The chemistry of

amidines and imidates

Volume 2

THE CHEMISTRY OF FUNCTIONAL GROUPS

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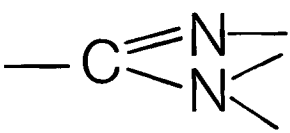

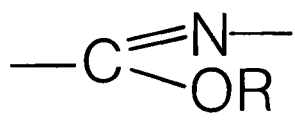

The chemistry of
amidines and imidates

Volume 2

Edited by

SAUL PATAI

and

ZVI RAPPOPORT

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Anat, Galit and Sara

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Foreword

The volume on *The chemistry of amidines and imidates* appeared in 1975 in the series *The chemistry of functional groups*. The size of the net text of that volume was 617 pages in a period when print sizes and distances between lines were considerably larger than in the more recent volumes of the Series. Even so, the present Volume 2 on the same topic contains 845 pages of net text, covering fifteen years of development of the subject. Another pleasing aspect to the editors is that while the twelve chapters of Volume 1 were written by authors in six countries, all in Europe and in the USA, in the sixteen chapters of Volume 2 authors from ten countries participated including several from what used to be behind the Iron Curtain (USSR, Poland) as well as from Japan, Italy, Finland, Sweden, Germany, UK, USA and Israel. Indeed the continued international character of the Series is a source of lasting satisfaction to the editors.

Two planned chapters failed to materialize for this volume: One on 'Biochemistry, pharmacology and toxicology' and the second on 'Isotopically substituted amidines, their preparation and uses'.

The literature coverage in most chapters is up to the end of 1989.

We would be grateful to readers who would draw our attention to mistakes or omissions in this volume.

Jerusalem
May 1991

SAUL PATAI
ZVI RAPPOPORT

The Chemistry of Functional Groups
Preface to the series

The series 'The Chemistry of Functional Groups' was originally planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the preparation, properties and reactions of the functional group treated and on the effects which it exerts both in the immediate vicinity of the group in question and in the whole molecule.

A voluntary restriction on the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series and in textbooks (i.e. in books which are usually found in the chemical libraries of most universities and research institutes), should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the topic. Therefore each of the authors is asked not to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level.

It is realized that no plan can be devised for a volume that would give a complete coverage of the field with no overlap between chapters, while at the same time preserving the readability of the text. The Editor set himself the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters. In this manner, sufficient freedom is given to the authors to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter deals with the general and theoretical aspects of the group.

(b) Chapters discuss the characterization and characteristics of the functional groups, i.e. qualitative and quantitative methods of determination including chemical and physical methods, MS, UV, IR, NMR, ESR and PES—as well as activating and directive effects exerted by the group, and its basicity, acidity and complex-forming ability.

(c) One or more chapters deal with the formation of the functional group in question, either from other groups already present in the molecule or by introducing the new group directly or indirectly. This is usually followed by a description of the synthetic uses of the group, including its reactions, transformations and rearrangements.

(d) Additional chapters deal with special topics such as electrochemistry, photochemistry, radiation chemistry, thermochemistry, syntheses and uses of isotopically labelled compounds, as well as with biochemistry, pharmacology and toxicology. Whenever applicable, unique chapters relevant only to single functional groups are also included (e.g. 'Polyethers'. 'Tetraaminoethylenes' or 'Siloxanes').

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the authors and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, some volumes may be published without giving consideration to the originally planned logical order of the chapters.

Since the beginning of the Series in 1964, two main developments occurred. The first of these is the publication of supplementary volumes which contain material relating to several kindred functional groups (Supplements A, B, C, D, E and F). The second ramification is the publication of a series of 'Updates', which contain in each volume selected and related chapters, reprinted in the original form in which they were published, together with an extensive updating of the subjects, if possible, by the authors of the original chapters. A complete list of all above mentioned volumes published to date will be found on the page opposite the inner title page of this book.

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editor.

The publication of this series would never have been started, let alone continued, without the support of many persons in Israel and overseas, including colleagues, friends and family. The efficient and patient co-operation of staff members of the publisher also rendered me invaluable aid. My sincere thanks are due to all of them, especially to Professor Zvi Rappoport who, for many years, shares the work and responsibility of the editing of this Series.

The Hebrew University
Jerusalem, Israel

SAUL PATAI

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
Alk	alkyl
All	allyl
An	anisyl
Ar	aryl
Bz	benzoyl (C_6H_5CO)
Bu	butyl (also *t*-Bu or Bu^t)
CD	circular dichroism
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
Cp	η^5-cyclopentadienyl
DBU	1,8-diazabicyclo[5.4.0] undec-7-ene
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulphoxide
ee	enantiomeric excess
EI	electron impact
ESCA	electron spectroscopy for chemical analysis
ESR	electron spin resonance
Et	ethyl
eV	electron volt
Fc	ferrocene
FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_3)
Hex	hexyl(C_6H_{13})
c-Hex	cyclohexyl(C_6H_{11})
HMPA	hexamethylphosophortriamide
HOMO	highest occupied molecular orbital
i-	iso
Ip	ionization potential

IR	infrared
ICR	ion cyclotron resonance
LCAO	linear combination of atomic orbitals
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	metal
M	parent molecule
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MNDO	modified neglect of diatomic overlap
MS	mass spectrum
n-	normal
Naph	naphthyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Pen	pentyl(C_5H_{11})
Pip	piperidyl($C_5H_{10}N$)
Ph	phenyl
ppm	parts per million
Pr	propyl (also *i*-Pr and Pr^i)
PTC	phase transfer catalysis
Pyr	pyridyl (C_5H_5N)
R	any radical
RT	room temperature
s-	secondary
SET	single electron transfer
SOMO	singly occupied molecular orbital
t-	tertiary
TCNE	tetracyanoethylene
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TMEDA	tetramethylethylene diamine
Tol	tolyl(MeC_6H_4)
Tos or Ts	tosyl(*p*-toluenesulphonyl)
Trityl	triphenylmethyl(Ph_3C)
Xyl	xylyl($Me_2C_6H_3$)

In addition, entries in the 'List of Radical Names' in *IUPAC Nomenclature of Organic Chemistry*, 1979 Edition. Pergamon Press, Oxford, 1979, p. 305–322, will also be used in their unabbreviated forms, both in the text and in formulae instead of explicitly drawn structures.

CHAPTER 1

General and theoretical aspects of amidines and related compounds

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The Chemistry of Amidines and Imidates, Volume 2
Edited by S. Patai and Z. Rappoport

I. INTRODUCTION

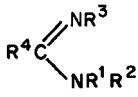
Amidines, the nitrogen analogues of carboxylic acids, are structural parts of numerous compounds of biological interest and form important medical and biochemical agents[1-3].

Since the publication of the monograph of this series[2] in 1975 these compounds have found wide interest with respect to determinations of molecular structures, quantum chemical calculations, physico-chemical properties and synthesis. Amidines find widespread applications in organic synthesis especially for the preparations of various heterocyclic systems. Methods of preparations and reactions of amidine systems have been reviewed lately by Granik[3] with 259 references for the period of 1971 to 1981.

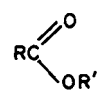
In this introductory chapter on general and theoretical aspects emphasis will be placed on molecular structure and properties of amidines and related compounds calculated by means of *ab initio* SCF MO procedures. These will concentrate on experimental and calculated molecular geometries, *E,Z* isomerism, rotational conformers, tautomerism, H-bonding effects and basicities.

II. GENERAL OVERVIEW

Amidines of the general formula **1** are nitrogen analogues of carboxylic acids (**2a**), esters (**2b**) or amides (**3**) which are each treated in separate volumes of the present series on functional groups[4-6]. The chemistry of amidines has already been reviewed three times[1-3].

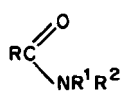


(1)



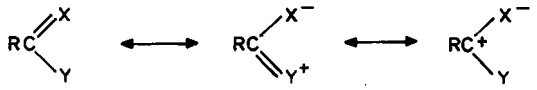
(2a) R′=H

(2b) R′= alkyl or aryl



(3)

These compounds are special cases of n–π conjugated heteroallylic systems which are isoconjugated to the allyl-anion (**4**: X = Y = CH_2) and described by the mesomeric formulae **4a–4c**. Further examples of hetero-allyl π-systems are collected in Table 1. Of



(4a) (4b) (4c)

TABLE 1. Heteroallylic π-systems **4**

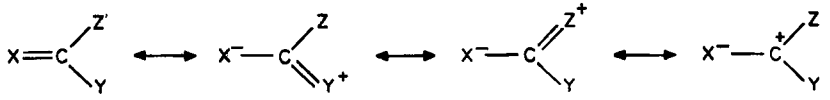
Class of compounds	X	Y	References
Carboxylic acids	O	OH	4,6
Carboxylates	O	O^-	4,6
Esters	O	OR	4,6
Acid halides	O	F, Cl, Br or I	7
Acid anhydrides	O	OCOR	
Amides	O	NR^1R^2	5
Thioamides	S	NR^1R^2	
Amide oximes	NOH	NR^1R^2	
Amidines	NR^3	NR^1R^2	1–3
Imidic acids	NR	OH	6
Imidates (imino ethers)	NR	OR′	2
Thioimidates	NR	SR′	
Imidoyl chlorides	NR	Cl	
Amidrazones	NR	$NHNH_2$	
Imidines	NR	$NR^1—C(=NR^2)—R^3$	

these imidic acids and imidates are especially related to amidines and will also be treated in this chapter.

Amidines contain two nitrogens of different functionality: a formally single-bonded amide-like amino nitrogen (denoted N_{am}) and a formally doubly-bonded imino nitrogen (N_{im}). Sometimes in the literature these two nitrogens have been (erronously) named sp^3 and sp^2 nitrogens[8–10], a problem which will be treated later.

As a consequence of conjugation, the formal CN double bond in **4a** will be slightly elongated and the formal CN single bond will be shortened by gaining some double-bond character as shown in the mesomeric form **4b**. This leads to an increase in the barrier of torsional rotation around the CN single bond with the possibility of rotational conformers.

An extension of the conjugation system leads to cross-conjugated or Y-delocalized hetero-π-systems[11,12] of the general type given by mesomeric formulae **5a** to **5d** for which chemical examples are given in Table 2. These are isoconjugated to the trimethylene dianion[12,13] (**5**: X = Y = Z = CH_2).

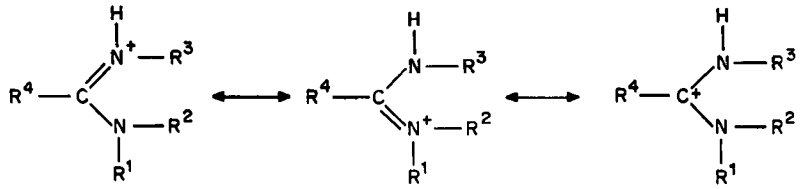


(5a) **(5b)** **(5c)** **(5d)**

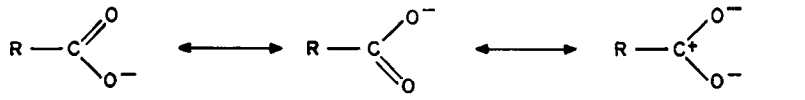
TABLE 2. Chemical examples of cross-conjugated π-systems **5**

Class of compounds	X	Y	Z
Carbonic acid	O	OH	OH
Dialkyl carbonates	O	OR	OR′
Urethanes	O	OR	NR^1R^2
Ureas	O	NR^1R^2	NR^3R^4
Thioureas	S	NR^1R^2	NR^3R^4
Guanidines	NR^5	NR^1R^2	NR^3R^4

Amidines (and especially guanidines) are strong organic bases. Their protonation occurs at the imino nitrogen[10,14] leading to the symmetrical amidinium cation **6** which is stabilized by conjugation as shown by the mesomeric formulae **6a–6c** that are similar to the isoelectronic carboxylate anions **7a–7c**, leading (depending on substituents R^1 to R^3) to equivalent CN bond lengths in **6**.

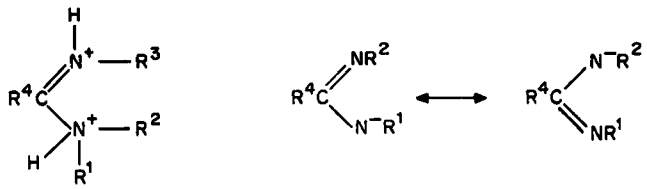


(6a) **(6b)** **(6c)**



(7a) **(7b)** **(7c)**

In strong acidic media double protonation leading to a dication **8** is observed[1,15,16] and **8** has a localized immonium C=N double bond.



(8) **(9a)** **(9b)**

With strong bases anionic amidinates **9** are formed[16] and may be stabilized by reactions with transition metal complexes[17,18].

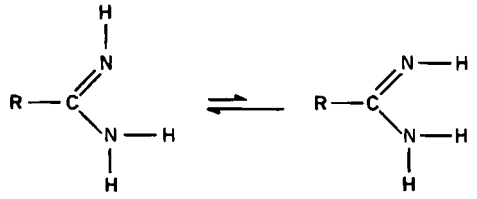
III. CLASSIFICATIONS AND NOMENCLATURE

The functional amidino group may be acyclic or part of different heterocyclic ring systems. Depending on the number and distribution of substituents (R may be H, alkyl or aryl, but usually not a heteroatom) acyclic amidines may be classified in six general types:

A. Acyclic Amidines

1. Unsubstituted amidines

As shown in formulae **10a** and **10b** these amidines occur as *E,Z* (*syn, anti* or *cis,trans*) isomers with respect to the C=N double bond. Generally the *E* form is energetically preferred[19].



(10a) *E* **(10b)** *Z*

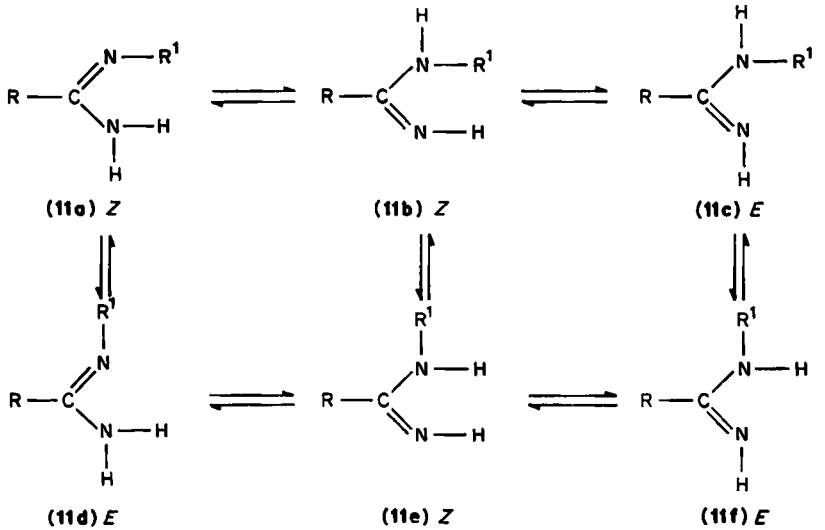
In the chemical literature amidines are named after the carboxylic acid or the amide which may be obtained from them by hydrolysis; thus R = H in **10** is formamidine, $R = CH_3$ is acetamidine and R = phenyl is benzamidine. As basic groups these three unsubstituted amidines will be considered later explicitly.

In *Chemical Abstracts* (CA) specific amidines are now named as amides of the corresponding imidic acid. Thus hexanimidamide is the name of the amidine derived from hexanoic acid by replacing the carboxyl group by $-C(=NH)NH_2$. The trivial name guanidine is retained for carbonimidic diamide: $H_2NC(=NH)NH_2$. Cyclic amidines are indexed at ring names. The locants N and N′ denote the amide and imide nitrogen atoms, respectively.

In the following text R, the substituent on the amidino carbon, may be hydrogen or any alkyl, aryl or heteroaryl substituent. If it is a hetero atom one deals with the Y-conjugated π-systems of Table 2. In these cases, i.e. when R is oxygen or fluorine[20], care must be taken with the application of the *E,Z* nomenclature because then the form **10a** must be denoted as *Z* due to the higher priority of oxygen or fluorine with respect to the amino nitrogen, and not *E* as in the case of R = H or alkyl. Substituents on nitrogens (R^1 to R^3) should be alkyl or aryl.

2. *N- or N′-Monosubstituted amidines*

Monosubstituted amidines should occur as pairs of tautomers as indicated by formulae **11a** and **11b** as well as **11d** and **11e**. But numerous experimental attempts to isolate or



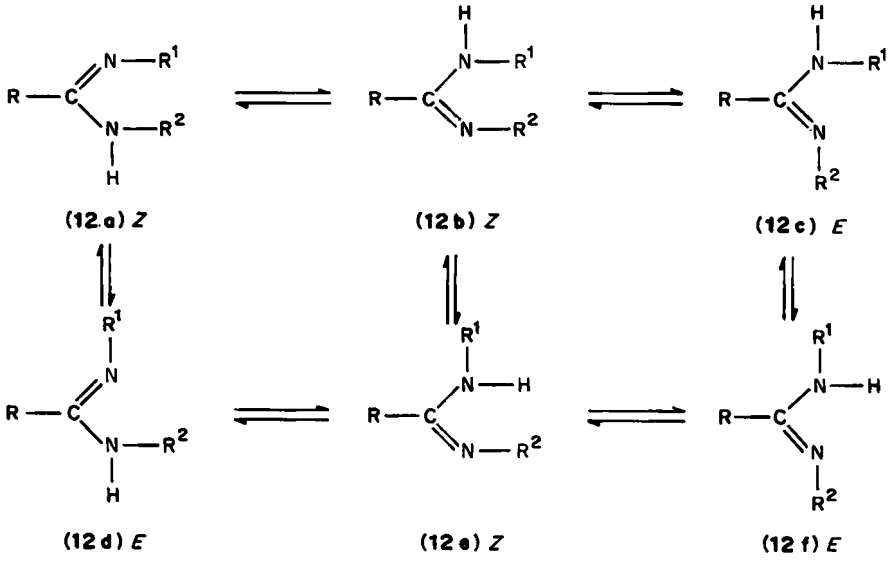
(11a) *Z* **(11b)** *Z* **(11c)** *E*

(11d) *E* **(11e)** *Z* **(11f)** *E*

prove the existence of both tautomers in equilibrium apparently all failed[21,22]. In addition *E,Z* isomerism with respect to the C=N double bond in **11a** versus **11d**, **11b** versus **11c** and **11e** versus **11f** should be observable as well as s-*cis* or s-*trans* rotamers with respect to the C—N single bond shown in **11b** versus **11e** and **11c** versus **11f**. By computations these six different configurations may be clearly distinguished (see Table 19).

3. *N,N'-Disubstituted amidines*

If the substituents R^1 and R^2 on nitrogens are different these *N,N'*-disubstituted amidines show the same kinds of isomerism as those of the monosubstituted amidines; tautomers: **12a** versus **12b** and **12d** versus **12e**; *E,Z* isomers: **12a** versus **12d**, **12b** versus **12c** and **12e** versus **12f**; rotamers: **12b** versus **12e** and **12c** versus **12f**.



4. *N,N-Disubstituted amidines*

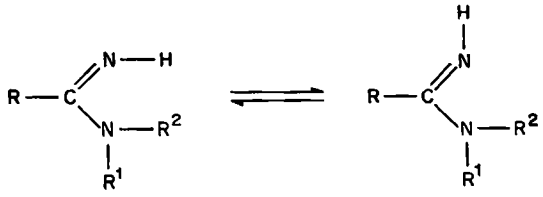
In these amidines the amino functionality is fixed by substitution and no tautomerism is possible. Only *E,Z* isomers **13a** and **13b** with corresponding rotamers **13c** and **13d** may be differentiated if R^1 and R^2 are different.

5. *N^1,N^1,N^2-Trisubstituted amidines*

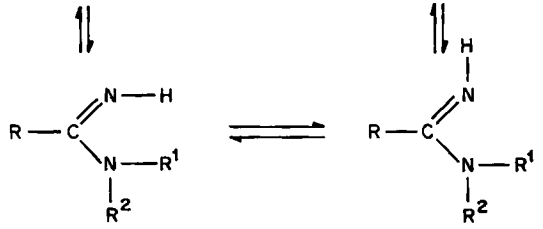
In these fully substituted amidines, as mentioned before, *E,Z* isomerism **14a** versus **14b** and **14c** versus **14d** as well as two pairs of rotamers **14a** versus **14c** and **14b** versus **14d** are possible if R^1 and R^2 are different.

6. *N,N,N',N'-Tetrasubstituted amidinium cations*

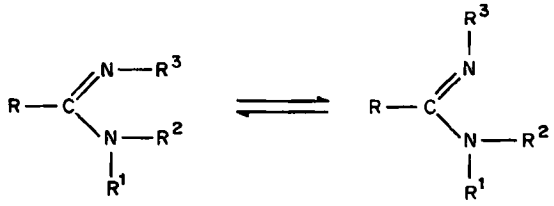
Each type of the amidines listed before may, by protonation or alkylation at the imino nitrogen, be converted into the symmetrical amidinium cation **15** in which the positive



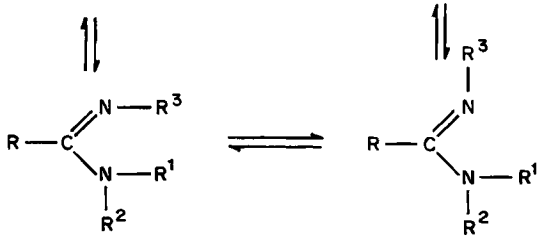
(13 a) *Z* (13 b) *E*



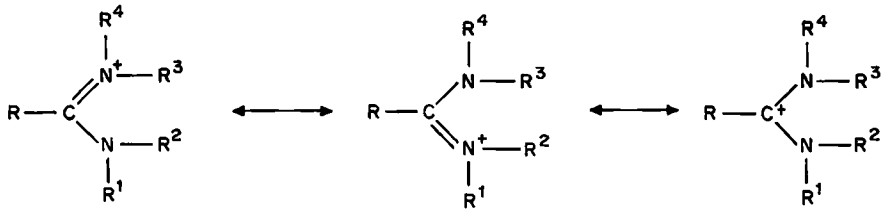
(13 c) *Z* (13 d) *E*



(14 a) *Z* (14 b) *E*



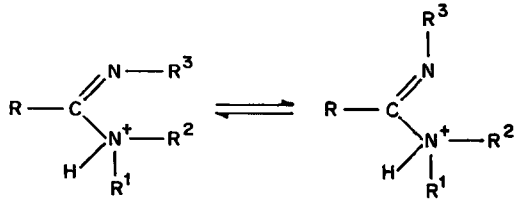
(14 c) *Z* (14 d) *E*



(15 a) (15 b) (15 c)

charge is evenly distributed in the heteroallyl π-system as indicated by the mesomeric forms **15a** to **15c**.

Protonation at the amino nitrogen leading to **16** is calculated[19] in the case of formamidine to be 37 kcal mol^{-1} higher in energy than the symmetrical cation **15**.



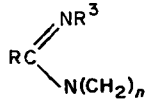
(16 a) *Z* **(16 b) *E***

B. Cyclic Amidines

Various types of rings may incorporate the amidino group into heterocyclic systems:

1. Amino group part of the heterocycle

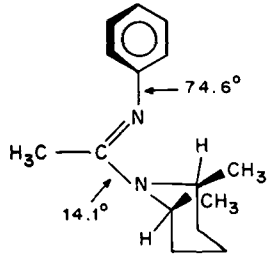
These amidines are a special case of the acyclic derivatives mentioned in Sections III.A.4 and III.A.5. For two derivatives of this class of compounds, namely 2,6-*cis*-



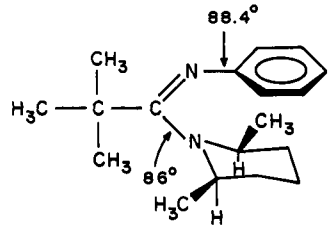
(a) n **= 4 pyrrolidino**
(b) n **= 5 piperidino**

(17) *Z*

dimethylpiperidyl-*N*-phenylacetamidine (**18**) and 2,6-*cis*-dimethylpiperidyl-*N*-phenyl-2,2-dimethylpropionamidine (**19**), an X-ray determination of molecular structures was reported by Gilli and Bertolasi[23]. The sterically demanding *tert*-butyl substituent in **19** forces the phenyl substituent in the usually not preferred *Z*-form out of the plane with a twist angle of 88.4°. The di-equatorial dimethylpiperidine ring is twisted by 86° out of the plane of the amidine group with a corresponding increase in the C—N bond lengths and with a short C=N double bond.



(18) *E*

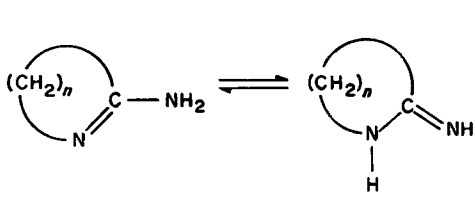


(19) *Z*

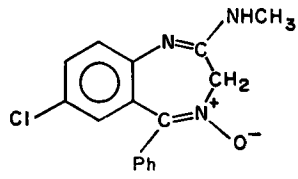
In **18** the phenyl substituent shows the generally preferred *E* orientation still with a large twist angle of 74.6°. The di-axial dimethylpiperidine group is only slightly twisted out of the plane of the amidine group (by 14.1°).

2. Imino group part of the heterocycle

These amidines may show tautomerism in which case the imino group may be endocyclic (**20a**) or exocyclic (**20b**). This substitution pattern is shown in the well-known tranquilizer chlordiazepoxide (Librium, **21**).



(**20a**) $n = 3$ $n = 4$ (**20b**)



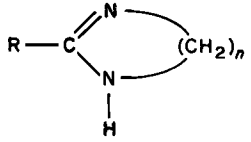
(**21**)

3. Amidino group incorporated in one heterocycle

If the amidino group is incorporated into one ring, a series of homologous compounds as shown in **22a** to **22e** is obtained. The three- and four-membered ring systems isodiazirine (**22a**) and 1,3-diazetidine (**22b**) are not known experimentally. *Ab initio* calculations[24] indicate that **22a** is the least stable of seven structural isomers of diazomethane, due to its iso-electronic relation to the Hückel anti-aromatic cyclopropenyl anion.

The five-, six- and seven-membered ring systems (**22c** to **22e**) are experimentally well known and may be synthesized in good yields by treatment of the appropriate diamines with HCN[25] or isonitriles[26].

The chemistries of Δ^2-imidazolines[27] (**22c**) and of 1,3-diazepines[28] (**22e**) have been reviewed separately. These cyclic amidines behave like the corresponding acyclic *N,N'*-disubstituted amidines (Section III.A.3).

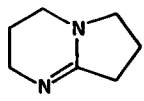


(**22**)

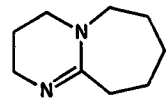
(**a**) $n = 0$ isodiazirine
(**b**) $n = 1$ 1,3-diazetidine
(**c**) $n = 2$ Δ^2-imidazoline
(**d**) $n = 3$ tetrahydro-Δ^2-pyrimidine
(**e**) $n = 4$ 1,3-diazepines

4. Bicyclic amidines

The amidino group may be part of two rings leading to bicyclic amidines. Of these 1,5-diazabicyclo[4.3.0]nonen-5 (DBN, **23**) and 1,8-diazabicyclo[5.4.0]undecen-7 (DBU, **24**) found wide applications as non-nucleophilic bases for dehydrohalogenations[29–31], aldol



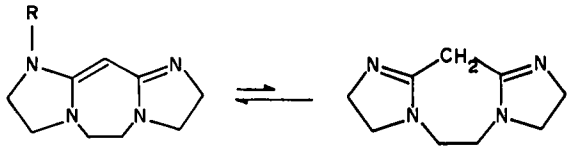
(23) DBN



(24) DBU

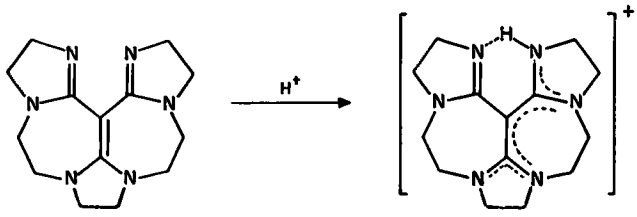
condensations[32] and preparations of Wittig reagents[33]. The chemistry of these compounds was reviewed recently[34,35].

Another class of bicyclic amidines, a series of so-called vinamidines (**25a–25c**), has been synthesized[36]. The ^{1}H-NMR spectrum of **25a** shows that the tautomeric malonic acid diamidine form **26a** is not detectably present. Modification of this structure[37] leads to **27**, which may act as a non-nucleophilic proton-sponge with strong delocalization of the positive charge in the cation **28**.



(25a) R=H
(25b) R=CH_3
(25c) R=$COCH_3$

(26a)



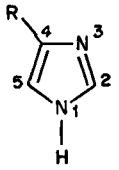
(27) (28)

C. Cyclic Heteroaromatic Amidines

The amidino group may be incorporated fully or partly in cyclically conjugated unsaturated ring systems. These heteroaromatic systems are mentioned here to show the wide distribution and importance of the amidino group in organic chemistry. The structural properties and basicities of the amidino group will be modified by cyclic conjugation in the aromatic ring[38].

1. Amidino group fully part of the ring

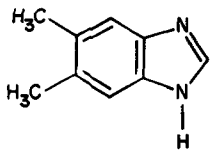
This structural principle occurs in odd-membered heterocycles. The most important example is imidazole[39–41] **29a** which occurs in the amino acid histidine **29b** and in the biogenic amine histamine **29c**. Dimethylbenzimidazole (**30**) is part of native vitamin B_{12}[42].



(29a) R = H

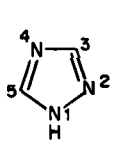
(29b) R = $CH_2CH(NH_2)COOH$

(29c) R = $CH_2CH_2NH_2$

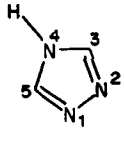


(30)

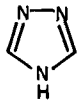
Other examples of azoles with an amidine structural unit are the 1*H*- and 4*H*-1,2,4-triazoles[43] **31a** and **31b**, 1,3,4-triazole[43] **32** and 1*H*-tetrazole[44] **33**.



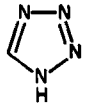
(31a)



(31b)

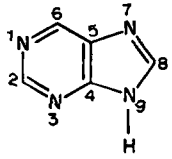


(32)

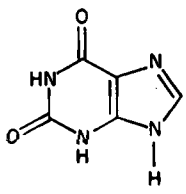


(33)

Bicyclic heteroaromatic compounds containing the amidino group are biologically active derivatives of 9*H*-purine[45] (**34**), which contains formally a monocyclic (7, 8, 9) and a bicyclic amidino group (3, 4, 9). Natural products are xanthine (**35**) and its methylation product caffeine (**36**).



(34)



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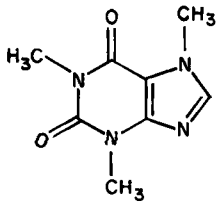
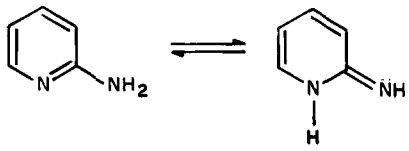


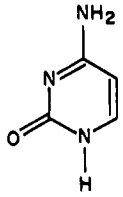
(36)

2. Amidino group only partly incorporated

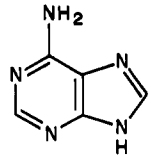
This situation is typically observed in α-amino pyridine (**37**) in which the possibility of tautomerism between an amino form (**37a**) and an imino form (**37b**) has to be taken into account.



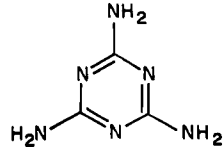
(37a) (37b)



(38)



(39)



(40)

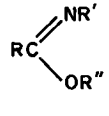
Important examples are the DNA and RNA constituents cytosine (**38**) and adenine (**39**) as well as melamine (**40**).

D. Amidine Related Compounds

1. Acyclic imidates

In Table 1 above various heteroallylic π-systems which are related to amidines are collected. Free imidic acids (**41a**) which are tautomers of amides (**41b**) are usually not observed in equilibrium[46] because the amide form is energetically much more favoured[47]. However, alkylation or arylation fixes the imino form **41a** in which case the chemical class of imidates (**42**, also named imino ethers, imido esters or imidic acid esters) is obtained. Their chemistry is treated separately in this volume.

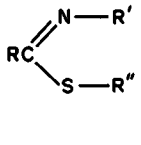
(41a) (41b)



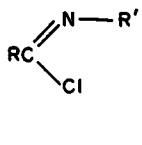
(42)

R′ = H, alkyl or aryl

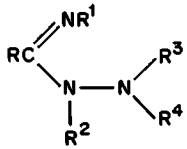
R″ = alkyl or aryl



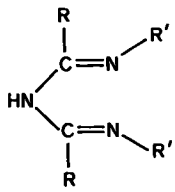
(43)



(44)



(45)

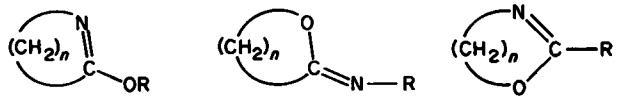


(46)

Further imidic acid derivatives are thioimidates (**43**), imidoyl chlorides (**44**), amidrazones (**45**) and imidines (**46**, nitrogen analogues of carboxylic acid anhydrides).

2. Cyclic imidates

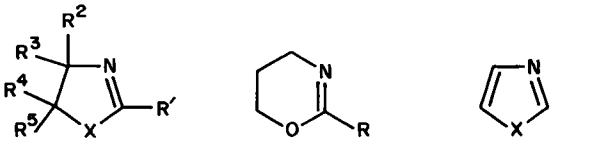
Of chemical importance are cyclic imidates and thioimidates either in exocyclic forms **47** and **48** or as endocyclic derivatives **49**.



(47) (48) (49)

Special cases of **49** are Δ^2-oxazolines (**50a**) whose chemistry was reviewed separately[48,49], Δ^2-thiazolines[26,50] (**50b**) and 5,6-dihydro-4*H*-1,3-oxazines[51] (**51**).

In a wide sense oxazole[52] (**52a**) and thiazole[53] (**52b**) form a special group of heteroaromatic imidates.



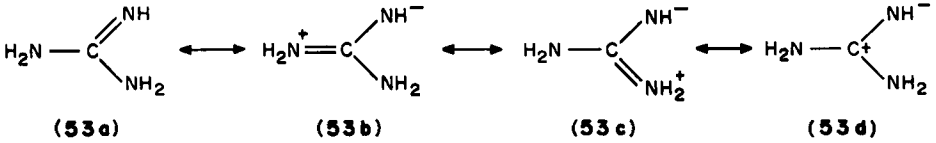
(50a) X = O
(50b) X = S

(51)

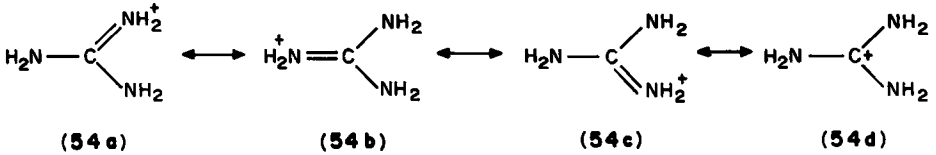
(52a) X = O
(52b) X = S

3. *Y-Conjugated systems: guanidines and guanidinium cations*

Of the Y- or cross-conjugated systems shown in Table 2 above guanidine (**53**) is most important and closely related to amidines. It is a very strong mono-acidic organic base, having a pK_a of 13.6, which is comparable to the basicity of the hydroxide anion. On protonation the symmetrically Y-delocalized guanidinium cation **54** is formed. For both forms four mesomeric structures, **53a** to **53d** and **54a** to **54d**, may be formulated. The first three are identical in energy for the cation but the fourth one apparently describes best the calculated charge distribution (see p. 51).

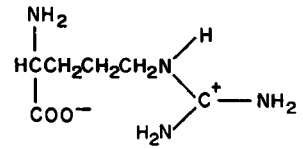


(53a) (53b) (53c) (53d)



(54a) (54b) (54c) (54d)

The guanidinium cation **54** has a singular structure with the possibility of so-called Y-conjugation[11,12] and the possibility to engage in patterns of hydrogen bonding which are rare, if not indeed unique. These properties may well account for the evolutionary selection of L-arginine (**55**) as one of the about 20 amino acids commonly found in proteins. In **55** the guanidinium group occurs as the zwitterionic internal salt.



(55)

IV. EXPERIMENTAL DETERMINATIONS OF MOLECULAR STRUCTURES

The structural chemistry of amidines and related species is treated by Krygowski in a separate chapter of this volume. Therefore here only results of highly accurate determinations of CN distances in basic structures are reported which are useful for comparison with calculated molecular geometries reported in Section VI.

A. CN Bond Distances for Comparison with Amidine Systems

Experimental CN bond lengths collected in Table 3 show a wide variety of distances as dependent on molecular structures, i.e. primary, secondary or tertiary nitrogen, the kind of hybridization at carbon and nitrogen, and of the state of aggregation [solid-state X-ray (XD) or neutron diffraction (ND) of single crystals versus gas-phase electron diffraction (ED) or microwave (MW) determinations].

Averaged gas-phase ED and MW data for C_{sp^3}—N_{sp^3} single bond lengths given in Table 4 show a small but significant reduction with increase in alkylation from 1.470 to 1.467 to 1.454 Å for primary, secondary and tertiary amines. However, averaged solid-state XD data of amides[54] indicate an increase in CN single bonds from 1.456 Å for secondary to 1.471 Å for tertiary amides. Quaternization leads to elongated XD CN distances of 1.499 Å. The unconjugated C_{sp^2}=N_{sp^2} double-bond MW distance is 1.273 ± 0.008 Å.

Solid-state XD data for amide-type C_{sp^2}—N_{sp^2} bonds, which are formally related to the amidino group and are, because of conjugation, intermediate between CN single and double bonds, show by statistical analysis[54] an increase from 1.322 to 1.331 to 1.346 Å for primary, secondary and tertiary amides. The corresponding C=O distances are slightly reduced in the same sequence from 1.234 to 1.231 to 1.228 Å.

Only for formamide and acetamide are both solid-state and gas-phase data available. These indicate 0.045 Å longer CN distances in the gas phase than in the solid state which is well above experimental errors. This difference must reflect the effect of the hydrogen-bonded network in the solid which is not present in the gas-phase determinations.

B. CN Distances in Neutral Amidines

For amidines and amidinium cations only solid-state X-ray determinations are reported in the literature, although *ab initio* calculated molecular geometries should be compared to gas-phase data.

Recently in the literature a large number of XD determinations of molecular structures of neutral amidines have appeared which are collected in Table 5. This reflects the widespread interest in such compounds because of their pharmaceutical use as well as their biological importance and bonding or ligand properties.

In Scheme 1 the structural formulae for the amidines of Table 5 are shown. These are classified according to the substitution pattern of acyclic amidines presented in

TABLE 3. Experimental CN distances (in Å) for comparison with amidine systems (quoted limits of error in parentheses)

Type of bond	Compound	Method/parameter[a]	C—N	C—O	Ref.
C_{sp^3}—$N^+_{sp^3}$	Ethylamine·HBr	XD	1.499(12)		55
	Taurine ($H_3\overset{+}{N}$—CH_2CH_2—SO_3^-)	XD	1.501(14)		56
	Piperidine·HCl	XD	1.497(10)		57
	Piperazine·2HCl·H_2O	XD	1.490(10)		58
			1.509(10)		
C_{sp^3}—N_{sp^3}	Methylamine	MW	1.474(5)		59
		ED r_g	1.465(2)		60
Secondary:	Dimethylamine	ED r_g	1.465(2)		61
		MW r_0	1.466(8)		62
	Piperidine	ED r_a	1.472(11)		63
	Piperazine	ED r_g	1.467(4)		64
Tertiary:	Trimethylamine	MW r_s	1.451(3)		65
		ED r_α°	1.458(2)		66
	Dimethylethylamine	ED r_g	1.452(2)		67
C_{sp^2}—N_{sp^3}	Aniline	ED r_g	1.401(2)		68
C_{sp^2}=N_{sp^2}	Methylene imine	MW r_0	1.273(8)		69
C_{sp^2}—N_{sp^2}	Formamide	MW r_s	1.352(12)	1.219(12)	70
		MW r_0	1.376(10)	1.193(20)	71
		ED r_g	1.367(4)	1.211(4)	72
		ED r_g	1.368(3)	1.212(3)	72
		ED + MW r_{av}	1.3665	1.210	72
		XD	1.318(1)	1.241(1)	73
	Acetamide	ED r_g	1.380(4)	1.220(3)	74
		XD	1.336(4)	1.243(4)	75
		ND, 23 K	1.337(1)	1.250(1)	76
	Diacetamide	ED r_g	1.402(2)	1.210(2)	77
	Urea	XD	1.360(6)	1.278(7)	78
	Tetramethylurea	ED r_g	1.397(4)	1.240(5)	79

[a]Definitions of ED and MW structureal parameters are well documented in the literature[80,81]. ED: r_a = constant distance argument in molecular scattering intensity curve; r_g = thermal average of the mean interatomic distance (the recommended value for comparisons with other structural parameters); r_α^0 = average distance in the ground vibrational state. MW: r_s = structure derived from isotopic substitution in the molecule; r_0 = effective ground-state structure.

TABLE 4. Averaged values of CN distances (in Å) from Table 3 and literature

Type of bond	Compound	Method/ parameter	C—N	C—O	Ref.
$C_{sp^3}—N_{sp^3}^+$	Quaternary CN^+	XD	1.499(10)		
$C_{sp^3}—N_{sp^3}$	Primary amines	MW	1.470(5)		
	Secondary amines	ED, MW	1.467(3)		
	Tertiary amines	ED	1.454(3)		
	Secondary amides	XD	1.456(14)		54
	Tertiary amides	XD	1.471(7)		54
$C_{sp^2}—N_{sp^2}^+$	Imines	MW	1.273(8)		69
$C_{sp^2}—N_{sp^2}$	Primary amides	XD	1.322(13)	1.234(11)	54
	Secondary amides	XD	1.331(11)	1.231(11)	54
	Tertiary amides	XD	1.346(10)	1.228(9)	54
	Formamide	XD	1.318(1)	1.247(1)	73
		ED, MW	1.366(4)	1.209(4)	
	Acetamide	XD, ND	1.337(3)	1.247(3)	
		ED	1.380(4)	1.220(3)	74

Section III.A. With the exception of N-monosubstituted **57** to **59** and trisubstituted (**19**) amidines the substituents at the imino nitrogens form *E* isomers with respect to the amino group. The *Z* configuration is forced by the bulky *tert*-butyl substituent on carbon in **19** and in **59**. In **58** the *p*-nitrophenyl ring is nearly perpendicularly twisted out of the plane of the amidino group which allows full conjugation with the lone electron pair on the imino nitrogen, but the phenyl ring on carbon is only twisted by 21.1° so that it is a sterically demanding substituent. In **57** internal hydrogen bonding between the amino group and the heterocyclic substituent may lead to the observed *Z* orientation.

Rotational isomerism with respect to the CN single bond shows s-*cis* rotamers for larger substituents in **60**, **61**, **66** and **67** as well as s-*trans* rotamers in **62** and **63**.

The most unusual molecular structures are shown by the *N,N'*-diarylformamidines **60** and **61**, which form two differently hydrogen-bonded dimers as shown in Scheme 1. In **60** the hydrogen bonding is similar to that observed in dimers of carboxylic acids, but in **61** one part of the dimer is a cationic amidinium form and the other is the negative imidinate form. Acetamidine (**56**) forms a hydrogen-bonding network connecting four molecules with hydrogen donation from the NH_2 groups and acception at imino nitrogens. The imino hydrogen is not involved in hydrogen bonding.

Krygowski and coworkers[87] showed that for experimental CN distances a shortening of formal single-bond distances is linearly related to the elongation of formal C=N distances of amidines with regression equation 1 for 8 data points and a linear regression coefficient $R = 0.966$.

$$d_{C=N} = 2.059 - 0.567 d_{C-N} \quad (1)$$

For 23 data points collected in Table 5 we obtain the corresponding equation 2 with the plot given in Figure 1. Our *R* value is 0.922 and the standard deviation is 0.009 Å. Only one point for **62** is far off the regression line.

$$d_{C=N} = 2.304 - 0.546 d_{C-N} \quad (2)$$

As a measure of conjugation in the amidino group[20] the difference of CN bond distances $\Delta = d_{am} - d_{im}$ as given in Table 5 may be used. This value is zero for bond equalization due

TABLE 5. XD experimental CN distances (in Å) in neutral amidines

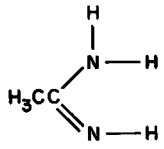
No.	Compound	C—N	C=N	C—X	Δ	Ref.
56a	Acetamidine	1.344(1)	1.298(1)	1.502(1)	0.046	82
56b	Acetamidine $CoClCO_3H_2O$	1.348(7)	1.298(8)	1.499(6)	0.050	83
57	5-(1-Aminoethylidene-amino)-3-chloromethyl-1,2,4-thiadiazole	1.327(5)	1.317(5)	1.493(6)	0.010	84
58	*N'-p*-Nitrophenylbenz-amidine	1.355(5)	1.280(5)	1.495(4)	0.075	85
59a	*N*-Pivaloylpivalamidine	1.320(5)	1.318(5)	1.552(6)	0.002	86
59b	*N*-Pivaloylpivalamidine	1.324(5)	1.323(5)	1.528(7)	0.001	86
60	*N,N'*-Diphenylformamidine	1.323(3)	1.311(3)		0.012	87
	dimer	1.314(3)	1.305(3)		0.009	
61	*N,N'*-Di-(*p*-bromophenyl)-formamidine dimer	1.311(5)	1.311(5)		0.000	88
		1.313(5)	1.313(5)		0.000	
62	*N,N'*-Diphenylbenzamidine	1.369(8)	1.310(8)	1.481(8)	0.059	89
		1.351(7)	1.295(6)	1.488(7)	0.056	
63	5-(1-Imino-*N*-methylethyl-amino)-3-methyl-1,2,4-thiadiazole	1.395(5)	1.264(3)	1.490(3)	0.131	90
64	*N,N*-Dimethylbenzamidine wolfram pentacarbonyl	1.349(7)	1.303(7)	1.486(8)	0.046	91
65	*N,N*-Pentamethylene-*N'*-(*p*-nitrophenyl)formamidine	1.334(5)	1.301(6)		0.033	92
66	*N'-p*-Bromophenyl-*N*-methyl-*N*-(*p*-tolyl) acetamidine	1.366(8)	1.273(8)	1.522(10)	0.093	93
18	2,6-*cis*-Dimethylpipe-ridyl-*N*-phenylacet-amidine	1.374(3)	1.278(3)	1.516(3)	0.096	23
19	2,6-*cis*-Dimethylpipe-ridyl-*N*-phenyl-2,2-dimethylpropionamidine	1.441(5)	1.263(5)	1.529(5)	0.178	23
		1.424(5)	1.263(5)	1.536(6)	0.162	23
67	*N*-Methyl-*N*-phenyl-*N'*-(*p*-tolyl)-benzamidine	1.365(5)	1.286(6)	1.490(6)	0.079	94
68	*N'*-(*m*-Chlorophenyl)-*N,N*-pentamethylene benzamidine	1.365(6)	1.290(6)	1.497(7)	0.075	95
69	*N'*-(*p*-Methoxyphenyl)-*N,N*-pentamethylene benzamidine	1.372(5)	1.283(5)	1.468(5)	0.089	96a
70	Bis-(*N'-p*-nitrophenyl-*N,N*-diethyl) oxamidine	1.343(3)	1.294(3)		0.049	96b
		1.348(3)	1.294(3)		0.054	

to complete conjugation (as in amidinium cations). Its maximum experimental value with 0.178 for no conjugation in a perpendicularly twisted amidino group in an amidine may be derived from **19** because the sterically large *t*-butyl substituent at the amidino carbon forces the substituted amidino nitrogen to be twisted by 90° from the plane of the amidino group.

C. Experimental Molecular Structures of Amidinium Cations

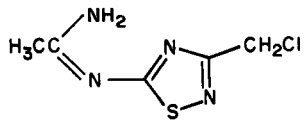
In Table 6 experimental XD CN distances for 17 amidinium cations with different substitution patterns are presented; molecular formulae are given in Scheme 2. Due to

1. Unsubstituted amidines (see Section III.A.1)

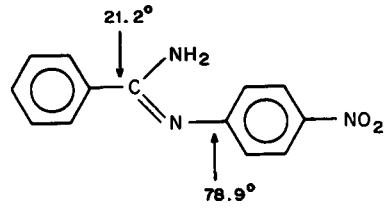


(56)

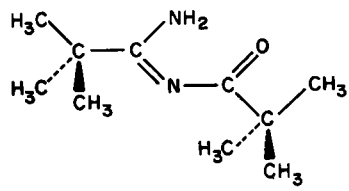
2. *N*-Monosubstituted amidines (see Section III.A.2)



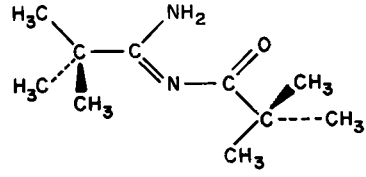
(57)



(58)

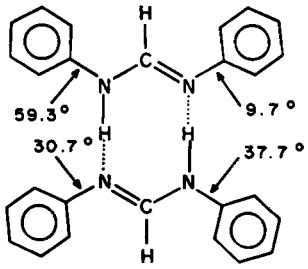


(59a)

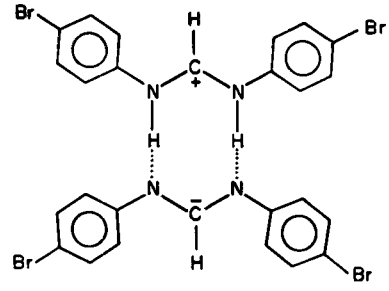


(59b)

3. *N*,*N*′-Disubstituted amidines (see Section III.A.3)

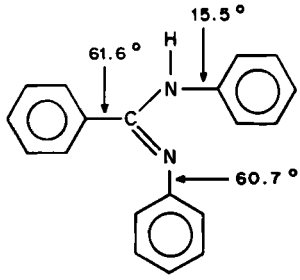


(60)



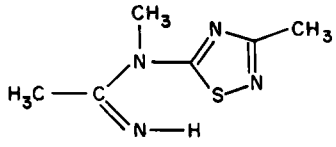
(61)

SCHEME 1 (*continued on next page*)

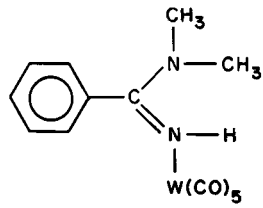


(62)

4. N^1,N^1-Disubstituted amidines (see Section III.A.4)

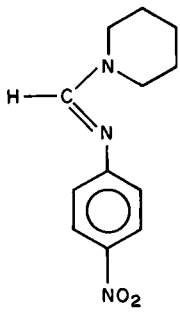


(63)

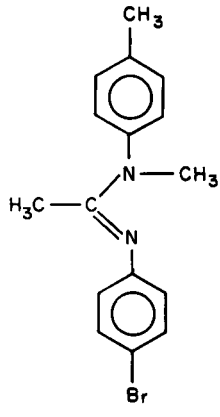


(64)

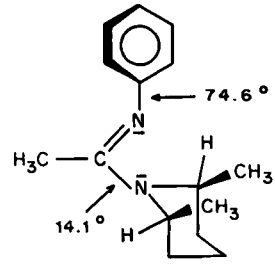
5. N^1,N^1,N^2-Trisubstituted amidines (see Section III.A.5)



(65)

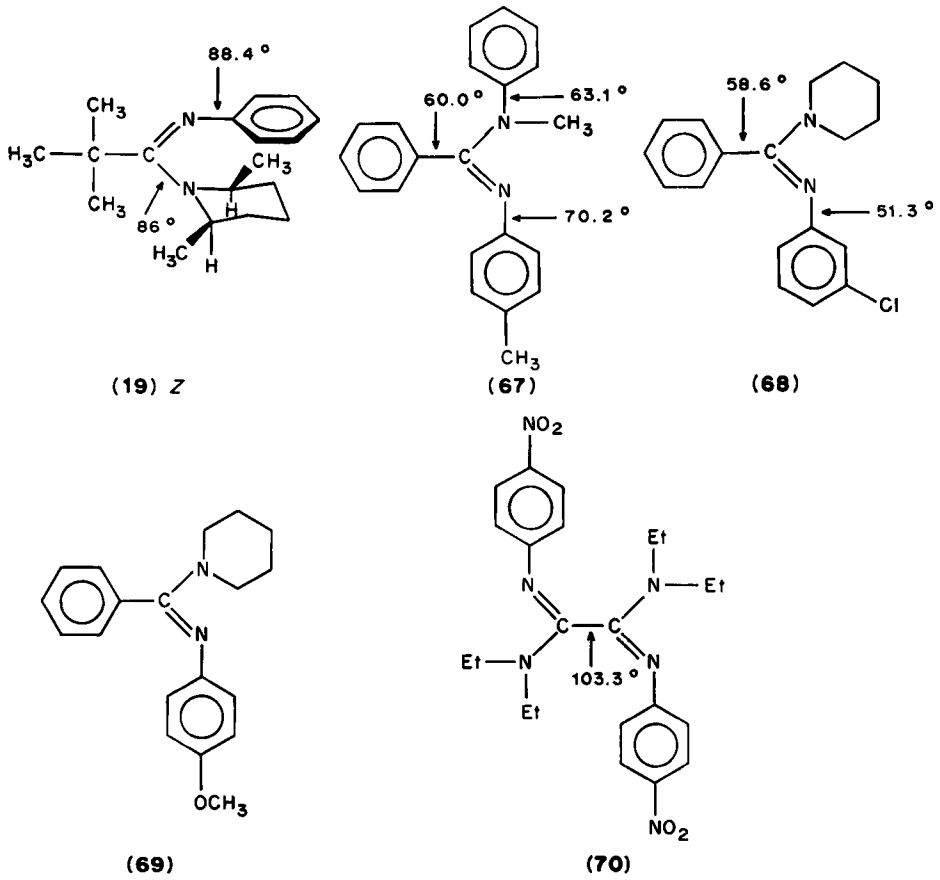


(66)



(18) *E*

SCHEME 1 (*continued*)



SCHEME 1. Structural formulae for XD data of neutral amidines presented in Table 5

delocalization in the protonated cations the CN distances are equal or differ only slightly. Krygowski and coworkers[87] derived equation 3 for seven amidinium cations where the shorter versus longer bond distances are linearly related, but, contrary to equations 1 and 2 of amidines, with a positive slope (R = 0.990).

$$d_{C=N} = -0.367 + 1.275 d_{C-N} \tag{3}$$

For 26 data from Table 6 we obtain the regression equation 4 with $R = 0.870$ and esd = 0.007 Å, shown graphically in Figure 2.

$$d_{C=N} = 0.246 + 0.807 d_{C-N} \tag{4}$$

D. Experimental XD Determinations In Amidinates

The molecular structure of amidinate anions (9) is preserved in transition metal derivatives of *N,N'*-diphenyl benz- or acetamidines with examples collected in Table 7 and molecular formulae shown in Scheme 3. The CN distances which differ not too much are

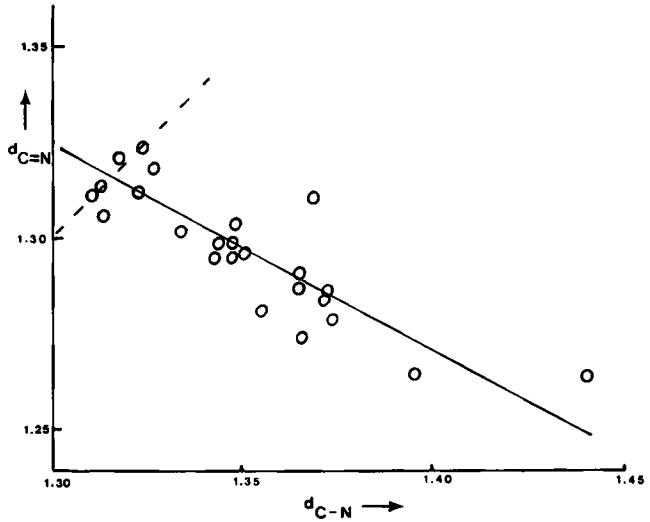


FIGURE 1. Plot of equation 2. Interrelation of experimental shorter and longer CN distances in amidines (----- shows unit slope)

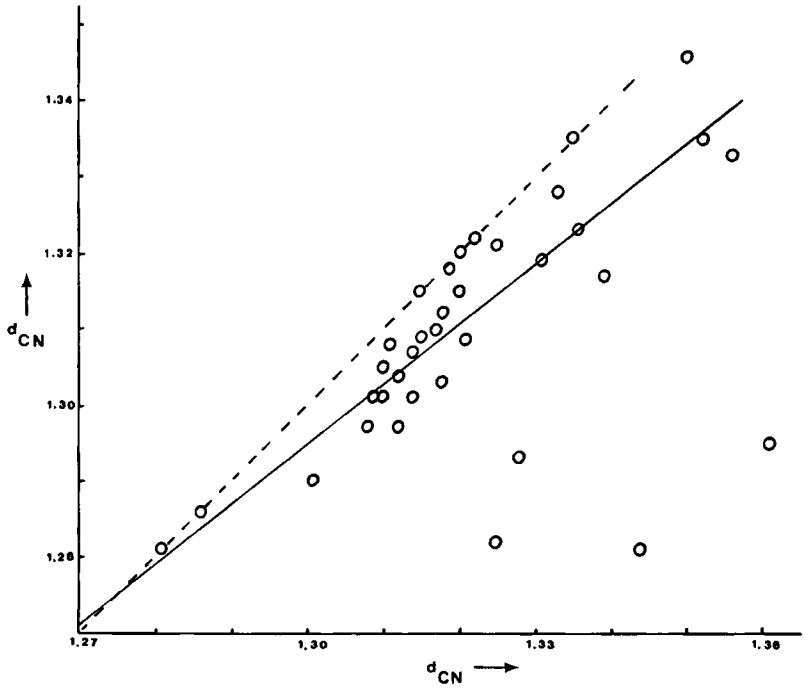
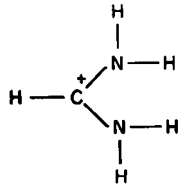


FIGURE 2. Plot of equation 4. Interrelation of experimental CN distances in amidinium cations

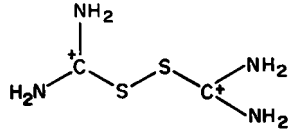
TABLE 6. Experimental CN distances (in Å) in amidinium cations

No.	Compound	C—N[1]	C—N[2]	C—X	Δ	Ref.
71a	Formamidinium·$FeCl_6$	1.281(9)	1.281(9)		0.000	97
71b	Formamidinium tris-formato·Zn(II)	1.286(4)	1.286(4)		0.000	98
72	Bis(α,α′-dithiobisform-amidinium hexachloro-rhenate(IV)·$3H_2O$	1.311(5)	1.308(5)		0.003	99
73a	Acetamidinium chloride	1.310(3)	1.305(2)	1.477(3)	0.005	100
73b	Bisacetamidinium carbonate·H_2O	1.315(5) 1.314(5)	1.309(5) 1.307(5)	1.495(5) 1.500(5)	0.006 0.007	101
73c	Acetamidinium nitrate	1.309(4)	1.301(4)	1.489(4)	0.008	102
	as above, at 116 K	1.321(5)	1.309(4)	1.481(5)	0.012	102
73d	Acetamidinium *N*-acet-imidoyldithiocarbamate	1.310(3)	1.301(2)	1.484(4)	0.009	103
74	Malonyldiamidinium sulphate	1.308(4)	1.297(4)	1.499(4)	0.011	104
75a	Benzamidinium chloride hydrate	1.328(7)	1.293(7)	1.471(8)	0.025	105
75b	Benzamidinium pyruvate	1.317(3)	1.310(3)	1.472(3)	0.007	106
75c	Benzamidinium tetracarbonyl rhenaacetylacetonate	1.314(7)	1.301(9)	1.488(9)	0.013	107
76	4-Amidinophenylacetic acid morpholide·HI	1.312(7)	1.304(7)	1.473(7)	0.008	108
77	*N*-Pivaloylpivalamidi-nium pyrosulphate	1.344(4) 1.361(4)	1.281(4) 1.295(5)	1.527(5) 1.509(4)	0.063 0.066	86
78	*N,N′*-Bis-(4-ethoxyphenyl) acetamidinium bis-*p*-nitro-phenyl phosphate·H_2O	1.319(8)	1.318(8)	1.492(10)	0.001	109
79	*N,N*-Dimethylchloroform-amidinium chloride·H_2O	1.325(5) prim.	1.282(6) tert.		0.043	110
80	2-Chloro-2-phenoxy-malonyldimethylamide-dimethylamidinium hydrochloride·H_2O	1.318(5)	1.303(5)		0.015	111
81	*N*-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]-dimethylformamidinium chloride	1.301(8)	1.290(8)		0.011	112
82	Tetrakis(dimethylamino)-ethene dication $2Cl^-$	1.320(3) 1.315(3)	1.315(3) 1.315(3)	1.524(3)	0.005 0.000	113
	as above, $2Br^-$	1.331(3) 1.312(3)	1.319(3) 1.297(3)	1.512(3)	0.012 0.015	113
83	Tetramethylformami-dinium phosphonate	1.336(3)	1.323(3)		0.013	114
84	Tetramethylformamidi-nium phosphonic anhydride	1.333(3)	1.328(3)		0.013	115
85	Tetramethylformamidi-nium phospha perchlorate	1.352(5)	1.335(5)		0.017	116
86	Tetramethylformamidi-nium methylphospha diiodide	1.318(12)	1.312(12)		0.006	116
87	Tetramethylformamidi-nium phosphinate perchlorate	1.335(5)	1.335(5)		0.000	117
88	Octamethyl-[bis-2,4-6-cycloheptatrien-1-yl]-3,3-dicarboxamidinium·$2J_3^-$	1.325(5)	1.321(5)		0.004	118

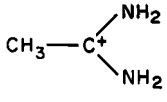
1. Unsubstituted amidinium cations



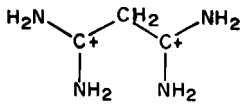
(71a) $\frac{1}{3}\,FeCl_6^{3-}$
(71b) $Zn(II)(HCO_2^-)_3$



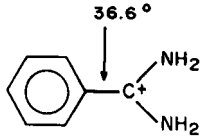
(72) $ReCl_6^{2-}\cdot 3H_2O$



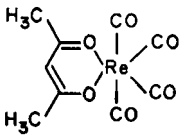
(73a) Cl^-
(73b) $\frac{1}{2}\,CO_3^{2-}\cdot H_2O$
(73c) NO_3^-
(73d) *N*-acetimidoyl-dithiocarbamate

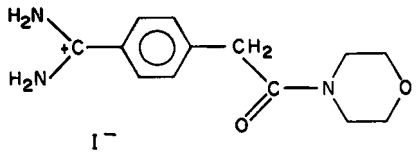


SO_4^{2-}
(74)



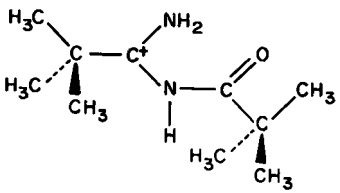
(75a) $Cl^-\cdot H_2O$
(75b) $CH_3CH(OH)CO_2^-$
(75c)





I^-
(76)

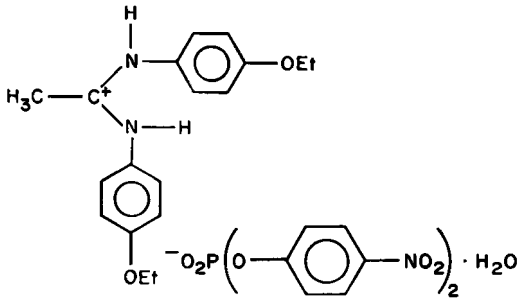
2. *N*-Monosubstituted amidinium cation



$\frac{1}{2}\,{}^-O_3S-O-SO_3^-$

(77)

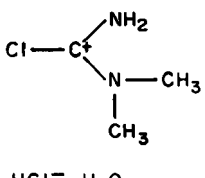
3. *N*,*N*'-disubstituted amidinium cation



(78)

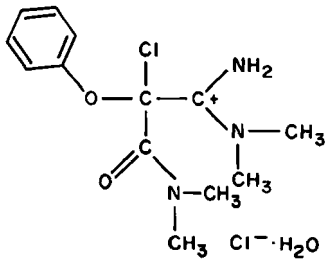
SCHEME 2 (*continued*)

4. N^1,N^1-disubstituted amidinium cations



$HCl^- \cdot H_2O$

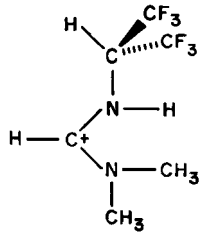
(79)



$Cl^- \cdot H_2O$

(80)

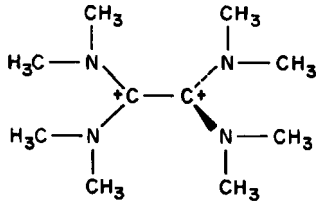
5. N^1,N^1,N^2-trisubstituted amidinium cations



Cl^-

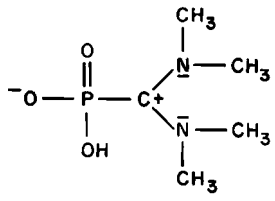
(81)

5. N,N,N',N'-tetrasubstituted amidinium cations

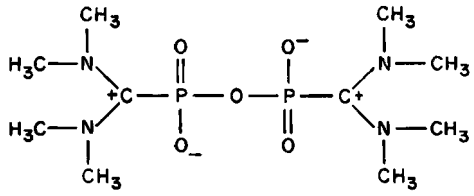


$2Cl^-$ or $2Br^-$

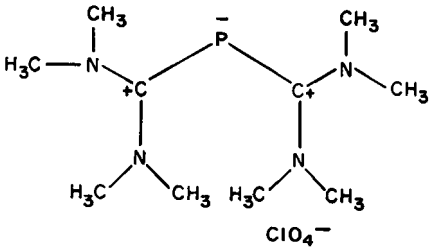
(82)



(83)

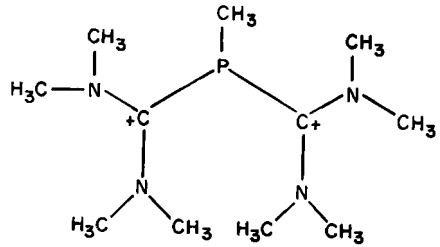


(84)



ClO_4^-

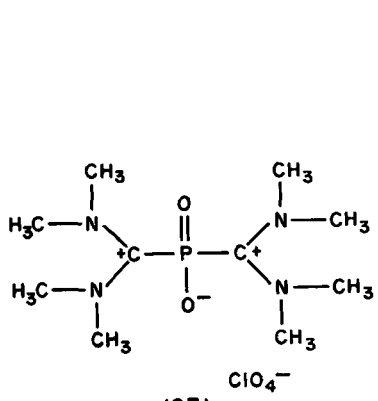
(85)



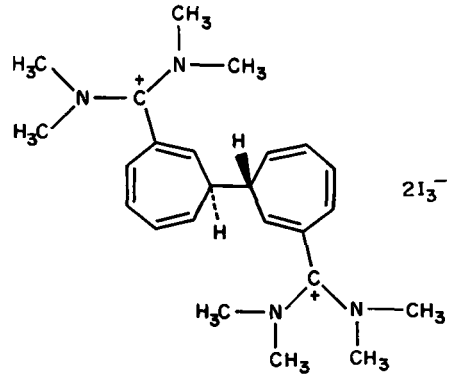
$2I^-$

(86)

SCHEME 2 (*continued on next page*)



(87)



(88)

SCHEME 2. Molecular structures of amidinium cations of Table 6

TABLE 7. CN bond lengths (in Å) of amidinates **9**

No.	Compound	C—N[1]	C—N[2]	C—X	Δ	Ref.
89a	*N,N'*-Diphenylbenzamidinate Rh cycloocta-1,5-diene	1.356(9)	1.331(9)	1.490(8)	0.025	17
89b	Bis(*N,N'*-diphenylbenzamidino) Pt(II)	1.340(7)	1.334(7)	1.493(8)	0.006	18b
90	(*N,N'*-Diphenylbenzamidinate)$_2$ Rh_2 (tetrafluorobarrelene)	1.350(7) 1.339(7)	1.346(7) 1.317(9)	1.501(6) 1.502(7)	0.004 0.012	17 17
91	(*N,N'*-Di-*p*-tolylacetamidino)$_2$ Pd(II)	1.322(4)	1.322(4)	1.512(9)	0.000	18a
92	*N,N'*-Diphenylacetamidino $Mo(\eta^5\text{-}C_5H_5)(CO)_2$	1.320(4)	1.320(4)	1.499(5)	0.000	18a

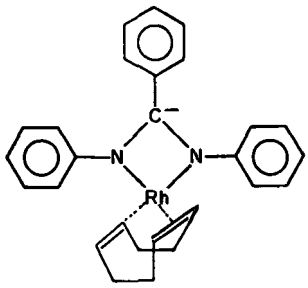
longer than in the cationic amidines or in neutral amidines. The distances fall on the regression line defined by amidinium cations (equation 4).

E. Molecular Structures of Neutral Guanidines

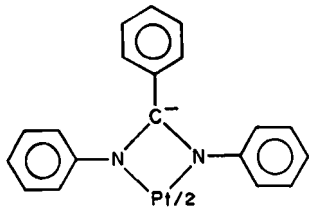
In Table 8 four XD determinations of molecular structures of neutral guanidines shown in Scheme 4 are presented. With the exception of **93** the formally double CN bond is relatively long, between 1.308 and 1.333 Å.

F. Molecular Structures of Guanidinium Cations

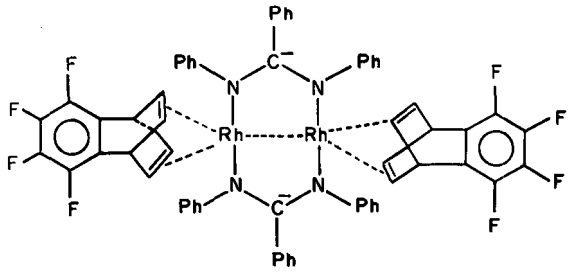
Experimental data for the unsubstituted guanidinium cation **54** are shown in Table 9 and structures in Scheme 5. This system is very often studied (17 determinations). Usually all three bonds differ slightly but mostly they are equal within the limit of three standard deviations (esd), unless the H-bonding situation is different. The average CN distance (of



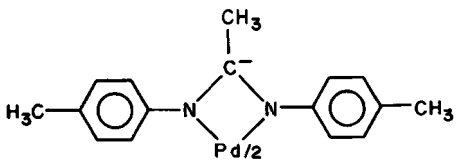
(89a)



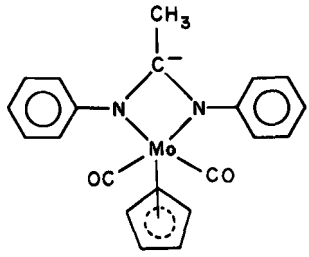
(89b)



(90)



(91)

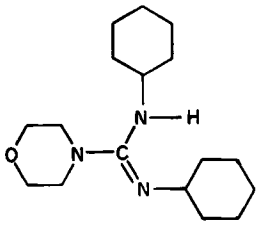


(92)

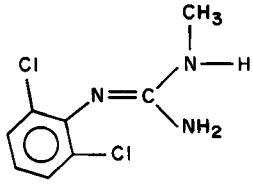
SCHEME 3. Molecular formulae of amidinates given in Table 7

TABLE 8. CN bond distances (in Å) in neutral guanidines

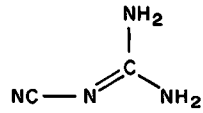
No.	Compound	C—N[1]	C—N[2]	C—N[3]	Ref.
93	(*E*)-*N*,*N*'-Dicyclohexyl-4-morpholinecarboxamidine	1.414(2)	1.381(2)	1.276(3)	119
94	2-(2,6-Dichlorophenyl)-1-methylguanidine	1.364(5)	1.339(4)	1.308(4)	120
95a	2-Cyanoguanidine	1.3414(3)	1.3391(3)	1.3327(3)	121
95b	2-Cyanoguanidine potassium cyanamide	1.348(6)	1.331(6)	1.329(6)	122



(93)



(94)

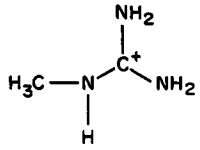


(95)

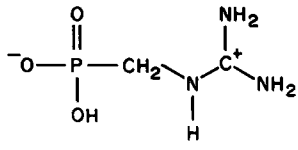
SCHEME 4. Molecular formulae for compounds of Table 8

TABLE 9. CN bond lengths (in Å) in guanidinium cations = GUAD

No.	Compound		C—N[1]	C—N[2]	C—N[3]	Ref.
96	GUAD·Cl^-		1.325(5)	1.325(5)	1.318(5)	123
97	GUAD·ClO_4^-		1.327(5)	1.327(5)	1.327(5)	124
98	GUAD·HCO_3^-		1.325(3)	1.325(2)	1.322(2)	125
99	Di-GUAD·CO_3^{2-}		1.358(6)	1.335(6)	1.333(6)	126
100	di-GUAD·CrO_4^{2-}		1.330(5)	1.325(4)	1.312(5)	127
			1.330(5)	1.328(5)	1.320(4)	
	thermal correction:		1.349(5)	1.333(4)	1.329(5)	
			1.341(5)	1.343(5)	1.334(5)	
101	Di-GUAD·$Zn(SO_4^{2-})_2$		1.319(4)	1.319(4)	1.316(3)	128
102	Di-GUAD·$(CH_3)_2AsMo_4O_{15}H$· H_2O		1.338(3)	1.322(3)	1.313(2)	129
			1.338(3)	1.326(2)	1.317(3)	
103	Di-GUAD·$B_4O_5(OH)_4·2H_2O$		1.340(5)	1.333(5)	1.314(5)	130
			1.325(5)	1.322(5)	1.321(5)	
104	GUAD·maleic acid		1.329(9)	1.325(7)	1.311(7)	131
105a	GUAD·crown·ClO_4^-		1.331(5)	1.330(5)	1.316(5)	132
105b	GUAD·dibenzo-27-crown-9		1.331(6)	1.324(7)	1.324(6)	132
105c	GUAD·dibenzo-30-crown-10		1.320(6)	1.320(6)	1.312(5)	132
106	Methylguanidinium·$H_2PO_4^-$		1.326(2)	1.325(2)	1.319(2)	133
107	Bis(methylguanidinium)· HPO_4^{2-}		1.328(2)	1.324(3)	1.322(3)	134
			1.331(2)	1.327(2)	1.330(2)	
108	Guanidinomethylphosphonic acid		1.341(3)	1.328(3)	1.323(3)	135
109	Guanidinoacetic acid (glycocyamine)		1.327(2)	1.324(2)	1.330(2)	136
110	Creatine·H_2O		1.346(6)	1.334(6)	1.324(6)	137
110	Creatine		1.334(2)	1.327(1)	1.336(2)	138
111	β-Guanidinopropionic acid		1.333(5)	1.322(4)	1.323(4)	139
55	L-Arginine·$2H_2O$	ND:	1.331(2)	1.329(2)	1.335(2)	140
		corr.	1.345	1.344	1.351	140
		XD:	1.340(8)	1.322(8)	1.351(8)	141
55	L-Arginine·HCl·H_2O		1.327(4)	1.326(3)	1.318(3)	142
			1.329(3)	1.325(3)	1.322(3)	142
55	L-Arginine·$H_3PO_4·H_2O$		1.326(4)	1.324(4)	1.315(3)	143
55	L-Arginine·L-aspartate		1.334(5)	1.328(5)	1.341(5)	144
94	2-(2,6-Dichlorophenyl)-1-methylguanidinium. HCl		1.349(6)	1.338(6)	1.312(6)	120



(106)



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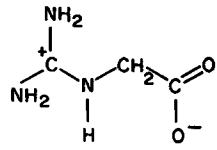

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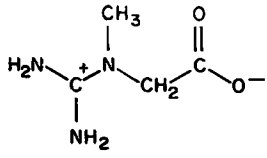
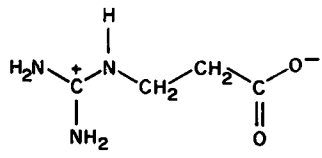


(110)



(111)

SCHEME 5. Structures for guanidinium cations collected in Table 9

TABLE 10. XD bond distances (in Å) in neutral and protonated forms of imidates

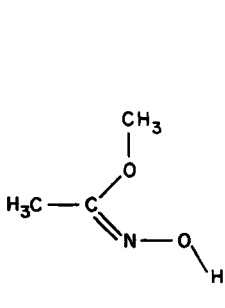
No.	Compound	C=N	C—O	C—C	Ref.
112	Methyl-Z-acetohydroximate	1.274(5)	1.336(3)	1.480(5)	145
113	Methylbenzimidate $W(CO)_5$	1.276(8)	1.309(8)	1.496(8)	91
114	4-Chlorophenylimino(trimethylsiloxy)methyl-phenyltrimethylsilylphosphan	1.275(2)	1.355(2)	—	146
115	*N,N'*-Bis-(trimethylsilyl)-oximidatebis(trimethylsilyl)-ester	1.282(9)	1.376(8)	1.508(16)	147
116	2-Methoxycarbonyl-1-naphthyl-*N*-(1-naphthyl)benzimidinate	1.261(4)	1.372(3)	1.482(4)	148
117	*trans*-Bis(dimethylglyoximato)-(ethyl)(methyl 4-pyridine-carboximidate)cobalt(III)	1.261(7)	1.333(7)	1.511(7)	149
118	Diiminooxalic acid diethyl-ester $K[I(CN)_2]$	1.252(3)	1.327(4)	1.511(7)	150
119	3-Cyano-1,2,4-thiadiazol-5-carboximidic acid methyl ester	1.245(3)	1.345(3)	1.483(3)	151
120	*N*-Benzoylethyl-benzimidate	1.262(5)	1.323(4)	1.498(5)	152
	thermal correction:	1.272	1.334	1.499	
121	*N*-(ethoxyphenylmethylene)-carbamic acid phenyl ester	1.274(4)	1.332(2)	1.484(3)	153
	thermal correction:	1.282	1.347	1.488	
122a	Acetamide hemihydrobromide at −160 °C	1.307(4)	1.264(4)	1.497(5)	154
122b	Acetamide nitrate	1.292(5)	1.287(5)	1.488(6)	155
123	*N,N*-Dimethyl-(*O*-ethyl)phenyl-propiolamidinium BF_4^-	1.315(8)	1.282(7)	1.488(9)	156

51 values) is 1.325 Å, which is definitely longer than the bond distances in amidinium cations (see Table 6). With thermal corrections[127] this value is even increased to 1.338 Å.

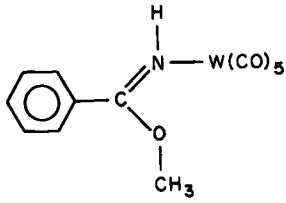
Some monosubstituted guanidinium cations are also included in Table 9. The CN bond to the substituted carbon (C—N^3) is generally shorter than the other two bonds.

G. Structural Data of Imidates and the Corresponding Cations

In Table 10 CN and CO distances of the functional group of neutral imidates **42** and of three protonated forms are shown, and structures are given in Scheme 6. The C=N double bond (average value of 1.267 Å, increased by thermal correction to 1.277 Å) is generally very short. The average of the C—O bond distances is 1.341 Å, which is very



(112)



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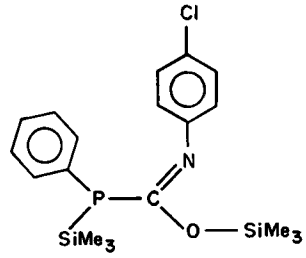

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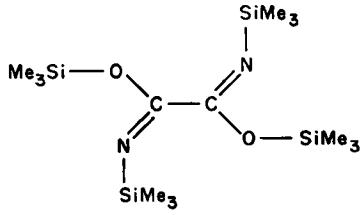

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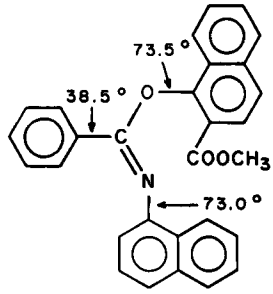

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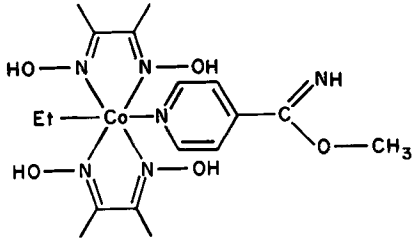

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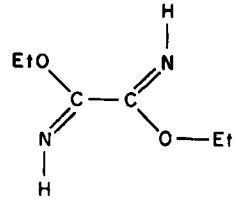
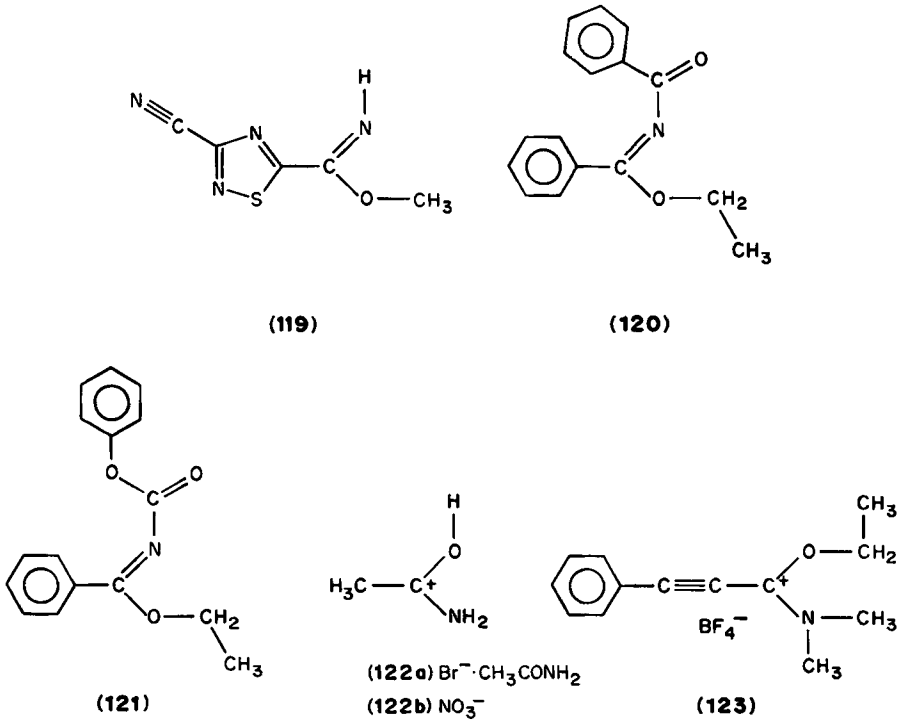


$K^+[I(CN)_2]$

(118)

SCHEME 6 (*continued*)



SCHEME 6. Structural formulae of imidates collected in Table 10

similar to the corresponding value of 1.340(14) Å derived for the carboxylic ester group[157]. Neither of these distances indicates a large interaction due to conjugational effects which should increase C=N and shorten C—O distances.

For three protonated imidates in Table 10 the average CN distance with 1.305 Å is appreciably elongated and the CO is shortened to 1.278 Å, showing the effective delocalization of the positive charge.

H. Structural Data of Neutral and Protonated Y-conjugated Systems

From cross- or Y-conjugated systems **5** of Table 2, bond distances of neutral nitrogen-containing examples are collected in Table 11 and protonated charged systems are given in Table 12. Structures are presented in Scheme 7.

I. Miscellaneous Compounds

1. Biguanide

Biguanide (**137**) is structurally related to guanidine (**53**). It forms a mono- and a bis-protonation product **138** and **139**, respectively (Scheme 8). The molecular structures of all three forms have been determined in two independent studies[104,172,173] with results shown in structures **137a**, **138a** and **139a**. The chemistry of biguanides was reviewed in 1968[174].

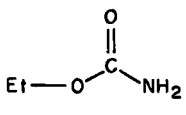
TABLE 11. Bond lengths (in Å) of neutral Y-conjugated systems

No.	Compound	CN	CX	CY	Ref.
124	Ethyl carbamate	1.341(4)	1.342(4)	1.219(4)	158
125	*N*-(Diphenoxymethylene)carbamic acid phenyl ester	1.264(2)	1.329(2)	1.325(2)	159
126	1,2-Bis(dimethylphosphinato)-Pt(II)-*N*-(*p*-chlorophenyl)-methoxy imidate	1.268(9)	1.386(7)	2.058(5)	160
127	Bis(1-*tert*-butyl-2,3-dimethylisourea)·$Pd(II)Cl_2$	1.311(8)	1.326(8)	1.327(8)	161
128	Fluorenylisothiourea	1.271(3)	1.339(3)	1.787(2)	162
129	Bis(*N*-methyl *O*-ethylthiocarbamate)·$Pd(II)(SCN)_2$	1.302(7)	1.331(6)	1.700(6)	163
130	Ethyl 2-imino-4-oxo-5-phenylimidazoline-1-carboximidate	1.259(3)	1.337(3)	1.399(2)	164

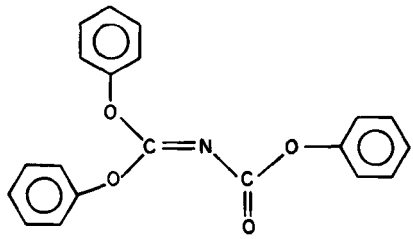
TABLE 12. Bond lengths (in Å) of charged Y-conjugated systems

No.	Compound		CN	CX	CY	Ref.
131	Uronium nitrate	ND:	1.315(1)	1.313(1)	1.298(2)	164
		XD:	1.309(3)	1.306(3)	1.302(3)	165
132	*O*-Methyluronium chloride	Cu[a]:	1.321(10)	1.294(11)	1.331(9)	166
		Mo[b]:	1.331(11)	1.289(11)	1.332(9)	166
			1.337(10)	1.312(10)	1.310(9)	167
	thermally corrected:		1.352(10)	1.318(10)	1.322(9)	167
133	3-(1,3-Diphenyl-1-oxo-2-propenyl)-tetramethyluronium triflate		1.320(3)	1.304(3)	1.343(3)	168
134	Azidoformamidinium chloride		1.314(4)	1.302(4)	1.393(4)	169
135	Thiuronium nitrate	Cu[a]:	1.321(5)	1.293(5)	1.735(4)	170
		Mo[b]:	1.312(5)	1.300(5)	1.739(4)	170
136	Thiourea *S,S*-dioxide		1.2972(4)	1.2972(4)	1.8615(4)	171

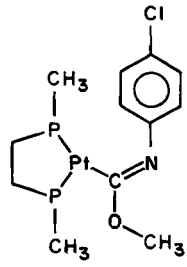
[a]XD using copper as radiation source.
[b]XD using molybdenum as radiation source.



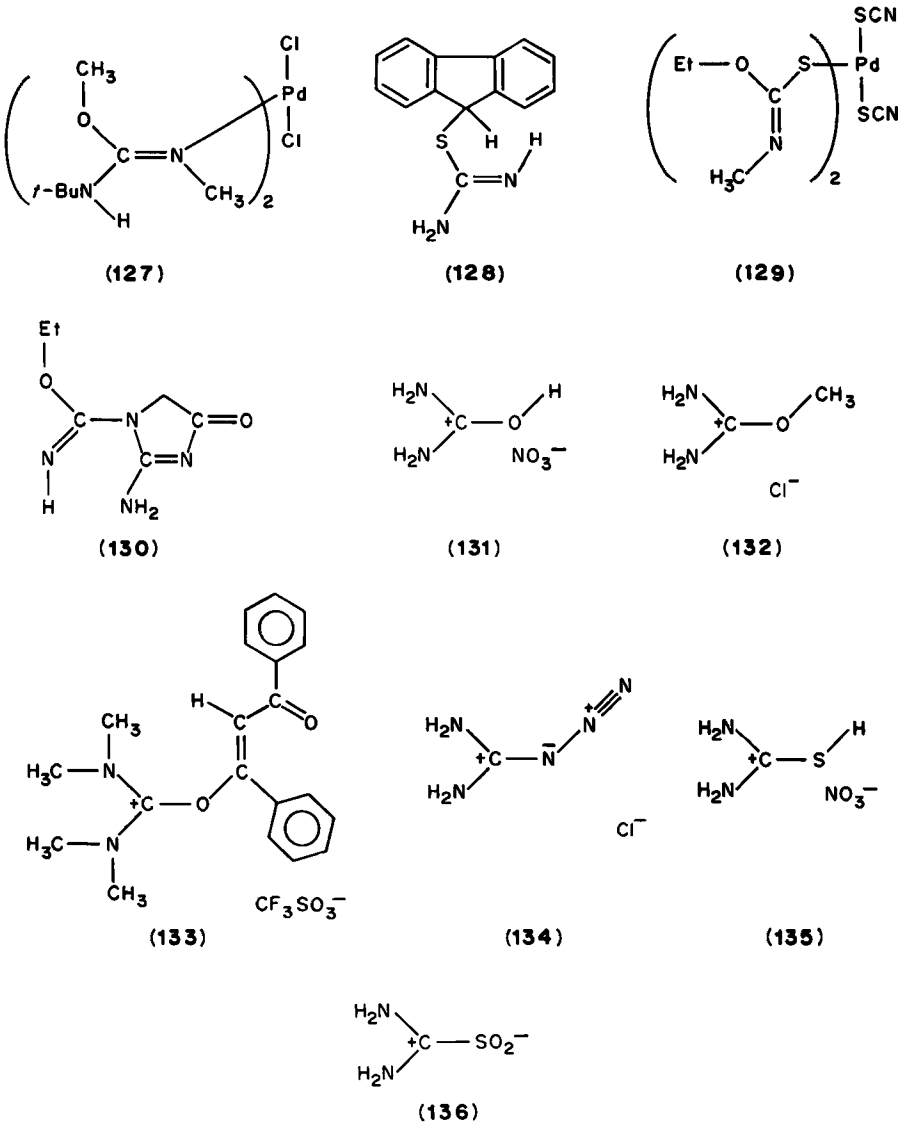
(124)



(125)



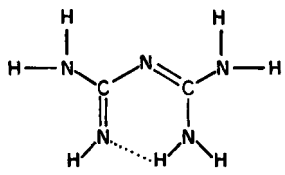
(126)



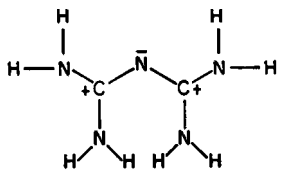
SCHEME 7. Molecular structures of compounds collected in Tables 11 and 12

2. *Bis(N^1-acetimidoylacetamidine-N^1,N^3)nickel(II) chloride trihydrate (**140**)*

A methanolic solution of acetamidine and nickel(II) chloride leads to crystals of **140** as the result of a self-condensation reaction possibly under the influence of the metal[175]. This chelate is a structural example of imidine **46**. The numbering is shown in Scheme 9 and bond lengths and angles are shown in Table 13.

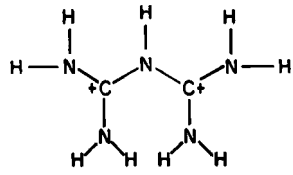


(137)



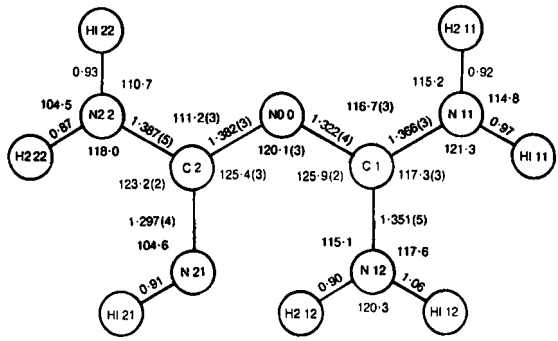
Cl^-

(138)

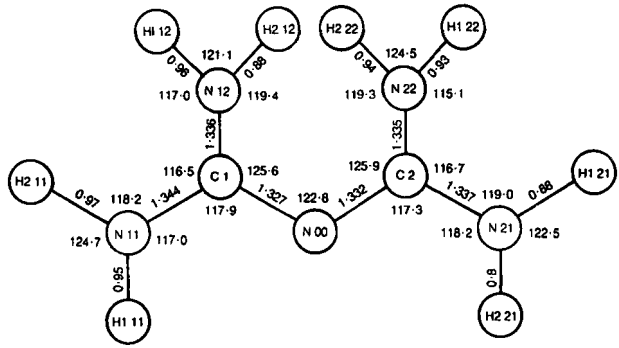


$2\,Cl^-$

(139)

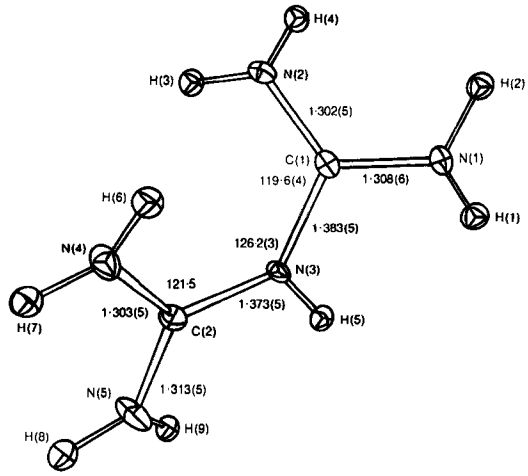


(137a)



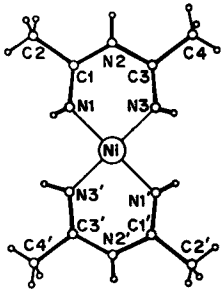
(138a)

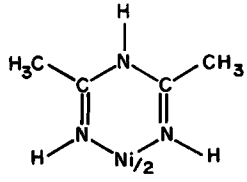
SCHEME 8 (*continued*)



(139 a)

SCHEME 8. Formulae and geometric parameters of biguanide (**137**) and its mono- and bis-protonation products: (**138**) and (**139**)





$2\,Cl^- \cdot 3\,H_2O$

(140)

SCHEME 9. Atomic labels of the square-planar chelate **140**

3. *Psychoactive amidines*

Several psychoactive drugs contain an amidino moiety. For four of these compounds (**21** and **141** to **143**) the molecular structures have been determined[176–178] with CN distances presented in Scheme 10.

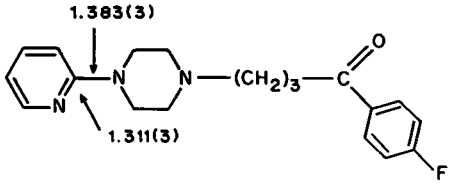
4. *6-Dimethylamino-5-azaazulene* (**144**)

In this molecule (**144**) the amidino group is incorporated into the heteroconjugated azulene ring[179] with rather long CN distances shown in the formula.

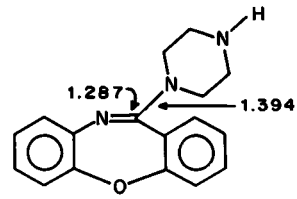
TABLE 13. Bond distances (in Å) and bond angles (in deg) between non-hydrogen atoms of **140**[a]

Parameter	Values	
Ni—N(1)	1.849(4)	1.861(4)
Ni—N(3)	1.858(4)	1.873(3)
C(1)—N(1)	1.282(6)	1.270(5)
C(1)—N(2)	1.367(5)	1.369(5)
C(1)—C(2)	1.510(6)	1.514(6)
C(3)—N(2)	1.362(5)	1.376(5)
C(3)—N(3)	1.285(6)	1.276(5)
C(3)—C(4)	1.508(5)	1.497(5)
N(1)—Ni—N(3)	89.9(2)	89.8(2)
N(1)—Ni—N(3')	90.3(2)	90.1(2)
Ni—N(1)—C(1)	129.9(3)	130.6(3)
N(1)—C(1)—N(2)	124.4(4)	122.3(4)
N(1)—C(1)—C(2)	122.1(4)	123.0(4)
C(2)—C(1)—N(2)	113.5(4)	114.6(4)
C(1)—N(2)—C(3)	121.7(4)	124.9(4)
Ni—N(3)—C(3)	129.7(3)	130.4(3)
N(3)—C(3)—N(2)	124.3(4)	121.7(4)
N(3)—C(3)—C(4)	121.5(4)	123.8(4)
C(4)—C(3)—N(2)	114.2(4)	114.5(4)

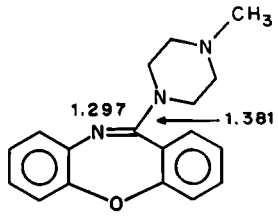
[a]Right column is for the primed atoms of Scheme 9



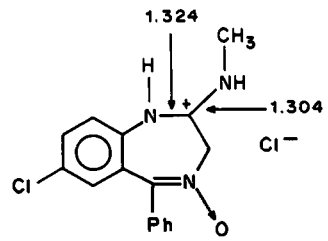
azaperone[176] (141)



amoxapine[177] (142)

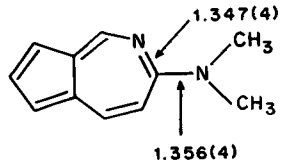


loxapine[177] (143)



librium[178] (21)

SCHEME 10. Molecular structures of psychoactive drugs containing the amidine group



(144)

V. THEORY: METHODS OF CALCULATION

The presently available quantum-mechanical procedures for calculations of molecular properties are shown in Table 14. The semi-empirical one-electron methods may be classified into those which neglect inter-electron repulsions, i.e. simple Hückel (HMO) π-electron theory[180] and Hoffmann's extended Hücked theory (EHT) for valence electrons[181], and those which include inter-electron repulsions and electron spin explicitly: the latter range from the Pariser, Pople and Parr (PPP) π-electron theory[182,183] to various 'neglect of differential overlap' (NDO) methods for valence electrons[184,185]. The PPP and Jaffé's CNDO/S methods[186] are still useful for calculations of electronic absorption spectra. For calculation of molecular geometries Dewar's semi-empirical procedures: MINDO-3[187], MNDO[188], or AM1[189], Pullman's PCILO method[190], or molecular force-field procedures (not included in Table 14) like MM2[191,192] may be used.

'*Ab initio* methods' are all quantum-chemical procedures which use the appropriate Hamiltonian and an appropriate kind of variational wave function for evaluation of all necessary integrals, and, in contrast to semi-empirical methods, do not use experimentally adjusted parameters. The background information about *ab initio* calculations is given in a series of excellent monographs[193–197]. The introduction of fast and large computers and efficient computer programs distributed through the quantum chemistry program

TABLE 14. Kinds of available procedures for quantum-mechanical calculations

Kind of Electrons	Electron repulsion Excluded	Included	Types of theories
π-Electrons, Only planar systems	HMO 1931 Hückel	PPP 1953 Pariser, Parr, Pople	Semiempirical methods
Valence shell electrons, non-planar and planar	EHT 1963 Hoffmann	CNDO/2 1965 INDO Pople, Santry, NDDO Segal CNDO/S 1968 Jaffé MINDO/3 1975–1985 MNDO Dewar	
$(\pi + \sigma)$-systems		AM1 PCILO 1972 Pullman	
All electrons = core and valence electrons, any molecular system		POLYATOM-2 Moskowitz IBMOL-4 1968 Veillard PHANTOM 1971 Clementi HONDO 1976 King TEXAS 1979 Pulay GAUSSIAN 70; 76; 80; 82; 86; 88 Pople	*ab initio* methods

exchange (QCPE) in Bloomington, Indiana to the scientific community went hand in hand. A selection of available *ab initio* programs is indicated in Table 14.

Theoretical calculations for amidines and related systems in the original volume of this series[2] have been based on Hückel and PPP procedures, but now we present results of *ab initio* Hartree–Fock MO calculations using Pople's GAUSSIAN 82 program system[198].

A. Assumptions of *ab initio* Hartree–Fock SCF MO Procedures

The considerations presented here are based on *ab initio* Hartree–Fock SCF MO calculations[193-197] with full optimization of molecular structures by means of the analytical gradient optimization of Murtagh and Sargent[199] implemented in the GAUSSIAN 82 (G 82) program system of Pople's group[198] on a COMPAREX 7/88 computer.

Inherent to all *ab initio* programs are the following assumptions:

The Born–Oppenheimer approximation[200] is the separation of the movement of electrons and atomic nuclei due to the large difference of masses. This leads to the formulation of chemical molecules with definite three-dimensional molecular geometry.

The orbital approximation: Although it is not possible experimentally to differentiate separate electrons in a molecule, each of these is treated by a one-electron wave function, named orbital, which leads to a model of independent enumerable particles.

A single-determinantal wave function: The many-electron wave function, i.e. for the ground-state configuration, is formulated as one Slater determinant of spin orbitals which takes care of the Pauli exclusion principle and of the change of sign of the total wave function on interchange of the label of two electrons.

Hartree–Fock SCF procedure in Roothaans's LCAO–MO formalism: For molecules one-electron molecular orbitals (MO) are obtained by linear combinations of atomic orbitals (LCAO) as first formulated for determinantal wave functions by Roothaan[201]. The Hartree–Fock Hamiltonian treats each electron in the effective field of the others and contains the interaction of electrons with same and opposite spins in a different manner. Therefore this self-consistent field (SCF) procedure is iterative. Starting from a first guess for electron distributions, Roothaan's equations are solved, inserting the resulting electron distributions until the total energy does not alter with respect to a predefined limit.

Use of Gaussian-type basis functions instead of Slater-type functions.

1. Gaussian basis sets

$$\phi_{nlm}(r, \Theta, \Phi) = N_n r^{n-1} \exp(-\xi r) Y_{lm}(\Theta, \Phi) \tag{5}$$

$$\phi_{nlm}(r, \Theta, \Phi) = N_n r^{n-1} \exp(-\alpha r^2) Y_{lm}(\Theta, \Phi) \tag{6}$$

Numerical many-electron atomic wave functions are Slater-type (STO) s, p, d or f functions[202] of the kind shown in equation 5 which are characterized for s electrons by a cusp at the nucleus and fall off by $\exp(-\xi r)$ as shown graphically in Figure 3, or Gaussian-type functions (GTF) as defined in equation 6 which show an $\exp(-\alpha r^2)$ dependence and are curved at the nucleus.

The notations used for atomic orbitals ϕ in equations 5 and 6 are defined in the following way[203]: r, Θ and Φ are spherical coordinates (radial coordinate r, equatorial angle Φ and azimuthal angle Θ) instead of cartesian coordinates x, y and z; n, l and m are quantum numbers used for the separation of atomic wave functions in spherical coordinates: n = main, l = angular momentum and m = magnetic quantum numbers; N are normalization constants and Y_{lm} are spherical harmonics indicating the angular dependence of atomic wave functions, which are the same for Slater- and Gaussian-type functions.

For molecules with many atoms, electron repulsion integrals between atomic orbitals at

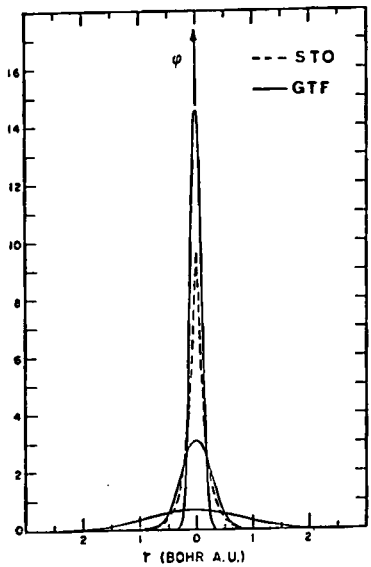


FIGURE 3. Comparison of a 1s Slater-type orbital (STO) and 1s Gaussian-type orbitals (GTF) as a function of r. (Repoduced by permission of Elsevier Science Publishers from Reference 193)

one, two, three and up to four centres have to be evaluated. This is difficult mathematically for STO functions. Use of GTF functions leads to much simpler integral evaluation because the product of two Gaussians at different centres is a new Gaussian in between, and the resulting many-electron repulsion integrals may be solved analytically. But Gaussian-type wave functions have no cusp and fall off too rapidly, as shown in Figure 3.

Therefore, in order to approximate each STO, at least three different Gaussians must be used as indicated in Figure 3 and equation 7.

$$\phi_\mu(r) = \sum_{i=1}^{N} d_{i\mu} \exp(-\alpha_i f^2 r^2) \tag{7}$$

In equation 7 the number N of Gaussians is called the degree of contraction, which ranges from 3 to 6. The linear factor $d_{i\mu}$ is called the contraction ocoefficient, α_i is the exponent and f is a scale factor, both α_i and f being characteristic for each atom. In Pople's GAUSSIAN program systems the exponents and scale factors for atomic 2s and 2p subshells are set equal (Pople constraint), which greatly simplifies calculations, but only contraction coefficients and angular dependence differentiate between 2s and 2p orbitals.

2. Notations for Gaussian basis sets

If one Slater-type orbital is approximated by a fixed number of Gaussians, one speaks of a minimal Gaussian basis set, termed STO-3G up to STO-6G[204]. Split-valence basis sets, named 3-21G[205], 4-31G[206], 6-31G[207] or 6-311G[208], are constructed by one block of 3, 4 or 6 Gaussians for core electrons (first number) and by two (indicated by 21 or 31) or three (311) blocks for valence electrons which are varied linearly and independently.

Although split-valence basis functions show larger flexibility, this may be further increased by the addition of so-called polarization functions which are three 2p orbitals for hydrogen, or five or six 3d orbitals for elements of the second row of the periodic system. The latter case is marked by the addition of one asterisk, i.e. STO-3G*[209], 3-21 G*[210] or 6-31G*[211]. Two asterisks, i.e. 6-31 G**[211] or 6-311 G**[208,212], indicate the additional presence of polarization 2p orbitals on hydrogen.

Especially for negatively charged systems, diffuse s- or p-type functions of high quantum numbers may be necessary. These are marked by + signs, i.e. 3-21 + G or 6-31 + G**.

Optimizations of molecular geometries may be performed with a simpler basis set followed by a single-point HF calculation with a larger basis set for this geometry. This is indicated by double bars, i.e. 6-31 G//STO-3G.

B. Gradient Optimizations of Molecular Structures

Until the end of the 1970s the optimization of molecular structures by means of *ab initio* calculations was a very tedious and time-consuming procedure and usually calculations had been performed for selected standard geometries or experimental values. But since the pioneering work of Pulay[213] efficient computer programs (GAUSSIAN 80, 82, 86 and 88 as well as other *ab initio* programs listed in Table 14) have been developed which use analytical gradients of the total energy with respect to internal coordinates to optimize molecular geometries. In our calculations we used the Murtagh–Sargent procedure[199], implemented in the G 82 program system[198].

C. Methods of Population Analysis

Methods of population analysis, the first of which was proposed by Mulliken[214], are designed to relate molecular electronic structures to intuitive concepts of chemistry. For this purpose one extracts from the wave function a set of quantities, such as bond orders or overlap populations and atomic charges, for a shorthand description of the electronic structure. But this procedure is ambiguous because these derived parameters are not observable and cannot be defined in a unique way. Two fundamentally different approaches are used for this purpose. The partitioning of the molecular electron density to define atomic charges is done either in the real three-dimensional Cartesian space (a), or in the Hilbert space spanned by the atomic orbital-like basis set (b).

1. Integrated Bader populations and integrated projected populations

The first kind (a) is used by Bader[215] and Streitwieser[216–218]. In Bader's analysis there is a set of partitioning surfaces which start at a saddle point in the electron distribution between a pair of atoms and follow paths of steepest descent through the electron distribution. These 'zero-flux surfaces' are mathematically well defined and lead to natural definitions of atoms in molecules. The electron populations that are obtained by integrations over the volumes defined by these surfaces are termed 'Integrated Bader Populations' or IBPs. Bader's method has the advantages that it partitions the molecule according to a real physical property, the charge distribution, and that it is independent of the quantum-mechanical model used. The disadvantage is that locating the zero-flux surface is not simple and the computation of IBP values is relatively slow and computer intensive. Streitwieser[216] introduced with 'Integrated Projected Populations', or IPPs, an approximation to Bader's method: the three-dimensional electron distribution is first integrated in a direction perpendicular to the plane of the molecule to give a two-dimensional projected electron density, which is partitioned by zero-flux lines. For gaussian basis sets this integration is analytic and rapid. A disadvantage is that relative

IPP values frequently differ from IBPs and the determination of IPPs for hydrogen is particularly difficult[218].

2. *Basis set population methods*

The basis set population methods (b) are used by Mulliken[214], Ahlrichs[219-221] and Weinhold[222,223]. Ahlrichs and coworkers, following Davidson[224] and Roby[225], construct from the *ab initio* molecular density operator a minimal set of modified atomic orbitals which are used to compute atomic occupation numbers (N) and shared electron numbers (SEN) for description of the molecular electron density distribution. In the Natural Population Analysis (NPA) of Weinhold's group.[222,223] the density matrix is transformed into a set of orthonormal but arbitrary atomic one-centre orbitals which are localized on the individual atoms. The occupancy of these natural orbitals gives the NPA values. An advantage of NPA over Mulliken population analysis (MPA) is the relative independence on basis sets.

3. *Mulliken population analysis*

For analysis of molecular wave functions obtained by full optimization of molecular geometries we had access only to Mulliken's population analysis[214], which is defined in the following way: for a MO ψ_j given in equation 8 as a linear combination of atomic orbitals φ_{r_k} on atoms k of a molecule (LCAO–MO), the projected electron density q_k at the nucleus k is named gross atomic population and is defined by equation 9, where b_j is the occupation number of MO ψ_j (equals 2, 1 or 0), c_{r_kj} and c_{s_lj} are linear expansion coefficients of equation 8 and $S_{r_ks_l}$ is the overlap integral between atomic orbitals at different atomic centres k and l.

$$\psi_j = \sum_{r_k} c_{r_kj}\phi_{r_k} \tag{8}$$

Gross atomic population on atom k:

$$q_k = \underbrace{\sum_j \sum_r b_j\left(c^2_{r_kj}\right)}_{q^n_k} + \underbrace{\sum_{l\neq k} c_{r_kj}c_{s_lj}S_{r_ks^l}}_{\frac{1}{2}p_{kl}} \tag{9}$$

net atomic population $\qquad$ $\frac{1}{2}$ overlap population

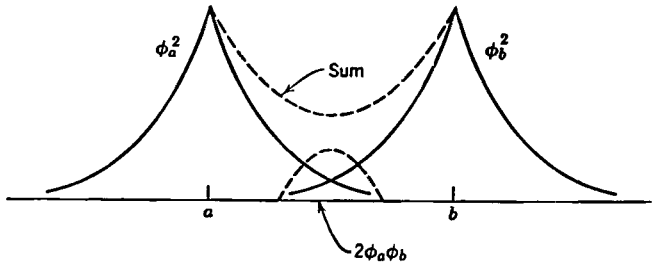


FIGURE 4. Origin of overlap population in molecular hydrogen. (From Reference 226)

In equation 9 the first sum is called the net atomic population q_k^n and the second sum is one-half of the so-called overlap population p_{kl}, which takes into account the electron distribution in the bonding region between atoms as indicated in Figure 4 and which is added equally to both atoms. This equal partitioning of the overlap population between bonded atoms is a weak point of the Mulliken population analysis, especially if these bonds are between atoms which differ in electronegativities. As shown by Flizár[227] it may be replaced by an experimental partitioning of overlap populations defined by an empirical scaling of atomic charges.

D. Post-Hartree–Fock Calculations

The Hartree–Fock limit in energy and geometry is the best possible solution obtainable with a single-determinantal wave function (Slater determinant) for a hypothetical basis of infinite members.

Improvements below the Hartree–Fock limit are possible by the use of configuration interaction[194,297] (CI). In this case excited-state structures are derived in which one or more electrons are shifted from occupied molecular orbitals (MO) into virtual antibonding MOs. Each of these numeral electron configurations is described by one Slater determinant and their contributions are determined by the quantum-mechanical variation principle. Depending on the type of excitation, this procedure is named CI–SDQ for single, double or quadruple excitations. As this CI method is only slowly converging, many configurations must be taken into account needing large computers and much computing time.

Another estimation of CI energies that result from imbalance in the treatment of electrons with like and unlike spin in the Hartree–Fock equation is possible by use of pertubation theory, which was suggested by Möller and Plesset[298] and may be applied to second, third or fourth order, named MP2, MP3 or MP4. Both CI or MP procedures are incorporated in Pople's GAUSSIAN programs but have not been applied by us for calculations related to amidines.

VI. RESULTS OF *AB INITIO* CALCULATIONS FOR AMIDINES

A. 3-21G Calculations for Formamidines

An extensive *ab initio* study with full optimization of molecular geometries and conformational preferences of neutral, protonated and deprotonated forms of formamidine as shown in Scheme 11 was reported by Zielinski and coworkers[19], using the 3-21G split valence basis set.

The species studied can be divided into four groups: anionic, neutral, cationic imino and amino protonated formamidines. The ten structures presented in Scheme 11 correspond to minima of the potential energy hypersurface. Relative stabilities are calculated as follows (see Table 15):

(1) **148** E > **149** Z: In neutral planar formamidine the E isomer is favoured over the Z isomer by only 2.5 kJ mol^{-1}.

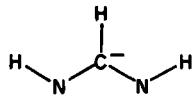
(2) **150** ≫ **151** > **152** > **153** > **154**: The planar symmetrical formamidinium cation **150** is the most stable molecule of Scheme 11.

The amino protonated formamidines **151** to **154** are higher in energy by at least 155 kJ mol^{-1} than **150**. As in the neutral molecule E isomers are more stable than Z isomers.

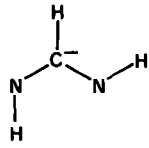
(3) **147** > **146** > **145**: Among anionic formamidinates the symmetrical E form **147** is the most stable.

Transition state structures, which may be obtained by rotations around CN bonds or by inversion at the imino NH bond, are shown in Scheme 12.

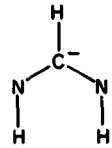
Anionic:



(145) C_{2v}

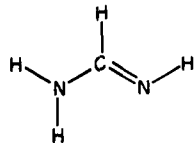


(146) C_s

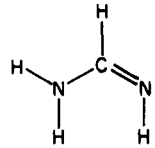


(147) C_{2v}

Neutral:

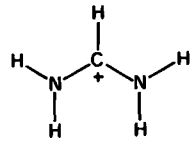


(148) *E* C_s



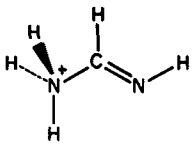
(149) *Z* C_s

Imino protonated:

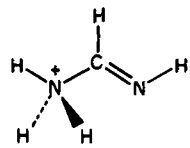


(150) C_{2v}

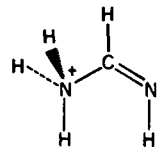
Amino protonated:



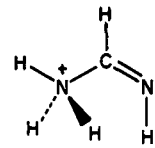
(151) C_s



(152) C_s



(153) C_s



(154) C_s

SCHEME 11. Minimum conformations of the potential energy surface for anionic deprotonated, neutral and cationic imino and amino protonated formamidines

Numerical values of 3-21G calculated bond lengths and angles are presented in Figures 5 and 6 for the compounds shown in Schemes 11 and 12.

Calculated total energies for minimum structures of molecules **145** to **154** and transition structures **155** to **164** are collected in Table 15. The entry order presents the number of negative eigenvalues of the Hessian matrix (these are second derivatives of the energy): structures of minima are zero-order critical points, saddle points have at least one negative eigenvalue and a chemical transition state may have only one negative eigenvalue.

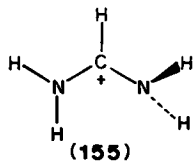
1. E,Z Formamidines

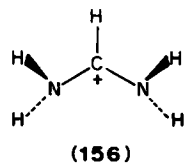
The planar *E* isomer **148** of neutral formamidine is calculated to be 2.5 kJ mol^{-1} more stable than the *Z* isomer **149**. The *E,Z* isomerization by in-plane inversion at the imino

TABLE 15. 3-21G *ab initio* total energies for formamidinium cations, formamidine and formamidinate anions[19] (1 hartree = 627.51 kcal mol^{-1} = 262.5 kJ mol^{-1})

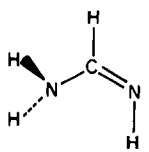
Compound	Formula	Order	E (hartree)	ΔE kcal mol^{-1}	ΔE kJ mol^{-1}
Imino protonated	**150**	0	− 148.643507	0.0	0.0
$HC(NH_2)_2^+$	**155**	1	− 148.597781	28.7	120.0
	156	2	− 148.486938	98.2	410.9
Neutral	**148** *E*	0	− 148.237764	0.0	0.0
$HC(=NH)NH_2$	**149** *Z*	0	− 148.236833	0.6	2.5
	157	1	− 148.221461	10.2	42.7
	158	1	− 148.219078	11.7	49.0
	159	1	− 148.200857	23.2	97.1
	160	3	− 148.174995	39.4	164.8
Anionic	**147**	0	− 147.591675	0.0	0.0
$HC(NH)_2^-$	**146**	0	− 147.585742	3.7	15.5
	145	0	− 147.572178	12.2	51.0
	161	1	− 147.555046	23.0	96.3
	162	1	− 147.542646	30.8	128.9
	163	2	− 147.490760	63.3	264.8
	164	2	− 147.482760	68.3	285.8
Amino protonated	**151**	0	− 148.584362	0.0	0.0
$HC(=NH)NH_3^+$	**154**	1	− 148.581463	1.8	7.5
	153	0	− 148.570176	8.9	37.2
	152	1	− 148.569122	9.6	40.2

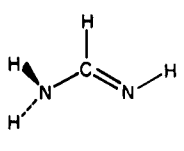
Imino protonated:

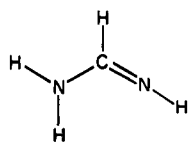


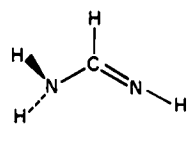


Neutral:

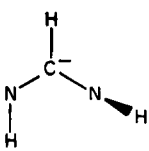


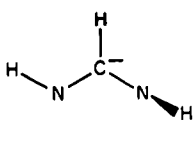


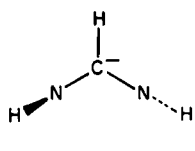


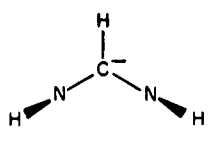


Anionic:









SCHEME 12. Molecular structures for transition state structures of protonated, neutral and anionic formamidines

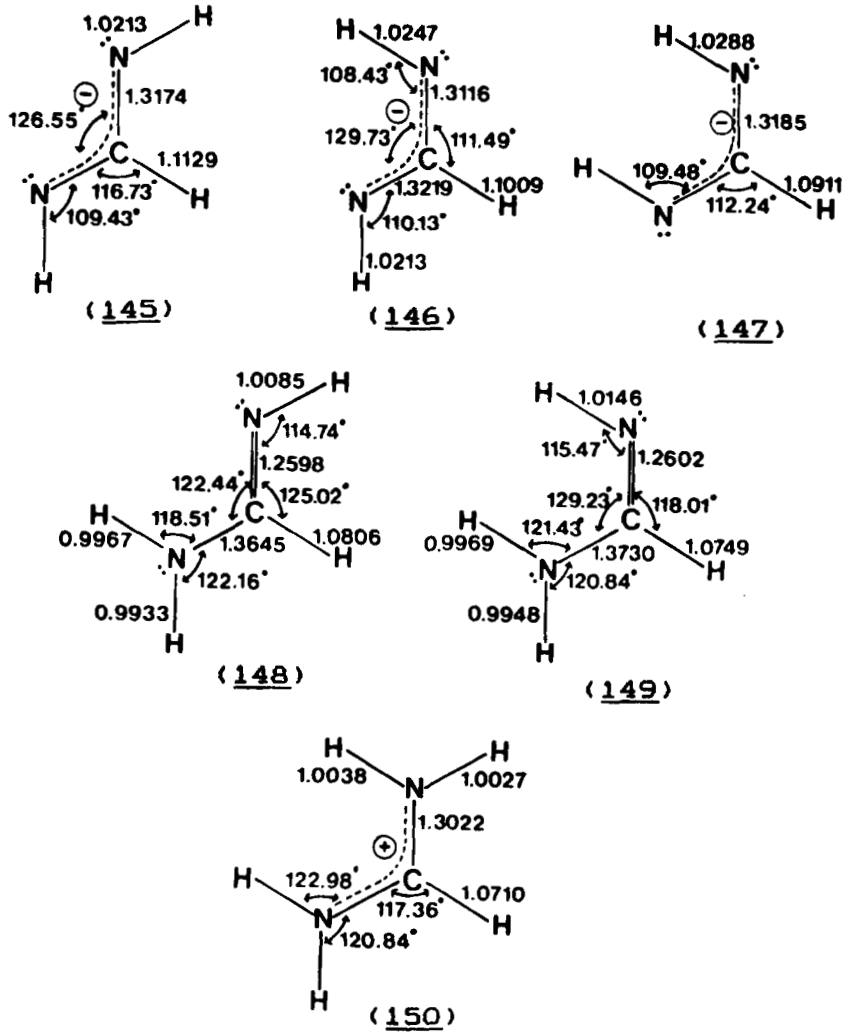


FIGURE 5. 3-21G optimized molecular geometries for minima of total energies of formamidine systems.(From Reference 19)

NH group through structure **159** was computed to be 97.1 kJ mol^{-1}. **160** corresponds to a maximum in the potential surface of order 3, since inversion at both N atoms as well as rotation around the CN bond correspond to negative eigenvalues of the Hessian matrix.

Barriers to rotation around the formal CN single bond are calculated to be 49.0 (**148** → **158** → **148**) and 40.2 kJ mol^{-1} (**149** → **157** → **149**) for **148** and **149**. These values are lower than 75–105 kJ mol^{-1} calculated for the CN rotational barrier in formamide using various geometries and basis sets[47] with an experimental range of values of 71–87.9 kJ mol^{-1}. This trend parallels the 3-21G calculated CN distances: 1.3534 Å for formamide[228] is shorter than 1.3645 or 1.3730 Å in **148** and **149**, indicating a higher degree of double-

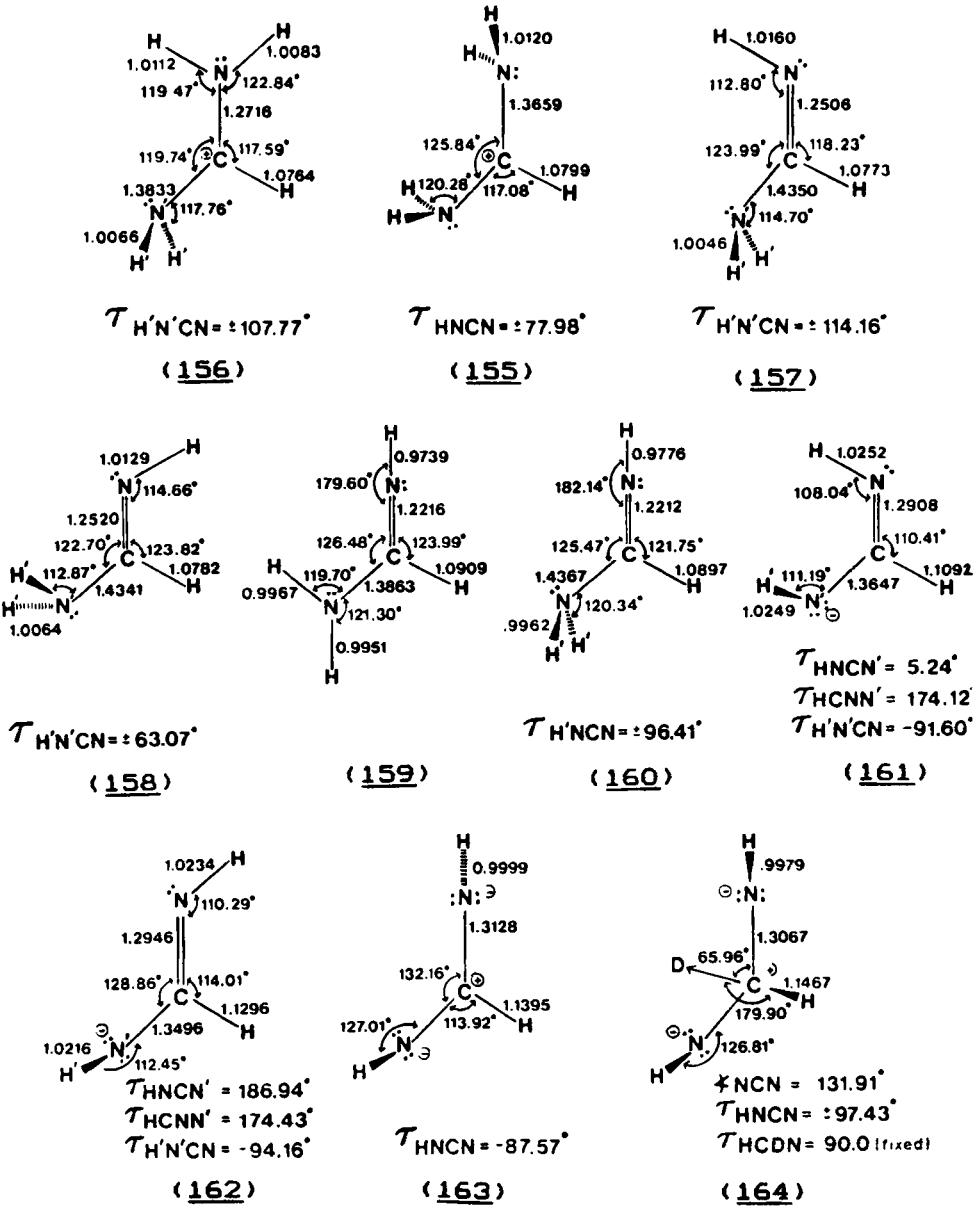
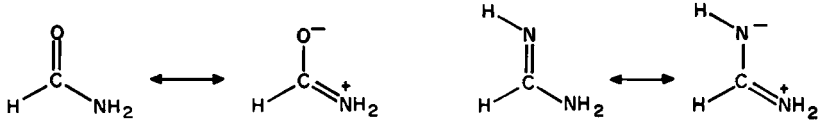


FIGURE 6. 3-21G optimized molecular geometries for first- and second-order critical points of the formamidine systems. (From Reference 19)

bond character in the CN bond of formamide than in formamidine. In terms of mesomeric forms, due to the more electronegative oxygen, the zwitterionic form **Ib** contributes more to formamide than **IIb** to formamidine.



(Ia) **(Ib)** **(IIa)** **(IIb)**

The gas-phase proton affinity of **148** at the imino nitrogen is calculated to be $-254.6\,kcal\,mol^{-1}$ ($1065\,kJ\,mol^{-1}$), comparable to the 4-31G value[273c] of $-249\,kcal\,mol^{-1}$ ($1042\,kJ\,mol^{-1}$). The proton affinity at the amino nitrogen, calculated as $-217.5\,kcal\,mol^{-1}$ ($910\,kJ\,mol^{-1}$), is much lower.

2. *Formamidinium cations*

The most stable cationic structure is the planar symmetric minimum (**150**) of order zero obtained by protonation at the imino nitrogen. The twisted structures **155** and **156** represent transition structures for the single and simultaneous double rotations around the CN bonds with computed rotational barriers of 28.7 and 98.2 kcal mol^{-1}, respectively. The first value is in close agreement with 28.2 kcal mol^{-1} calculated by Kollman and coworkers[273c] using the 4-31G basis set but with only partial optimization of molecular geometry.

The 3-21G calculated CN distances with 1.302 Å are longer than the experimental value[98] of 1.286(4) Å. The angle of 125.28° at the planar central carbon is in close agreement with the experimental value of 125.6° but deviates strongly from the hypothetical value of 120.0°.

Protonation at the amino group leads to **151** as the most stable form of the series **151** to **154** which is 155 kJ mol^{-1} higher in energy than **150**. Barriers for $C—NH_3^+$ rotation are very low: 2.9 kJ mol^{-1} for the *Z* (**153** → **154** → **153**) and 7.5 kJ mol^{-1} for the *E* conformers (**151** → **152** → **151**). These *E*,*Z* isomers have significantly different molecular geometries as may be seen by comparison of **151** with **153** and **152** with **154** in Figure 7.

3. *Anionic formamidinates*

The minimum energy conformation for anionic formamidinate is **147** with isomers **146** and **145** 15.5 and 15.0 kJ mol^{-1} higher in energy. The barrier to rotation of **147** to **146** *E* via **161** is 96.3 kJ mol^{-1} and of **146** to **145** via **162** is 113.0 kJ mol^{-1}. A conversion from **146** to **145** through simultaneous double rotation via the conformational maxima **163** or **164**, representing disrotatory or conrotatory movement of the hydrogens, is not likely to occur due to the high barriers, around 250 kJ mol^{-1}, for this process.

The proton affinity of **147** is computed to be $-405.4\,kcal\,mol^{-1}$ ($1696\,kJ\,mol^{-1}$). Thus anionic formamidinate is very unstable compared to the neutral and cationic forms. In agreement with experimental observations (Table 7), calculated CN bond lengths of Figure 7 are longer than in cationic species.

B. Basis Set Dependence of Calculated Molecular Structures

Single determinantal wave functions with increase of basis sets approach asymptotically the Hartree–Fock (HF) limit of total energy from one side as a consequence of the

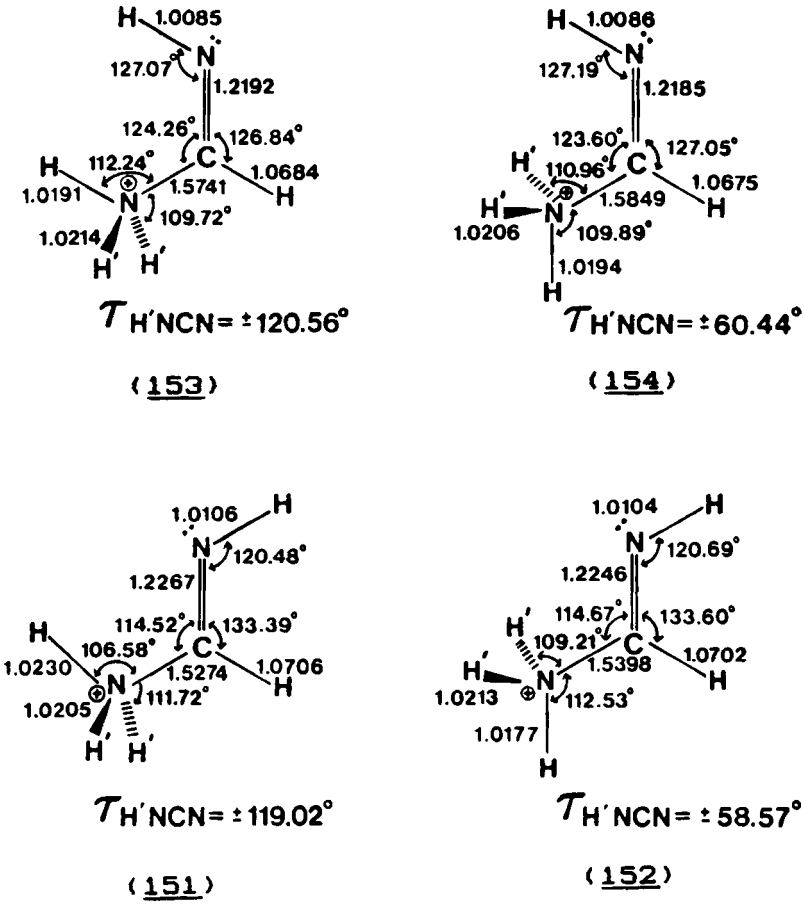


FIGURE 7. Optimized geometries for the amino-protonated forms of the formamidinium cation. (From Reference 19)

quantum-mechanical variation principle[193–197]. Gradient optimizations of molecular structures are dependent on the kind of applied basis sets[196] and calculated bond distances may be longer or shorter than the theoretical r_{HF} distances or the scarcely known experimental r_e distances. We had shown[229b] that out of eight tested basis sets for unstrained CC distances the 6-31G basis set gives statistically the best agreement with experimental gas-phase ED r_g bond lengths, although it was not the best with respect to total energies.

For our *ab initio* calculations on amidine systems with Pople's GAUSSIAN 82 (G82)[198] we applied only three basis sets: STO-3G[204] as the economically cheapest one, 3-21G because of comparison with extensive calculations of Zielinski[19,230–232] and 6-31G because of expected accuracy. Some 6-31G* values from the literature[228] have also been used.

1. Comparison of calculated CN distances with experimental values

In Table 16 for ten small CN systems which cover the range from single over double to triple bonds, STO-3G, 3-21G and 6-31G* basis set calculations taken from Reference 228 have been correlated by linear least squares to experimental gas-phase data. The regression equations 10 to 12 for 13 data points ($CH_3NH_3^+$ was discarded because it is a solid-state XD value and it was trimethylamine because its 6-31G* value is missing) show high statistical relevance with the linear correlation coefficient R increasing from 0.9967 over 0.9994 to 0.9998 and standard deviations esd decreasing from 0.011 over 0.005 to 0.003 Å for STO-3G, 3-21G and 6-31G* basis sets. These equations may be used to predict experimental gas-phase distances from calculated CN bond lengths.

$$r_{CN}^{exp} = 0.914\, r_{CN}^{STO-3G} + 0.101 \qquad (R = 0.9967;\ \text{esd} = 0.011) \tag{10}$$

$$r_{CN}^{exp} = 0.943\, r_{CN}^{3-21G} + 0.087 \qquad (R = 0.9994;\ \text{esd} = 0.005) \tag{11}$$

$$r_{CN}^{exp} = 0.980\, r_{CN}^{6-31G} + 0.046 \qquad (R = 0.9998;\ \text{esd} = 0.003) \tag{12}$$

Equation 11 is shown graphically in Figure 8. Of interest is the isodistance point $r^i = a/(1-m)$, which gives from slope m and intercept a of the regression the value of the intersection of the regression line with that of slope 1.0. If the slope of the derived regression equation is smaller than 1.0, all calculated distances larger than r^i are decreased by application of the regression, and distances smaller than r^i are increased. The STO-3G r^i value with 1.185 Å is close to the range of CN triple bonds, i.e. most calculated CN distances are decreased. The 3-21G value with 1.511 Å is in the range of bonds to quaternary nitrogen, i.e. most calculated CN distances are increased by application of the regression. The 6-31G* value with 2.352 Å is far outside the range of accessible CN bonds, therefore all distances are increased.

2. Formamidines, acetamidines, benzamidines and corresponding cations

In Table 17 the basis set dependence of our calculated CN bond lengths for E,Z isomers of formamidine, acetamidine and benzamidine and the corresponding cations protonated

TABLE 16. Basis set dependence of calculated CN distances (in Å) in comparison to experimental ED and MW data (collected in Table 3)

Compound	STO-3G	3-21G	6-31G*	Experimental	Method	Ref.
$Me—NH_3^+$	1.5288	1.5473	1.5075	1.499(10)	XD	55
$Me—NH_2$	1.4855	1.4716	1.4532	1.474(5)	MW	59
				1.465(2)	ED	60
$(Me)_2NH$	1.4844	1.4656	1.4470	1.466(8)	MW	61
				1.465(2)	ED	62
$(Me)_3N$	1.486	1.464	—	1.451(3)	MW	65
				1.458(2)	ED	66
$H_2C{=}NH$	1.2729	1.2564	1.2614	1.273(8)	MW	69
$H_2C{=}NOH$	1.2814	1.2553	1.2494	1.276(5)	MW	233a
$HCO\text{-}NH_2$	1.4028	1.3534	1.3489	1.367(4)	ED	72
				1.368(3)	ED	72
				1.3665	ED + MW	72
$HC{\equiv}N$	1.1530	1.1372	1.1325	1.1568(2)	MW	233b
				1.1158(3)	ED	234
$MeC{\equiv}N$	1.1543	1.1390	1.1348	1.159(2)	ED	234
$C{\equiv}\overset{+}{N}H$	1.1703	1.1596	1.1542	1.1726(2)	MW	233b

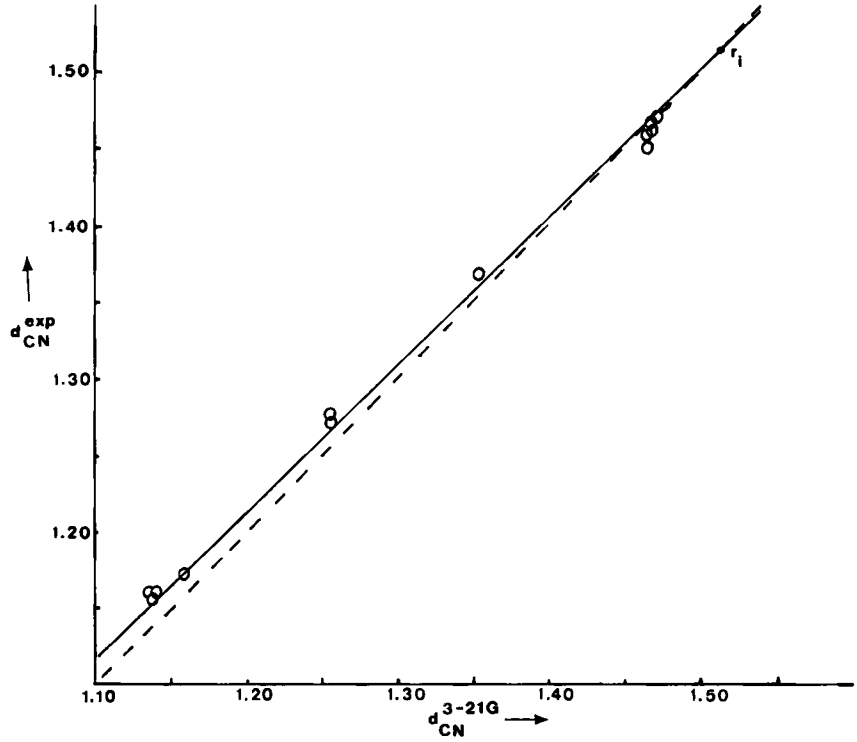


FIGURE 8. Plot of equation 11. Experimental versus 3-21G calculated CN distances

at the imino nitrogen is shown. (Angles are given in Table 18 and total energies in Table 19.)

The STO-3G minimum basis set predicts for *E* and *Z* formamidine a non-planar tetrahedral amino group, as was found also by CNDO/2[235] and MNDO calculations[236]. The calculated difference $\Delta = R_{am} - R_{im}$ with 0.16 Å is close to the maximum value (0.18 Å) for a non-conjugated amidine system obtained from 3-21G data by Zielinski[19] for the twisted amino group and also close to the experimental value of 0.178 Å. Assumed planarity as a constraint leads to $\Delta = 0.12$ Å, a value close to the range of 0.09 to 0.11 Å found for other basis sets and is characteristic for normal amidine conjugation. Split-valence basis sets leads to coplanar geometry of the amidino group with all hydrogen substituent atoms in the plane. In the case of fluorine substitution on amino nitrogen the 3-21G calculation leads to non-planar tetrahedral geometry of the amino group[20].

Formamidine may be compared to formamide in which difficulties exist in the precise determination of the experimental geometry[70–72,75] as well as in *ab initio* calculations of the molecular structure[75,237–241], the results of which vary with the applied basis set whether or not the lowest-energy geometry is planar. Recent MP2 calculations[241] favour a single, slightly non-planar minimum energy geometry although the HF potential energy surface for formamide exhibits a very flat region near its global minimum. It should be remembered that the experimental geometry of aniline shows also a non-planar tetrahedral geometry of the amino group[68].

Numerical data in Table 17 show that increase of the basis set reduces the formal CN

single bond, R_{am}, in the sequence STO-3G to 6-31G*. However, for the formal CN double bond, R_{im}, 6-31G values are longer than 3-21G and 6-31G* data. For *Z*-formamidine the R_{am} values are slightly longer than in the more stable *E* isomer and R_{im} values are very similar for both series. For the formamidinium cation both equal CN bond lengths vary in the series STO-3G > 6-31G > 3-21G and the data are close to the average of the corresponding CN single and double bonds in neutral formamidine. Experimental distances (Table 6) are 0.02 Å longer than calculated values.

NH bond distances are about 1.00 Å with the bond of the hydrogen *syn* (*Z*) to the imino nitrogen being longer than that of the *anti* (*E*) hydrogen in the neutral amidines and cations. This may be related to a study of Perrin and coworkers[242] of the kinetics of base-catalysed proton exchange in amidinium cations: H_Z exchanges 25 to 100% faster than H_E which was explained as 'the most acidic proton exchanges fastest'. We may conclude: the weaker-bound hydrogen (longer NH bond) exchanges faster. It should be noted that in acid-catalysed proton exchange[243], in 80% H_2SO_4, H_E exchanges faster than H_Z but this reaction proceeds via the dication [$RC(—NH_3^+)=NH_2^+$]. Surprisingly, the imino NH bond is about 0.01 Å longer than the amino NH bond.

In acetamidine, both CN distances are longer than in the corresponding formamidine isomers and the CC distance is between 1.53 and 1.50 Å. Experimental XD distances for acetamidinium cations in Table 6 show very good agreement with 3-21G and 6-31G data. The agreement for acetamidine (Table 5) is less satisfactory and may be due to the hydrogen-bonding effects in the crystal, neglected in the calculation.

In benzamidine, the phenyl ring and the amidine group are twisted by 42° (STO-3G) or 46° (3-21G) for the minimum-energy *E* conformation and by 30° (STO-3G), 21° (3-21G) or 26° (6-31G) for the *Z* isomer. Both *E*,*Z* isomers have the same 3-21G energy. In the *Z* isomer, less sterical strain between the imino NH and *ortho* hydrogens of the phenyl group leads to a smaller torsional angle. The torsional angle in *E*-benzamidine is very similar to that calculated and determined for gaseous biphenyl[244a] (STO-3G: 38.6°; 6-31G: 44.7°; ED r_g: 44.4°) indicating similar sterical requirements. As in the case of biphenyl, the molecular geometry may be optimized for the constraint of coplanarity or for a fixed twist angle of 90° with results presented in Table 17. CN bond lengths vary only slightly as dependent on the torsional angle.

STO-3G optimization for benzamidinium cation leads to a torsional angle of 32.3° for STO-3G and to 44.4° for 3-21G basis sets, in agreement with a CNDO/2 calculation[235] which yields a twist angle of 35.7° compared to the experimental angle of 36.6° (Table 6). Due to conjugative interactions the CN bonds are 0.007 Å longer in the coplanar form than in the perpendicularly twisted molecule.

3. *Guanidine and guanidinium cation*

Ab initio SCF optimizations of molecular structures of several Y-conjugated hetero-π-systems using STO-3G and 3-21G basis sets have been reported by Williams and Gready[244b]. The results for guanidine and its cation are shown in Figure 9.

In the free base guanidine (**53**) the two bonds to amino groups differ by 0.004 Å (STO-3G) or 0.009 Å (3-21G), the longer bond being *cis* to the imino NH group. Protonation at the imino nitrogen leads to the highly symmetrical planar guanidinium cation (**54**) in which all three CN bonds are equal at 1.355 (STO-3G) or 1.324 Å (3-21G). The second value is very close to the experimental average of 1.325 Å, Calculated CN distances are related linearly to Mulliken π-bond orders[244b].

4. *Basis set dependence of calculated angles*

In Table 18 our calculated angles of *E*,*Z* isomers of formamidine, acetamidine, benzamidine and corresponding cations are shown for STO-3G, 3-21G, 6-31G and

TABLE 17. Basis set dependence of calculated distances (in Å) in amidines and corresponding cations

Compound	Basis	R_{am}	R_{im}	N1—H1	N1—H2	N2—H4 N2—H5	C—X3	Δ^a
E-Formamidine tetr.[b]	STO-3G	1.435	1.276	1.028	1.029	1.044	1.095	0.159
(148) plan.[c]	STO-3G	1.397	1.281	1.012	1.013	1.043	1.096	0.116
plan.	3-21G	1.364	1.260	0.993	0.997	1.009	1.081	0.105
plan.	6-31G	1.359	1.268	0.988	0.992	1.002	1.080	0.092
plan.	6-31G*	1.359	1.268	0.988	0.992	1.002	1.080	0.092
Z-Formamidine tetr.	STO-3G	1.436	1.276	1.027	1.028	1.048	1.092	0.160
(149) plan.	STO-3G	1.401	1.279	1.013	1.014	1.047	1.093	0.121
plan.	3-21G	1.373	1.260	0.995	0.997	1.015	1.075	0.112
plan.	6-31G	1.369	1.267	0.990	0.992	1.008	1.074	0.102
plan.	6-31G*	1.363	1.257	0.992	0.994	1.007	1.102	0.107
Formamidinium plan.	STO-3G	1.330	1.330	1.025	1.026	1.025 1.026	1.102	0.000
(150)	3-21G	1.302	1.302	1.003	1.004	1.003 1.004	1.071	0.000
	6-31G	1.306	1.306	0.996	0.998	0.996 0.998	1.072	0.000
E-Acetamidine plan.	STO-3G	1.402	1.284	1.012	1.013	1.042	1.535	0.119
	3-21G	1.370	1.262	0.994	0.996	1.009	1.518	0.109
	6-31G	1.367	1.272	0.989	0.991	1.002	1.509	0.095
Z-Acetamidine plan.	STO-3G	1.406	1.282	1.013	1.014	1.046	1.531	0.123
(56)	3-21G	1.378	1.263	0.995	0.997	1.014	1.511	0.115
	6-31G	1.376	1.272	0.990	0.991	1.007	1.501	0.106
Acetamidinium plan.	STO-3G	1.338	1.337	1.023	1.024	1.023 1.024	1.533	0.001
(73)	3-21G	1.310	1.307	1.002	1.003	1.001 1.003	1.505	0.003
	6-31G	1.316	1.313	0.995	0.997	0.995 0.997	1.497	0.003
H-Perpendicular[d]	3-21G	1.309	1.309	1.001	1.003	1.001 1.003	1.504	0.000
E-Benzamidine twist[e]	STO-3G	1.403	1.287	1.012	1.013	1.042	1.520	0.116
	3-21G	1.368	1.264	0.993	0.996	1.009	1.497	0.104
	6-31G	1.368	1.264	0.988	0.991	1.002	1.495	0.104
Z-Benzamidine twist	STO-3G	1.406	1.286	1.011	1.014	1.046	1.516	0.119
	3-21G	1.373	1.265	0.992	0.996	1.012	1.497	0.109
	6-31G	1.374	1.274	0.988	0.991	1.006	1.491	0.100

Z-Benzamidine plan.	STO-3G	1.405	1.287	1.010	1.014	1.045	1.519	0.118
E-Benzamidine plan.	STO-3G	1.405	1.288	1.009	1.013	1.040	1.527	0.117
E-Benzamidine perp.[f]	STO-3G	1.402	1.285	1.013	1.014	1.043	1.525	0.117
Benzamidinium twist	STO-3G	1.344	1.344	1.021	1.023	1.021 1.023	1.495	0.000
	3-21G	1.312	1.312	1.001	1.002	1.001 1.002	1.474	0.000
	6-31G	1.319	1.319	0.994	0.996	0.994	1.473	0.000
Benzamidinium plan.	STO-3G	1.346	1.346	1.019	1.022	1.019 1.022	1.497	0.000
Benzamidinium perp.	STO-3G	1.339	1.339	1.023	1.024	1.023 1.024	1.520	0.000
N^1-Phenylformamidine[c]	STO-3G	1.409	1.280	1.018	1.427	1.043	1.095	0.129
twist = 46.6°	STO-3G	1.415	1.277	1.018	1.436	1.044	1.093	0.137
N^2-Phenylformamidine[c]	STO-3G	1.394	1.283	1.013	1.014	1.454	1.093	0.111
twist = 69.5°	STO-3G	1.397	1.281	1.013	1.013	1.463	1.094	0.116
N-Phenylform-amidiniun cation[c]	STO-3G	1.336	1.330	1.023	1.467	1.023 1.020	1.100	0.005
N-Methylformamidines[c]:								
(174)	STO-3G	1.399	1.278	1.012	1.013	1.487	1.096	0.145
(174)	3-21G	1.366	1.255	0.993	0.996	1.464	1.083	0.112
(175)	3-21G	1.361	1.262	0.994	1.458	1.009	1.081	0.099
(176)	3-21G	1.372	1.261	0.995	1.456	1.013	1.075	0.111
(177)	3-21G	1.363	1.261	1.456	0.997	1.009	1.082	0.102
(178)	3-21G	1.376	1.257	0.994	0.994	1.467	1.076	0.119
(179)	3-21G	1.371	1.261	1.458	0.999	1.015	1.076	0.110
N-Methylformamidinium cations[c]:								
(180)	3-21G	1.307	1.298	1.002	1.002	1.002	1.071	0.009
(181)	3-21G	1.308	1.296	1.002	1.003	1.004	1.072	0.012

[a] $\Delta = R_{am} - R_{im}$.
[b] tetr. = tetrahedral non-planar amino group in the amidine system.
[c] plan. = planar amidine system.
[d] One hydrogen of the methyl group perpendicular to the planar amidino group (C_{2v} symmetry).
[e] twist = torsion by angle ϕ (twist) between the planar amidine group and the phenyl substituent:

E-Benzamidine: $\Phi = 42.4°$ (STO-3G); 45.5° (3-21G); 45.8° (6-31G),
Z-benzamidine: $\Phi = 29.6°$ (STO-3G); 21.0° (3-21G); 26.3° (6-31G),
benzamidinium: $\Phi = 32.3°$ (STO-3G); 44.4° (3-21G); 41.4° (6-31G),

[f] perp. = perpendicular orientation between the amidine plane and the plane of the phenyl ring ($\Phi = 90°$).

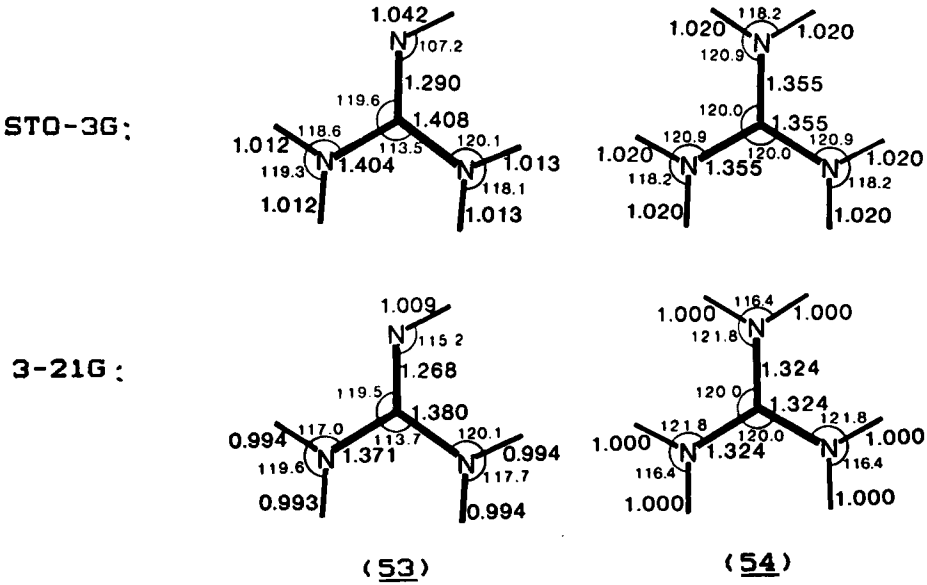
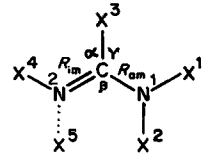


FIGURE 9. STO-3G and 3-21G optimized bond lengths and angles for guanidine (**53**) and guanidinium cation (**54**). (From Reference 244b)

6-31G* basis sets (data for formamidines are from References 19 and 228, except 6-31G values). Numerical values show relatively small basis set dependent variations between angles for heavy atoms of at most 1.5°. The angle N1CN2 (β in the notation of **181a**) differs very much for *E, Z* isomers. For all *E* isomers this angle is smaller than in the cation and the *Z* isomer. 6-31G values, which are usually intermediate between STO-3G and 3-21G angles, are in the formamidine series 122.2° for *E*, 124.8° for the cation and 128.8° for *Z*. The angle XCN2 (α) behaves in just the opposite manner: 124.3° for *E* and 117.7° for the *Z* isomer and the cation. The angle XCN1(γ) remains small: 113.6° and 113.7° in the *E, Z* isomers and 117.5° in the cation. These trends reflect stereochemical requirements: in *E*-formamidine H^4–H^3 interactions open angle α and in *Z*-formamidine H^4–H^2 interactions open angle β. In symmetrical formamidinium cations the H^5–H^2 interaction opens angle β. Substitution at functional carbon either with methyl or with phenyl leads to the same pattern of angular variation at the amidine group.

Angles to hydrogen atoms show larger dependences on basis sets, thus especially the CN2H4 angle at the imino nitrogen varies up to 8°. The angle H1N1H2 of the amino group lies between 116° and 119°.



(**181a**)

Notation for molecules of Tables 17 to 19

TABLE 18. Basis set dependence of calculated angles (in deg) in amidines and corresponding cations

Compound	Basis	β N1CN2	γ X3CN1	α X3CN2	CN2X4	CN1X1	CN1X2 CN2X5	X1N1X2 X4N2X5
E-Formamidine tetr.[b]	STO-3G	120.98	113.03	125.98	108.46	110.67	109.70	108.89
(148) plan.[c]	STO-3G	121.30	112.59	126.10	107.75	121.39	119.78	118.83
plan.	3-21G	122.45	112.54	125.01	114.74	122.16	118.53	119.32
plan.	6-31G	122.17	113.57	124.26	115.38	122.05	118.81	119.14
plan.	6-31G*	122.82	112.80	124.38	110.93	121.94	119.09	118.97
Z-Formamidine tetr.	STO-3G	127.55	113.29	119.16	108.53	111.30	111.46	108.76
(149) plan.	STO-3G	128.05	112.85	119.11	108.15	121.07	121.04	117.89
plan.	3-21G	129.26	112.76	117.99	115.50	120.85	121.39	117.76
plan.	6-31G	128.79	113.72	117.49	116.61	120.82	121.56	117.62
plan.	6-31G*	129.06	112.71	118.23	112.33	120.90	121.39	112.71
Formamidinium[c]	STO-3G	124.23	117.89	117.89	120.19	120.19	122.19	117.62
(149)	3-21G	125.26	117.37	117.37	120.87	120.87	122.96	116.17
	6-31G	124.84	117.65	117.51	120.68	120.68	123.18	116.14
E-Acetamidine plan.	STO-3G	118.84	113.83	127.33	107.92	121.81	119.38	118.81
	3-21G	120.02	113.26	126.73	114.92	122.59	118.05	119.37
	6-31G	119.42	114.45	126.13	115.21	122.63	118.23	119.14
Z-Acetamidine plan.	STO-3G	125.71	114.12	120.17	108.12	121.37	120.88	117.76
(56)	3-21G	126.75	113.58	119.66	115.06	121.19	121.16	117.65
	6-31G	125.90	114.51	119.59	115.99	121.32	121.21	117.48
Acetamidinium	STO-3G	120.53	119.20	120.27	120.47	120.35	122.20	117.46
(73)								117.41
	3-21G	121.65	118.40	119.95	121.26	120.99	122.84	116.17
	6-31G	120.94	119.01	120.06	121.04	120.92	123.00	116.08
								116.07
H-Perpendicular[d]	3-21G	121.62	119.18	119.20	121.15	121.15	122.74	116.12
E-Benzamidine twist[e]	STO-3G	118.56	115.10	126.34	107.89	121.94	119.11	118.96
	3-21G	120.09	114.41	125.50	114.86	122.64	117.73	119.63
	6-31G	119.27	115.50	125.23	115.22	122.67	117.93	119.40
Z-Benzamidine twist	STO-3G	124.93	116.31	118.77	108.09	122.12	120.13	117.75
	3-21G	125.72	116.06	118.22	115.33	122.53	120.09	117.38
	6-31G	125.01	116.33	118.66	115.92	122.30	120.32	117.38

(continued)

TABLE 18. (*continued*)

Compound	Base	β N1CN2	γ X3CN1	α X3CN2	CN2X4	CN1X1	CN1X2 CN2X5	X1N1X2 X4N2X5
Z-Benzamidine plan.	STO-3G	124.07	117.53	118.41	108.09	122.97	119.60	117.43
E-Benzamidine plan.	STO-3G	116.16	116.85	127.00	109.04	123.74	117.76	118.50
E-Benzamidine perp.	STO-3G	119.21	114.23	126.56	107.74	121.50	119.52	118.98
Benzamidinium twist	STO-3G	118.89	120.55	120.56	120.49	120.51	121.92	117.57
								117.58
(75)	3-21G	121.24	119.38	119.38	120.54	120.55	122.75	116.70
								116.70
	6-31G	120.14	119.93	119.93	120.65	120.64	122.82	116.54
								116.54
Benzamidinium plan.	STO-3G	117.05	121.60	121.47	121.60	121.60	121.23	117.17
Benzamidinium perp.	STO-3G	120.43	119.82	119.76	119.79	119.79	122.53	117.69
N^1-Phenylformamidine[c]	STO-3G	124.50	110.52	124.99	107.50	115.34	129.16	115.50
twist = 46.6°	STO-3G	130.25	111.18	118.57	109.18	116.19	127.00	116.82
N^2-Phenylformamidine[c]	STO-3G	120.33	112.58	127.09	118.62	121.25	119.82	118.93
twist = 69.5°	STO-3G	129.35	112.67	118.00	116.94	120.51	121.32	118.17
N-Phenylform-	STO-3G	128.98	115.50	115.52	118.96	112.99	134.27	112.74
amidinium cation[c]							123.57	117.47
N-Methylformamidines[c]:								
(174)	STO-3G	121.35	113.04	125.62	114.81	121.25	119.85	118.90
(174)	3-21G	123.21	113.24	123.56	119.92	122.09	118.54	119.38
(175)	3-21G	121.89	113.04	125.08	114.83	119.94	120.45	119.61
(176)	3-21G	129.00	112.97	118.03	116.07	118.78	122.49	118.74
(177)	3-21G	122.61	112.46	124.93	114.66	123.37	116.59	120.04
(178)	3-21G	130.05	112.30	117.65	123.41	120.05	122.47	117.48
(179)	3-21G	129.36	112.67	117.97	115.57	123.63	118.64	117.72
N-Methylformamidinium cations[c]:								
(180)	3-21G	125.00	117.22	117.77	118.11	120.81	122.93	116.26
							124.67	117.22
(181)	3-21G	125.66	117.00	117.34	123.23	120.86	122.82	116.32
					122.82		120.04	116.72

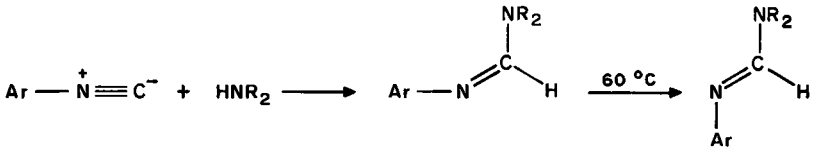
See the footnotes at the end of Table 17.

C. *E,Z* Isomerism of Amidines

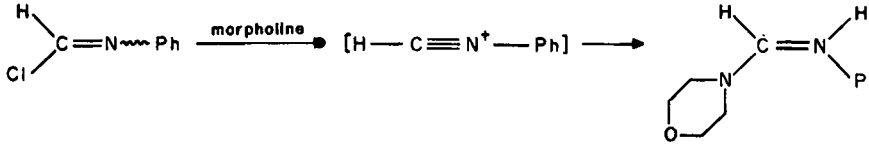
1. Experimental results

Acyclic amidines may show *Z,E* (*syn, anti* or *cis,trans*) isomerism with respect to the formal C=N double bond. Whereas the *E* isomer is mostly energetically more favoured than the *Z* form[19], the actual geometry depends on the kind and number of substituents at the amidine fragment. The adopted geometry depends mainly on the steric requirements of the substituents and the XD data on amidines in Table 5 and cations in Table 6 show the occurrence of both kinds of isomers.

Hegarty and Chandler[245] described the stereospecific preparation of thermodynamically unstable *Z*-amidines by 1,1-addition of secondary amines to isonitriles in the presence of AgCl below 0 °C (equation 13) or by solvolysis[246] of *N*-phenylformohydrazonyl chloride in water in the presence of morpholine (equation 14).



(13)



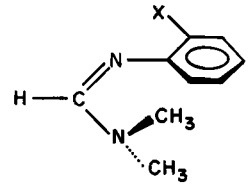
(14

By acid catalysis or by reflux in chloroform (6h) the *Z* form may be converted into the *E* form. The stereochemistry was deduced from the ^{1}H NMR spectrum of the N—CH_2 signals of the morpholino group which, owing to the effect of the adjacent aryl group in *Z*, are shielded by 0.65 ppm in $CDCl_3$ relative to *E*. In addition this signal shows a smaller solvent-induced shift for the *Z* isomer when measured in benzene relative to chloroform (0.15 ppm for *Z* and 0.33 ppm for *E*) due to the fact that the intramolecular *N*-aryl group already 'solvates' the morpholino group.

The temperature dependence of ^{1}H NMR spectra[247] of the *E* isomer shows that the signals of the NMe_2 groups are equivalent at 34 °C but, on cooling to − 30 °C, separate signals of equal intensity are obtained with a coalescence temperature of − 5 °C. This temperature, and thus the energy barrier for CN bond rotation, is raised when Ar contains an electron-withdrawing group which increases by conjugation the bond order of the formal CN single bond.

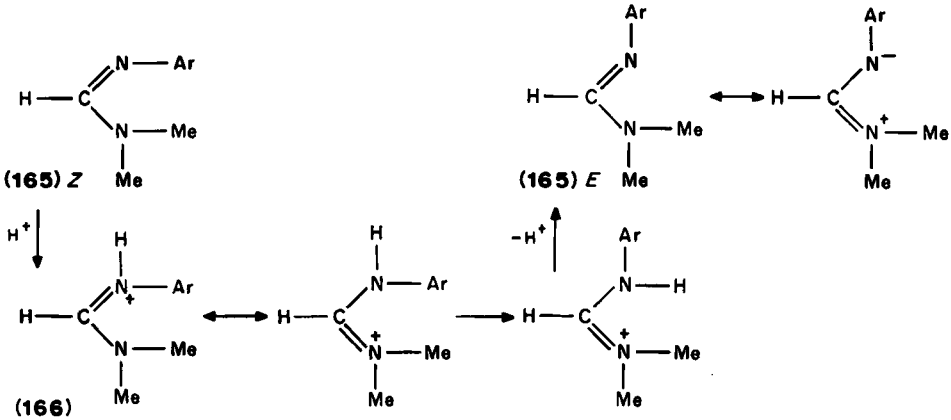
The *Z* isomer presents quite a different situation, since the signal for the NMe_2 group remains as a singlet over the temperature range from − 80 to 34 °C. This is explained by the possibility that the *Z* isomer is frozen even at 34 °C in a twisted conformation (**165a**) in which the perpendicular methyl groups are in equivalent positions. When the aryl group

contains an *ortho* substituent, the two Me groups become non-equivalent, a fact clearly pointing to a fixed conformation around the CN single bond and the *N*-aryl bond.



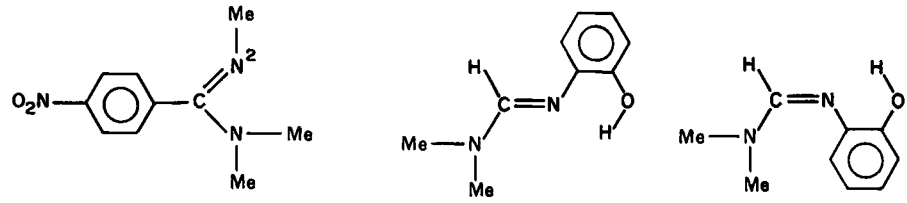
(165a)

The $Z \rightarrow E$ isomerization of **165** is pH-independent from pH 0 to 8 and then decreases. Thus the protonated form **166** is undergoing the isomerization as shown in Scheme 13. No evidence was found for isomerization of the free base by direct nitrogen inversion[248].



SCHEME 13. Mechanism of proton-catalysed-$Z \rightarrow E$ isomerization[248]

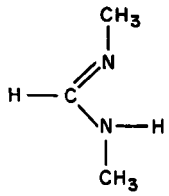
A direct proof of the presence of the *E* isomer of N^1,N^1,N^2-trimethyl-*p*-nitrobenzamidine (**167**) in $CDCl_3$ solution was given by Exner and coworkers[249]. They observed in the ^1H NMR a nuclear Overhauser effect as an intensity enhancement of the signals of protons H^2 and H^6 of the phenyl ring on selective irradiation of the $=N-CH_3$ signal. The intensities of other signals remain unaffected.



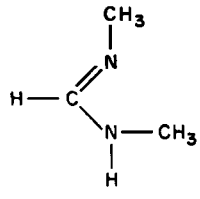
(167) (168)

For N^2-(2-hydroxyphenyl)-N^1,N^1-dimethylformamidine (**168**) in $CDCl_3$ solution the occurrence of both *E*,*Z* isomers but with 80% predominance of *E* was shown[250] in the ^1H NMR spectrum at room temperature.

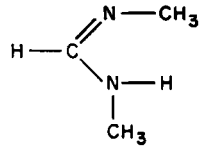
^1H NMR and IR studies of neat *N*,*N'*-dimethylformamidine have shown[251] that of structures **169a** to **169d** the *E* isomer **169a** is present exclusively. It undergoes tautomerism which is proposed to occur through a hydrogen-bonded cyclic dimer **170**. At 25 °C $k_{taut} = 820\,s^{-1}$ and $E_a = 41.5 \pm 1.5\,kJ\,mol^{-1}$.



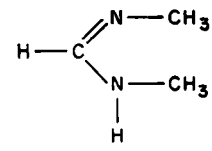
(**169a**)



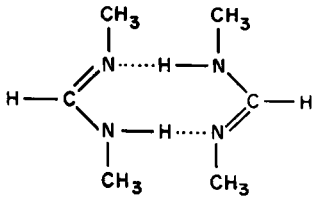
(**169b**)



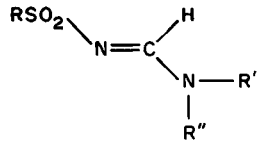
(**169c**)



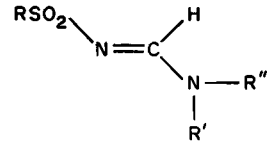
(**169d**)



(**170**)

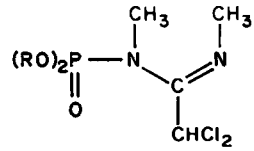


(**171a**)

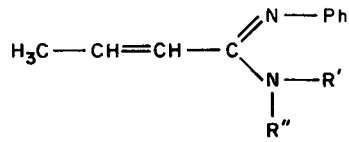


(**171b**)

For N^2-sulphonyl formamidines (**171**), using ^1H and ^{13}C NMR and IR spectroscopy the occurrence of the *E* isomer and of two rotamers **171a** and **171b** was shown[252,253]. In phosphorylated amidines **172** the presence of both *E*,*Z* isomers in solution in different ratios was found[254] by ^1H, ^{13}C and ^{31}P NMR spectroscopy.



(**172**) *Z*



(**173**) *Z*

However, for several propenyl amidines (**173**) the predominance of the *Z* isomer by about 60% was indicated[255] by ^{13}C NMR spectroscopy. The free energy of activation for rotation around the formal single CN bond was determined[256] from the temperature dependence of the ^{13}C NMR signals as 49.4 kJ mol^{-1} for the *E* isomer and 36.4 kJ mol^{-1} for the *Z* isomer.

2. *Calculated energy differences between E,Z isomers*

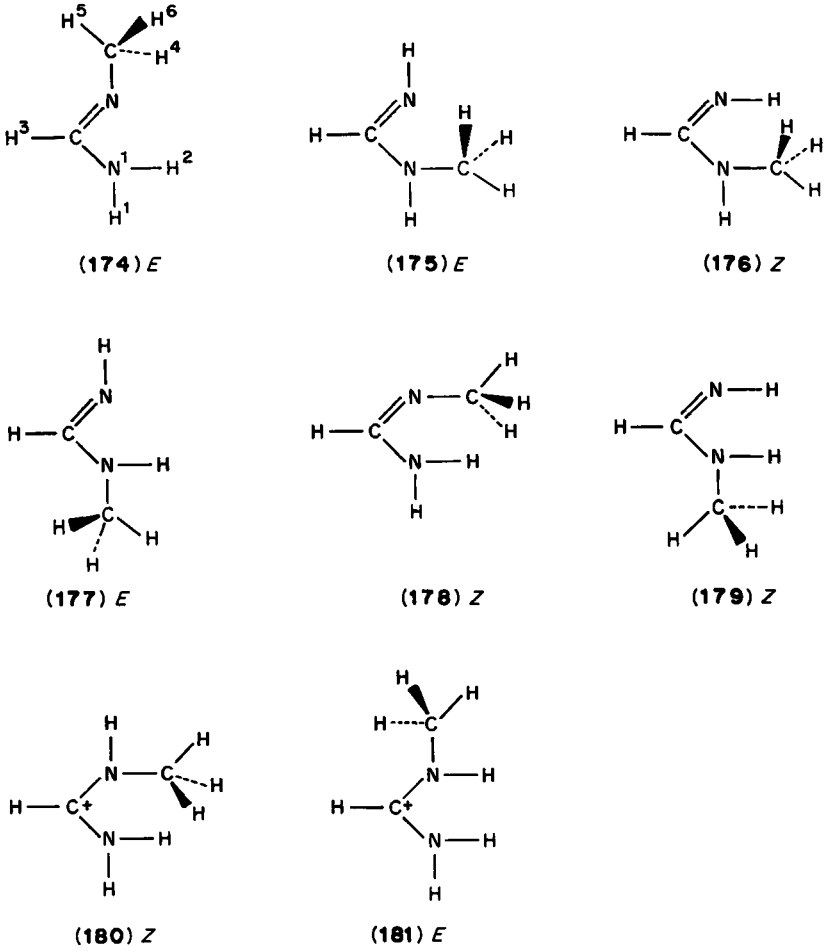
Numerical values of total energies of several amidines in various basis sets are given in Table 19 (see also Scheme 14). The basis set dependence of the differences between *E* and *Z*

TABLE 19. Basis set dependence of calculated total energies (in hartree units). For formamidine systems all basis sets, except 6-31G, are given in References 19 and 228. All others are taken from our own calculations using G82

Compound	STO-3G	3-21G	6-31G	6-31G*	4-31G[229a]
E-Formamidine tetr.[b]	−147.15397				
(148) plan.[c]	−147.14828	−148.23777	−149.01146	−149.07504	−148.85427
Z-Formamidine tetr.	−147.15338				
(149) plan.	−147.14885	−148.23684	−149.00849	−149.07289	−148.85178
Formamidinium[c] **(150)**	−147.61022	−148.64351	−149.41073	−149.46382	−149.25493
E-Acetamidine plan.	−185.73694	−187.06495	−188.03882		
Z-Acetamidine plan.	−185.73769	−187.06488	−188.03756		
Acetamidinium[c] **(73)**	−186.21172	−187.48061	−188.44858		
H perpendicular[d]		−187.48055			
E-Benzamidine twist	−373.90719	−376.51247	−378.48626		
Z-Benzamidine twist[e]	−373.90798	−376.51247	−378.48505		
Z-Benzamidine plan.	−373.90749				
E-Benzamidine plan.	−373.90375				
E-Benzamidine perp.[f]	−373.90469				
Benzamidinium twist	−374.39168	−376.93263	−378.90185		
Benzamidinium plan.	−374.39010				
Benzamidinium perp.	−374.38572				
N^1-Phenylformamidine[e]	−373.90811				
twist = 46.6°	−373.90349	−376.50129			
N^2-Phenylformamidine[e]	−373.90657				
twist = 69.5°	−373.90563	−376.50937			
N-Phenylformamidinium cation plan.	−374.36957				

N-Methylformamidines[c]:		
(**174**)*E*	−185.73034	−187.05215
(**175**)*E*		−187.05184
(**176**)*Z*		−187.04968
(**177**)*E*		−187.04889
(**178**)*Z*		−187.04865
(**179**)*Z*		−187.04803
Z-*N*-Methylform-amidinium cation[c] (**180**)		−187.46404
E-*N*-Methylform-amidinium cation[c] (**181**)		−187.46196
Fluoro-substituted formamidines[20]:		
E-N^2-Fluoroformamidine[c] (**182a**)		−246.50086
Z-N^2-Fluoroformamidine[c] (**183a**)		−246.50642[g]
Z-Fluoroformamidine[c,h] (**182b**)		−246.58021
E-Fluoroformamidine[c,h] (**183b**)		−246.57319[g]
E-N^1-Fluoroformamidine[b] (**182c**)		−246.46863
Z-N^1-Fluoroformamidine[b] (**183c**)		−246.47665[g]
Z-N^1-Fluoroformamidine[b] (**184c**)		−246.47308[g]
Protonated fluoroformamidines[20]:		
Z-*N*-Fluoroformamidinium cation[c]		−246.85027
E-*N*-Fluoroformamidinium cation[c]		−246.85613
Fluoroformamidinium cation[c]		−246.95835

[a–f] See the footnotes at the end of Table 17.
[g] New values which are not included in Reference 20.
[h] Change in stereochemical *E*,*Z* notation due to higher priority of fluorine over nitrogen.



SCHEME 14. Geometrical isomers of *N*-methylformamidines

energies for formamidine is given in Table 20. Neglecting the extreme values of non-planar and planar STO-3G energies, the Hartree–Fock results for split-valence basis sets yield energy differences between 2.4 and 7.8 kJ mol^{-1}. The 4-31G value is taken from Reference 236.

TABLE 20. Differences between total energies for *E* and *Z* isomers of formamidine as dependent on the applied basis sets

ΔE *E*–*Z*	STO-3G tetr.	STO-3G planar	3-21G	4-31G	6-31G	6-31G*	MP2[257a]	MP3[257a]
hartree	0.00569	0.00057	0.00093	0.00249	0.00296	0.00236	0.00355	0.00341
kJ mol^{-1}	14.94	1.50	2.44	6.54	7.78	6.20	9.32	8.95

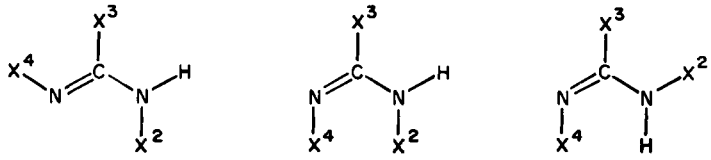
Moeller–Plesset post-Hartree–Fock calculations by Wiberg and coworkers[257a] using the extremely large 6-311 + + G** basis set (with diffuse functions and polarization functions on all atoms) at 6-31 G* optimized geometries give slightly increased energy differences of 9.3 kJ mol^{-1} for MP2 and 9.0 kJ mol^{-1} for MP3. The energy differences between *E* and Z isomers are relatively small but the 3-21G calculated barrier of activation for inversion[19] with a linear =N—H bond (**159**) is rather high (96.9 kJ mol^{-1}).

For all six stereochemical isomers of *N*-methyl formamidine, **174** to **179**, 3-21G optimized bond lengths are shown in Table 17, angles in Table 18 and energies in Table 19. The structures in Scheme 14 show four pairs of *Z*,*E* isomers: the methyl group *E*,*Z* isomers **174** and **178** show a difference of 9.18 kJ mol^{-1} in 3-21G energies, and in the cations, **180** versus **181**, a value of 5.46 kJ mol^{-1}. For the s-*cis* isomeric pair **175** and **176** the difference of 18.03 kJ mol^{-1} is rather high, due to steric interaction. In the s-*trans* isomers **177** and **179** the energy difference is only 2.26 kJ mol^{-1}.

For acetamidine, the STO-3G basis favours the *Z* isomer over *E* by 1.97 kJ mol^{-1} (Table 19) but 3-21G and 6-31G show calculated stabilities of *E* versus *Z* higher by 0.18 and 3.31 kJ mol^{-1}.

For benzamidine, STO-3G and 3-21G predict higher stability for the *Z* isomer by −2.1 and −0.02 kJ mol^{-1} but in the 6-31G basis the *E* form is more stable by 3.18 kJ mol^{-1}.

We reported[20] 3-21G optimizations of seven fluorine-substituted formamidines (Scheme 15) with up to three fluorine atoms at the positions at imino nitrogen, amino nitrogen and functional carbon, all in *E* configuration **182**, since we assumed from steric reasons that these isomers are the most stable. To our surprise, the *Z* isomers **183a** and **183c** were calculated to be energetically more stable by 14.6 and 21.1 kJ mol^{-1}. This may be explained by the same factors which determine the greater stability of *cis*-1,2-dichloroethylene over the *trans* form[257b]. This result shows that the predominance of *E* or *Z* isomers is not determined only by steric effects but also by electronic effects.



(182) (183) (184)

FHH (a) $X^4 = F$; $X^3 = X^2 = H$
HFH (b) $X^3 = F$; $X^4 = X^2 = H$
HHF (c) $X^2 = F$; $X^3 = X^4 = H$
FFH (d) $X^4 = X^3 = F$; $X^2 = H$
FHF (e) $X^4 = X^2 = F$; $X^3 = H$
HFF (f) $X^3 = X^2 = F$; $X^4 = H$
FFF (g) $X^2 = X^3 = X^4 = F$

SCHEME 15. Geometrical isomers of fluorine-substituted formamidines

D. Hindered Rotation Around the Formal CN Single Bond

1. *Experimental facts*

Substituents on the amino nitrogen of amidines are magnetically non-equivalent as in the case of dimethylformamide[258]. Therefore the temperature dependence of NMR

spectra allows the determination of coalescence temperatures and activation energy parameters for rotation around the formally single CN bond. A collection of experimental data up to 1971 was presented in the first volume on this subject[259] (Table 27 and 28, pp. 68 and 70) and need not be repeated here.

For unsubstituted formamidinium chloride[260] the barrier to rotation about one of the CN bonds was found to decrease with an increase in the dielectric constant of the solvent: $E_a = 124$ kJ mol^{-1} in chloroform, 105 kJ mol^{-1} in acetone and 77 kJ mol^{-1} in DMSO.

For the N^1,N^2-dimethyl(trideuteroacet)amidinium cation[261] in DMSO-d_6 E_a is 89 ± 1 kJ mol^{-1}.

N^1,N^2-dimethylbenzamidine[262] in $CDCl_3$ shows a value for E_a of 76.1 kJ mol^{-1}, which may be affected by a hydrogen bond of about 12.6 kJ mol^{-1}.

In N^1,N^1-dimethyl-N^2-*t*-butylformamidine[263] in pyridine-d_5 E_a is as low as 46 ± 3 kJ mol^{-1} with a coalescence temperature of -48 °C.

The free enthalpy of activation ($\Delta G^{\ddagger}$) is in the range of 46 to 63 kJ mol^{-1} for variously substituted N^1,N^1-dimethylamidines[256,263-266], while for amidinium cations[260,261,266,267] the values are higher, in the range of 70 to 92 kJ mol^{-1}. These different energy values may be taken as an indication of stronger bond orders in the amidinium cations due to mesomeric bond-length equalization.

Recently[268] barriers to rotation in N^1,N^1-dimethyl-N^2-substituted phenylacetamidines with 12 different substituents on the phenyl ring have been determined from line shape analysis of dynamic ^{1}H and ^{13}C NMR spectra. The values of $\Delta G^{\ddagger}$ are 51.2–58.7 kJ mol^{-1}. Their correlation with Hammett σ-values indicate an important contribution of substituents to the barrier height. Correspondingly substituted formamidines[256,269] show a higher barrier of 63 kJ mol^{-1}. This decrease of about 10 kJ mol^{-1} in the parent compounds is probably due to steric interaction of the methyl group with the aromatic ring that leads to non-planarity and a decrease in conjugation of this phenyl ring with the amidine group. However, this may be compensated by conjugation to the lone pair on imino nitrogen.

Similar differences were observed[270,271] for N^2 heteroaryl substituted N^1,N^1-dimethyl formamidines (73–84 kJ mol^{-1}) and acetamidines (39–59 kJ mol^{-1}).

The influence of aryl substitution at N^2 and of alkyl substitution at the functional carbon (R^3) on ^{13}C NMR was studied at low temperature by Wawer[269] for ten N^1,N^1-dimethylformamidines, five acetamidines and five isobutyramidines. With an increase in the steric demand of substituent R^3 the enthalpy of activation decreases from 63.3 to about 30 kJ mol^{-1} as shown in Table 21.

The rotational barriers of eleven N^2-phosphorylated N^1,N^1-dimethylamidines have reported[272] $\Delta G^{\ddagger}$ values between 45.6 and 90 kJ mol^{-1}.

For *N,N,N',N'*-tetramethyl-formamidinium and -acetamidinium cation[273a] $\Delta G^{\ddagger}$ was determined as 64.4 and 44.2 kJ mol^{-1}. Thus in the cation the methyl substituent at the

TABLE 21. Influence of substituents (R^3) at the functional carbon on chemical shifts, δC_F, and the barrier to rotation around C—N^1 in N^1,N^1-dimethyl-N^2-phenylamidines

R^3	Isomer	δC_F (ppm)	$\Delta G^{\ddagger}$ (kJ mol^{-1})	Solvent	Ref.
H	*E*	153.5	63.3	acetone-d_6	269
CH_3	*E*	157.0	53.8	acetone-d_6	268
C_2H_5	*E*	160.5	45.9	$CDCl_3$	256
n-C_4H_9	*E*	160.0	45.9	$CDCl_3$	256
i-C_3H_7	*E*	162.5	30(?)	acetone-d_6	269

functional carbon has a larger influence on the rotational barrier than in the neutral base. In *N,N*-dimethyl-*N',N'*-diethylformamidine[273a] the rotational barrier of the dimethylamino group is 66.8 kJ mol^{-1} and of the diethylamino group, 63.9 kJ mol^{-1}.

2. *Calculations of rotational barriers*

MNDO and *ab initio* STO-3G, 4-31G and pseudo-potential calculations with determinations of rotational barriers have been reported[236] for formamidine, acetamidine, N^1,N^1-dimethylformamidine and N^2-cyanoformamidine. Calculated barriers are given in Table 22. The MNDO values are lower by a factor of 2 to 3 than *ab initio* pseudopotential calculations. Contrary to experimental results the rotational barrier is lower in formamidine than in acetamidine with the exception of the H4 basis set. For *N,N*-dimethylformamidine the calculated barrier to rotation is considerably lowered in all cases. An electron-withdrawing cyano substituent at the imino nitrogen raises by conjugative influence the barrier of rotation around CN^1. This effect is similar to N^2 phenyl-substituted formamidines[269] where the *p*-nitrophenyl substituent at the imino nitrogen (N^2) increases and a *p*-anisyl group decreases the rotational barrier with respect to the unsubstituted compound.

Zielinski's[19] 3-21G calculations yield rotational barriers of 49.1 kJ mol^{-1} for the *E* isomer and 40.4 kJ mol^{-1} for the *Z* isomer. The first value is very close to the pseudopotential H31* calculation[236].

A calculation by a MNDO effective charge model[273b] which introduces the solvent effect into MO calculations yielded, for the barrier to rotation of the formamidinium cation, 68.4, 64.9 and 54.2 kJ mol^{-1} for dielectric constants of 1, 2 and 10, respectively.

The *N*-methyl substituted formamidines and **174** to **181** from Scheme 14 contain three pairs of rotamers which yield, from 3-21G optimizations (Table 19), the following ground-state energy differences: the *E* isomers **175** and **177** differ by 7.73 kJ mol^{-1}, the *Z* isomers **176**

TABLE 22. Calculated rotational barriers in formamidines (in kJ mol^{-1})[236]

Compound	MNDO	Pseudo-potentials H4	Pseudo-potentials H31	Pseudo-potentials H31*	*ab initio*[19] HF 3-21G
Formamidine	27.2	77.0	66.5	48.5	49.1(*E*); 40.4(*Z*)
Acetamidine	28.0	69.5	68.6	50.6	
N^1,N^1-Dimethyl-formamidine	7.9	49.0	51.9	67.8	
N^2-Cyanoformamidine	36.8	92.0	89.1	67.8	

TABLE 23. Calculated rotational barriers[273c] of amino-substituted carbenium carbon (kJ mol^{-1})

	$H_2C^+—NH_2$ (185)	$H_2N—CH^+—NH_2$ (186)	$H_2N—C^+(NH_2)—NH_2$ (187)	$H_2N—C^+(Me)—NH_2$ (188)
STO-3G	341	144	84	
4-31G	295	118	59	112

and **179** differ by 4.33 kJ mol^{-1} and the cations **180** and **181** which are *E,Z* isomers as well as rotamers yield 5.46 kJ mol^{-1} energy difference with *Z* being more stable than *E*.

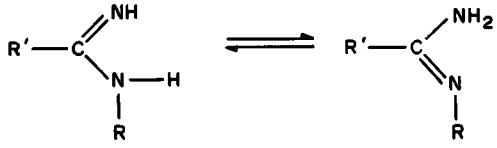
Immonium (**185**), formamidinium (**186**) and guanidinium (**187**) cations may be considered as carbenium cations, which are very effectively stabilized by amino substituents as indicated in the given structures. Rotational barriers collected in Table 23 have been calculated by partial optimization of molecular geometry by use of STO-3G and 4-31G basis sets[273c]. The bond lengths increase and rotational barriers decrease in the sequence from left to right.

E. Tautomerism

N-mono- and *N,N'*-disubstituted amidines may occur in two different tautomeric forms. This problem was studied experimentally mainly by the use of IR and ^{15}N NMR spectroscopy.

1. Experimental IR determinations

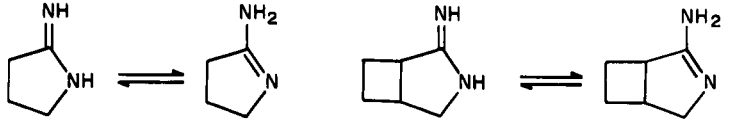
For N-monosubstituted amidines the preference in the tautomeric equilibrium in equation 15 depends on the electronic type of the substitutent R on nitrogen[274–281].



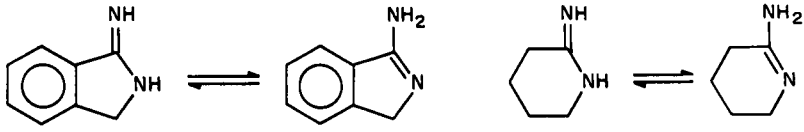
imino form amino form (15)

For R = alkyl the equilibrium prefers the imino form due to the +I effect of the substituent[275], although in chloroform solution both forms are present.

For R = aryl the amino form is dominant[275,277,278] due to the −I and −M effect of the substituent, which may conjugate in a planar geometry with the amidine system, and even in the twisted orientation it can still conjugate with the lone pair on imino nitrogen.



(189) (190)



(191) (192)

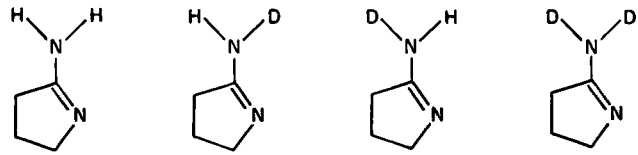
Sieveking and Lüttke[281] studied the tautomerism of cyclic amidines **189** to **192** by application of IR spectroscopy. In these the electronic influence of substituents is combined with steric factors, which include the preference of endo- or exocyclic C=N double bonds in five- or six-membered rings[276].

TABLE 24. Expectation values and assignment of characteristic IR vibrations of monomeric cyclic amidines[281] (in cm^{-1})

Amino form		Imino form	
assignment	region	assignment	region
ν_{as} NH_2	3540–3490	ν sec NH	3460–3420
ν_s NH_2	3420–3390	ν =NH	3370–3250
ν C=N (amidine I)	1680–1600	ν C=N (amidine I)	1680–1600
δ_s NH_2 (amidine II)	1610–1580	δ sec NH (amidine II)	1410–940?
ν C—N (amidine III)	1450–1350	ν C—N (amidine III)	1310–1200
γ_{as} NH_2 (twisting)	1250?	δ = NH	1450–1050
δ_{as} NH_2 (rocking)	1100	γ =NH	900–850
γ_s NH_2 (wagging)	650	γ sec NH (amidine IV)	780–420

The expected values for characteristic IR vibrations of the cyclic amino and imino forms are shown in Table 24.

All four cyclic amidines studied exist completely in the amino rather than the imino form. The characteristic group frequencies depend strongly on the state of aggregation, the solvent and the concentration, that is on the state of association. They have been studied specifically by means of partial and full deuterium exchange. Mono-deuteration of the amino group of **189** leads to four bands in the region of NH(D) valence vibrations: 3475, 3450, 2565 and 2535 cm^{-1}. These bands have been interpreted by the presence of two rotamers, **189a** and **189b**, as shown in Scheme 16. The absorptions at higher frequencies in each pair are assigned to the NH or ND group which is *s-trans* to the C=N bond.



ν_{as}: 3513 3475[a] 3450[b] 2628

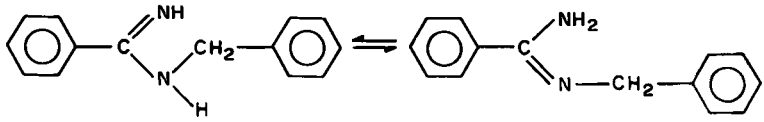
ν_s: 3410 2535[b] 2565[a] 2489

[a] = νNH or νND (*trans*). [b] = νNH or νND (*cis*)

(189a) **(189b)**

SCHEME 16. NH and ND valence vibrations[281] of **189**

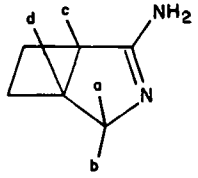
Deuteration of the acyclic *N*-benzyl benzamidine (**193**), which occurs mainly in the imino form (**193a**), shows a different picture. Besides the bands at 3450 (ν sec NH) and



(193a) **(193b)**

3320 cm^{-1} (ν=NH) only two further deuteration bands at 2251 (ν sec ND) and 2455 cm^{-1} (ν=ND) are observed.

In addition, the presence of the amino form of **190** is inferred from the 100 MHz ^1H NMR spectrum: the proton H_b shows a double triplet at $\delta = 3.43$ ppm with coupling constants $J_{ab} = 13.5$ Hz and $J_{bc} = J_{bd} = 1.5$ Hz. Due to the spatial arrangement of protons H_b and H_c a 'homoallylic coupling' is to be assumed which may occur only through the endocyclic double bond of the amino form[281].



(190)

2. ^{15}N NMR study

Natural abundance ^{15}N NMR spectroscopy[282,283] is a useful tool for the study of tautomeric equilibria in nitrogen-containing heterocycles. This method was applied by Clement and Kämpchen[284] for the study of tautomerism in N-monosubstituted amidines. Due to fast proton exchange, signal averaging occurs and no NH coupling could be observed. Experimental ^{15}N chemical shifts for tautomeric equilibria **194** and **195** as well as structurally fixed non-tautomeric amidines **196** to **199** are given in Scheme 17.

In the case of the *N*-methyl substituted benzamidine (**195**) both N signals are rather similar at 141.6 and 145.1 ppm, which indicates the presence of both exchanging tautomers in about equal amounts. However, in *N*-phenylbenzamidine (**194**) there is a difference of 145 ppm between the two nitrogen signals. The reference signals of the non-tautomeric amidines **196** to **199** allow the estimation of the presence of the less stable tautomer **194a** as 11% in the equilibrium mixture. In agreement with Prevoršek's[275] IR determinations for *N*-phenyl substituted amidines the amino form **194b** is dominant whereas for *N*-alkyl substituted amidines (**195**) both forms seem to be present in about equal amounts.

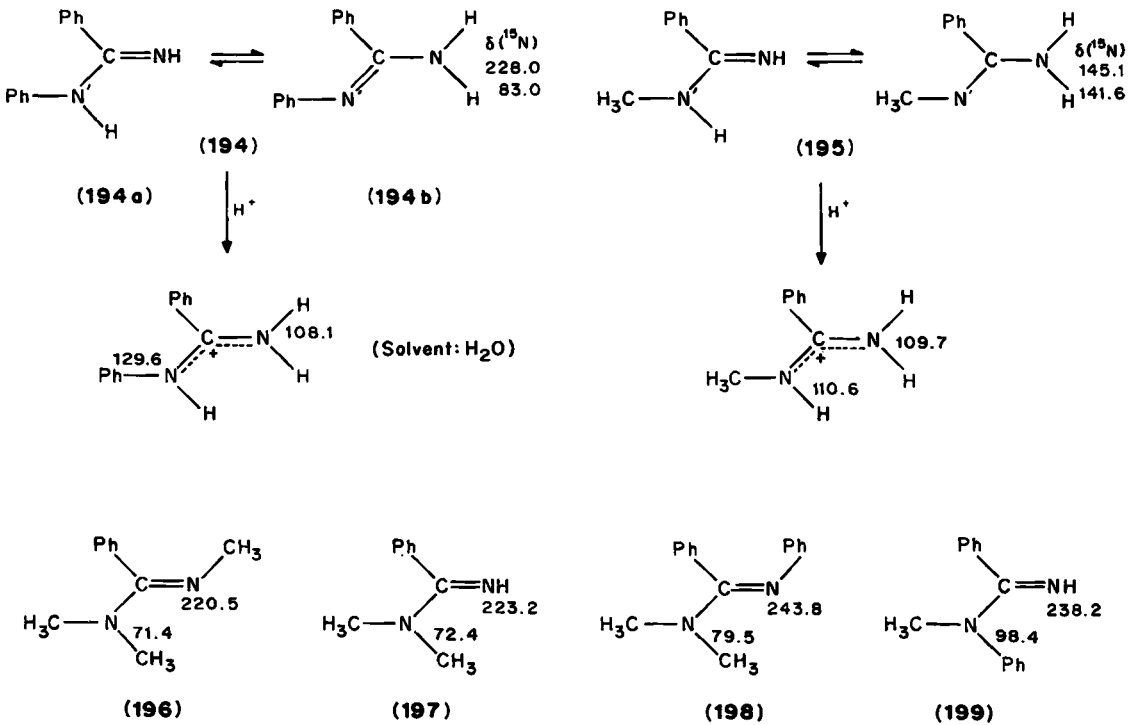
3. Experimental determinations of pK_T

Oszczapowicz and Raczyńska[22,285,286] proposed the prediction of pK_T values of tautomeric equilibria of amidines based on Hammett σ^0 substituent constants and measured macroscopic pK_a values of methylated derivatives. For *N*-phenyl formamidine pK_T was calculated as 1.8, showing the predominance of the amino form by 98.5%. For *N*-phenylacetamidine this value is 2.7, yielding a practically 100% presence of the amino tautomer.

Katritzky and coworkers[287,288] employed UV spectroscopy to determine the tautomeric equilibrium constant of *N*-acyl and *N*-sulphonyl substituted amidines. Values for K_T are about 30 for the acyl and 10^7 for the sulphonyl compounds, favouring the amino (H_2N—CR=NY) tautomer as in the case of phenyl substituents. For *N*-phenylacetamidine[288] pK_T is 2.4, in agreement with the above-mentioned value of 2.7.

4. Calculated energy differences of tautomeric amidines

The 3-21G calculations on *N*-methylformamidines of Scheme 14 show two kinds of tautomeric relations. The lowest-energy isomer **174** is the amino form with the methyl



SCHEME 17. ^{15}N NMR values in DMSO (δ values in ppm relative to NH_3). (Reproduced by permission of VCH Verlagsgesellschaft mbH from Ref. 284)

group on imino-*N E* or *anti* to NH_2, but the tautomer **175** with the methyl substituent s-*cis* to the *E*-imino NH is only 0.82 kJ mol^{-1} higher in energy. This negligible difference explains why *N*-alkyl substituted amidines occur usually as tautomeric mixtures. Energy differences of **174** compared to other tautomeric isomers **176**, **177** and **179** are with 6.5, 8.5 and 10.8 kJ mol^{-1} higher, but still relatively small. Starting from the other amino form **178** with the methyl substituent in *Z* arrangement, the smallest difference in energy of 0.64 kJ mol^{-1} is towards the more stable isomer **177**.

STO-3G calculations for twisted *N*-phenyl substituted formamidines lead to 5.6 kJ mol^{-1} stabilization for the amino tautomer with a torsional angle of 69.5° between the phenyl substituent and the amidino group.

In the case of fluorine as a substituent in formamidines we found[20] much larger energy differences for two pairs of tautomers appearing in equations 16 and 17. The energy difference for the tautomers in equation 16 is 84.6 and for equation 17, 53.0 kJ mol^{-1}, both in favour of the isomer with the fluorine on the imino nitrogen. A second fluorine substituent on the functional carbon decreases the energy difference. These data are in accord with an earlier conclusion[289] that the less basic tautomer predominates in the equilibrium mixture of tautomers and with the more basic amidines the difference between the energy of the two tautomeric forms is larger.

$$FN{=}CH{-}NH_2 \rightleftharpoons FNH{-}CH{=}NH \qquad (16)$$

$$FN{=}CF{-}NH_2 \rightleftharpoons FNH{-}CF{=}NH \qquad (17)$$

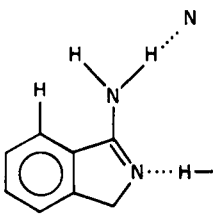
F. Molecular Association

Amidines with at least one hydrogen on nitrogen may show intermolecular hydrogen bonding leading to dimers or polymers in the crystal, the melt or in unpolar solvents. In polar solutions, hydrogen bonding from solvent protons to the basic imino nitrogen or of the NH protons to basic centres of the solvent may also occur. Experimentally, these problems may be studied by IR and Raman or ^{1}H NMR spectroscopy.

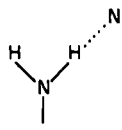
1. Experimental IR results

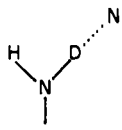
Intermolecular associates of amidines leading to dimers have been detected in cyclic amidines[281], N^1,N^1-diethylacetamidine[290], *N*,*N*′-diphenylformamidine (both in the crystal[87] and in benzene solution[291]) and in *N*,*N*′-diphenylacetamidine[292]. In the case of *N*,*N*′-diphenylbenzamidine no association was observed[292]; this was explained as a result of sterical shielding by the bulky phenyl groups allowing no hydrogen bonding.

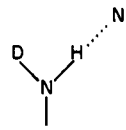
The solid-state IR spectrum of 3-amino-1*H*-isoindole (**191**) in CsI shows an interesting

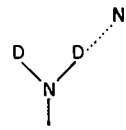


(**191**)









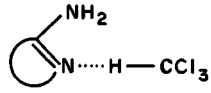
sharp: ν_{free} :	3451	3445	2567	2539
broad: $\nu_{assoc.}$:	3050	2280	3050	2280

SCHEME 18. IR NH and ND valence vibrations (in cm^{-1}) of partially deuterated 3-amino-1*H*-isoindole[281] (**191**)

feature[281]. In the region of NH valence vibrations a sharp and intense absorption band at 3451 cm^{-1} and a broad band about 3050 cm^{-1} is observed, which on partial deuteration leads to four bands with values shown in Scheme 18.

These bands prove the presence of the amino form and a partial association of $-NH_2$ as shown in structure **191**. The NH which is s-*trans* to the C=N bond is sterically shielded by the annelated phenyl ring so that only the s-*cis* proton may be engaged in hydrogen bonding, which may be dimeric or polymeric.

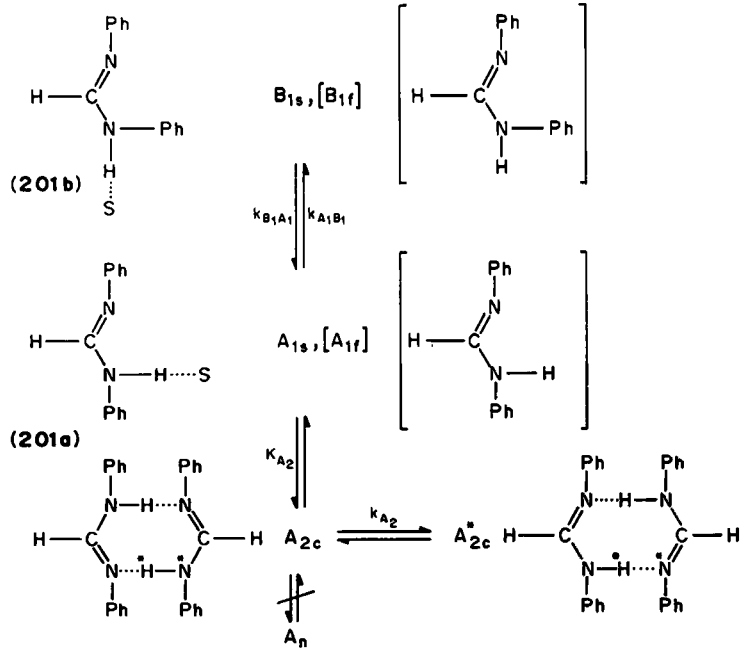
In chloroform, a specific hydrogen bonding to the imino nitrogen is observed from shifts of IR frequencies[281] (**200**).



(200)

2. ^1H NMR studies of molecular association

N,N'-Diphenylformamidine (**201**) in THF forms a hydrogen-bonded s-*trans* conformer (**201a**) and a s-*cis* conformer (**201b**), which interconvert slowly on the NMR time scale[293]. According to recent ^1H NMR results[294] **201** is subject to the complex reaction scheme shown in Scheme 19. Both rotamers form hydrogen bonds to the solvent, but only the s-

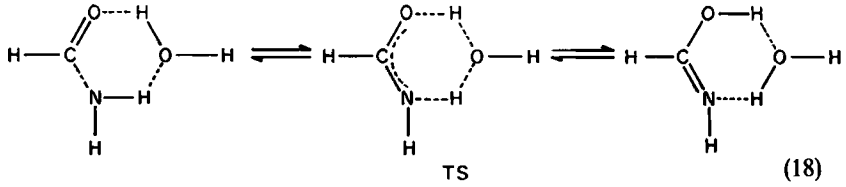


SCHEME 19. Rotation, association, and proton transfer of diphenylformamidine (**201**) in tetrahydrofuran[294]. S = solvent, A_{1s} = solvated s-trans monomer (**201a**), B_{1s} = solvated s-cis monomer (**201b**), k = rate constants, K = equilibrium constant, *denotes proton transfer, A_{2c} = cyclic dimer, A_{1f} and B_{1f} = free monomers, A_n = higher associates. A_{1f} and B_{1f} are intermediates present only in small concentrations. (Reproduced by permission of VCH Verlagsgesellschaft mbH from Ref. 194)

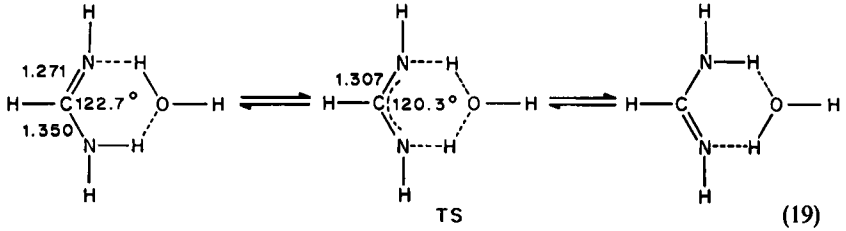
trans conformer (**201a**) is capable of forming a cyclic dimer and of double proton exchange in the latter. The energy of activation for this exchange is about 17 kJ mol^{-1} and a kinetic HH/HD isotope effect of 5 to 6 was found at 298 K. Higher associates were not observed.

3. 3-21G calculation of water-mediated tautomerism of formamidine

Zielinski and coworkers[230] performed 3-21G optimizations for the water-mediated tautomerism between formamide and formamidic acid (equation 18) and for formamidine (equation 19).



(18)



(19)

Optimized geometries for the water-bounded systems and corresponding energies are reported in the paper[230]. Two possible orientations of the water molecule have been considered: first, water being coplanar, bifurcating the water oxygen lone pairs by the NH proton. The second type with non-planar water was obtained by rotation of the water plane relative to the carbonyl hydrogen bond plane, bringing one of the water lone pairs into the formamide plane. The latter case is energetically favoured.

The bonds involved in hydrogen bonding were slightly extended and hydrogen bonds are bent by about 140°.

The minimum-energy formamide–water complex is 74.6 kJ mol^{-1} more stable than the isolated monomers, leading to 37.3 kJ mol^{-1} per hydrogen bond. For the formamidine–water complex these values are 78.5 kJ mol^{-1}, yielding 39.3 kJ mol^{-1} per hydrogen bond.

The activation energy for proton transfer is 101.9 kJ mol^{-1} from the formamide–water side to the transition state and 41.3 kJ mol^{-1} from the formamidic acid–water side. The corresponding energy difference of 60.6 kJ mol^{-1} is 13 kJ mol^{-1} smaller for hydrated molecules than for isolated molecules.

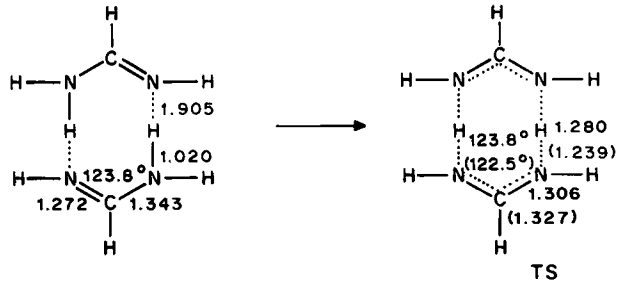
The activation energy for the bifunctional water-mediated proton transfer in formamidine–water is 71.6 kJ mol^{-1} in the 3-21G basis. Use of the 6-31G basis at 3-21G optimized geometries lowers all dimerization energies and increases the activation barriers of the proposed tautomerization mechanism.

4. 3-21G calculations of the hydrogen-bonded dimer of formamidine

Amidines were shown experimentally to form hydrogen-bonded dimers in the crystal or in non-aquous solutions.

Ab initio 3-21G optimizations for hydrogen-bonded dimers of formamide, formamidic acid and formamidine have been performed by Zielinski[231]. STO-3G data for the formamidine dimer were reported by Ahlberg and coworkers[295]. The 3-21G interaction energy for formamide dimer is $-97.3\,kJmol^{-1}$, for formamidic acid dimer $124.7\,kJ\,mol^{-1}$ and $-83.4\,kJ\,mol^{-1}$ for formamidine dimer leading to energies of -48.7, -62.4 and $-41.7\,kJ\,mol^{-1}$ per hydrogen bond.

The formamidine dimer and the symmetrical transition state have the calculated geometry shown in Scheme 20. The shorter CN distance is elongated relative to free formamidine and the longer bond is shortened as a result of hydrogen bonding. The hydrogen bond deviates with 175.5° slightly from linearity. In the transition state structure both CN distances are equal at 1.306 Å, which is very close to the average value of 1.308 Å for both CN distances in the dimer. The hydrogen bond remains bent with 176°. The activation energy for symmetrical hydrogen transfer is $66.9\,kJ\,mol^{-1}$, slightly lower than in the water-mediated reaction.

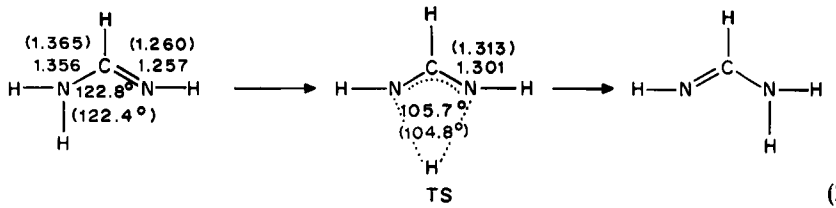


SCHEME 20. 3-21G optimized geometries[231] of hydrogen-bonded dimer of formamidine and transition state of symmetrical hydrogen transfer (values in parentheses are from STO-3G calculations[295])

5. *3-21G calculation of the 1,3-hydrogen shift in formamidine*

Zielinski and coworkers[232] studied the 1,3-hydrogen shift in formamidine using 3-21G and 6-31G** basis sets. By application of the Woodward–Hoffmann rules[296] the shift is antarafacially symmetry allowed as a thermal process.

6-31G** optimized geometrical parameters for formamidine and for the symmetrical transition state for the 1,3-hydrogen shift are include in equation 20. (Values in parentheses are 3-21G data.) The 6-31G** distances are shorter than the corresponding 3-21G values.



(20)

For the transition state, the most noticeable change besides the equalization of the CN distances is the narrowing of the NCN angle by 17° on the path from the minimum to the transition state.

For derivation of highly reliable energies, 3-21G and 6-31G** geometries have been

used for single-point calculations with the 6-31G basis set using configuration interaction[297] (CI) for single and double excitations (CISD) and up to quadruple excitations (CISD-DQ). The calculated activation energy for equation 20 is 247.6 kJ mol^{-1} (3-21G//3-21G) or 254.9 kJ mol^{-1} (6-31 G**//6-31 G**) at the Hartree–Fock level. Application of CI reduces this value to 220.1 kJ mol^{-1} for (6-31G/CISD-DQ). But the activation energy for the 1,3-hydrogen shift is much higher than in the case of water-mediated or dimeric hydrogen transfer.

VII. EXPERIMENTS AND CALCULATIONS OF PHYSICO-CHEMICAL PROPERTIES

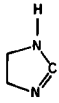
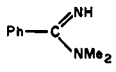
A. Dipole Moments of Amidines

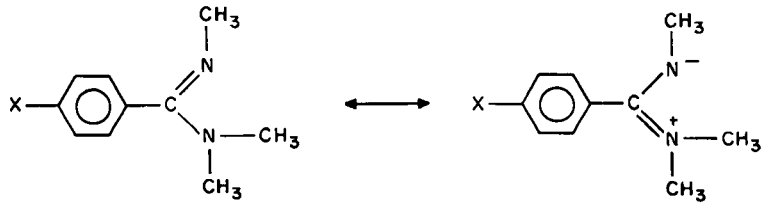
1. Experimental determinations of mesomeric dipole moments

Experimental dipole moments of alkyl- and aryl-substituted amidines collected in Table 25 span the range of 2.2 to 3.4 debyes. In the case of N^1,N^1-dimethyl-N^2-phenyl formamidines[249] *p*-Br and *p*-NO_2 substitution at the N^2-phenyl ring increase this value to 4.56 and 7.70 debyes.

Lumbroso[299–301] calculated a mesomeric moment, which is the vector difference between the actual dipole moment and that calculated for a classical structural formula, of 1.9 ± 0.2 D for the Me_2N—C=NH group of *N*,*N*-dimethylbenzamidines. Exner and collaborators[249] derived for this group in *E*-N^1,N^1,N^2-trimethylbenzamidine a lower value of 0.88 D. Comparison to mesomeric dipole moments in *N*,*N*-dimethylbenzamide[302] (1.4 D), *N*,*N*-dimethylthiobenzamide[303] (2.55 D) and methyl benzoate[304] (0.24 D) shows a low value for amidines, indicating a small contribution of the mesomeric formula **202b**. Since, in **202b**, complete electron transfer is estimated to result in a dipole moment of 11 D, the actual contribution of this form is estimated at about 8%.

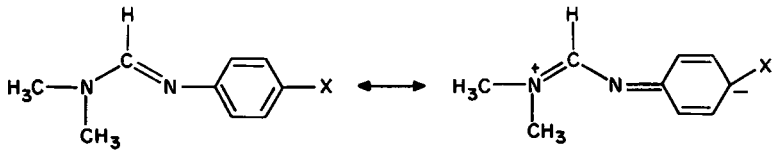
TABLE 25. Experimental dipole moments of amidines (debye)

Compound	Structure	Solvent	μ	Ref.
N,*N*′-Diphenylformamidine	**60**	dioxane	2.20	305
2-Ethyl-Δ^2-imidazoline	 R = Et	benzene	3.42	299
2-Phenyl-Δ^2-imidazoline	R = phenyl	benzene	3.08	299
N^1,N^1-Dimethylbenzamidine		benzene	2.83	300, 301
		dioxane	3.00	300, 301
DBN (**23**)		benzene	3.29	299
DBU (**24**)		benzene	3.41	299
N^1,N^1,N^2-Trimethylbenzamidines (**202**)	X = H	benzene	2.48	249
	X = Me		2.62	
	X = Br		1.98	
	X = NO_2		3.19	
N^1,N^1-Dimethyl-N^2-phenylformamidines (**203**)	X = H	benzene	3.21	249
	X = Me		2.99	
	X = Br		4.56	
	X = NO_2		7.70	



(202a) (202b)

The mesomeric dipole moment in N^1,N^1-dimethyl-N^2-phenyl formamidine[249] (**203a**) is 1.81 D, which is an indication of extended conjugation as shown in the mesomeric formula **203b**.



(203a) (203b)

2. Basis set dependence of ab initio *calculated dipole moments*

Calculated dipole moments as dependent on basis sets are presented in Table 26. Numerical values increase with increase in basis sets and are similar to experimental values in the range of 2.2 to 3.9 debyes. With the exception of benzamidine the dipole moments of the *Z*-forms are larger than those of the *E*-forms. The difference of dipole moments between *Z* and *E* isomers is most pronounced for formamidine, yielding 0.70 D for STO-3G, 0.88 D for 3-21G and 0.87 D for 6-31G basis sets. For acetamidine this difference is smaller: 0.39 D (STO-3G), 0.49 D (3-21G) and 0.39 D (6-31G); and for benzamidine in the two split-basis sets the *Z* form has a smaller dipole moment: 0.033 D (STO-3G), − 0.064 D (3-21G) and − 0.252 D (6-31G).

In the series of six *N*-methylformamidines **174** to **179** the *Z* isomer always has the larger value with differences from 0.8 to 1.9 D. The fluoro-substituted formamidines **182** and **183** show no regular pattern for dipole moments of *E* and *Z* isomers, but numerical values may be as large as 5.1 D.

B. Basicity (Proton Affinities)

1. Experimental results

The basicity of amidines is measured in solution by their pK_a values defined by equation 21 as the acidity of the corresponding protonated base. (The higher the number, the stronger is the basicity.) The parentheses in equation 21 denote molecular activities.

$$pK_a = -\log \frac{(H^+)\cdot(\text{base})}{(\text{base}^+ - H)} \tag{21}$$

Some characteristic pK_a values of nitrogen bases are collected in Table 27 (see Scheme 21). These values are solvent- and temperature-dependent. Oszczapowicz and collaborators[306,307] introduced the use of azeotropic ethanol (95.6% aqueous ethanol) as

TABLE 26. Basis set dependence of calculated dipole moments (debye)

Compound	STO-3G		3-21G		6-31G	
	μ	$\Delta(Z-E)^a$	μ	$\Delta(Z-E)^a$	μ	$\Delta(Z-E)^a$
E-Formamidine	2.416	0.699	2.829	0.877	3.073	0.866
NH_2 tetrahedral	2.245					
Z-Formamidine	3.245		3.706		3.939	
NH_2 tetrahedral	2.634					
E-Acetamidine	2.639	0.386	3.051	0.487	3.355	0.394
Z-Acetamidine	3.025		3.538		3.749	
E-Benzamidine, twist.	2.747	0.033	3.218	−0.064	3.571	−0.252
Z-Benzamidine, twist.	2.780		3.154		3.319	
Z-Benzamidine, planar	2.658					
E-Benzamidine, perp.	2.704					
N^1-Phenylformamidine	2.644		3.442			
N^2-Phenylformamidine	2.297		3.138			
N-Methylformamidines:						
(174) *E*			2.382	0.790	**178 − 174**	
(175) *E*			2.720	1.139	**176 − 175**	
(176) *Z*			3.859			
(177) *E*			2.863	1.897	**179 − 177**	
(178) *Z*			3.172			
(179) *Z*			3.829			
Fluoro-substituted formamidines:						
E-FHH (182a)			5.061	−0.145		
Z-FHH (183a)			4.916			
Z-FFH[b] (182b)			1.954	2.762		
E-HFH[b] (183b)			4.716			
E-HHF (182c)			4.474	−1.797		
Z-HHF (183c)			2.677			
Z-FFH[b] (182d)			4.955	−0.357		
E-FFH[b] (183d)			4.598			
E-FHF (182e)			4.622	0.408		
Z-FHF (183e)			5.030			
Z-HFF[b] (182f)			2.623	−0.184		
E-HFF[b] (183f)			2.439			
Z-FFF (182g)			3.742	−0.024		
E-FFF (183g)			3.718			

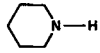
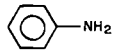
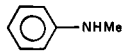
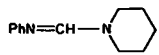
[a]Difference of calculated dipole moments between *Z* and *E* isomers.
[b]Change of stereochemical *E,Z*-notation due to higher priority of fluorine with respect to nitrogen.

an experimentally well-defined solvent with good solution properties for the measurement of pK_a values of amidines and nitrogen bases.

The basicity of amidines depends on the extent and type of substitution at three sites: at both the amino and imino nitrogens, and at the functional carbon atom. The protonation occurs at the imino nitrogen (im) atom. Therefore, substitution at this site exerts the strongest influence on the pK_a values of amidines, followed by substitution at the functional carbon.

In the review of Ševčik and Grambal[308] the following order of increasing basicity is

TABLE 27. pK_a values of nitrogen bases in solution at 25 °C

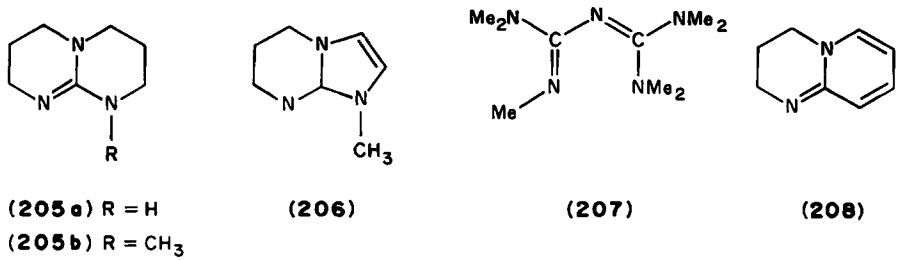
Compound	Structure	pK_a	Solvent[a]	Ref.
Ammonia	NH_3	9.245	water	324
Methylamine	CH_3NH_2	10.657	water	325
Dimethylamine	$(CH_3)_2NH$	10.732	water	325
		9.56(4)	az. EtOH	311
Trimethylamine	$(CH_3)_3N$	9.752	water	325
n-Propylamine	$CH_3CH_2CH_2NH_2$	11.03	98.5% aq. EtOH	309
Piperidine		9.59(2)	az. EtOH	311
Pyridine		5.23(5)		326
Aniline		4.65	water	327
N-Methylaniline		3.49(5)	az. EtOH	311
Formamidines:				
RN=CH—NHR	R = *n*-propyl	12.22	98.5% EtOH	309
	R = phenyl	7.17	98.5% EtOH	328
RN=CH—NMe_2	R = *n*-propyl	10.84(5)	az. EtOH	306
	R = phenyl	7.45(5)	az. EtOH	306
		8.69	98.5% EtOH	316
	PhN=CH—NMePh	5.29(5)	az. EtOH	319
Acetamidines:				
Unsubstituted acetamidine		12.40	water	329
N,N'-Diphenylacetamidine		8.30	water	329
		8.35(5)	98.5% EtOH	328
RN=CMe—NMe_2	R = *n*-propyl	12.46(7)	az. EtOH	310
	R = phenyl	8.32(7)	az. EtOH	310
PhN=CMe—NMePh		6.96(1)	az. EtOH	319
Benzamidines:				
Unsubstituted benzamidine		11.6	water	330
		11.23	50% aq. EtOH	331
		11.1	75% aq. EtOH	332
HN=CPh—N(*n*-Bu)$_2$		11.27	50% aq. MeOH	333
PhN=CPh—$N(Me)_2$		7.59(4)	az. EtOH	312
PhN=CPh—N(Me)Ph		5.75(7)	az. EtOH	320
		7.56(5)	50% aq. EtOH	308
PhN=CPh—N		7.45(5)	99.8% EtOH	307
		6.89(14)	az. EtOH	307
		6.67(3)	50% aq. EtOH	307
PhN=CPh—NH_2		7.71(9)	50% aq. EtOH	308
PhN=CPh—NHMe		6.66(9)	50% aq. EtOH	308
PhN=CPh—NHPh		6.92(9)	50% aq. EtOH	308
		7.43(5)	98.5% EtOH	328

(*continued*)

TABLE 27. (*continued*)

Compound	Structure	pK_a	Solvent[a]	Ref.
Guanidines:				
Guanidine		13.6	water	334
Tetramethylguanidine		13.6	water	335
Pentamethylguanidine		15.6	water	336
n-Butyltetramethylguanidine		14.83(10)	az. EtOH	315
Phenyl tetramethylguanidine		11.52(7)	az. EtOH	315
(205a) R = H		13.46	CH_3CN[b]	337
(205b) R = CH_3		12.93	CH_3CN[b]	337
(206)		12.05	CH_3CN[b]	338
Heptamethylbiguanid **(207)**		17.1	water	336
Bicyclic amidines[337]:				
DBN **(23)**		11.29	CH_3CN[b]	338
DBU **(24)**		11.82	CH_3CN[b]	338
(25b)		14.46	CH_3CN[b]	36
(27)		17.46	CH_3CN[b]	37
(208)		11.50	CH_3CN[b]	337

[a]Percentages refer to aqueous ethanol (EtOH); az. EtOH is azeotropic ethanol (95.6% aqueous EtOH).
[b]Experimental absolute pK_a values determined in acetonitrile[337] have been converted by subtraction of 12.5 units to relative values, based on pK_a of 9-phenylfluorene = 18.49.



(205a) R = H **(206)** **(207)** **(208)**
(205b) R = CH_3

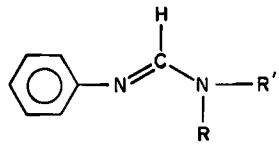
SCHEME 21. Structures of compounds in Table 27

indicated if no strongly polar substituents are present:

N,N,N'-trisubstituted amidines < *N,N'*-disubstituted amidines

< *N*-monosubstituted amidines < *N,N*-disubstituted amidines < unsubstituted amidines

Oszczapowicz and coworkers[306,309-315] showed for amino- and imino-substituted amidines linear relations of pK_a values of amidines with pK_a values of corresponding primary or secondary amines. For example, for N^1,N^1-disubstituted-N^2-phenylformamidines **(204)** the regression equation 22 shown in Figure 10 was obtained[311]. This figure shows an interesting and important feature of the basicity of amidines: the bisection of the axes (dotted line) is crossing the regression line between the experimental points. This means that only amidines derived from secondary amines whose pK_a value is below this intersection are stronger bases than the corresponding amines,



(204)

otherwise the amidines are weaker bases than secondary amines.

$$pK_a(\text{amidine}) = (0.35 \pm 0.04)pK_a(\text{sec. amine}) + 3.97 \quad (22)$$

$$R = 0.991; \quad \text{esd} = 0.018$$

For aryl ring substituted amidines pK_a values obey Hammett-type correlations with σ^- substituent constants; this was shown by Oszczapowicz and coworkers in numerous papers[306,307,310,312-320]. From the slope of regressions, the sensitivity to substituent effects is largest for substitution at the imino nitrogen[315,316], which is at the centre of protonation. Substitution at the amino nitrogen is of less influence than at the functional carbon. The extent of mutual interaction of substituents at these three sites was modelled by *ab initio* 3-21G calculations of fluorine-substituted formamidines with one to three fluorine substituents[20], with the same result as experimental conclusions.

In cyclic amidines the pK_a values depend significantly on the ring size[321-323]. The basicity decreases in the sequence $C_6 > C_7 > C_8 \cong C_5$ for systems **209**.

2. *Calculations of protonation energies*

In Table 28 calculated protonation energies, ΔE_p, as the difference of total energies between protonated amidines (AmH^+) and corresponding neutral amidines (Am) are

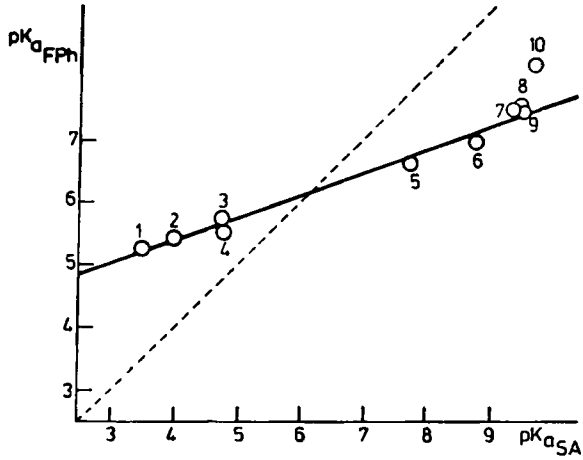
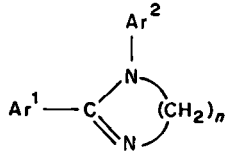


FIGURE 10. Plot of equation 22. Correlation of pK_a values of N^1,N^1-disubstituted N^2-phenylformamidines (FPh) with pK_a of corresponding secondary amines (SA). (Reproduced with permission from Reference 311)



(209)

(a) $n = 2$; five-membered ring[321]
(b) $n = 3$; six-membered ring[322]
(c) $n = 4$; seven-membered ring[323]
(d) $n = 5$; eight-membered ring[323]

given for three basis sets: STO-3G, 3-21G and 6-31G, derived from values of Table 19. With increase in basis sets ΔE_p decreases. Quantity ΔE_p estimates protonation energies in the gas phase at 0 K without consideration of the zero-point energy which was calculated[339] as 10.2 kcal mol^{-1} for formamidine. Del Bene[339] calculated for *E*-formamidine a 6-31G**//6-31 G* Hartree–Fock value for $\Delta E_p = -246.7$ kcal mol^{-1} which is slightly lower than our 6-31G energy of -250.6 kcal mol^{-1}. Post-Hartree–Fock calculations[339] by Möller–Plesset perturbation methods, MP2 and MP3, lead to a further reduction to -242.4 and -244.7 kcal mol^{-1} for MP2 and MP3, respectively. The enthalpy of protonation of *E*-formamidine in the gas phase was calculated as $\Delta H^{298} = -236.0$ kcal mol^{-1}.

Substituted amidines are mostly more basic than methylamine and the 3-21G values of protonation energies in Table 28 show the following calculated sequence of decreasing basicity:

E- and *Z*-benzamidine > Z-acetamidine > *E*-acetamidine methylformamidines: **178 > 176 > 179 > 177 > 175 > 174** > *Z*-formamidine > *E*-formamidine > fluoro-substituted formamidines: **182c > 183b > 184c > 183c > 182b** > methylamine > ammonia > **182a > 183a** > water.

TABLE 28. Basis set dependence of *ab initio* calculated protonation energies ($\Delta E_p = E_{AmH^+} - E_{Am}$) from data of Table 19

Compounds		STO-3G	3-21G	6-31G
Water[228]	hartree:	−0.36249	−0.30527	−0.27581[a]
	kcal mol^{-1}:	−227.47	−191.56	−173.08
	kJ mol^{-1}:	−951.7	−801.5	−724.1
Ammonia[228]	hartree:	−0.41343	−0.36166	−0.34641[a]
	kcal mol^{-1}:	−259.44	−226.95	−217.38
	kJ mol^{-1}:	−1085.5	−949.5	−909.5
Methylamine[228]	hartree:	−0.42777	−0.37768	−0.36366[a]
	kcal mol^{-1}:	−268.43	−237.00	−228.20
	kJ mol^{-1}:	−1123.1	−991.6	−954.8
E-Formamidine[228]	hartree:	−0.45625	−0.40574	−0.39927
	kcal mol^{-1}:	−286.31	−254.61	−250.55
	kJ mol^{-1}:	−1197.9	−1065.3	−1048.2
Z-Formamidine[228]	hartree:	−0.45684	−0.40667	−0.40224
	kcal mol^{-1}:	−286.68	−255.19	−252.41
	kJ mol^{-1}:	−1123.1	−991.6	−954.8
E-Acetamidine	hartree:	−0.47478	−0.41566	−0.40976
	kcal mol^{-1}:	−297.93	−260.83	−257.13
	kJ mol^{-1}:	−1246.5	−1091.3	−1075.8
Z-Acetamidine	hartree:	−0.47403	−0.41573	0.41102
	kcal mol^{-1}:	−297.46	−260.88	−257.92
	kJ mol^{-1}:	−1244.6	−1091.5	−1079.1

(*continued*)

TABLE 28. (*continued*)

Compounds		STO-3G	3-21G	6-31G
E-Benzamidine	hartree:	−0.48449	−0.42016	−0.41559
twisted	kcal mol^{-1}:	−304.03	−263.66	−260.79
	kJ mol^{-1}:	−1272.0	−1103.1	−1091.1
Z-Benzamidine	hartree:	−0.48370	−0.42016	−0.41680
twisted	kcal mol^{-1}:	−303.53	−263.66	−261.55
	kJ mol^{-1}:	−1267.0	−1103.1	−1094.3
N^1-Phenylformamidine	hartree:	−0.46146		
planar	kcal mol^{-1}:	−289.57		
	kJ mol^{-1}:	−1211.6		
N-Methylformamidines:				
ΔE(181 − 174)[b]	hartree:		−0.40981	
	kcal mol^{-1}:		−257.16	
	kJ mol^{-1}:		−1076.0	
ΔE(180 − 175)[b]	hartree:		−0.41220	
	kcal mol^{-1}:		−258.66	
	kJ mol^{-1}:		−1082.2	
ΔE(180 − 176)[b]	hartree:		−0.41436	
	kcal mol^{-1}:		−260.02	
	kJ mol^{-1}:		−1087.9	
ΔE(181 − 177)[b]	hartree:		−0.41307	
	kcal mol^{-1}:		−259.21	
	kJ mol^{-1}:		−1084.5	
ΔE(180 − 178)[b]	hartree:		−0.41539	
	kcal mol^{-1}:		−260.67	
	kJ mol^{-1}:		−1090.6	
ΔE(181 − 179)[b]	hartree:		−0.41393	
	kcal mol^{-1}:		−259.75	
	kJ mol^{-1}:		−1086.8	
Fluoro-substituted formamidines:				
(182a)	hartree:		−0.34941	
	kcal mol^{-1}:		−219.26	
	kJ mol^{-1}:		−917.4	
(183a)	hartree:		−0.34385	
	kcal mol^{-1}:		−215.77	
	kJ mol^{-1}:		−902.8	
(182b)	hartree:		−0.37814	
	kcal mol^{-1}:		−237.29	
	kJ mol^{-1}:		−992.8	
(183b)	hartree:		−0.38516	
	kcal mol^{-1}:		−241.70	
	kJ mol^{-1}:		−1011.2	
(182c)	hartree:		−0.38750	
	kcal mol^{-1}:		−243.16	
	kJ mol^{-1}:		−1017.4	
(183c)	hartree:		−0.37948	
	kcal mol^{-1}:		−238.13	
	kJ mol^{-1}:		−996.3	
(184c)	hartree:		−0.38305	
	kcal mol^{-1}:		−240.37	
	kJ mol^{-1}:		−1005.7	

[a]6-31G* values from Reference 228.
[b]Energy differences between the protonated and unprotonated amidines.

The calculated gas-phase basicity of benzamidine is higher than that of acetamidine, in contrast to the experimental pK_a values of Table 27 which are 12.4 for acetamidine and 11.6 for benzamidine in water solution.

C. Mass Spectra

Mass spectra are mainly reported for various *N*-substituted formamidines[340-344] but 18 symmetrical amidines [R'—N=C(R)—NHR'] including formamidines, acetamidines, benzamidines and *tert*-butylamidines have been studied recently by Kilner and coworkers[345]. The fragmentation of all the molecular ions is characterized by skeletal

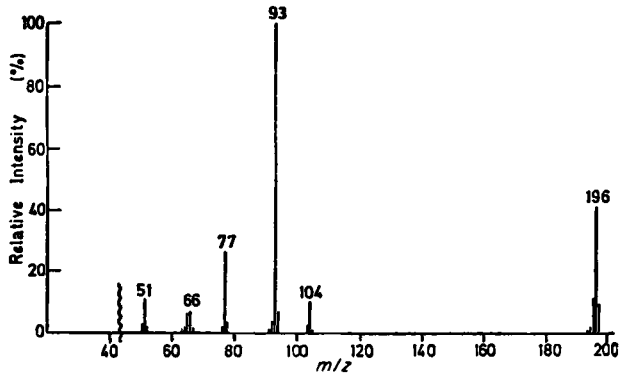
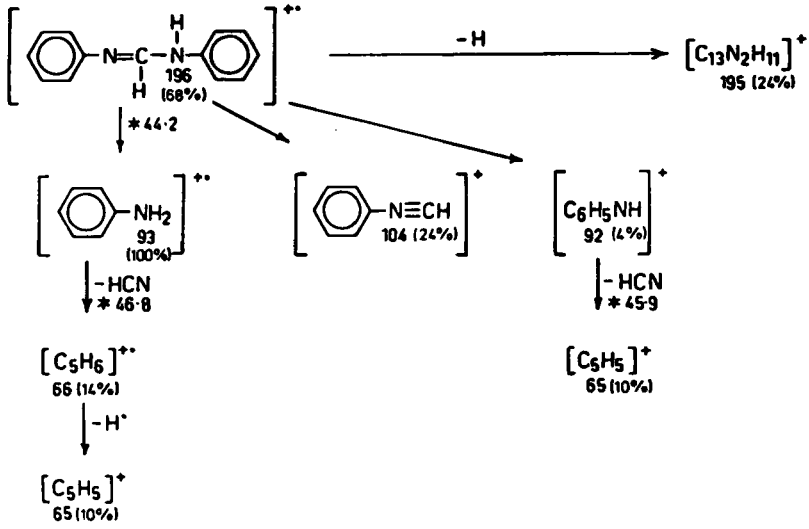


FIGURE 11. Mass spectrum of *N*,*N'*-diphenylformamidine, $C_6H_5N{=}CH{-}NHC_6H_5$, mol. wt. = 196. (Reproduced with permission from Reference 343)



SCHEME 22. Fragmentation pattern of *N*,*N'*-diphenylformamidine[345]

carbon–nitrogen bond cleavage to form $[R'—N{=}CR]^+$ and $[R'—NH]^+$ fragments, both of which are observed. For formamidines (R = H), the positive charge remains with the $[R'—NH]^+$ fragment which leads, for R′ = phenyl, to the base peak at *m/z* 93 corresponding to $[C_6H_5—NH_2]^{+\cdot}$. In contrast, for acetamidines and benzamidines the charge prefers to remain on the $[R'—N{=}CR]^+$ fragment which gives the base peaks for

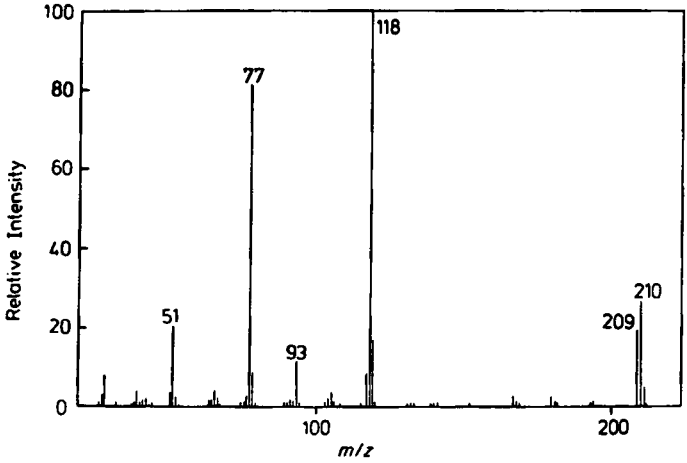
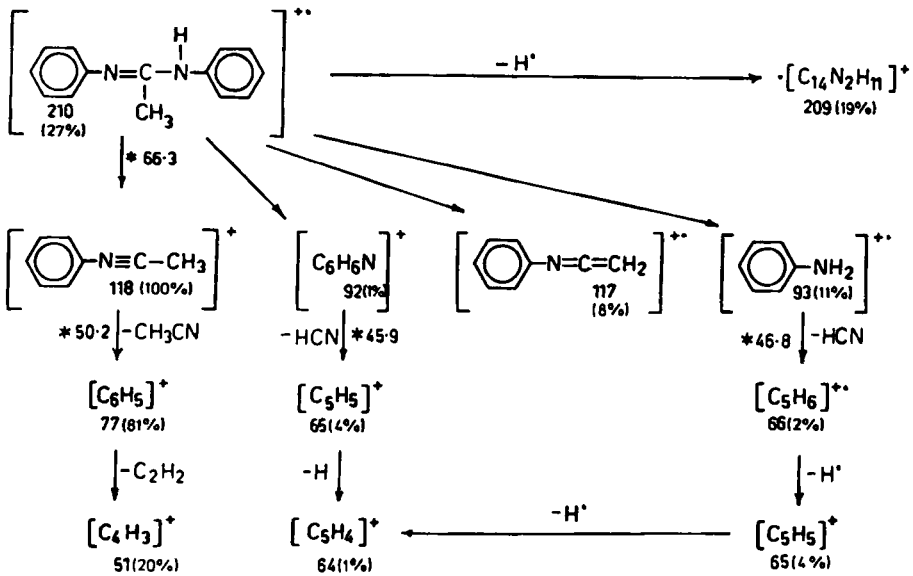


FIGURE 12. Mass spectrum of *N,N′*-diphenylacetamidine, $C_6H_5N{=}C(CH_3)—NHC_6H_5$, mol. wt. = 210. (From Reference 345)



SCHEME 23. Fragmentation pattern of *N,N′*-diphenylacetamidine[345]

the compounds corresponding to $[C_6H_5—N=CR]^+$ with *m/z* 118 and 180 for R = CH_3 and C_6H_5, respectively.

The fragmentation pattern of *N,N'*-diphenyl derivatives of formamidine, acetamidine and benzamidine are summarized in Schemes 22 to 24 with the corresponding mass spectra shown in Figures 11 to 13. In all three cases the M^+ as well as the $[M-1]^+$

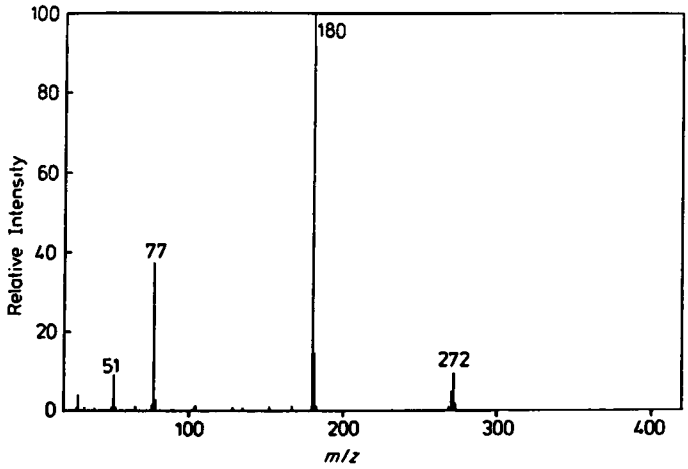
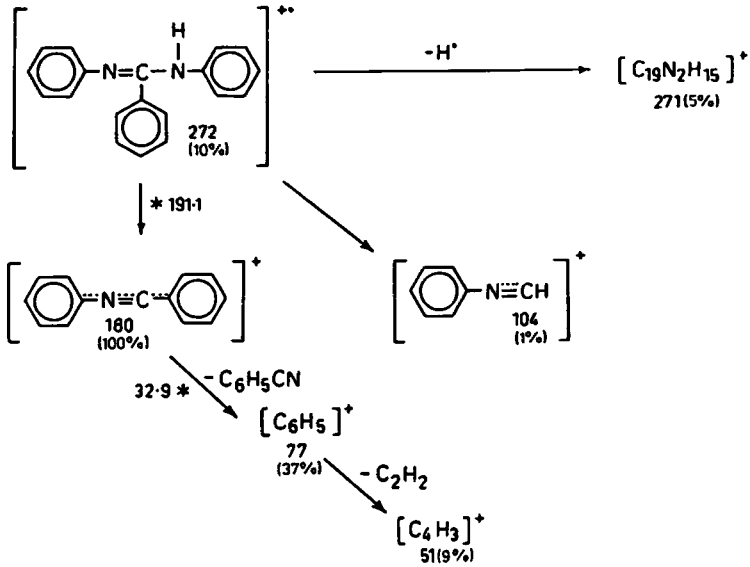


FIGURE 13. Mass spectrum of *N,N'*-diphenylbenzamidine, $C_6H_5N=C(C_6H_5)—NHC_6H_5$, mol. wt. = 272. (From Reference 345)



SCHEME 24. Fragmentation pattern of *N,N'*-diphenylbenzamidine[345]

molecular ions were observed with different intensities. Many of the fragmentation routes shown in Schemes 22 to 24 are supported by the presence of metastable ion peaks as indicated.

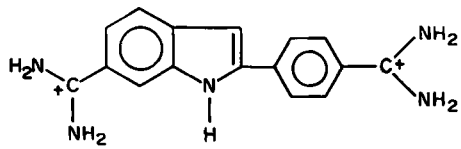
The spectra of unsubstituted amidines [HN=C(R)NH_2] are characterized by cleavage of the substituent at carbon from the NCN skeleton, $[HN{=}CNH_2]^+$ (*m/z* 43) being produced in all cases.

The fragmentation of N^1,N^1-dimethyl-N^2-phenylformamidine occurs through the $[M-1]^+$ peak which is due to loss of hydrogen at the *ortho* position leading to benzimidazolium cations[340,341] as discussed explicitly in the first volume on this subject in this series[259].

D. Electronic Spectra

Ultraviolet absorption spectra of *para*-substituted derivatives of benzamidine are reported by Nelson and coworkers[346]. The shift of absorption maxima due to *p*-substituents correlates linearly with those of the corresponding benzoic acids.

The dication of 4',6-diamidino-2-phenylindole (**210**) binds specifically to double-stranded DNA with a concomitant increase in fluorescence quantum yield. The electronic properties in the UV-vis spectrum of **210** have been studied by means of linear dichroism, fluorescence polarization anisotropy, circular dichroism and magnetic circular dichroism measurements[347].



(210)

VIII. MO THEORETICAL DESCRIPTIONS

This section will be based only on calculations for *E*- and *Z*-formamidine and for the corresponding formamidinium cation.

A. Basis Set Dependence of MO Diagrams

In Table 29 MO orbital energies are given for STO-3G, 3-21G and 6-31G basis sets. Numerical values increase with increase in basis sets. As usual for MO functions the MOs are delocalized, containing contributions from all AOs of appropriate symmetry. Leading AO contributions (atomic orbitals coefficients > 0.3) are indicated in Table 29 and 6-31G values for valence orbitals are plotted in Figure 14.

The three lowest MOs 1 to 3 refer to 1s core AOs on heavy atoms in the sequence NH_2 > NH > C. MOs 4 to 6 are mainly 2s AO contributions of nitrogen and carbon (MO 6). The MOs 7 to 9 show leading $2p_x$ and $2p_z$ AOs contributions at nitrogen and carbon in combination with hydrogen 1s AOs. MOs 8 and 9 are mostly affected by the change in molecular geometry: in the *E* form they are very close together with only 0.013 hartree 6-31G difference, but in the *Z* form the separation is 0.115 hartree (6-31G). MOs 10, 12 and 13 are of pure π-symmetry ($2p_y$) with the frontier orbitals, 12 being the HOMO and 13 the LUMO. The corresponding HOMO–LUMO gap, which may be related to molecular stability, is 0.559 for *E*-formamidine, 0.570 for *Z*-formamidine and 0.578 for formamidinium cation (6-31G

TABLE 29. Basis set dependence of molecular orbitals (MO ε_j) of *E*- and *Z*-formamidines and formamidinium cation with leading atomic orbital contributions

Compound	ε_j	Type	STO-3G	3-21G	6-31G
E-Formamidine	1	1s NH_2	−15.3431	−15.4768	−15.5654
(**148**)	2	1s NH	−15.3094	−15.4312	−15.5245
	3	1s C	−11.1166	−11.2502	−11.3206
	4	2s N,C	−1.1892	−1.2484	−1.2626
	5	2s N	−1.0816	−1.1368	−1.1476
	6	2s C,N	−0.7578	−0.8171	−0.8328
	7	$2p_x$, $2p_z$, H	−0.6615	−0.7379	−0.7494
	8	$2p_x$, $2p_z$, H	−0.5556	−0.6268	−0.6401
	9	$2p_x$, $2p_z$, H	−0.5425	−0.6159	−0.6271
	10	$2p_y$: π_1	−0.4538	−0.5202	−0.5254
	11	N^2: n	−0.3560	−0.3899	−0.3980
	12	$2p_y$: π_2	−0.3038	−0.3440	−0.3518
	13	$2p_y$: π_3	0.3100	0.2320	0.2074
HOMO–LUMO gap:			0.6138	0.5760	0.5592
Z-Formamidine	1	1s NH_2	−15.3430	−15.4899	−15.5790
(**149**)	2	1s NH	−15.2863	−15.4360	−15.5289
	3	1s C	−11.1196	−11.2510	−11.3216
	4	2s N, C	−1.1845	−1.2532	−1.2678
	5	2s N	−1.0721	−1.1410	−1.1516
	6	2s C,N	−0.7748	−0.8312	−0.8464
	7	$2p_x$, $2p_z$, H	−0.6504	−0.7168	−0.7302
	8	$2p_x$, $2p_z$, H	−0.6123	−0.6882	−0.7007
	9	$2p_x$, $2p_z$, H	−0.5115	−0.5746	−0.5859
	10	$2p_y$: π_1	−0.4666	−0.5251	−0.5307
	11	N^2: n	−0.3455	−0.3946	−0.4017
	12	$2p_y$: π_2	−0.2843	−0.3527	−0.3604
	13	$2p_y$: π_3	0.3320	0.2332	0.2091
HOMO–LUMO gap:			0.6138	0.5760	0.5695
Formamidinium cation	1	1s N	−15.6806	−15.7603	−15.8362
(**150**)	2	1s N	−15.6805	−15.7602	−15.8361
	3	1s C	−11.4881	−11.5496	−11.6122
	4	2s N,C	−1.5032	−1.5495	−1.5496
	5	2s N	−1.3901	−1.4363	−1.4417
	6	2s C,N	−1.0889	−1.1222	−1.1325
	7	$2P_x$, $2p_z$, H	−0.9816	−1.0234	−1.0269
	8	$2p_x$, $2p_z$, H	−0.9369	−0.9851	−0.9891
	9	$2p_x$, $2p_z$, H	−0.8595	−0.8990	−0.9051
	10	$2p_x$, $2p_z$, H	−0.8072	−0.8340	−0.8407
	11	$2p_y$: π_1	−0.7788	−0.8072	−0.8049
	12	$2p_y$: π_2	−0.6072	−0.6454	−0.6466
	13	$2p_y$: π_3	−0.0019	−0.0543	−0.0688
HOMO–LUMO gap:			0.6053	0.5911	0.5778

values). MO 11 may be considered as a mainly lone pair MO on imino nitrogen with 2s, $2p_x$ and $2p_z$ AO contributions. This MO is mostly shifted (by 0.503 hartree in the 6-31G basis) in the change to the MOs of the protonated formamidinium cation. All other valence MOs in the cation are lowered by a nearly constant difference of −0.286 hartree with respect to Z-formamidine.

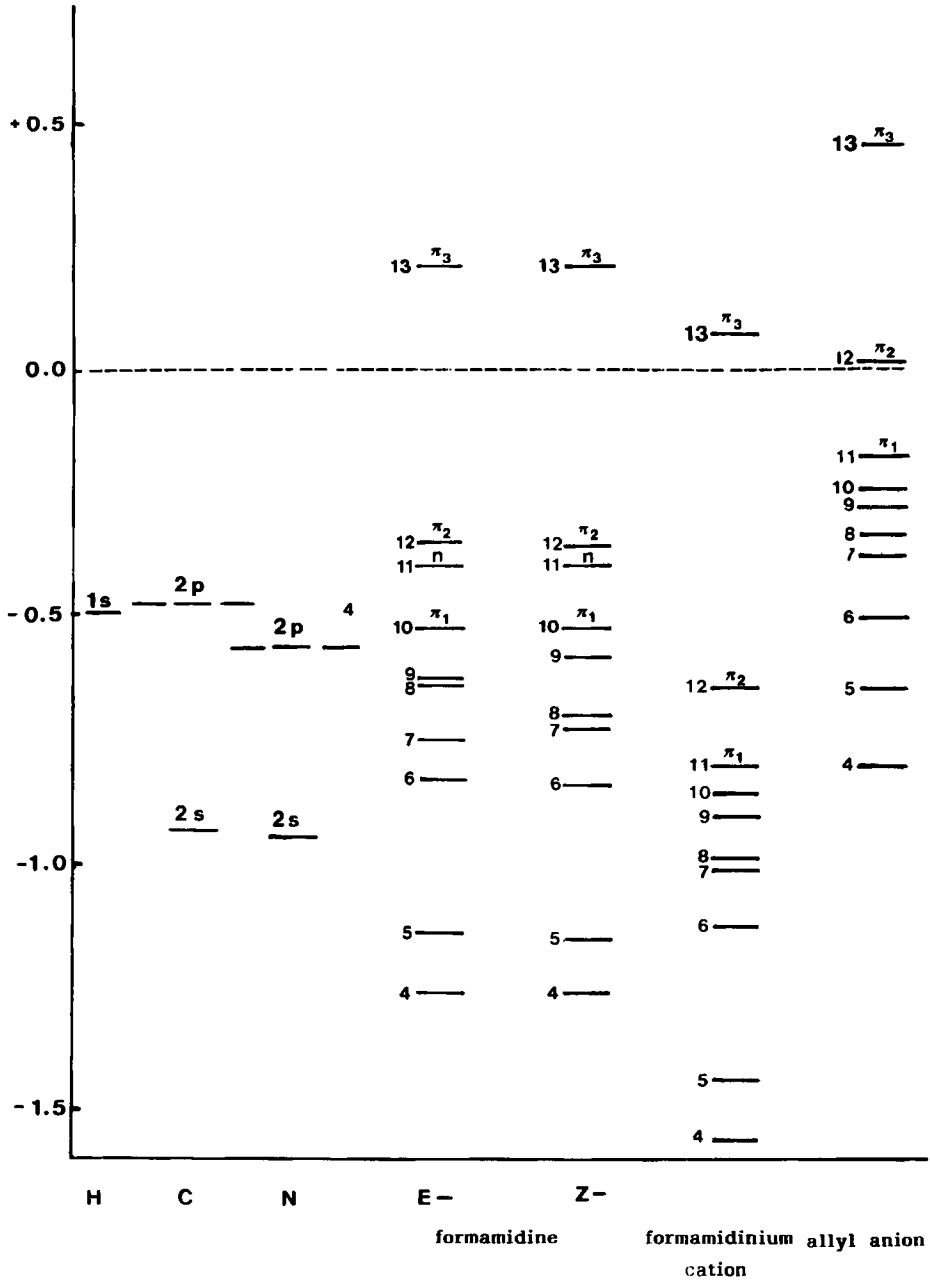


FIGURE 14. 6-31G MO orbital energies ε_j (in hartree)

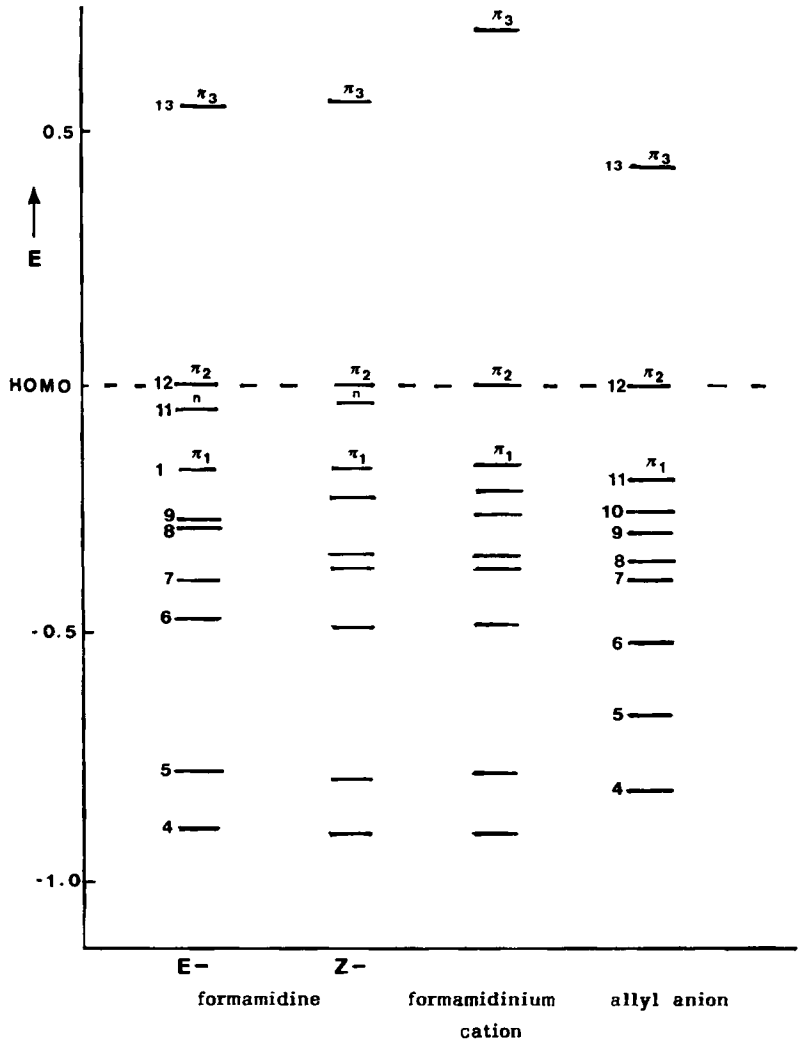


FIGURE 15. 6-31G MO orbital energies of formamidines and the allyl anion placed for comparison at the same HOMO energy

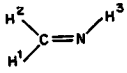
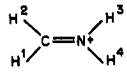
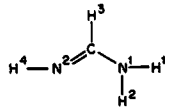
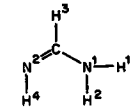
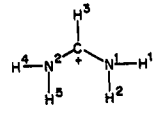
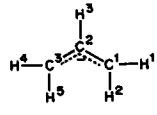
The similarity of the MO diagrams of formamidines with the iso-electronic allyl anion is seen clearly in Figure 15, where the HOMOs of both molecules are placed for comparison at the same energy.

B. Basis Set Dependence of Mulliken Charge Densities

1. Total charges

In Table 30 Mulliken total charge densities ($\Delta q^{tot} = Z\text{-}q^{tot}$ with Z = atomic nuclear charge) for three basis sets are collected for formamidines in comparison to formimine,

TABLE 30. Basis set dependence of Mulliken total charge densities ($\Delta q^{tot} = Z - q^{tot}$)

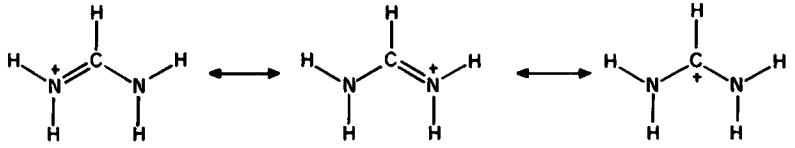
Compound	Atom	STO-3G	3-21G	6-31G
 Formimine	C	−0.0091	−0.1104	−0.0919
	N	−0.2762	−0.5802	−0.5312
	H^1	0.0734	0.2163	0.1752
	H^2	0.0606	0.1826	0.1471
	H^3	0.1514	0.2918	0.3009
 Formiminium cation	C	0.2005	0.1003	0.1330
	N	−0.2826	−0.7495	−0.7061
	$H^1 = H^2$	0.2066	0.3617	0.3123
	$H^3 = H^4$	0.3345	0.4629	0.4743
 *E*-Formamidine	C	0.1803	0.4409	0.3507
	N^1	−0.3514	−0.9050	−0.9022
	N^2	−0.4264	−0.7150	−0.6572
	H^1	0.1952	0.3421	0.3652
	H^2	0.2065	0.4390	0.3837
	H^3	0.0611	0.2033	0.1701
	H^4	0.1346	0.2759	0.2897
 *Z*-Formamidine	C	0.1786	0.4281	0.3598
	N^1	−0.4321	−0.9137	−0.9217
	N^2	−0.3406	−0.6991	−0.6442
	H^1	0.1997	0.3484	0.3682
	H^2	0.1935	0.3402	0.3717
	H^3	0.0764	0.2366	0.1923
	H^4	0.1245	0.2595	0.2739
 Formamidinium cation	C	0.3414	0.6628	0.5874
	$N^1 = N^2$	−0.3551	−0.8762	−0.8528
	$H^1 = H^4$	0.3008	0.4366	0.4528
	$H^2 = H^5$	0.2885	0.4228	0.4435
	H^3	0.1901	0.3706	0.3256
 Allyl anion	C^2	−0.0506	−0.1488	0.0005
	$C^1 = C^3$	−0.3440	−0.6202	−0.5747
	$H^1 = H^4$	−0.0621	0.0664	0.0205
	$H^2 = H^5$	−0.0554	0.0767	0.0323
	H^3	−0.0265	0.1031	0.0435

formiminium cation and allyl anion. Numerical values of the 6-31G basis set are mostly between those of the STO-3G and 3-21G basis sets, but closer to the latter.

In formimine, a large negative total charge is accumulated on nitrogen which is about half-compensated by the positive charge on N—H hydrogens. On protonation at the imino nitrogen this atom carries a negative charge of − 0.706, which is in contrast to the usual chemical notation in formula **185a**, so that this system is better described by the mesomeric formula **185b**. However, the positive charge is most effectively distributed onto the hydrogen atoms.

(185 a) **(185 b)**

In *E*- and *Z*-formamidine, negative total charges are calculated for both nitrogen atoms, with a larger value at the amino nitrogen N^1. Positive charges are found at carbon and in similar magnitude at hydrogens decreasing in the sequence: $H^2 > H^1 > H^4 > H^3$. (For numbering, see Table 30). Differences of charges between *E*- and *Z*-formamidine are relatively small (< 0.02 hartree) and not characteristic. Again, on protonation, negative charge accumulates on both nitrogens and positive charge on carbon as indicated by the mesomeric structure **186c** but most of the positive charge is transferred to the hydrogen atoms, as was observed for charged hydrocarbons[348].



(186a) **(186b)** **(186c)**

2. π-Electron charges

In Table 31 Mulliken π-electron charges ($\Delta q^\pi = Z^\pi - q^\pi$ with Z^π = number of π-electrons) are given for our three basis sets. The numerical values increase with increase in basis sets. The sum of π-electron charges add in all cases to zero, indicating that in the 2π-electron systems (formimine and its cation) and in the 4π-electron systems (*E*- and *Z*-formamidine, their cation and the allyl anion) there is no resultant π-electron charge but only π-electron polarization.

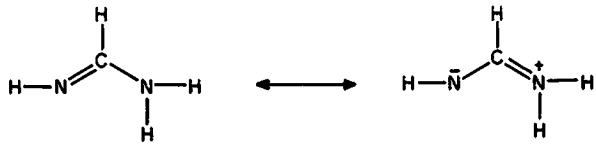
In the formamidinium cation and allyl anion we have an ambiguity in the description of the π-electron charge distribution, which may be referred either to structure **186c**, leading to $\Delta q^\pi_{q_C} = -0.6728$ and $\Delta q^\pi_{q_N} = 0.3364$, or to the superposition of **186a** and **186b**, which places 1.5 π-electrons on the equivalent nitrogens and one π-electron on carbon with resultant values as given in Table 31.

The π-electron charges in *E*- and *Z*-formamidine are rather similar. As described with resonance structures **211a** and **211b** the imino nitrogen N^2 carries a partial negative π-

TABLE 31. Basis set dependence of Mulliken π-electron charge densities ($\Delta q^\pi = Z^\pi - q^\pi$)

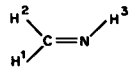
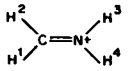
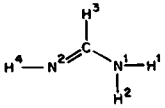
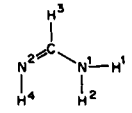
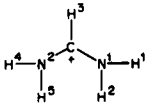
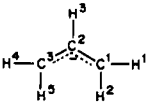
Compound	Atom	STO-3G	3-21G	6-31G
Formimine	C	0.0446	0.0751	0.1190
	N	−0.0446	−0.0751	−0.1190
Formiminium cation	C	0.4247	0.4475	0.4849
	N	−0.4247	−0.4475	−0.4849
E-Formamidine	C	0.0704	0.1218	0.1695
	N^1	0.1415	0.1651	0.1525
	N^2	−0.2119	−0.2869	−0.3220
Z-Formamidine	C	0.0728	0.1264	0.1777
	N^1	0.1358	0.1566	0.1402
	N^2	−0.2086	−0.2830	−0.3180
Formamidinium cation	C	0.2960	0.3273	0.3739
	$N^1 = N^2$	−0.1480	−0.1636	−0.1869
Allyl anion	C^2	0.0678	0.1071	0.1225
	$C^1 = C^3$	−0.0339	−0.0536	−0.0612

electron charge of -0.20 to -0.32 and the amino nitrogen N^1 shows a positive charge between 0.14 and 0.16 with about the same positive charge at carbon.



(211a) (211b)

TABLE 32. Basis set dependence of Mulliken total and π-electron overlap populations (p^{tot} and p^{π})

Compound	Bond	STO-3G	3-21G	6-31G
 Formimine	C=N	1.0410	1.0252	1.0430
	C—H^1	0.7776	0.7510	0.7638
	C—H^2	0.7702	0.7258	0.7684
	N—H^3	0.6224	0.6416	0.6466
	p^{π}: C=N	0.3722	0.4806	0.4884
 Formiminium cation	C=N	1.0196	0.6784	0.6820
	C—H^1; C—H^2	0.7636	0.7238	0.7648
	N—H^3; N—H^4	0.6836	0.6326	0.6262
	p^{π}: C=N	0.3200	0.3968	0.3854
 *E*-Formamidine	C—N^1	0.7792	0.7074	0.2538
	C=N^2	1.0152	1.0266	1.2056
	N^1—H^1	0.7242	0.6818	0.6668
	N^1—H^2	0.7170	0.6552	0.6334
	N^2—H^4	0.6322	0.6552	0.6678
	C—H^3	0.7672	0.7356	0.8072
	p^{π}: C—N^1	0.0746	0.0674	0.0322
	p^{π}: C=N^2	0.3420	0.4444	0.4616
 *Z*-Formamidine	C—N^1	0.7630	0.3748	0.2560
	C=N^2	1.0195	1.1652	1.2398
	N^1—H^1	0.7213	0.6684	0.6516
	N^1—H^2	0.7276	0.6710	0.6474
	N^2—H^4	0.6192	0.6498	0.6600
	C—H^3	0.7778	0.7668	0.8016
	p^{π}: C—N^1	0.0720	0.0644	0.0282
	p^{π}: C—N^2	0.3442	0.4454	0.4616
 Formamidinium cation	C—N	0.9342	0.7014	0.7124
	N^1—H^1	0.7074	0.6528	0.6436
	N^1—H^2	0.7014	0.6524	0.6456
	C—H^3	0.9408	0.7364	0.7718
	p^{π}: C—N	0.2108	0.2564	0.2470
 Allyl anion	C^1=C^2	1.0602	0.9952	1.1023
	C^1—H^1	0.7874	0.8002	0.7674
	C^1—H^2	0.7824	0.8048	0.7840
	C^2—H^3	0.7540	0.7758	0.7538
	p^{π}: C^1—C^2	0.2390	0.3052	0.3044

C. Basis Set Dependence of Mulliken Overlap Populations

In Table 32 Mulliken total and π-electron overlap populations are shown for STO-3G, 3-21G and 6-31G basis sets. (The values given in Table 32 are two times the printout values, because in the program only half of the overlap populations are calculated.) Numerical values show no regular basis set dependent trends, therefore the discussion will be based on 6-31G values.

The total overlap population of the unconjugated C=N bond in formimine is 1.043, which is lowered to 0.682 in the corresponding cation. Surprisingly, in *E*- and *Z*-formamidine this value is increased to 1.206 and 1.240. Protonation again reduces this parameter to 0.712. The C—N single bond shows a total overlap population of 0.254 and 0.256 for *E*- and *Z*-formamidine. Bonds between carbon and hydrogen have overlap populations between 0.76 and 0.80. Those between nitrogen and hydrogen are in the range of 0.63 and 0.66 with the largest value for the imino N^2—H^4 bond.

The π-electron overlap populations are closer to chemical intuition: the value of 0.4884 for the unconjugated C=N bond in formimine reduces to 0.385 on protonation and to 0.462 in the conjugated π-system of the *E*- and *Z*-formamidine which, in turn, is reduced to 0.247 on protonation. With 0.032 and 0.028 the π-electron overlap for the C—N^1 single bond is rather small.

Linear least-squares correlations for 6-31G calculated distances with either p^{tot} or p^{π} for 7 values of Table 32 lead to results shown in equation 23 and 24. Statistically the regression with p^{π} is highly significant and satisfactory.

$$d_{CN} = -0.102 \cdot p^{tot} + 1.379 \qquad (23)$$

$$R = 0.909;\ \text{sd} = 0.021$$

$$d_{CN} = -0.227 \cdot p^{\pi} + 1.369 \qquad (24)$$

$$R = 0.991;\ \text{sd} = 0.007$$

IX. REFERENCES

1. R. L. Shriner and F. W. Neumann, *Chem. Rev.*, **35**, 351 (1944).
2. S. Patai (Ed.), *The Chemistry of Amidines and Imidates*, Interscience, London, 1975.
3. V. G. Granik, *Russ. Chem. Rev.*, **52**, 377 (1983); *Usp. Khim.*, **52**, 669 (1983).
4. S. Patai (Ed.), *The Chemistry of Carboxylic Acids and Esters*, Wiley–Interscience, London, 1969.
5. J. Zabicky (Ed.), *The Chemistry of Amides*, Wiley–Interscience, London, 1970.
6. S. Patai (Ed.), *Supplement B. The Chemistry of Acid Derivatives*, Wiley–Interscience, Chichester, 1979.
7. S. Patai (Ed.), *The Chemistry of Acyl Halides*, Wiley–Interscience, London, 1972.
8. R. Mecke and W. Kutzelnigg, *Spectrum. Acta*, **16**, 1216 (1960).
9. H. Gonçalves and A. Secches, *Bull. Soc. Chim. Fr.*, 2589 (1970).
10. Z. B. Kiro, Yu. A. Teterin, L. N. Nikolenko and B. I. Stepanov, *Zh. Org. Khim.*, **8**, 2573 (1972); *Chem. Abstr.*, **78**, 15210z (1973).
11. P. Gund, *J. Chem. Educ.*, **49**, 100 (1972).
12. J. Klein, *Tetrahedron*, **39**, 2733 (1983).
13. D. Wilhelm, H. Dietrich, T. Clark, W. Mahdi, A. J. Kos and P. von R. Schleyer, *J. Am. Chem. Soc.*, **106**, 7279 (1984).
14. A. Kotera, T. Morita, S. Aoyagi, Y. Kakiuchi, S. Nagakura and K. Kume, *Nippon Kagaku Zassi*, **82**, 302 (1961); *Chem. Abstr.*, **55**, 15128e (1961).
15. A. Hantsch, *Ber. Dtsch. Chem. Ges.*, **63**, 1782 (1930).
16. M. E. Runner, M. L. Kilpatrick and E. C. Wagner, *J. Am. Chem. Soc.*, **69**, 1406 (1947).
17. F. J. Lahoz, A. Tiripicchio, M. Tiripicchio-Camellini, L. A. Oro and M. T. Pinilos, *J. Chem. Soc., Dalton Trans.*, 1487 (1985).
18. (a) J. Barker, N. Cameron, M. Kilner, M. M. Mahoud and S. C. Wallwork, *J. Chem. Soc., Dalton Trans.*, 1359 (1986).

(b) J. Barker, M. Kilner and R. O. Gould, *J. Chem. Soc., Dalton Trans.*, 2687 (1987).
19. T. J. Zielinski, M. R. Peterson, I. G. Csizmadia and R. Rein, *J. Comput. Chem.*, **3**, 62 (1982).
20. J. Oszczapowicz, C. U. Regelmann and G. Häfelinger, *J. Chem. Soc., Perkin Trans. 2*, 1551 (1990).
21. R. Delaby, J. V. Horisse and S. H. Renard, *Bull. Soc. Chim. Fr.*, **11**, 227 (1944).
22. E. Raczyńska and J. Oszczapowicz, *Tetrahedron*, **41**, 5175 (1985).
23. G. Gilli and V. Bertolasi, *J. Am. Chem. Soc.*, **101**, 7704 (1979).
24. J. B. Moffat, *J. Mol. Struct.*, **52**, 275 (1979).
25. W. Jentsch and M. Seefelder, *Chem. Ber.*, **98**, 1342 (1965).
26. Y. Ito, Y. Inubushi, M. Zenbayashi, S. Tomita and T. Saegusa, *J. Am. Chem. Soc.*, **95**, 4447 (1973).
27. R. J. Ferm and J. C. Riebsomer, *Chem. Rev.*, **54**, 593 (1954).
28. F. D. Popp and A. C. Noble, *Adv. Heterocycl. Chem.*, **8**, 21 (1967).
29. E. Truscheit and K. Eiter, *Justus Liebigs Ann. Chem.*, **658**, 65 (1962).
30. H. Oediger and F. Möller, *Angew. Chem.*, **79**, 53 (1967).
31. C. W. Spangler, R. Eichen, K. Silver and B. Buntzlaff, *J. Org. Chem.*, **36**, 1695 (1971).
32. E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas and R. E. K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968).
33. H. Oediger, H. J. Kobbe, F. Möller and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).
34. H. Oediger, F. Möller and K. Eiter, *Synthesis*, 591 (1972).
35. I. Hermecz, *Adv. Heterocycl. Chem.*, **42**, 83 (1987).
36. R. Schwesinger, *Angew. Chem.*, **99**, 1209 (1987).
37. R. Schwesinger, M. Mißfeldt, K. Peters and H. G. von Schnering, *Angew. Chem.*, **99**, 1210 (1987).
38. A. R. Katritzky, *Adv. Heterocycl. Chem.*, **17**, 255 (1974).
39. M. R. Grimmett, *Adv. Heterocycl. Chem.*, **12**, 103 (1970).
40. M. R. Grimmett, *Adv. Heterocycl. Chem.*, **27**, 241 (1980).
41. R. J. Sundberg and R. B. Martin, *Chem. Rev.*, **74**, 471 (1974).
42. R. Bonnett, *Chem. Rev.*, **63**, 573 (1963).
43. J. Catalan, J. L. M. Abboud and J. Elguero, *Adv. Heterocycl. Chem.*, **41**, 187 (1987).
44. R. N. Butler, *Adv. Heterocycl. Chem.*, **21**, 323 (1977).
45. B. Pullman and A. Pullman, *Adv. Heterocycl. Chem.*, **13**, 77 (1971).
46. C. A. Grob and B. Fischer, *Helv. Chim. Acta*, **38**, 1794 (1955).
47. I. G. Csizmadia, M. R. Peterson, C. Kozmutza and M. A. Robb, in *Supplement B. The Chemistry of Acid Derivatives* (Ed. S. Patai), Wiley–Interscience, Chichester, 1979, pp. 1–57.
48. R. H. Wiley and L. L. Bennett, Jr., *Chem. Rev.*, **44**, 447 (1949).
49. J. A. Freemp, *Chem. Rev.*, **71**, 483 (1971).
50. H. Wenker, *J. Am. Chem. Soc.*, **57**, 1079 (1935).
51. Z. Eckstein and T. Urbański, *Adv. Heterocycl. Chem.*, **23**, 1 (1978).
52. I. J. Turchi and M. J. S. Dewar, *Chem. Rev.*, **75**, 389 (1975).
53. J. M. Sprague and A. H. Land, in *Heterocyclic Compounds* (Eds. R. C. Elderfield), Vol. 5, Wiley, New York, 1957, pp. 484–722.
54. P. Chakrabarti and J. D. Dunitz, *Helv. Chim. Acta*, **65**, 1555 (1982).
55. F. Jellinek, *Acta Crystallogr.*, **11**, 626 (1958).
56. H. H. Sutherland and D. W. Young, *Acta Crystallogr.*, **16**, 897 (1963).
57. C. Rérat, *Acta Crystallogr.*, **13**, 72 (1960).
58. C. Rérat, *Acta Crystallogr.*, **13**, 459 (1960).
59. D. R. Lide, *J. Chem. Phys.*, **27**, 343 (1957).
60. H. K. Higginbotham and L. S. Bartell, *J. Chem. Phys.*, **42**, 1131 (1965).
61. M. D. Harmony, V. W. Laurie, R. L. Kuczowski, R. H. Schwendeman, D. A. Ramsey, F. J. Lovas, W. J. Lafferty and A. G. Maki, *J. Phys. Chem. Ref. Data*, **8**, 619 (1979).
62. J. E. Wollrab and V. W. Laurie, *J. Chem. Phys.*, **48**, 5058 (1968).
63. G. Gundersen and D. W. H. Rankin, *Acta Chem. Scand.*, A37, 865 (1983).
64. A. Yokozeki and K. Kuchitsu, *Bull. Chem. Soc. Jpn.*, **44**, 2352 (1971).
65. J. E. Wollrab and V. W. Laurie, *J. Chem. Phys.*, **51**, 1580 (1969).
66. B. Beagley and A. R. Medwid, *J. Mol. Struct.*, **38**, 229 (1977).
67. J. H. M. Ter Brake, V. Mom and F. C. Mijlhoff, *J. Mol. Struct.*, **65**, 303 (1980).
68. D. G. Lister, J. K. Tyler, J. H. Hög and N. W. Larsen, *J. Mol. Struct.*, **23**, 253 (1974).
69. R. Pearson, Jr. and F. J. Lovas, *J. Chem. Phys.*, **66**, 4149 (1977).
70. E. Hirota, R. Sugisaki, C. Nielsen and G. Q. Sörensen, *J. Mol. Spectrosc.*, **49**, 251 (1974).

71. C. C. Costain and M. J. Dowling, *J. Chem. Phys.*, **32**, 158 (1969).
72. M. Kitano and K. Kuchitsu, *Bull. Chem. Soc. Jpn.*, **47**, 67 (1974).
73. E. D. Stevens, *Acta Crystallogr.*, **B34**, 544 (1978).
74. M. Kitano and K. Kuchitsu, *Bull. Chem. Soc. Jpn.*, **46**, 3048 (1973).
75. T. Ottersen, *Acta Chem. Scand.*, **A29**, 939 (1975).
76. G. A. Jeffrey, J. R. Ruble, R. K. McMullan, D. J. DeFrees, J. S. Binkley and J. A. Pople, *Acta Crystallogr.*, **B36**, 2292 (1980).
77. K. L. Gallaher and S. H. Bauer, *J. Chem. Soc., Faraday Trans. 2*, **71**, 1423 (1975).
78. A. Caron and J. Donohue, *Acta Crystallogr.*, **B25**, 404 (1969).
79. L. Fernholt, S. Samdal and R. Seip, *J. Mol. Struct.*, **72**, 217 (1981).
80. L. V. Vilkov, V. S. Mastryukov and N. I. Sadova, *Determination of the Geometrical Structure of Free Molecules*, Mir Publishers, Moscow, 1983.
81. K. Kuchitsu, in *MTP International Review of Science* (Ed. G. Allen), *Phys. Chem. Series* 1, Vol. 2, Chap. 6, Medical and Technical Publ. Co. and University Park Press, Baltimore, 1972, pp. 203–239.
82. R. Norrestam, S. Mertz and I. Crossland, *Acta Crystallogr.*, **C39**, 1554 (1983).
83. R. Norrestam, *Acta Crystallogr.*, **C41**, 873 (1985).
84. F. Iwasaki and K. Akiba, *Acta Crystallogr.*, **B37**, 185 (1981).
85. K. Surma, M. Jaskólski, Z. Kosturkiewicz and J. Oszczapowicz, *Acta Crystallogr.*, **C44**, 1031 (1988).
86. J. Hvoslef, M. L. Tracy and C. P. Nash, *Acta Crystallogr.*, **C42**, 353 (1986).
87. R. Anulewicz, T. M. Krygowski and B. Pniewska, *J. Cryst. Spectrosc., Res.*, **17**, 661 (1987).
88. R. Anulewicz, T. M. Krygowski, J. Jaroszewska-Manaj and B. Pniewska, *Pol. J. Chem.*, **63**, (1990), in press.
89. N. W. Alcock, J. Barker and M. Kilner, *Acta Crystallogr.*, **C44**, 712 (1988).
90. F. Iwasaki and K. Akiba, *Acta Crystallogr.*, **B37**, 180 (1981).
91. H. G. Raubenheimer, G. J. Kruger, F. Scott and R. Otte, *Organometallics*, **6**, 1789 (1987).
92. J. Krajewski, Z. Urbańczyk-Lipowska, P. Gluzinski, J. Oszczapowicz, I. Busko-Oszczapowicz, J. B. Bleidelis and A. Kemme, *Pol. J. Chem.*, **55**, 1015 (1981).
93. E. Cisazk, M. Gdaniec and Z. Kosturkiewicz, *Acta Crystallogr.*, **B43**, 1362 (1987).
94. J. Oszczapowicz, E. Tykarska, M. Jaskólski and Z. Kosturkiewicz, *Acta Crystallogr.*, **C42**, 1816 (1986).
95. E. Tykarska, M. Jaskólski and Z. Kosturkiewicz, *Acta Crystallogr.*, **C42**, 208 (1986).
96. (a) E. Tykarska, M. Jaskólski and Z. Kosturkiewicz, *Acta Crystallogr.*, **C42**, 740 (1986). (b) H. Gotthardt, T. Löhr and D. J. Brauer, *Chem. Ber.*, **120**, 751 (1987).
97. U. Demant, E. Conradi, U. Müller and K. Dehnike, *Z. Naturforsch.*, **B40**, 443 (1985).
98. R. E. Marsh, *Acta Crystallogr.*, **C42**, 1327 (1986).
99. T. Lis and P. Starynowicz, *Acta Crystallogr.*, **C41**, 1299 (1985).
100. J. R. Cannon, A. H. White and A. C. Willis, *J. Chem. Soc., Perkin Trans. 2*, 271 (1976).
101. R. Norrestam, *Acta Crystallogr.*, **C40**, 297 (1984).
102. M. Hjorth and R. Norrestam, *Acta Crystallogr.*, **C43**, 1589 (1987).
103. W. Eul, G. Kiel and G. Gatow, *Z. Anorg. Allg. Chem.*, **542**, 182 (1986).
104. A. A. Pinkerton and D. Schwarzenbach, *J. Chem. Soc., Dalton Trans.*, 989 (1978).
105. V. G. Thailambal, V. Pattabhi and T. N. G. Row, *Acta Crystallogr.*, **C42**, 587 (1986).
106. B. Kratochvil, J. Ondraček, J. Krechl and J. Hasek, *Acta Crystallogr.*, **C43**, 2182 (1987).
107. P. G. Lenhert, C. M. Lukehart, P. D. Sotiropoulos and K. Srinivasan, *Inorg. Chem.*, **23**, 1807 (1984).
108. G. Reck, V. Hagen and G. Wagner, *Cryst. Struct. Commun.*, **11**, 1099 (1982).
109. M. Sax, J. Pletcher, C. S. Yoo and J. M. Stewart, *Acta Crystallogr.*, **B27**, 1635 (1971).
110. T. Chivers, J. F. Richardson and N. R. M. Smith, *Inorg. Chem.*, **24**, 2453 (1985).
111. J. Galloy, J.-P. Putzeys, G. Germain, J.-P. Declercq and M. van Meersche, *Acta Crystallogr.*, **B30**, 2460 (1974).
112. H. Grützmacher, H. W. Roesky, M. Noltemeyer and G. M. Sheldrick, *Z. Naturforsch.*, **42b**, 1245 (1987).
113. H. Bock, K. Ruppert, K. Merzweiler, D. Fenske and H. Goesman, *Angew. Chem.*, **101**, 1715 (1989).
114. J. J. Daly, *J. Chem. Soc., Dalton Trans.*, 1048 (1972).
115. F. Sanz and J. J. Daly, *J. Chem. Soc., Dalton Trans.*, 2267 (1972).

116. R. O. Day, A. Willhalm, J. M. Holmes, R. R. Holmes and A. Schmidtpeter, *Angew. Chem.*, **97**, 775 (1985).
117. A. Schmidtpeter, K.-H. Zirzow, A. Willhalm, J. M. Holmes, R. O. Day and R. R. Holmes, *Angew. Chem.*, **98**, 471 (1985).
118. J. Daub, A. Hasenhündl, E. Salbeck, A. Gieren and T. Hübner, *Z. Naturforsch.*, **40b**, 1390 (1985).
119. F. Belluci, V. Bertolasi, V. Feretti and G. Gilli, *Acta Crystallogr.*, **C41**, 544 (1985).
120. A. Carpy, J.-M. Leger, C.-G. Wermuth and G. Leclerc, *Acta Crystallogr.*, **B37**, 885 (1981).
121. F. L. Hirshfeld and H. Hope, *Acta Crystallogr.*, **B36**, 406 (1980).
122. M. J. Begley, A. Harper and P. Hubberstey, *J. Chem. Res. (S)*, 398 (1979).
123. D. J. Haas, D. R. Harris and H. H. Mills, *Acta Crystallogr.*, **19**, 676 (1965).
124. Z. Pajak, M. Grottel and A. E. Koziol, *J. Chem. Soc., Faraday Trans. 2*, 1048 (1972).
125. D. A. Baldwin, L. Denner, T. J. Egan and A. J. Markwell, *Acta Crystallogr.*, **C42**, 1197 (1986).
126. J. M. Adams and R. W. H. Small, *Acta Crystallogr.*, **B30**, 2191 (1974).
127. M. Cygler, M. J. Grabowski, A. Stepień and E. Wajsman, *Acta Crystallogr.*, **B32**, 2391 (1976).
128. C. N. Morimoto and E. C. Lingafelter, *Acta Crystallogr.*, **B26**, 335 (1970).
129. K. M. Barkigia, L. M. Rajkovic-Blazer, M. T. Pope, E. Prince and C. O. Quicksall, *Inorg. Chem.*, **19**, 2531 (1980).
130. T. J. R. Weakley, *Acta Crystallogr.*, **C41**, 377 (1985).
131. L. Golic, I. Leban, S. Detoni, B. Orel and D. Hadzi, *J. Cryst. Spectrosc. Res.*, **15**, 215 (1985).
132. J. A. A. de Boer, J. W. H. M. Uiterwijk, J. Geevers, S. Harkema and D. N. Reinhoudt, *J. Org. Chem.*, **48**, 4821 (1983).
133. F. A. Cotton, V. W. Day, E. E. Hazen, Jr. and S. Larsen, *J. Am. Chem. Soc.*, **95**, 4834 (1973).
134. F. A. Cotton, V. W. Day, E. E. Hazen, Jr., S. Larsen and S. T. K. Wong, *J. Am. Chem. Soc.*, **96**, 4471 (1974).
135. W. Sawka-Dobrowolska, T. Głowiak and R. Tyka, *Acta Crystallogr.*, **C40**, 174 (1984).
136. J. Berthou, A. Laurent and S. Nakajima, *Acta Crystallogr.*, **B32**, 1529 (1976).
137. Y. Kato, Y. Haimoto and K. Sakurai, *Bull. Chem. Soc. Jpn.*, **52**, 233 (1979).
138. J. C. Hanson, L. H. Jensen and J. R. Herriott, *Acta Crystallogr.*, **A40**, S 40 (1984).
139. E. G. Steward, D. Warner and G. R. Clarke, *Acta Crystallogr.*, **B30**, 813 (1974).
140. M. S. Lehmann, J. J. Verbist, W. C. Hamilton and T. F. Koetzle, *J. Chem. Soc., Faraday Trans. 2*, 133 (1973).
141. I. L. Karle and J. Karle, *Acta Crystallogr.*, **17**, 835 (1964).
142. J. Dow, L. H. Jensen, S. K. Mazumdar, R. Srinivasan and G. N. Ramachandran, *Acta Crystallogr.*, **B26**, 1662 (1970).
143. W. Saenger and K. G. Wagner, *Acta Crystallogr.*, **B28**, 2237 (1972).
144. D. M. Salunke and M. Vuayan, *Acta Crystallogr.*, **B38**, 1328 (1982).
145. A. Kjaer, I. Kjoller-Larsen and P. Sivertsen, *Acta Chem. Scand.*, **B31**, 415 (1977).
146. G. Becker and O. Mundt, *Z. Anorg. Allg. Chem.*, **459**, 87 (1979).
147. U. Thewalt and D. Rinne, *Z. Anorg. Allg. Chem.*, **420**, 51 (1976).
148. M. Kimura, *J. Chem. Soc., Perkin Trans. 2*, 205 (1987).
149. L. G. Marzilli, M. F. Summers, J. H. Ramsden, Jr, N. Bresciani-Pahor and L. Randaccio, *J. Chem. Soc., Dalton Trans.*, 511 (1984).
150. K.-F. Tebbe and R. Fröhlich, *Z. Anorg. Allg. Chem.*, **505**, 7 (1983).
151. H. W. Roesky, H. Hofmann, K. Keller, W. Pinkert, P. G. Jones and G. M. Sheldrick, *Chem. Ber.*, **117**, 2681 (1984).
152. R. Kupfer, M. Nagel, E.-U. Würthwein and R. Allmann, *Chem. Ber.*, **118**, 3089 (1985).
153. R. Allmann, M. Krestel, R. Kupfer, M. Nagel and E.-U. Würthwein, *Chem. Ber.*, **119**, 2444 (1986).
154. P. Groth, *Acta Chem. Scand.*, **B31**, 607 (1977).
155. A. I. Gubin, A. I. Yanovsky, Yu. T. Struchkov, B. A. Berimzhanov, N. N. Nurakhmetov and M. Zh. Buranbaev, *Cryst. Struct. Commun.*, **9**, 745 (1980).
156. P. M. van Meerssche, G. Germain and J. P. Declercq. *Acta Crystallogr.*, **B33**, 1622 (1977).
157. W. B. Schweizer and J. D. Dunitz, *Helv. Chim. Acta*, **65**, 1547 (1982).
158. B. H. Bracher and R. W. H. Small, *Acta Crystallogr.*, **23**, 410 (1967).
159. R. Kupfer, E.-U. Würthwein, M. Krestel and R. Allmann, *Chem. Ber.*, **119**, 3236 (1986).
160. N. W. Alcock, J. M. Brown and T. D. MacLean, *J. Chem. Soc., Chem. Commun.*, 1689 (1984).
161. F. W. B. Einstein and J. S. Field, *Acta Crystallogr.*, **B35**, 1696 (1979).
162. P. Gronski, K. Hartke, H. Burzlaff, R. Böhme and A. Shaukat, *Chem. Ber.*, **119**, 3689 (1986).

163. R. Bardi, A. del Pra, A. M. Piazzesi, L. Sinellari and B. Zarli, *Inorg. Chim. Acta*, **47**, 231 (1981).
164. J. E. Worsham, Jr. and W. R. Busing, *Acta Crystallogr.*, **B25**, 572 (1969).
165. S. Harkema and D. Feil, *Acta Crystallogr.*, **B25**, 589 (1969).
166. J. N. Brown and E. A. Meyers, *Acta Crystallogr.*, **B26**, 1178 (1970).
167. J. C. B. White and S. A. Mason, *Acta Crystallogr.*, **B26**, 2068 (1970).
168. B. Feith, H.-M. Weber and G. Maas, *Justus Liebigs Ann. Chem.*, 2123 (1986).
169. H. Henke and H. Baeringhausen, *Acta Crystallogr.*, **B28**, 1100 (1972).
170. D. Feil and W. Song Loong, *Acta Crystallogr.*, **B24**, 1334 (1968).
171. E. Hough and J. S. Lomas, *Acta Crystallogr.*, **C40**, 1938 (1984).
172. S. R. Ernst and F. W. Cagle, Jr., *Acta Crystallogr.*, **B33**, 235 (1977).
173. S. R. Ernst, *Acta Crystallogr.*, **B33**, 237 (1977).
174. F. Kurzer and E. D. Pitchfork, *Fortschr. Chem. Forschung*, **10/3**, 375 (1968).
175. R. Norrestam, *Acta Crystallogr.*, **C40**, 955 (1984).
176. M. H. J. Koch, G. German, J. P. Declercq and M. van Meerssche, *Acta Crystallogr.*, **B33**, 1975 (1977).
177. D. B. Cosulich and F. M. Lovell, *Acta Crystallogr.*, **B33**, 1147 (1977).
178. C. Hernstadt, D. Mootz, H. Wunderlich and H. Möhrle, *J. Chem. Soc., Perkin Trans. 2*, 735 (1979).
179. H. J. Lindner, *Chem. Ber.*, **102**, 2464 (1964).
180. A. Streitwieser, Jr., *Molecular Orbital Theory for Organic Chemists*, Wiley, New York, 1961.
181. R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963).
182. R. G. Parr, *The Quantum Theory of Molecular Electronic Structure*, Benjamin, New York, 1966.
183. L. Salem, *The Molecular Orbital Theory of Conjugated Systems*, Benjamin, New York, 1966.
184. J. A. Pople and D. L. Beveridge, *Approximate MO Theory*, McGraw-Hill, New york, 1970.
185. J. Sadlej, *Semi-Empirical methods of Quantum Chemistry. CNDO, INDO, NDDO*, Ellis Horwood, Chichester, 1985.
186. J. Del Bene and H. H. Jaffé, *J. Chem. Phys.*, **48**, 1807 (1968).
187. R. C. Bingham, M. J. S. Dewar and D. H. Lo, *J. Am. Chem. Soc.*, **97**, 1285, 1294, 1302, 1307 (1975).
188. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899, 4907 (1977).
189. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
190. P. Claverie, J. P. Daudey, S. Diener, C. Giessner-Prettre, M. Gilbert, J. Langlet, J. P. Malrieu, U. Pincelli and B. Pullman, *QCPE*, **11**, 220 (1972).
191. U. Burkert and N. L. Allinger, *Molecular Mechanics*, ACS Monograph No. 177, Washington, 1982.
192. S. R. Niketic and K. Rasmussen, *The Consistent Force Field*, Springer, Berlin, 1977.
193. I. G. Csizmadia, *Theory and Practice of MO-Calculations on Organic Molecules*, Elsevier, Amsterdam, 1976.
194. P. Čarsky and M. Urban, *Ab initio Calculations*, Lecture Notes in Chemistry, Vol. 16, Springer, Berlin, 1980.
195. A. Szabo and N. S. Ostlund, *Modern Quantum Chemistry. Introduction to Advanced Electron Structure Theory*, MacMillan, New York, 1982.
196. W. J. Hehre, L. Radom, P. V. R. Schleyer and J. A. Pople, *Ab initio Molecular Orbital Theory*, Wiley, New York, 1986.
197. C. E. Dykstra, *Ab initio Calculations of the Structures and Properties of Molecules*, Elsevier, Amsterdam, 1988.
198. J. S. Binkley, M. J. Frisch, D. J. DeFrees, K. Raghavachari, A. Whiteside, H. B. Schlegel, E. M. Flunder and J. A. Pople, *GAUSSIAN 82*, Carnegie-Mellon University, Pittsburgh, 1984.
199. B. A. Murtagh and R. W. H. Sargent, *Comput. J.*, **13**, 185 (1970).
200. M. Born and J. R. Oppenheimer, *Ann. Phys.*, **84**, 457 (1927); M. Born, *Gött. Nachr. Math. Phys., Kl.*, 1 (1951).
201. C. C. J. Roothaan, *Rev. Mod. Phys.*, **23**, 69 (1951); **32**, 179 (1960).
202. E. Clementi and D. L. Raimondi, *J. Chem. Phys.*, **38**, 2686 (1968).
203. L. Pauling and E. B. Wilson, *Introduction to Quantum Mechanics*, McGraw-Hill, New York, 1935.
204. STO-3G to STO-6G: W. J. Hehre, R. F. Stewart and J. A. Pople, *J. Chem. Phys.*, **51**, 2657 (1969).
205. 3-21G: J. S. Binkley, J. A. Pople and W. J. Hehre, *J. Am. Chem. Soc.*, **102**, 939 (1980).

206. 4-31G: R. Ditchfield, W. J. Hehre and J. A. Pople, *J. Chem. Phys.*, **54**, 724 (1971).
207. 6-31G: W. J. Hehre, R. Ditchfield and J. A. Pople, *J. Chem. Phys.*, **56**, 2257 (1972).
208. 6-311G and 6-311G**: R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys.*, **56**, 2257 (1972).
209. STO-3G*: J. B. Collins, P. von R. Schleyer, J. S. Binkley and J. A. Pople, *J. Chem. Phys.*, **64**, 5142 (1976).
210. 3-21G*: W. J. Pietro, M. M. Francl, W. J. Hehre, D. J. DeFrees, J. A. Pople and J. S. Binkley, *J. Am. Chem. Soc.*, **104**, 5039 (1982).
211. 6-31G* and 6-31G**: P. C. Hariharan and J. A. Pople, *Theor. Chim. Acta*, **28**, 213 (1973); M. M. Francl. W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees and J. A. Pople, *J. Chem. Phys.*, **77**, 3654 (1982).
212. 6-311G**: R. Krishnan, J. S. Binkley, R. Seeger and J. A. Pople, *J. Chem. Phys.*, **72, 650** (1980).
213. P. Pulay, *Mol. Phys.*, **17**, 197 (1969); P. Pulay, in *Modern Theoretical Chemistry*. Vol. 4, *Application of Electronic Structure Theory* (Ed. H. F. Schaefer III), Plenum Press, New York, 1977, pp. 153–186.
214. R. S. Mulliken, *J. Chem. Phys.*, **23**, 1833, 1841, 2338, 2343 (1955).
215. R. F. W. Bader, *Acc. Chem. Res.*, **18**, 9 (1985).
216. J. B. Collins and A. Streitwieser, Jr., *J. Comput. Chem.*, **1**, 81 (1980).
217. R. S. McDowell, D. L Grier and A. Streitwieser, Jr., *Comput. Chem.*, **9**, 165 (1985).
218. S. M. Bachrach and A. Streitwieser, Jr., *J. Comput. Chem.*, **10**, 514 (1989).
219. R. Ahlrichs and C. Ehrhardt, *Chem. Unserer Zeit*, **19**, 120 (1986).
220. R. Heinzmann and R. Ahlrichs, *Theor. Chim. Acta*, **42**, 33 (1976).
221. C. Ehrhard and R. Ahlrichs, *Theor. Chim. Acta*, **68**, 231 (1985).
222. A. E. Reed and F. Weinhold, *J. Chem. Phys.*, **78**, 4066 (1983).
223. A. E. Reed, R. B. Weinstock and F. Weinhold, *J. Chem. Phys.*, **83**, 735 (1985).
224. E. D. Davidson, *J. Chem. Phys.*, **46**, 3320 (1967).
225. K. R. Roby, *Mol. Phys.*, **27**, 81 (1974).
226. K. B. Wiberg, *Physical Organic Chemistry*, Wiley, New York, 1964.
227. S. Flizár, *Charge Distributions and Chemical Effects*, Springer, Berlin, 1983.
228. A. Whiteside, J. S. Binkley, R. Krishnan, D. J. DeFrees, H. B. Schlegel and J. A. Pople, Carnegie-Mellon Quantum Chemistry Archive. Department of Chemistry, Carnegie-Mellon University, Pittsburg, 3rd Ed., 1984.
229. G. Häfelinger, C. U. Regelmann, T. M. Krygowski and K. Woźniak, *J. Comput. Chem.*, **10**, 329 (1989).
230. T. J. Zielinski, R. A. Poirer, M. R. Peterson and I. Csizmadia, *J. Comput. Chem.*, **4**, 419 (1983).
231. T. J. Zielinski and R. A. Poirer, *J. Comput. Chem.*, **5**, 466 (1984).
232. R. A. Poirer, D. Majlessi and T. J. Zielinski, *J. Comput. Chem.*, **7**, 464 (1986).
233. (a) J. N. Levine, *J. Chem. Phys.*, **38**, 2327 (1963).
(b) E. F. Pearson, R. A. Creswell, M. Winnewisser and G. Winnewisser, *Z. Naturforsch.*, **31**, 1394 (1976).
234. K. Karakida, T. Fukiyama and K. Kuchitsu, *Bull. Chem. Soc. Jpn.*, **47**, 229 (1974).
235. P. Scharfenberg, *Z. Chem.*, **21**, 328 (1981).
236. W. Kinasiewicz, A. Leś and I. Wawer, *J. Mol. Struct.*, **168**, 1 (1988).
237. N. R. Carlsen, L. Radom, N. V. Riggs and W. R. Rodwell, *J. Am. Chem. Soc.*, **101**, 2223 (1979).
238. L. Radom and N. V. Riggs, *Aust. J. Chem.*, **33**, 249 (1980).
239. J. E. Boggs and Z. Niu, *J. Comput. Chem.*, **6**, 46 (1985).
240. M. H. Palmer, *Chem. Phys.*, **127**, 335 (1988).
241. G. M. Wright, R. J. Simmonds and D. E. Parry, *J. Comput. Chem.*, **9**, 600 (1988).
242. C. L. Perrin, D. A. Schiraldi and G. M. L. Arrhenius, *J. Am. Chem. Soc.*, **104**, 196 (1982).
243. C. L. Perrin, E. R. Johnston and J. L. Ramirez, *J. Am. Chem. Soc.*, **102**, 6299 (1980).
244. (a) G. Häfelinger and C. U. Regelmann, *J. Comput. Chem.*, **6**, 368 (1985); **8**, 1057 (1987).
(b) M. L. Williams and J. E. Gready, *J. Comput. Chem.*, **10**, 35 (1989); M. J. Jordan and J. E. Gready, *J. Comput. Chem.*, **10**, 186 (1989).
245. A. F. Hegarty and A. Chandler, *Tetrahedron Lett.*, **21**, 885 (1980).
246. M. T. McCormack and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1701 (1976); G. Leroy, M. T. Nguyen, M. Sana, K. J. Dignam and A. F. Hegarty, *J. Am. Chem. Soc.*, **101**, 1988 (1979).
247. A. F. Hegarty and A. Chandler, *J. Chem. Soc., Chem. Commun.*, 130 (1980).
248. I. D. Cunningham and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 537 (1986).

249. O. Exner, M. Budesinsky, D. Hnyk, V. Vsetecka and E. D. Raczyńska, *J. Mol. Struct.*, **178**, 147 (1988).
250. E. D. Raczyńska, *J. Chem. Res. (S)*, 410 (1987).
251. J. D. Halliday, E. A. Symons and P. E. Binder, *Can. J. Chem.*, **56**, 1470 (1978).
252. P. Jacobsen and S. Treppendahl, *Tetrahedron*, **33**, 3137 (1977).
253. P. Jacobsen and S. Treppendahl, *Tetrahedron*, **37**, 829 (1981).
254. V. V. Negrebetskii, L. Ya. Bogel'fer, A. D. Sinitsa, V. I. Kal'chenko and V. S. Krishtal, *Zh. Prikl. Khim.*, **51**, 1485 (1981); *J. Gen. Chem. USSR*, **51**, 1260 (1981).
255. N. Naulet, M. L. Filleux, G. J. Martin and J. Pornet, *Org. Magn. Reson.*, **7**, 326 (1975).
256. M. L. Filleux, N. Naulet, J. P. Dorie, G. J. Martin, J. Pornet and L. Miginiac, *Tetrahedron Lett.*, 1435 (1974).
257. (a) K. B. Wiberg, C. M. Breneman and T. J. LePage, *J. Am. Chem. Soc.*, **112**, 61 (1990).
(b) K. S. Pitzer and J. L. Hollenberg, *J. Am. Chem. Soc.*, **76**, 1493 (1954); M. I. Davis, H. A. Kappler and D. J. Cowan, *J. Phys. Chem.*, **68**, 2005 (1964).
258. M. Rabinowitz and H. Pines, *J. Am. Chem. Soc.*, **91**, 1585 (1969).
259. G. Häfelinger, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Chap. 1, Wiley–Interscience, London, 1975, 1–84.
260. R. J. F. M. Staps, J. W. Scheeren, F. W. Pijpers and R. J. F. Nivard, *Rec. Trav. Chim. Pays-Bas*, **98**, 445 (1979).
261. R. C. Neumann, Jr. and V. Jonas, *J. Phys. Chem.*, **75**, 3532 (1971).
262. G. Schwenker and H. Rosswag, *Tetrahedron Lett.*, 2691 (1968).
263. D. L. Harris and K. M. Wellman, *Tetrahedron Lett.*, 5225 (1968).
264. D. J. Bertelli and J. T. Gerig, *Tetrahedron Lett.*, 2481 (1967).
265. Z. Rappoport and R. Ta-Shma, *Tetrahedron Lett.*, 5281 (1972).
266. J. S. McKennis and P. A. S. Smith, *J. Org. Chem.*, **37**, 4173 (1972).
267. R. C. Neumann, Jr. and L. B. Young, *J. Phys. Chem.*, **69**, 2570 (1965).
268. I. Wawer, *Magn. Reson. Chem.*, **26**, 601 (1988).
269. I. Wawer, *Magn. Reson. Chem.*, **27**, 577 (1989).
270. M. Zupan, V. Pirc, A. Pollak, B. Stanovnik and M. Tisler, *J. Heterocycl. Chem.*, **11**, 525 (1974).
271. M. Drobnič-Košorok, S. Polanc, B. Stanovnik, M. Tišler and B. Verček, *J. Heterocycl. Chem.*, **15**, 1105 (1978).
272. V. V. Negrebetskii, L. Ya. Bogel'fer, A. D. Sinitsa, V. I. Kal'chenko and V. S. Krishtal, *Zh. Prikl. Khim.*, **51**, 1493 (1981); *J. Gen. Chem. USSR*, **51**, 1267 (1981).
273. (a) C. Rabiller, G. Ricolleau, M. L. Martin and G. J. Martin, *Nouv. J. Chim.*, **4**, 35 (1980).
(b) T. Kozaki, K. Morihashi and O. Kikuchi, *J. Mol. Struct.*, **168**, 265 (1988).
(c) P. Kollmann, J. McKelvey and P. Grund, *J. Am. Chem. Soc.*, **97**, 1640 (1975).
274. J. C. Grivas and A. Taurins, *Can. J. Chem.*, **37**, 795 (1959); *Can. J. Chem.*, **39**, 414 (1961).
275. D. Prevoršek, *Bull. Soc. Chim. Fr.*, 840 (2958); *J. Phys. Chem.*, **66**, 769 (1962).
276. A. R. Forrester and R. H. Thomson, *Spectrochim. Acta*, **19**, 1481 (1963).
277. A. G. Moritz, *Spectrochim. Acta*, **20**, 1555 (1964).
278. R. A. Cummins and A. G. Moritz, *Aust. J. Chem.*, **18**, 1107 (1965).
279. G. Schwenker and K. Bösl, *Pharmazie*, **24**, 653 (1969).
280. P. Reynaud, J.-D. Brion and G. Menard, *Bull. Soc. Chim. Fr.* II, 449 (1978).
281. H. U. Sieveking and W. Lüttke, *Justus Liebigs Ann. Chem.*, 189 (1977).
282. G. C. Levy and R. L. Lichter, *Nitrogen-15 NMR Spectroscopy*, Wiley, New York, 1979.
283. G. J. Martin, M. L. Martin and J. P. Gouesnard, *^{15}N NMR Spectroscopy, in NMR—Basic Principles and Progress*, Vol. 18, Springer, Berlin, 1981.
284. B. Clement and T. Kämpchen, *Chem. Ber.*, **119**, 1101 (1986).
285. E. D. Raczyńska, *J. Chem. Soc., Perkin Trans. 2*, 1189 (1986).
286. E. D. Raczyńska, *J. Chem. Res. (S)*, 256 (1986).
287. S.-O. Chua, M. J. Cook and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 546 (1974).
288. M. J. Cook, A. R. Katritzky and S. Nadji, *J. Chem. Soc., Perkin Trans. 2*, 211 (1976).
289. E. Raczyńska and J. Oszczapowicz, *Tetrahedron*, **41**, 5175 (1985).
290. J. Fabian, M. Legrand and P. Poirer, *Bull. Soc. Chim. Fr.*, 1499 (1956).
291. N. E. White and M. Kilpatrick, *J. Phys. Chem.*, **59**, 1044 (1955).
292. P. Sohár, *Acta Chim. Sci. Hung.*, **54**, 91 (1967).

293. H.-H. Limbach, H. Rumpel, L. Meschede, B. Wehrle, M. Schmalbach and G. Scherer, *J. Mol. Struct.*, **177**, 143 (1988).
294. L. Meschede, D. Gerritzen and H.-H. Limbach, *Ber. Bunsenges. Phys. Chem.*, **92**, 469 (1988).
295. P. Svensson, N.-A. Bergman and P. Ahlberg, *Z. Naturforsch.*, **44A**, 473 (1989).
296. R. B. Woodward and R. Hofmann, *Angew. Chem.*, **81**, 797 (1969).
297. I. Shavitt, *The Method of Configuration Interaction*, in *Modern Theoretical Chemistry*. Vol. 3. *Methods of Electronic Structure Theory* (Ed. H. F. Schaefer III), Plenum Press, New York, 1977, pp. 189–275.
298. C. Möller and M. S. Plesset, *Phys. Rev.*, **46**, 618 (1934).
299. C. Pigenet and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 3743 (1972).
300. H. Lumbroso, C. Pigenet, H. Rosswag and G. Schwenker, *C.R. Acad. Sci. Paris, Ser. C*, **266**, 1479 (1968).
301. H. Lumbroso and G. Pifferi, *Bull. Soc. Chim. Fr.*, 3401 (1972).
302. O. Exner and Z. Papoušková, *Collect. Czech. Chem. Commun.*, **45**, 2410 (1980).
303. O. Exner and K. Waisser, *Collect. Czech. Chem. Commun.*, **47**, 828 (1982).
304. B. Plesničar and O. Exner, *Collect. Czech. Chem. Commun.*, **46**, 490 (1981).
305. O. A. Osipov, A. M. Simonov, V. I. Minkin and A. D. Garnovskii, *Dokl. Akad. Nauk SSR*, **137**, 1374 (1961); *Chem. Abstr.*, **55**, 24173f (1961).
306. J. Oszczapowicz and E. Raczyńska, *Polish J. Chem.*, **57**, 419 (1983).
307. J. Oszczapowicz, E. Raczyńska and T. Pawlik, *Polish J. Chem.*, **58**, 117 (1984).
308. J. Ševčik and F. Grambal, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Chap. 12, Wiley–Interscience London, 1975, p. 565.
309. J. Oszczapowicz and R. Orliński, *Polish J. Chem.*, **54**, 1901 (1981).
310. J. Oszczapowicz and E. Raczyńska, *J. Chem. Soc., Perkin Trans. 2*, 1643 (1984).
311. E. Raczyńska, J. Oszczapowicz and M. Wojtkowska, *Polish J. Chem.*, **59**, 945 (1985).
312. J. Oszczapowicz, W. Krawczyk, J. Osek and E. Raczyńska, *Polish J. Chem.*, **60**, 157 (1986).
313. J. Oszczapowicz and K. Ciszkowski, *J. Chem. Soc., Perkin Trans. 2*, 663 (1987).
314. J. Oszczapowicz and W. Krawczyk, *J. Chem. Soc., Perkin Trans. 2*, 21 (1989).
315. J. Oszczapowicz and J. Osek, *Polish J. Chem.*, **57**, 93 (1983).
316. J. Oszczapowicz, R. Orliński and H. Walczyńska, *Polish J. Chem.*, **53**, 2531 (1979).
317. J. Oszczapowicz, J. Osek and R. Orliński, *Polish J. Chem.*, **54**, 1191 (1980).
318. J. Oszczapowicz, E. Raczyńska and R. Orliński, *Polish J. Chem.*, **55**, 2031 (1981).
319. E. Raczyńska, J. Oszczapowicz and M. Walczak, *J. Chem. Soc., Perkin Trans. 2*, 1087 (1985).
320. J. Oszczapowicz, E. Raczyńska and I. Barecka, *Polish J. Chem.*, **59**, 387 (1985).
321. B. Fernandez, I. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans. 2*, 1371 (1973).
322. B. Fernandez, I. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans. 2*, 1416 (1974).
323. B. Fernandez, I. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans. 2*, 2068 (1977).
324. R. P. Bell, *The Proton in Chemistry*, Cornell University Press, Ithaca, New York, 1959, p. 65.
325. H. S. Herned and B. B. Owen, *J. Am. Chem. Soc.*, **52**, 5079 (1930).
326. A. Gero and J. J. Markham, *J. Org. Chem.*, **16**, 1835 (1951).
327. N. F. Hall and M. R. Sprinkle, *J. Am. Chem. Soc.*, **54**, 3469 (1932).
328. J. Oszczapowicz, R. Orliński and E. Hejchman, *Polish J. Chem.*, **53**, 1259 (1979).
329. G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1162 (1940).
330. A. Albert, G. Goldacre and J. Philips, *J. Chem. Soc.*, 2240 (1948).
331. J. N. Baxter and J. Cymerman-Craig, *J. Chem. Soc.*, 1490 (1953).
332. J. Goerdeler, D. Krause-Loevenich and B. Wedekind, *Chem. Ber.*, **90**, 1638 (1957).
333. E. Lorz and R. Baltzly, *J. Am. Chem. Soc.*, **71**, 3992 (1949).
334. A. Albert, R. Goldacre and J. Phillips, *J. Chem. Soc.*, 2240 (1948).
335. J. F. Coetzee and G. R. Padmanabhan, *J. Am. Chem. Soc.*, **87**, 5005 (1965).
336. K. G. Flynn and D. R. Nenortas, *J. Org. Chem.*, **28**, 3527 (1963).
337. R. Schwesinger, *Chimia*, **39**, 269 (1985); R. Schwesinger and H. Schlemper, *Angew. Chem.*, **99**, 1212 (1987).
338. R. Schwesinger, *Nachr. Chem. Tech. Lab.*, **38**, 1214 (1990).
339. J. E. Del Bene, *J. Comput. Chem.*, **5**, 381 (1984).
340. A. K. Bose, I. Kugajevsky, P. T. Funke and K. G. Das, *Tetrahedron Lett.*, 3065 (1965).
341. H. F. Grützmacher and H. Kuschel, *Org. Mass. Spectrom.*, **3**, 605 (1970).

342. H. Kuschel and H. F. Grützmacher, *Org. Mass. Spectrom.*, **9**, 395, 403, 408 (1974)
343. N. G. Keats, J. E. Rockley and L. A. Summers, *Z. Naturforsch.*, **32b**, 1156 (1977).
344. A. A. H. Saeed and S. A. Selman, *Can. J. Spectrosc.*, **27**, 123 (1982).
345. J. Barker, M. Jones and M. Kilner, *Org. Mass. Spectrom.*, **20**, 619 (1985).
346. E. Rogman, D. L. Nelson and M. Mares-Guia, *J. Am. Chem. Soc.*, **97**, 6844 (1975).
347. M. Kubista, B. Akerman and B. Albinson, *J. Am. Chem. Soc.*, **111**, 7031 (1989).
348. G. Häfelinger, *Properties of Hydrogen as a Substituent in Planar Organic π-Systems in Similarity Models in Organic Chemistry* (Eds. T. M. Krygowski, J. Shorter and R. Zalewski), Elsevier, Amsterdam (in print).

CHAPTER 2

Structural chemistry of amidines and related systems

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ABBREVIATIONS

$A^{-\delta}$	hydrogen bond accepting atom in B—H···A complex
CN(l)	longer of the two CN bonds
CN(s)	shorter of the two CN bonds
CSD	Cambridge Structural Database
esd	estimated standard deviation
P_i, P_j	structural parameters
r	correlation coefficient
SA	sum of all valence angles
Δ	deviation of the central C atom from the N^1N^2X plane
σ	estimated standard deviation
X^i	the first atom of the group R^i
σ_x	the first atom of the group R^3 attached to the carbon atom of the amidine skeleton.

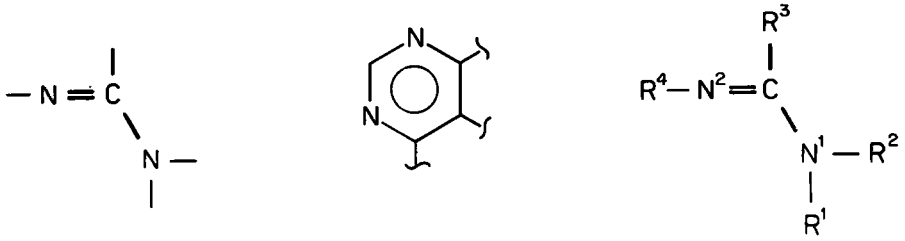
I. INTRODUCTION

The structure of a molecule may be interpreted either as the electron structure or as the geometrical structure of the chemical species in question. These two meanings of the molecular structure are interrelated by the quantum chemical approach which gives both of them as a final result. In this chapter we take into account only the geometrical meaning of the molecular structure. The main sources of structural data are the X-ray diffraction technique and, to a much lesser degree, the neutron- and electron-diffraction techniques, and finally the microwave measurements. In the case of complex organic systems X-ray techniques are used to obtain most, perhaps 95% or more, of the geometrical information. Hence, the experimental geometries presented in this chapter originate from such measurements and they were retrieved from the Cambridge Structural Database[1] (CSD) by July 1989.

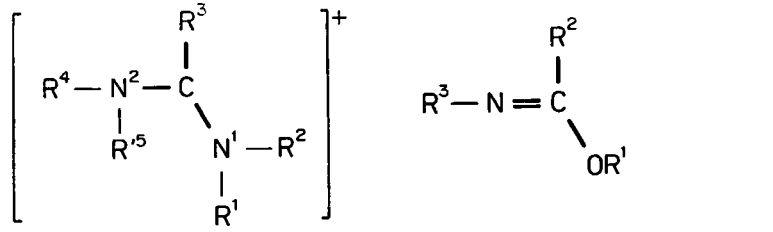
The geometry of a molecule is usually defined by means of bond lengths, bond or valence angles, torsional angles and dihedral angles. Only in some exceptional situations are other terms used. Often, some of the already-mentioned concepts are used in a complex way, such as in linear combinations or the like. The above-mentioned geometrical (or structural) parameters differ by their resistance to forces which tend to deform the molecules. It is usually accepted[2,3] that the force needed for deformation of bonds by

stretching is one order of magnitude larger than that required for (in-plane) deformation of the bond angle. Torsion deformation is again one order of magnitude less costly energetically than the latter. A similar situation occurs in the case of out-of-plane bending deformations. Hence it is often decided[3] to discuss changes in the molecular geometry separately for the case of bond lengths and bond angles, which are called hard structural parameters, and for torsional angles and dihedral angles, which are referred to as soft structural parameters. Hydrogen bonds and interatomic distances in EDA complexes belong also to the soft structural parameters. The hard parameters may often be used as indicators of intramolecular interactions between various parts of molecules, whereas the soft parameters have been mainly used to study the flexibility of molecular conformations. Hard parameters are supposed[4] to be hardly deformed by intermolecular interactions, particularly in rigid molecular systems (aromatic rings and polycyclic aromatics), but recently this point of view has often been criticized[2,5]. Nevertheless, in the case of structural parameters which are averaged values over sets of many molecular systems the concepts of Kitajgorodzki[4] are still valid. Individual structural parameters may be studied as dependent on intermolecular interactions due to the crystal lattice forces.

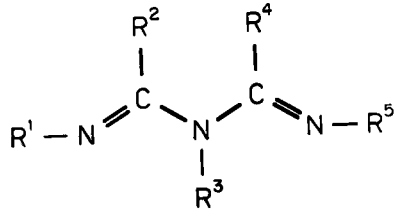
The amidine moiety **1** may be either included in cyclic systems, as e.g. **2**, or may exist in acyclic molecules of the general form **3**.



(1) **(2)** **(3)**



(3') **(4)**



(5)

SCHEME 1

Since systems like **2** are mostly treated as amines, they are not taken into account here. In this chapter only derivatives of **3**, their cationic forms (amidinium salts) **3'** and additionally imidates **4** and imidines **5** are taken into consideration. Guanidines in which R^3 is NR'R", and their salts are treated within groups **3** and **3'** (although for some purposes these two subgroups are treated separately).

Table 1 gives the numbers of crystal and molecular structures which belong to these three (four) groups solved by X-ray diffraction and neutron diffraction techniques retrieved from CSD[1]. The data in CSD are divided, into groups according to their precision described by the AS designation. For AS = 1 the mean value of the estimated standard deviation, hereafter abbreviated as esd or σ, for all bond lengths between non-hydrogen atoms is in the range 0.001–0.005 Å. The group indicated as AS $\geqslant$ 2 corresponds to all less precise geometries, whereas those with unknown precision are denoted as AS = 0.

Some 15 years ago Häfelinger[6] reviewed the general and theoretical aspects of amidines. That review dealt with the quantum chemical approach and with the structural chemistry obtained mostly from X-ray diffraction studies, as well as with various physicochemical properties considered from the structural point of view. Since that time, in all those directions significant developments occurred and hence these fields of research are updated in the present chapter, without repeating what has already been written in the previous review[6], presenting here an extension and continuation of the former work. In the last two decades an enormous volume of structural information has been published chiefly due to the development of computer techniques and of the theoretical basis for solving crystal and molecular structures by X-ray diffraction. Since so much information is available, statistical methods must be used to draw reasonable conclusions from these data, lest the review be transformed into something like a telephone directory. We use the statistical approach to describe the most important structural patterns of the amidine and imidate moieties in the compounds in question. Moreover, in order to obtain more precise and reliably averaged information on structural parameters, further partitioning into smaller, more homogeneous groups has been carried out in this chapter. Although we try to supplement our elaboration with short notes about statistical techniques applied, for those who are either ignorant of statistics or who wish to understand deeper the statistical tools used, two references may be recommended[7,8].

The material considered in this chapter, as mentioned above, consists of three main groups: amidine derivatives and their salts assigned as **3** and **3'**, respectively; imidate derivatives referred to as **4**, and imidine derivatives named **5**. All these groups are shown in Scheme 1, with possible substituents attached to all allowed sites. The first atoms of the

TABLE 1. Number of compounds retrieved from the Cambridge Structural Database by July 1989 and presented in Scheme 1

Group of compounds	Number of compounds
3	342
3'	234
4	79
5	13
3 with X = N[a]	197
3' with X = N[a]	146

[a]X is the first atom of the R^3 group, i.e. the one linked directly to the functional carbon atom.

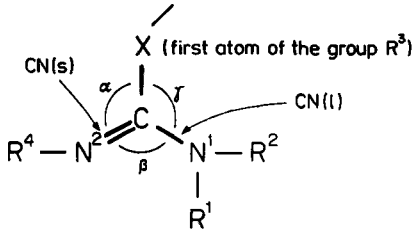
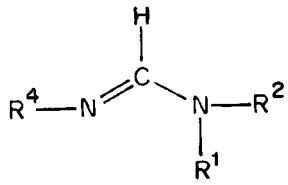


FIGURE 1. Scheme of labelling for amidine derivatives (group 3). In the case of amidinium cation derivatives (group 3') the fifth substituent R^5 is attached at nitrogen atom N^2

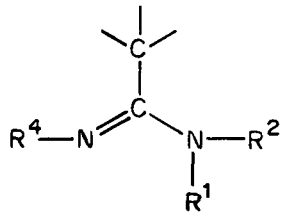
substituents R^1–R^5 are assigned as X^1–X^5, respectively. The three main groups of compounds, **3** + **3'**, **4** and **5**, are first treated as three independent samples and then divided into smaller subsamples. Within each of these three samples, and then within the many subsamples, statistical analyses of structural parameters are carried out, including the lengths of those bonds which, in Scheme 1, are drawn in bold lines, and all bond angles between those bonds. Additionally, the planarity of the main skeleton is analyzed. For the structural parameters, which for amidine derivatives are presented in detail and assigned in Figure 1, the tables give the number of data points in the subsample, *n*, the mean value for the structural parameter, its variance (var) and estimated standard deviation (esd), as well as both the minimal and maximal values of the parameter within a given sample or subsample.

Apart from the presentation of the data, an analysis of the relationship between various structural parameters is also carried out. The results of these analyses are described in this chapter if they are chemically informative. Since this analysis is often not conclusive in a chemically reasonable way, it is usually not discussed in detail. This procedure is applied to all main groups (**3** + **3'**, **4** and **5**) and also to those subgroups which are chemically important and sufficiently numerous. The division of the subgroups is as follows. As a principle of this division we select one of the bonds between the skeleton of the functional group of (**3** + **3'**), **4** or **5** and one of the possible substituents R^1 through R^4 for **3**, R^1 through R^3 (for **4**) and R^1 through R^5 (for **3'** and **5**). We can distinguish between various bonds according to the nature of X^i, i.e. the atom linking the substituent to the functional group. Then we can select subsamples according to the nature of X^i, say X^i = C,N,H,O,S, etc., until we explore all reasonable possibilities. This procedure may only be used for cases where the subsamples are sufficiently numerous, since otherwise the statistical conclusions would not be reliable enough.

To illustrate the method let us consider subsample **3**, i.e. amidine derivatives. We select compounds in which X^3 = const, e.g. X^3 = H. Thus we obtain the X^3 subsample which contains formamidine derivatives:



In this subsample R^1, R^2 and R^4 are unrestricted and may be any substituent. If we choose next $X^3 = C$, we obtain another X subsample whose structure may be represented by the general formula:



In this subsample there are included acetamidines, benzamidines and all derivatives of amidines in which the first atom of R^3, i.e. X^3, is a carbon atom, $X^3 = C$, independently of what is attached further to this carbon and what substituents are represented by R^1, R^2 and R^4. Next we can put $X^3 = N,S,O$, etc., obtaining subsets in which the differentiating feature is the difference in the C—X^3 bond. Within these subsets with C—X^3 equal to CH, CC, CN.... statistical analysis is carried out. The same can be done for X^1, X^2 and X^4 giving for amidine subsample **3** four possible ways of division. In addition, more complex substitutions may be taken into account as well.

These problems will be dealt within more detail during the analysis of particular subsamples.

While considering the main skeleton in **3**, **3'**, **4** and **5** some common problems arise.

First of all, from the formal point of view the functional carbon atom should be sp^2-hybridized due to the double bond between the C and N^2 atoms and hence the NC(X)N skeleton should be planar. This means that both nitrogen atoms N^1 and N^2, the carbon atom and the X atom linked to the latter should lie in the plane at least in nonionic derivatives of **3**, **4** and **5**. Figure 1 illustrates the labelling used for amidine derivatives and designates the structural parameters considered in the chapter. Similar schematic structures are then given for other main groups (**3'**, **4** and **5**). Throughout this chapter, unless stated otherwise, X is always the first atom of group R^3. Opposite to the C—X bond is situated always the bond angle β. The shorter of the two CN bonds is labelled CN(s), and the longer one CN(l). The bond angle opposite to CN(s) is always designated γ and that opposite to CN(l) is always designated α.

Other problems while considering variously substituted amidines **3** and their salts **3'** are to what extent the structural parameters of the amidine skeleton depend upon one another and how they are influenced by substituent effects. Both these problems will be treated before any more detailed analysis. Similar problems arise for compounds of groups **4** and **5**, but since these groups are much less numerous (cf. Table 1) statistical conclusions which may be drawn for them are much less significant. Nevertheless, when justified, these data will also be taken into consideration. It must be remembered that throughout the chapter most often the mean geometry parameters are considered and the data for classes or subclasses are averaged values, except in cases when individual compounds are shown as examples for important structural patterns.

II. ANALYSIS OF AMIDINE AND AMIDINIUM CATION DERIVATIVES (3 + 3' GROUP)

Before presenting a more detailed analysis of structural parameters of the subgroups included in groups (3 + 3') we give the results of the analysis for the whole group (3 + 3') and make some methodological remarks. We should be aware of the fact that the really fixed part of the NC(X)N skeleton is only the amidine moiety NCN. The CX bond varies

more, but due to its key importance for the NCN group it is regarded as an important part of the skeleton under study.

A. Planarity of the NC(X)N Skeleton in Amidine Derivatives and their Salts

For a long time the NC(X)N skeleton has been regarded as being planar[6]. In order to check this hypothesis we have retrieved from the Cambridge Structural Database the whole sample consisting of 576 compounds included in the general structures **3** and **3'** with subsamples in which R^3 was NRR' (343 compounds), CR'R"R"' (146 compounds), SR (53 species), PR'R"R"' (8 compounds) and OR (11 compounds). These subsamples are labelled throughout this chapter 3(CN), 3(CC), 3(CS), 3(CP) and 3(CO), indicating in parentheses the kind of bond between the carbon atom of the amidine group and the X atom of group R^3 (Scheme 1 and Figure 2); the numeral 3 represents the numeral which defines the substituent in question, R^3 in this case. If salts are considered, these labels are marked by primes; e.g. 3(CN)' means a guanidinium salt $[N(R^1R^2)C(R^3)N(R^4R^5)]^+Anion^-$.

The three atoms N^1, N^2 and X define a plane as shown in Figure 2. In the special case when the NC(X)N is planar, the deviation Δ of the central C atom from the plane N^1N^2X is equal to zero ($\Delta = 0$) and the sum of all valence angles, SA, at the central C atom is equal to 360° ($SA = \alpha + \beta + \gamma = 360°$). Thus, for the whole group we have estimated mean values of Δ and SA and found them equal to: $\bar{\Delta} = 0.019$ Å with the sample variance 7.9×10^{-4} Å^2 and $\overline{SA} = 359.83°$ with the sample variance 1.17°^{2}. In order to check the hypothesis regarding the planarity of the N^1N^2XC skeleton we have to test two null hypotheses:

$$H_0: \ \bar{\Delta}^t = 0, \quad \text{against } H_1: \ \bar{\Delta}^t > 0,$$

and

$$H_0: \ \overline{SA^t} = 360°, \quad \text{against } H_1: \ \overline{SA^t} < 360°.$$

H_1 stands for the alternative hypothesis which we accept after rejecting the null hypothesis at a given significance level. The superscript t stands for the true value of a parameter, i.e. either Δ or SA for the whole population. We cannot study the whole population of all possible amidine and amidinium cation derivatives (**3** and **3'**) but only those for which the molecular structure has been determined, i.e. our groups with 576 entries. Even so, we try to draw conclusions about the whole population of amidine and amidinium cation derivatives by studying only this available sample group. That is why we have to apply tests for checking the above-mentioned hypotheses instead of directly by comparing Δ or $\overline{SA}$ values with 0 Å and 360°, respectively. (For details of applying statistics in structural studies cf. Reference 8.) Applying Student's t test at the significance level $\alpha = 0.05$, both hypotheses must be rejected. This means that, with the probability of error in 5% of the cases, we can accept an alternative hypothesis that the NC(X)N skeleton in **3** and **3'** is not planar. To show how frequently those nonplanar skeletons occur in comparison with those which are planar, Figures 3 and 4 show histograms of Δ and SA distributions for all structural data. It is worth mentioning that when applying statistical methods to obtain reliable scientific conclusions, there is a need to use as many data of the highest precision as possible[8]. If, however, we wish to recognize the nature of the distribution, it is better to use all possible data excluding only those which are methodologically incorrect. In Figures 3

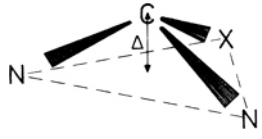


FIGURE 2. Definition of the N^1XN^2 plane with the functional carbon atom deviating from the plane by the distance Δ

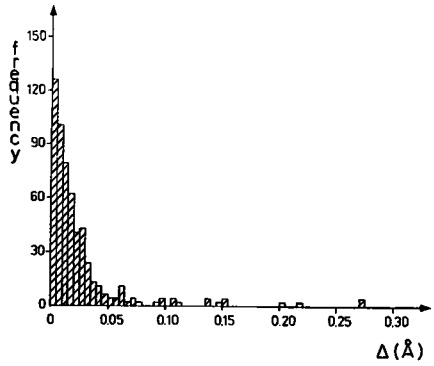


FIGURE 3. Frequency histogram of Δ for the (3 + 3′) group (i.e. amidine and amidinium cation derivatives) for all data irrespective of precision

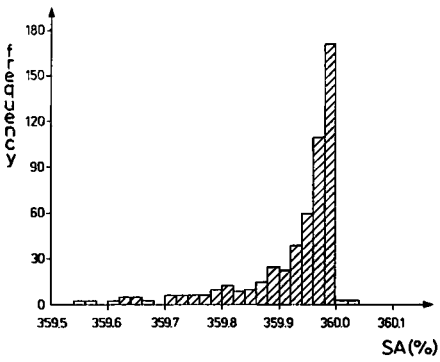


FIGURE 4. Frequency histogram of SA for the (3 + 3′) group; cf. Figure 3

and 4 we can observe distributions which are similar to the normal one (Gauss-type distribution). This may be easily checked by using proper statistical tests.

We can summarize that nonplanarity of the NC(X)N skeleton in amidine and amidinium salt derivatives is very slight, but statistically significant, and at least in some particular cases it should be taken into account while analyzing chemical or physicochemical (spectral !) properties of these systems. From the histograms (Figures 3 and 4) it is apparent that Δ is a more sensitive parameter in describing nonplanarity than SA and in the following analyses only Δ will be taken into consideration. When we consider the dependence of the planarity of the NC(X)N group on the nature of R^3 we find that for all but one (X = Cl) subsamples mentioned at the beginning of this section, the hypothesis of planarity can be rejected at $\alpha = 0.05$. This means that accepting the alternative hypothesis H_1 that the NC(X)N skeleton is not planar, we are in error in 5% or less cases. However, when we compare $\bar{\Delta}_i$ values of subsamples i with the mean nonplanarity parameter of the general sample, $\bar{\Delta}$, we can see that only one of the $\bar{\Delta}_i$ values is significantly greater than $\bar{\Delta}$ of

TABLE 2. Mean values of nonplanarity parameters Δ and SA and their significances at $\alpha = 0.05$ for various groups of amidine and amidinium cation derivatives[a]

Å	$\bar{\Delta}$ (Å)	Significance of deformation	$\overline{SA}$ (deg)	Significance of deformation
Total	0.019	+	359.83	+
CN	0.019	+	359.78	+
CC	0.018	+	359.84	–
CO	0.014	+	359.94	–
CP	0.047	+	359.63	+
CCl	0.011	–	359.95	–
CS	0.016	+	360.06	–
3	0.023	+	359.77	+
3'	0.014	+	359.94	–
4	0.016	+	359.92	–
5	0.013	+	359.95	–

[a]The + sign indicates a significant deformation from planarity.

the general sample. This takes place particularly for X = P. With R^3 representing in this case PR'R"R/A. It is seen more clearly by looking at the data of Table 2, where apart from the mean values of Δ and SA there are given also the results of testing the null hypotheses H_0: $\bar{\Delta}_i = 0$ or $\overline{SA}_i = 0$ (*i* enumerates the group or subgroups) at the significance level $\alpha = 0.05$. When the + sign appears in the "significance" column, we can reject H_0 and accept H_1, i.e. the nonplanarity of the NC(X)N skeleton. As we can see Δ is more sensitive than SA.

A significantly larger value of $\bar{\Delta}_i$ for the subsample with R^3 = PR'R"R"' and a still larger value of $\bar{\Delta}_i$ for SR' may be interpreted in a very simple way. In both these cases X (i.e. P or S) belong to the third period of the Periodic Table and their covalent radii are greater than those of atoms of the second period, i.e. C, N and O. The values are 1.04 Å and 1.10 Å for sulfur and phosphorus, respectively, while for oxygen, carbon and nitrogen they vary from 0.66 Å to 0.77 Å. The elongation of the CX bond for the derivatives of S and P gives the effect on Δ, as presented in Figure 5.

For a very strong deformation from planarity it may be expected that rather strong intermolecular interactions must occur. Let us consider as an example the crystal and molecular structure of guanidinium tricarbonatotrifluorothorate(IV)[9] for which Δ = 0.274 Å. All five guanidinium units of this system are involved in strong interactions with negatively charged oxygen atoms (of the carbonate anions), or fluoride anions. We should be aware that all of them are N—H···$A^{-\delta}$-type interactions with the shortest contacts N—H···$O^{-\delta}$ ranging from 2.79 Å and N—H···$F^{-\delta}$ ranging from 2.70 Å. So short contacts may imply rather strong N—H···$A^{-\delta}$ interactions which in turn may affect

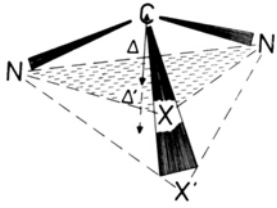


FIGURE 5. Comparison of NCN planes for mean geometries of (3 + 3') groups for the case of X from the second, and X' from the third row of the Periodic Table (e.g. X and X' may be considered as C and P atoms, respectively)

the planarity of the NC(X)N system. No deeper analysis on the energy of interactions may be given here since in the structure determinations of guanidinium tricarbonatrotrifluorothorate(IV)[9] the final results were given with very low precision and without giving the positions of the hydrogen atoms. Comparison of the above-mentioned $N—H\cdots A^{-\delta}$ contacts with standard H-bonding systems with the same constituents suggests relatively strong H-bond interactions.

It should be mentioned that the out-of-plane deformations of the NC(X)N skeleton cannot be observed in cases when the deformation forces give a resultant force close to zero. Nevertheless, it should be stressed that if in any individual case $\Delta > 3\sigma$ for a given sample or subsample (the values of σ(= esd) are given in the tables of this chapter), one should consider the possibility of relatively strong interactions in the crystal lattice. Very low force constants[2,3] for out-of-plane deformations should also be taken into consideration.

In general, it can be concluded that for individual cases or for smaller subsamples as well as for subsamples **3** or **3'** we should always be aware of the fact that the amidine skeleton may be slightly but significantly deformed from planarity.

B. Substituent Effects on Structural Parameters of the Amidine Skeleton

When six structural parameters of the amidine group, CN(s), CN(l), CX (if, in the assignment CX, there is no superscript it means that we deal with CX^3) and α, β, γ, are exposed to substituent effects which can come from various substituents, R^1, R^2, R^3, R^4 and even R^5, one may expect a very complex picture. And indeed it is so, since not only various electronic substituent effects may act, but also direct steric effects of bulky substituents in too close a neighborhood may affect the geometry of the amidine skeleton. In order to simplify the situation we apply first the principal component analysis to the set of six structural parameters of the sample built up of 576 species retrieved from the CSD.

C. Principal Component Analysis Applied to CN(s), CN(l), CX^3, α, β and γ

When many factors operating in a quantitatively unknown way affect the experimental data, it is convenient to use the principal component analysis[10]. This method relies on a simple mathematical procedure which reduces the multidimensional space built up upon not necessarily independent vectors, into the lowest number of linearly independent orthogonal vectors which reproduce the initial data set with the required precision. For details of this technique and for its particular application in chemistry, see reference 10. When this technique was applied to the full data matrix with structural parameters CN(s), CN(1), CX, α, β and γ retrieved for 576 amidines of the groups **3** and **3'**, the results shown in Table 3 were obtained. This table contains a number of factors (or components) with their weights, i.e. percent of explanation of the total variance of the structural parameters analyzed.

In order to understand better the information obtained by using principal component analysis let us recall what variance means. Each set of numerical data $x_1, x_2, \ldots, x_n$ may be characterized by the mean value:

$$\bar{x} = (1/n)\left(\sum_{i=1}^{n} x_i\right)$$

The dispersion of x_i around $\bar{x}$, however, may be differentiated. A numerical description of this dispersion is given by the variance:

$$\mathrm{var}(x) = \left[\sum_{i=1}^{n} (x - x_i)^2/(n-1)\right]^{1/2}$$

TABLE 3. Factors needed to reproduce the total variance of the initial set of structural data CN(l), CN(s), CX, α, β and γ for amidines and amidinium cations in their derivatives (3 and 3' groups)

Factor number[a]	Percent of explanation of the total variance by factors in subgroups of 3 + 3'					
	Total	CN	CC	CS	CP	CO
1	29.4	37.6	32.5	45.6	64.5	71.4
2	27.2	27.5	27.6	29.1	27.6	14.6
3	18.3	21.0	17.3	10.7	5.1	9.6
4	14.2	8.5	16.7	10.0	2.4	2.6
5	10.5	5.0	5.7	4.5	0.4	1.8
6	0.4	0.5	0.2	0.1	0.0	0.0

[a]Factors are ordered according to their decreasing magnitudes.

Thus the variation of a given property among n elemental sets of systems is described by variance. If we assume that this property depends on many various causes ('factors'), then each of them may describe only some part of the total variance. The first factor may describe, say, 30% of the total variance. Then, the next one may describe another part, say 20% of that part which was not explained by the first factor. Principal component analysis gives the numerical forms of factors which if all of them are used, reproduce exactly the initial set of data, i.e. describe the whole variance for these data. However, each factor represents another weight in reproducing the initial data set, or each factor explains another percentage of the total variance.

What is the chemical content of these data? First of all, the sixth factor has always been close to zero, never greater than 1%. This is an obvious consequence of the constraint that $\alpha + \beta + \gamma = 360°$. Even if the NC(X)N system is not fully planar, deviations from planarity are rather small (the mean value of $\alpha + \beta + \gamma$ is 359.83). Thus, only five structural parameters may be treated as fully geometrically independent. Indeed, when the whole sample (3 + 3') is taken into consideration five factors are necessary to explain more than 95% (99.6% in this case) of the total variance (as shown in the second column of Table 3). A very similar situation is observed for subsamples CN, CC and CS. However, quite different situation is found for the CP and CO subsamples for which only three factors are necessary to explain > 95% of the total variance (97.2% and 95.6%, respectively). This is a distinct difference, but may be the result of the set of data being too small in these two groups, $n = 8$ and 11, respectively. In such cases conclusions should be drawn only with great care. Another possible reason for the above-described situation may be that these two groups constitute, perhaps by chance, a more homogeneous set of data. Chemically this can be understood, since intramolecular interactions present in molecules belonging to these two group are more concerted, i.e. more strongly correlated one to another. In general, however, the result that so many factors must be applied to reproduce the six structural parameters exposed to the nonhomogeneous substituent effect means that the mutual interactions between the structural parameters of the amidine skeleton are rather weakly intercorrelated. In other words, the amidine skeleton does not follow readily concerted structural changes as a result of variations in interactions in the structure comprising the NCN(X) skeleton.

D. Analysis of the Mean Values of the Structural Parameters in the Amidine Skeleton Affected by Substituent Effects

It results from the former section that structural parameters describing variations of geometry in the amidine skeleton affected by substituent effects are rather weakly

interrelated. However, in subsamples which exhibit some structural similarity they cannot be excluded. For limited and rather homogeneous samples it was found, for example, that there exists quite a good linear dependence between CN(s) and CN(l)[11]. In both cases the slope observed was negative and it could be interpreted[11] as a compensation in bond-length changes due to π-electron delocalization.

Before we try to analyze the interrelation between structural parameters generally called P_j; namely CN(s), CN(l), CX, α, β and γ (cf. labelling in Figure 1), we will first consider mean values of these parameters in groups of compounds containing different substituents at the functional carbon. Table 4 presents the mean values of structural parameters P_j, their variances var(P) and estimated standard deviations, esd(P). Then the minimal P(min) and the maximal P(max) values of the parameters are also shown. Under the label of the sample (or subsample) in the parentheses the number of compounds included in this calculation is given. Additionally, in the last column on the right the values of the planarity parameters Δ are given.

Since the amidine skeleton of compounds **3** + **3'** contains two fixed bonds, CN(l) and CN(s), while CX is being varied, the analysis of this group must be carried out according to a division dependent on the type of the link C—X[3]. Table 4 shows these subgroups by indicating in the first column the type of the C—X[3] bond.

Data are presented first for the total sample of **3** + **3'** structures and then in three versions each for X = N (guanidine derivatives) and X = C in order to check the hypothesis regarding the dependence of the mean structural and statistical parameters on the quality of data. In these two cases (CN and CC) data are given first for the whole subsample. Then for two sets of differing precision: (a) for the subsample in which the precision of the data is the highest, in which the reliability factor $R \leqslant 0.035$; and (b) for the subsample with $R \leqslant 0.05$. For less numerous samples with X = S, Cl and P no such divisions are made, and only the whole group was analyzed.

Table 5 presents the results of the statistical analysis of the significance or insignificance in the differences between the two parameters in question. This information is chemically important—we may decide in which cases the parameters differ as a result of almost random action of the substituent effect on them.

TABLE 4. Structural and statistical data for amidine and amidinium cation derivatives. Differentiation of the sample is at C—X[3] bond. All other substituents R[1], R[2], R[4] and R[5] (if present) are unrestricted. Formamidine derivatives are included in the total sample, but are considered separately in Table 9

Type of subsample (number of entires)	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Total	$\bar{P}$	1.306	1.341	1.436	120.21	121.03	118.60	0.019
(576)	var (P)	0.0010	0.0007	0.0229	17.5	18.0	17.1	0.0008
	esd(P)	0.033	0.031	0.151	4.2	4.2	4.1	0.028
	P(min)	1.103	1.158	0.938	89.19	103.37	97.14	0.000
	P(max)	1.476	1.481	1.938	140.19	136.50	137.81	0.274
CN[a]	$\bar{P}$	1.307	1.333	1.355	120.06	121.34	118.38	0.019
(343)	var(P)	0.0012	0.0006	0.0011	10.7	13.0	13.2	0.0009
	esd(P)	0.035	0.025	0.033	3.3	3.6	3.6	0.030
	P(min)	1.103	1.158	1.252	106.85	110.78	105.23	0.000
	P(max)	1.423	1.442	1.499	135.84	136.50	128.12	0.274

TABLE 4. (*continued*)

Type of subsample (number of entries)	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
CN[a]	$\bar{P}$	1.316	1.331	1.349	119.76	121.52	118.65	0.011
(114)	var(*P*)	0.0002	0.0002	0.0007	8.4	12.7	10.7	0.0001
	esd(*P*)	0.015	0.015	0.027	2.9	3.6	3.3	0.010
$R < 0.05$	*P*(min)	1.263	1.295	1.308	112.43	113.33	110.33	0.000
	P(max)	1.381	1.381	1.484	130.37	136.50	125.94	0.037
CN[a]	$\bar{P}$	1.314	1.329	1.343	120.21	120.70	119.06	0.010
(41)	var(*P*)	0.0003	0.0002	0.0006	5.7	5.2	9.9	0.0001
	esd(*P*)	0.016	0.014	0.024	2.4	2.3	3.1	0.010
$R < 0.035$	*P*(min)	1.263	1.302	1.314	115.89	117.12	110.33	0.000
	P(max)	1.336	1.381	1.416	128.54	128.23	125.93	0.035
CC[a]	$\bar{P}$	1.302	1.353	1.492	119.88	121.03	118.93	0.018
(146)	var(*P*)	0.0009	0.0014	0.0016	27.6	19.8	17.2	0.0007
	esd(*P*)	0.030	0.037	0.040	5.3	4.5	4.1	0.027
	P(min)	1.252	1.266	1.354	89.19	103.37	103.35	0.000
	P(max)	1.476	1.481	1.734	133.19	131.90	137.81	0.274
CC[a]	$\bar{P}$	1.298	1.350	1.486	119.41	122.23	118.33	0.014
(81)	var(*P*)	0.0003	0.0008	0.0005	18.7	12.5	13.1	0.0002
	esd(*P*)	0.018	0.029	0.023	4.3	3.5	3.6	0.013
$R < 0.05$	*P*(min)	1.252	1.306	1.394	108.68	108.67	103.35	0.000
	P(max)	1.352	1.447	1.551	133.19	131.90	128.63	0.059
CC[a]	$\bar{P}$	1.301	1.336	1.492	119.70	121.61	118.53	0.015
(13)	var(*P*)	0.0004	0.0004	0.0001	5.1	15.3	6.3	0.0003
	esd(*P*)	0.019	0.020	0.009	2.3	3.9	2.5	0.016
$R < 0.035$	*P*(min)	1.274	1.306	1.482	115.77	109.58	116.46	0.000
	P(max)	1.352	1.364	1.514	124.40	124.98	126.01	0.059
CS	$\bar{P}$	1.302	1.355	1.765	121.38	120.65	118.03	0.016
(53)	var(*P*)	0.0005	0.0013	0.0016	27.6	26.1	33.2	0.0012
	esd(*P*)	0.021	0.036	0.039	5.3	5.1	5.8	0.011
	P(min)	1.235	1.297	1.659	110.23	108.64	97.14	0.000
	P(max)	1.349	1.472	1.862	140.89	132.39	125.92	0.051
CO	$\bar{P}$	1.321	1.348	1.291	123.25	120.27	116.42	0.014
(11)	var(*P*)	0.0008	0.0015	0.0032	16.4	28.2	8.8	0.0002
	esd(*P*)	0.029	0.039	0.056	4.1	5.3	3.0	0.013
	P(min)	1.285	1.300	1.213	114.80	110.58	112.70	0.000
	P(max)	1.378	1.430	1.383	131.77	126.51	122.34	0.037
CP	$\bar{P}$	1.324	1.337	1.858	119.21	119.70	120.71	0.047
(8)	var(*P*)	0.0001	0.0002	0.0017	8.3	2.7	17.5	0.0005
	esd(*P*)	0.011	0.014	0.041	2.9	1.7	4.2	0.022
	P(min)	1.303	1.308	1.791	115.79	117.07	112.73	0.016
	P(max)	1.337	1.354	1.890	124.57	122.15	126.38	0.092
CCl	$\bar{P}$	1.300	1.330	1.724	119.97	120.85	119.12	0.11
(8)	var(*P*)	0.0002	0.0002	0.0002	5.8	3.9	10.4	0.0002
	esd(*P*)	0.015	0.032	0.015	2.4	2.0	3.2	0.014
	P(min)	1.282	1.313	1.703	117.06	119.07	115.25	0.002
	P(max)	1.317	1.355	1.744	123.60	125.02	122.72	0.043

[a]For the differences between the three different CN and three different CC subsamples, see text.

TABLE 5. Statistical analysis of differences between the mean values of structural parameters $\bar{P}_j$ [CN(l), CN(s), CX, α, β and γ]. The sample includes both **3** (amidines) and **3'** (amidinium cations). Full subsamples are taken into account (irrespective of precision). Assignments of subgroups are as in Table 4. The significant differences are assigned the sign of inequality and insignificant differences by the sign of approximate equality $\cong$

CN(s)	CCl	$\cong$	CS	$\cong$	CC	$\cong$	CN	$<$	CO	$\cong$ CP
CN(l)	CCl	$\cong$	CN	$\cong$	CP	$\cong$	CO	$\cong$	CS	$\cong$ CC
CX	CO	$<$	CN	$<$	CC	$<$	CCl	$<$	CS	$<$ CP
α	CP	$\cong$	CC	$\cong$	CCl	$\cong$	CN	$<$	CS	$\cong$ CO
β	CP	$\cong$	CO	$\cong$	CS	$\cong$	CCl	$\cong$	CC	$\cong$ CN
γ	CO	$\cong$	CS	$\cong$	CN	$\cong$	CC	$\cong$	CCl	$\cong$ CP

The mean values of a given structural parameter, say $\bar{P}_i$ [e.g. in Table 5 in the first row $\bar{P}_i$ = CN(s)] are ordered in a sequence according to increasing magnitudes. Then, the analysis carried out is based on the application of Student's t test to verify the null hypothesis H_0, when two parameters $\bar{P}_j$ and $\bar{P}_i$ are equal, i.e. H_0: $\bar{P}_j = \bar{P}_i$, against the alternative hypothesis H_1: $P_j \neq P_i$. It is carried out in the following way. The t statistics is defined as:

$$t = (\bar{P}_j - \bar{P}_i)/[(1/N_i - 1/N_j)(N_j s_j^2 + N_i s_i^2)/(N_j + N_i - 2)]^{1/2} \quad (1)$$

where $\bar{P}_j$ and $\bar{P}_i$ denote the mean values for a given structural parameter in subsamples j and i, while s_j^2 and s_i^2 denote the subsample variances; N_j and N_i are the numbers of data points in these subsamples. This test works even when the assumption, that variances of both subsamples are different, is true. For each pair of $\bar{P}_j$ and $\bar{P}_i$, of which we want to know if the difference $(\bar{P}_j - \bar{P}_i)$ is significantly different from zero, we compare the value of t for our pair with the value $t_{\alpha,f}$ taken from the statistical tables[12] at a given significance level (called α) and for a given degree of freedom f. Usually, we accept $\alpha = 0.05$ and this means that when we reject the null hypothesis at $\alpha = 0.05$ we may be in error in 5 out of 100 cases. In such an event we may accept the alternative hypothesis, i.e. that $\bar{P}_i \neq \bar{P}_j$ at this probability is in error.

Both Tables 4 and 5 contain a great deal of chemical information. Anybody interested in the differences between structural parameters P_j in variously substituted NC(X)N systems (containing both **3** and **3'**), may find in Table 4 the relevant number for the mean value of a given subsample and compare it with the value for another subsample. The differences between the mean values of parameters within a given subsample may also be found from Table 4, which makes it possible to test the hypothesis about the equality of two bond lengths or two bond angles in question. Let us consider an example to illustrate how to utilize the contents of Table 4. Two CN bonds in groups (**3**, **3'**) differ from one another. The shorter CN(s) has mean length 1.307 Å, whereas the longer CN(l) has mean length 1.333 Å. The difference is evident and amounts to 0.026 Å. Is it statistically significant? To answer this question we assume the null hypothesis, that for this case these bonds are of equal length, H_0: R[CN(s)] = R[CN(l)] and calculate the Student's t value following equation 1. Taking the values of variances for these two bonds from Table 4, 1.23×10^{-3} and 0.61×10^{-3} Å^2, we obtain $|t| = 10.830$. Comparison with the $t_{\alpha,f} = t_{0.05,324} = 1.967$ value from the statistical table at the significance level $\alpha = 0.05$ for $326 - 2 = 324$ degrees of freedom allows us to conclude that we have to reject this null hypothesis. However, accepting the alternative hypothesis, namely, that the lengths of bonds CN(s) and CN(l) are significantly different, we are in error only in 5 out of 100 cases. The same can be done for any two parameters, P_j and P_i, which we wish to compare.

Another, alternative way of estimating the significance of the difference between two structural parameters (or their mean values) in question is applying the so-called 3σ rule. This rule, very popular among crystallographers, states (and this results from the statistical properties of a normal distribution[7]) that if the difference between two structural parameters P_i and P_j is greater than the threefold value of the estimated standard deviation of these two parameters, then the difference is statistically significant at $\alpha = 0.0027$ (0.27%), and we are in error in 0.27% of cases. How to use this rule? Let us consider once again the example with the bond lengths CN(l) and CN(s). The difference is $(1.333 - 1.307)\text{Å} = 0.026\,\text{Å}$. The value of the estimated standard deviation for the difference is

$$\{[\sigma^2(\text{CN(l)})]^2 + [\sigma(\text{CN(s)})]^2\}^{1/2} = \{\text{var}[\text{CN(l)}] + \text{var}[\text{CN(s)}]\}^{1/2} = 0.043.$$

However, in the case when we do not compare two individual data but two mean values, the formula for the estimated standard deviation of the mean values has to be divided by $n^{1/2}$. Thus, we have to divide 0.043 by $(326)^{1/2}$ and obtain 0.0023. Dividing 0.026 by 0.0023 we end up with $10.92 > 3$. So we can reject the hypothesis (at $\alpha = 0.0027$) that the lengths of CN(s) and CN(l) are equal. The conclusion is in line with the former one. It should be stressed strongly here that when we apply statistical tests to verify hypotheses, we should always apply the same level of significance, α. Otherwise, we may assign various weights to conclusions drawn from various experiments or sets of experiments.

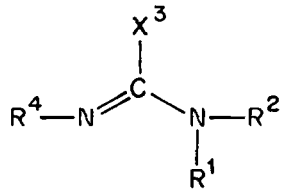
We must return to the problem of drawing conclusions from the sets of data. By increasing the precision, the data become less numerous and the distribution becomes more difficult to correctly characterize. However, the mean values of structural parameters do not change much when coming from larger sets of less precise data or from smaller sets of more precise data. This is well illustrated (Table 4) by the data for subsamples CN(3, 3′) and CC(3, 3′) each considered in three versions: as the whole subsample, as precise data ($R \leqslant 0.05$) and as very precise data ($R \leqslant 0.035$). This conclusion is worth remembering and can be applied in all cases except in those when data strongly deviating from the standard precision are present in the data set.

Table 5 presents the mean values $\bar{P}_j$ of the structural parameters, where $\bar{P}_j$ stands for $\overline{\text{CN(s)}}$, $\overline{\text{CN(l)}}$, $\overline{\text{CX}}$, $\bar{\alpha}$, $\bar{\beta}$ and $\bar{\gamma}$. For each subsample NC(X)N with X = C, N, S, Cl, H, P, O these parameters are arranged in the order of increasing value of the parameter. If two adjacent parameters in a row, P_i and P_j, differ one from another in a significant way, which was checked by the use of Student's t test at the significance level $\alpha = 0.05$, then we put between these two parameters the sign of inequality, $P_i < P_j$. When the above-mentioned difference is insignificant, then we indicate this situation as $P_i \cong P_j$, which may either mean that $\bar{P}_i = \bar{P}_j$ exactly or $\bar{P}_i$ is less than $\bar{P}_j$ but in a statistically insignificant way. Thus, the structural parameters on the left side of this relationship are almost always smaller than those on the right side, but only sometimes are they smaller in a significant way. Let us consider as an example the first row of Table 5, showing the relative magnitudes of the bond lengths for CN(s) in the six subsamples. The CN(s) bond length is insignificantly shorter for subsample NC(Cl)N than for NC(S)N, and the latter is insignificantly smaller for NC(S)N than for NC(C)N and so on. The only sharp inequality is between CN and CO, the latter being significantly larger. Finally, it may be monitoned that the CN(s) bond is the longest for the NC(P)N group, but this is only insignificantly longer than the CN(s) bond in the NC(O)N subsample. The total difference between the shortest CN(s) and the longest one is 0.026 Å. Interestingly for the CN(l) bond lengths the sequence is reversed (except for the CCl subgroup). In the third row of Table 5, the covalent radii of X_3 equal to O, N, C, Cl, S and P increase very distinctly in the sequence, and hence in this row all differences are statistically significant.

Considering the variations of the $\bar{\alpha}$, $\bar{\beta}$ and $\bar{\gamma}$ values (Table 4) we observe that $\bar{\gamma}$ is the smallest (118.60°) in comparison to $\bar{\beta} = 121.03°$ and $\bar{\alpha} = 120.21°$. The variances for all three angles are comparable[2], between $17.1°^2$ and $18.0°^2$, and the values of esd are rather large, about 4.2°. Hence, no significant conclusion can be drawn from these differences. Moreover the sequences of increase for $\bar{\alpha}$, $\bar{\beta}$ and $\bar{\gamma}$ are also not conclusive in these series, and except for the CN < CS case, the inequalities are not sharp and not significant statistically. The opposite directions in the sequence of the $\bar{\alpha}$ and $\bar{\gamma}$ angles may also be mentioned.

E. Analysis of Interrelations Between Structural Parameters in Amidine Derivatives with Varying X^3

In the previous section we presented mean geometries and a simple statistical analysis of structural parameters compared between subsamples (Tables 4 and 5). This, however, does not help one to understand the dependences between them while varying substituents R^1 through R^4 (R^5 for the 3′ group). In this section we will try to relate structural parameters within subsamples which are selected, as formerly, by dividing the material according to the C—X^3 link, as in the structure below:



R^1, R^2 and R^4 are unrestricted.

1. *Group with X^3 = N (guanidine derivatives)*

The mean geometry of the amidine moiety for this group is given in Figure 6. The main feature distinguishing the geometry of this subgroup from the others is the relatively small differentiation between CN(s), CN(l) and CX, even though the differences between them are significant. An interesting fact is that an increase in a bond length opposite a bond angle implies an increase in this angle. For the series of CN bond lengths 1.307 Å, 1.333 Å and 1.355 Å the opposite bond angles increase to the values 118.38°, 120.06° and 121.30°, respectively.

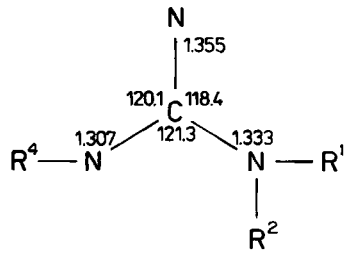


FIGURE 6. Mean geometry of the amidine moiety of guanidine and guanidinium cation derivatives

Table 4 shows that the data for all three groups: the whole sample (343 entries), the sample with $R \leqslant 0.035$ (41 entries) and the sample with $R \leqslant 0.05$ (114 entries), all give equivalent results. The mean values of the structural parameters are similar and, even if they differ from each other in the three precision-dependent subsamples, the differences are small and statistically insignificant (at $\alpha = 0.05$). Hence the analysis of interrelations between structural parameters was carried out for the whole set of 343 entries. It must be said that no chemically important and conclusive interrelations of the type have been found for P_i and P_j, being either bond lengths or bond angles. The same was found for analysis of mixed structural parameters, when either P_i or P_j was bond length while the other was bond angle. The following problem may arise: if the substituents R^1, R^2 (R^3), R^4 and R^5 vary in a random way, why should the structural parameters follow any regularity? This is even further corroborated by the fact that factor analysis gives in this case the following weights of subsequent, fully independent factors: 29.4, 27.2, 18.3, 14.2, 10.5, 0.4. In order to avoid the complexity of mutual interactions affecting variations in structural parameters, we have undertaken another kind of analysis, looking for dependences between differences in structural parameters $\delta_{ij} = P_i - P_j$ plotted against another parameter P_k or one of the constituents of δ_{ij}:

$$P_i = aP_j + b \tag{2}$$

$$\delta_{ij} = a'P_k + b' \tag{3}$$

Thus we have found a few weak relationships, such as $\delta_{ij} = \mathrm{CN(l)} - \mathrm{CN(s)}$ plotted against CN(l). In this case the correlation coefficient was equal to 0.76, and for $\delta_{ij} = \mathrm{CN(l)} - \mathrm{CX}$ and $\delta_{ij} = \mathrm{CX} - \mathrm{CN(s)}$ vs CX the correlation coefficients r were -0.73 and 0.74, respectively. It seems that in these cases the variability of the constituents of δ_{ij} affects the δ_{ij} value sufficiently to find a relationship between these two parameters.

Thus in differences δ_{ij} might dominate the contributions resulting from the variations in CN(l) and CX, and hence the δ_{ij} values were found to depend on the CN(l) and CX values. This effect may be regarded as chiefly geometrical in nature.

Much higher dependences are found for δ_{ij} for bond angles. Quantity δ_{ij} is found to depend on P_i or P_j in all cases if either P_i or P_j is present in the difference defined, for example, $\alpha - \beta$ vs α or β, β-γ vs β or γ, etc. For all these cases $|r|$ is always greater than 0.8. Once again these relationships seem to illustrate geometrical constraints rather than electronic effects of substituents. Additionally, we should be aware of the constraint that $\alpha + \beta + \gamma \cong 360°$.

2. *Groups with* $X^3 = C$

The mean geometry of the NC(C)N skeleton is given in Figure 7. The main difference between this subsample and the previous one is that CN(s) is significantly shorter than CN(l) (at $\alpha = 0.05$). The difference is equal to 0.051 Å. This means that substitution of the amidine carbon by a substituent bound to the latter by a C atom causes stronger localization of the double bond in the amidine moiety. Again, opposite CN(s) is an angle with a smaller value (118.93°) than that opposite CN(l) (119.88).

Similarly, as in the case of guanidine derivatives, no strong regularities of the form of equation 2 could be observed for this group. In the analysis we have considered the data for the full sample (146 entries) even though it was found that the mean values of the structural parameters for this sample are not fully equivalent to those with more precisely measured subsamples. The picture observed is very similar to that for guanidine derivatives, for both equations 2 and 3. For equation 2 no dependence was found, with the correlation coefficient $|r| > 0.40$. However, better dependences are observed for equation 3, when the

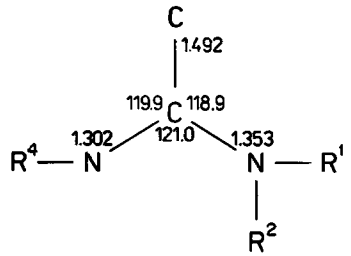


FIGURE 7. Mean geometry of the amidine skeleton of the (3 + 3') group with R^1, R^2 and R^3 unrestricted and $X^3 = C$

structural parameters are bond angles. This effect may be due to the constraint $\alpha + \beta + \gamma = 360°$ (or close to 360° when the NC(X)N atoms do not form an exact plane). Stronger linear dependences were found for equation 3. Correlation coefficients for plotting δ_{ij} vs P_j or P_i in the case of bond lengths attained the values -0.85, -0.80 and 0.86. For bond angles these coefficients were even better: 0.90, -0.84 and 0.85. Once again, geometrical effects should be taken as the main reason for these regularities. They may also be due to greater variability of the structural parameters for this group, compared to derivatives of guanidine. Simple comparison of variances for P_i values (cf. Table 4) shows that in almost all cases var_i for this group is greater than var_i for guanidines.

3. *Group with $X^3 = O$*

The mean geometry of the amidine skeleton for this group is given in Figure 8. The difference between CN(s) and CN(l) is significant and in the same range as for the derivatives of guanidine, whereas the C—O bond is surprisingly short. Angles α, β and γ differ from one another considerably. In this group α is much larger than γ ($\alpha = 123.25°$ and $\gamma = 116.42°$) in spite of the fact that CN(s) and CN(l) differ only slightly from one another (1.321 Å and 1.348 Å, respectively).

Only 11 entries belong to this group and hence no significant statistical study may be carried out. Nevertheless, it is interesting that for this small sample equation 2 is observed quite well. The lowest correlation coefficient $|r|$ observed for interrelations between bond

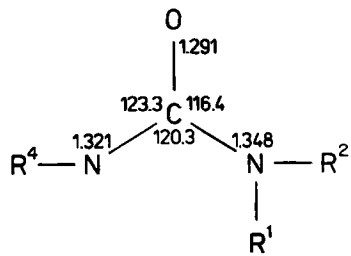


FIGURE 8. Mean geometry of the amidine skeleton of the (3 + 3') group with R^1, R^2 and R^3 unrestricted and $X^3 = O$

lengths was equal to 0.721, but those for bond angles were even worse. The angles NCN(β) plotted against the CN(l) bond lengths gave some weak regularity with a correlation coefficient $r = -0.867$, and similar plots against CN(s) and CO gave $r = 0.721$ and -0.805, respectively. The picture for the regression (equation 3) is better and similar to the previous case. It must be remembered, however, that interrelations in these groups, even if statistically significant, have very low predictive power. They may only indicate some trends in cooperative effects in the electron structure due to multiple and varied substitution in the amidine (or amidinium) moiety.

4. *Group with $X^3 = S$*

The mean geometry of this group is given in Figure 9. The most striking feature is the relatively great difference between CN(s) and CN(l): 0.053 Å. Again the relation $\alpha < \gamma$ exists, but to a lesser degree than for derivatives with $X^3 = O$, in spite of the large difference between Cn(s) and Cn(l).

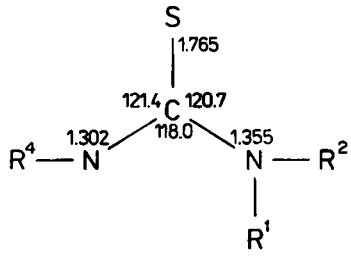


FIGURE 9. Mean geometry of the amidine skeleton of the (3 + 3′) group with R^1, R^2 and R^3 unrestricted and $X^3 = S$

5. *Groups with $X^3 = Cl$ and P*

These two groups are not numerous, each having only 8 entries. For Cl and particularly for P derivatives, there are rather small differences in the CN(s) and CN(l) bond lengths, as well as between α, β and γ. Moreover, the regularity $\alpha > \gamma$ is not observed for P derivatives. Due to small numbers of data in these three sets, these observations cannot be regarded as conclusive. Figure 10 presents the mean geometry of these two classes of compounds.

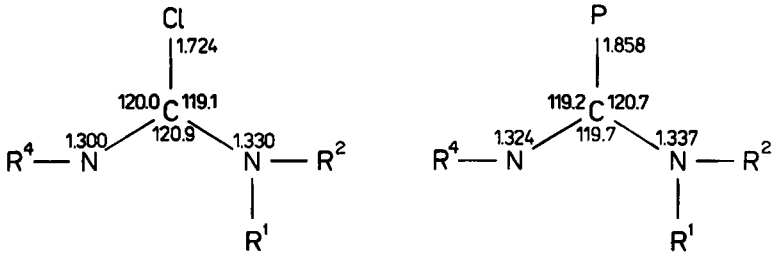


FIGURE 10. Mean geometry of the amidine skeleton of the (3 + 3′) group with R^1, R^2 and R^3 unrestricted and X^3 = Cl and P

F. Analysis of Other Subsamples Selected from the (3 + 3′) Group

1. Analysis of amidine derivatives with R^1, R^2 and R^3 unrestricted

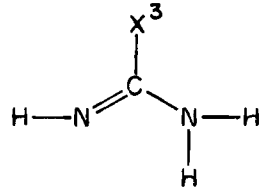
This sample contains 54 fragments and may be represented by the mean structure presented in Figure 11. Even a cursory examination of the group reveals interesting patterns: CN(s) ≪ CN(l), $\alpha \gg \gamma$ and $\beta < 120°$. These results are rather surprising. Table 6 contains all the structural and statistical data for the main group as well as for subgroups which may be drawn from the main group.

Table 7 presents the sequences of structural parameters ordered according to increasing value. In all cases the amidine skeleton NC(X)N is significantly deformed from planarity.

There are many possible selections of subsamples which may be derived from amidine and amidinium salt derivatives. We have selected a few of them in order to get more homogenous groups, and then within these groups we proceeded as previously. We use the same scheme of labelling as in Scheme 1 and Figure 1.

2. Analysis of systems with $X^1 = X^2 = X^4 = H$

The general structure for this group of amidine derivatives is shown below:



The total number of entries of this kind is 35, but in 30 of the cases $X^3 = N$. Figure 12 presents the mean geometry for these 30 guanidine derivatives. The most striking feature for this group is the quite small difference in the CN bond lengths. Table 8 contains all the structural data. An interesting finding is that, in the factor analysis of this subgroup, only three factors are necessary to reproduce 94.3% of the total variance (the explaining powers of factors being: for the first factor 61%, for the second one 20.2% and for the third one 13.1%). This must mean that within this group strong cooperative interactions operate. In other words, substitution at the functional carbon with no other substituents ($R^1 = R^2 = R^3 = H$) produces more concerted changes in the structural parameters than was

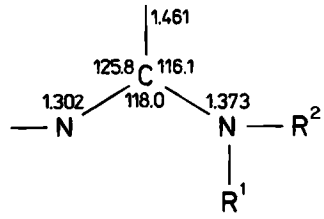


FIGURE 11. Mean geometry of the amidine skeleton of the (3 + 3′) group with R^1 and R^2 unrestricted

TABLE 6. Structural and statistical data for unrestricted amidine and amidinium cation derivatives

Type of subsample (number of entries)	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Total	$\bar{P}$	1.302	1.373	1.461	125.82	118.04	116.06	0.014
(54)	var(*P*)	0.0008	0.0031	0.029	28.1	17.6	18.7	0.0003
	esd(*P*)	0.028	0.055	0.170	5.3	4.2	4.3	0.017
	P(min)	1.235	1.273	1.037	116.25	110.93	91.74	0.000
	P(max)	1.355	1.484	1.827	140.19	128.07	121.18	0.101
$X^3 = C$	$\bar{P}$	1.288	1.370	1.501	124.74	118.14	117.07	0.014
(24)	var(*P*)	0.0004	0.0022	0.0005	8.1	5.4	2.5	0.0001
	esd(*P*)	0.020	0.047	0.022	2.9	2.3	1.6	0.010
	P(min)	1.252	1.295	1.473	119.48	111.31	91.74	0.000
	P(max)	1.329	1.481	1.559	132.01	122.31	120.36	0.038
$X^3 = N$	$\bar{P}$	1.322	1.414	1.331	129.17	114.97	115.84	0.009
(17)	var(*P*)	0.0005	0.0025	0.0004	35.2	23.9	9.4	0.0001
	esd(*P*)	0.023	0.050	0.021	5.9	4.9	3.1	0.008
	P(min)	1.272	1.337	1.305	116.25	110.93	110.33	0.000
	P(max)	1.350	1.484	1.379	136.50	125.07	119.12	0.023
$X^4 = C$	$\bar{P}$	1.291	1.369	1.435	125.15	119.79	114.89	0.018
(22)	var(*P*)	0.0007	0.0022	0.041	31.2	15.9	37.4	0.0006
	esd(*P*)	0.026	0.047	0.203	5.6	4.0	6.1	0.025
	P(min)	1.235	1.273	1.037	116.25	113.02	91.74	0.000
	P(max)	1.339	1.460	1.827	140.19	128.07	121.18	0.101
$X^3 = N$	$\bar{P}$	1.318	1.392	1.427	128.38	115.41	116.18	0.011
(16)	var(*P*)	0.0006	0.0046	0.216	35.7	20.7	8.47	0.0001
	esd(*P*)	0.025	0.068	0.147	6.0	4.5	2.9	0.008
	P(min)	1.270	1.295	1.305	120.32	110.93	110.94	0.002
	P(max)	1.350	1.484	1.734	136.50	122.31	120.08	0.027
$X^1 = C$	$\bar{P}$	1.303	1.355	1.487	124.58	119.02	116.27	0.015
(43)	var(*P*)	0.0007	0.0017	0.029	19.2	14.8	21.0	0.0003
	esd(*P*)	0.028	0.042	0.170	4.4	3.8	4.6	0.019
	P(min)	1.235	1.273	1.037	116.25	113.02	91.74	0.000
	P(max)	1.355	1.416	1.827	140.19	128.07	121.18	0.101

TABLE 7. Statistical analysis of differences between the mean values of structural parameters $\bar{P}_j$[CN(l), CN(s), CX, α, β and γ]. Analysis is carried out in sequence of a given *j*. The subsample consists of both **3** and **3'** species, i.e. both amidine and amidinium cation derivatives are taken into consideration. Full subsamples are taken into account (irrespectively of precision). The sequence for given parameters with significant differences is assigned by the sign of inequality <, and for insignificant differences by the sign of approximate equality ≅

CN(s)	$(X^3 = C)$	≅	$(X^4 = C)$	≅	Total	≅	$(X^1 = C)$	≅	$(X^4 = N)$	≅	$(X^3 = N)$
CN(l)	$(X^1 = C)$	≅	$(X^4 = C)$	≅	$(X^3 = C)$	≅	Total	≅	$(X^4 = N)$	≅	$(X^3 = N)$
CX	$(X^3 = N)$	<	$(X^4 = N)$	≅	$(X^4 = C)$	≅	Total	≅	$(X^1 = C)$	≅	$(X^3 = C)$
α	$(X^1 = C)$	≅	$(X^3 = C)$	≅	$(X^4 = C)$	≅	Total	≅	$(X^4 = N)$	≅	$(X^3 = N)$
β	$(X^3 = N)$	≅	$(X^4 = N)$	≅	Total	≅	$(X^3 = C)$	≅	$(X^1 = C)$	≅	$(X^4 = C)$
γ	$(X^4 = C)$	≅	$(X^3 = N)$	≅	Total	≅	$(X^4 = N)$	≅	$(X^1 = C)$	≅	$(X^3 = C)$

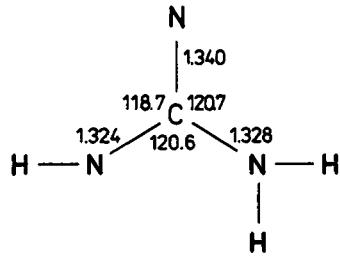


FIGURE 12. Mean geometry of the amidine skeleton of the (3 + 3') group with $R^1 = R^2 = R^4 = H$ and $X^3 = N$

TABLE 8. Structural and statistical data for amidine and amidinium cation derivatives with $X^1 = X^2 = X^4 = H$. The only variation is in the C—X^3 bond and this is taken as a base for differentiation of the sample

Type of subsample (number of entries)	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Total	$\bar{P}$	1.319	1.330	1.387	121.29	120.80	117.87	0.013
(35)	var(*P*)	0.0004	0.0005	0.018	11.1	4.2	12.4	0.0001
	esd(*P*)	0.021	0.022	0.13	3.3	2.1	3.5	0.010
	P(min)	1.268	1.279	1.309	117.00	117.72	109.46	0.002
	P(max)	1.342	1.389	1.794	130.37	125.33	121.78	0.028
$X^3 = N$	$\bar{P}$	1.324	1.328	1.340	120.71	120.56	118.69	0.014
(30)	var(*P*)	0.0002	0.0005	0.0016	7.9	3.7	6.8	0.0001
	esd(*P*)	0.015	0.023	0.040	2.8	1.9	2.6	0.010
	P(min)	1.288	1.279	1.309	117.00	116.72	111.13	0.002
	P(max)	1.342	1.897	1.524	130.37	125.09	121.78	0.028

observed for less homogeneous samples. The bond lengths CN(l) vs CN(s) exhibit a weak but statistically significant correlation (with $r = -0.610$). We should also note the very small differences between CN(l) and CN(s), which result from dimer formation in the crystal lattice. This is usually the case when, at the amine nitrogen, at least one of the substituents is H. This situation is presented in Figure 13. Due to dimer formation the π-electron delocalization in the amidine skeleton is enhanced in most cases in which, at one of the two nitrogen atoms, a hydrogen atom may serve as an H-donor. Some other interrelations have also been found to be statistically significant, but they are all without any predictive power and chemical value.

3. *Analysis of systems with $X^3 = H$ (formamidine derivatives)*

This group of structures is not numerous (17 entries), but it seems to be important. Table 9 contains structural data for this group. It is apparent that the differences between CN(l) and CN(s) are large and significant. Also, one of the bond angles is $\beta = 122.56°$, i.e. significantly greater than 120°. The full geometry is given in Figure 14.

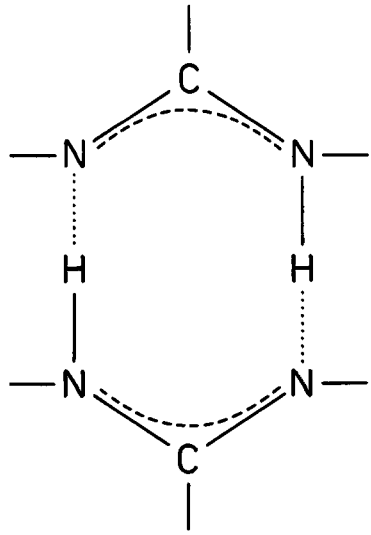


FIGURE 13. Scheme of π-electron delocalization in the NCN moiety for amidine derivatives forming dimers via H-bonds

TABLE 9. Structural and statistical data for formamidine and formamidinium cation derivatives with R^1, R^2 and R^4 unrestricted

Type of subsample number of entries)	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Formamidines	$\bar{P}$	1.289	1.340	0.977	117.85	122.56	119.31	0.015
17)	var(P)	0.0006	0.0016	0.0058	32.0	12.0	27.1	0.0008
	esd(P)	0.024	0.040	0.076	5.7	3.5	5.2	0.028
	P(min)	1.216	1.283	0.819	105.58	113.53	104.92	0.0
	P(max)	1.315	1.420	1.092	132.93	128.04	130.94	0.101

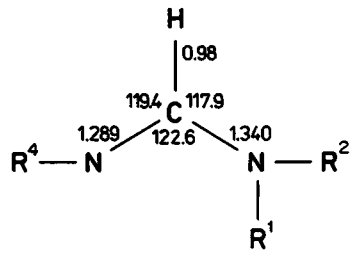


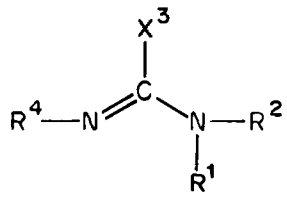
FIGURE 14. Mean geometry of the amidine skeleton for formamidine and formamidinium derivatives. X^3 = H, R^1, R^2 and R^4 unrestricted

The value of the variance for the β angle is the lowest among the three bond angles. This may be due to the fixed substituent $X^3 = H$. However, the fact is that $\beta > 120$ cannot be explained on the basis of the Walsh rule[13,3] since the electronegativity of H ($\kappa = 2.1$) is not much different from that for NR_2 (2.4 for NMe_2)[14]. The only reasonable explanation may be based on the repulsion between two rather bulky groups (=NR and NR_2).

The relationship between CN(l) and CN(s) is weak but significant. Factor analysis shows that, to explain about 95% of the total variance, four factors must be used (their weights are: 1st 40.6%, 2nd 26.7%, 3rd 15.7% and 4th 13.7%).

4. Analysis of systems with $X^4 \neq H$ and X^1 or $X^2 = H$

The general structure for these systems is given below:



R^1 or $R^2 = H$, $R^4 \neq H$.

Within this group one can select subsamples e.g., by taking $X^2 = C(n = 31)$, $X^3 = C(n = 12)$, $X^3 = N(n = 16)$ and $X^4 = C(n = 21)$. Table 10 contains structural and statistical data for these subsamples as well as for the whole group. For all cases there are only small differences between the CN(l) and CN(s) bond lengths. Even more, differences between equivalent bonds for various subsamples are usually small as presented in Table 11. In spite of small differences between CN(s) and CN(l), the differences between α and γ are sometimes very considerable (for $X^3 = C$ and $X^3 = N$ these differences are 4.65° and 1.75°, respectively. The only sharp inequalities in this table are for CX bonds, which are easy to understand, due to the variation of X. The reason for the strong equalization of the CN(s) and CN(l) bond lengths lies in the possibility of dimer formation and in enhanced π-electron delocalization in the NCN fragment, as shown in Fig. 13.

The results of factor analysis show that in all these groups strong cooperative interactions exist, since the number of factors necessary to explain 95% of the variance is either four or, in two cases, only three. Table 12 contains the relevant data. This decrease of the number of independent factors necessary to explain the total variance of all six structural parameters may be associated with the finding that CN(l) $\cong$ CN(s). This, in turn, results from the fact that structures of this group exist in the crystal lattice mostly as dimers.

5. Analysis of amidine and amidinium derivatives substituted at imine nitrogen and functional carbon

This subsample was extracted from the (3 + 3') set of Scheme 1 for getting less complex interactions in the NC(X)N skeleton as a result of substitution. The substituents are

TABLE 10. Structural and statistical data for amidine and amidinium cation derivatives with R^1 or $R^2 = H$ and $R^3 \neq H$

Type of subsample (number of entries)	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Total	$\bar{P}$	1.330	1.324	1.465	118.61	123.22	118.09	0.018
(32)	var(*P*)	0.0014	0.0012	0.0210	22.6	17.4	16.7	0.0002
	esd(*P*)	0.037	0.034	0.145	4.8	4.2	4.1	0.014
	P(min)	1.273	1.272	1.302	110.33	114.83	109.35	0.0
	P(max)	1.400	1.381	1.839	128.63	132.39	126.64	0.059
$X^3 = C$	$\bar{P}$	1.327	1.328	1.488	120.93	122.64	116.28	0.028
(12)	var(*p*)	0.0026	0.0011	0.0008	22.3	6.9	10.45	0.0003
	esd(*P*)	0.051	0.034	0.027	4.7	2.6	3.2	0.016
	P(min)	1.273	1.272	1.436	115.00	117.89	109.35	0.0
	P(max)	1.400	1.368	1.527	128.63	127.70	120.30	0.059
$X^3 = N$	$\bar{P}$	1.329	1.331	1.365	117.90	122.41	119.65	0.011
(16)	var(*P*)	0.0009	0.0011	0.0017	20.0	21.7	21.1	0.0001
	esd(*P*)	0.030	0.033	0.041	4.5	4.7	4.6	0.010
	P(min)	1.275	1.272	1.328	110.33	114.83	112.28	0.0
	P(max)	1.382	1.381	1.460	128.18	130.93	126.64	0.035
$X^4 = C$	$\bar{P}$	1.327	1.322	1.455	118.01	123.18	118.76	0.017
(21)	var(*P*)	0.0009	0.0095	0.0260	21.9	21.8	19.9	0.0001
	esd(*P*)	0.030	0.031	0.162	4.7	4.5	0.012	0.012
	P(min)	1.275	1.272	1.328	110.33	116.95	112.28	0.0
	P(max)	1.382	1.381	1.839	126.73	132.39	126.64	0.042
$X^2 = C$	$\bar{P}$	1.322	1.331	1.468	118.57	123.21	118.14	0.016
(31)	var(*P*)	0.0014	0.0011	0.0214	23.4	18.8	17.1	0.0001
	esd(*P*)	0.037	0.033	0.146	4.8	4.2	4.1	0.012
	P(min)	1.273	1.272	1.328	110.33	114.83	109.35	0.0
	P(max)	1.400	1.381	1.839	128.63	132.39	126.64	0.059

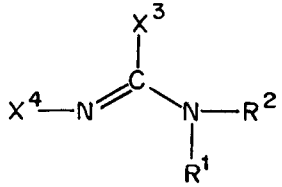
TABLE 11. Statistical analysis of the differences between the mean values of structural parameters $\bar{P}_j$[CN(l), CN(s), CX, α, β and γ] for amidine and amidinium cation derivatives with R^1 or $R^2 = H$ and $R^3 \neq H$. The sequence for a given parameter with significant differences is assigned by the sign of inequality <, whereas for insignificant differences by the sign of approximate equality ≅

CN(s)	$(X^2 = C) \cong (X^4 = C) \cong (X^3 = C) \cong (X^3 = N) \cong$ Total
CN(1)	$(X^4 = C) \cong$ Total $\cong (X^3 = C) \cong (X^3 = N) \cong (X^2 = C)$
CX	$(X^4 = C) < (X^3 = N) \cong$ Total $\cong (X^2 = C) \cong (X^3 = C)$
α	$(X^3 = N) \cong (X^4 = C) \cong (X^2 = C) \cong$ Total $\cong (X^3 = C)$
β	$(X^3 = N) \cong (X^3 = C) \cong (X^4 = C) \cong (X^2 = C) \cong$ Total
γ	$(X^3 = C) \cong$ Total $\cong (X^2 = C) \cong (X^4 = C) \cong (X^3 = N)$

TABLE 12. Results of factor analysis for amidine and amidinium cation derivatives

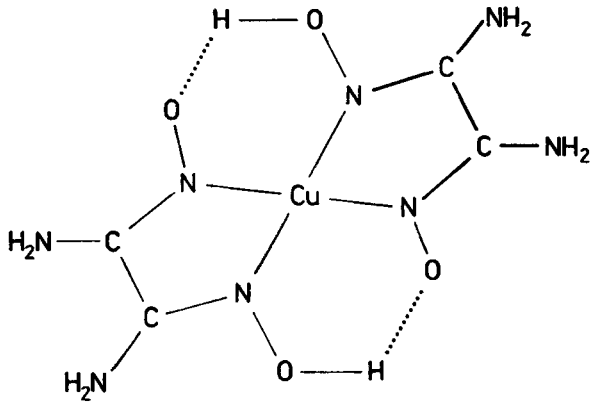
Factor number	Total	$X^3=C$	$X^3=N$	$X^4=C$	$X^2=C$
1	44.8	39.8	52.2	50.0	44.7
2	28.8	36.0	38.7	35.7	28.9
3	16.3	16.4	4.6	9.8	16.2
4	8.5	7.5	3.3	3.0	8.5
5	1.6	0.2	1.2	1.6	1.6
6	0.0	0.0	0.0	0.0	0.0

attached in this subsample only at the functional carbon and at the imine nitrogen, as shown below:



This subsample is quite numerous ($n = 53$) and its mean geometry (together with other statistical data) is given in Table 13. The table also includes data for five smaller subsamples in which X^3 is either N (34 entries) or C (13 entries) and those where X^4 is C (22 entries), N (14 entries) or O (12 entries).

The analysis of planarity gives the same results for the sample and for all smaller subsamples: H_0: $\Delta = 0$ has to be rejected at $\alpha = 0.05$. Since in this group and all its subgroups an N—H bond exists, all these compounds form dimers in crystals. As a result, CN(l) and CN(s) have very similar lengths, with small variances for both. The only exceptions are two subsamples: that with $X^3 = C$ and the other with $X^4 = O$, in which both CN(s) and CN(l) differ significantly. In these two groups the amidine group may be a part of a larger group and may be involved in strong interactions as with a complexation agent. Scheme 2 shows the structure of bis(oxamide oximato)copper(II)-oxamide oxime[15]. In this



SCHEME 2

TABLE 13. Structural and statistical data for amidine and amidinium cation derivatives substituted at imine nitrogen and functional carbon. Thus $R^1 = R^2 = H$, X^3 and X^4 are unrestricted

Type of subsamples	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Total	$\bar{P}$	1.317	1.339	1.418	119.64	121.08	119.21	0.014
(53)	var(*P*)	0.0013	0.0015	0.020	25.6	26.4	7.7	0.0002
	esd(*P*)	0.036	0.039	0.14	5.1	5.1	2.8	0.014
	P(min)	1.184	1.150	1.252	111.11	110.78	115.32	0.0
	P(max)	1.398	1.407	1.832	130.50	129.13	130.72	0.076
$X^3 = N$	$\bar{P}$	1.329	1.329	1.339	120.64	119.81	119.50	0.013
(34)	var(*P*)	0.0012	0.0019	0.0006	32.6	29.5	10.7	0.0002
	esd(*P*)	0.035	0.043	0.025	5.7	5.4	3.3	0.015
	P(min)	1.184	1.150	1.305	111.13	110.78	115.32	0.0
	P(max)	1.398	1.407	1.408	130.50	129.13	130.72	0.076
$X^3 = C$	$\bar{P}$	1.283	1.362	1.493	116.33	123.73	119.10	0.018
(13)	var(*P*)	0.0003	0.0005	0.0002	1.68	12.8	4.3	0.0004
	esd(*P*)	0.016	0.022	0.014	1.3	3.6	2.1	0.021
	P(min)	1.269	1.322	1.463	113.10	118.10	116.67	0.0
	P(max)	1.330	1.391	1.515	118.18	128.42	123.88	0.076
$X^4 = C$	$\bar{P}$	1.333	1.334	1.345	119.76	121.10	119.05	0.016
(22)	var(*P*)	0.0005	0.0004	0.0019	21.0	14.1	5.3	0.0003
	esd(*P*)	0.024	0.021	0.044	4.6	3.8	2.3	0.017
	P(min)	1.285	1.295	1.282	111.13	113.40	116.13	0.0
	P(max)	1.383	1.371	1.495	127.04	125.69	123.88	0.076
$X^4 = N$	$\bar{P}$	1.317	1.329	1.494	122.34	116.64	120.98	0.013
(14)	var(*P*)	0.0024	0.005	0.054	38.4	32.9	14.8	0.0002
	esd(*P*)	0.050	0.065	0.233	6.2	5.7	3.9	0.031
	P(min)	1.184	1.150	1.305	111.92	110.78	117.81	0.0
	P(max)	1.398	1.407	1.382	133.50	129.13	130.72	0.051
$X^4 = O$	$\bar{P}$	1.283	1.365	1.493	116.18	125.47	118.29	0.017
(12)	var(*P*)	0.0003	0.0004	0.0002	1.5	1.7	1.3	0.0001
	esd(*P*)	0.017	0.021	0.014	1.2	1.3	1.1	0.011
	P(min)	1.269	1.322	1.463	113.10	122.64	116.66	0.002
	P(max)	1.330	1.391	1.515	117.91	128.42	121.19	0.032

compound, as is clear from the scheme, the amidine skeleton (in bold lines) is involved in strong interactions with Cu(II) and contains links as mentioned previously. These strong interactions may be responsible for localizing the double bonds and hence causing a significant difference between CN(s) and CN(l).

The application of factor analysis to the data of the main sample and smaller subgroups mentioned above shows that, except in the subsample with $X^4 = O$, usually four or even five factors must be applied to explain 95% of the total variance for the three bonds and three bond angles taken into account. Thus, it seems that in this subsample the intercorrelations between structural parameters describing the NC(X)N skeleton are rather weak. And indeed, while correlating structural parameters according to equation 2, only in one case is $|r| > 0.84$, namely for the plot of bond angles NCR^3 vs NCN. This is not particularly strange considering the obvious constraint that the three bond angles sum up to almost 360° or slightly less.

6. Analysis of amidine and amidinium derivatives substituted at amine nitrogen

Another subsample which can be selected from the (3 + 3′) sample is the group of compounds in which substitution is at the amine nitrogen atom, as shown in Figure 15. One of the substituents at the amine nitrogen atom R^1 or R^2 is H. There are 42 entries of this group, from which two smaller subsamples with $X^2 = C$ ($n = 33$) and $X^2 = N$ ($n = 7$) may be selected. An important feature of this group is that both CN bonds are of almost equal length and, again, this results from the possibility of dimer formation in the crystal lattice. The differences in the CN bond lengths in the subgroup with $X^2 = N$ may result from the fact that the molecules of this group may form more complex H-bonding networks in which there is no reason for the equalization of the CN bonds.

Table 14 contains structural and statistical data for the group and both subgroups. Table 15 presents the sequence of increasing structural parameters for the amidine

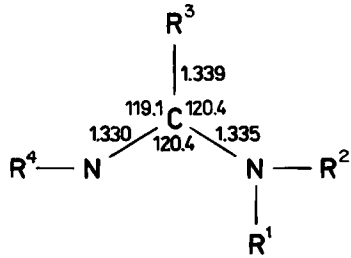


FIGURE 15. Mean geometry of the amidine skeleton of the (3 + 3′) group for derivatives with R^1, R^2 and R^4 unrestricted, but R^1 or R^2 must be H

TABLE 14. Structural and statistical data for amidine and amidinium cation derivatives with R^1 or $R^2 = H$; other substituents unrestricted. If $R^2 \neq H$ then two subsamples may be extracted

Type of subsample	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Total	$\bar{P}$	1.330	1.335	1.339	119.07	120.43	120.43	0.018
(42)	var(*P*)	0.0003	0.0003	0.0006	6.7	9.8	12.8	0.0001
	esd(*P*)	0.017	0.017	0.023	2.6	3.1	3.6	0.01
	P(min)	1.303	1.288	1.279	115.15	114.13	112.03	0.0
	P(max)	1.386	1.371	1.418	126.63	125.79	126.02	0.049
$X^2 = C$	$\bar{P}$	1.332	1.332	1.342	118.54	120.78	120.62	0.018
(33)	var(*P*)	0.0003	0.0003	0.0005	6.3	8.8	12.1	0.0001
	esd(*P*)	0.016	0.017	0.021	2.5	3.0	3.5	0.01
	P(min)	1.305	1.288	1.320	115.15	117.02	112.03	0.003
	P(max)	1.386	1.351	1.418	126.63	125.79	125.93	0.035
$X^2 = N$	$\bar{P}$	1.322	1.350	1.323	121.86	118.71	119.35	0.017
(7)	var(*P*)	0.0003	0.0002	0.0007	1.4	7.9	12.3	0.0003
	esd(*P*)	0.018	0.012	0.026	1.2	2.8	3.5	0.02
	P(min)	1.303	1.332	1.279	119.92	114.13	114.97	0.0
	P(max)	1.356	1.371	1.358	123.80	122.89	124.07	0.049

TABLE 15. Statistical analysis of differences between the mean values of structural parameters $\bar{P}_j$ [CN(l), CN(s), CX, α, β and γ] for amidine and amidinium cation derivatives with R^1 or $R^2 = H$; other substituents unrestricted. The sequence for a given parameter with significant differences is assigned by the sign of inequality $<$, and for insignificant differences by the sign of approximate equality $\cong$

CN(s)	$(X^2 = N) \cong X \cong (X^2 = C)$
CN(l)	$(X^2 = C) \cong X < (X^2 = N)$
CX	$(X^2 = N) \cong X \cong (X^2 = C)$
α	
β	$(X^2 = N) \cong X \cong (X^2 = C)$
γ	$(X^2 = N) \cong X \cong (X^2 = C)$

skeleton. The application of factor analysis leads to the conclusion that the subgroup with $X^2 = C$ needs five factors to describe 95% of the total variance, whereas the other subgroup with $X^2 = N$ needs only three factors for the same purpose. This may be interpreted as follows: $X^2 = N$ is a structural component which facilitates mutual interactions, since in this case all three atoms linked to the functional carbon of the amidine moiety are nitrogen atoms and have very similar electronegativities. This may decrease the number of independent factors affecting the geometry of the NC(X)N skeleton.

III. ANALYSIS OF AMIDINIUM SALT DERIVATIVES (3' GROUP)

The general scheme for this group and the labelling of the structural parameters is in principle the same as for the 3 group (Figure 1) provided there are attached two substituents R^4 and R^5 at the N^2 atom. Since in this group very often both CN bonds are of the same length, CN(s) and CN(l) are chosen randomly. If, however, one of them is shorter than the other, it is labelled as CN(s). All other assignments are as in the scheme for amidine derivatives (group 3). The mean geometry for the amidine skeleton is presented in Figure 16. The equalization of CN(s) and CN(l) observed in this group is due to the almost identical chemical state of both nitrogen atoms: both are trivalent and differences may be due only to the nature of the substituents, or even to the nature of interactions between NR^1R^2 and NR^4R^5 with the environment. This is a particularly important factor if $R^1 = R^2 = R^4 = R^5 = H$. Table 16 contains the structural and statistical data for the large group (234 entries) which was divided into four subsamples, differing in the nature

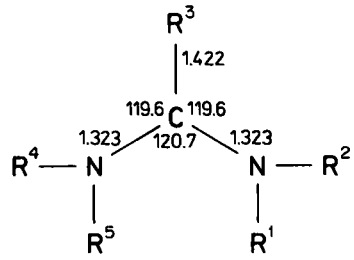


FIGURE 16. Mean geometry of the amidine skeleton of group 3' (amidinium cation derivatives)

TABLE 16. Structural and statistical data for amidinium cation derivatives (3′ group)

Type of subsample	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Total	$\bar{P}$	1.323	1.323	1.422	119.60	120.73	119.60	0.014
(234)	var(*P*)	0.0005	0.0005	0.0236	9.3	5.9	9.3	0.0002
	esd(*P*)	0.022	0.022	0.154	3.0	2.4	3.1	0.01
	P(min)	1.266	1.266	0.967	103.35	107.92	103.35	0.0
	P(max)	1.447	1.447	1.890	133.19	126.51	133.19	0.107
$X^3 = C$	$\bar{P}$	1.323	1.323	1.473	118.95	122.06	119.16	0.016
(54)	var(*P*)	0.0010	0.0010	0.0025	12.7	4.1	12.7	0.0036
	esd(*P*)	0.032	0.032	0.050	3.6	2.0	3.6	0.020
	P(min)	1.274	1.274	1.324	103.35	116.08	103.35	0.0
	P(max)	1.447	1.447	1.551	133.19	125.11	133.19	0.107
$X^3 = N$	$\bar{P}$	1.324	1.324	1.353	119.78	120.35	119.78	0.012
(146)	var(*P*)	0.0002	0.0002	0.0060	6.3	3.3	6.3	0.0001
	esd(*P*)	0.015	0.015	0.078	2.5	1.8	2.5	0.01
	P(min)	1.266	1.266	1.308	111.23	107.92	103.35	0.0
	P(max)	1.416	1.416	1.431	129.83	126.51	129.83	0.039
$X^3 = N$ $R^1 = R^2 = R^4$ $= R^5 = H$	$\bar{P}$	1.322	1.322	1.350	119.87	120.16	119.87	0.012
	var(*P*)	0.0002	0.0002	0.0063	6.1	3.1	6.1	0.0001
(102)	esd(*P*)	0.013	0.013	0.079	2.5	1.8	2.5	0.010
	P(min)	1.266	1.266	1.308	111.23	115.86	111.23	0.0
	P(max)	1.380	1.380	1.388	128.54	126.28	128.54	0.039
$X^3 = C$ $R^1 = R^2 = R^4$ $= R^5 = H$	$\bar{P}$	1.313	1.313	1.476	119.36	121.39	119.36	0.007
	var(*P*)	0.0002	0.0002	0.0015	19.7	2.0	19.7	0.0001
(13)	esd(*P*)	0.015	0.015	0.038	4.4	1.4	4.4	0.007
	P(min)	1.297	1.297	1.394	103.95	118.95	103.35	0.0
	P(max)	1.375	1.375	1.529	133.19	123.46	133.19	0.026

of the C—X^3 link with unrestricted R^1, R^2, R^4 and R^5 substituents. The other two subgroups are similar but with $R^1 = R^2 = R^4 = R^5 = H$.

The typical pattern of the geometry of the NC(X)N skeleton shows very little differentiation between CN(l) and CN(s), with very small variances for both. The same is observed for the bond angles α and γ. This corroborates the recognized fact that both nitrogen atoms as well as both CN bonds are chemically very similar. Table 16 contains structural and statistical data for the amidine skeleton for the whole group as well as for the four subgroups, which will be discussed separately.

Table 17 presents the sequences of increasing structural parameters. For both CN(s) and CN(l) the inequalities are mostly weak ones, and the same is true for the α, β and γ angles. The only significant difference is for CX bonds and results from the variation in the chemical nature of X. Factor analysis gives a surprising result, namely that except in one subgroup (two unsubstituted NH_2 groups with $X^3 = C$), always all five factors are necessary to reproduce the total variance for the main group as well as for the remaining three subgroups.

TABLE 17. Statistical analysis of differences between the mean values of structural parameters $\bar{P}_j$ [CN(l), CN(s), CX, α, β and γ] for amidinium cation derivatives. The sequence for a given parameter with significant differences is assigned by the sign of inequality $<$, and for insignificant differences by the sign of approximate equality $\cong$

CN(s)	$(X^3 = C) \cong (X^3 = C, R^1 = H) \cong \text{Total} \cong (X^3 = N, R^1 = H) \cong (X^3 = N)$
CN(l)	$(X^3 = C, R^1 = H) < (X^3 = N, R^1 = H) \cong (X^3 = N) \cong \text{Total} \cong (X^3 = C)$
CX	$(X^3 = N, R^1 = H) \cong (X^3 = N) < \text{Total} < CX^3 = C) \cong (X^3 = C, R^1 = H)$
α	$(X^3 = C) \cong \text{Total} \cong (X^3 = N) \cong (X^3 = N, R^1 = H) \cong (X^3 = C, R^1 = H)$
β	$(X^3 = N, R^1 = H) \cong (X^3 = N) < \text{Total} \cong (X^3 = C, R^1 = H) \cong (X^3 = C)$
γ	$(X^3 = C, R^1 = H) \cong (X^3 = C) \cong \text{Total} \cong (X^3 = N) \cong (X^3 = N, R^1 = H)$

A. Analysis of the Subgroup with R^1, R^2, R^4 and R^5 Unrestricted but $X^3 = C$

This group is quite numerous ($n = 54$). While looking at its geometry it is important to say that both CN bonds are of the same length, whereas angles α and γ differ only slightly. This reflects the similarity of the chemical nature of both nitrogen atoms and might suggest a relatively concerted substituent effect on the π-electron system of NCN(X)N which results in equalization in bond lengths and bond angles, although the latter is to a much lesser extent.

B. Analysis of the Subgroup with R^1, R^2, R^4 and R^5 Unrestricted but $X^3 = N$

This numerous group ($n = 146$) consists of guanidinium cation derivatives. Compared to the former group ($X^3 = C$), variances for all structural parameters are smaller. Even the deviations from the planarity of this group are less exhibited than in the former one. This may result from the easier delocalization of the π-electrons due to equal (or almost equal) electronegativities of all three nitrogen atoms involved in the skeleton.

C. Analysis of the Subgroups with $R^1 = R^2 = R^4 = R^5 = H$ and either $X^3 = C$ or $X^3 = N$

These two groups differ rather slightly from each other. The CN bond lengths for the $X^3 = N$ group are somewhat longer than for the $X^3 = C$ group. A greater difference is found for the β angle which, for the $X^3 = N$ group, is 1.23° smaller than for the $X^3 = C$ group. The greater equalization of α, β and γ values in the $X^3 = N$ group may result from possible interactions of NH fragments with anions in the environment, involving all three nitrogen atoms in question. The application of the factor analysis to the structural parameters of this group and its subgroups shows that all five factors are necessary to reproduce the total variance (the fifth smallest factor is still larger than 9.0%). This seems to suggest low cooperative effects due to variations of the substituents in the NCN group in amidinium cation derivatives.

IV. ANALYSIS OF SUBGROUPS OF AMIDINE DERIVATIVES

This group consists of 346 entries and may be described by the mean geometry as presented in Figure 17. Full geometrical and statistical data for this group and all its subgroups are given in Table 18. The most important characteristics of this group are: a significant difference between CN(s) and CN(l) equal to 0.041 Å, and $\alpha > \gamma$, by 1.76°. This picture for bond lengths becomes even more distinct while coming to subgroups with $X^3 = C$ with CN(l) − CN(s) = 0.056 and for $X^3 = S$ with CN(l) − CN(s) = 0.069 Å, respectively. For the latter case $\alpha - \gamma = 4.35°$. The difference in CN bond lengths is the smallest

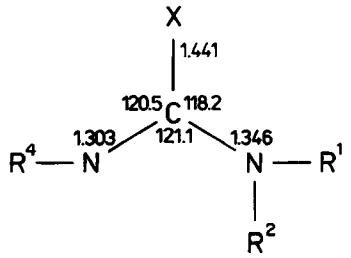


FIGURE 17. Mean geometry of the amidine skeleton of group 3 (amidine derivatives)

for the $X^3 = N$ group. Undoubtedly, the three nitrogen atoms bound to the same functional carbon atom behave similarly and hence delocalization of the π-electrons in the NCN fragment is easy, with CN(l) − CN(s) = 0.035 Å. The sequential relationships between the structural parameters of this group and all its subgroups are given in Table 19. The whole group as well as all subgroups exibit deformations from planarity. The mean geometries for the subgroups are presented in Figures 18, 19 and 20. Regressional analysis carried out within group 3 and its subgroups has not given any chemically important results. The results of the factor analysis are given in Table 20. In all cases (except $X^3 = S$)

TABLE 18. Structural and statistical data for amidine derivatives. Differentiation of the sample is by the C—X^3 bond. All other substituents R^1, R^2, R^4 and R^5 (if present) are unrestricted

Type of subsample	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Total	$\bar{P}$	1.303	1.346	1.441	120.48	121.05	118.24	0.023
(342)	var(P)	0.0015	0.0012	0.0215	22.9	23.3	21.4	0.0011
	esd(P)	0.038	0.035	0.147	4.8	4.8	4.6	0.034
	P(min)	1.103	1.158	0.938	89.19	103.37	97.14	0.000
	P(max)	1.476	1.481	1.938	140.19	136.40	137.81	0.274
CN(3)	$\bar{P}$	1.301	1.336	1.363	120.17	121.84	117.64	0.025
(197)	var(P)	0.0018	0.0009	0.0014	14.7	18.0	16.3	0.0001
	esd(P)	0.043	0.030	0.037	3.8	4.2	4.0	0.037
	P(min)	1.103	1.158	1.252	106.85	110.78	105.23	0.000
	P(max)	1.423	1.442	1.499	135.84	136.50	128.12	0.274
CC(3)	$\bar{P}$	1.303	1.359	1.488	120.21	120.27	119.29	0.022
(94)	var(P)	0.0013	0.0015	0.0011	34.3	27.3	21.1	0.0010
	esd(P)	0.036	0.039	0.032	5.9	5.2	4.6	0.032
	P(min)	1.252	1.266	1.354	89.19	103.37	110.25	0.000
	P(max)	1.476	1.481	1.607	132.19	131.90	137.81	0.274
CS(3)	$\bar{P}$	1.299	1.368	1.767	122.06	120.33	117.71	0.016
(35)	var(P)	0.0005	0.0010	0.0010	34.3	35.5	42.5	0.0001
	esd(P)	0.022	0.032	0.032	5.9	6.0	6.5	0.010
	P(min)	1.235	1.327	1.719	110.23	108.64	97.14	0.003
	P(max)	1.338	1.472	1.839	140.89	132.39	125.92	0.051

TABLE 19. Statistical analysis of differences between the mean values of structural parameters $\bar{P}_j$ [CN(l), CN(s), CX, α, β and γ] for amidine derivatives. Differentiation of the sample is by the C—X^3 bond. All other substituents R^1, R^2, R^4 and R^5 (if present) are unrestricted. The sequence for a given parameter with significant differences is assigned by the sign of inequality <, and for insignificant differences by the sign of approximate equality ≅

CN(s)	CS ≅ CN ≅ Total ≅ CC
CN(l)	CN < Total < CC ≅ CS
CX	CN < Total < CC < CS
α	CN ≅ CC ≅ Total = CS
β	CC < CS ≅ Total < CN
γ	CS < CC ≅ Total < CN

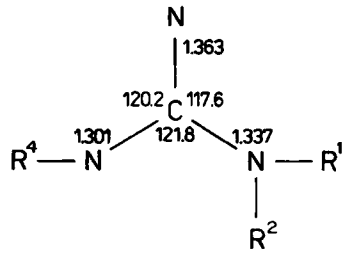


FIGURE 18. Mean geometry of the amidine skeleton of group 3 with $X^3 = N$. R^1, R^2 and R^4 are unrestricted

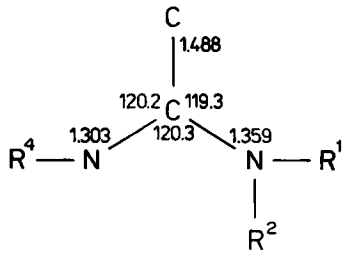


FIGURE 19. Mean geometry of the amidine skeleton of group 3 with $X^3 = C$. R^1, R^2 and R^4 are unrestricted

five factors are necessary to reproduce more than 95% of the total variance. In the case of the $X^3 = S$ group, four factors are needed to give a 96.3% explanation.

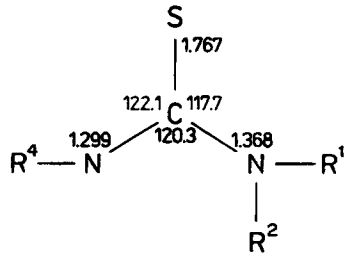


FIGURE 20. Mean geometry of the amidine skeleton of group 3 with $X^3 = S$. R^1, R^2 and R^4 are unrestricted

TABLE 20. Results of factor analysis for amidine derivatives. Differentiation of the sample is by the C—X^3 bond

Factor number	Percent of explanation of the total variance by factors in subgroups of 3			
	Total	CN	CC	CS
1	29.9	37.0	34.9	46.1
2	27.6	28.7	24.6	29.3
3	18.2	20.8	17.3	11.4
4	14.6	7.8	14.3	10.6
5	9.3	5.0	5.5	3.6
6	0.4	0.6	3.4	0.1

A. Structural Comparison of the Mean Geometries of NC(X)N Skeletons in Amidine and Amidinium Salt Derivatives

Both groups of compounds, 3 and 3′, i.e. amidine and amidinium salt derivatives, are of comparable amounts, containing 346 and 234 entries, respectively. The amidine derivatives 3 exhibit the greater mean value of deviation from planarity $\bar{\Delta} = 0.023$ Å in comparison to 0.014 for the 3′ group. The analysis of the shape of the distribution of Δ values for the 3 and 3′ groups supports the conclusion that the NC(X)N skeleton in the amidinium salt derivatives is often less deformed from planarity.

An obvious difference is in the CN bond lengths, the mean values of which for group 3′ are equal to each other and have a very small value of variance 0.0005 Å, whereas for group 3 these bonds are significantly (at $\alpha = 0.05$) differentiated in length with much larger values of variances, 0.0015 and 0.0012 for CN(s) and CN(l), respectively. Undoubtedly, in group 3′ the equalization of the CN bond lengths as well as the more planar shape of the NC(X)N skeleton results from the delocalization of the positive charge via the π-electron effect. This effect is weaker in group 3, except in cases of dimers formed in the crystal lattice by amidine derivatives with R^1 or $R^2 = H$.

The differences in bond angles in the NC(X)N fragment of the 3 and 3′ groups fit our previous conclusions. In the amidinium salt derivatives the mean value of α is equal to the mean value of γ with $\beta = 120.73$. In the case of amidine derivatives $\beta = 121.05$, and it is only slightly larger than in the 3′ group, but $\bar{\alpha} > \bar{\gamma}$, with the difference being quite large, 2.24°.

V. STRUCTURAL ANALYSIS OF IMIDATE DERIVATIVES

Imidates and their derivatives belong to class 4 of Scheme 1 and retrieval from CSD gave 79 imidate entries. The labelling of bonds and bond angles is given in Figure 21. Imidates may be again classified according to the nature of the C—X^3 link, and four subgroups have been selected from the total sample. The mean geometry of the imidate skeleton is given in Figure 22.

The most striking fact observed in the mean geometries of all subsamples is the large value of α. Since this angle is opposite the C—O bond, it may be interpreted within the frame of the Walsh rule[13,3]. The electronegativity of the oxygen atom ($\chi = 3.5$) may cause the increase in the value of α. The structural and statistical data for imidates and some subsamples are gathered in Table 21.

We can analyze the planarity of the N=CX^3O skeleton in a way similar to that employed before, applying as a measure of deviation from planarity the value of Δ defined previously (Figure 1). The mean value of Δ for the total sample (0.016 Å) is significantly different from zero at the significance level $\alpha = 0.05$. This observation is in line with that for amidines (groups 3 and 3′ in Scheme 1). Table 22 presents the results of the statistical analysis of the sequence for the changes of structural parameters for the total group of imidate derivatives and for all its subgroups as well.

The application of principal component analysis to the data of the whole sample of imidate derivatives as well as to the above-mentioned subsamples leads to the results collected in Table 23. The main conclusion is that, except for the X^3 = C subsample, for all subsamples five or four factors are enough to reproduce from 90 to 95% of the total variance (in the case of X^3 = O, even three factors). This could support the conclusion that, in the imidate derivatives, the substituents affect the skeleton in a way giving more concerted changes in the structural parameters.

A. Analysis of Subsamples with either R^1 and R^3 or R^3 and R^4 Unrestricted

The sample containing 79 entries is not a group of homogeneous systems. The substituents (R^1, R^3, R^4) may differ by the first atom linked directly to the atoms of the

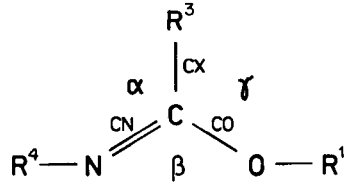


FIGURE 21. Assignment of bonds and angles for imidate derivatives

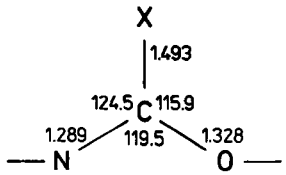


FIGURE 22. Mean geometry of the imidate skeleton

TABLE 21. Structural and statistical data for imidate derivatives with R^1 and R^3 unrestricted

Type of subsample	Parameter	CN(s)	CO	CX	α	β	γ	Δ
Total	$\bar{P}$	1.289	1.328	1.493	124.55	119.51	115.86	0.016
(79)	var(P)	0.0010	0.0010	0.0415	10.8	18.0	19.3	0.0002
	esd(P)	0.032	0.032	0.229	3.3	4.2	4.4	0.015
	P(min)	1.205	1.224	1.170	115.10	108.06	107.21	0.0
	P(max)	1.387	1.418	2.099	133.17	126.75	124.26	0.058
$X^2 = S$	$\bar{P}$	1.276	1.332	1.744	124.21	117.68	118.03	0.024
(8)	var(P)	0.0011	0.0010	0.0016	5.1	26.4	39.0	0.0002
	esd(P)	0.033	0.031	0.040	2.3	5.1	6.2	0.014
	P(min)	1.205	1.304	1.17	121.02	113.21	107.21	0.004
	P(max)	1.302	1.398	1.804	127.41	124.97	124.26	0.052
$X^2 = N$	$\bar{P}$	1.302	1.324	1.319	123.48	120.49	115.98	0.012
(14)	var(P)	0.0001	0.0006	0.0002	2.048	12.9	8.6	0.0001
	esd(P)	0.008	0.024	0.014	1.4	3.6	2.9	0.015
	P(min)	1.285	1.299	1.298	121.75	114.80	112.69	0.0
	P(max)	1.311	1.383	1.336	126.51	123.51	121.56	0.037
$X^2 = O$	$\bar{P}$	1.311	1.334	1.285	125.61	117.75	116.49	0.021
(11)	var(P)	0.0020	0.0006	0.0083	9.7	53.7	24.2	0.0004
	esd(P)	0.044	0.025	0.091	3.1	7.3	4.9	0.021
	P(min)	1.264	1.291	1.173	120.54	108.06	111.92	0.0
	P(max)	1.387	1.366	1.484	129.72	125.01	123.80	0.058
$X^2 = C$	$\bar{P}$	1.284	1.323	1.492	124.15	119.23	115.56	0.014
(41)	var(P)	0.0009	0.0012	0.0041	12.7	9.8	113.7	0.0002
	esd(P)	0.030	0.035	0.064	3.6	3.1	4.4	0.014
	P(min)	1.231	1.224	1.415	115.10	115.01	109.17	0.0
	P(max)	1.346	1.418	1.850	130.94	126.75	121.92	0.048

TABLE 22. Statistical analysis of differences between the mean values of structural parameters $\bar{P}_j$ [CN(l), CN(s), CX, α, β and γ] for imidate derivatives with R^1 and R^3 unrestricted. The sequence for a given parameter with significant differences is assigned by the sign of the inequality $<$, and for insignificant differences by the sign of approximate equality $\cong$

CN(s)	$(X^3 = S) \cong (X^3 = C) \cong$ Total $\cong (X^3 = N) \cong (X^3 = O)$
CN(l)	$(X^3 = C) \cong (X^3 = N) \cong$ Total $\cong (X^3 = S) \cong (X^3 = O)$
CX	$(X^3 = O) \cong (X^3 = N) < (X^3 = C) \cong$ Total $< (X^3 = S)$
α	$(X^3 = N) \cong (X^3 = C) \cong (X_3 = S) \cong$ Total $\cong (X^3 = O)$
β	$(X^3 = S) \cong (X^3 = O) \cong$ Total $\cong (X^3 = C) \cong (X^3 = N)$
γ	$(X^3 = C) \cong$ Total $< (X^3 = N) \cong (X^3 = O) \cong (X^3 = S)$

TABLE 23. Results of factor analysis for imidate derivatives with R^1 and R^3 unrestricted

Factor number	Total	$X^3 = O$	$X^3 = N$	$X^3 = C$
1	44.6	81.7	44.2	50.1
2	27.9	11.8	24.7	19.5
3	15.5	4.0	20.2	15.2
4	7.3	2.3	9.7	8.1
5	4.7	0.2	1.2	7.1
6	0.0	0.0	0.0	0.0

TABLE 24. Structural and statistical data for two groups of imidate derivatives, the first with R^1 and R^2 unrestricted ($X^3 = C$, $X^3 = H$ and $X^3 = N$), and the other with R^2 and R^3 unrestricted ($X^1 = C$ and $X^1 = H$)

Type of subsample	Parameter	CN(s)	CO	CX	α	β	γ	Δ
$X^3 = C$	$\bar{P}$	1.288	1.332	1.565	125.51	118.70	115.68	0.022
(39)	var(*P*)	0.0012	0.0009	0.0665	9.7	19.5	20.3	0.0003
	esd(*P*)	0.034	0.030	0.258	3.1	4.4	4.5	0.017
	P(min)	1.205	1.282	1.173	119.79	108.06	107.21	0.0
	P(max)	1.387	1.398	2.099	133.17	125.01	124.26	0.058
$X^3 = H$	$\bar{P}$	1.284	1.317	1.413	124.25	120.38	115.36	0.010
(19)	var(*P*)	0.0008	0.0002	0.0081	3.9	11.4	18.7	0.0001
	esd(*P*)	0.030	0.015	0.090	2.0	3.4	4.3	0.010
	P(min)	1.231	1.299	1.298	121.44	115.37	109.17	0.0
	P(max)	1.312	1.344	1.527	127.35	124.16	121.56	0.041
$X^3 = N$	$\bar{P}$	1.293	1.326	1.429	121.60	122.24	116.14	0.014
(8)	var(*P*)	0.0005	0.0045	0.0078	24.9	8.4	10.9	0.0002
	esd(*P*)	0.022	0.067	0.088	5.0	2.9	3.3	0.015
	P(min)	1.266	1.224	1.318	115.10	188.5	111.90	0.0
	P(max)	1.325	1.418	1.521	129.61	126.75	121.20	0.041
$X^1 = C$	$\bar{P}$	1.287	1.331	1.495	124.94	119.27	115.70	0.017
(70)	var(*P*)	0.0010	0.0008	0.0468	9.2	17.8	19.1	0.0002
	esd(*P*)	0.032	0.028	0.216	3.0	4.2	4.4	0.016
	P(min)	1.205	1.282	1.173	118.23	108.06	107.21	0.0
	P(max)	1.387	1.418	2.099	133.17	126.75	124.26	0.058
$X^1 = H$	$\bar{P}$	1.309	1.289	1.402	121.81	118.92	119.26	0.008
(10)	var(*P*)	0.0001	0.0010	0.0086	11.7	10.3	5.5	0.0001
	esd(*P*)	0.010	0.032	0.093	3.4	3.2	2.3	0.008
	P(min)	1.298	1.224	1.298	115.10	115.37	115.36	0.004
	P(max)	1.325	1.314	1.521	124.83	123.70	121.56	0.017

imidate skeleton (X^1, X^3 and X^4, respectively) and may produce quite different structural changes of the skeleton. Figure 22 presents the labelling of the structural parameters, whereas Table 24 contains the structural and statistical parameters for subsamples extracted from imidate derivatives (group 4) by fixing $X^3 = C$, $X^3 = H$ and $X^3 = N$.

The most numerous subsample, $n = 41$, is the one with $X^2 = C$ and X^1 and X^3 being varied.

First of all, testing the hypothesis on the planarity of the NX^2CO skeleton leads to the same conclusion as for the whole sample, that is, $\Delta = 0.014$ Å is significantly different from zero at $\alpha = 0.05$. The other structural parameters, two of them being chemically fixed, i.e. $C—N^2$ and C—O bonds, vary very strongly and in a way which makes it difficult to carry out any analysis. These two types of bonds, however, in spite of the possibility of being involved in the π-electron conjugation, in general, do not interact in an expected way. If this conjugation occurred, one would expect a mutual dependence between the lengths of the CN and CO bonds with a negative slope. In this kind of plot the correlation coefficient $r = -0.51$ was obtained, and it is significantly different from $r = 0$ at the $\alpha = 0.05$ level. This kind of dependence, however, gives no perspectives for any quantitative interpretation. Of many other plots, only two seem to be interesting and significant: α vs CN and α vs CO bond lengths give $r = 0.64$ and -0.58, respectively, and they support the conclusion

that the electronic effects of the substituents at various sites affect these three parameters in a relatively concerted way, as already shown above for the CN vs CO bond lengths.

The application of principal component analysis shows that three main factors explain 50.1, 19.5 and 15.2% of the total variance, i.e. altogether 84.8%. The next two explain 8.0 and 7.1%, being distinctly lower in significance. The last factor is close to zero, which results from the almost complete planarity of the skeleton and from the restriction that the three angles must add up to 360°.

Apart from subsamples whose structural parameters are given in Table 21, one can consider another partitioning in which the principle of division involves atoms linked to the nitrogen (N—X group) and oxygen (O—X group) atoms. Table 24 also contains structural and statistical parameters for these subsamples. The most interesting features are relatively short CN bond lengths, the longest being for the OX^1 subgroup (1.309 Å) for which the CO bond is the shortest (1.289 Å).

VI. ANALYSIS OF IMIDINE DERIVATIVES

From this group of compounds (**5** in Scheme 1) only 13 fragments could be retrieved from CSD. The mean geometry of this group is presented in Figure 23, whereas the full geometrical and statistical characteristics are presented in Table 25.

An important feature of the mean geometry of the NCN skeleton is that CM(l) is considerably longer than CN(s), 1.384 Å and 1.314 Å, respectively. The largest of all bond angles is the central CNC angle equal to 122.33° with a relatively large variance 11.8°^{2}, which is significantly greater than 120° at $\alpha = 0.05$. The large value of this angle seems to result from the repulsion of substituents at both functional carbon atoms. Factor analysis applied to NC(X)N fragments shows that to reach more than 95% of the explanation of the total variance, five factors have to be used.

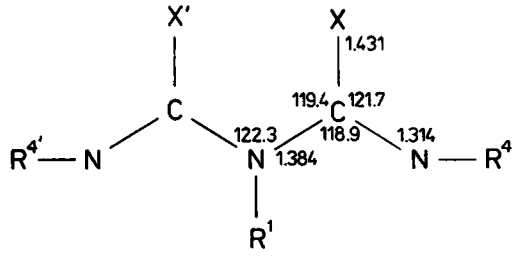


FIGURE 23. Mean geometry of the imidine skeleton of group **5**

TABLE 25. Structural and statistical data for imidine derivatives (**5**). All substituents R^1, R^2, R^4 and R^5 (if present) are unrestricted

Type of subsample	Parameter	CN(s)	CN(l)	CX	α	β	γ	Δ
Total	$\bar{P}$	1.314	1.384	1.431	121.74	118.85	119.36	0.013
(13)	var(*P*)	0.0009	0.0010	0.0316	24.0	21.8	13.7	0.0002
	esd(*P*)	0.030	0.031	0.178	4.9	4.7	3.7	0.013
	P(min)	1.264	1.307	1.213	109.35	110.33	112.29	0.000
	P(max)	1.381	1.460	1.762	131.77	127.70	128.63	0.048

VII. GENERAL REMARKS AND FINAL CONCLUSIONS

A. Planarity of the NC(X)N and NC(X)O Skeletons

While considering the NC(X)N skeleton in amidines, amidinium cations and imidine derivatives and the NC(X)O skeleton in imidate derivatives and looking through all tables one can conclude that for all groups and subgroups the NC(X)N and NC(X)O fragments treated as averaged structures should not be taken as planar. The largest value of $\Delta = 0.274$ Å observed for guanidinium tricarbonatotrifluorothorate(IV)[9] is quite large, but this is rather an exception and the mean values of Δ are in the range 0.009Å–0.050 Å. Chemical implications due to this nonplanarity seem not to be important even if the mean values of Δ are always different from zero in a statistically significant way at the significance level $\alpha = 0.05$. How to interpret this finding? It is well known that the force constants for out-of-plane deformations in rigid systems such as in aromatic ones, are one order of magnitude smaller than for the deformation of the bond angles[2,3]. The packing forces, which operate in the crystal lattice are strong enough to cause deformations from planarity, which indeed are observed. Only in a small fraction of the systems (4.8% of the cases) do we observe planarity (i.e. $\Delta_i = 0$). In these cases the forces operating may be either very weak and hence little deforming, or quite strong but operating in opposite directions and cancelling each other in the skeleton in question. Table 26 presents the frequency distribution of Δ values calculated for the whole sample of amidine and amidinium salt derivatives.

TABLE 26. Frequency of deviation of the carbon atom from the N^1XN^2 plane for the whole sample

Range of Δ (Å)	% of NC(X)N entries
0.000	4.8
0.000–0.005	22.6
0.005–0.010	17.7
0.010–0.015	14.2
0.015–0.020	10.9
0.020–0.025	7.3
0.025–0.030	7.5
0.030–0.035	4.5
0.035–0.040	2.0
0.040–0.050	2.5
0.050–0.100	3.7
> 0.100	2.3

B. Equalization of NC Bond Lengths in the NCN Fragment

Another general feature of the amidine skeleton is the relation between the shorter and longer CN bond lengths, i.e. CN(s) and CN(l), respectively. In many cases these two bonds are of similar length. In general, this is observed for two situations: (a) when amidines can form dimers in the crystal lattice and (b) in the case of amidinium salt derivatives. Additionally, it may occur in the case of amidine derivatives with substituents acting by a push–pull effect. Let us illustrate all three cases.

(a) Equalization of CN bond length due to dimer formation in the crystal lattice. In the case of amidine derivatives with at least one N—H bond at one of the nitrogen atoms in the NCN skeleton, dimerization may be observed in the crystal lattice (see Figure 13).

As an illustration let us consider the crystal and molecular structure of *N,N'*-diphenylformamidine[11] presented in Figures 24 and 25. Figure 24 shows the arrangement of the dimers of *N,N'*-diphenylformamidine in the crystal lattice. The NCN planes as shown in Figure 25 are not coplanar in both parts of the dimer; the dihedral angle between them is equal to 180–40.4 = 139.6°. This makes the situation even more complex, but this noncoplanarity results from the very low value of the force constant of N—H... N bond bending.

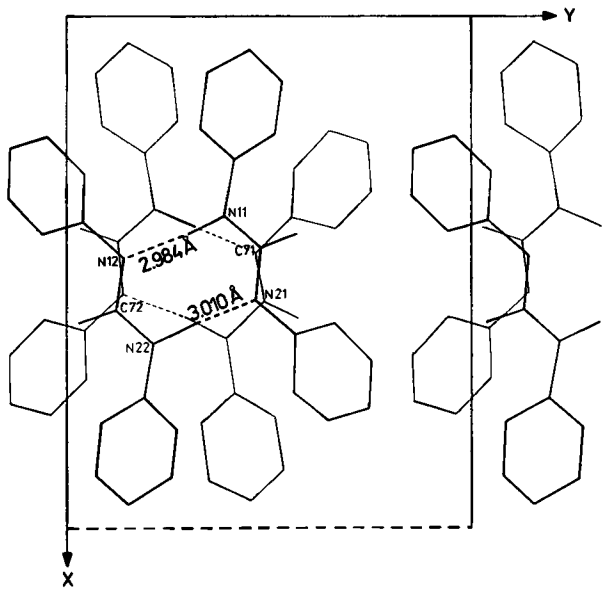


FIGURE 24. Projection of the cell content along the *Z*-axis. Only half of the cell is presented

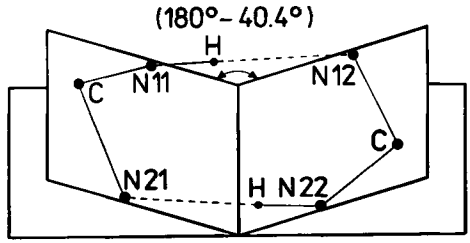


FIGURE 25. Scheme of the spatial arrangement for NCN skeletons in dimers of *N,N'*-diphenylformamidine[11]

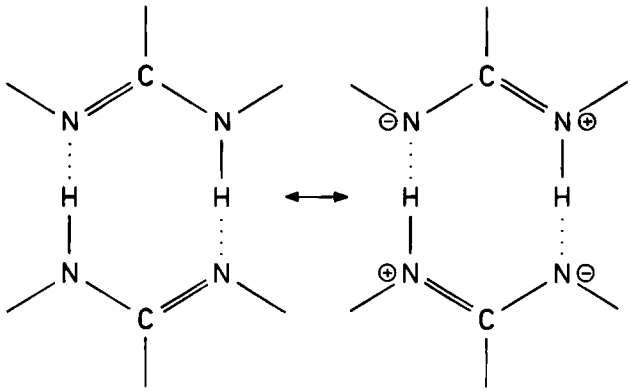


FIGURE 26. Canonical structures for (NCNH) in dimers

To understand the nature of the interactions we apply the approximate estimation of the N—H...N interaction energy given recently[16,17] by equation 4:

$$E(\text{N}\ldots\text{H}) = E(\text{N—H})\exp\{\alpha[R(\text{N—H}) - R(\text{N}\ldots\text{H})]\} \tag{4}$$

where E(N—H) and R(N—H) stand for the energy and bond length of the N—H bond in ammonia, respectively, whereas E(N...H) and R(N...H) stand for the energy of the N...H bond (interaction) with the interatomic distance R(N...H), respectively. Quanitity α is an empirical constant estimated for the case when R(N...H) and E(N...H) are known (for $H^+\ldots N^-$ interaction $\alpha = 4.015$). The application of this formula to N—H...N interactions in the above-mentioned dimer yields $E = 29.2\,\text{kJ mol}^{-1}$. This relatively strong interaction causes the two canonical structures of the NCN skeleton to be taken into account while analyzing its geometry in the dimer. This is shown in Figure 26. It seems that both canonical structures participate with almost equal weights, resulting in equalization of CN bond lengths.

(b) Equalization of CN bond lengths in the case of amidinium cation derivatives. It is usually accepted that in the case of amidinium cation derivatives the values of the two CN bond lengths are CN(s) ≅ CN(l). This is well supported by the mean values of CN bond lengths for this class of compounds (Table 16). However, in many individual cases the intramolecular structure of the compound would suggest the equality of CN bond lengths, whereas the observed values are not equal to each other. This is particularly well observed for cases with $R^1 = R^2 = R^3 = R^4 = R^5 = H$. Let us consider a typical example: the molecular structure of guanidinium carbonate[18] for which Figure 27 presents the geometry and the closest contacts. When equation 4 is applied to NH...O interactions one can obtain $E(N^1H\ldots O^{-\delta}) = 13.0\,\text{kJ mol}^{-1}$, whereas for the $N^2H\ldots O^{-\delta}$ and $N^3H\ldots O^{-\delta}$ interactions the energies are considerable larger, 23.6 and 33.7 kJ mol^{-1}, respectively. In these calculations α (the empirical constant in equation 4) is estimated to be equal to 4.338[16,17]. It is immediately apparent that the C—N bond with the NH_2 group must weakly interacting with the oxygen atoms of the carbonate anion is the longest (1.358 Å). This may be understood, since in the two other NH_2 groups much stronger H-bond interactions cause the appearance of a negative charge at the nitrogen atom which may be partly delocalized along the CN bond. Hence, these two CN bonds are considerably shorter.

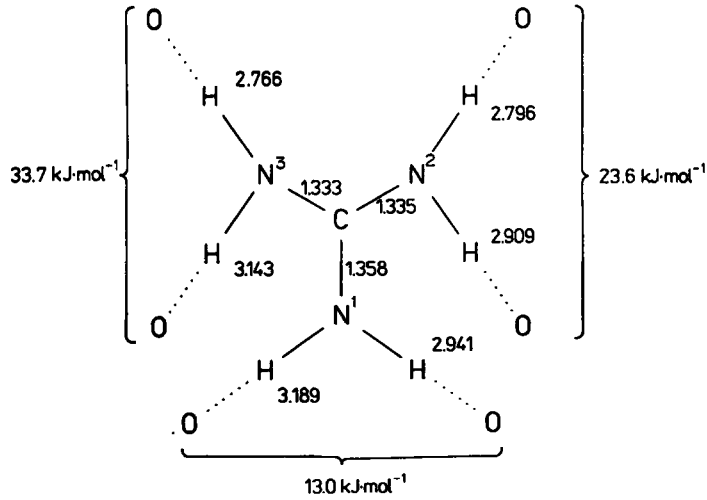
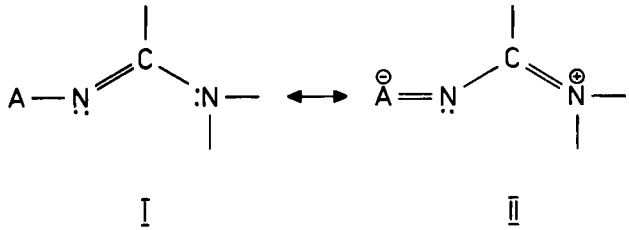


FIGURE 27. Geometry and H-bonding net for the guanidinium cation in its carbonate salt[12]. The numbers at the H atoms are the N···O interatomic distances



I II

FIGURE 28. Canonical structures for amidine derivatives with an electron-accepting substituent attached at imine nitrogen atom

(c) Equalization of CN bond lengths as a result of substituent effects via push–pull interactions. In the case of an electron-accepting group attached to the imine nitrogen atom, one can expect an increase in the weight of the canonical structure II with a localized negative charge at the accepting group A (Figure 28). This intramolecular charge transfer should be reflected in the equalization of the CN bond lengths. Let us consider as an illustration the molecular geometry of *N,N*-dimethyl-*N*-sulfonylamidine[19] in which the CN bond lengths are equal to 1.307(5) Å and 1.314(4) Å. The application of the HOSE model[20] (i.e., the model which allows to obtain the weights of canonical structures directly from the geometry of the π-electron molecule or a fragment of it), gives weights for the first and second canonical structures equal to 53 and 47%, respectively. In the case of a weaker accepting substituent[21], i.e. *p*-nitrophenyl, these values are 67 and 33%, respectively. It should be noted here that the delocalization of the π-electrons in the NCN skeleton depends not only on the accepting properties of the R^4 substituent at the functional carbon, and in the case of R^3 = *tert*-butyl[21] these weights are 85.2 and 14.8%

respectively. Undoubtedly, conformational conditions may affect in these cases the π-electron delocalization[19]. These two effects, namely the push–pull one from the R^4 substituent (if it is electron accepting) and the steric one from R^3, make the general situation very complex.

C. Sequence of the Variation of Structural Parameters Analyzed along Main Groups

The data in Table 27 show the results of the sequence analysis of the structural parameters for all main groups including the structures **3**, **3'**, **4**, **5** and **(3 + 3')**. The most

TABLE 27. Sequence of parameters in all main groups of amidine and amidinium cation derivatives

CN(s)	$4 < 3 \cong (3+3') \cong 5 \cong 3'$
CN(l)	$3' \cong 4(C{-}O) < (3+3') < 3 < 5$
CX	$3' \cong 5 \cong (3+3') \cong 3 < 4$
α	$3' < (3+3') \cong 3 \cong 5 < 4$
β	$5 \cong 4 < 3' \cong (3+3') \cong 3$
γ	$4 < 3 \cong (3+3') \cong 5 \cong 3'$
Δ	$5 \cong 3' \cong 4 < (3+3') < 3$

planar NC(X)N skeletons [or NC(X)O skeletons] are in the systems belonging to groups **5**, **3'** and **4**. The NC(X)N skeleton in group **(3 + 3')** is significantly more deformed than the former ones. Most deformed are the NC(X)N skeletons in structures of group **3**.

With a few exceptions the sequences of $\bar{\alpha}$ and $\bar{\gamma}$ angles are generally opposite in direction, and this is true also for the CN(s) and CN(l) bond lengths.

These observations are very approximate and true only for averaged structures. In individual cases they may often not be maintained.

D. Variation of the Angle β and the Problem of the Configuration of Amidine Derivatives

The amidine derivatives (group **3**) may be considered in terms of geometrical isomerism around the CN(s) double bond. Formally, one can select four possible isomers as shown in Figure 29 for the case when R—one of the substituents at N^1—is a hydrogen atom. The spatial relations between the substituents at N^1, N^2 and the functional carbon atom follow the rules given by Cahn, Ingold and Prelog (Figure 29).

An interesting observation that the angle β depends on the size of R^3 and on the configuration at N^2 has been made by Ciszak[22]. She has found that for formamidines, benzamidines and acetamidines, all in configuration $N^2(E)$, the angle β is 122.9, 119.0 and 118.5°, respectively. For those amidines which are in configuration $N^2(Z)$, the angle β is as large as 125.9°. These results, although observed on a relatively small sample, are very important. First, the sample was chosen from not very complex systems and with well-solved geometry. Second, it shows a relation between the configuration at N^2 and the NCN angle, which is of great interest in the field of amidine derivatives. She has also found that for $\beta \leqslant 124°$ mostly the $N^2(Z)$ configuration occurs. Moreover, the fact that in the series of formamidines, benzamidines and acetamidines the β value decreases for the $N^2(E)$ configuration may simply mean that the β value depends on spatial requirements of R^3. Considering the values of $\bar{\beta}$ for the **(3 + 3')** group (Tables 4 and 9) it can be seen that $\bar{\beta}$ for formamidines has indeed the largest value, supporting broadly the former conclusion.

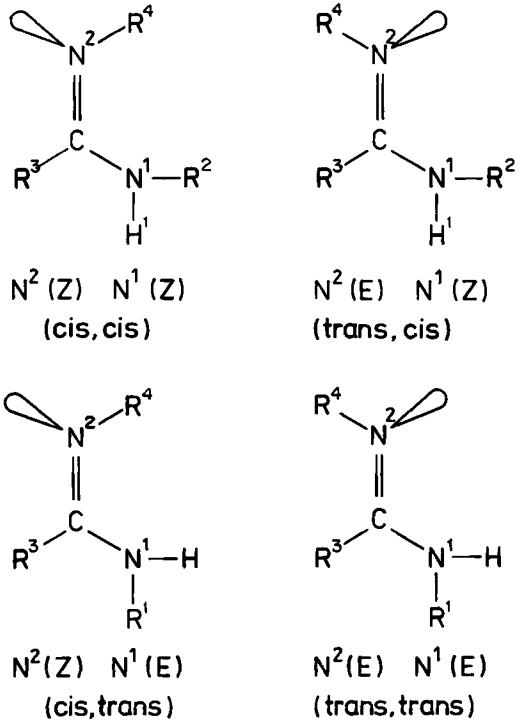


FIGURE 29. Assignment of the spatial arrangements for the amidine skeleton according to Cahn, Ingold and Prelog

VIII. ACKNOWLEDGEMENTS

This work was supported by project G-MEN 178/90 of the Polish Ministry of National Education.

IX. REFERENCES

1. Cambridge Structural Database (CSD); for details see F. H. Allen, S. Bellard, M. D. Brice, B. A. Cartwright, A. Doubleady, H. Higgs, T. Hummelink, B. G. Hummelink-Peters, O. Kennard, W. D. S. Matherwell, J. R. Rogers and D. G. Watsan, *Acta Crystallogr.*, **B35**, 2331 (1979), See also F. H. Allen, O. Kennard and R., Taylor, *Acc. Chem. Res.*, **16**, 146 (1989) and F. H. Allen, 'The retrieval and analysis of precise structural information from CSD files', Lecture Notes of *11th* Course of International School of Crystallography, Erice, Italy, 24 May–6 June, 1985: *Static and Dynamic Implications of Precise Structural Information*, CNR Reports, Technografico, Roma, 1985.
2. J. C. D. Brand and J. C. Speakman, *Molecular Structure, the Physical Approach*, Arnold, London, 1960; see also J. Bernstein, Lecture Notes (quoted in Ref. 1), p. 269.
3. T. M. Krygowski, *Prog. Phys. Org. Chem.*, **18**, 291 (1990).
4. A. I. Kitajgorodzki, *Molecular Crystals and Molecules*, Academic Press, New York, 1973.
5. T. M. Krygowski and I. Turowska-Tyrk, *Chem. Phys. Lett.*, **138**, 90 (1987).
6. G. Häfelinger, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, London, 1975, pp. 1 ff.
7. J. B. Czerminski, A. Iwasiewicz, Z. Paszek and A. Sikorski, *Statistical Methods in Applied Chemistry*, Elsevier, Amsterdam, 1990.

8. T. M. Krygowski and K. Woźniak, in *Similarity Models in Organic Chemistry, Biochemistry and Related Fields* (Eds. R. I. Zalewski, T. M. Krygowski and J. Shorter), chap. 1, Elsevier, Amsterdam, 1991.
9. S. Voliotis, *Acta Crystallogr.*, **B35**, 2899 (1979).
10. R. I. Zalewski, in *Similarity Models in Organic Chemistry, Biochemistry and Related Fields* (Eds. R. I. Zalewski, T. M. Krygowski and J. Shorter), Elsevier, Amsterdam, 1991.
11. R. Anulewicz, T. M. Krygowski and B. Pniewska, *J. Cryst. Spectr. Res.*, **17**, 661 (1987).
12. D. B. Owen, *Handbook of Statistical Tables*, Addison-Wesley, Reading, 1962.
13. H. A. Bent, *Chem. Rev.*, **61**, 275 (1961).
14. J. E. Huheey, *J. Phys. Chem.*, **69**, 3284 (1965).
15. H. Endres, N. Genc and D. Nöthe, *Acta Crystallogr.*, **C39**, 701 (1983).
16. T. M. Krygowski and S. J. Grabowski, submitted.
17. T. M. Krygowski, M. K. Kalinowski, I. Turowska-Tyrk, P. C. Hiberty, P. Milart, A. Silvestro, R. D. Topsom and S. Dähne, *Struct. Chem.*, **2** (1991).
18. J. M. Adams and R. W. Small, *Acta Crystallogr.*, **B30**, 2191 (1974).
19. R. Anulewicz, T. M. Krygowski, Ch. Laurence and E. D. Raczyńska, *J. Phys. Org. Chem.*, in press.
20. T. M. Krygowski, R. Anulewicz and J. Kruszewski, *Acta Crystallogr.*, **B39**, 732 (1983).
21. E. Ciszak, M. Gdaniec, M. Jaskóski, Z. Kosturkiewicz, J. Owsiański and E. Tykarska, *Acta Crystallogr.*, **C45**, 433 (1989).
22. E. Ciszak, PhD Thesis, The University of A. Mickiewicz, Poznań, 1988.

CHAPTER 3

Stereochemical aspects of amidines, imidates and related compounds

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The Chemistry of Amidines and Imidates, Volume 2
Edited by S. Patai and Z. Rappoport

I. INTRODUCTION

A. Scope

This chapter is a review of recent developments in the stereochemical aspects of amidines, imidates and related compounds. It is an updating of parts of two chapters from the 1975 volume on amidines and imidates: 'General and Theoretical Aspects of Amidines and Imidic Acid Derivatives', by Häfelinger[1], and 'Constitution, Configurational and Conformational Aspects, and Chiroptical Properties of Imidic Acid Derivatives', by Fodor and Phillips[2]. The literature has been surveyed from 1974 to early 1990, and little effort was devoted to coverage of any pre-1974 publications that may have been omitted from the earlier volume. One other review on amidines, emphasizing their synthesis and reactions, has been published by Granik[3].

The structures under consideration all have the functional group N—C=N or O—C=N, as in amidines $RC(NR'_2)=NR''$ or imidates $RC(OR')=NR''$. Consideration is extended to thioimidates $RC(SR')=NR''$, as well as to conjugate bases and conjugate acids, including alkylated species. Further extensions are to amidines and imidates substituted with an oxygen or nitrogen heteroatom at nitrogen, as in amidoximes $RC(NR'_2)=NOH$ or hydrazidates $RC(OR')=NNR''_2$, or substituted with a heteroatom at carbon, as in guanidines $R_2NC(NR'_2)=NR''$ or iminocarbonates $ROC(OR')=NR''$. We omit doubly heterosubstituted amidines and imidates, such as hydroxyamidoximes $RC(NHOH)=NOH$ or aminoguanidines $R_2NC(NR'_2)=NNR''_2$. Also we omit heterocycles that incorporate the N—C=N or O—C=N grouping, except where these exemplify the behavior of amidines or imidates independently of their presence in a heterocyclic ring. If there is a proton on the singly bonded nitrogen (or oxygen), there is the further complication of tautomerism, and this is discussed in another chapter of this supplement[4].

The emphasis is on configurations and conformations of amidines and imidates. The principal topic is the characterization of the stereochemistry of the C—N double or partial-double bond and of the C—N or C—O single bond. A further aspect is the interconversion of those configurations and conformations, by such mechanisms as nitrogen inversion and rotation about double, partial-double and single bonds. Most of the results presented will be NMR results, since NMR is such a powerful technique for answering such questions, far more direct than the older IR methods that rely on correlations of bands with structural features. However, little attention will be paid to the assignment of NMR signals, since chemical-shift correlations are now complemented by measurement of *n*-bond coupling constants ^nJ and nuclear Overhauser enhancements (NOEs), which are more secure.

Further aspects of stereochemistry concern reactivity. Diastereotopic groups in an amidine or imidate molecule can react at different rates. Also diastereoisomeric

(diastereomeric) amidines or imidates can have different reactivity, and they may be formed at different rates, so that the product that is obtained synthetically is not necessarily the equilibrium material. Also, the stereochemistry of an amidine or imidate may induce configurational or conformational features in intermediates along the reaction pathway, and these may determine the course of the chemical reaction, or its regiochemistry or stereochemistry. In particular, there are often stereochemical aspects of amidines (and imidates) that arise from chiral (stereogenic) centers, either in the amidine or imidate itself or in reaction intermediates or products derived therefrom.

This review is organized according to the stereochemical questions that are considered. First the structural aspects are surveyed: What are the configurations of amidines and imidates—the stereochemistry about the C—N double bond? What are the conformations of amidines and imidates—the stereochemistry about the C—N or C—O single bond? Then the interconversions of these stereoisomers are surveyed—rates of *E*–*Z* stereoisomerization and rates of rotation about the single bond. Finally the consequences of stereochemistry for reactivity are surveyed: Which stereoisomers are obtained from a chemical reaction? What are the relative reactivities of the different diastereoisomers (diastereomers) or of diastereotopic groups in the same molecule?

Within each category of stereochemical questions the various functional groups are considered in turn. The order is approximately an order of increasing molecular complexity: amidines, imidic acids and esters, thioimidates, ionic conjugate acids and bases (amidinium ions, amidinate anions, imidatonium ions, imidate anions, plus metal complexes), amidines and imidates with sp^2-C substituents (*N*-alkylidene amidines, *N*-acylamidines, imidines, *N*-acylimidates), N-heterosubstituted amidines and imidates (*N*-aminoamidines, amidrazones, amidoximes, hydrazidates, hydroximates), C-heterosubstituted amidines and imidates (guanidines, isoureas, isothioureas, haloformamidines, haloformimidic acids and their conjugate acids). There are frequent gaps in the record, where some stereochemical question has not been addressed for some functional group, and it is hoped that this review will encourage researchers to answer these questions.

We neglect the extensive investigations into chiroptical properties—optical activity, optical rotatory dispersion and circular dichroism—that were included in the original volume[2]. Although these are influenced by the amidine chromophore, the amidine itself does not carry the chirality, since it is planar. Instead we focus on those stereochemical aspects that are consequences of the chemistry of the amidine functional group.

B. Nomenclature

Amidines are characterized by the $RC(NR'_2)=NR''$ fragment, with the singly bonded nitrogen formally sp^3 hybridized and the doubly bonded nitrogen sp^2 hybridized. Imidate esters are characterized by the $RC(OR')=NR''$ fragment, and imidic acids are $RC(OH)=NR'$, although this is the unstable tautomer of an amide $RCONHR'$ and cannot readily be studied directly.

The conjugate acids (amidinium ions and imidatonium ions) are obtained by protonating or alkylating these species on sp^2 nitrogen, to create a resonance-stabilized cation. It should be noticed that an imidatonium ion is $RC(OR')=NR''^+_2$, and the conjugate acid of an imidate ester is $RC(OR')=NHR''^+$, both of which are quite similar to the conjugate acid of an amide $RC(OH)=NR'^+_2$, except that the latter is protonated on oxygen rather than alkylated. However, the conjugate acids of amides are discussed in another volume of this series. The conjugate bases of interest here (amidinate anions and imidate anions) are obtained by deprotonating from singly bonded nitrogen or from oxygen, respectively. The imidate anion $RC(—O^-)=NR'$ is also the conjugate base of an amide $RCONHR'$, and these are discussed here. Also, amidines and imidate esters can

form metal complexes $RC(NR'_2)=NR''\rightarrow M$ or $RC(OR')=NR''\rightarrow M$, where a metal is bound to the sp^2 nitrogen. Since the metal is a Lewis acid akin to a proton, these complexes are analogous to amidinium or imidatonium ions.

Thioimidates are characterized by the RC(SR')=NR" fragment. These are synthetically more accessible than ordinary imidates, but the stereochemical aspects are quite similar.

N-Alkylidene and *N*-acyl derivatives are characterized by an sp^2 carbon (or phosphoryl phosphorus or sulfonyl sulfur) attached to a nitrogen, as in *N*-alkylidene amidines $RC(N=CR'_2)=NR''$, *N*-acylamidines $RC(NR'_2)=NCOR''$ or $RC(=NR')-N(R'')COR'''$ (or phosphorylated or sulfonated amidines), imidines (the tri-nitrogen equivalent of a carboxylic anhydride) $RC(=NR')-N(R'')CR'''(=NR''')$ or $RC(NR'_2)=NC(R'')=NR'''$, and *N*-acylimidates $RC(OR')=NCOR''$.

N-Heterosubstituted amidines and imidates have the grouping N—C=NX or O—C=NX, where X is a nitrogen or oxygen substituent. These include *N*-aminoamidines $RC(NR'_2)=NNR''_2$, amidrazones $RC(NR'_2)=NN=CR''_2$, amidoximes $RC(NR'_2)=NOR''$, hydrazidates $RC(OR')=NNR''_2$ and hydroximates $RC(OR')=NOR''$. These are often configurationally more stable to inversion of the sp^2 nitrogen than ordinary amidines and imidates, so that their stereochemistry has been more extensively studied.

The C-heterosubstituted amidines and imidates include guanidines $(R_2N)_2C=NR'$, isoureas $ROC(NR'_2)=NR''$, isothioureas $RSC(NR'_2)=NR''$, haloformamidines $XC(NR_2)=NR'$ and haloformimidates $XC(OR)=NR'$, as well as their conjugate acids, such as guanidinium ions $(R_2N)_3C^+$ and isouronium ions $ROC(NR'_2)_2{}^+$. These often show quantitatively different stereochemical features because the additional heteroatom is conjugated with the amidine or imidate group and reduces the conjugation of the lone pair on the singly bonded nitrogen or oxygen.

The stereochemical designations of amidines and imidates are indicated by the structures **1*Z-syn***, **1*Z-anti***, **1*E-syn*** and **1*E-anti*** in Figure 1. These use the Cahn–Ingold–Prelog sequence rules of the IUPAC nomenclature system of organic chemistry. In Figure 1 it is assumed that the group R on carbon ranks lower than the group Y (O or NH) and that the group R' on Y ranks lower than N. (This is true in the usual case that R or R' is a carbon substituent.) The C—N double or partial-double bond is designated as *Z* or *E*, according to whether the higher ranking groups are on the same side or opposite sides of the bond. The C—N or C—O single bond is designated as *syn* or *anti*, also according to whether the higher ranking groups are on the same side or opposite sides of the bond. Notice that the designation *syn* or *anti* does not depend simply on the relationship of the singly bonded substituents on that single bond, but it considers the doubly bonded nitrogen as a group. This is opposite to the convention in the original 1975 volume of this series, and it is not always the way the stereochemistry was designated in the original publications summarized here, but for consistency we choose the same system not only for double bonds but also for single bonds that have double-bond character. For *N,N'*-disubstituted amidinium ions with different substituents there are *ZZ* (**2*ZZ***), *EE* (**2*EE***), *ZE* (**2*ZE***) and *EZ* (**2*EZ***) forms, as shown in Figure 2. The latter two are distinguished by

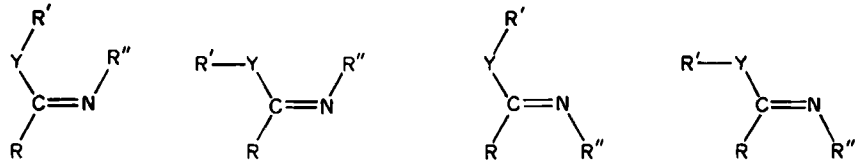


FIGURE 1. Stereochemical designations of amidines (Y = NH) and imidates (Y = O)

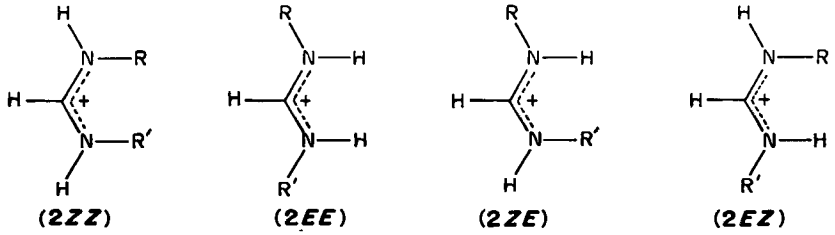


FIGURE 2. Stereoisomers of *N,N'*-dialkylformamidinium ions

specifying that the first descriptor refers to the nitrogen whose alkyl substituent ranks higher according to the sequence rules.

The transition state for *E–Z* interconversion by rotation about the double bond is shown as **3**. The transition state for *E–Z* interconversion by nitrogen inversion is shown as **4**. NMR methods for measuring activation energies are designated with the nucleus (^{1}H or ^{13}C or other) and with the technique for extracting rates from spectra [time dependence of signal intensities NMR(*t*), coalescence temperature T_c, line shape analysis LSA or saturation transfer ST]. All rate constants have been expressed in terms of the free energy of activation $\Delta G^{\ddagger}$. For uniformity in tables any activation energies reported in kJ mol^{-1} have been converted to kcal mol^{-1}, with 1 kcal = 4.184 kJ. Entries in tables are listed in order of increasing complexity of each successive substituent group.

II. CONFIGURATION ABOUT C—N DOUBLE BONDS

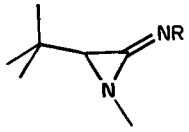
A. Configurations of Amidines and Imidates

1. Configurations of amidines

We begin with the question of whether amidines $RC(NR'_2)=NR''$ are of *Z* or *E* configuration. Much progress has been made in determining the stereochemistry of amidines since the previous volume, when only formamidoxime, azobis(*N*-chloroformamidine) and *N,N*-dimethylbenzamidine could be assigned as *E*, and none was found as a mixture of two forms.

Usually the stable form of an *N,N,N'*-trisubstituted amidine is *E*[5]. Indeed, chemical shifts for 65 different *N*-arylamidines and guanidines could be correlated using additivity parameters, so that all must be of the same *E* configuration[6]. In a survey of the Cambridge Crystallographic Database nine *N,N,N'*-trisubstituted amidines were found[7] to be of *E* stereochemistry. One disubstituted amidine was also found to be *E*. Two monosubstituted amidines, as well as the unsubstituted $MeC(NH_2)=NH$, were found to be *Z*. In solution *N,N,N'*-trimethyl-*p*-nitrobenzamidine could be confirmed as *E* by NOE data. Moreover, the resonance contribution to the dipole moment is only 0.88*D* in this compound, lower than the 1.81*D* in $HC(NMe_2)=NAr$, where the small hydrogen permits coplanarity and thus delocalization of the nitrogen lone pair into the C—N double bond. Despite this general

preference for a single stereoisomer, some cases show two forms, as listed in Tables 1 and 2. For the adamantylidene derivatives, the *Z* and *E* forms were assigned[9] by comparison of NMR chemical shifts with those of other aziridinimines, and the *E* structure could be confirmed by X-ray analysis. Another case where two forms are observed is when hydrogen bonding provides stabilization to the *Z* form, as in HC(=NAr)—NMe_2 with Ar = *o*-hydroxyphenyl[14], and the hydrogen bond could be confirmed by IR spectroscopy. For phenyliminopyrrolidine (**6**, $n = 5$, X = H) there is a complication due to the presence of the amino tautomer, so that early assignments and estimates of the *E*:*Z* ratio, based on chemical shifts, are questionable[13]. On the basis of kinetic proton acidities in the conjugate acid, it was concluded[15] that the more stable configuration of *N*,*N*′-dimethylacetamidine MeC(NHMe)=NMe is *Z*. This is the one that permits rotation about the C—NHMe bond to relieve methyl–methyl repulsions.



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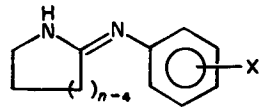


(6)

TABLE 1. Equilibrium between *Z* and *E* forms of amidines, RC(NR′R″)=NR‴

R	R′	R″	R‴	Solvent	%Z	Ref.
H	H	*o*-Tol	CH_2CH_2OMe	$CDCl_3$	75(25?)	8
	—*t*-BuCH—[a]	Me	Me	CCl_4	30	9
	—*t*-BuCH—[a]	Me	*t*-Bu	CCl_4	22	9
CH_3CH=CH	Me	Me	Ph	CCl_4	56	5
CH_3CH=CH	Ph	H	Ph	CCl_4	> 50	5
Ph	CH_2CH=CH_2	Me	Me	Cl′d[b]	0	10
Ph	CH_2CH=CH_2	Me	Me	$C_6D_5CD_3$	15	10
Ph	CH_2CH=CH_2	Me	Me	CD_3COCD_3	15	10
Ph	Me	Me	CH_2CH=CH_2	$CDCl_3$	0	11
Ph	Me	Me	CH=$CHCH_3$	$CDCl_3$	> 0	11
—2-Admantylidene—		*t*-Bu	Me	$CDCl_3$	10	9

[a]cf. 5.
[b]Various chlorinated solvents.

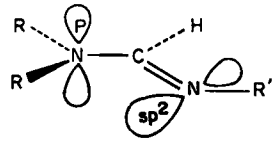
TABLE 2. Equilibrium between *Z* and *E* forms of cyclic amidines, **6**

n	X	Solvent	%Z	Ref.
5	H	$CDCl_3$	100	12
5	H	$CDCl_3$	0	13
5	2,6-Me_2	$CDCl_3$	90	12
5	2,6-Cl_2	$CDCl_3$	20	12
5	2,6-Cl_2	CD_3OD	90	12
6	H	$CDCl_3$	64	13
6	H	CD_3COCD_3	14	13
6	H	CD_3OD	100	13
6	2,6-Cl_2	$CDCl_3$	> 0	12
7	H	$CDCl_3$	85	13
7	H	CD_3OD	100	13

TABLE 3. Calculated energies (kcal mol^{-1}) of stereoisomeric formamidines, HC(NHR)=NR'

R	R'	E(E)	E(Z)	method	Ref.
H	H	0	>0	CNDO/2	16
H	H	0	0.6	3-21G	17
H	H	0	2.94	4-31G	18
H	H	0	1.6	4-31G	19
H	H	0	2.1	6-311++G**/MP3	20
$(CH_2)_3NH_2$	H	0	0.08	MNDO	21
$(CH_2)_3NH_2$	H	0	1.00	STO-3G	21
H	Ph	0	0.72	MNDO	22

Molecular orbital calculations on some formamidines HC(NHR)=NR' generally show that the *E* form is most stable. The results for these derivatives are summarized in Table 3. The preference is not large, so that steric interactions of substituents can readily reverse the stabilities. Also, according to CNDO/2 MO calculations[16] on HC(NH$_2$)=NH, the molecule is not planar, but the singly bonded nitrogen is pyramidalized. However, this is likely to be an artifact, as in some calculations on amides. According to the X-ray structure of *N*-hexamethylene-*N'*-*p*-nitrophenylformamidine, an amidine (7) is planar[23], in order to achieve resonance stabilization or delocalization of the lone pair on the singly bonded nitrogen. Therefore this nitrogen is only formally sp^3, and it is actually sp^2, like the other nitrogen. The difference between them is that the doubly bonded nitrogen has its lone pair in an sp^2 orbital, whereas the singly bonded nitrogen has a lone pair that is p.



(7)

2. *Configurations of imidate esters and imidic acids*

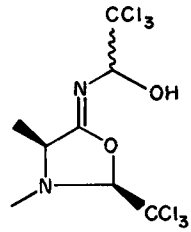
Since the earlier review in this series[2], it is now thoroughly established[24] that the *E* form of imidate esters is more stable than the *Z*. The dipole moment of MeC(OMe)=NMe is nearly the same as that of 2-methoxy-Δ^1-pyrroline, whose cyclic structure constrains it to be *E*. The NMR signals of RC(OR')=NMe can be assigned unambiguously to *Z* and *E* isomers on the basis of the $^5J_{RCNMe}$, as well as through lanthanide-induced shifts. Moreover, it was possible to detect a long-range through-space $^6J_{HF}$ in the *E* form of $(CH_3)_2CHC(OMe)=NC_6H_4F$-*o*, which confirms the stereochemical assignments. The proportion of *Z* form for various imidate esters is listed in Table 4. The proportion of the *Z* form is increased by polar solvents[27]. Likewise, hydrogen bonding to added acids, such as phenols, increases the proportion of the *Z* form of PhC(OMe)=NMe, and the proportion increases with the acidity of the phenol, from 7.2% with *p*-*t*-butylphenol in PhNO$_2$ to 17.5% with *p*-bromophenol. It can be seen that electron-withdrawing groups in the aryl ring of MeC(OAr)=NMe stabilize the *E* form[26], since these favor coplanarity, which is not possible in the *Z* form. Another general situation where there are appreciable amounts of the *Z* imidate ester is when steric effects destabilize the *E* form. Thus HC(OMe)=NBu-*t* and PhC(OMe)=NMe are exclusively *E*, but PhC(OMe)=NBu-*t* at -10 °C is a mixture of 62% *E* and 38% *Z*, assigned[25] by NMR chemical-shift correlations and nuclear

TABLE 4. Equilibrium between *Z* and *E* forms of imidate esters, RC(OR′)=NR″

R	R′	R″	Solvent	%*E*	Ref.
H	Me	*t*-Bu	CD_2Cl_2	100	25
H	Et	*m*-ClC_6H_4	$CDCl_3$	< 100	5
Me	Me	Me	CCl_4	100	24
Me	Me	Me	CD_3OD	95	24
Me	Me	Et	CCl_4	100	24
Me	Me	Et	CD_3OD	95	24
Me	Ph	Me	CCl_4	69	24
Me	Ph	Me	CD_3OD	56	24
Me	*p*-Tol	Me	CCl_4, $CDCl_3$	67	26
Me	*p*-Tol	Me	CD_3CN	80	26
Me	*p*-ClC_6H_4	Me	$CDCl_3$	80	26
Me	*p*-$O_2NC_6H_4$	Me	$CDCl_3$	90	26
t-Bu	Me	Me	CCl_4	87	24
t-Bu	Me	Me	CD_3OD	71	24
Ph	Me	Me	$CDCl_3$	98	27
Ph	Me	Me	CD_2Cl_2	100	25
Ph	Me	Me	CD_3OD	93	27
Ph	Me	Me	PhOH-$PhNO_2$	89	27
Ph	Me	*i*-Pr	PhOH-$PhNO_2$	82	27
Ph	Me	*t*-Bu	CD_2Cl_2	62	25
Ph	Me	Cl	$CDCl_3$	25	28
o-Tol	Me	*i*-Pr	PhOH-$PhNO_2$	91	27
o-FC_6H_4	Me	*i*-Pr	PhOH-$PhNO_2$	85	27
o-ClC_6H_4	Me	*i*-Pr	PhOH-$PhNO_2$	89	27
o-BrC_6H_4	Me	*i*-Pr	PhOH-$PhNO_2$	90	27
o-IC_6H_4	Me	*i*-Pr	PhOH-$PhNO_2$	88	27
o-$O_2NC_6H_4$	Me	*i*-Pr	PhOH-$PhNO_2$	92	27
1-Naph	Me	*i*-Pr	PhOH-$PhNO_2$	86	27

Overhauser enhancements. On the other hand, *ortho* substituents on the aryl ring of ArC(OMe)=NPr-*i* shift the equilibrium toward the *E* form[27].

A cyclic imidate ester (**8**), formed as a mixture of diastereomers, has been assigned[29] as the *Z* isomer, on the basis of the generalization[2] that this is the more stable. Although the generalization is not universal, it does apply for this cyclic case, where the C—O bond is constrained to be *syn* (see Section III.A.2 below). Besides, here there is an intramolecular hydrogen bond that stabilizes the *Z* form.



(**8**)

X-ray analysis[30] of PhC(OMe)=NC(NMe_2)=Cr($CO)_5$ shows that this too is the *E* stereoisomer. This contrasts with PhC(OCOPh)=NC(*t*-Bu)=Cr$(CO)_5$[31], where the

CNC angle is nearly 180°. The latter structure is better viewed as $PhC(OCOPh)=N^+=C(t\text{-}Bu)Cr(CO)_5^-$, so that *Z* and *E* lose significance. The nitrogen lone pair here is needed to stabilize the carbene, whereas the Me_2N nitrogen is sufficient in the contrasting $PhC(OMe)=NC(NMe_2)=Cr(CO)_5$.

N-Chloroimidate esters[28] may be an exception where the *Z* form is more stable, if the NMR assignments are reliable. This is consistent with the relative stabilities of stereoisomeric hydroximate esters RC(OR)=NOH (Section II.D.5). However, according to MNDO calculations[32] the *E* stereoisomer of HC(OR)=NCl is more stable than the *Z* by 0.4 kcal mol^{-1} for R = Et and by 2.6 kcal mol^{-1} for R = Me_3Si. In agreement, for

TABLE 5. *E*/*Z* equilibrium[27,33] for thioimidate esters, RC(SR')=NR"

R	R'	R"	Solvent	%E
Me	Me	Me	$CDCl_3$	64
Me	Me	Me	C_6D_6	76
Me	Me	Et	C_6D_6	74
Me	Me	Pr	C_6D_6	73
Me	Me	*i*-Pr	C_6D_6	77
Me	Me	Bu	C_6D_6	74
Me	Me	*t*-Bu	C_6D_6	84
Me	Me	Ph	C_6D_6	95
Me	Et	Me	C_6D_6	73
Me	Et	Ph	C_6D_6	95
Me	*i*-Pr	Me	C_6D_6	75
Me	*t*-Bu	Me	C_6D_6	92
Me	$PhCH_2$	Me	$CDCl_3$	79
Me	$PhCH_2$	Ph	C_6D_6	94
Me	Ph	Me	C_6D_6	10
Me	*p*-$O_2NC_6H_4$	Me	$CDCl_3$	85
Et	Me	Me	$CDCl_3$	50
Et	Me	Me	C_6D_6	57
Pr	Me	Me	$CDCl_3$	38
t-Bu	Me	Me	$CDCl_3$	0
t-Bu	Me	Ph	$CDCl_3$	0
$PhCH_2$	Me	*i*-Pr	C_6D_6	69
$PhCH_2$	Me	Ph	C_6D_6	90
Ph	Me	Me	$PhNO_2$	56
Ph	Me	*i*-Pr	$CHBr_3$	39
Ph	Et	Me	C_6D_6	58
Ph	Et	*t*-Bu	$CDCl_3$	17
Ph	Et	Ph	$CDCl_3$	56
Ph	*i*-Pr	Me	C_6D_6	42
Ph	*i*-Pr	Ph	$CDCl_3$	49
Ph	*t*-Bu	Me	C_6D_6	52
Ph	*t*-Bu	Ph	$CDCl_3$	86
Ph	Ph	Me	C_6D_6	6
o-HOC_6H_4	Me	Me	$CDCl_3$	0
o-HOC_6H_4	Me	Me	DMSO	57
o-HOC_6H_4	Me	$PhCH_2$	$CDCl_3$	0
o-HOC_6H_4	Me	$PhCH_2$	DMSO	69
o-HOC_6H_4	Me	Ph	$CDCl_3$	0
o-HOC_6H_4	Me	Ph	Py-d_5	87
o-HOC_6H_4	Me	1-Naph	$CDCl_3$	0
o-HOC_6H_4	Me	1-Naph	$CDCl_3$-DMSO	60

RC(OEt)=NCl (R = Me, Pr, Bu, *s*-Bu) the NMR spectrum indicates that the former is a mixture, but the latter is a single isomer.

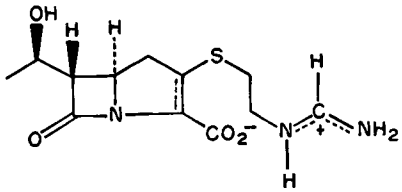
3. *Configurations of thioimidates*

The separate *Z* and *E* forms of thioimidate esters, RC(SR′)=NR″, can be distinguished by ^{1}H NMR and the peaks assigned[27,33]. The proportion of *E* form at equilibrium is given in Table 5, and additional data for *ortho*-substituted thiobenzimidate esters ArC(SMe)=NPr-*i* are available. Also, the configurations of some of these in the crystal were determined by comparing the NMR spectra after dissolving the crystalline material. As with ordinary imidate esters (Section II.A.2) the *E* isomer is usually more stable. It can further be seen that bulky R groups at carbon favor the *Z* form, whereas bulky R′ at sulfur or R″ at nitrogen favor the *E*, but only slightly. As with ordinary *N*-isopropyl benzimidate esters ArC(OMe)=NPr-*i*, *ortho* substituents shift the equilibrium toward the *E* form. The position of the equilibrium depends on solvent, with more polar solvents favoring the *Z* form. For example, for MeC(SBu-*t*)=NMe, which is 92% *E* in C_6D_6, there is 80% *E* in $CDCl_3$ and only 60% *E* in CD_3OD. Also, as with ordinary imidate esters the proportion of (*Z*)-PhC(SMe)=NMe increases with the acidity of an added phenol, from 73.6% with *p*-*t*-butylphenol in $PhNO_2$ to 83.9% with *p*-bromophenol. With *S*-methyl *o*-hydroxythiobenzimidates, *o*-$HOC_6H_4C(SMe)$=NR, the configuration in $CDCl_3$ is entirely *Z*, since only this configuration can form an intramolecular hydrogen bond with the *ortho* hydroxyl, but in solvents that compete for the hydrogen bond there are again substantial amounts of the *E* form.

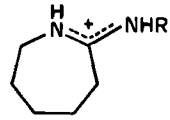
B. Configurations of Conjugate Acids and Bases

1. *Configurations of amidinium ions*

The antibiotic imipenem (**9**) and a model *N*-alkyl formamidinium ion H_2NCH=NHR^+ (R = $CH_2CH_2SC_6H_4CO_2^-$-*o*) are present[34] at equilibrium in water as a 2:1 mixture of *Z* and *E* stereoisomers. They could be characterized by ^{1}H and ^{13}C NMR, and they are separable by HPLC or crystallization. X-ray analysis verified that the major form is *Z*.



(**9**)



(**10**)

In $CDCl_3$ the cyclic amidinium ion **10** (R = *p*-TolCHPO_2OMe$^-$) is present[35] as a 30:70 mixture of *Z* and *E* forms, assigned on the bais of ^{1}H NMR chemical shifts. With other ring sizes the proportions change slightly, but in CD_3OD these are entirely the *Z* isomer. In CF_3COOH the tri-substituted formamidinium ion $HC(NEt_2)(NHPh)^+$ shows[5] a $^3J_{HCNH}$ of 17.3 Hz, consistent only with an *E* stereoisomer.

The previous cases were simple, in that their substitution patterns permit only *Z* and *E* isomers. With patterns of lower symmetry the question of isomerism is more complicated, since each C—N partial double bond can be *Z* or *E*. As Figure 2 shows, there can then be up to four stereoisomers, although the *ZZ* isomer (**2ZZ**) is usually absent, owing to severe

TABLE 6. Equilibrium between *ZE* and *EZ* stereoisomers of amidinium ions $RC(NR'Me)(NHR'')^+$

R	R′	R″	%*ZE*	Ref.
H	H	Me	5(%*EE*)	37
Me	H	H	96(%Z)	38
Me	Me	Me	<2(%Z)	38
Me	H	*i*-Pr	54	38
Me	H	Bu	52	38
Me	H	neoPen	61	38
Me	H	CH_2Ph	38	38
Me	H	*t*-Bu	85	38
Me	H	$CH_2CMe{=}CH_2$	38	39

steric repulsions, and with identical nitrogens the *EZ* (**2*EZ***) is not different from the *ZE* (**2*ZE***). The *ZE* stereoisomer of *N,N′*-diphenylacetamidinium ion $MeC(NHPh)_2^+$ has been verified[36] by X-ray crystallography.

The ^1H NMR spectrum of *N,N′*-dimethylformamidinium ion[37] $HC(NHMe)_2^+$ in aqueous HCl shows two *N*-methyl peaks, at δ 3.70 and δ 3.49, corresponding to the inequivalent methyls of the dominant *ZE* stereoisomer. There is also a peak at δ 3.62, due to the *EE* isomer. These peaks were assigned on the basis of the ^4J.

N,N′-Dialkylamidinium ions with two different alkyl groups exist almost exclusively as a mixture of *ZE* (**2*ZE***) and *EZ* (**2*EZ***) stereoisomers (Figure 2), although formamidinium ions have an additional *EE* form (**2*EE***). These may be assigned on the basis of NMR chemical shifts, since an *E* substituent is generally downfield of the *Z*, as in amides. The proportion of *ZE* form for a series of *N*-alkyl-*N′*-methyl amidinium ions in DCl/D_2O is listed in Table 6. Also included are the monomethyl and trimethyl acetamidinum ions.

The NMR spectrum of the drug mifentidine, $HC(NHPr\text{-}i)(NHAr)^+$, Ar = *p*-imidazolylphenyl, shows[40] two different CH signals, in the ratio 6:4. These are attributed to the *EE* plus the *ZE* or *EZ* forms.

The puzzling equilibrium constants in *N*-*t*-butyl-*N′*-aryl- and *N,N′*-diaryl-formamidinium ions can now be understood. It had been observed[41] that electron-donating substituents shift the equilibrium toward the *ZE* form. This was considered to be contrary to resonance theory that predicts that the *EE* isomer, which can be coplanar, will be stabilized by electron-donating substituents. Therefore the *ZE* form was considered to be stabilized by dipolar interactions. However, it is clear that electron-donating substituents cannot delocalize the positive charge of the amidinium ion, even when it is planar, whereas electron-withdrawing substituents can delocalize the lone pair on the nitrogen and stabilize the *EE* form, as observed.

Relative stabilities of stereoisomeric *N*-methyl-*N′*-phenylformamidinium ions $HC(NHMe)(NHPh)^+$ have been calculated[42] by MO theory. The *EE* isomer is most stable, with the *EZ* 0.56 kcal mol^{-1} higher energy, and the *ZZ* > 0.65 kcal mol^{-1} higher. Since it is likely that the relative stabilities are determined by steric interactions in a structure constrained to be planar, molecular mechanics calculations might be useful in estimating stereoisomer energies for a wider range of such ions.

2. *Configurations of amidinate anions*

It is surprising that the stereochemistry of amidinate anions $RC(NR')_2^-$ is so poorly established. They are isoelectronic to the well-known case of carboxylic acids, where lone pair repulsions or dipole–dipole interactions strongly favor the *Z* form. Therefore

it might be expected that the *ZZ* form of an amidinate anion would be favored. However, mutual repulsions of bulky substituents on the nitrogens could favor the *ZE* form, and solvation or counterion effects might favor the *EE* form.

A 3-21G MO calculation[17] on $HC(NH)_2^-$ shows that the *ZZ* form is most stable, with the *ZE* form 3.7 kcal mol^{-1} less stable, and the *EE* form 12.2 kcal mol^{-1} less stable. A 6-311 + + G**/MP3 calculation[20] shows that the *ZZ* form is most stable, with the *EE* form 5.5 kcal mol^{-1} higher in energy.

In CD_3NH_2 the ^1H NMR of the anion $HC(NMe)_2^-$ shows[37] equivalent methyl peaks down to $-56\,°C$. From the $^4J_{HCNCH}$ of 0.5 Hz it was concluded that this is the *EE* stereoisomer.

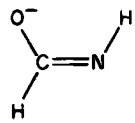
In order to account for the preferential formation of the *Z* stereoisomer of **5**, it was proposed[9] that lone pair repulsions favor the *ZZ* stereoisomer of the amidinate *t*-BuCHBrC(NMe)(NR)$^-$, not only for R = Me but also for R = *t*-Bu.

3. *Configurations of conjugate acids of imidate esters and of imidatonium ions*

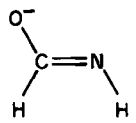
The equilibrium between *Z* and *E* isomers of protonated imidate esters is indicated in Table 7. For the conjugate acid MeC(OTol-*p*)=NHMe$^+$ only the *Z* form could be detected[26], even though the imidate ester itself is 80% *E*. The reversal is attributed to interference of the hydrophobic aryl group with solvation of the proton. Also, for the imidatonium ion HC(OMe)=NMeAr$^+$ (Ar = 2,6-Xyl)[43] the equilibrium favors the *E* form by *ca* 3:1.

4. *Configurations of imidate anions*

An imidate anion RC(—O$^-$)=NR is isoelectronic to carboxylic acids and esters RC(=O)—OR. Since these are *syn* as regards the C—O single bond, owing to lone-pair or dipole–dipole repulsions that destabilize the *anti* conformer, an imidate anion may be expected to be *Z* (**11*Z***) rather than *E* (**11*E***) as regards the C—N double bond. Results of MO calculations on the conjugate bases of formimidic acids are listed in Table 8. They all agree with this analogy to carboxylic acids and esters. However, according to calcul-



(**11*Z***)



(**11*E***)

TABLE 7. Equilibrium between *Z* and *E* stereoisomers of protonated imidate esters, RC(OR')=NHR''$^+$

R	R'	R''	Solvent	%*Z*	Ref.
H	Et	Me	CD_3NO_2	< 100	44
Me	*p*-Tol	Me	H^+/H_2O	> 87	26
t-Bu	Me	Ph	H_2SO_4	81.0	27
Ph	Me	*i*-Pr	CF_3COOH	91.8	27
Ph	Me	Ph	CF_3COOH	60.6	27
Ph	Me	Ph	$CHCl_2COOH$	68	27
Ph	Me	2,6-Xyl	CF_3COOH	65.3	27
o-FC_6H_4	Me	*i*-Pr	CF_3COOH	91.4	27
o-ClC_6H_4	Me	*i*-Pr	CF_3SO_3H	84.7	27

ations[47] solvation by a molecule of water stabilizes the *E* form more than the *Z*, so that the relative stabilities may be reversed in solution.

Although stereochemical aspects of amides have long been studied, imidate anions were neglected until recently. The stereoisomeric *N*-alkylformimidate anions, HC(—O⁻)=NR, have been characterized[48] by ^{1}H NMR. Each exists as an equilibrium mixture of *Z* and *E* forms. Rapid reprotonation preserves that mixture's proportions and creates the parent *N*-alkylformamide in a nonequilibrium mixture of its *Z* and *E* forms, which equilibrate on standing. The *E*/*Z* equilibrium constants for the imidate anions are listed in Table 9. With few exceptions the *E* stereoisomer is more stable than the *Z*, and even those exceptions disappear if the imidate anion is compared with its amide, where the *Z* form has an inherently greater stability. This is contrary to the simple molecular orbital calculations above, but it is consistent with the calculated effect of solvation. Indeed, the $\Delta S°$ for isomerization of *E* imidate anion to *Z* is $+10-20\,\text{cal mol}^{-1}\,\text{deg}^{-1}$, suggesting a difference in solvation. The discrepancy between the calculated stabilities and the experimental ones can then be attributed to steric hindrance by the *N*-alkyl group to

TABLE 8. Calculated relative stabilities (kcal mol^{-1}) of stereoisomeric formimidate anions, HC(—O⁻)=NR

R	*E*(*Z*)	*E*(*E*)	Method	Ref.
H	0	7.0	3-21G	45
H	0	>0	4-31G	46
H	0	6.9	4-31G	47
H	0[a]	2.7[a]	4-31G	47
H	0	5.4	MP4SDQ	47
H	0	3.6	6-311++G**/MP3	20
Me	0	4.7	6-31G**	47

[a]Imidate monohydrated.

TABLE 9. Equilibrium constants, $K=[Z]/[E]$, for *N*-alkylformimidate anions, HC(—O⁻)=NR, at 22 °C

R	Solvent	*K*	Ref.
Me	DMSO-d_6	4.09	48
t-Bu	DMSO-d_6	0.19	48
CH_2Ph	THF	<0.03	48
CH_2Ph	DMSO-d_6	0.26	48
Ph	THF	<0.07	48
Ph	*c*-HexOH-dioxan	0.17	48
Ph	*c*-HexOH	0.42	48
Ph	DMSO-d_6	~0.3	48
Ph	$HOCH_2CH_2OH$	1.02	48
Ph	EtCONHMe	0.37	49
m-Tol	EtCONHMe	0.30	49
p-Tol	EtCONHMe	0.25	49
3,5-Xyl	EtCONHMe	0.22	49
m-$MeOC_6H_4$	EtCONHMe	0.41	49
p-$MeOC_6H_4$	EtCONHMe	0.31	49
p-BrC_6H_4	EtCONHMe	0.29	49
m-$O_2NC_6H_4$	EtCONHMe	0.26	49

solvation of the *Z* form, and the solvent dependence of the equilibrium constant is consistent with this interpretation.

The relative stabilities of stereoisomeric imidate anions correspond to the relative acidities of diastereotopic protons of amides. It follows from thermodynamics that the greater stability calculated for (*Z*)-HC(—O$^-$)=NH means that H_E is the more acidic proton of formamide. This contrasts with protonated or *O*-alkylated acyclic amides (see Section VII.B.2), where H_Z is more acidic than H_E. The difference arises because relative stabilities of the stereoisomeric imidate anions are determined by lone-pair/lone-pair repulsions, whereas stabilities of the imidate esters are determined by dipole/dipole interactions. As further evidence for the greater acidity of H_E in formamide, it has been found[50] by STO-3G molecular orbital calculation that OH^- hydrogen bonds more strongly to this proton. Moreover, it is quite a general observation[51] for primary amides that H_E undergoes base-catalyzed proton exchange faster than H_Z. However, in nonpolar solvents it is H_Z that is faster, and in secondary amides[52] and a lactam[53] it is also H_Z that is faster. These results were rationalized by recognizing that an *E* imidate anion can be stabilized more than the *Z* by solvent or counterion, and that a *Z N*-alkyl group interferes with that stabilization, as described above to account for the relative stabilities of stereoisomeric *N*-alkylformimidate anions.

5. *Configurations of metal complexes of amidines*

Amidines (and imidate esters) can form metal complexes $RC(NR_2)=NR\rightarrow M$ [or $RC(OR)=NR\rightarrow M$], with a metal bound to the sp^2 nitrogen. These are analogous to amidinium (or imidatonium) ions. However, since the metal is a high-ranking substituent according to the Cahn–Ingold–Prelog sequence rules, the metal complex of a *Z* ligand is of *E* stereochemistry, and *vice versa*.

In $CDCl_3$ the methyl(dimethylglyoxime)cobalt(III) complex of *N*,*N*′-dimethylformamidine, $HC(NHMe)=NMe\rightarrow M$ [M = $MeCo(DMGH)_2$], is a 1:2 mixture of *Z* and *E* isomers, distinguishable[54] by the larger $^4J_{HCNCH_3}$ of 1.5 Hz in the *E* isomer. For the bis(amidine) complex, $[HC(NHMe)=NMe\rightarrow]_2M$ [M = $Co(DMGH)_2$], in CD_3CN each of the amidine fragments can be *Z* or *E* independently, but only the *EE* isomer, with a $^4J_{HCNCH_3}$ of 0.5 Hz, could be detected. The *E* stereochemistry is presumably favored on steric grounds.

The nickel complex, $MeC(NRR')=NH\rightarrow NiL$, where L is a tridentate ligand, is a mixture of *Z* and *E* forms, distinguishable[55] by ^1H NMR. For R = R′ = Me, there is only 9% *Z* in $CDCl_3$, and none in DMSO. For R = Et, R′ = H, there is an 8:7 mixture.

The $PtCl_2(N{\equiv}CPh)$ complex of $PhC[N(t\text{-}Bu)CH_2CH_2NHBu\text{-}t]=NH$ is a mixture of stereoisomers[56] about the C—N double bond. By comparison of the NH chemical shifts with those of chelated model compounds that must be *Z*, it was concluded that the major form is *E*, present to 90% in CD_2Cl_2, or 67% in $CDCl_3$. In support, the crystalline form was found to be *E* by X-ray analysis.

6. *Configurations of metal amidinates*

Treatment of *N*,*N*′-dimethylacetamidine with Me_3M (M = Al, Ga, In) produces[57] the Me_2M^+ salt of the amidinate, $MeC(NMe)_2^-$. According to mass spectrometry this is dimeric, and the IR/Raman spectra show that it is centrosymmetric. Therefore the stereochemistry must be *ZZ*, with an eight-membered ring.

Many metal complexes of amidinates have the metal bonded equivalently to both nitrogens, and the *ZZ* configuration of the complex, or the *EE* configuration of the ligand itself, can be confirmed by X-ray analysis. Among the complexes are $MoCl_4^+$ and $ReCl_4^+$ complexes[58] of $ClC(NPr\text{-}i)_2^-$, $AlCl_2^+$ and $SnCl_3^+$ complexes[59] of $PhC(NSiMe_3)_2^-$, the

Me_2Al^+ complex[60] of $PhC(NSiMe_3)_2^-$, 2:1 complexes[61] of this amidinate with $TiCl_2^{+2}$ and MoO_2^{+2}, and anionic complex[62] of this amidinate with $SnCl_3F$, vanadium complexes[63] of $HC(NTol\text{-}p)_2^-$, the 2:1 complex[64] of $MeC(NTol\text{-}p)_2^-$ with Pd^{+2}, and $CpMo(CO)_2^+$ complexes[65] of $RC(NPh)_2^-$ [R = 2,4-cyclopentadienyl and $CpMo(CO)_3$]. Also, there are various dimetal (Ag_2, Cu_2, Ir_2, quadruply bonded Mo_2, Re_2, Cr_2 and Rh_2) salts with 2, 3 or 4 amidinate counterions such as $PhC(NPh)_2^-$, $PhC(NMe)_2^-$ or $HC(NTol\text{-}p)_2^-$ that have the two metals in close proximity. This again requires the *ZZ* configuration of the complex, or the *EE* configuration of the amidinate ligand itself, which is confirmed[66] by X-ray analysis. A similar structure is seen[67] with the tetrameric $[HC(NPh)_2^-Au^+]_4$. The further complication of chiral centers at the metal and at both alpha carbons is seen with the $CpMo(CO)_2^+$ complex[68] of $PhC(NCHRPh)(NCHR'Ph)^-$.

7. *Configurations of metal complexes of imidate esters and imidate anions*

Reaction of the nickel acetonitrile complex, $MeCN—NiL_2Ar$ ($Ar = C_6Cl_5$, $L = PhPMe_2$) with methanol or ethanol produces[69] $MeC(OR)=NH \rightarrow NiL_2Ar$ as a mixture of stereoisomers, in ratio 5:3 for R = Me or 8:5 for R = Et. With the phenylacetonitrile complex these ratios are 5:1 and 7:2. For the bulkier $L = Ph_2PMe$ only one isomer is formed. Although the *Z* and *E* stereoisomers could be distinguished by their NMR spectra, they were not assigned.

Similarly, various tungsten complexes, $RC(OR')=NH \rightarrow Mo(CO)_5$, appear[70] as a mixture of *Z* and *E* forms, with different ^1H and ^{13}C NMR spectra. No interconversion could be detected up to 60 °C. The chromium analog is a single stereoisomer.

Subsequently, the ^1H NMR spectra of such stereoisomers, but of the cationic complexes $RC(OMe)=NH \rightarrow NiL^+$ (R = Me, Et or Ph, L = a tridentate ligand), have been assigned[55] on the basis of the proximity of substituents to the deshielding nickel. The *E* form of the complex (with *Z* imidate as ligand) predominates, to 60–75%, and the proportion of the *E* form increases at lower temperature.

Addition of one or two moles of methanol to the coordinated benzonitrile ligands of either *cis*- or *trans*-$(PhCN)_2PtCl_2$ produces[71] the mono or di PhC(OMe) = NH complexes of the platinum. For the mono complex $PhC(OMe)=NH \rightarrow PtCl_2(NCPh)$ there are *Z* and *E* forms (with *E* or *Z* imidate ester as ligand, respectively), and for the di complex $[PhC(OMe)=NH \rightarrow]_2PtCl_2$ there are *ZZ*, *ZE* and *EE* forms. The NMR spectra were assigned on the basis of a downfield chemical shift for the methoxy or *ortho*-hydrogen that is *cis* to the platinum. The stereoisomers can be separated by chromatography or crystallization, and often a nonequilibrium distribution of stereoisomers precipitates from the reaction mixture. At equilibrium in $CDCl_3$ there is a 1:8:3 mixture of *ZZ*, *ZE* and *EE* stereoisomers for the *trans*-diimidato platinum complexes, and a 1:10:7 mixture for the *cis*. Despite the proximity of the bulky phenyl and platinum, the *E* imidate complex is favored over the *Z*, especially in the *cis*, where a reciprocal influence of the two ligands is thought possible.

The crystal structure of the Cu(II) complex of a bicyclic $RC(OMe)=NR'$ shows[72] that the stereochemistry is *E*, as required by the polycyclic nature of the complex, and that the C—O single bond is *anti*.

The crystal structures of the dichromium complex of an *N*-arylacetimidate anion, η^2-$(MeCONAr)_4Cr_2$ (Ar = 2,6-Xyl) and of its molybdenum isomorph have been determined[73]. Since this is an η^2 complex, it is necessarily *Z*, with an *E* imidate anion. Similarly, the η^2 nature of the isocyanate or carbamate ligand of Cp*Ir(CO)(*t*-BuNCO) or Cp*Ir(OCONBu-*t*) requires[74] that the imidate anions be of *Z* stereochemistry as regards the C—N partial double bond.

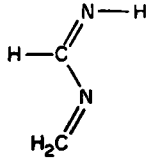
Most metal imidates whose stereochemistry is known involve coordination at nitrogen. One *O*-metallated exception[75] is the difluoroboron complex of *N*-(4-fluoro-2-

pyridyl)acetimidate anion. Its unusually high stability, relative to other difluoroboron complexes of enolic species, was attributed to intramolecular hydrogen bonding to the pyridine nitrogen. This then requires that the imidate be *Z*, and with a *syn* C—O bond.

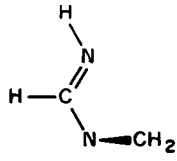
C. Configurations of Amidines and Imidates with sp^2-C Substituents

1. Configurations of N-alkylidene amidines

Molecular orbital calculations agree that the most stable form of $HC(N{=}CH_2){=}NH$ is the planar *Z-anti* stereoisomer (**12**). According to STO-3G MO calculations[76] the *E-syn* is 2.31 kcal mol^{-1} higher is energy. According to double-zeta SCF MO calculations[77] the *E-syn*, *E-anti* and *Z-syn* stereoisomers are respectively 1.0, 3.1 and 8.4 kcal mol^{-1} less stable, with the last destabilized simply by steric repulsion. According to high-level *ab initio* MO calculations[78] the most stable form is again *Z-anti*, although the *E* form, with the C—N single bond twisted by 60° (**13**), is only 0.59 kcal mol^{-1} higher in energy, and twisting the *Z* form by 43° requires only 1.33 kcal mol^{-1}. The X-ray analysis of $PhC(N{=}CHAr){=}NBu\text{-}t$ ($Ar = p\text{-}MeOC_6H_4$) does indeed show that the stereochemistry is *Z* about the C=NBu-*t* bond. However, the CHAr group is twisted 110° from the amidine plane, so that the sp^2 lone pair on the CHAr nitrogen can be delocalized into the amidine C—N double bond.



(**12**)



(**13**)

2. Configurations of N-acylamidines

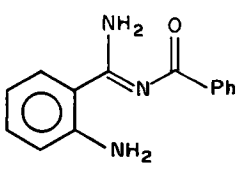
In general *N*-acylamidines $RC(NR'_2) = NCOR''$[79] are exclusively of *E* stereochemistry. This probably arises because the N—C=N—C=O must be coplanar so as to delocalize the lone pair of the distant nitrogen into the carbonyl group. This means that the acyl group is effectively too bulky to give the *Z* isomer, where it would interfere with the *syn N*-

TABLE 10. Equilibrium between Z and E forms of acylamidines and phosphorylamidines $RC(=NR')—NR''R'''$

R	R′	R″	R‴	Solvent	%Z	Ref.
H	*p*-Tol	*p*-Tol	$COCH_3$	CCl_4	0	80
Cl_2CH	Me	Me	$PO(OEt)_2$	CCl_4	48	81
Cl_2CH	Me	Me	$PO(OPr)_2$	CCl_4	44	81
Cl_3C	Me	Me	$PO(OEt)_2$	$CDCl_3$	100	81
Cl_2CH	Me		$=PPh_3$	C_6D_6	68	81
Cl_2CH	Me		$=PPh_3$	CD_3CN	79	81
Cl_2CH	*t*-Bu		$=PPh_3$	C_6D_6	48	81
Cl_2CH	$PhCH_2$		$=PPh_3$	CD_3COCD_3	77	81
Cl_2CH	$PhCH_2$		$=PPh_3$	C_6D_6	57	81
Cl_2CH	Ph		$=PPh_3$	C_6D_6	0	81

alkyl groups. Nevertheless many *N*-phosphoryl amidines, RC(=NR')—N(R")PX_3, show two forms, perhaps because the phosphoryl group can delocalize electrons without strong conformational constraints. The *E*:*Z* proportions for some *N*-phosphoryl amidines in nonpolar solvents are listed in Table 10. In more polar solvents the *Z* form becomes more favored[81].

According to X-ray analysis[82] the acylamidine **14** is in the *Z* form, stabilized by intramolecular hydrogen bonding. In **15** the C—N double bond is exclusively *E*, according to the observed ^5J of 0.88 Hz, which is substantially lower than the 1.76 Hz seen in a model for the *Z* stereoisomer.



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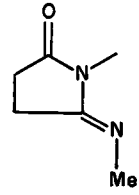

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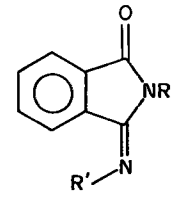

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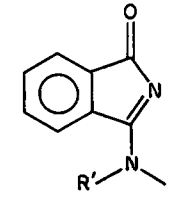


(17)

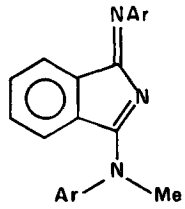
For the iminoisoindolone **16** (R = Me, R' = aryl) only one stereoisomer is observed, assigned[83] as *E* according to the shielding of the benzo ring by the aryl group, which is twisted perpendicular to the plane of the rest of the molecule. The same shielding was seen in the *anti* aminoisoindolinone **17** (R = Me, R' = aryl). However, for **16** (R = H, R' = aryl) there is a mixture of the *E* stereoisomer shown and the *Z* form, which predominates to the extent of 87–88% (or 100% for 2-pyridyl derivatives, which are capable of internal hydrogen bonding) in $CDCl_3$ and to 69–100% in DMSO.

Similar behavior is seen[84] with other compounds **16** (R = H, R' = Me or Bu), which are 95–96% *Z*. In contrast, for R = R' = Me, NOE measurements show that the molecule is 100% *E*. For R = H, R' = Me there is 11–12% *Z*, although in $CDCl_3$ the barrier to interconversion is low, so that the separate forms can be seen only below −50 °C. It is especially unusual to see the separate forms, since proton exchange usually interconverts them.

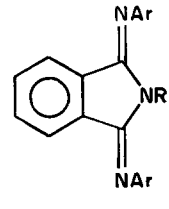
N-Sulfonylformamidines, HC(NR'_2)=NSO_2R", have been assigned[85] as *E* according to CMR and IR spectra and analogy to other amidines.

3. *Configurations of imidines*

In $CDCl_3$ at 263–298 K the aminoiminoisoindoline **18** (Ar = *p*-Tol) occurs[86] as a mixture of 90% *Z* and 10% *E* about the exocyclic C—N double bond. The diimino species **19** is exclusively *EE* for Ar = Ph and R = Me, but for R = H there is a mixture of *ZZ* and *ZE* forms. The proportion of *ZE* isomer increases from 28% for Ar = *p*-$MeOC_6H_4$ to 37% for Ar = Ph, which is relatively electron-withdrawing and provides resonance stabilization when it is coplanar with the imidine. Electronic effects are not the only determinant, since for electron-withdrawing Ar = 2-pyridyl, the material is 100% *ZZ*, owing to an internal hydrogen bond, even in DMSO. These stereoisomers can be distinguished[87] on the basis of chemical shifts. The *ZE* isomer is less symmetric and shows an ABCD pattern for the benzo ring, as well as inequivalent *N*-aryls if these carry methyl groups that can be resolved. The *ZZ* and *EE* forms show an AA'BB' pattern, and the benzo ring is more shielded in the *EE* form. For **19** (R = H) the proportion of *ZZ* form is increased at higher temperature or in more polar solvents, whereas the *ZE* form is favored in solvents like DMSO and pyridine, which are hydrogen-bond acceptors that bind at the NH and repel the *N*-aryl.



(18)



(19)

The nickel(II) salt of the imidine $HN(CMe{=}NH)_2$ is necessarily *ZZ* (*EE* imidine) in order to chelate the nickel, and this is confirmed[88] by X-ray analysis.

D. Configurations of *N*-Heterosubstituted Amidines and Imidates

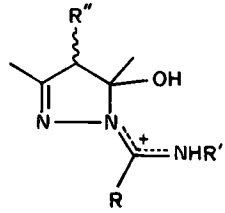
Much progress has been made through studies of *N*-hydroxy, *N*-alkoxy and *N*-amino amidines and imidates, where the configurational stability makes structure determination easier than in simple amidines or imidates. Hegarty[89] has reviewed this topic, from the viewpoint of the reactivity of nitrilium ions.

1. *Configurations of N-aminoamidines*

According to a STO-3G molecular orbital calculation[90] the more stable stereoisomer of $NCC(NH_2){=}NNH_2$ is *Z*.

2. *Configurations of amidrazones*

The equilibria between *Z* and *E* stereoisomers of amidrazones $PhC(NHR){=}NN{=}CMeCH_2COR'$ and also of their enamine tautomers $PhC(NHR){=}NNHCMe{=}CHCOR'$ in CCl_4 have been determined[91] by ^1H NMR. All are entirely *Z* except for one enamine with R = Me, which is 70% *E*. The corresponding conjugate acids are a mixture. For example, for R = H and R′ = OEt the N-protonated keto form is 20% *E* and the N-protonated enamine is 50% *E*. For some cyclic amidrazonium ions (**20**), the *E*/*Z* equilibria are given in Table 11.



(20)

TABLE 11. *E*/*Z* equilibrium[91] in some amidrazonium ions, **20**

R	R′	R″	%*E*
Me	H	H	35
Ph	H	H	33
Ph	H	Me	20
Ph	Me	H	15

3. Configurations of amidoximes

Since amidoximes are configurationally more stable than amidines, it seems that it would be easier to elucidate their stereochemistry. However, there have been several complications. One is that the *Z* stereoisomer is often the one that is formed more quickly by amine addition to a nitrile oxide, and this then rearranges at a measureable rate to the *E* isomer. Another complication is that the stable configuration of *N,N*-dialkyl amidoximes is different from that of *N*-alkyl or unsubstituted amidoximes. Besides, the resonance contribution to the dipole moment was sufficiently uncertain that some amidoximes were misassigned.

The kinetically formed benzamidoximes $ArC(NMe_2)=NOH$ (Ar = *p*-$MeOC_6H_4$, *p*-Tol, Ph, *p*-ClC_6H_4, *p*-$O_2NC_6H_4$) were assigned[92] as *Z* through the use of paramagnetic shift reagents, and on heating each is converted to the more stable *E* form. Although these assignments contradict those based on dipole moments, further evidence was obtained[93] from chemical shift correlations, aromatic solvent induced shifts and nuclear Overhauser enhancements. Conclusively, an X-ray analysis of the stable form of $PhC(NMe_2)=NOH$ showed that it is indeed *E*, as had been found[94] for $MeC(NMe_2)=NOH$. Further NMR studies indicated that the kinetic product from addition of morpholine to the nitrile oxide *p*-$O_2NC_6H_4CNO$ is the *Z* form, which is converted to the more stable *E* form by heating or treatment with acid, and these assignments are in agreement with the dipole moments and with X-ray analysis[95] of the stable form. Likewise, X-ray analysis[96] showed that the stable isomer of $PhC(NEt_2)=NOH$ is *E*. Further dipole moment studies[97] showed that various $RC(NMe_2)=NOH$ and $RC(NMe_2)=NOAc$ are *E*. Nevertheless crystalline $ArC(NHPh)=NOH$ (Ar = 2,6-$Cl_2C_6H_3$)[98] is *Z* (and *anti* about N—O and C—N). Also, $ArCH(OH)C(NH_2)=NOH$ [Ar = 3,4-(methylenedioxy)phenyl][99], $PhC(NH_2)=NOH$[96] and the parent $HC(NH_2)=NOH$[100] are found to be *Z-anti*, and these assignments agree with dipole moment measurements and chemical shift correlations[101,102] on $ArC(NH_2)=NOH$ and $ArC(NH_2)=NOCOAr'$. Further evidence from ^{15}N NMR[103] shows that $PhC(NHR)=NOH$ (R = H, Me or Ph) are *Z*, whereas $PhC(NR_2)=NOH$ [R,R = Me, Me or Ph, Me or $(CH_2)_5$] are *E*, or perhaps a mixture of *Z* and *E*.

The resolution of these apparently contradictory assignments is that with *N,N*-disubstituted amidoximes, the initially formed *Z* isomer can be converted by heating to the more stable *E* isomer. Howwever, with *N*-monosubstituted or-unsubstituted amidoximes, the initially formed *Z* isomer is also the more stable one, owing perhaps to internal hydrogen bonding[93]. Thus the stabilities depend on the substitution pattern. The *E* form is the more stable for *N,N*-disubstituted amidoximes, but the *Z* form is more stable for *N*-unsubstituted and -monosubstituted[104].

TABLE 12. Equilibrium between *Z* and *E* forms of amidoximes, $RC(NR'R'')=NOR'''$

R	R′	R″	R‴	Solvent	%*Z*	Ref.
o-Tol	H	Ph	H	DMSO-d_6	83.5	105
p-Tol	—$(CH_2)_4$—		Me	dioxan	12	106
2,6-$Cl_2C_6H_3$	H	Ph	H	DMSO-d_6	62	105
Mes[a]	H	Ph	H	DMSO-d_6	67	105
p-$MeOC_6H_4$	—$(CH_2)_4$—		Me	dioxan	12	106
p-ClC_6H_4	—$(CH_2)_4$—		Me	dioxan	13	106
3,5-Cl_2Mes[a]	H	Ph	H	DMSO-d_6	62	105
p-$O_2NC_6H_4$	Me	Ph	H	H_2O	67	107
p-$O_2NC_6H_4$	—$(CH_2)_5$—		Me	dioxan	12	106

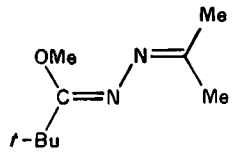
[a] Mes = 2,4,6-$Me_3C_6H_2$.

Some amidoximes are a mixture of *Z* and *E* stereoisomers, even though dipole moment measurements on ArC(NHR)=NOH, as well as cyclization by $COCl_2$ or $SOCl_2$, had suggested[105] that these are of *Z* configuration. The proportions of the two forms are indicated in Table 12. *N,N*-Pentamethylene-*p*-nitrobenzamidoxime shows the interesting feature[106] of isomerizing in the solid to the *E* form, even though this is the less stable one in solution.

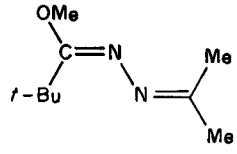
4. Configurations of hydrazide derivatives

In general, the more stable stereoisomer of a hydrazidate ester $RC(OR')=NNR''_2$ is *E*, although the *Z* isomer is often the one formed faster[108]. This is discussed in Section VI.C.3. For RC(OMe)=NNMeAr [R = Ph or t-Bu, Ar = Ph, p-$O_2NC_6H_4$ or 2,4-$(O_2N)_2C_6H_3$] the equilibrium proportion of *E* stereoisomer ranges from 20 to 78%.

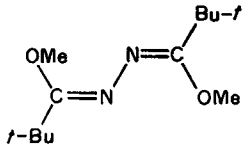
Most hydrazonate esters $RC(OR')=NN=CR''_2$ are a single stereoisomer, according to NMR[109]. However, with pivalate derivatives, which contain a *t*-butyl group, two forms (**21Z, 21E**) can be detected, and three for a molecule with two hydrazonate groups (**22ZZ**, plus *ZE* and *EE* forms). Since a *t*-butyl group can destabilize only the *E* form, it can be concluded that the simpler compounds that are a single form must be *E*. Relative to other imidates, these show a greater preference for the *E* form. This may be due to a greater destabilization of the *Z* form by repulsion between the *O*-alkyl and the other nitrogen, in the *anti* conformation, or to repulsions between the oxygen and nitrogen lone pairs in the *syn* conformation.



(21Z)



(21E)



(22ZZ)

According to 6-31G**/MP2 calculations[110] the *Z* stereoisomer of the hydrazidoyl fluoride $HCF=NNH_2$ is 4.3 kcal mol^{-1} more stable than the *E* isomer. In agreement, the only available hydrazidoyl chlorides are the *Z*. This is opposite to the situation described above for hydrazidate esters, where the *E* form is slightly more stable. Perhaps the stability of the *Z* halide is due to a generalized anomeric effect, arising from delocalization of the nitrogen lone pair into the C—X σ^* orbital.

5. Configurations of hydroximates and related derivatives

Hydroximoyl and alkoximoyl halides had been a problem for several years. There had been some confusion from misassignment on the basis of dipole moment studies, but X-ray analyses have been definitive. In particular, the stable isomers of p-$O_2NC_6H_4CCl=NOH$[111] and p-$O_2NC_6H_4CCl=NOMe$[112] were found to be *Z-anti*.

Equilibration with catalytic HCl shows[113] that the *Z* forms of various ArCCl=NOMe (Ar = Ph, p-$O_2NC_6H_4$, p-Tol, p-ClC_6H_4, p-*t*-BuC_6H_4) are much more stable than the *E*. Originally these assignments had been mistakenly reversed, but the X-ray analyses show that the stable form is the *Z* isomer. This is also consistent with the ^1H NMR spectra, where the methoxy group of the *E* form is shifted upfield by proximity to the aromatic ring, just as in hydroximate esters, ArC(OR)=NOMe. These in turn are of certain assignment, since several have been assigned by chemical interconversion and by correlation of ^1H and ^{13}C NMRs and melting points with the higher-melting isomer of MeC(OMe)=NOH,

whose structure was confirmed[114] as *Z* by X-ray crystallography. Moreover, a series of hydroximoyl chlorides[115] shows consistency of the infrared and NMR spectra, so that all of these are *Z*.

Although the *Z* isomer of an oximoyl halide is considerably more stable than the *E*, the stabilities of the alkoximate esters are more closely balanced. For PhC(OMe)=NOMe in acetic acid, the equilibrium mixture[113] contains 32% *Z*, and 20% in benzene. With other substituents the equilibrium is hardly changed, except that with *o*-TolC(OMe)=NOMe there is only 12% *Z* in acetic acid. The contrast between halides and esters is not clear. Rationales based on dipole moments suggest that the *E* halide should be more stable. Therefore the stability of the *Z* halide may again be due to a generalized anomeric effect, as proposed (Section II.D.4) for hydrazidoyl halides.

E. Configurations of C-Heterosubstituted Amidines

1. Configurations of isothioureas

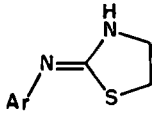
N-Arylisothioureas, $MeSC(NH_2)=NAr$, exist as a mixture[116] of *Z* and *E* stereoisomers, in nearly equal amounts. For *N*-aryl-*N'*-methylisothioureas[117] the *Z* form is slightly favored, especially in more polar solvents. The proportion of *Z* form increases with electron-withdrawing groups on the aryl ring, since the SMe is bulkier than the NH_2 and interferes with a coplanar aryl. Similar behavior is seen[118] for 2-(arylimino)thiazolidines in $CDCl_3$–CD_3OD, but in $CDCl_3$ intermolecular hydrogen bonding shifts the equilibrium to the *Z* form (**23**). *N*-Phosphorylated isothioureas (**24**, **25**) also exist as a mixture of *Z* and *E* forms, distinguishable[119–121] by ^{31}P and ^{13}C NMR. The proportions of the stereoisomers are listed in Tables 13 and 14.

TABLE 13. Equilibrium between *Z* and *E* forms of isothioureas MeSC(NHR)=NR'

R	R'	Solvent	%*E*	Ref.
H	aryl	$CDCl_3$-CS_2	33–50	116
alkyl	alkyl	$CDCl_3$	100	121
Me	Ph	$CDCl_3$	100	121
Me	Ph	$CDCl_3$-CS_2	33	117
Me	MeP(O)OPh	CD_3COCD_3	67	120
Me	MeP(O)OPh	CD_3OD	41	119
Me	MeP(S)OEt	CD_3COCD_3	86	119
Me	MeP(S)OEt	CD_3COCD_3	75	120
Me	MeP(S)OEt	CD_3OD	71	119
Me	MeP(S)OEt	CD_3OD	58	120
Me	MeP(S)OPh	CD_3COCD_3	86	119
Me	MeP(S)OPh	CD_3COCD_3	55	120
Me	MeP(S)OPh	CD_3OD	76	119
Me	MeP(S)OPh	CD_3OD	44	120
Me	$PO(OEt)_2$	CD_3COCD_3	85	119
Me	$PO(OEt)_2$	CD_3OD	33	119
Me	$PS(OEt)_2$	CD_3COCD_3	78	119
Me	$PS(OEt)_2$	CD_3COCD_3	66	120
Me	$PS(OEt)_2$	CD_3OD	66	119
Me	$PS(OEt)_2$	CD_3OD	50	120
t-Bu	$PO(OEt)_2$	$CDCl_3$	10	122
t-Bu	$PO(OEt)_2$	CD_3OD	90	122

TABLE 14. Equilibrium between *Z* and *E* forms of *N*-phosphorylated isothioureas $RSC[N(R')PO(OEt)_2]=NR''$

R	R′	R″	Solvent	%*E*	Ref.
Me	Me	Me	C_6D_6	42	121
Me	Me	Me	CD_3CN	46	123
Me	Me	Et	C_6D_6	47	121
Me	Me	Et	C_6D_6	50	123
Me	Me	*i*-Pr	C_6D_6	52	121
Me	Me	*t*-Bu	C_6D_6	100	121
Me	Et	Me	C_6D_6	36	121
Me	Et	Me	C_6D_6	41	123
Me	*i*-Pr	Me	C_6D_6	40	121
Me	*t*-Bu	Me	C_6D_6	0	121
Et	Me	Et	C_6D_6	48	121
Et	Me	*i*-Pr	C_6D_6	46	121
Et	Et	Me	C_6D_6	32	121
Et	*i*-Pr	Me	C_6D_6	31	121



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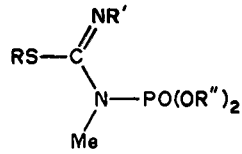

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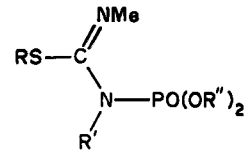


(25)

The *E*/*Z* equilibrium constants have been determined[124] for a series of isothiouronium ions, $RSC(NR'_2)_2^+$. Even if the two groups on a nitrogen are as disparate as hydrogen, methyl, benzyl or aryl there is little preference for one stereoisomer over the other.

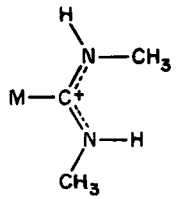
2. *Configurations of haloformamidines and haloformimidates*

In CD_3OD the ^1H NMR spectrum of $ClC(NHMe)_2^+$ shows[125] *N*-methyl peaks at δ 2.9, 3.1 and 3.2, in a ratio of 1.2:1.0:1.0. These were attributed to 30% of the *EE* stereoisomer, plus 70% of the *ZE*, which has inequivalent methyls. However, the chemical shift of the (*E*)-*N*-methyl of the *ZE* isomer ought to be closer to that of the *N*-methyls of the *EE* isomer, and it may be that hydrolysis produced some $CD_3OC(NHMe)_2^+$. The stereochemistry of this simple ion should be reinvestigated in an aprotic solvent.

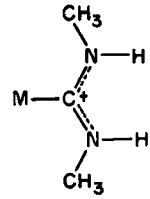
According to MNDO calculations[126] the *E-syn* forms of FC(OH)=NH and ClC(OH)=NH are 1.8 and 0.1 kcal mol^{-1}, respectively, more stable than the *Z-anti* forms.

3. *Configurations of C-metallosubstituted amidines*

Just as with simple amidinium ions, the ^1H NMR spectrum of the cationic gold complex $Au[C(NHMe)_2]_2^+$, with two *N*,*N*′-dimethylamidinium ligands, shows[127] two different *N*-methyls, so that it must be the *ZE* stereoisomer (**26ZE**, $M = Au_{1/2}$). This is an Au(I) complex, but the same behavior is seen with the Au(III) complex.



(26ZE)



(26ZZ)

Dimethylglyoximecobalt(III) complexes with *N,N'*-dimethylamidinium ligands appear[54] as a mixture of *ZE* [**26ZE**, M = Me(DMGH)$_2$Co] and *ZZ* (**26*ZZ***) stereoisomers. For the *ZE* isomer, the upfield ^{1}H NMR peak was assigned to the *E* methyl by comparison with $HC(NHMe)_2^+$, and the other isomer was assigned as *ZZ* on the basis of comparison of chemical shifts. In $CDCl_3$ there is a 1:1 mixture of the two, but the proportion of the *ZE* form increases in more polar solvents. For bis(amidinio)cobalt complexes (**26*ZE***, **26*ZZ***, M = $[(DMGH)_2Co]_{1/2}$) each of the amidinium fragments can be *ZE* or *ZZ* independently, but the presence of a mixture of isomers leads to an unresolved multiplicity of peaks. With the $(DMGBF_2)_2Co[C(NHMe)_2]_2$ complex there is only one form, assigned as the *EE* structure on the basis of the steric effect expected from the BF_2 group, but with a chemical shift that is appropriate for the *ZZ*.

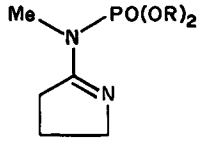
III. CONFORMATION ABOUT C—N AND C—O SINGLE BONDS

A. Conformations of Amidines and Imidates

1. *Conformations of amidines*

Nearly all the amidines studied have two identical groups attached to the singly bonded nitrogen. Therefore there is no conformational equilibrium, but only the dynamics of rotation about the C—N single bond (Section V.A.1). Two exceptions are $Ph(NMeCH_2SMe)=NMe$[10], which exists as a mixture of two conformers, in unequal but unspecified proportion, and $HC(=NPh)—NHPh$[128], which is a 2.92:1 mixture of *anti* and *syn* conformers, although at higher concentrations the equilibrium shifts further to the *anti*, which can form a hydrogen-bonded dimer.

In contrast to many experimental and theoretical values indicating a planar structure for amidines, with a significant barrier to rotation about the C—N single bond, the low $^3J_{CCNP}$ in **27** (R = Et or Ph) suggests[123] that the phosphoryl group is rotated nearly perpendicular to the five-membered ring.



(27)

2. *Conformations of imidate esters and imidic acids*

Stereochemical information regarding conformations of imidate esters could be obtained[129] through ^{1}H nuclear Overhauser enhancements. For PhC(OMe)=NBu-*t* enhancements could be detected at the *ortho* positions on saturating the *t*-butyl group of

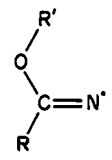
TABLE 15. Calculated relative energies (kcal mol^{-1}) of stereoisomeric imidates, RC(OR')=NR"

R	R'	R"	*E*(*E-anti*)	*E*(*E-syn*)	*E*(*Z-anti*)	*E*(*Z-syn*)	Method	Ref.
H	H	*a*	0	1.65	0	1.65	MNDO	32
H	H	H	8.33	0	3.77	6.66	4-31G	18
H	H	H	0	>0	>0	>0	CNDO/2	16
H	H	H	9.1	0	4.0	3.2	3-21G	45
H	H	H	9.1	0	<9.1	<9.1	3-21G	130
H	H	H	—	0.9	0	—	MNDO	126
H	H	H	—	0	4.21	3.93	6-31G**	131
H	H	H	7.3	0	4.4	3.8	6-311++G**/MP3	20
H	Me	H	7.43	0	1.65	6.11	4-31G	132
H	Me	H	—	0	4.7	—	MNDO	126
H	Me	H	5.0	0.28	0	9.4	4-31G	133
H	OH	H	—	1.11	1.52	0	STO-3G/6-31G	134
Me	H	Me	6.01	3.61	0.88	0	MINDO/3	135
Me	Me	H	7.95	4.65	0.58	0	MINDO/3	135
Me	Me	Me	4.07	8.40	0	36.6	CNDO/2	136

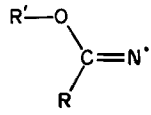
[a]Iminyl free radicals (**28***syn* and **28***anti*), neither *Z* nor *E*.

the *E* isomer and on saturating the methoxy group of the *Z*. This means that the C—O bond of the *E* isomer is *anti* and that of the *Z* isomer is *syn*. Likewise MeC(OMe)=NMe shows mutual enhancements between *C*-methyl and *N*-methyl, but none involving the *O*-methyl, so that this is *E-anti*.

The results of molecular orbital calculations on formimidic acid and its derivatives, RC(OR')=NR", are summarized in Table 15. Some of the calculations found only the optimum geometry or neglected unstable conformers. It can be seen that the *E-syn* form is generally the most stable, but that steric effects can shift the equilibrium toward the *Z* form, as is seen experimentally[24] for imidate esters. It is not clear why two 4-31G calculations[132,133] give such different results.



(28*syn*)



(28*anti*)

The preference for the *syn* form is due to dipole–dipole interactions, as in carboxylic acids and esters, which also have a strong preference for a *syn* C—O single bond. In the *syn* conformer of an imidate ester the interaction between the dipoles of the nitrogen and oxygen lone pairs is more favorable in the *E* stereoisomer. However, if the C—O single bond is somehow constrained to be *anti*, then the interaction of these dipoles is more favorable in the *Z* stereoisomer.

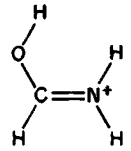
B. Conformations of Conjugate Acids

1. Conformations of imidatonium ions

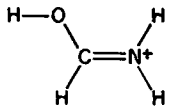
According to NOEs[137], the C—O single bond of HC(OMe)=NMe$_2^+$ is *anti*. According to X-ray analysis[138] the *Z* stereoisomer of HC(OMe)=NMeAr$^+$, Ar = 2,6-

Xyl, has its C—O bond *anti*. These conformations are surely a consequence of steric effects.

MO calculations at the 3-21G level[45] have been carried out for the conjugate acid of formimidic acid. The *syn* conformation of $HC(OH)=NH_2^+$ (**29***syn*) is 3.1 kcal mol^{-1} less stable than the *anti* (**29***anti*). This is in agreement with the experimental results even though steric effects are minimal in this model.



(**29** *syn*)



(**29** *anti*)

2. Conformations of metal complexes of amidines

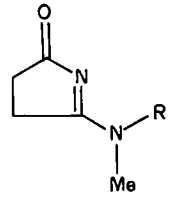
The (dimethylglyoxime)cobalt(III) complexes[54] of *N,N'*-dimethylformamidine, HC(NHMe)=NMe→M [M = MeCo(DMGH)$_2$] and [HC(NHMe)=NMe→]$_2$M [M = Co(DMGH)$_2$], are of *anti* conformation, according to the large $^3J_{HCNH}$ of 13–14 Hz. This holds for both the *Z* and *E* stereoisomers of the former complex.

C. Conformations of Amidines and Imidates with sp^2-C Substituents

1. Conformations of N-acylamidines

For HC(=NTol-*p*)-N(COMe)Tol-*p*, which is the *E* stereoisomer at the C—N double bond, the C—N single bond is exclusively *anti*[80], according to Kerr constant and dipole moment measurements.

For the cyclic acylamidine **30** (R = H)[139] both *syn* and *anti* forms can be seen, in ratio 3:1 in $CDCl_3$ and 9:1 in DMSO. The *syn* form could be distinguished by the long-range ^5J of 0.67 Hz between the *N*-methyl and $H_{(4)}$. In contrast **30** (R = Ph) shows only one *N*-methyl in the ^{1}H NMR, so that one conformer must predominate. Also the aminoisoindolinone **17** (R = Me, R' = aryl) is *anti*, according to the shielding of the benzo ring by the aryl[83].



(**30**)

N-Sulfonylformamidines HC(=NSO_2R)—NR'Ar[85] exist as an unequal mixture of conformers, with hindered rotation about the C—N single bond. For R' = H, the $^3J_{HCNHS}$ of 12.5 Hz and 5.5 Hz permit assignment as *syn* and *anti* forms, respectively. The equilibrium proportions in DMSO-d_6 are given in Table 16. The two forms of HC(=NSO_2Me)—$NHCH_2CH_2NHPh$ can be separated by crystallization, but on dissolution they show the same NMR and IR spectra. These had been considered[140] to be *Z* and *E* forms, but they show the same chemical shifts for the SO_2R groups, so that they differ at the NR'Ar portion of the molecule.

TABLE 16. Equilibrium[85] between *syn* and *anti* conformers of *N*-sulfonylformamidines HC(=NSO_2R)—NR'Ar in DMSO-d_6

R	R'	Ar	% *syn*
Me	H	Ph	42
Me	Ph	$(CH_2)_2NHPh$	20(80?)
Me	H	*p*-Tol	33
Ph	H	Ph	37
p-Tol	H	*c*-Hex	25
p-Tol	H	Ph	43

According to NMR coupling constants between CH and P, the further stereochemistry of the C—$NPPh_3$ single bond of the various $Cl_2CHC(=NR)—N=PPh_3$ in Table 10 (Section II.C.2) could be assigned[81] as *anti* in the *Z* stereoisomers and *syn* in the *E*, although for $Cl_2CHC(N=PPh_3)=NBu$-*t* the Ph_3P is twisted out of the plane.

2. Conformations of imidines

In $CDCl_3$ at 263–298 K both the *Z* and *E* stereoisomers of the aminoiminoisoindoline **18** (Ar = *p*-Tol)[86] are exclusively the *anti* stereoisomer about the exocyclic C—N single bond.

3. Conformations of N-acylimidates

According to 3-21G MO calculations[141] the most stable form of *N*-carboxyformimidic acid, HC(OH)=NCOOH, is *E-syn*, with a barrier of only 4.8 kcal mol^{-1} for rotation about the N—COOH bond. Indeed, the X-ray structure of PhC(OEt)=NCOOPh shows that the molecule is *E-syn*, with the COOPh rotated nearly perpendicular to the C—N double bond. No dynamic NMR behavior could be detected even at low temperature. Similarly, the structure of PhC(OEt)=NCOPh[142] in the crystal is *E-syn*. The N—COPh dihedral angle is 71.6°, so that the carbonyl π system overlaps the nitrogen lone pair, rather than the imidate π system. A 3-21G MO calculation of the parent HC(OH)=NCHO indicates that the *E-syn* form (with the amide C—N also *syn*) is most stable even though the lowest-energy form is calculated as the *Z-syn-syn*, which is stabilized by an intramolecular hydrogen bond that is absent in the actual molecules studied.

D. Conformations of *N*-Heterosubstituted Amidines and Imidates

1. Conformations of amidoximes

Dipole moment measurements[105] on ArC(NHR)=NOH show that these are of *Z* configuration, with antiperiplanar conformations about the C—N and N—O single bonds.

Molecular orbital calculations generally suggest that the most stable configuration of a simple amidoxime is *Z*, with a preferred *anti* conformation about the N=O bond. Results are listed in Table 17. These calculations are in agreement with the experimental data (Section II.D.3), except that for N,N-dimethyl-substituted amidoximes the stabilities are reversed, owing to steric repulsion. For the tautomeric RC(NROH)=NR″ there are also syn and anti conformers about the N—O single bond, but only the more stable conformer is listed in the table.

TABLE 17. Calculated relative energies (kcal mol^{-1}) of stereoisomeric amidoximes, RC(=NOR')—NR''_2

R	R	R''	*E*(*E-anti*)	*E*(*E-syn*)	*E*(*Z-anti*)	*E*(*Z-syn*)	Method	Ref.
H	H	H	1.4	8.1	0	11.04	STO-3G	100
H	H	H	4.0	—	0	—	3-21G	100
H	H	H	3.66	—	0	—	dbl-zeta	143
H	H	Me	0	—	23.5	—	MNDO	144
Me	H	H	5.0	14.75	0	13.05	6-31G*	145
Me[a]	H	H	11.2	0	11.7	8.15	6-31G*	145
Me	H	Me	0	—	9.2	—	MNDO	144
Ph	Ac	H	5.90	—	0	—	CNDO/2	146
Ph	CONHPh	H	> 0	> 0	0	> 0	CNDO/2	147

[a]RC(NR'OH)=NR''.

TABLE 18. Calculated relative energies (kcal mol^{-1}) of stereoisomeric formohydroximic acid derivatives, HC(OH)=NOR

R	*E*(*E-anti*)	*E*(*E-syn*)	*E*(*Z-anti*)	*E*(*Z-syn*)	Method	Ref.
H	6.5	2.5	4.9	0	STO-3G	148
H	—	2.64	—	0	dbl-zeta	143
$^-$(anion)	18.7	9.6	27.0	0	4-31G/CI	149

2. *Conformations of hydroximates*

In contrast to imidic acids, where the *E-syn* form is most stable, molecular orbital calculations on hydroximic acid derivatives RC(OH)=NOR' generally show that the *Z-syn* form is most stable. The results for these derivatives are summarized in Table 18. For the neutral HC(OH)=NOH there is the further possibility of *syn/anti* stereoisomerism about the N—O bond, but the values in the table are for whichever N—O conformer is the more stable. The experimental data on ArC(OMe)=NOMe[113] indicate that the *E* form is slightly more stable, but this may be due to steric repulsions between the methoxy groups in the *Z* form.

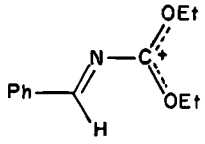
E. Conformations of C-Heterosubstituted Amidines and Imidates

1. *Conformations of guanidinium ions*

The ^{1}H NMR spectrum[150] of $(Me_2N)_2CN(CH_2Ar)_2^+$ shows an AB pattern for the CH_2Ar groups, so that the ion cannot be planar, but must be twisted.

2. *Structure of iminocarbonates*

Some *N*-alkylidene iminocarbonatonium ions show an interesting contrast. For $PhCH{=}N^+{=}C(OEt)_2$ the ^{13}C NMR spectrum[151] at $< -54\,°C$ shows two sets of ethyl signals, corresponding to a structure bent at nitrogen (**31**). In contrast $t\text{-}Bu_2C{=}N^+{=}C(OEt)_2$ shows no separation of signals even at $-90\,°C$, and this is consistent with a linear structure (**32**) as indicated by the IR band at 1750 cm^{-1} and verified by an X-ray structure. A 3-21G MO calculation on $H_2C{=}N^+{=}C(OH)_2$ suggests that the linear form is most stable, although the bent form is only 2.56 kcal mol^{-1} less stable.



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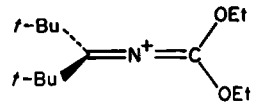

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F. X-Ray Structures of Amidines, Imidates and Related Compounds

Structures of many amidines and a few imidates have been determined by X-ray analysis. Table 19 lists the amidines, including some amidoximes and C-heterosubstituted derivatives, along with the stereochemistries of the C—N double and single bonds. One molecule (**38**) bears two amidine functionalities, one of them *Z* and the other *E*. It is necessary to remember that the designations *Z* or *E* and *syn* or *anti* apply to the ranking of substituents, so that they do not have a uniform significance as regards heteroatom substituents. An asterisk (*) marks those molecules where the ranking reverses the stereochemistry from that shown in Figure 1.

Clearly X-ray analysis is a powerful method for determining stereochemistry. The structures themselves carry a great deal of additional information regarding bond lengths and bond angles, as well as dihedral angles that define the conformations, and the reader is referred to the originals for such details. The examples in the table are representative, rather than comprehensive, and a complete set can be obtained through the Cambridge Crystallographic Database.

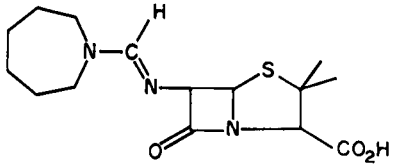
TABLE 19. Stereochemistry of crystalline amidines, RC(NR'R")=NR"'. Molecules where the geometry differs from that in Figure 1 are marked with *. Molecules where the stereochemistry is required by the cyclic structure are marked with †

R	R'	R"	R"'	Stereochem.	Ref.
H	H	H	OH	*Z*	100
H	H	Ph	Ph	*E-anti*	152
H	Me	Me	*p*-$O_2NC_6H_4$	*E*	153
H	Me	Me	H,$CH(CF_3)_2$[a]	*E*	154
H	—$(CH_2)_6$—		*p*-$O_2NC_6H_4$	*E*	23
H	—$(CH_2)_6$—		R"[b]	*E*	155
H	—$(CH_2)_6$—		H,R"[a,c]	*E*	156
Me	H	H	H	*Z*	157
Me	H	H	R"[d]	*Z*	158
Me	H	H	CS_2^-	*Z*	159
Me	H	Me	R"[e]	*E-syn*	160
Me	H	Ph	H,Ph[a]	*ZE*	36
Me	H	*p*-Tol	*p*-Tol	*E-syn*	156
Me	H	R"[f]	H	*E-syn*	160
Me	Me	Me	*p*-$O_2NC_6H_4$	*E*	153
Me	Me	Me	OH	*E*	94
Me	—*cis*-MeCH$(CH_2)_3$CHMe—		Ph	*E*	98
$[(NC)_2C]_{1/2}(CH_2)_2$	H	*t*-Bu	2,6-$Cl_2C_6H_3$	*E-syn*	161
—2-Adamantylidene—		*t*-Bu	Me	*e-anti*†	9
t-Bu	H	H	COBu-*t*	*Z*	162

Table 19. (*continued*)

R	R′	R″	R‴	Stereochem.	Ref.
t-Bu	H	COBu-*t*	H,H[a]	*Z*	162
t-Bu	Me	Me	*p*-$O_2NC_6H_4$	*Z*	153
t-Bu	—*cis*-MeCH$(CH_2)_3$CHMe—		Ph	*Z*	98
Ph	H	H	*p*-$O_2NC_6H_4$	*Z*	163
Ph	H	H	C(=S)NEt_2	*Z*	164
Ph	H	H	OH	*Z*	96
Ph	H	H	Cl	*Z*	165
Ph	H	CH_2Ph	OH	*Z-anti*	166
Ph	H	(*S*)-PhCHMe	(*S*)-PhCHMe	*E-syn*	167
Ph	H	Ph	Ph	*E-syn*	168
Ph	H	Ph	C(=S)NEt_2	*Z-anti*	169
Ph	Me	Me	OH	*E*	93
Ph	Me	Me	SMe	*E*	170
Ph	Me	Ph	*p*-Tol	*E-anti*	171
Ph	Et	Et	OH	*E*	96
Ph	*t*-Bu	$(CH_2)_2NHBu$-*t*	$PtCl_2$(NCPh)	*E**	56
Ph	—$(CH_2)_6$—		*m*-ClC_6H_4	*E*	172
Ph	—*p*-$MeOC_6H_4CH$—		*t*-Bu	*Z*	78
Ph	*p*-$MeOC_6H_4$	2,4,6-$(O_2N)_3C_6H_2$	*p*-$MeOC_6H_4$	*E-syn*	173
Ph	$SiMe_3$	$SiMe_3$	$SiMe_3$	*E*	59
p-$O_2NC_6H_4$	—$(CH_2)_2O(CH_2)_2$—		OH	*Z*	95
2,6-$Cl_2C_6H_3$	H	Ph	OH	*Z-anti*	98
R[g]	Et	Et	SO_2Tol-*p*	*E*	174
ArCHOH[h]	H	H	OH	*Z*	99
HC(=NOH)	H	H	OH	*Z*	175
MeC(=NOH)	Me	Me	OH	*E*	176
H_2NC(=NOH)	H	H	OH	*Z*	175
$O[(CH_2)_2]_2N$	H	*c*-Hex	*c*-Hex	*E-anti**	177
H_2N	*p*-BrC_6H_4	R‴[i]	*p*-BrC_6H_4	*E-syn**	178
F	CF_3	CF_3	H,CF_3[a]	*Z**	179
—SCH_2—		Ph	Ph	*Z-syn**[†]	180
—SCH_2—		SO_2Tol-*p*	SO_2Tol-*p*	*Z-anti**[†]	181
—$S(CH_2)_2$—		H	Ph	*Z-syn**[†]	182
—$S(CH_2)_2$—		H	2,6-Xyl	*Z-syn**[†]	183
—$S(CH_2)_3$—		H	Ph	*Z-syn**[†]	184
—SC(=CMeX)—[j]		Me	*t*-Bu	*Z-syn**[†]	174
—SC(=O)—		Ph	SO_2Tol-*p*	*Z-syn**[†]	185
—SC(=S)—		Ph	SO_2Tol-*p*	*Z-syn**[†]	186
Cl	—$(CH_2)_4$—		R‴[k]	*Z**	187
—$(Me_3P)_2(OC)_2FeC(=CH_2)$—[l]		*c*-Hex	*c*-Hex	*Z-anti**[†]	188
Cp_3U	Et	Et	2,6-Xyl	*E**	189

[a] Cationic.
[b] R″ = 6-Penicillanyl acid (cf. **33**).
[c] R″ = 6-Penicillanyl acid 1-(ethoxycarbonyloxy)-1-ethyl ester (cf. **34**).
[d] R″ = 3-(Chloromethyl)-5-1,2,4-thiadiazolyl (cf. **35**).
[e] R″ = 3,4-Dimethyl-5-1,2,4-thiadiazolylium (cf. **36**).
[f] R″ = 3-Methyl-5-1,2,4-thiadiazolyl (cf. **37**).
[g] R = MeC=[cyclo-[CSC(=NBu-*t*)NMe]] (cf. **38**).
[h] Ar = 3,4-(Methylenedioxy)phenyl.
[i] R″ = 3-(*p*-Bromophenyl)-5-1,2,4-thiadiazolyl (cf. **39**).
[j] X = $(Et_2N)C{=}NSO_2$Tol-*p* (cf. **38**).
[k] R″ = cyclo-[CC(=O)C(=O)CPh] (cf. **40**).
[l] cf. **41**.



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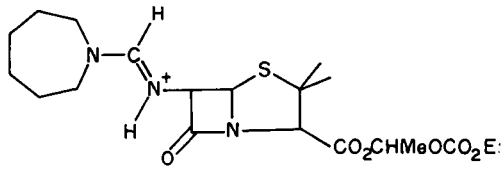

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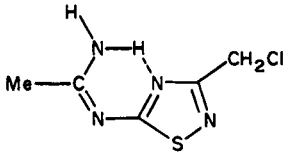

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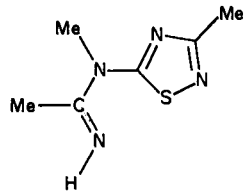

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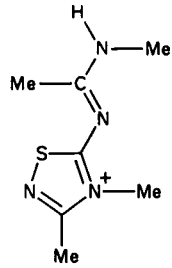

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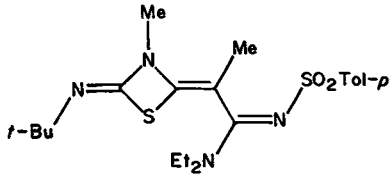

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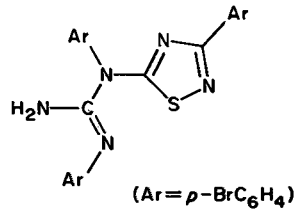

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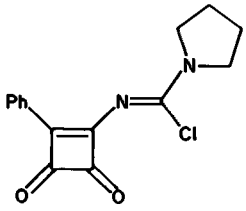

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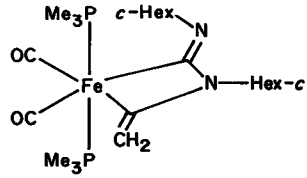

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IV. INVERSION AT NITROGEN AND ROTATION ABOUT C—N DOUBLE BONDS

A. Stereoisomerization of Amidines and Imidates

1. E–Z stereoisomerization of amidines

The interconversion of *Z* and *E* forms of amidines has not often been studied, since the equilibrium usually lies far to one side. For the few *N,N,N'*-trisubstituted amidines where there is an appreciable amount of each isomer, interconversion proceeds via nitrogen

inversion, with a barrier of *ca* 25 kcal mol^{-1}. For example, for $CH_3CH{=}CHC(NMe_2){=}NPh$ the barrier to *E–Z* interconversion[5] is *ca* 26 kcal mol^{-1}. For the iminoaziridines **5**[9] the barrier to *E–Z* interconversion is 23.3 kcal mol^{-1} (R = Me) or 21.4 kcal mol^{-1} (R = *t*-Bu). Although these values correspond to a relatively slow process, it is fast enough that isomerization can occur under laboratory conditions. Therefore the ratios in Table 1 (Section II.A.2) presumably refer to true equilibrium.

For some amidines other mechanisms can provide lower barriers. For example, $\Delta G^{\ddagger}$ for the cyclic amidine **6** ($n = 5$, X = H)[12] is *ca* 15 kcal mol^{-1}, and this was originally viewed as proceeding by nitrogen inversion, since tautomerization was expected to be slow in $CDCl_3$. Yet for the cyclic amidine **6** ($n = 7$, X = H)[13] $\Delta G^{\ddagger} = 15.9$ kcal mol^{-1}, and the mechanism for this *E–Z* interconversion is certainly rotation about the C—N single bond of the amino tautomer, which could be detected by NMR in the mixture of amidine structures. Likewise, for $HC(NMe_2){=}NAr$, with Ar = *o*-hydroxyphenyl, the barrier to *E–Z* interconversion[14] is low, and this was attributed to rotation about the partial double bond of the tautomer, $HC(NMe_2)(NHC_6H_4O^-)^+$.

According to 3-21G MO calculations[17] the transition state for interconversion of the *Z* and *E* stereoisomers of $HC(NH_2){=}NH$ by nitrogen inversion lies at 23.2 kcal mol^{-1} above the *E* reactant.

2. *E–Z stereoisomerization of imidate esters*

For a series of methyl *N*-isopropylbenzimidates, the rate of *E–Z* interconversion could be measured from the NMR coalescence behavior of the separate *Z* and *E* signals or from the time dependence of the integrated NMR intensities after dissolving one crystalline form of the conjugate acid of the imidate in $CDCl_3$-pyridine. The results are shown in Table 20. It can be seen that both experimental methods give the same $\Delta G^{\ddagger}$, even though they involve different temperatures. Therefore $\Delta S^{\ddagger}$ is near zero.

TABLE 20. Activation barriers (kcal mol^{-1}) to *E–Z* interconversion of imidate esters, $RC(OR'){=}NR''$

R	R′	R″	Solvent	Method	$\Delta G^{\ddagger}$	Ref.
Me	Ph	Me	*o*-$C_6H_4Cl_2$	^1H T_c	19.8	24
Me	*p*-Tol	Me	CCl_4	NMR(*t*)	20.4	26
t-Bu	Me	Me	CCl_4	^1H T_c	15.9	24
Ph	Me	Me	PhOH-$PhNO_2$	^1H T_c	18.9	27
Ph	Me	*i*-Pr	PhOH-$PhNO_2$	^1H T_c	18.7	27
Ph	Me	*t*-Bu	CD_2Cl_2	^1H T_c	14.0	129
Ph	Me	*t*-Bu	$CDCl_3$	^1H T_c	14.2	129
o-Tol	Me	*i*-Pr	PhOH-$PhNO_2$	^1H T_c	19.4	27
o-FC_6H_4	Me	*i*-Pr	PhOH-$PhNO_2$	^1H T_c	18.9	27
o-FC_6H_4	Me	*i*-Pr	$CDCl_3$-Py-d_5	NMR(*t*)	18.8	27
o-ClC_6H_4	Me	*i*-Pr	PhOH-$PhNO_2$	^1H T_c	19.3	27
o-ClC_6H_4	Me	*i*-Pr	$CDCl_3$-Py-d_5	NMR(*t*)	19.2	27
o-BrC_6H_4	Me	*i*-Pr	PhOH-$PhNO_2$	^1H T_c	19.6	27
o-BrC_6H_4	Me	*i*-Pr	$CDCl_3$-Py-d_5	NMR(*t*)	19.5	27
o-IC_6H_4	Me	*i*-Pr	PhOH-$PhNO_2$	^1H T_c	19.2	27
o-IC_6H_4	Me	*i*-Pr	$CDCl_3$-Py-d_5	NMR(*t*)	19.0	27
o-$O_2NC_6H_4$	Me	*i*-Pr	PhOH-$PhNO_2$	^1H T_c	18.8	27
o-$O_2NC_6H_4$	Me	*i*-Pr	$CDCl_3$-Py-d_5	NMR(*t*)	19.3	27
1-Naph	Me	*i*-Pr	PhOH-$PhNO_2$	^1H T_c	19.5	27

In contrast to the behavior of the conjugate acids (below), which isomerize by rotation about the C—N double bond, the rates for the imidate esters are independent of the steric bulk of the *ortho* substituents. Therefore, the substituents on nitrogen can remain in the molecular plane, which means that the isomerization proceeds by nitrogen inversion. For MeC(OAr)=NMe in CCl_4 the mechanism is nitrogen inversion, but in aqueous solution there is catalysis by bases such as tertiary amines, and stereoisomerization by tautomerization to CH_2=C(OAr)—NHMe could be confirmed[26] by deuterium incorporation into the *C*-methyl.

On heating to 100 °C for 40 minutes the *Z* and *E* isomers of the *N*-chloroimidate[28] PhC(OMe)=NCl equilibrate. This represents a slower sp^2 nitrogen inversion than in ordinary imidates, as expected from the electronegative chlorine.

According to 3-21G MO calculations[45] the activation energy for nitrogen inversion in the *syn* conformer of formimidic acid HC(OH)=NH is 20.3 kcal mol^{-1}, whereas in peroxyformimidic acid HC(=NH)—OOH[134] it is 15.9 kcal mol^{-1} by 6-31G calculations.

3. *E–Z stereoisomerization of thioimidate esters*

The barriers to *E–Z* interconversion[33] of various thioimidate esters, RC(SR′)=NR″, are given in Table 21, and additional data for aryl-substituted thiobenzimidate esters ArC(SMe)=NPr-*i*[27] are available. For a few of these methyl *N*-isopropylbenzothioimidates, the rate of *E–Z* interconversion could be measured not only from the coalescence behavior of the separate *Z* and *E* NMR signals but also from the time

TABLE 21. Activation barriers[33] (kcal mol^{-1}) to *E–Z* interconversion of thioimidate esters, RC(SR′)=NR″

R	R′	R″	Solvent	$\Delta G^{\ddagger}$
Me	Me	Me	*o*-$C_6H_4Cl_2$	21.6
Me	Me	Et	$PhNO_2$	21.2
Me	Me	*i*-Pr	$CHBr_3$	19.6
Me	Me	*t*-Bu	C_6D_6	16.7
Me	Et	Me	*o*-$C_6H_4Cl_2$	21.6
Me	Et	Ph	$CDCl_3$	16.0
Me	*i*-Pr	Me	*o*-$C_6H_4Cl_2$	21.6
Me	*t*-Bu	Me	$PhNO_2$	21.4
Me	$PhCH_2$	Me	*o*-$C_6H_4Cl_2$	21.2
Me	$PhCH_2$	Ph	$CDCl_3$	15.7
Me	Ph	Me	$PhNO_2$	20.3
Me	*p*-$O_2NC_6H_4$	Me	$PhNO_2$	20.8
Et	Me	Me	$CHBr_3$	20.4
Pr	Me	Me	$PhNO_2$	19.7
i-Pr	Me	Ph	$CDCl_3$-C_6D_6	13.9
$PhCH_2$	Me	*i*-Pr	*o*-$C_6H_4Cl_2$	19.6
$PhCH_2$	Me	Ph	CD_3OD	15.7
Ph	Me	Me	*o*-$C_6H_4Cl_2$	19.8
Ph	Me	*i*-Pr	$CHBr_3$	19.5
Ph	Me	Ph	$CDCl_3$	14.2
Ph	Et	Me	$PhNO_2$	20.4
Ph	Et	Ph	$CDCl_3$	14.2
Ph	*i*-Pr	Me	$PhNO_2$	20.3
Ph	*i*-Pr	Ph	$CDCl_3$	14.2
Ph	*t*-Bu	Me	$PhNO_2$	20.6
Ph	*t*-Bu	Ph	$CDCl_3$	13.8

dependence of the integrated NMR intensities after dissolving one crystalline form of the thioimidate in $CDCl_3$. The barrier to *E–Z* interconversion is nearly independent of solvent[33], although there are slight increases[27] in the presence of phenol. For $MeC(SC_6H_4NO_2\text{-}p)$=NMe in CD_3OD—$CDCl_3$ the rate of stereoisomerization is the same as that of deuterium incorporation, so that the mechanism for this ester involves tautomerization to CH_2=C(SAr)—NHMe and rotation about the C—N single bond. For the others, which lack alpha hydrogens or acidifying aryl groups, the mechanism is simply nitrogen inversion.

B. Stereoisomerization of Conjugate Acids and Bases

1. *E–Z* stereoisomerization of amidinium ions

In the previous review[2] there were very few examples of rotation about the partial C—N double bonds of amidinium ions, and except for $PhC(NMePh)(NMe_2)^+$[190], where steric effects lower the barrier, these clustered close to a $\Delta G^{\ddagger}$ of 21 kcal mol^{-1}. Subsequently it has been possible to find lower barriers, and to measure them. Barriers to rotation about the partial C—N double bonds in various amidinium ions are listed in Table 22. For *N,N*-dimethylacetamidinium ion[191] the rate is independent of counterion (nitrate or chloride) even in 1,1,2,2-tetrachloroethane solvent, and it is the same as in DMSO. Therefore the process is indeed rotation about the C—N partial double bond, rather than rotation about a C—N single bond of a covalent adduct. For this ion and for the seven-membered ring amidinium ion **10**[35] the activation parameters were also determined. For the latter the rate is higher in the presence of Et_3N, since isomerization can occur by rotation about the exocyclic C—N single bond of the amidine free base.

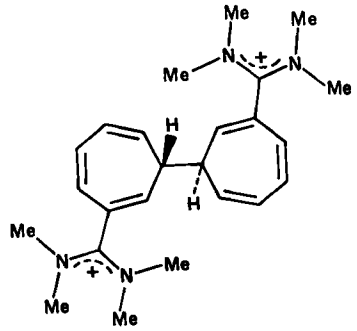
Solvent and counterion effects have been studied[195] more extensively for $HC(NMe_2)_2^+$. With perchlorate counterion the rate is nearly independent of solvent, and the same rate is seen in DMSO with iodide or tosylate counterion. However, the activation enthalpy is higher with chloride in DMSO or tosylate in $CDCl_3$, and there is a large increase in $\Delta H^{\ddagger}$ with iodide in $CDCl_3$ or chloride in $CDCl_3$ or acetone-d_6. However, these latter cases show a compensating large increase in $\Delta S^{\ddagger}$, so that the rate is nearly the same. This is most likely due to stereoisomerization via formation of the covalent intermediate $(Me_2N)_2CHX$ (X = Cl, I, OTs) in these nonpolar media.

For imipenem (**9**) kinetic analysis[34] by HPLC (not NMR) indicates that reequilibration of the *Z* and *E* forms takes several hours at 0 °C at pH 5.5 or only a few minutes at room temperature at pH 7. The base catalysis indicates that this isomerization proceeds via deprotonation and rotation about the C—N single bond of the amidine.

TABLE 22. Activation barriers (kcal mol^{-1}) to rotation about C—N partial double bond of amidinium ions

Ion	Solvent	$\Delta G^{\ddagger}$	Method	Ref.
$CD_3C(NH_2)$=NMe_2^+	$C_2H_2Cl_4$	22.1	^{1}H LSA	191
$^+H_3NC(NH_2)$=NMe_2^+	FSO_3H-SbF_5-SO_2	15	^{1}H T_c	192
Me_2NCH=NMe_2^+	$CDCl_3$	15.6	^{13}C T_c	193
Me_2NCH=NMe_2^+	$CDCl_3$	15.4	^{13}C T_c	194
Et_2NCH=NMe_2^+	$CDCl_3$	16.0	^{13}C T_c	194
Me_2NCH=NEt_2^+	$CDCl_3$	15.3	^{13}C T_c	194
Et_2NCMe=NEt_2^+	$CDCl_3$	15.5	^{13}C T_c	193
Et_2NCMe=NEt_2^+	$CDCl_3$	14.9	^{13}C T_c	194
10, R = *p*-TolCHPO_2OMe^-	$CDCl_3$	19.7	^{1}H LSA	35

For the dimeric amidinium ion **42**, obtained as the *meso* isomer, the ^{1}H NMR spectrum[196] shows four *N*-methyl peaks at 253 K, and these coalesce to two with a $\Delta G^{\ddagger}$ *ca* 14.6 kcal mol^{-1}. The X-ray structure shows that the molecule has an inversion center, so that the two amidinium fragments are equivalent to each other. However, each amidinium fragment is twisted relative to the seven-membered ring, so that the *Z* methyls on the two nitrogens of the same amidinium fragment are not equivalent and neither are the *E* methyls. The dynamic behavior could be due to restricted rotation about either the C—N partial double bond or the C—C bond between the amidinium fragment and the ring. If the process were C—N rotation, then the two kinds of C—N bonds are in different environments and should show different $\Delta G^{\ddagger}$. Since there is only a single $\Delta G^{\ddagger}$ for the coalescence of both pairs of *N*-methyls, the dynamic process is most likely the C—C rotation. This then means that the barrier to C—N rotation is considerably higher than 14.6 kcal mol^{-1}. This is consistent with the other studies above on amidinium ions.



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Around 120 °C in DMSO-d_6 the ^{1}H NMR peaks of the inequivalent *N*-methyls of (*ZE*)-*N*,*N*′-dimethylformamidinium ion $HC(NHMe)_2^+$ coalesce[197]. This represents an isomerization of both C—N partial double bonds, presumably via the *EE* isomer as intermediate.

From the NMR coalescence temperature the barrier to interconversion of the two forms of mifentidine [HC(NHPr-*i*)(NHAr)$^+$, Ar = *p*-imidazolylphenyl][40] is 16.1 kcal mol^{-1}. Equilibration presumably occurs by deprotonation (pK_a 8.88), followed by rotation about the C—N single bond. The barrier is sufficiently low that under physiological conditions the *ZE* or *EZ* distomer (inactive stereoisomer) can convert to the *EE* eutomer, which is the active form that binds to the histamine receptor.

The calculated barriers to rotation about the partial C—N double bonds in various amidinium ions are listed in Table 23. The experimental barriers in Table 22 are significantly lower, because steric repulsions of the N-alkyl groups destabilize the planar amidinium ion relative to its transition state.

TABLE 23. Calculated activation energies (kcal mol^{-1}) for rotation about the C—N double bond of amidinium ions

Ion	E_A	Method	Ref.
$H_2NCH{=}NH_2^+$	34.5	STO-3G	198
$H_2NCH{=}NH_2^+$	28.7	3-21G	18
$H_2NCH{=}NH_2^+$	28.2	4-31G	198
$H_2NC(Me){=}NH_2^+$	26.8	4-31G	198

According to MNDO calculations and an effective charge model[199] to account for solvation of both planar and twisted $HC(NH_2)_2^+$, the activation energy for rotation about the C—N double bond decreases with increasing solvent dielectric constant. This is in general agreement with the experimental results above. The decrease occurs because the positive charge is more localized in the transition state for rotation.

2. *E–Z* stereoisomerization of amidinate anions

According to a 3-21G MO calculation[17] the barrier to *ZZ*-to-*ZE* isomerization by C—N rotation in $HC(NH)_2^-$ is calculated to be 23.0 kcal mol^{-1} and that for *ZE*-to-*EE* is 27.1 kcal mol^{-1}. According to a 6-311 + + G**/MP3 calculation[20] the barrier to rotation about one C—N bond of (*ZZ*)-$HC(NH)_2^-$ is 21.1 kcal mol^{-1}. It is surprising that there are no experimental data in so simple a system, although it might be difficult to distinguish C—N rotation from nitrogen inversion.

3. *E–Z* stereoisomerization of imidatonium ions and protonated imidate esters

In $C_2H_2Cl_4$ the barrier to rotation[200] about the C—N double bond in $HC(OMe)=NMe_2^+$ is greater than 19.7 kcal mol^{-1}. The ^{1}H NMR spectrum of the imidoyl chloride, $HCCl=NMe_2^+$, shows coalescence of the inequivalent methyl groups around 240 K. The $\Delta G^{\ddagger}$ is only 10.5 kcal mol^{-1}, far too low to be due to rotation about the C—N double bond. Indeed the rate in acetonitrile increases with increasing substrate concentration, so that the stereoisomerization must occur by chloride exchange, to form Cl_2CHNMe_2 as intermediate. In methylene chloride the rate constant decreases with increasing substrate concentration, and although this suggested a more complicated mechanism, it may be simply due to a polarity effect, whereby the substrate stabilizes the $HCCl=NMe_2^+ Cl^-$ ion pair, relative to the covalent intermediate. Equilibration of the stereoisomeric formimidatonium ions $HC(OMe)=NMeAr^+$ (Ar = 2,6-Xyl)[43] proceeds rapidly in aqueous medium or with Et_3N in CH_2Cl_2 or CH_3CN. The mechanism involves reversible formation of a tetrahedral intermediate. In contrast, deuterium incorporation[201] confirmed a tautomeric mechanism, via $CH_2=C(OEt)$-NMePr-*i*, for *E–Z* stereoisomerization of the acetimidatonium ion, $MeC(OEt)=NMePr\text{-}i^+$, in aqueous alkali.

Activation barriers to *E–Z* isomerization of protonated imidate esters are listed in Table 24. The rates are independent of the counterion (dichloroacetate, bisulfate or trifluoromethanesulfonate), so that the mechanism for these conjugate acids is rotation about the C—N double bond, rather than via deprotonation to the imidate ester. Comparisons of entries in the table show that *ortho* substituents retard the rotation, since they are above or below the molecular plane, where they interfere with the rotating groups on nitrogen.

TABLE 24. Activation barriers[27] (kcal mol^{-1}) to rotation about C—N double bond of protonated *O*-methyl imidate esters, $RC(OMe)=NHR'^+$

R	R′	Solvent	Method	$\Delta G^{\ddagger}$
t-Bu	Ph	H_2SO_4	NMR(*t*)	22.6
Ph	*i*-Pr	CF_3COOH	NMR(*t*)	24.2
Ph	Ph	CF_3COOH	NMR(*t*)	20.9
Ph	Ph	$CHCl_2COOH$	^{1}H T_c	20.8
Ph	2,6-Xyl	CF_3COOH	NMR(*t*)	24.7
o-FC_6H_4	*i*-Pr	CF_3COOH	NMR(*t*)	25.8
o-ClC_6H_4	*i*-Pr	CF_3SO_3H	NMR(*t*)	28.4

MO calculations at the 3-21G level[45] on protonated formimidic acid $HC(OH)=NH_2^+$ suggest a barrier to rotation about the C—N double bond of 39.7 kcal mol^{-1}. Other calculations[202] suggest a barrier of 75.1 kcal mol^{-1}. Both of these are overestimates, compared to the experimental values.

4. E–Z stereoisomerization of imidate anions

For $HC(—O^-)=NH$ the barrier to *Z*-to-*E* interconversion by rotation about the C—N double bond is calculated at the 3-21G level[45] to be 30.6 kcal mol^{-1}. The barrier to nitrogen inversion is still higher, 37.7 kcal mol^{-1}, but this is not a proper transition state. According to MP4SDQ/631 + + G calculations[47] these barriers are 27.5 (also at the 6-311 + + G**/MP3 level[20]) and 34.0 kcal mol^{-1}, respectively. For $MeC(—O^-)=NH$ these barriers are 31.1 and 38.6 kcal mol^{-1}, respectively, according to a 6-31G** calculation. Thus it would seem that the operative mechanism for stereoisomerization is rotation about the C—N double bond. This is not the common mechanism for imines, but delocalization of the oxyanion electrons, as in the resonance form $RC(=O)—NH^-$, reduces the double-bond character. Rotation is thereby facilitated and might become competitive.

Rates of *E–Z* interconversion in various *N*-arylformimidate anions $HC(—O^-)=NAr$ could be measured by ^1H NMR saturation transfer. The experimental activation barriers[48] are 19–23 kcal mol^{-1}, quite similar to the barriers in other imines that are known to interconvert by nitrogen inversion. It was therefore concluded that nitrogen inversion is also the mechanism in imidate anions. However, the molecular orbital calculations above[45,47] suggest that the lower-enegy pathway is rotation about the C—N partial double bond. Nevertheless the Hammett ρ for stereoisomerization of a series of *N*-arylformimidate anions[49] is + 2.2, quite close to ρ for other imine stereoisomerizations known to proceed by nitrogen inversion and far from the + 3.8 expected for rotation about the C—N bond. It was therefore concluded that *E–Z* interconversion in imidate anions proceeds by nitrogen inversion.

5. E–Z stereoisomerization of thioimidatonium ions and protonated thioimidate esters

The barriers to rotation about the C—N double bond in a series of thioimidatonium ions, $RC(SR')=NR''R'''^+$, and protonated thioimidate esters in various solvents, are given in Table 25. According to a molecular orbital calculation[202] the barrier to rotation about the C—N double bond of $HSCH=NH_2^+$ is 57.3 kcal mol^{-1}. This is clearly an overestimate.

TABLE 25. Activation barriers (kcal mol^{-1}) to rotation about the C—N double bond of protonated thioimidates and thioimidatonium ions, $RC(SR')=NR''R'''^+$

R	R′	R″	R‴	$\Delta G^{\ddagger}_{E\rightarrow Z}$	Ref.
H	Me	Me	Me	> 19.5	193
t-Bu	$PhCH_2$	H	Me	26.5	203
Ph	Me	H	*i*-Pr	26.5	203
Ph	Me	H	Ph	21.75	203
Ph	Me	Me	Ph	22.3	203
Ph	Me	H	*o*-Tol	21.9	203
Ph	Me	H	2,6-Xyl	26.7	203
Ph	*t*-Bu	H	Ph	21.5	203
Ph	Ph	Me	Ph	23.7	203
o-Tol	Me	H	Ph	24.0	203

6. *E–Z stereoisomerization of metal complexes of amidines and of imidate esters*

Metal complexes $RC(NR'_2)=NR'' \rightarrow M$ or $RC(OR')=NR'' \rightarrow M$, with a metal bound to the sp^2 nitrogen, are analogous to amidinium ions or imidatonium ions. The formal single bond and the formal double bond of the amidine or imidate ester both become partial double bonds, so that rotation about the double bond becomes faster. On the other hand, the rate of sp^2 nitrogen inversion is markedly reduced.

The barrier to interconversion of the two stereoisomers of the $PtCl_2(NCPh)$ complex of $PhC[N(t\text{-}Bu)CH_2CH_2NHBu\text{-}t]=NH$[56] is only 10.8 kcal mol^{-1}, which is too low for rotation about a C—N double bond, but dissociation of the Pt, followed by nitrogen inversion, also seems unlikely. Nucleophilic attack by the free amino group has been suggested[71], although deprotonation of the sp^2 nitrogen, followed by inversion via a transition state with 180° C=N—Pt angle, is also possible.

For the cationic complexes $RC(OMe)=NH \rightarrow NiL^+$ (R = Me, Et, or Ph, L = a tridentate ligand) the observation[55] that the equilibrium between *Z* and *E* stereoisomers can be established at different temperatures means that the barrier to interconversion is not so high as to freeze the mixture, even though the interconversion cannot be detected by NMR lineshape changes. This is a system whose kinetics might be followed by saturation transfer.

Only for the platinum complexes $PhC(OMe)=NH \rightarrow PtCl_2(NCPh)$ and $[PhC(OMe)=NH \rightarrow]_2PtCl_2$[71] has interconversion of *Z* and *E* (or *ZZ*, *ZE* and *EE*) complexes of imidate esters been seen. The interconversion is catalyzed by base. The mechanism involves reversible addition of methoxide, rather than simply deprotonation and nitrogen inversion, since in deuteriomethanol both isomerization and deuterium incorporation occur simultaneously.

C. Stereodynamics of Amidines and Imidates with sp^2-C Substituents

1. *Stereodynamics of N-alkylidene amidines*

The transition states for inversion of the $N=CH_2$ nitrogen in $HC(N=CH_2)=NH$ are calculated[78] to be around 20 kcal mol^{-1} higher in energy than the reactant, and the transition state for inversion of the =NH nitrogen is 30.8 kcal mol^{-1} higher, but no dynamic behavior of the *N*-alkylidene amidine $PhC(N=CHC_6H_4OMe\text{-}p)=NBu\text{-}t$ could be detected by ^{13}C NMR, even at −90 °C.

2. *E–Z stereoisomerization of N-acylamidines and N-acylimidates*

For most ordinary acylamidines the equilibrium lies so far toward the *E* stereoisomer that rates of equilibration cannot be measured. Interconversion of the *Z* and *E* forms of some *N*-phosphoryl amidines, $Cl_2CHC(=NMe)\text{-}N(Me)PO(OR)_2$ and $Cl_2CHC(=NR)—N=PPh_3$[81], proceeds with a $\Delta G^{\ddagger}$ of 18–22 kcal mol^{-1}, and the reactivity parallels the rate of exchange at the $CHCl_2$ group. Therefore the mechanism involves a tautomerization and rotation about the C—N single bond of the enediamine (ketene aminal).

Although X-ray analysis shows that the acylamidine **14** is the *Z* form, this can be cyclized[82] to a benzopyrimidine. Therefore the *E* form must be accessible as a reaction intermediate.

For **16** (R = H, R′ = *p*-Tol)[83] the barrier to *E–Z* interconversion is 18.6 kcal mol^{-1}.

According to MINDO/3 calculations[204] on *N*-nitrosoformamidine, HC(=NH)NHN=O, the barrier to *E–Z* isomerization by sp^2 nitrogen inversion is 9.2 kcal mol^{-1}. A 3-21G calculation[142] on HC(OH)=NCHO shows that *E–Z* isomerization occurs by nitrogen inversion and rotation of the carbonyl to overlap with the lone pair.

3. E–Z stereoisomerization of imidines

For **19** (R = H) the *ZZ* and *ZE* forms interconvert[87] with a $\Delta G^{\ddagger}$ varying from 16.5 to 18.8 kcal mol^{-1}, depending on substitution. Dynamic NMR behavior is also seen for **19** (R = Me), although only the *EE* form is detectable. A similarity of rates indicates that all these stereoisomerizations occur by nitrogen inversion, rather than tautomerization. However, for **19** (R = H, Ar = unhindered aryl) the rates are concentration dependent, suggesting equilibration by tautomerization. This permits interconversion of the inequivalent aryls of the *ZE* form via the *ZZ* isomer. It was claimed that the kinetics could not be fit by a four-site model, with independent *E–Z* isomerization of the two aryls, nor by synchronous isomerizations of both aryls. However, the exchange matrix used to analyze the NMR spectra appears to be incorrect. This is a system that might well be studied by 2D NMR exchange spectroscopy[205].

D. Stereoisomerization of *N*-Heterosubstituted Amidines and Imidates

1. E–Z stereoisomerization of N-aminoamidines

Stereoisomerization of (*Z*)-MeC(NMe$_2$)=NNMeAr to its *E* isomer[206] could be followed by UV spectrophotometry in aqueous buffers. The reaction proceeds at different rates in acid and base, with a transition region at the pK_a of the protonated substrate, corresponding to separate reactions of the free base and its conjugate acid, protonated on the sp^2 nitrogen. The mechanisms could be elucidated from the Hammett ρ for variation of Ar. For reaction of the conjugate acid, $\rho > 0$, corresponding to rotation about the C—N partial double bond. For the free base, $\rho < 0$, so it cannot be by rotation about the C—N double bond. Nor can the mechanism be by tautomerization to CH$_2$=C(NMe$_2$)—NHNMeAr, since in D$_2$O there is insufficient deuterium incorporation. Therefore it was concluded that the mechanism is nitrogen inversion. For Ar = 2,4-(O$_2$N)$_2$C$_6$H$_3$ there is an additional OH$^-$-catalyzed reaction, corresponding to addition to the C—N double bond and rotation about the C—N bond that becomes single in the tetrahedral intermediate.

E–Z stereoisomerization of some amidrazonium ions, **20** (R = Ph, R′ = H), has been studied[91] by ^{1}H NMR. For R″ = H and Me the activation barriers are 20.3 and 19.1 kcal mol^{-1}, respectively.

2. E–Z stereoisomerization of amidoximes

Interconversion of *Z* and *E* stereoisomers of amidoximes RC(NR$_2$)=NOH was not recognized until rather recently, since the dynamic process was thought to be rotation about the C—N single bond. With ArC(NHR)=NOH bearing *ortho*-substituted aromatic rings two forms could be detected[105] in the ^{1}H NMR spectrum, with a coalescence temperature near 120 °C. These were mistakenly assigned as different conformers about the C—N single bond. Likewise, the stereoisomerizations of ArC(NHPh)=NOH were originally thought[207] to be rotations about the C—N single bond, since the barrier near 20 kcal mol^{-1} seemed too small for an *E–Z* interconversion. However, comparison with ArC(N[CH$_2$CH$_2$]$_2$O)=NOH showed[107] that *E–Z* isomerization does proceed with such a low barrier, and comparison with ArC(NMe$_2$)=NOH[208] showed that rotation about the C—N single bond has a much lower barrier. Therefore the process in ArC(NHR)=NOH is indeed *E–Z* interconversion, perhaps proceeding via tautomerization to ArC(NHOH)=NR, which can rotate about its C—N single bond.

The kinetics of conversion of (*Z*)-*N*,*N*-dimethyl-*p*-nitrobenzamidoxime to its *E* stereoisomer could be determined[93] by following the time course of NMR intensities. Table 26 lists the activation barriers to several such amidoximes. It is surprising that these barriers are not much higher than those of ordinary amidines (Section IV.A.1), inasmuch

TABLE 26. Activation barriers (kcal mol^{-1}) to isomerization of a *Z* amidoxime ArC(NRR')=NOH to its *E* isomer

Ar	R	R'	Solvent	$\Delta G^{\ddagger}$	Ref.
o-Tol	Ph	H	DMSO-d_6	21.5	207
p-Tol	Me	Me	$CDCl_3$	24.7	92
p-ClC_6H_4	—([CH_2CH_2]$_2$O)—		H_2O	24.56	107
p-ClC_6H_4	—([CH_2CH_2]$_2$O)—		H^+/H_2O	16.04	107
3,5-Cl_2-2,4,6-Me_3C_6	Ph	H	DMSO-d_6	19.9	207
p-$O_2NC_6H_4$	Me	Me	C_6D_6	24.5	93
p-$O_2NC_6H_4$	Me	Me	CD_3CN	23.7	93
p-$O_2NC_6H_4$	Me	Me	MeOH	23.3	93
p-$O_2NC_6H_4$	Me	Me	Pyridine	25.5	93

as an attached hydroxyl group generally raises the barrier to sp^2 nitrogen inversion, and the barrier in an *N*-chloroimidate ester is higher than in ordinary imidate esters (Section IV.A.2).

For *E–Z* isomerization of ArC(NMe_2)=NOH with a series of *C*-aryl groups[93] electron-donating substituents accelerate the reaction, with a Hammett ρ of -0.56. The reaction in pyridine is slow because of a negative $\Delta S^{\ddagger}$. The mechanism may be rotation about the C=NOH double bond because the rate increase in more polar solvents can be attributed to stabilization of the charge-separated resonance form, ArC(=$\overset{+}{N}Me_2$)—N^-OH. However, it is more likely that the mechanism involves tautomerization to ArC(=$\overset{+}{N}Me_2$)—NHO^-, which can rotate about the C—NO single bond. This then accounts for the retardation by pyridine, which removes the proton.

In aqueous solution the stereoisomerization of ArC(NR_2)=NOH (Ar = *p*-ClC_6H_4, R_2NH = morpholine) could be followed[107] by UV spectrophotometry. Both the substrate and its conjugate acid react, but the latter is 10^5-fold faster, since rotation about the C—N partial double bond is easier. For a series of aryl groups, the Hammett ρ for the reaction of the conjugate acid is -0.28, which is in accord with reduction of the double-bond character by electron-donating substituents. For the amidoxime itself there is no need to invoke stereoisomerization via the ArC(NR_2)=NH^+O^- tautomer, since ArC(NR_2)=NOR' reacts at nearly the same rate. The oximate, ArC(NR_2)=NO^-, is unreactive toward stereoisomerization.

The *Z* and *E* stereoisomers of MeC(=NOH)C(NHR)=NOH (R = Me, Et, *i*-Pr, *t*-Bu), differing at the amidoxime C—N double bond, interconvert slowly enough that they could be distinguished[209] by NMR. However, they interconvert too fast to be separated by liquid chromatography.

3. *E–Z stereoisomerization of hydrazide derivatives*

Methoxide ion catalyzes the isomerization[210] of the kinetically formed hydrazidate ester (*Z*)-RC(OMe)=NNMeAr [R = *p*-$MeOC_6H_4$, Ar = 2,4-$(O_2N)_2C_6H_3$] to the more stable *E* stereoisomer. The kinetics of this conversion could be followed by analyzing aliquots of the reaction mixture by HPLC. The mechanism involves reversible addition of methoxide, to form $RC(OMe)_2N^-NMeAr$.

According to 6-31G**/MP2 calculations[110] the barrier to *E–Z* isomerization of the hydrazidoyl fluoride $HCF=NNH_2$ is 25.3 kcal mol^{-1}. The lowest-energy pathway is nitrogen inversion.

The equilibrium of the hydrazonate esters (**21Z** and **21E**, or **22*ZZ*** plus *ZE* and *EE*

forms)[109] is established too rapidly to permit taking the NMR spectrum of an unequilibrated stereoisomer. Nevertheless no coalescence of the signals could be seen even at 120 °C, so the $\Delta G^{\ddagger}$ is greater than 15.9 kcal mol^{-1}.

4. *E–Z stereoisomerization of hydroximates*

Isomerization of the *E* stereoisomer of the imidoyl halides ArCCl=NOMe (Ar = Ph, *p*-$O_2NC_6H_4$, *p*-Tol, *p*-ClC_6H_4, *p*-$MeOC_6H_4$, *o*-Tol) to the more stable *Z*[211] can be effected with HCl in dioxane. With DCl the reaction is 2.3 times as fast, so that the reaction involves a prior equilibrium protonation. With $H^{36}Cl$ the exchange of chlorine proceeds half as fast as the isomerization, showing that the mechanism of isomerization is not simply rotation about the C—N double bond, but involves nucleophilic addition of Cl^-, to produce an intermediate that can lose either of two equivalent chlorines. Incorporation of ^{36}Cl into the more stable *Z* isomer proceeds only 1/210 as fast as into the *E* isomer. Although this was attributed to a greater basicity of the *E* form, it is a necessary consequence of their relative stabilities, since the exchange reactions of the two stereoisomers proceed by an identical intermediate.

According to 4-31G/CI calculations[149] on the anion $HC(OH)=NO^-$, the activation energy for stereoisomerization of the *Z* isomer to the *E* by nitrogen inversion is 46.9 kcal mol^{-1}.

E. Stereoisomerization of C-Heterosubstituted Amidines and Imidates

1. *E–Z stereoisomerization of guanidines*

It is now firmly established[212] that stereoisomerization about the C—N double bond of guanidines proceeds by nitrogen inversion, rather than rotation. However, if there are protons on one of the other nitrogens, stereoisomerization can proceed by tautomerization and rotation about a C—N single bond. Thus ^{15}N NMR[213] of arginine, $(H_2N)_2C=NR$ [$R = (CH_2)_3CH(NH_2)CO_2^-$], in 50% aqueous DMSO shows inequivalent NH_2 nitrogens, which coalesce with a $\Delta G^{\ddagger}$ of 10.4 kcal mol^{-1}. This is much lower than the 18.8 kcal mol^{-1} for nitrogen inversion in pentamethylguanidine, so that the mechanism must involve tautomerization to $RNHC(=NH)—NH_2$ and rotation about the C—NHR bond that has become single.

In contrast, ^{13}C NMR indicates that $\Delta G^{\ddagger}$ for making equivalent the methyls of the acylguanidine $ArCON=C(NHMe)_2$ (Ar = 2-amino-5-chlorophenyl or 3,5-diamino-6-chloro-2-pyrazinyl, the side chain of amiloride)[214] is 14.7 kcal mol^{-1}. Since the ^{15}N spectrum of $ArCON=C(NH_2)_2$ shows that NH exchange is slow, the mechanism cannot be via tautomerization but must involve direct isomerization of the C—N double bond.

TABLE 27. Calculated activation energies (kcal mol^{-1}) for rotation about the C—N double bond of guanidines, $(H_2N)_2C=NR$

R	Method	E_A	Ref.
H	CNDO/2	30.4	215
H	6-31G	24.10	216
Me	6-31G	27.09	216
NH_2	6-31G	48.16	216
F	6-31G	42.45	216
Ph	CNDO/2	24.8	214
COAr[a]	CNDO/2	15.8	214

[a] Ar = 3,5-diamino-6-chloro-2-pyrazinyl (amiloride side chain).

Moreover, the barrier in $ArCON{=}C(NMe_2)_2$ is < 10 kcal mol^{-1}, and this permits only the direct isomerization. The acyl group reduces the double-bond character and lowers the barrier to rotation.

Calculated barriers to rotation about the C—N double bond of N-substituted guanidines are listed in Table 27. These are not very informative, since nitrogen inversion is the more common mechanism for *E–Z* stereoisomerization.

2. *E–Z stereoisomerization of guanidinium ions*

The experimentally determined barriers to rotation about the C—N partial double bonds in guanidinium ions are listed in Table 28. Calculated barriers are listed in Table 29.

TABLE 28. Activation barriers (kcal mol^{-1}) to rotation about the C—N partial double bond of guanidinium ions, $(R_2N)(R'_2N)C(=NR''R'''^{+})$

R	R′	R″	R‴	Solvent	$\Delta G^{\ddagger}$	Method	Ref.
H	H	H	H	liq. cryst.	< 12–13	^{1}H LSA	150
H	H,Me	Me	$CH_2CO_2^-$	CD_3OD	11.05	^{1}H LSA	215
Me	$ArCH_2$	Me	Me	$CDCl_3$	14.6–15.7	^{1}H LSA	217
Me	Me	$ArCH_2$	$ArCH_2$	$CDCl_3$	13.8–15.2	^{1}H LSA	217
H,Me	H,Me	H	ArCO[a]	DMSO-d_6–CD_3OD	14.8	^{13}C T_c	214
H	H	H	R‴[b]	50% aq. DMSO	12.9	^{14}N LSA	213

[a] Ar = 3,5-diamino-6-chloro-2-pyrazinyl (amiloride side chain).
[b] R‴ = $(CH_2)_3CH(NH_3^+)COOH$ (arginine side chain).

TABLE 29. Calculated activation energies (kcal mol^{-1}) for rotation about the C—N partial double bond of guanidinium ions, $(RNH)(H_2N)C(=NHR'R''^{+})$

R	R′	R″	Method	E_A	Ref.
H	H	H	MINDO/3	8.9	150
H	H	H	STO-3G	20.1	198
H	H	H	4-31G	14.1	198
H	H	H	CNDO/2	21.9	215
H	Me	Me	CNDO/2	19.7	215
Me	Me	$CH_2CO_2^-$	CNDO/2	22.6	215
H	H	CH=O	4-31G	17.7	218
H	H	COAr[a]	CNDO/2	16.2	214
H	H	H	STO-3G	22.76	219
H	H	H	4-31G	14.97	219
H	H	H	6-31G	14.73	220
H	H	NH_2	6-31G	22.79	221
syn-H_2N	H	H	6-31G	23.40	221
anti-H_2N	H	H	6-31G	12.97	221
H	H	Me	6-31G	16.78	221
syn-Me	H	H	6-31G	15.21	221
anti-Me	H	H	6-31G	13.47	221
H	H	F	6-31G	19.70	221
syn-F	H	H	6-31G	19.33	221
anti-F	H	H	6-31G	11.53	221
H	H	$CH{=}CH_2$	6-31G	14.67	222
syn-$CH{=}CH_2$	H	H	6-31G	13.42	222
anti-$CH{=}CH_2$	H	H	6-31G	13.54	222

[a] Ar = 3,5-diamino-6-chloro-2-pyrazinyl (amiloride side chain).

TABLE 30. Activation barriers (kcal mol^{-1}) to rotation about the C—N partial double bond of *O*-alkyl isouronium ions

Ion	Solvent	$\Delta G^{\ddagger}$	Ref.
$MeOC(NMe_2)=NMe_2^+$	CH_2Cl_2	10.3	193
$MeOC(NMe_2)=NMe_2^+$	$CDCl_3$	10.2	194
$MeOC(NEt_2)=NMe_2^+$	$CDCl_3$	9.8	194
$MeOC(NMe_2)=NEt_2^+$	$CDCl_3$	8.9	194
$MeOC(NEt_2)=NEt_2^+$	$CDCl_3$	9.5	194

Under acidic conditions the experimental $\Delta G^{\ddagger}$ of 12.9 kcal mol^{-1} for arginine, $(H_2N)_2CNHR^+$, R = $(CH_2)_3CH(NH_3^+)COOH$, is higher than the $\Delta G^{\ddagger}$ of 10.4 kcal mol^{-1} for the basic form, but it is independent of pH[213]. Therefore the mechanism for making the NH_2 groups equivalent must be rotation about the C—NHR partial double bond, rather than deprotonation to $(H_2N)_2C=NR$ and nitrogen inversion. The 4-31G and 6-31G calculated barriers are in good agreement with the experimental values. The increased barriers[221] calculated for *N*-amino- and *N*-fluoroguanidinium ions are due to a hydrogen bond to these substituents, and the decreased barrier for the H_2N *anti* to the substituent is due to the reduced electron density on the nitrogen bearing the substituent.

3. *E–Z stereoisomerization of isourea derivatives*

Rates of rotation about C—N partial bonds of *O*-alkyl isouronium ions, $ROC(NR'_2)_2^+$, measured by ^{13}C coalescence temperatures, are listed in Table 30. These are significantly lower than for corresponding amidinium ions, $RC(NR'_2)_2^+$, since the alkoxy group stabilizes the positive charge in the transition state for rotation.

4. *E–Z stereoisomerization of isothioureas*

The barriers to interconversion of *Z* and *E* stereoisomers of *N*-arylisothioureas, MeSC(NHR)=NAr, and some *N*-phosphorylated isothioureas, MeSC(NHMe)=NPX_3 and RSC[N(R')PO(OEt)$_2$]=NR", are listed in Tables 31 and 32. These barriers are similar to values found in imine derivatives known to isomerize by nitrogen inversion, so it was inferred[116] that this is the process in these molecules. For variation of substituents on the aromatic ring of *N*-aryl-*N'*-methylisothioureas[117] the Hammett ρ (versus σ^-) of 1.1 does not distinguish between nitrogen inversion and rotation about the C—N double bond, but acceleration by an *ortho* methyl indicates that the former is the operative mechanism. Relative to *N*-phosphorylated benzamidines, the sulfur substituent reduces the activation barrier[121].

The barriers to interconversion of *Z* and *E* stereoisomers of isothiouronium ions, $RSC(NR'_2)_2^+$, are listed in Table 33. In CF_3COOH there is no exchange of NH protons with solvent OH[124], so that the mechanism involves rotation about the C—N partial double bond. However, in methanol the interconversion is faster if one of the substituents on nitrogen is a hydrogen, since this permits proton loss and rotation about a C—N single bond of the isothiourea, so that the barrier is reduced.

5. *Stereoisomerization of iminocarbonates*

For $PhCH=N^+=C(OEt)_2$ (**31**) the interchange of *syn* and *anti* ethoxy groups[151] proceeds with an experimental $\Delta G^{\ddagger}$ of 10.0 kcal mol^{-1}. This corresponds to nitrogen inversion, via a linear transition state like the stable form of the analogous di-*t*-butyl derivative (**32**).

TABLE 31. Activation barriers (kcal mol^{-1}) to *E–Z* interconversion of isothioureas MeSC(NHR)=NR′

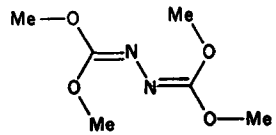
R	R′	Solvent	$\Delta G^{\ddagger}$	Ref.
H	2,6-Xyl	$CDCl_3$–CS_2	13.1	116
H	Mes[a]	$CDCl_3$–CS_2	13.3	116
H	2,6-$Et_2C_6H_3$	$CDCl_3$–CS_2	13.2	116
Me	Ph	$CDCl_3$–CS_2	12.4	117
Me	MeP(O)OPh	CD_3OD	15.0	119
Me	MeP(S)OEt	CD_3COCD_3	14.3	119
Me	MeP(S)OEt	CD_3OD	13.8	119
Me	MeP(S)OPh	CD_3COCD_3	14.6	119
Me	MeP(S)OPh	CD_3OD	14.3	119
Me	$PO(OEt)_2$	CD_3COCD_3	14.8	119
Me	$PO(OEt)_2$	CD_3OD	15.6	119
Me	$PS(OEt)_2$	CD_3COCD_3	14.4	119
Me	$PS(OEt)_2$	CD_3OD	14.8	119
23	2,6-Xyl	CD_3OD–$CDCl_3$	12	183

[a]Mes = 2,4,6-$Me_3C_6H_2$.

TABLE 32. Activation barriers (kcal mol^{-1}) to *E–Z* interconversion of *N*-phosphoryl isothioureas RSC-[N(R′)PO(OEt)$_2$]=NR″ in C_6D_6[121]

R	R′	R″	$\Delta G^{\ddagger}_{Z\rightarrow E}$
Me	Me	Me	17.9
Me	Me	Et	17.6
Me	Me	*i*-Pr	17.4
Me	Et	Me	18.0
Et	Me	Et	17.5
Et	Et	Me	17.6
i-Pr	Me	Et	17.5
i-Pr	Et	Me	17.6

For the *N*-acyliminocarbonates $(RO)_2C{=}NCOR'$ and $(RO)_2C{=}NCOOR'$[224,225] the R groups are equivalent in ^1H and ^{13}C NMR, corresponding to a barrier to nitrogen inversion of < 9 kcal mol^{-1}. In support, a 3-21G MO calculation on the model compound, $(HO)_2C{=}NCHO$, indicates that the transition state for nitrogen inversion lies at 9.5 kcal mol^{-1} above the reactant. However, $(MeO)_2C{=}NN{=}C(OMe)_2$[226] shows inequivalent methoxy groups in both ^1H and ^{13}C NMR, and the X-ray structure verifies that the structure is centrosymmetric (43), as is consistent with the IR/Raman spectra. The



(43)

TABLE 33. Activation barriers (kcal mol^{-1}) to interconversion of *Z* and *E* stereoisomers of isothiouronium ions MeSC(NRR′)=NR″R‴ $^+$

R	R′	R″	R‴	Solvent	$\Delta G^{\ddagger}$	Ref.
H	H	H	Me	CF_3COOH	17.7	124
H	H	H	CH_2Ph	CF_3COOH	16.9	124
H	H	H	Ph	CF_3COOH	14.3	124
H	H	H	*p*-ClC_6H_4	CF_3COOH	14.1	124
H	H	H	*p*-$MeOC_6H_4$	CF_3COOH	14.6	124
H	H	H	2,6-Xyl	CF_3COOH	20.0	124
H	H	H	2,6-Xyl	CD_3OD	18.1	124
H[a]	H	H	2,6-Xyl	CF_3COOH	18.5	124
H[b]	H	H	2,6-Xyl	CF_3COOH	20.4	124
H[c]	H	H	2,6-Xyl	CF_3COOH	20.1	124
H	H	H	2,6-$Et_2C_6H_3$	CF_3COOH–$PhNO_2$	20.6	124
H	H	H	4-Br-2,6-Xyl	CF_3COOH	20.0	124
H	H	H	3-O_2N-4-Br-2,6-Xyl	CF_3COOH	19.6	124
H	H	Me	2,6-Xyl	CF_3COOH–$PhNO_2$	22.9	124
H[b]	H	Me	2,6-Xyl	CF_3COOH–$PhNO_2$	23.9	124
H[c]	H	Me	2,6-Xyl	CF_3COOH–$PhNO_2$	23.9	124
H	H	Me	2,6-$Et_2C_6H_3$	$PhNO_2$	24.3	124
H	H	Et	2,6-Xyl	CF_3COOH–$PhNO_2$	22.7	124
H	Me	H	2,6-Xyl	CF_3COOH	17.6	124
H	Me	Me	2,6-Xyl	CF_3COOH–$PhNO_2$	22.9	124
H	Et	H	2,6-Xyl	CF_3COOH	17.7	124
H	*t*-Bu	H	2,6-Xyl	CF_3COOH	16.8	124
H	PhCHMe	H	2,6-Xyl	CF_3COOH	17.6	124
Me	Me	H	2,6-Xyl	CF_3COOH	14.0	124
Me	Me	H	2,6-$Cl_2C_6H_3$	CF_3COOH	16.0	124
Me	Me	Me	Me	$CDCl_3$	9.4	194
Me	Me	Me	Me	CH_2Cl_2	10.3	223
Me	Me	Me	2,6-Xyl	CF_3COOH–$PhNO_2$	21.1	124
Me[c]	Me	Me	2,6-Xyl	CF_3COOH–$PhNO_2$	21.9	124
Me	Me	Me	2,6-$Et_2C_6H_3$	CF_3COOH–$PhNO_2$	23.2	124
Et	Et	Me	2,6-Xyl	CF_3COOH–$PhNO_2$	19.0	124
Ph	Ph	Me	Me	CH_2Cl_2	15.06	223
—*o*,*o*′-$C_6H_4C_6H_4$—		Me	Me	CH_2Cl_2	> 15.5	223
—*o*,*o*′-$C_6H_4SC_6H_4$—		Me	Me	CH_2Cl_2	12.7	223

[a] *S*-Phenyl.
[b] *S*-Ethyl.
[c] *S*-*s*-Butyl.

barrier to nitrogen inversion is lower in the previous compounds because the electron-withdrawing acyl group stabilizes the p lone pair on nitrogen in the transition state.

The barrier to *E*–*Z* stereoisomerization by nitrogen inversion in the iminodithiocarbonate $(MeS)_2C{=}NC(NR_2){=}NCN$[227] (R = CH_2Ph) is *ca* 10 kcal mol^{-1}.

V. RATES OF ROTATION ABOUT SINGLE BONDS

Hindered internal rotation has been reviewed by Umemoto and Ouchi[228]. Included is rotation about the C—N single bond of amidines, as well as some examples where the C—N double bond of the amidine is incorporated into an aromatic heterocycle.

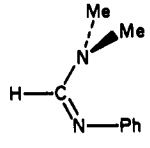
A. Rotation about Single Bonds of Amidines and Imidates

1. Rates of C—N rotation in amidines

Rates of rotation about the C—N single bond of amidines have been studied by various NMR methods. It is usually necessary to use reduced temperatures, since the barrier to rotation is low. Data are listed in Table 34, and many earlier values are tabulated in an earlier review[2]. Unless otherwise noted, all these amidines are known or presumed to be of *E* configuration. Rotational barriers for many additional RC(=NHet)—NR'_2 with bicyclic heterocycles (Het)[235] not included in Tables 34 were also measured. Restricted rotation about the C—N bond was also seen for *N*-phosphoniobenzamidines, $ArC(=NP^+Ph_3)—NMe_2$, and related compounds[237], but no activation barriers were determined. The large $\Delta S^‡$ previously reported for C—N rotation in $phC(=NH)—NMe_2$[38] could be corroborated[239] as 11.4 cal mol^{-1} deg^{-1}, but this was considered to be an anomaly due to the high viscosity of the solvent $CDCl_3$ near its freezing point. Indeed, in CHF_2Cl the $\Delta S^‡$ is not significantly different from 0. Solvent dependence of $\Delta G^‡$ is ordinarily slight. The barriers for the various HC(=NHet)—NMe_2[229] hardly change from DMSO to CS_2, and for $HC(NMe_2)$=NPh the barriers vary only from 14.5 to 14.7 kcal mol^{-1} across a wide range of solvents[240], although added CF_3COOH raises the barrier considerably by protonating the lone pair. With $HC(=^{15}NC_6D_5)—^{15}NHC_6D_5$[128] the ^{15}N label simplifies the spin system so that the $^3J_{HCNH}$ can be seen and used to assign *anti* and *syn* forms. The inverconversion of these by C—N rotation could be followed by line-shape analysis, which was complicated by NH exchange of the *syn* isomer, and the temperature dependence was fit as $k = 10^{13.8}e^{-14.27/RT}$.

It is generally found that the barrier to rotation is lowered by steric bulk of substituents, which destabilizes the planar ground state of the moelcule. The effect is rather small for formamidines[22]. The contrast[5,230] between the *Z* and *E* forms of $CH_3CH=CHC(=NPh)—NMe_2$, differing in the stereochemistry of the C—C double bond, is particularly significant, in that the *Z* form shows the lower barrier. A similar dichotomy is seen with $RC(=NAr)—NMe_2$, where the barriers for R = H or Me are measurable, but the barrier for R = *i*-Pr[22], which is the *Z* stereoisomer according to ^{13}C chemical shifts, is < 7 kcal mol^{-1}. Likewise, the comparison[234] between the *Z* and *E* forms of HC(=NPh)—NMe_2, differing at the C—N double bond, shows that rotation of the *Z* form is too fast to measure even at − 80 °C. The same behavior is found for the conjugate acids, in CF_3COOD or with DOAc in $CDCl_3$. All these results can be explained by destabilization of a coplanar NMe_2 group by the bulky *Z* substituent. However, these authors unfairly reject the conclusion that C—N rotation would be freer in the more congested stereoisomer. Instead they conclude that the methyls are statically equivalent, in a twisted structure (**44**). In support of this interpretation, the ^1H NMR spectra of amidines HC(=NAr)—NMe_2 with *ortho*-substituted aryl groups show inequivalent *N*-methyls, and the inequivalence persists from − 80 to + 34 °C. This is certainly a puzzling observation.

Electronic effects are now clear, even though there was a controversy described in an earlier review in this series[2] due to complications from steric effects. Electron-withdrawing



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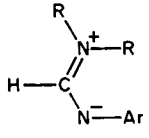

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TABLE 34. Activation barriers (kcal mol^{-1}) to rotation about the C—N single bond of amidines, RC(=NR')—NR"R"

R	R'[a]	R"	R"	Solvent	$\Delta G^{\ddagger}$	Ref.
H	Pr	Me	Me	DMSO-d_6	13.0	229
H	Pr	Me	Me	CD_3COCD_3	12.1	22
H	*i*-Pr	Me	Me	CD_3COCD_3	12.1	22
H	Bu	Me	Me	CD_3COCD_3	12.1	22
H	*i*-Bu	Me	Me	CD_3COCD_3	12.1	22
H	Hex	Me	Me	CD_3COCD_3	12.0	22
H	$PhCH_2$	Me	Me	CD_3COCD_3	12.5	22
H	*p*-$ClC_6H_4CH_2$	Me	Me	CD_3COCD_3	12.6	22
H	*m*-$MeOC_6H_4CH_2$	Me	Me	CD_3COCD_3	12.4	22
H	*p*-$TolCH_2$	Me	Me	CD_3COCD_3	12.4	22
H	Ph	Me	Me	$CDCl_3$	14.9	230
H	Ph	Me	Me	CD_3COCD_3	14.8	231
H	Ph	Me	Me	DMSO-d_6	14.9	229
H	Ph	Et	Et	$CH_2{=}CCl_2$	14.3	230
H	Ph	—$(CH_2)_5$—		DMSO-d_6	14.4	232
H	Ph	—$(CH_2)_6$—		DMSO-d_6	16.5	232
H	Ph	—$[(CH_2)_2O(CH_2)_2]$—		CD_3COCD_3	13.6	233
H	*m*-ClC_6H_4(*E*)	Me	Me	$CDCl_3$	14.3?	234
H	*m*-ClC_6H_4(*Z*)	Me	Me	$CDCl_3$	< 10?	234
H	2-Py	Me	Me	DMSO-d_6	16.6	229
H	3-Me-2-Py	Me	Me	DMSO-d_6	16.4	229
H	4-Me-2-Py	Me	Me	DMSO-d_6	16.7	229
H	5-Me-2-Py	Me	Me	DMSO-d_6	16.6	229
H	3-CN-2-Py	Me	Me	?	19.1	235
H	5-O_2N-2-Py	Me	Me	?	19.1	235
H	2-Pym	Me	Me	?	18.1	235
H	2-Pyz	Me	Me	?	17.5	235
H	5-Cl-2-Pyz	Me	Me	?	18.6	235
H	3,5-Br_2-2-Pyz	Me	Me	?	19.9	235
H	3-Pydz	Me	Me	DMSO-d_6	17.4	229
H	6-Cl-3-Pydz	Me	Me	DMSO-d_6	18.4	229
H	2-N-$MePy^+$	Me	Me	DMSO-d_6	23.0	229
H	N,3-Me_2-2-Py^+	Me	Me	DMSO-d_6	21.1	229

H	N,4-Me_2-2-Py^+	Me	Me	DMSO-d_6	22.4	229
H	N,5-Me_2-2-Py^+	Me	Me	DMSO-d_6	22.8	229
H	$N_{(2)}$-Me-3-$Pydz^+$	Me	Me	DMSO-d_6	23.1	229
H	4-Cl-$N_{(2)}$-Me-3-$Pydz^+$	Me	Me	DMSO-d_6	> 25.2	229
H	6-Cl-3-Pydz-1-O	Me	Me	DMSO-d_6	19.7	229
H	6-Cl-3-Pydz-2-O	Me	Me	DMSO-d_6	19.3	229
Me	Hex	Me	Me	CD_3COCD_3	< 10	22
Me	*c*-Hex	Me	Me	CD_3COCD_3	< 10	22
Me	Ph	Me	Me	$CDCl_3$	12.7	236
Me	Ph	Me	Me	CD_3COCD_3	12.4	22
Me	2-Py	Me	Me	?	< 10.4	235
Me	3-CN-2-Py	Me	Me	?	13.0	235
Me	3-Me-2-Py	Me	Me	?	< 9.4	235
Me	4-Me-2-Py	Me	Me	?	13.2	235
Me	3-Pydz	Me	Me	?	14.0	235
Me	6-Cl-3-Pydz	Me	Me	?	14.0	235
Me	4-Me-6-Cl-3-Pydz	Me	Me	?	< 9.4	235
Me	5-Me-6-Cl-3-Pydz	Me	Me	?	14.2	235
Me	4,5-Me_2-6-Cl-3-Pydz	Me	Me	?	< 9.7	235
Me	2-Pym	Me	Me	?	< 9.3	235
Me	2-Pyz	Me	Me	?	13.9	235
Et	Ph	Me	Me	$CH_2{=}CCl_2$	11.0	230
i-Pr	Ar	Me	Me	CD_3COCD_3	< 7	22
Bu	Ph	Me	Me	$CDCl_3$	11.0	230
$-(CH_2)_5-$		H	R‴ [b]	$CDCl_3$	15.3	35
(*E*)-$CH_3CH{=}CH$	Ph	Me	Me	$CH_2{=}CCl_2$	11.5	5
(*Z*)-$CH_3CH{=}CH$	Ph	Me	Me	$CH_2{=}CCl_2$	8.5	5
$(CH_3)_2C{=}CH$	Ph	Me	Me	$CH_2{=}CCl_2$	11.6	5
Ph	Me	Me	Me	$C_6D_5CD_3$	11.1	10
Ph	Me	CH_2SMe	Me	$C_6D_5CD_3$	11–12	10
Ph	Ph	Me	Me	$CDCl_3$	12.8	230

[a] Pym = pyrimidyl, Pyz = pyrazyl, Pydz = pyridazyl.
[b] R‴ = *p*-TolCHPO_2OMe^- (compound 10).

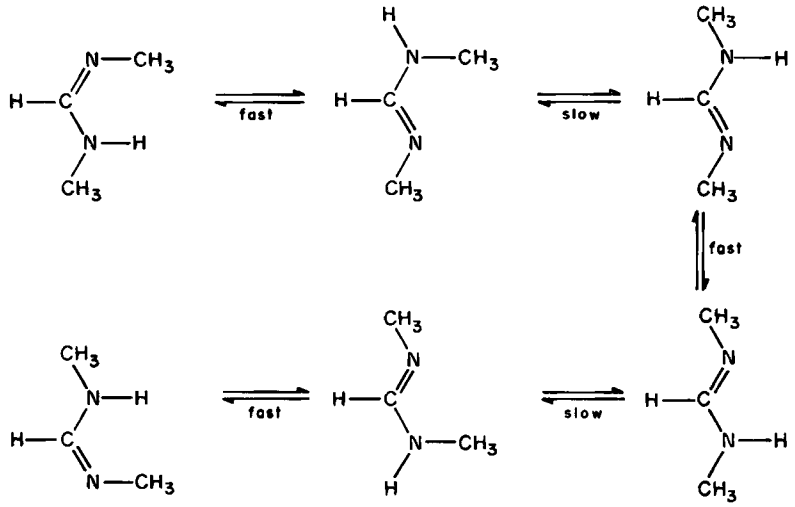
aryl or heterocyclic groups on the singly bonded nitrogen retard the rotation, since the resonance form **45**, with a full double bond about which rotation must occur, is stabilized[241,242]. By the same reasoning, electron-withdrawing groups on the doubly bonded nitrogen can accelerate the rotation, although fewer of these have been studied, since the experimental method is easiest for *N,N*-dimethyl-substituted amidines. For a series of HC(=NAr)—NMe_2[231] the activation barriers can be fitted to the Hammett equation as $\Delta G^{\ddagger} = 14.8 + 2.39\sigma$, but two *m*-alkoxyphenyl derivatives deviate positively, and this has been attributed[236] to a steric effect. In support of a steric effect, the acetamidine analogs, MeC(=NAr)—NMe_2 show a higher rate of rotation and a lower slope ρ of 1.67, since the greater size of the methyl group reduces the amidine conjugation. For the hexamethyleneimine analogs HC(=NAr)—$N[(CH_2)_6]$[232] the fit to the Hammett equation is $\Delta G^{\ddagger} = 16.5 + 1.99\sigma$. For the piperidine analogs HC(=NAr)—$N[(CH_2)_5]$[233] the equation is $\Delta G^{\ddagger} = 1.44 + 2.04\sigma$, and for the morpholine analogs HC(=NAr)—$N[(CH_2)_2]_2O$ it is $\Delta G^{\ddagger} = 13.7 + 1.70\sigma$. The reduced barrier in this last case is due to the electron-withdrawing power of the oxygen. The barrier with the seven-membered ring is higher than with the six, owing to different conformations of the ring. This is a general observation, also seen in urea derivatives and enamines.

According to 3-21G MO calculations[17] on HC(=NH)—NH_2, the barrier to rotation about the C—N single bond is 10.2 kcal mol^{-1}. According to a pseudopotential method and a polarized double-zeta basis[19] the barrier to C—NH_2 rotation is 12.0 kcal mol^{-1}, but for HC(=NCN)—NH_2 the barrier rises to 16 kcal mol^{-1}.

In CD_3NH_2, *N,N'*-dimethylformamidine HC(NHMe)=NMe[37] shows an interesting dynamic behavior. At $-56.5\,^{\circ}C$ the ^1H NMR spectrum shows inequivalent *N*-methyls. The peak at δ 2.68 shows a ^4J to the formyl CH proton of 0.52 Hz, and the one at δ3.02 shows a ^4J of 0.98 Hz. Therefore the former one was assigned to the singly bonded C—NHMe of the *E-anti* stereoisomer, and the latter to the doubly bonded C=NMe. In $CDCl_3$ these coalesce around $-15\,^{\circ}C$, with an activation energy of *ca* 9.8 kcal mol^{-1}, dependent on amidine concentration, but far lower than the barrier to rotation about the C—N double bond. The mechanism was therefore considered simply as a tautomerization of the *E-anti* stereoisomer, whose presence was inferred from the IR spectrum. However, the absence of splitting of the *N*-methyls by the NH proton shows that proton exchange is very fast. Therefore the two *N*-methyl peaks must be assigned to 'inside' (*Z* and *syn*) and 'outside' (*E* and *anti*) methyls of *E-syn* and *Z-anti* stereoisomers. The interconversion must then proceed by rapid tautomerization, plus slower rotation about the C—N single bond (Scheme 1). The two equivalent tautomers of the *E-anti* stereoisomer are then the key intermediates.

Similar behavior is seen[243] for *N*-alkyl-*N'*-methylbenzamidines. At $-40\,^{\circ}C$ in $CDCl_3$–acetone-d_6 *N,N'*-dimethylbenzamidine shows two methyl peaks in both ^1H and ^{13}C NMR. These were ascribed to the inequivalent methyls of PhC(NHMe)=NMe, which become equivalent at higher temperature through tautomerization. For higher homologs the doubling of signals at $-40\,^{\circ}C$ was ascribed to a mixture of PhC(NHMe)=NR and PhC(NHR)=NMe (R = Et or *i*-Pr), and the relative amounts of these two was solvent-dependent. For R = *t*-Bu or Ph only one form was observed, as is reasonable from the acidifying nature of phenyl, but not so obvious for the *t*-butyl derivative. By analogy to the above case, where $^3J_{HCNH}$ is not seen, it seems more likely instead that tautomerization is fast, and that the dynamic process involved is the interconversion of *E-syn* and *Z-anti* stereoisomers. Then the phenyl and *t*-butyl derivatives can be viewed as cases where the *Z-anti* stereoisomer predominates, owing to the bulk of these substituents.

This same behavior is also seen with *N,N'*-diphenylacetamidine MeC(NHPh)=NPh[244]. In DMSO-d_6 (and in the solid) there are separate ^1H and ^{13}C NMR signals for *Z* and *E* phenyl geoups, but in $CDCl_3$ these are coalesced. By HPLC it is possible to separate two compounds, in 1:1 molar ratio, but these interconvert too quickly to permit purification. Again it is likely that the mechanism involves rapid tautomerization plus



SCHEME 1. Proposed mechanism for equivalencing 'inside' and 'outside' *N*-methyls of rapidly tautomerizing *N,N'*-dimethylformamidine

slower rotation (Scheme 1), with two equivalent tautomers of the *E-anti* (or *Z-syn*) stereoisomer as key intermediates.

2. Conformational interconversion of imidates and thioimidates

According to molecular orbital calculations[132] the barrier to rotation about the C—OMe bond of methyl formimidate HC(OMe)=NH is 23.57 kcal mol^{-1}. The 6-31G-calculated[134] barrier to rotation about the C—O bond of peroxyformimidic acid, HC(OOH)=NH, is 6.61 kcal mol^{-1}.

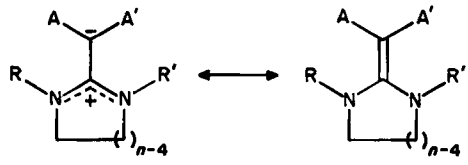
Photolysis of RC(OR')=NCl[32] produces the radical, RC(OR')=N·, whose ESR spectrum shows a temperature dependence of the ^{14}N coupling. This is viewed as arising from slow interconversion of *syn* (**28** *syn*) and *anti* (**28** *anti*) radicals, with different coupling constants. According to MNDO calculations on HC(OH)=N·, the $\Delta G^{\ddagger}$ for conversion of *anti* to *syn* is 4.5 kcal mol^{-1}, which is consistent with the ESR behavior.

Further stereochemical features can be seen with some N- or C-isopropyl thioimidate esters, whose NMR spectra[27] show inequivalent methyls owing to restricted rotation of a bulky aryl ring. For methyl *N*-(*o*-phenylphenyl)isobutyrthioimidate, the barrier to *N*-aryl rotation is *ca* 8 kcal mol^{-1}. for various methyl *N*-isopropylbenzothioimidates with *ortho* substituents in the benzene ring, as well as *i*-PrC(SMe)=N-Naph – 1, the barrier to C–Ar rotation is near 19 kcal mol^{-1} although it is 12.5 kcal mol^{-1} for *i*-PrC(SMe)=NC$_6$H$_4$F-*o* and 22.7 kcal mol^{-1} for the *ortho*-iodo analog.

B. Rotation In Conjugate Acids and Bases

1. Racemization of chiral amidinium ions and similar conformational interconversions

Sandström and his coworkers[245] have carried out a series of elegant studies on stereodynamics of amidinium ions bearing an electron-donor substituent (**46**, A,A' = CN,

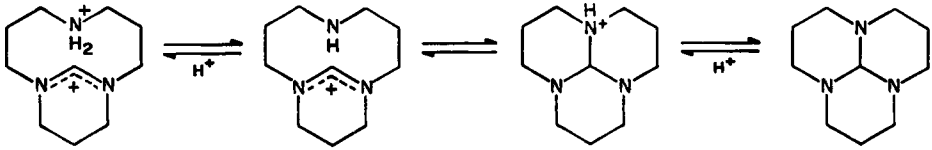


(46) (47)

COMe, COPh, CSMe, etc.) that permits an additional ketene aminal resonance form (47). To achieve the C—C double bond of the latter, the molecule must be planar and therefore achiral. Many of these molecules are indeed planar, but show a dynamic NMR behavior that makes A and A′ or R and R′ equivalent. This corresponds to rotation about the C—C double bond, with a barrier unusually low owing to resonance stabilization of the perpendicular transition state by amidinium resonance form **46**. For example, for the acyclic $PhC(CN)=C(NMe_2)_2$ $\Delta G^{\ddagger}$ is only 19.3 kcal mol^{-1}.

For many other such molecules steric repulsions destabilize the planar form, and electron-accepting substituents A and A′ stabilize the twisted form. If A ≠ A′ and R ≠ R′ the molecule is then chiral. In some cases these can be resolved into enantiomers, and the rates of racemization measured polarimetrically. Some faster reactions can be measured by NMR, when R = *i*-Pr or $PhCH_2$, which provides a prochiral group. For example, for **46** ($n = 6$, R = *i*-Pr, R′ = $PhCH_2$, A = A′ = MeCO) $\Delta G^{\ddagger}$ is 30.3 kcal mol^{-1}. Generally it is found that $\Delta S^{\ddagger}$ is large and positive, since solvent is liberated on converting the zwitterionic reactant to the less polar transition state.

The amidinium ion **48**[246] shows the interesting feature of an apparent D_{3h} symmetry in its ^{1}H NMR spectrum. This requires deprotonation to the monocation **49** and closure to **50**, which is the actual form of the monocation even though this too shows apparent D_{3h}



(48) (49) (50)

symmetry in the ^{1}H NMR. Deprotonation and reprotonation at another nitrogen makes the nitrogens equivalent, to produce effective C_{3v} symmetry, and to achieve the full D_{3h} symmetry the 10-membered ring of **48** or **49** must undergo rapid inversion. Although this example would require additional substitution to make it a racemization of a chiral amidine, it is included here because it involves conformational interconversions, plus bonding changes, to produce an apparently higher symmetry than the static structure.

2. *Rates of C—N rotation in amidinate ions*

Conjugate bases of amidines have not often been characterized. However, one likely candidate is $ArC(=N^-)—N(SiMe_3)_2$[247], which might show a readily measurable barrier near 11 kcal mol^{-1} for rotation about the C—N single bond.

3. *Rates of C—O rotation in imidatonium ions*

MO calculations[45] at the 3-21G level on protonated formimidic acid $HC(OH)=NH_2^+$ suggest a barrier to *anti*-to-*syn* interconversion by C—O rotation of 17.6 kcal mol^{-1}.

C. Rotation of Amidines and Imidates with sp^2-C Substituents

1. *Rates of C—N rotation in N-acylamidines*

The cyclic acylamidine **30** (R = Me)[248] shows two *N*-methyls in the ^1H NMR. Therefore rotation about the C—N single bond must be slow.

Rates of rotation about the C—N single bond of acylamidines have been measured by NMR methods. Data are listed in Table 35. Unless otherwise specified, the C—N double bond is of the more stable *E* configuration. For some of the *N*-acylamidines in the table rotational barriers in other solvents[79,251] have been determined. Also, for some acylamidines the activation parameters have been evaluated[250], and $\Delta S^{\ddagger}$ is negative but small. As with ordinary amidines (Section V.A.1) the rotation is retarded by an electron-withdrawing group on the doubly bonded nitrogen. Thus the barrier for the *N*-trifluoroacetyl derivative is higher than for the *N*-trichloroacetyl derivative, and for the phosphoryl series, the barrier increases[250] in the order $P(—OCH_2CH_2O—) < PO(OR)_2 < P(Tol\text{-}p)_3^+ < PPh_3^+$, and this correlates with ^{13}C chemical shifts. It is also necessary to consider steric effects, since bulky R groups such as trichloromethyl lower the barrier, despite their electron-withdrawing power.

TABLE 35. Activation barriers (kcal mol^{-1}) to rotation about C—N single bond of acylamidines, sulfonylamidines and phosphorylamidines RC(=NR')—NR"R"

R	R'	R"	R"'	Solvent	$\Delta G^{\ddagger}$	Ref.
H	$COCF_3$	Me	Me	$C_2H_2Cl_4$	20.1	79
H	$COCHCl_2$	Me	Me	$C_2H_2Cl_4$	21.7	79
H	$COCCl_3$	Me	Me	CCl_4	21.7–23.1	249
H	SO_2Me	H	Ph	DMSO-d_6	19.0	85
H	SO_2Me	H	*p*-Tol	DMSO-d_6	19.6	85
H	SO_2Me	Ph	$(CH_2)_2NHPh$	DMSO-d_6	19.5	85
H	SO_2Ph	H	Ph	DMSO-d_6	19.8	85
H	SO_2Tol-*p*	H	Ph	DMSO-d_6	19.4	85
Me	$COCF_3$	Me	Me	CCl_4	17.2	249
Me	$COCHCl_2$	Me	Me	$C_2H_2Cl_4$	17.9	79
Cl_2CH	Me	Me	PPh_3^+	CD_3CN	18.2	250
Cl_2CH	Me	Me	$P(Tol\text{-}p)_3^+$	CD_3CN	17.8	250
Cl_2CH	Me	Me	$PO(OMe)_2$	CD_3CN	16.1	250
Cl_2CH	Me	Me	$PO(OPr)_2$	CD_3CN	15.7	250
F_3C	Me	Me	PPh_3^+	CD_3CN	17.9	250
F_3C	Me	Me	$PO(OEt)_2$	CD_3CN	14.6	250
Cl_3C	Me	Me	PPh_3^+	$CDCl_3$	14.2	250
Cl_3C	Me	Me	POOMe	CD_3COCD_3	10.8	250
Ph	Me	Me	PPh_3^+	CD_3CN	21.4	250
Ph	Me	Me	$P(—OCH_2CH_2O—)$	CD_3CN	14.5	250
Ph	$COCHCl_2$	Me	Me	$Cl_2CDCDCl_2$	15.8	79
Ph	$COCF_3$	Me	Me	$CHCl_3$	18.1	249
Ph	$COCCl_3$	Me	Me	C_2Cl_4	16.1	249
2-Py	$COCF_3$	Me	Me	$CDCl_3$	16.7	251
3-Py	$COCCl_3$	Me	Me	$CDCl_3$	16.1	251
4-Py	$COCF_3$	Me	Me	$CDCl_3$	16.6	251

According to MINDO/3 calculations[204] on *N*-nitrosoformamidine, HC(=NH)NHN=O, the barriers to C—N and N—N single bond rotation are 11.6 and 4.0 kcal mol^{-1}, respectively.

D. Rotation of *N*-Heterosubstituted Amidines and Imidates

1. *Rates of C—N rotation in N-aminoamidines*

Rates of rotation of *N*-aminoformamidines and *N*,*N*-dimethyl-*N'*-(acylamino) formamidines about their C—N single bond were determined by ^{1}H NMR. Activation barriers are listed in Table 36. The higher barrier found when the *N*-acylamido group is *Z* is attributed to more extensive conjugation of the lone pair on the dimethylamino nitrogen.

2. *Rates of C—N rotation in amidoximes*

Rates of rotation about the C—N single bond of amidoximes have been studied by various NMR methods. Data are listed in Table 37. The barrier to rotation about the C—N single bond is lower in (*Z*)-ArC(NMe$_2$)=NOH than in the *E* isomer[92], owing to steric interaction between the methyls and the OH.

TABLE 36. Activation barriers (kcal mol^{-1}) to rotation about the C—N single bond of *N*-aminoformamidines, HC(=NNRR')—NR"R"'

R	R'	R"	R"'	Solvent	$\Delta G^{\ddagger}$	Ref.
Me	Me	H	CH_2Ph	$CDCl_3$	14.8	252
Me	Me	H	2-Py	$CDCl_3$	17.4	252
Me	Ph	H	Me	$CDCl_3$	14.9	252
Me	Ph	H	CH_2Ph	$CDCl_3$	14.9	252
Me	Ph	H	2-Py	$CDCl_3$	17.5	252
Me	Ph	Me	Me	CD_3COCD_3	9.7	252
i-Pr	*i*-Pr	H	CH_2Ph	$CDCl_3$	15.6	252
CH_2Ph	CH_2Ph	H	CH_2Ph	$CDCl_3$	15.2	252
(*Z*)-HCO	Me	Me	Me	CD_3COCD_3	13.4	253
(*E*)-HCO	Me	Me	Me	CD_3COCD_3	10.9	253
(*Z*)-HCO	*i*-Pr	Me	Me	CD_3COCD_3	13.2	253
(*E*)-HCO	*i*-Pr	Me	Me	CD_3COCD_3	< 10.0	253
(*Z*)-HCO	*t*-Bu	Me	Me	CCl_4	13.2	253

TABLE 37. Activation barriers (kcal mol^{-1}) to rotation about the C—N single bond of amidoximes, RC(=NOR')—NMe$_2$

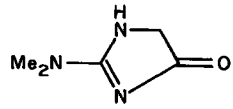
R	R'	Solvent	$\Delta G^{\ddagger}$	Method	Ref.
Ar[a]	(*E*)-H	CD_2Cl_2	9.7	^{1}H T_c	92
Ar[a]	(*E*)-Me	CD_2Cl_2	9.7	^{1}H T_c	92
Ar[a]	(*Z*)-H or Me	$CDCl_3$?	$T_c < 90$ °C		92
Mes	H	CD_2Cl_2	11.2	^{1}H LSA	208

[a]Ar = *p*-MeOC$_6$H$_4$, *p*-Tol, Ph, *p*-ClC$_6$H$_4$, *p*-O$_2$NC$_6$H$_4$, without significant variation in $\Delta G^{\ddagger}$.

E. Rotation of C-Heterosubstituted Amidines

1. Rates of C—N rotation in guanidines

The barrier to rotation about the C—NMe_2 single bond of the acylguanidine **51**[218] is 15.6 kcal mol^{-1}. In acid, $\Delta G^{\ddagger}$ is 17.7 kcal mol^{-1}, and the rate is independent of the acid concentration, so that this represents rotation about the C—NMe_2 partial double bond of protonated **51**. Similarly, the barrier to rotation about the C—$N(CH_2Ph)_2$ single bond of



(51)

$Ar_2C{=}NC(=NCN)—N(CH_2Ph)_2$[227] is 17.3 kcal mol^{-1} in toluene-d_8, and it is higher in more polar solvents. Such restricted rotation is probably responsible for the inequivalence of the R_2N ^1H and ^{13}C NMR signals[254] in AdNC(=NCOAr)—NR_2 (AdNH = adenine, R_2NH = piperidine, pyrrolidine, Me_2NH, morpholine). These barriers are higher than in most other guanidines because the electron-withdrawing carbonyl or cyano group increases the double-bond character.

Calculated barriers to rotation about the C—N single bonds of guanidines are listed in Table 38. The variations in activation energies are attributed[216] to hydrogen bonding to the substituent, which stabilizes the planar form. The increase in activation energy due to a carbonyl substituent is in agreement with experimental results[218].

2. Rates of C—N rotation in isothioureas

Barriers to rotation about the C—NMe_2 single bond of some *N*-phos-

TABLE 38. Calculated activation energies (kcal mol^{-1}) for rotation about the C—N single bonds of stereoisomeric $(H_2N)C(=NH)—NHR$ or $(H_2N)C(=NH)—NR_2$

R	C=N	C—N	Method	$E_A(NH_2)$	E_A(NHR)	Ref.
H	—	?	CNDO/2	14.4	—	215
H	—	?	4-31G	12.2	—	218
H	—	*syn*	6-31G	7.50	—	216
H	—	*anti*	6-31G	11.90	—	216
Me	*Z*	*syn*	6-31G	12.97	8.16	216
Me	*Z*	*anti*	6-31G	12.30	9.36	216
Me	*E*	*syn*	6-31G	—	13.19	216
Me	*E*	*anti*	6-31G	—	14.39	216
Me_2	?	—	CNDO/2	11.6	—	215
CHO	?	?	4-31G	17.0	—	218
NH_2	*Z*	*syn*	6-31G	19.31	14.80	216
NH_2	*Z*	*anti*	6-31G	10.84	11.20	216
NH_2	*E*	*syn*	6-31G	—	19.29	216
NH_2	*E*	*anti*	6-31G	—	19.40	216
F	*Z*	*syn*	6-31G	16.98	13.13	216
F	*Z*	*anti*	6-31G	9.89	8.53	216
F	*E*	*syn*	6-31G	—	15.84	216
F	*E*	*anti*	6-31G	—	7.26	216

TABLE 39. Activation barriers (kcal mol^{-1})[255] to rotation about the C—N single bond of phosphorylated isothioureas MeSC(=NR)—NMe_2

R	Solvent	$\Delta G^{\ddagger}$
MeP(O)OPh	$CDCl_3$-CD_3COCD_3	10.5
$PO(OEt)_2$	$CDCl_3$	11.5
PO(OEt)(SEt)	$CDCl_3$	11.6
$PS(OEt)_2$	$CDCl_3$-CD_3COCD_3	11.0

phonioisothioureas[255] are listed in Table 39. The barriers are lower than in the corresponding *N*-phosphonioamidines, perhaps owing to steric repulsion from the bulkier methylthio group.

3. *Rotation of haloformamidines*

In contrast to most other *N*-acylamidines, the ^{1}H NMR spectrum of ClC(=NCOPh)—NMe_2 in $CDCl_3$ shows[256] a single *N*-methyl peak. Therefore rotation about the C—N single bond must be fast.

4. *Rotation of C-metallosubstituted amidines*

The ^{1}H NMR spectrum[127] of the cationic gold complex, $Au[C(NHMe)(NMe_2)]_2^+$, with two *N,N,N'*-trimethylamidinium ligands, shows two different methyls on the dimethylamino nitrogen. Likewise $Au[C(NHMe)_2]_2^+$, with two *N,N'*-dimethylamidinium ligands, shows two different *N*-methyls. Therefore rotation about the C—N partial double bonds must be slow. These are Au(I) complexes, but the same behavior is seen with the corresponding Au(III) complexes. The behavior parallels that of simple amidinium ions, in contrast to amidines, where rapid rotation about the C—N single bond leads to equivalent *N*-methyls.

The ^{1}H NMR spectrum[189] of $Cp_3UC(NEt_2)$=NXyl-2,6 shows inequivalent *N*-ethyl resonances, so that rotation about the C—N single bond is slow. Moreover, there are inequivalent cyclopentadienyl ligands, so that rotation about the U—C bond is also restricted.

VI. STEREOCHEMICAL EFFECTS ON FORMATION OF AMIDINES, IMIDATES AND RELATED COMPOUNDS

A. Formation of Stereoisomeric Amidines and Imidates

1. *Formation of stereoisomeric amidines*

Since the *E* stereoisomer of a trisubstituted amidine is the more stable, this is usually the product formed. However, it is sometimes possible to take advantage of kinetic control to produce the *Z* form. In particular, the *Z* stereoisomer of **5** is formed preferentially, and this has been attributed[9] to the preferred stereochemistry of the precursor. Another case is addition of secondary amines to isonitriles (equation 1)[257], where reaction at -15 °C

$$R_2NH + R'NC \rightarrow (Z)\text{-}HC(NR_2)=NR' \rightarrow (E)\text{-}HC(NR_2)=NR' \qquad (1)$$

leads to the *Z* form, which is isomerized to the *E* form only on refluxing in chloroform. The *Z* form could be distinguished by the 0.65 ppm shielding of the substituents on nitrogen. The mechanism for preferential formation of the *Z* stereoisomer is viewed as proceeding

via the silver complex of the isonitrile, nucleophilic addition of amine, N-protonation and 1,2-hydrogen shift. Alternatively, addition of nucleophile *anti* to the lone pair is preferred stereoelectronically, and this establishes the stereochemistry immediately while allowing external proton to displace the silver. The *Z* form could also be obtained from HCCl=NAr plus secondary amine, and this seems to be the result of stereoelectronically preferred addition to $HC{\equiv}NAr^+$.

Another example is the reaction[258] of CH_3CN, ArN(Me)SPh ($Ar = p\text{-}O_2NC_6H_4$) and $RC{\equiv}CH$ (R = Bu or Ph), catalyzed by $BF_3{-}OEt_2$, which produces a mixture of stereoisomeric PhSCH=CRN=CMe—NMeAr, which slowly converts to a single material. By analogy with other reactions it was concluded that the kinetic product is the *Z* form as regards the C—N double bond, and that the thermodynamic product is the *E* isomer.

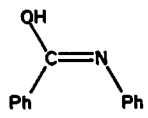
2. *Formation of stereoisomeric imidic acids and imidate esters*

Photolysis of *N*-phenylbenzamide PhCONHPh[259] produces a long-wavelength fluorescence whose intensity, at constant absorbance, increases with concentration. Although similar fluorescence is seen with *N*-methyl-*N*-phenylbenzamide, the width of the emission band in *N*-phenylbenzamide varies with solvent polarity, so it is composite and can be attributed[260] partly to emission from the tautomeric imidic acid. Since the amide catalyzes conversion to the emitting state, presumably by a double proton transfer, the imidic acid is claimed to be created in its *E* configuration (**52**), but the evidence is weak.

Reaction of PhC(OMe)=NH with NaOCl produces the *N*-chloroimidate[28] PhC(OMe)=NCl as a 9:1 mixture of *Z* and *E* isomers. Only on heating do these equilibrate, so that this is indeed a kinetically determined mixture.

3. *Formation of stereoisomeric thioimidates*

Methylation of the *N*-pyridinium betaine $ArC(-S^-)=N(NC_5H_5{}^+)$[261] produces only the *Z* stereoisomer of the *S*-methyl *N*-(1-pyridinio)thioimidate (**53**, R,R′ = H, Me). This



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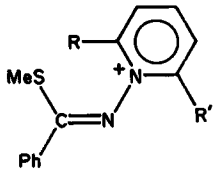


(**53**)

means that the reactant must have been present predominantly as its *Z* configuration. On heating the product to 70 °C, an equilibrium is established, with the *E* isomer predominating for R = R′ = H and with the *Z* predominating for R = H, R′ = Me. For R = R′ = Me no equilibration could be detected, and this was attributed to retardation of equilibration by steric hindrance. However, it is more likely that the equilibrium simply favors strongly the *Z* form.

B. Formation of Stereoisomeric Conjugate Acids

1. *Formation of stereoisomeric amidinium ions*

Reaction of $RC{\equiv}NMe^+$ (R = Me or Ph) with $R'NH_2$ [R′ = *cis*-(NC)C(NH$_2$)=(NC)C][262] produces *N*,*N*′-dialkylamidinium ions as a mixture (1.4:1 or 1.5:1) of *ZE* and

EZ isomers (**2*ZE*, 2*EZ***), in nearly equal amounts. It is not clear why addition across the C—N triple bond is not *anti*, as in the cases above (Section VI.A.1) and below (Sections VI.D.1–4). Nor is it clear how the material that crystallizes from the reaction can be a mixture of stereoisomers.

2. *Formation of stereoisomeric imidatonium ions*

By *O*-alkylation of the separate *Z* and *E* amide stereoisomers it is possible to prepare stereoisomeric imidatonium ions[43] that can sometimes be enriched or separated by crystallization and characterized by NMR.

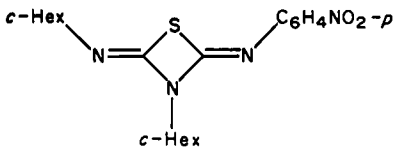
3. *Formation of stereoisomeric metal complexes of amidines*

The $W(CO)_5$ complex of $PhC(NMe_2)=NH$[70] is formed as a 1:3 mixture of *Z* and *E* isomers, from which the *E* can be separated by crystallization. This material is then stable to stereoisomerization to the *Z* form. Since the precursor $PhC(OMe)=NH \rightarrow W(CO)_5$ was a 1.2:1 mixture of stereoisomers, its reaction with Me_2NH is not stereospecific, but proceeds by an addition–elimination mechanism.

C. Formation of Stereoisomeric Amidines with sp^2-C Substituents

1. *Formation of stereoisomeric imidines*

According to X-ray analysis[263] [2 + 2] cycloaddition of *c*-HexN=C=NHex-*c* with *p*-$O_2NC_6H_4N=C=S$ produces the *ZZ* imidine **54**. Although previous studies had suggested that steric effects would favor kinetic formation of the *ZE* stereoisomer, the *ZZ* form is the most stable. Since the barrier to isomerization is likely to be low, the *ZE* form might be formed initially, but then be rapidly isomerized to the *ZZ*. In contrast, another four-membered ring imidine (**55**, Ar = *p*-Tol)[264] is the *EZ* form shown, owing to the steric bulk of the diphosphine ligand.



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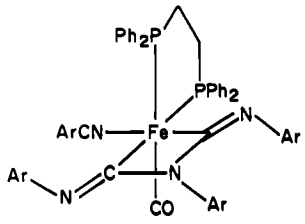

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D. Formation of Stereoisomeric *N*-Heterosubstituted Amidines and Imidates

N-Hetero-amidines and -imidates show the unusual feature that the kinetic product may be different from the thermodynamic product.

1. *Formation of stereoisomeric aminoamidines*

Reaction of various MeCCl=NNMeAr with Me_2NH[206] produces (*Z*)-$MeC(NMe_2)$=NNMeAr as kinetic product, by stereospecific addition to $MeC{\equiv}N^+NMeAr$. For Ar = 2,4-$(O_2N)_2C_6H_3$ this product can be crystallized and kept as the *Z* stereoisomer at

– 20 °C, but with other aryl groups impure crystals are obtained or the material does not crystallize, and such substances more readily convert to the *E* stereoisomer.

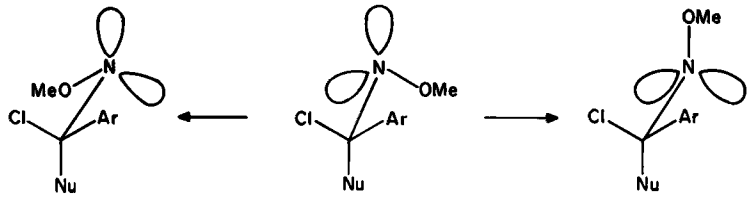
2. *Formation of stereoisomeric amidoximes*

The *Z* stereoisomer of an amidoxime is often the one that is formed more quickly by amine addition to a nitrile oxide, and this then rearranges at a measureable rate to the more stable *E* stereoisomer. Thus the kinetically formed $ArC(NMe_2)=NOH$[92] is *Z*, and on heating this is converted to the *E* form. Further NMR studies[95] indicated that the kinetic product from addition of morpholine to the nitrile oxide $p\text{-}O_2NC_6H_4CNO$ is the *Z* form, which is converted to the more stable *E* form by heating or treatment with acid. Another example[265] is the addition of Me_3SiNEt_2 to MeCNO, to produce (*Z*)-$MeC(NEt_2)=NOSiMe_3$, which takes days to isomerize to its *E* isomer. However, with *N*-monosubstituted or -unsubstituted amidoximes[93], the initially formed *Z* isomer is also the more stable one, and this persists in the reaction mixture. Thus the general addition of amine R_2NH to nitrile oxide ArCNO produces (*Z*)-$ArC(NR_2)=NOH$ as kinetic product. If at least one of the R groups is hydrogen, this is the stable product. However, if both R groups are alkyl, the product isomerizes to the more stable *E* stereoisomer, especially under acidic conditions. To obtain the *Z* form, it is necessary to carry out the synthesis near 0 °C.

A MNDO calculation[266] on the addition of NH_3 to fulminic acid HCNO or acetonitrile oxide MeCNO shows that (*Z*)-$RC(NH_3^+)=NO^-$ is formed faster. Rapid proton transfer then produces the more stable *Z* amidoxime $RC(NH_2)=NOH$.

Reaction of hydroximoyl and alkoximoyl chlorides with amines[106] shows interesting sterochemical features. Reaction of (*Z*)-ArCCl=NOMe (Ar = *p*-Tol, *p*-ClC_6H_4 or *p*-$MeOC_6H_4$) with R_2NH (pyrrolidine) produces (*Z*)-$ArC(NR_2)=NOMe$ as kinetic product, but on heating this is converted to an equilibrium mixture of *Z* and *E* stereoisomers. Reaction with RNH_2 produces (*Z*)-ArC(NHR)=NOMe as the stable form. In contrast, (*E*)-ArCCl=NOMe is unreactive toward R_2NH or RNH_2, even though this stereoisomer is reactive toward the better nucleophile methoxide. With the still more nucleophilic R_2NLi (*N*-lithiopyrrolidine) the *E* stereoisomer is reactive, but only one-sixth as fast as the *Z*. The *Z* alkoximoyl chloride reacts stereospecifically to form (*Z*)-ArC(NHR)=NOMe, but the *E* gives a 57:43 mixture of *Z* and *E* products.

These results have been interpreted in terms of a stereoelectronic effect, whereby cleavage of an alkoxide leaving group requires two antiperiplanar lone pairs, but cleavage of the better leaving group chloride requires only one. Thus addition of nucleophile Nu to (*Z*)-ArCCl=NOMe produces intermediate **56**, which cleaves to the *Z* product. Addition of Nu to (*E*)-ArCCl=NOMe produces intermediate **57**. If the nucleophile is R_2NH, there is no lone pair antiperiplanar to Cl, and this intermediate reverts to reactant faster even than it can rotate about the C—N single bond. Thus the *E* reactant cannot lead to product. If the nucleophile is R_2N^- or MeO^-, there is a lone pair antiperiplanar to Cl, and



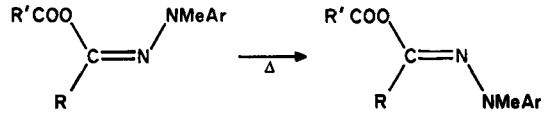
(56) **(57)** **(58)**

this intermediate can lose Cl^- or rotate to other conformations with two lone pairs antiperiplanar to Cl, one of which (**56**) gives *Z* product and the other of which (**58**) gives *E*.

The same behavior is seen[209] in addition of amines to MeC(=NOH)CNO, formed as an intermediate from MeC(=NOH)C(Cl)=NOH. Addition of ammonia gives only the *Z* amidoxime. Addition of primary amines gives 1.5–4.0% *E* amidoxime, except that *t*-butylamine gives 10% of the *E* isomer. The stereoisomers could be distinguished by their ^1H NMR spectra, especially the chemical shift of the amidoxime hydroxyl. With secondary amines, the *E* amidoxime is the kinetic product that can only be detected by NMR, since it isomerizes rapidly to the more stable *Z*.

3. *Formation of stereoisomeric hydrazide derivatives*

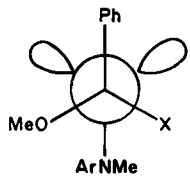
Reaction of hydrazidoyl halides with nucleophiles also can lead to a kinetic product that is not the more stable stereoisomer. For example, reaction of various RCX=NNMeAr [Ar = 2,4-$(O_2N)_2C_6H_3$] with silver acetate[267] produces the *Z* stereoisomer of the hydrazidoyl carboxylates, **59Z** (R′ = Me). On heating these in inert solvents, they isomerize to the *E* form (**59E**), which then undergoes a 1,3-acyl shift. The kinetics could be



(59*Z*) **(59*E*)**

followed by UV and NMR, but the intermediate *E* form could not be detected. Nevertheless, the substituent effects indicate that the nitrogen inversion is rate-limiting.

This same behavior is seen[108] with methoxide as a nucleophile. Only the *Z* methyl hydrazidate RC(OMe)=NNMeAr is formed, but this can be isomerized to the *E* on heating. Moreover, the starting halide could be confirmed as the *Z* stereoisomer by X-ray studies. Therefore, the substitution occurs with retention of configuration. The mechanism is an addition–elimination, via an intermediate (**60**, X = Cl, Br). Since the methoxy can enter



(60)

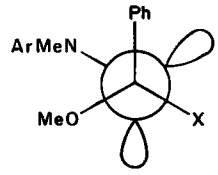
antiperiplanar to a lone pair on the imino nitrogen, and since halide can leave antiperiplanar to a second lone pair on that nitrogen, the lifetime of the intermediate is too short to permit rotation about its C—N single bond. It should be noted that with methoxide as nucleophile the reaction is further complicated by methoxide catalysis[210] of the isomerization of the *Z* product to the more stable *E*.

All these studies were limited to the available *Z* reactant. To compare the stereoselectivities of the *Z* and *E* forms, it was necessary to prepare the *E* form. Although

TABLE 40. Product stereochemistry[210] from reaction of stereoisomeric *O*- or *S*-*p*-nitrophenyl benzo(thio)hydrazidates $ArC(XC_6H_4NO_2\text{-}p)=NNMeC_6H_3(NO_2)_2\text{-}2,4$ with sodium methoxide

Ar	X	Reactant	%*E*
p-$O_2NC_6H_4$	O	*Z*	16
p-$MeOC_6H_4$	S	*Z*	16
p-$MeOC_6H_4$	S	*E*	49
p-$O_2NC_6H_4$	S	*Z*	10
p-$O_2NC_6H_4$	S	*E*	62

this was not possible, even by photolysis, for the hydrazidoyl halides, reaction with thiophenols[210] could produce either stereoisomer of RC(SAr')=NNMeAr. The *Z* form is the kinetic product, obtainable if the reaction is carried out at room temperature. The *E* form is thermodynamically more stable, and it predominates if the reaction is carried out at 65 °C. The two forms could then be purified by chromatography. These are still reactive toward nucleophilic substitution, since $Ar'S^-$ is a good enough leaving group. According to substituent effects the reaction is again an addition–elimination. The product composition is shown in Table 40. The *E* thiophenolates produce a mixture of *Z* and *E* products, since there is no nitrogen lone pair antiperiplanar to the leaving group in the initial intermediate (**61**, X = SAr'). Therefore this undergoes rotation either to **60**

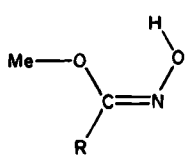


(61)

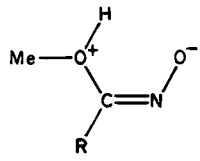
(X = SAr'), which gives *Z* product, or to another rotamer, which gives *E*. However, in contrast to the reaction of the hydrazidoyl chlorides, the reaction of the *Z* thiophenolates (or phenolate) is not so stereospecific, and 10–16% of *E* product is formed. This is because the thiophenoxide or phenoxide is not as good a leaving group as chloride, so that some of the intermediates (**60**, X = SAr' or OAr') live long enough to rotate about their C—N bond.

4. Formation of stereoisomeric hydroximates

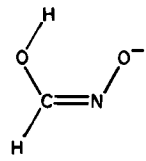
According to 4-31G calculations[149] on the reaction coordinate for addition of OH^- to fulminic acid HCNO, the simplest nitrile oxide, the activation energy for formation of the *Z* product is 32 kcal mol^{-1}, substantially lower than the 61 kcal mol^{-1} for formation of the *E* product. This same result was obtained qualitatively for addition of methanol[268] (or water[269]) to RCNO (R = H, Me, Ph); according to MNDO calculations the *Z* product (**62**) is formed via a kinetically preferred stereoisomer (**63**) of the intermediate, which transfers a proton with little barrier. A MNDO calculation[270] on the initial adduct of HCNO and OH^- is also of relevance to the question of stereoelectronic control. Although the



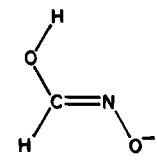
(62)



(63)



(64Z)



(64E)

preferential formation of the *Z*-stereoisomer can be attributed, through the principle of microscopic reversibility, to a preference for cleavage of a leaving group that is antiperiplanar to a nitrogen lone pair, the C—O bond length of the *Z* adduct (**64*Z***) does not show any weakening, compared to the *E* adduct (**64*E***).

Formation of hydroximates from hydroximoyl or alkoximoyl halides is stereoselective. As formed by action of PCl_5 on hydroxamic acids or esters, an oximoyl halide is exclusively (99.5%) the *Z* stereoisomer[113] (equation 2). On photolysis of this material, a photostationary state can be set up, with detectable amounts of the *E* form. The reactivities of the two stereoisomeric alkoximoyl chlorides[271] are quite different. The *Z* form undergoes S_Ni reaction 470 times as fast as the *E* even though the equilibrium favors the *Z* form by at least 99.5%. This represents a strong preference for a nitrogen lone pair antiperiplanar to the leaving group, just as in the E1cB reaction of vinyl halides. Then, by the principle of microscopic reversibility, there should be a strong preference for an incoming nucleophile to enter antiperiplanar to the lone pair on the nitrogen. This then leads to the *Z* product (equation 3). Indeed, both stereoisomers of the reactant give only the same *Z* product, PhC(OMe)=NOMe, since both proceed via the common intermediate, $ArC{\equiv}NOMe^+$. In support, this same *Z* product is obtained[271] if the intermediate is generated by diazotization of the amidoxime, $PhC(NH_2){=}NOMe$.

$$ArCONHOR + PCl_5 \longrightarrow (Z)\text{-}ArCCl{=}NOR \tag{2}$$

$$\begin{gathered} ArCX{=}NOMe \longrightarrow ArC{\equiv}NOMe^+ + X^- \\ ArC{\equiv}NOMe^+ + Nu^- \longrightarrow (Z)\text{-}ArCNu{=}NOMe \end{gathered} \tag{3}$$

$$ArC(-O^-){=}NOR + AcCl \longrightarrow (Z)\text{-}ArC(OAc){=}NOR \tag{4}$$

Similarly the intermediate nitrilium ion, $ArC{\equiv}NOPr^+$, formed by diazotization of $ArC(NH_2){=}NOPr$, can be trapped[272] with acetate, to form $(Z)\text{-}ArC(OAc){=}NOPr$. Alternatively, acylation of the silver salt of an *N*-alkoxyimidate anion produces the *Z* stereoisomer of the *O*-acylalkoxyimidate (equation 4). This product is stable to O-to-N acyl shift, since the lone pair on the nitrogen is *trans* to the acyl group. Photolysis produces a mixture of *Z* and *E* forms, which can often be separated by chromatography. The stereochemical assignment is confirmed by the observation that the *E* form does undergo an O-to-N acyl shift. Preferential formation of the *Z* stereoisomer was attributed to chelation of the Ag^+ counterion, which favors the *Z* stereoisomer of the reactant. However, the chelation effect of silver is not necessary, since treatment of $PhCONHOCH_2Ph$ with acetic anhydride and pyridine[273] produces the *Z* stereoisomer of $PhC(OAc){=}NOCH_2Ph$, so that this is a general feature of the reactant stereochemistry.

The same behavior is shown in addition to nitrile oxides[274]. Addition of ethoxide produces the *Z* hydroximate, with the nucleophile entering *anti* to the nitrogen lone pair (equation 5, Ar = $p\text{-}O_2NC_6H_4$). Photolysis produces a mixture of *Z* and *E* forms, and the

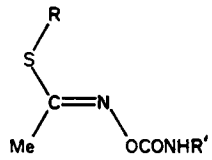
$$ArC{\equiv}N^+O^- + EtO^- \longrightarrow (Z)\text{-}ArC(OEt){=}NOH \tag{5}$$

E form can be distinguished by a 0.9 ppm upfield shift of the OH resonance. With acetate as nucleophile, the initial adduct is not stable, but undergoes a 1,4-acyl transfer to produce ArCONHOAc. This transfer requires that the initial addition product be *Z*. With azide as nucleophile, the *Z* hydroximoyl azide, $ArC(N_3)=NOH$, could be obtained, whereas if the product had been the *E* isomer, it would have cyclized to a hydroxytetrazole, which is known to form when there are catalysts that isomerize the double bond.

Under S_N2 conditions the formation of alkoximates from alkoximoyl chlorides is not always so stereospecific[275]. Reaction of (*Z*)-ArCCl=NOR with alkoxide produces exclusively the *Z* alkoximate ester, within limits of detectability. In contrast, the *E* chloride produces a mixture of *Z* and *E* esters, with the *E* predominating. The *Z* and *E* forms react at nearly the same rate, and the kinetic behavior is consistent with an addition–elimination mechanism.

Although formation of hydroximate esters usually leads to the *Z* form, from the more stable *Z* stereoisomer of the hydroximoyl halide, alternative routes can produce a mixture of stereoisomers. In particular, complexation of benzyl methyl ether with chromium tricarbonyl activates the methylene toward nitrosation, and the resulting η^6-$Cr(CO)_3$ complex of methyl benzohydroximate, PhC(OMe)=NOH, is formed[276] as a 55:45 mixture of *Z* and *E* forms.

Reaction of *S*-alkyl-*N*-hydroxy thioacetimidates MeC(SR)=NOH with isocyanates[277] produces *N*-(carbamoyloxy)thioacetimidates (**65**). These are a mixture of *Z* and *E* forms,



(65)

whose NMR spectra could be assigned. However, the formation of a mixture is due to the trivial fact that the reactant is also a mixture. Such compounds are important because methomyl (**65**, R = R′ = Me) is an insecticide, active as its *Z* form[278].

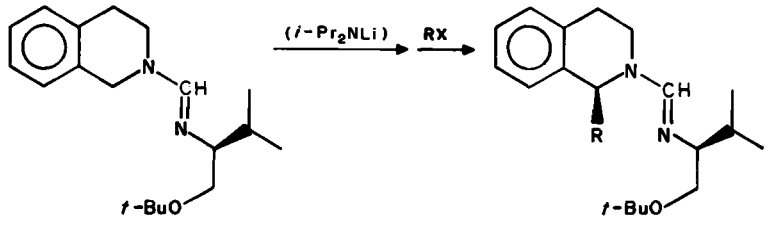
VII. STEREOCHEMICAL EFFECTS IN REACTIONS OF AMIDINES, IMIDATES AND RELATED COMPOUNDS

One of the principles of stereochemistry is that enantiotopic groups or enantiomeric structures must show identical reactivity (in the absence of optically active coreagents), but that diastereotopic groups or diastereomeric structures can show different reactivities. Certainly different stereoisomers can show different reactivities, since diastereomers are genuinely different. Reaction may be stereospecific, if each stereoisomeric reactant leads to a different product. If the two stereoisomers can be studied independently, their separate reactivities can be determined. However, it is quite possible that they interconvert under the reaction conditions, especially if they are simply conformers, interconverting by rotation about single bonds. It is then necessary to take account of the Curtin–Hammett principle[279]. The observed rate is not the rate of either individual reactant. Also, even if the reaction is stereospecific, the mixture of products represents neither the mixture of reactant stereoisomers nor simply their relative reactivities. It is quite possible that the dominant product arises from a greater reactivity of a minor stereoisomer.

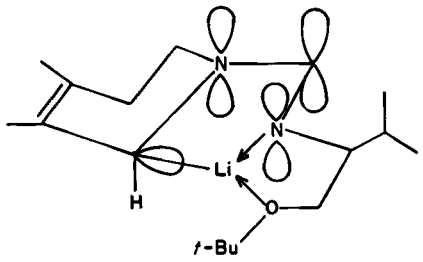
A. Stereochemical Effects on Reactivity of Amidines and Imidates

1. Reactions of chiral amidines

Meyers[280] has used chiral amidines to synthesize chiral amines in high enantiomeric purity. For example, alpha-deprotonation of amidine **66**, derived from valinol, followed by alkylation, produces **67**, which can be hydrolyzed to alkylated amine. The model for diastereoselection is alkylation of chelated organolithium **68** with retention of configur-



(66) **(67)**

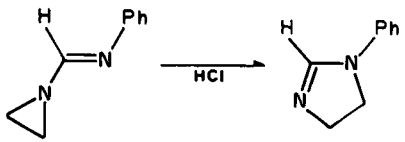


(68)

ation. Although the chirality cannot reside in the amidine functional group, it is the chemistry of the amidine functionality that permits the transfer of chirality from a group on one nitrogen to one on the other.

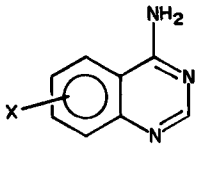
2. Relative reactivities of stereoisomeric amidines

The *Z* and *E* stereoisomers of amidines can show different reactivities. Obviously substituents that are to react must be on the same side of the double bond. Thus cyclization of *N*-aryl-*N'*-cyanoformamidines HC(NHAr)=NCN to 4-aminoquinazolines **(69)**[281] requires the *Z-syn* stereoisomer so that the electrophilic cyano and nucleophilic aryl can be in proximity. Likewise ring expansion of the aziridine derivative (equation 6)[257]

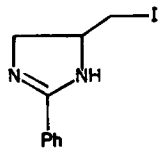


(6)

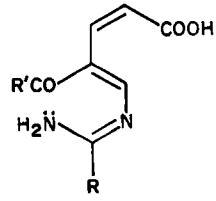
succeeds only with the *E* form shown, since this one has the nitrogen lone pair properly disposed for substitution. (It is likely that this reaction proceeds via a 2-chloroethyl derivative, since direct opening of the aziridine would be a 5-*endo-tet* reaction[282].) Another example is the conversion of *N*-allylbenzamidine $PhC(=NH)NHCH_2CH=CH_2$ to 2-phenyl-4-(iodomethyl)imidazoline (**70**)[283] with *N*-iodosuccinimide, where the cyclization



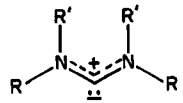
(**69**)



(**70**)



(**71**)



(**72**)

requires proximity of the nitrogen lone pair and the allyl group on the other nitrogen. Likewise, cyclization of the adduct from an amidine and a pyrone derivative (**71**, R′ = H or OMe)[284] requires proximity between nitrogen and carbonyl. In both these kinds of cyclization, the stereochemical description depends on whether the attacking nucleophile is an amino nitrogen or an imino nitrogen, but the necessity for proximity is obvious.

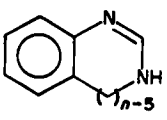
The intramolecular 1,3-phosphoryl shift in various N-phosphorylated amidines also obviously requires the *Z* stereoisomer, and it could be verified by line-shape analysis[243] that the *E* stereoisomer is unreactive and must convert to the *Z* form in order to undergo the rearrangement.

The stereochemical requirement is less obvious for the alkyl migration in a diaminocarbene (**72**)[285]. With R = R′, as in the bispyrrolidine carbene studied, it is not possible to determine whether the *Z* or *E* alkyl migrates. However, with R = Me, $R'R' = (CH_2)_3$, the product may be expected to be either a tetrahydropyrimidine or an iminopyrrolidine, so that this is a practical experiment to do.

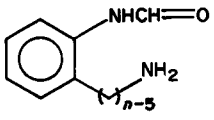
3. *Stereoelectronic effects in reactivity of amidines*

Hydrolysis of amidines has been used as evidence both for and against the theory of stereoelectronic control[286], according to which preferential cleavage of tetrahedral intermediates occurs when there are two lone pairs antiperiplanar to the leaving group. This is an especially good system for testing the theory, since the positions of the nitrogen lone pairs can usually be specified unambiguously.

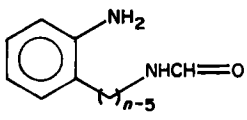
Hydrolysis of the cyclic amidines **73**[8] can lead to two possible products, depending on which C—N bond is cleaved. Since an alkyl amine is more basic, it ought to be cleaved more readily, to produce **74**, even though **75** is more stable. For $n = 7$ *ca* 50% of the kinetic product **74** was indeed detected, but for $n = 6$, only **75** was obtained. A possible explanation is that the tetrahedral intermediate **76** ($n = 6$) cannot achieve a conformation



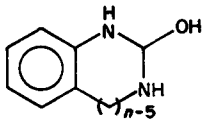
(**73**)



(**74**)



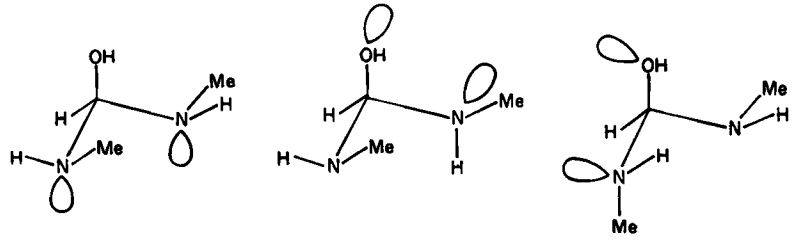
(**75**)



(**76**)

with two lone pairs antiperiplanar to the more basic nitrogen, and therefore this must cleave the other C—N bond, to produce **75**. However, an alternative explanation is that the kinetic product **74** ($n = 6$) is formed, but it is too transient to detect.

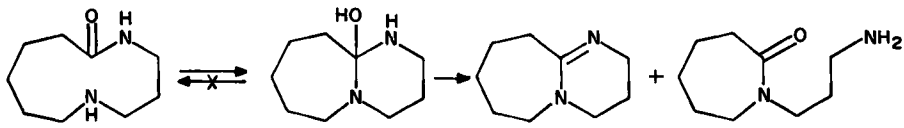
Hydrolysis of *N,N'*-dimethylformamidine[287] produces predominantly or exclusively the less stable *E* stereoisomer of *N*-methylformamide, which converts to the *Z* stereoisomer under the reaction conditions. The reaction involves hydroxide attack on the predominant *ZE* stereoisomer of the amidinium ion. Because the initial tetrahedral intermediate (**77**) lacks two lone pairs antiperiplanar to any nitrogen leaving group, rotation about a C—N single bond is required for cleavage. Rotation of the nitrogen that was originally *E* (at the rear of the structure as illustrated) would produce **78**, which is sterically crowded. Therefore rotation of the other nitrogen is preferred, to produce **79**.



(77) (78) (79)

This now has two lone pairs antiperiplanar to the rear nitrogen, whose cleavage produces (*E*)-*N*-methylformamide. Although this result had been taken as evidence for stereoelectronic control, it should be noted that **79** is a unique conformation of the intermediate, free of *gauche* butane or other 1,4 H–H repulsions, and this can cleave only to the (*E*) amide, regardless of whether stereoelectronic control operates.

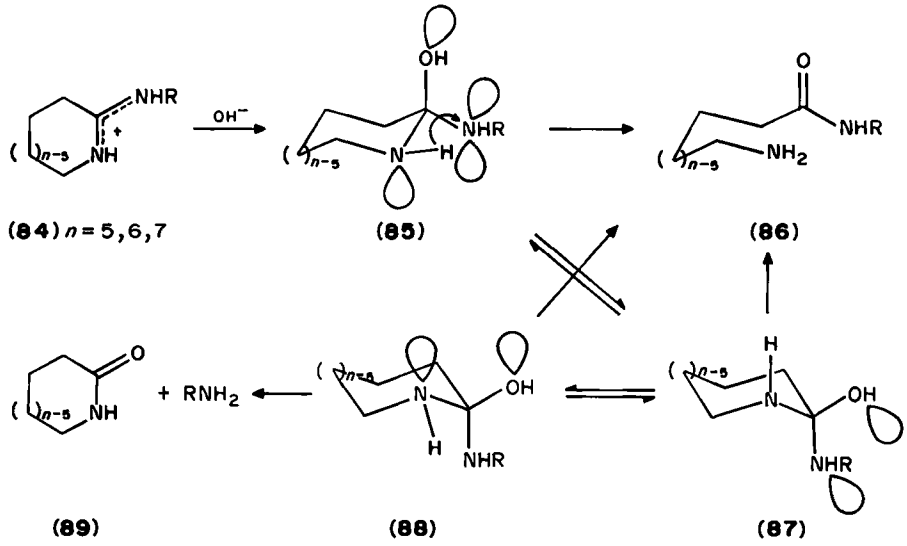
Another case is the cleavage of intermediate **80**[288], not to precursor azalactam **81**, but to amidine **82** and aminoamide **83**. Although this was viewed as a consequence of



(81) (80) (82) (83)

stereoelectronic control, the products are determined simply by thermodynamic stabilities, and no kinetic effects need be invoked.

Hydrolysis of appropriate cyclic amidines provides a definitive test for stereoelectronic control in cleavage of tetrahedral intermediates. The predictions[289] of stereoelectronic control are shown in Scheme 2. Hydroxide is expected to attack the amidinium ion **84** antiperiplanar to the lone pairs on the two nitrogens, to form **85** as initial intermediate. Following rotation about the exocyclic C—N single bond, there are lone pairs on oxygen and on one nitrogen antiperiplanar to the endocyclic C—N bond, which can cleave to produce **86**. Ring inversion of **85** produces **87**, which also has lone pairs on oxygen and on



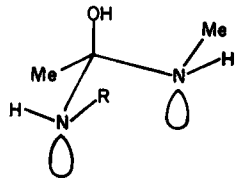
SCHEME 2. Stereoelectronic control in hydrolysis of cyclic amidines

nitrogen antiperiplanar to the endocyclic C—N bond, so it too can cleave to **86**. However, neither **85** nor **87** has two lone pairs antiperiplanar to the exocyclic C—N bond. To cleave this bond, it is necessary also to invert the ring nitrogen, to produce **88**. Now there are lone pairs on oxygen and on ring nitrogen antiperiplanar to the exocyclic C—N bond. Cleavage of this bond produces lactam **89** plus amine RNH_2. This has the advantage over hydrolysis of imidatonium ions (see Section VII.B.2), where the comparison is between oxygen and nitrogen leaving groups and between amide plus alcohol and ester (or lactone) plus amine products, which are not comparable. In contrast, here the leaving groups are uniformly nitrogens, and the products are amide or lactam plus amines. Moreover, the rate constant for nitrogen inversion is estimated as *ca* $10^5\ s^{-1}$, significantly lower than the $10^8\ s^{-1}$ estimated for cleavage of intermediate **85** or **87**. Therefore, conformations like **88** are inaccessible during the lifetime of the intermediate. In summary, then, **86** is expected to be the predominant product if stereoelectronic control is operative.

Initial results[289] were in accord with this expectation. For **84** (R = H, $n = 5,6$) the aminoamide **86** is the only product, within the experimental error. However, control experiments[38] showed that the leaving abilities of the two nitrogens are not balanced. Therefore it was necessary to balance the leaving abilities with **84** (R = Me, $n = 5,6,7$)[290]. For the six-membered ring the product is 93% aminoamide **86**, just as expected from stereoelectronic control. However, for the five- and seven-membered rings the products include 56–58% lactam **89** plus $MeNH_2$. These are formed through the use of the *syn* lone pair on the ring nitrogen, so that stereoelectronic preference for an antiperiplanar lone pair cannot be universal. Indeed, this is entirely parallel to well-known *syn* eliminations in five- and seven-membered rings. Even the 93% aminoamide product from six-membered rings represents only a weak preference, of $< 2\ kcal\ mol^{-1}$, in this most favorable case.

Hydrolysis of *N,N'*-dialkylamidines can show an unusual configurational effect[38]. For *N*-alkyl-*N'*-methylacetamidinium ions, which exist as a mixture of *ZE* and *EZ* stereoisomers (**2ZE** and **2EZ**), there is a preference for cleavage of the nitrogen whose alkyl group is *Z*. This arises from weak stereoelectronic effects[286] in formation and cleavage of the

tetrahedral intermediate. Thus, hydroxide is expected to add antiperiplanar to the nitrogen lone pairs of the *ZE* ion to produce **90**. After rotation about C—N single bonds, which preserves the absolute configurations at both nitrogens, there are only two conformations (**91** and **92**) that are free of steric repulsion, that have a leaving group



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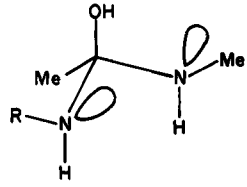

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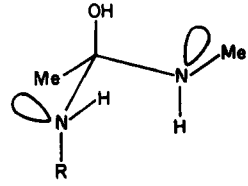


(92)

antiperiplanar to two lone pairs and that can cleave to repulsion-free *Z*-amide products. In both these conformations the leaving group is not $MeNH_2$ but RNH_2, the amine whose alkyl group was *Z* in the original ion. Correspondingly the *EZ* ion is expected to lead to cleavage of $MeNH_2$. For R = *i*-Pr, Bu or *t*-Bu the experimental results[38] are in fair agreement with this expectation, kif the relative reactivities of the two stereoisomeric ions are such that they react at the same rate rather than with the same rate constant. However, for R = neoPen or $PhCH_2$, leaving abilities that arise from unequal basicities of the two nitrogens also influence the direction of cleavage.

4. Relative reactivities of stereoisomeric imidate esters

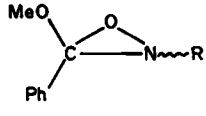
The stereochemistry of imidate esters is of importance for their reactivity. The intramolecular Diels–Alder cyclization of ethyl *N*-(3,5-hexadienoyl)acrylimidates[291] requires that the C—N double bond be *E*. Fortunately the barriers to conformational interconversion are low, so that all conformations can be explored, including the reactive ones.

A more elaborate case of differing reactivities of imidate stereoisomers occurs in the hydrolysis of aryl *N*-methylacetimidates[26]. These differ in their basicities, and spectrophotometric titration shows that for MeC(OTol-*p*)=NMe the pK_a of N-protonated $Z{\cdot}H^+$ is 8.0 whereas the pK_a of $E{\cdot}H^+$ is 6.55. Observation of biphasic kinetics suggests that the two stereoisomers also react at different rates, such that the rate of interconversion is comparable to the rate of hydrolysis of the slower isomer. In acid the *Z* isomer is 4 times as reactive as the *E*, whereas in base the *E* isomer is 3 times as reactive as the *Z*. The rate-limiting step must be nucleophilic attack on the N-protonated substrate, since if breakdown of the tetrahedral intermediate were rate-limiting, the reactants would equilibrate rapidly and biphasic kinetics would not be observed. By correcting the relative reactivities for the basicities, it could be concluded that $E{\cdot}H^+$ is 3.0 times as reactive as $Z{\cdot}H^+$ toward H_2O, 4.0 times as reactive toward $MeNH_2$, 10 times toward carbonate and 7 times toward OH^-.

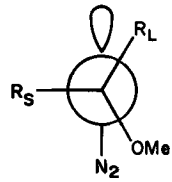
With peracids the stereoisomeric PhC(OMe)=NR could be oxidized to oxaziridines, which were obtained[25] as a mixture of *cis* and *trans* forms (**93**), even from PhC(OMe)=NMe, where the *Z* form is undetectable by NMR. Since the oxidation should be stereospecific, this result means that the *Z* form, present in low concentrations, is more reactive than the *E*.

Photolytic conversion of azides to imidate esters[292] presents an interesting stereochemical problem. On heating $RR'C(OMe)N_3$ to 360 °C, there is loss of N_2 and preferential

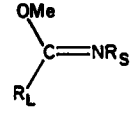
migration of the smaller alkyl group to the electron-deficient nitrogen. Alternatively, the migration can be induced photochemically, without any migration preference. This rearrangement is modeled by a transition state (**94**) with the alkyl group migrating to the vacant 2p atomic orbital on nitrogen rather than opposite to the N_2 that is being lost. Yet any such migration will not place the migrating alkyl coplanar with the methoxy and other alkyl, as it must become in the product imidate (**95**). It would be of interest to determine the stereochemistry of the product from the photochemical reaction.



(**93**)



(**94**)



(**95**)

5. Relative reactivities of stereoisomeric thioimidates

Iodolactonization of γ,δ-unsaturated *S*-methyl-*N*-benzylthioimidates[293] clearly requires the *Z* stereoisomer, so that the nitrogen lone pair can serve as nucleophile.

B. Stereochemical Effects on Reactivity of Conjugate Acids

1. Relative reactivities of diastereotopic groups in amidinium ions

An unsubstituted or *N,N'*-dialkyl-substituted amidinium ion $RC(NHR')_2^+$ (R' = H or alkyl) has diastereotopic *Z* and *E* protons. These have identical bonds and might be naively expected to show identical reactivities. However, the protons are in different environments, and they can and do show different reactivities.

Base-catalyzed proton exchange of amidinium ions shows the remarkable stereochemical feature of positional selectivity in an encounter-controlled reaction[15]. The rate constants are shown in Table 41. Although the diastereotopic protons in a molecule exchange at nearly identical rates, the differences are significant. In all these cases it is the more acidic proton, or the proton that is expected to be more acidic, that exchanges faster. This is remarkable, in that hydroxide is a sufficiently strong base to remove any proton in an encounter-controlled reaction, so that acidity ought not to matter. These results were originally interpreted in terms of a mechanism where the breaking of a hydrogen bond in an amidine hydrate is partially rate-limiting. However, more recent results[39] suggest that

TABLE 41. Rate constants for OH^--catalyzed exchange[15] in amidinium ions RC(NHR')(NHR'')$^+$

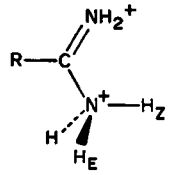
R	R'	R''	Method	$k_E(s^{-1})$	$k_Z(s^{-1})$	k_Z/k_E
H	H	H	^{1}H LSA	4.2	8.6	2.0
Me	H	H	^{1}H ST	3.8	4.81	1.28
Ph	H	H	^{1}H LSA	15.6	19.5	1.25
Me	Me	Me	^{1}H LSA	0.48	0.35	0.73
Me	Me	Me	NMR(*t*)	6.8×10^{-4a}	1.8×10^{-4a}	3.8
Ph	Me	Me	^{1}H LSA	0.77	0.85	~1
—$(CH_2)_3$—		H	^{1}H ST	3.8	14.3, 6.2	3.8, 1.6

[a] D_2O-catalyzed.

the relative reactivities are governed by the rate at which hydroxide diffuses to the ion, along channels of hydrogen bonds in the solvent.

Acid-catalyzed proton exchange of amidinium ions shows an intriguing stereochemical feature. The reaction occurs only in strongly acidic solutions. The mechanism is protonation on one of the nitrogens, to produce a dication. It had originally been observed[294] that H_E of (*ZE*)-*N*,*N*′-dimethylacetamidinium ion, $MeC(NHMe)_2^+$, exchanges 6.4 times as fast as H_Z. Likewise, in 66% H_2SO_4 the NH protons of (*ZE*)-*N*,*N*′-dimethylformamidinium ion[37] undergo exchange with solvent, and the *E* proton, the one on the nitrogen with the upfield (*Z*) *N*-methyl, exchanges faster. These observations were attributed to an inherently greater basicity of the nitrogen that bears H_E. However, comparison with the isoelectronic alkenes suggests that the difference in basicities is not so large. Indeed, it was observed[295] that H_E of benzamidinium ion, $PhC(NH_2)_2^+$, exchanges faster than H_Z, and here the nitrogens must be of identical basicity. Similar behavior is seen[296] with *p*-toluamidinium ion, and saturation-transfer measurements on $p\text{-}^+H_3NC_6H_4C(NH_2)_2^+$ indicate that H_E exchanges 1.44 times as fast as H_Z.

The key to the greater reactivity of H_E lies in the structure of the intermediate, $RC(=NH_2^+)\text{-}NH_3^+$. The preferred conformation of this intermediate is **96**, and the initial



(96)

protonation creates this intermediate with the protons as labelled. It would seem that rotation about the C—N single bond would render the three protons of the $-NH_3^+$ group equivalent, so that H_E and H_Z would necessarily exchange at identical rates. Nevertheless, even though that rotation is extremely fast, so is deprotonation, since the intermediate is so strong an acid. (The rate constant for deprotonation of a strong acid in water has been estimated[297] as 1.6×10^{10} s^{-1}). Therefore the protons do not become equivalent. Loss of H_E from the intermediate can proceed readily, but exchange of H_Z requires prior rotation about the C—N bond. Thus exchange of H_E can proceed faster, as observed.

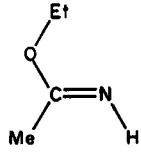
In 97% H_2SO_4 there is also coalescence of the *Z* and *E* *N*-methyls of (*ZE*)-*N*,*N*′-dimethylformamidinium ion[37]. This occurs by rotation of the N-protonated intermediate, to produce the *EE* stereoisomer as further intermediate.

In CD_3CN with added CF_3COOH the gold(I) complex (**26E**, $M = Au_{1/2}$)[54] undergoes proton exchange. The upfield *N*-methyl doublet, corresponding to the *E* methyl, exchanges faster. Different rates are expected, since the NH groups are inequivalent. Specifically, exchange of the *Z* methyl requires rotation about the $C—NH_2Me$ single bond, and this is competitive with deprotonation[295,296]. At higher CF_3COOH concentrations the two *N*-methyls coalesce with each other, by acid-catalyzed rotation about the C—N bonds, and via the *ZZ* or *EE* form, in which the methyls are equivalent.

2. *Relative reactivities of stereoisomeric imidatonium ions and of diastereotopic groups in imidatonium ions*

With sodium iodide in acetonitrile each of the two stereoisomeric $HC(OMe)=NMeXyl\text{-}2,6^+$ is demethylated stereospecifically[43] to the corresponding formamide.

In dilute aqueous acid, primary amides $RCONH_2$ with electron-withdrawing substituents have been shown[298] to undergo acid-catalyzed proton exchange via the conjugate acid $RC(OH)=NH_2^+$. The NH protons are diastereotopic and might exchange at different rates. In particular, it is found that the amide proton H_Z often exchanges faster than H_E. Also, in 46% sulfuric acid $MeC(OEt)=NH_2^+$, the conjugate acid of ethyl acetimidate, undergoes water-catalyzed proton exchange[299], and the proton H_Z exchanges 2.0 times as fast as H_E. In contrast, for 2-iminotetrahydrofuran hydrochloride in wet DMSO-d_6 it is H_E that exchanges 1.15 times as fast as H_Z. There is no intramolecular proton exchange, so that the mechanism does involve deprotonation to the imidic acid or imidate ester, which is configurationally stable during its lifetime before reprotonation. Since the more acidic proton is the one likely to exchange faster, these results indicate that **97** and **98** are the more stable stereoisomers, in agreement with MO calculations and



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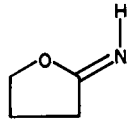
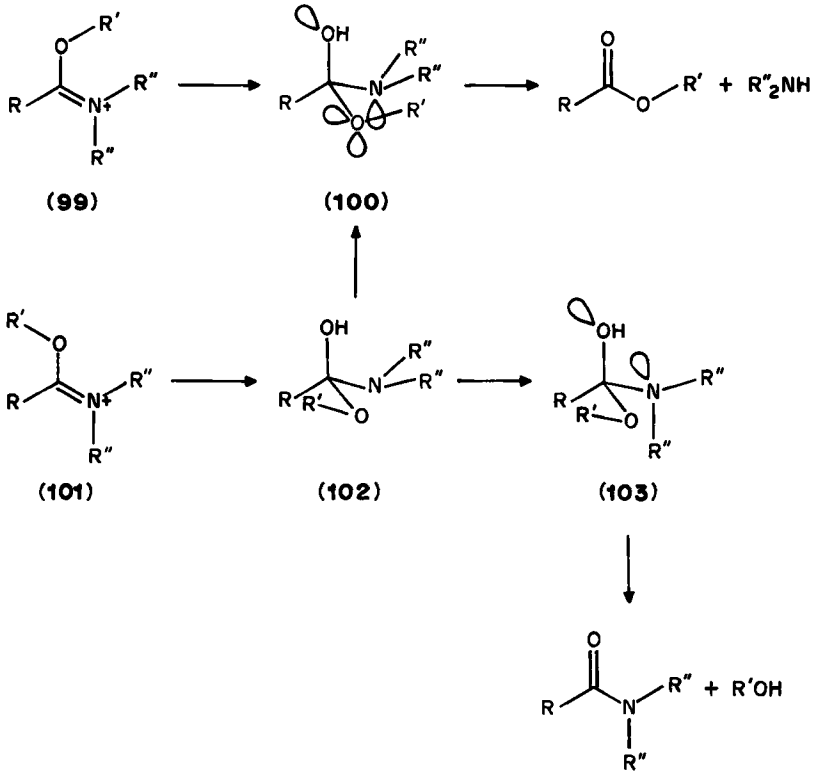


(98)

considerations of dipole–dipole interactions (Section III.A.2). The contrast arises because the C—O single bond of the cyclic imidate ester is *anti*, whereas in the acyclic one it is *syn*.

The reactivities of stereoisomeric imidatonium ions under alkaline conditions show a dependence on the conformation of the C—O bond, and the product mixtures have been presented[137] as evidence for a stereoelectronic effect in formation and cleavage of the tetrahedral intermediate. The results have been interpreted in terms of preferential cleavage of a leaving group that is antiperiplanar to two lone pairs, or preferential attack of nucleophile antiperiplanar to two lone pairs. The consequences of stereoelectronic control are shown in Scheme 3. Attack on the *syn* imidatonium ion **99** is expected to produce intermediate **100**, which has two lone pairs antiperiplanar to the nitrogen. If this undergoes cleavage faster than it undergoes conformational change, it will produce only ester plus amine. In contrast, attack on the *anti* imidatonium ion **101** is expected to produce intermediate **102**, which lacks two lone pairs antiperiplanar to any leaving group (except the OH). This then has time to rotate either about the C—OR′ bond, to produce **100**, or about the C—N bond, to produce **103**. As before, **100** can cleave to ester plus amine, but **103** can cleave to amide plus alcohol. Thus it is expected that a *syn* imidatonium ion should produce only ester plus amine, but an *anti* ion should produce a mixture of products. The experimental results[137,300] are given in Table 42, along with the presumed conformation of the C—O bond. It can be seen that the results are in accord with the expectations, and there are additional bicyclic cases not included in the table. Therefore these results seem to be excellent evidence in support of the proposed stereoelectronic effect. However, in some cases reactant conformations were unknown independently and simply assumed in order to fit the products. Also, a key assumption is that if there are two lone pairs antiperiplanar to a leaving group, then cleavage occurs faster than conformational equilibration.

Further interesting results are obtained with some cyclic six-membered-ring form-imidatonium ions[301] that necessarily have the C—O bond *anti*. Under basic conditions hydrolysis, via C—O cleavage, produces hydroxyamide, but as a nonequilibrium mixture of amide stereoisomers. These results were interpreted in terms of initial C—N cleavage,



SCHEME 3. Stereoelectronic effects in hydrolysis of imidatonium ions

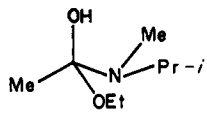
TABLE 42. Product mixture (% C—N cleavage to ester + amine)[137,300] from alkaline hydrolysis of imidatonium ions, RC(OR′)=NMeR″ +

R	R′	R″	C—O	%C—N Cleavage
H	Et	Me	*anti*	50
Me	Et	Me	*anti* or mixt.	81
c-Hex	Et	Me	*anti* or mixt.	75
t-Bu	Et	Me	*syn*	100
Ph	Et	Me	*syn*	100
Me	—$(CH_2)_2$—		*syn*	100
Ph	—$(CH_2)_2$—		*syn*	100
Ph	—$(CH_2)_3$—		*syn*	100
—$(CH_2)_3$—		Me	*anti*	50
—$(CH_2)_4$—		Me	*anti*	33
—$[(CH_2)_3]_{1/2}$— Et		—$[(CH_2)_3]_{1/2}$—	*anti*+*syn*	65
—$[(CH_2)_4]_{1/2}$— Et		—$[(CH_2)_4]_{1/2}$—	*anti-syn*	83

when steric effects permit, followed by reclosure and C—O cleavage from two possible conformations leading to the two different amide stereoisomers. With a hindered nitrogen, C—O cleavage is assumed to occur directly from a half-boat conformation of the intermediate.

Similar results have been obtained[302] in reactions of cyclic five-membered-ring imidatonium ions with HS^-. The kinetic product is obtained with C—N cleavage, even though the thermodynamic product requires C—O cleavage. The C—N cleavage is interpreted in terms of a stereoelectronic effect, but it is necessary to make assumptions about conformational equilibria.

The reactivities of the two stereoisomeric ethyl *N*-methyl-*N*-isopropylacetimidatonium ions, MeC(OEt)=NMePr-*i*$^+$, are nearly identical, but their partitionings to products[201] have important implications for the theory of stereoelectronic control[286]. Studies of *N,N*-dimethyl and *N,N*-diisopropyl analogs had shown that alkaline hydrolysis leads to 80% Me_2NH but only 6% *i*-Pr_2NH. This was attributed to steric repulsion in the tetrahedral intermediate between the *Z*-isospropyl group and the *O*-ethyl, which is thereby forced into an *anti* position, in place of an antiperiplanar lone pair on oxygen that is needed to assist in expulsion of amine. Then it would be expected that the product mixture from (*Z*)-MeC(OEt)=NMePr-*i*$^+$ would resemble that from the *N,N*-diisopropyl analog, whereas (*E*)-MeC(OEt)=NMePr-*i*$^+$ would resemble the *N,N*-dimethyl analog. Nevertheless, the two stereoisomers produce identical product mixtures, with up to 65% *i*-PrNHMe in alkali. It is not possible to account for this in terms of equilibration of reactants, although this does occur to some extent. Instead it is necessary to conclude that the tetrahedral intermediates (**104**, **105**) equilibrate, by sp^3 nitrogen inversion and C—N rotation, before they cleave to products. If such conformational processes do not occur during the lifetime of the intermediate, then there is no need to reject conformations like **106**, and the



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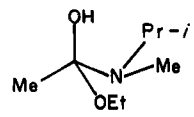

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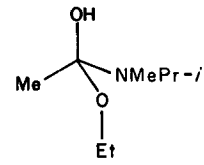


(106)

stereoelectronic explanation for the difference between *N,N*-dimethyl and *N,N*-diisopropyl analogs is weakened. Indeed, a key assumption in applying the theory of stereoelectronic control to hydrolysis of imidatonium ions is that if there are two lone pairs antiperiplanar to a leaving group, then cleavage occurs faster than conformational equilibration, and this does not seem to be the case.

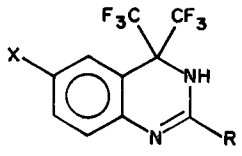
Similar results have been obtained[43] in hydrolysis of some formimidatonium ions. The stereoisomeric HC(OEt)=NMeCH_2Ph$^+$ and HC(OMe)=NMeAr$^+$ (Ar = Ph or 2,6-Xyl) are hydrolyzed in base nonstereospecifically to the same equilibrium mixture of *N,N*-dialkylformamides.

How then can the results in Table 42 be accounted for? The question is not a simple one, since it is necessary to compare cleavage of oxygen vs nitrogen leaving groups. It may be that C—N cleavage is favored by steric repulsions in the tetrahedral intermediate, as suggested[303] for the analogous hydrolysis of tertiary amides. The occurrence of C—O cleavage from some of the *anti* precursors can be attributed simply to the instability of the lactone product[289,304].

C. Stereochemical Effects on Reactivity of Amidines with sp^2-C Substituents

1. Relative reactivities of N-alkylidene amidines

The six-electron electrocyclization (followed by 1,5-hydrogen shift) of $RC(=NC_6H_4X\text{-}p)N=C(CF_3)_2$ to a 4,4-bis-(trifluoromethyl)-3,4-dihydroquinazoline (**107**)[305] obviously



(107)

requires that the stereochemistry be *Z*, since the $C(CF_3)_2$ group cannot reach to the aromatic ring in the *E* stereoisomer. It is also of interest that the $C(CF_3)_2$ group in the reactant is perpendicular to the amidine plane.

D. Stereochemical Effects on Reactivity of *N*-Heterosubstituted Amidines and Imidates

1. Relative reactivities of stereoisomeric amidoximes

The kinetics of cyclization of $PhC(NH_2)=NOCOPh$ to a 1,2,4-oxadiazole[306] have been followed. This is an obvious case where reaction requires that the stereochemistry be *Z*, since the *E* stereoisomer cannot cyclize.

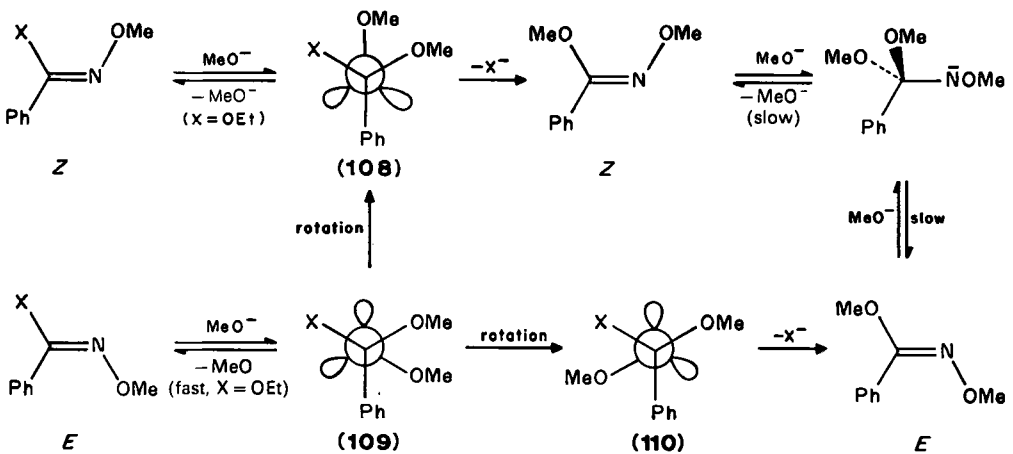
2. Relative reactivities of stereoisomeric hydrazidates

The two stereoisomers of *S*-*p*-nitrophenyl benzothiohydrazidates $ArC(SC_6H_4NO_2\text{-}p)=NNMeC_6H_3(NO_2)_2\text{-}2,4$ react with sodium methoxide at different rates[210]. Kinetics could be followed by UV, and substituent effects indicate that the mechanism is an addition–elimination. At 30 °C the *Z* form reacts 8.9 (Ar = *p*-$MeOC_6H_4$) or 13.8 (Ar = *p*-$O_2NC_6H_4$) times as fast as the *E*. This is an unusual case where the more stable stereoisomer is nevertheless the more reactive one, but presumably the intermediate from the *Z* reactant (**60**, X = SAr') is stabilized by an anomeric effect of having nitrogen lone pairs antiperiplanar to methoxy and to thiophenoxy groups.

3. Relative reactivities of stereoisomeric hydroximates

The stereoisomeric oximoyl chloride anions $PhCCl=NO^-$ react to form PhCNO at rates differing by more than 10^7-fold[307]. These anions could be generated by hydrolysis of PhCCl=NOAc, whose two stereoisomers could be separated from the photostationary state by preparative TLC. The rate constants were found to be $k_Z = 4 \times 10^5\,s^{-1}$ and $k_E = 6.6 \times 10^{-3}\,s^{-1}$.

The reactivities of the stereoisomeric hydroximate esters[275] provide a further contrast to their formation. With ethoxide, the *Z* stereoisomer of the methyl ester, PhC(OMe)=NOMe, could be transesterified to PhC(OEt)=NOMe, and the reaction proceeds with retention of configuration. The *E* stereoisomer is inert. In the reverse direction, with the ethyl ester plus methoxide, the *Z* form reacts 300 times as fast as the *E*, even though the *E* reactant leads predominantly to the *Z* product. This behavior is quite different from that of



SCHEME 4. Stereoelectronic effects in nucleophilic substitution reactions of alkoximoyl chlorides (X = Cl) and alkoximate esters (X = OEt)

the corresponding alkoximoyl chlorides (Section VI.D.4), where the *E* isomer is as reactive as the *Z* but leads to a mixture of products.

The stereochemical outcome of the transesterification is complicated by the equilibration of the stereoisomers under the reaction conditions. Although the *Z* isomer is the kinetic product, under these conditions the equilibrium strongly favors (> 98%) the *E*. This is in marked contrast to the alkoximoyl chlorides, where the equilibrium favors the *Z* isomer.

The stereochemical dichotomies could be rationalized in terms of stereoelectronic effects, which favor loss of a leaving group that is antiperiplanar to a lone pair. Addition of methoxide to the *Z* chloride produces an intermediate (**108**, X = Cl) with a nitrogen lone pair antiperiplanar to the chloride, which can be lost faster than the intermediate undergoes rotation about the C—N single bond (Scheme 4). Addition of methoxide to the *E* chloride produces an intermediate (**109**, X = Cl) with no nitrogen lone pair antiperiplanar to the chloride, so that the intermediate has time to undergo C—N rotation. Rotation to conformer **110** (X = Cl) leads to the *E* product, corresponding to retention of configuration, but rotation to **108** (X = Cl) permits formation of the *Z* product, corresponding to inversion.

In the transesterifications, addition of alkoxide to a *Z* ester leads to an intermediate (**108**, X = OEt) that can rapidly lose either of the two alkoxides, to revert to reactant or to produce product, but with retention of configuration (Scheme 4). Addition to the *E* ester leads to an intermediate (**109**, X = OEt) that rapidly reverts to reactant. Progress toward transesterification requires rotation about the C—N bond, to form **108** and **110** (X = OEt), which lead to a mixture of *Z* and *E* products.

E. Stereochemical Effects on Reactivity of *N*-Heterosubstituted Amidines

1. Relative reactivities of stereoisomeric isoureas and isothioureas

Cyclization to a dihydropyrimidine of the Michael adduct from *O*-methylisourea or *O*-(*p*-methoxybenzyl)isothiourea plus ArCH=C(COOR)COMe[308] clearly requires the *Z-anti* stereoisomer of the N-alkylated adduct, so that the lone pair on the nitrogen is in a position to condense onto the ketone.

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IX. REFERENCES

1. G. Häfelinger, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, New York, 1975.
2. G. Fodor and B. A. Phillips, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, New York, 1975.
3. V. G. Granik, *Russ. Chem. Rev. (Engl. Transl.)*, **52**, 377 (1983).
4. J. Oszczapowicz, this volume.
5. M. Naulet, M. L. Filleux, G. J. Martin and J. Pornet, *Org. Magn. Reson.*, **7**, 326 (1975).
6. J. Oszczapowicz, E. Raczyńska and J. Osek, *Magn. Reson. Chem.*, **24**, 9 (1986).
7. O. Exner, M. Buděšinský, D. Hnyk, V. Všetečka and E. D. Raczyńska, *J. Mol. Struct.*, **178**, 147 (1988).
8. B. A. Burdick, P. A. Benkovic and S. J. Benkovic, *J. Am. Chem. Soc.*, **99**, 5716 (1977).

9. H. Quast and E. Schmitt, *Angew. Chem., Int. Ed. Engl.*, **9**, 381 (1970); H. Quast, P. Schäfer, K. Peters and H. G. von Schnering, *Chem. Ber.*, **113**, 1921 (1980).
10. H.-M. Wolff and K. Hartke, *Arch. Pharm.*, **313**, 215 (1980).
11. S. D. Worley, K. G. Taylor, B. Venugopalan and M. S. Clark, Jr., *Tetrahedron*, **34**, 833 (1978).
12. L. M. Jackman and T. Jen, *J. Am. Chem. Soc.*, **97**, 2811 (1975).
13. V. V. Negrebetskii, T. V. Aleshnikova, A. F. Prokof'eva, A. F. Grapov and N. N. Mel'nikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **57**, 1650 (1987).
14. E. D. Raczyńska, *J. Chem. Res. (S)*, 410 (1987).
15. C. L. Perrin, D. A. Schiraldi and G. M. L. Arrhenius, *J. Am. Chem. Soc.*, **104**, 196 (1982).
16. J. Teysseyre, J. Arriau, A. Dargelos, J. Elguero and A. R. Katritzky, *Bull. Soc. Chim. Belges*, **85**, 39 (1976).
17. T. J. Zielinski, M. R. Peterson, I. G. Csizmadia and R. Rein, *J. Comput. Chem.*, **3**, 62 (1982).
18. L. Radom, W. J. Hehre and J. A. Pople, *J. Am. Chem. Soc.*, **93**, 289 (1971).
19. W. Kinasiewicz, A. Leś and I. Wawer, *J. Mol. Struct.*, **168** (*Theochem.*, **45**), 1 (1988).
20. K. B. Wiberg, C. M. Breneman and T. J. LePage, *J. Am. Chem. Soc.*, **112**, 61 (1990).
21. M. Sabio and S. Topiol, *Eur. J. Med. Chem.*, **24**, 189 (1989).
22. I. Wawer, *Magn. Reson. Chem.*, **27**, 577 (1989).
23. J. W. Krajewski, Z. Urbańczyk-Lipkowska, P. Gluziński, I. Buśko-Oszczapowicz, J. Oszczapowicz, J. Bleidelis and A. Kemme, *Pol. J. Chem.*, **55**, 1015 (1981).
24. C. O. Meese, W. Walter and M. Berger, *J. Am. Chem. Soc.*, **96**, 2259 (1974).
25. O. Gonzalez C., D. E. Gallis and D. R. Crist, *J. Org. Chem.*, **51**, 3266 (1986).
26. A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7045 (1974).
27. W. Walter and C. O. Meese, *Chem. Ber.*, **110**, 2463 (1977).
28. A. J. Papa, *J. Org. Chem.*, **35**, 2837 (1970).
29. M. Laspéras, J. Taillades and A. Commeyras, *New J. Chem.*, **12**, 147 (1988).
30. H. Fischer, U. Schubert and R. Märkl, *Chem. Ber.*, **114**, 3412 (1981).
31. W. D. Wulff, V. Dragisich, J. C. Huffman, R. W. Kaesler and D. C. Yang, *Organometallics*, **8**, 2196 (1989).
32. S. A. Glover and A. L. J. Beckwith, *Aust. J. Chem.*, **40**, 701 (1987).
33. W. Walter and C. O. Meese, *Chem. Ber.*, **109**, 922 (1976).
34. R. W. Ratcliffe, K. J. Wildonger, L. Di Michele, A. W. Douglas, R. Hajdu, R. T. Goegelman, J. P. Springer and J. Hirshfield, *J. Org. Chem.*, **54**, 653 (1989).
35. T. V. Aleshnikova, A. F. Prokof'eva, V. V. Negrebetskii, A. F. Grapov and N. N. Mel'nikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **56**, 2217 (1986).
36. B. Kratochvil, J. Novotny, S. Smrčkova and J. Krechl, *Collect. Czech. Chem. Commun.*, **55**, 479 (1990).
37. J. D. Halliday, E. A. Symons and P. E. Bindner, *Can. J. Chem.*, **56**, 1470 (1978).
38. C. L. Perrin and O. Nuñez, *J. Am. Chem. Soc.*, **109**, 522 (1987).
39. T. J. Dwyer, Ph.D. Thesis, Univ. of Calif., San Diego, 1988.
40. C. Bazzano, P. C. Vanoni, M. Mondoni, A. Gallazzi, E. Cereda and A. Donetti, *Eur. J. Med. Chem.*, **21**, 27 (1986).
41. K. M. Wellman and D. L. Harris, *J. Chem. Soc., Chem. Commun.*, 256 (1967).
42. A. Donetti, G. Trummlitz, G. Bietti, E. Cereda, C. Bazzano and H.-U. Wagner, *Arzneim.-Forsch.*, **35**, 306 (1985).
43. P. Deslongchamps, U. O. Cheriyan, J.-P. Pradère, P. Soucy and R. J. Taillefer, *Nouv. J. Chim.*, **3**, 343 (1979).
44. H. Kohn and R. A. Olofson, *J. Org. Chem.*, **37**, 3504 (1972).
45. T. J. Zielinski, R. A. Poirier, M. R. Peterson and I. G. Csizmadia, *J. Comput. Chem.*, **3**, 477 (1982).
46. A. C. Hopkinson and M. H. Lien, *Int. J. Quantum Chem.*, **13**, 349 (1978).
47. M. T. Nguyen and A. F. Hegarty, *J. Org. Chem.*, **51**, 4703 (1986).
48. C. L. Perrin, C. P. Lollo and C.-S. Hahn, *J. Org. Chem.*, **50**, 1405 (1985).
49. C. L. Perrin and J. D. Thoburn, *J. Org. Chem.*, **54**, 764 (1989).
50. G. Alagona, E. Scrocco and J. Tomasi, *J. Am. Chem. Soc.*, **97**, 6976 (1975).
51. C. L. Perrin, *J. Am. Chem. Soc.*, **96**, 5628 (1974).
52. C. L. Perrin, E. R. Johnston, C. P. Lollo and P. A. Kobrin, *J. Am. Chem. Soc.*, **103**, 4691 (1981).
53. I. Yavari and J. D. Roberts, *J. Am. Chem. Soc.*, **100**, 5217 (1978).

54. D. J. Doonan, J. E. Parks and A. L. Balch, *J. Am. Chem. Soc.*, **98**, 2129 (1976).
55. P. Paul and K. Nag, *Inorg. Chem.*, **26**, 1586 (1987).
56. L. Maresca, G. Natile, F. P. Intini, F. Gasparrini, A. Tiripicchio and M. Tiripicchio-Camellini, *J. Am. Chem. Soc.*, **108**, 1180 (1986).
57. F. Gerstner and J. Weidlein, *Z. Naturforsch.*, **33B**, 24 (1978).
58. G. Rajca, W. Schwarz, J. Weidlein and K. Dehnicke, *Z. Anorg. Allgem. Chem.*, **522**, 83 (1985).
59. C. Ergezinger, F. Weller and K. Dehnicke, *Z. Naturforsch.*, **43B**, 1621 (1988).
60. R. Lechler, H.-D. Hausen and J. Weidlein, *J. Organomet. Chem.*, **359**, 1 (1989).
61. H. W. Roesky, B. Meller, M. Noltemeyer, H.-G. Schmidt, U. Scholz and G. M. Sheldrick, *Chem. Ber.*, **121**, 1403 (1988).
62. J. D. Kildea, W. Hiller, B. Borgsen and K. Dehnicke, *Z. Naturforsch.*, **44B**, 889 (1989).
63. F. A. Cotton and R. Poli, *Inorg. Chim. Acta*, **141**, 91 (1988).
64. J. Barker, N. Cameron, M. Kilner, M. M. Mahoud and S. C. Wallwork, *J. Chem. Soc., Dalton Trans.*, 1359 (1986).
65. H. Brunner, W. Meier, J. Wachter, I. Bernal and E. Raabe, *J. Organomet. Chem.*, **362**, 95 (1989).
66. F. A. Cotton, T. Inglis, M. Kilner and T. R. Webb, *Inorg. Chem.*, **14**, 2023 (1975); F. A. Cotton and L. W. Shive, *Inorg. Chem.*, **14**, 2027 (1975); A. Bino, F. A. Cotton and W. Kaim, *Inorg. Chem.*, **18**, 3566 (1979); F. A. Cotton and R. Poli, *Organometallics*, **6**, 1743 (1987); F. A. Cotton and R. Poli, *Inorg. Chim. Acta*, **122**, 243 (1986); F. A. Cotton, X. Feng, M. Matusz and R. Poli, *J. Am. Chem. Soc.*, **110**, 7077 (1988); F. A. Cotton, X. Feng and M. Matusz, *Inorg. Chem.*, **28**, 594 (1989); P. Piraino, G. Bruno, G. Tresoldi, S. Lo Schiavo and F. Nicolò, *Inorg. Chem.*, **28**, 139 (1989).
67. E. Hartmann and J. Strähle, *Z. Naturforsch.*, **44B**, 1 (1989).
68. M. W. Creswick and I. Bernal, *Inorg. Chim. Acta*, **74**, 241 (1983).
69. M. Wada and T. Shimohigashi, *Inorg. Chem.*, **15**, 954 (1976).
70. H. G. Raubenheimer, G. J. Kruger, F. Scott and R. Otte, *Organometallics*, **6**, 1789 (1987).
71. F. P. Fanizzi, F. P. Intini and G. Natile, *J. Chem. Soc., Dalton Trans.*, 947 (1989).
72. D. G. Fortier and A. McAuley, *J. Am. Chem. Soc.*, **112**, 2640 (1990).
73. S. Baral, F. A. Cotton and W. H. Ilsley, *Inorg. Chem.*, **20**, 6696 (1981).
74. D. S. Glueck, F. J. Hollander and R. G. Bergman, *J. Am. Chem. Soc.*, **111**, 2719 (1989).
75. E. S. Hand and D. C. Baker, *Synthesis*, 905 (1989).
76. J. Kao, *J. Comput. Chem.*, **9**, 905 (1988).
77. D. E. Bernholdt, J. D. Irwin, J. P. Lacosse, S. K. Loushin, K. J. Mattson, J. B. Miers, K. D. Park, L. K. Tanaka and C. E. Dykstra, *J. Mol Struct.*, **153** (*Theochem.*, **38**), 175 (1987).
78. P. Luthardt, M. H. Möller, U. Rodewald and E.-U. Würthwein, *Chem. Ber.*, **122**, 1705 (1989).
79. N. N. Zobova, A. V. Aganov, V. V. Klochkov and A. Z. Nazyrova, *J. Gen. Chem. USSR* (*Engl. Transl.*), **57**, 1848 (1987).
80. S. B. Fulgarevich, T. A. Yusman, O. A. Lukova, D. Ya. Movshovich, L. N. Olekhnivich, I. E. Mikhailov and V. I. Minkin, *J. Gen. Chem. USSR* (*Engl. Transl.*), **57**, 1214 (1987).
81. V. V. Negrebetskii, L. Ya. Bogel'fer, A. D. Sinitsa, V. I. Kal'chenko and V. S. Krishtal', *J. Gen. Chem. USSR* (*Engl. Transl.*), **51**, 1260 (1981).
82. D. Korbonits, P. Kiss, K. Simon and P. Kolonits, *Chem. Ber.*, **117**, 3183 (1984).
83. L. I. Spiessens and M. J. O. Anteunis, *Bull. Soc. Chim. Belges*, **91**, 763 (1982).
84. L. I. Spiessens and M. J. O. Anteunis, *Bull. Soc. Chim. Belges*, **92**, 965 (1983).
85. P. Jakobsen and S. Treppendahl, *Tetrahedron*, **33**, 3137 (1977); **37**, 829 (1981).
86. L. I. Spiessens and M. J. O. Anteunis, *Bull. Soc. Chem. Belges*, **93**, 205 (1984).
87. V. V. Negrebetskii, O. V. Balitskaya, and M. Yu. Kornilov, *J. Gen. Chem. USSR* (*Engl. Transl.*), **53**, 2320 (1983).
88. R. Norrestam, *Acta Crystallogr.*, **C40**, 955 (1984).
89. A. F. Hegarty, *Acc. Chem. Res.*, **13**, 448 (1980).
90. J. B. Moffat, *J. Mol. Struct.*, **94** (*Theochem.*, **11**), 261 (1983).
91. V. A. Khrustalev, O. V. Solod, and K. N. Zelenin, *J. Org. Chem. USSR* (*Engl. Transl.*), **22**, 444 (1986).
92. H. Gozlan, R. Michelot and R. Rips, *Tetrahedron Lett.*, 859 (1975).
93. H. Gozlan, R. Michelot, C. Riche and R. Rips, *Tetrahedron*, **33**, 2535 (1977).
94. D. Bright, H. A. Plessius and J. de Boer, *J. Chem. Soc., Perkin Trans. 2*, 2106 (1973).
95. K. J. Dignam, A. F. Hegarty and M. J. Begley, *J. Chem. Soc., Perkin Trans. 2*, 704 (1980).
96. E. Arte, J. P. Declercq, G. Germain and M. Van Meerssche, *Bull. Soc. Chim. Belges*, **87**, 573 (1978).

97. O. Exner and N. Motekov, *Collect. Czech. Chem. Commun.*, **47**, 814 (1982).
98. A. Dondoni, G. Gilli and M. Sacerdoti, *J. Chem. Soc., Perkin Trans. 2*, 1036 (1976).
99. H. Gozlan and C. Riche, *Acta Crystallogr.*, **B32**, 1662 (1976).
100. G. A. Jeffrey, J. R. Ruble, R. K. McMullan, D. J. DeFrees and J. A. Pople, *Acta Crystallogr.*, **B37**, 1381 (1981).
101. O. Exner and N. Motekov, *Collect. Czech. Chem. Commun.*, **43**, 2740 (1978).
102. O. Exner and N. Motekov, *Collect. Czech. Chem. Commun.*, **51**, 1444 (1986).
103. B. Clement and T. Kämpchen, *Chem. Ber.*, **118**, 3481 (1985).
104. K. J. Dignam, A. F. Hegarty, and P. L. Quain, *J. Chem. Soc., Perkin Trans. 2*, 1457 (1977).
105. O. Exner, V. Jehlička, A. Dondoni and A. C. Boicelli, *J. Chem. Soc., Perkin Trans. 2*, 567 (1974).
106. J. E. Johnson, A. Ghafouripour, M. Arfan, S. L. Todd and D. A. Sitz, *J. Org. Chem.*, **50**, 3348 (1985).
107. K. J. Dignam and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1437 (1979).
108. A. F. Hegarty, M. T. McCormack, B. J. Hathaway and L. Hulett, *J. Chem. Soc., Perkin Trans. 2*, 1136 (1977).
109. D. Keus and J. Warkentin, *J. Org. Chem.*, **49**, 3466 (1984).
110. R. Benassi and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1629 (1985).
111. J. P. Declercq, G. Germain and M. Van Meerssche, *Acta Crystalllogr.*, **B31**, 2894 (1975).
112. V. Bertolasi, M. Sacerdoti and D. Tassi, *Cryst. Struct. Commun.*, **6**, 335 (1977).
113. J. E. Johnson, E. A. Nalley, Y. K. Kunz and J. R. Springfield, *J. Org. Chem.*, **41**, 252 (1976).
114. A. Kjaer, I. K. Larsen and P. Sivertsen, *Acta Chem. Scand.*, **B31**, 415 (1977).
115. J. Smolíková, O. Exner, G. Barbaro, D. Macciantelli and A. Dondoni, *J. Chem. Soc., Perkin Trans. 2*, 1051 (1980).
116. G. Tóth and L. Toldy, *Acta Chim. Acad. Sci. Hung.*, **80**, 349 (1974).
117. A. P. Engoyan, T. F. Vlasova, Yu. N. Sheinker and L. A. Ignatova, *Doklady-Chem. (Engl. Transl.)*, **225**, 687 (1975).
118. G. Tóth and J. Hemela, *Acta Chim. Acad. Sci. Hung.*, **95**, 71 (1977).
119. L. Ya. Bogel'fer, V. N. Zontova, V. V. Negrebetskii, A. F. Grapov, S. F. Dymova and N. N. Mel'nikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **48**, 1579 (1978).
120. V. V. Negrebetskii, L. Ya. Bogel'fer, A. F. Grapov, V. N. Zontova and N. N. Mel'nikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **49**, 61 (1979).
121. V. V. Negrebetskii, A. F. Grapov, V. N. Zontova, V. I Ivanchenko and N N. Mel'nikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **53**, 272 (1983).
122. L. Ya. Bogel'fer, A. F. Grapov, V. V. Negrebetskii, V. N. Zontova and N. N. Mel'nikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **51**, 1017 (1981).
123. V. V. Negrebetskii, A. F. Grapov, V. N. Zontova, V. I. Ivanchenko and N. N. Mel'nikov, *Doklady-Chem. (Engl. Transl.)*, **265**, 205 (1982); A. F. Grapov, V. V. Negrebetskii, E. A. Chertopolokhova and N. N. Mel'nikov, *Doklady-Chem. (Engl. Transl.)*, **265**, 191 (1982).
124. G. Tóth, L. Toldy, I. Tóth and B. Rezessy, *Tetraheddron*, **30**, 1219 (1974).
125. G. Birke, H. P. Latscha and A. Schmidt, *Z. Anorg. Allgem. Chem.*, **424**, 287 (1976).
126. B. C. Challis, J. N. Iley and H. S. Rzepa, *J. Chem. Soc., Perkin Trans. 2*, 1037 (1983).
127. J. E. Parks and A. L. Balch, *J. Organomet. Chem.*, **71**, 453 (1974).
128. L. Meschede, D. Gerritzen and H.-H. Limbach, *Ber. Bunsenges. Phys. Chem.*, **92**, 469 (1988).
129. D. E. Gallis and D. R. Crist, *Magn. Reson. Chem.*, **25**, 480 (1987).
130. H. B. Schlegel, P. Gund and E. M. Fluder, *J. Am. Chem. Soc.*, **104**, 5347 (1982).
131. J. Elguero, P. Goya, I. Rozas, J. Catalán, and J. L. G. de Paz, *J. Mol. Struct.*, **184** (*Theochem.*, **53**), 115 (1989).
132. H. Lumbroso and G. C. Pappalardo, *J. Mol. Struct.*, **43**, 97 (1978).
133. A. Greenberg and R. Winkler, *J. Mol. Struct.*, **63**, 131 (1980).
134. T. J. Lang, G. J. Wolber and R. D. Bach, *J. Am. Chem. Soc.*, **103**, 3275 (1981).
135. B. Hoesterey, W. C. Neely and S. D. Worley, *Chem. Phys. Lett.*, **94**, 311 (1983).
136. H. Lumbroso, A. Pilotti and G. C. Pappalardo, *J. Chim. Phys.*, **71**, 1433 (1974).
137. P. Deslongchamps, S. Dubé, C. Lebreux, D. R. Patterson and R. J. Taillefer, *Can. J. Chem.*, **53**, 2791 (1975).
138. G. I. Birnbaum, unpublished, via Reference 43.
139. L. I. Spiessens and M. J. O. Anteunis, *Bull. Soc. Chim. Belges*, **93**, 191 (1984).
140. J. Hocker and R. Merten, *Ann. Chem.*, **16** (1978).
141. R. Allmann, M. Krestel, R. Kupfer and E.-U. Würthwein, *Chem. Ber.*, **119**, 2444 (1986).

142. R. Kupfer, M. Nagel, E.-U. Würthwein and R. Allmann, *Chem. Ber.*, **118**, 3089 (1985).
143. M. T. Nguyen and T.-K. Ha, *J. Mol. Struct.*, **88** (*Theochem.*, **5**), 127 (1982).
144. M. N. Ramos, *Acta Sud Am. Quim.*, **2**, 45 (1982).
145. G. La Manna, M. Cignitti, and C. E. Notaro, *J. Mol. Struct.*, **166** (*Theochem.*, **43**), 439 (1988).
146. R. M. Srivastava, M. N. Ramos and L. M. Mendes e Silva, *Gazz. Chim. Ital.*, **113**, 845 (1983).
147. M. N. Ramos, R. M. Srivastava, M. B. Brito and G. F. de Sá, *J. Chem. Res.* (*S*), 228 (1984).
148. M. T. Nguyen, M. Sana, G. Leroy, K. J. Dignam and A. F. Hegarty, *J. Am. Chem. Soc.*, **102**, 573 (1980).
149. G. Leroy, M. T. Nguyen, M. Sana, K. J. Dignam and A. F. Hegarty, *J. Am. Chem. Soc.*, **101**, 1988 (1979).
150. T. Bally, P. Diehl, E. Haselbach and A. S. Tracey, *Helv. Chim. Acta*, **58**, 2398 (1975).
151. M. Krestel, R. Kupfer, R. Allmann and E.-U. Würthwein, *Chem. Ber.*, **120**, 1271 (1987).
152. R. Anulewicz, T. M. Krygowski and B. Pniewska, *J. Cryst. Spectr. Res.*, **17**, 661 (1987).
153. E. Ciszak, M. Gdaniec, M. Jaskólski, Z. Kosturkiewicz, J. Owsiański and E. Tykarska, *Acta Crystallogr.*, **C45**, 433 (1989).
154. H. Grützmacher, H. W. Roesky, M. Noltemeyer and G. M. Sheldrick, *Z. Naturforsch.*, **42B**, 1245 (1987).
155. J. W. Krajewski, Z. Urbańczyk-Lipkowska, P. Gluziński, L. Lebioda, I. Buśko-Oszczapowicz and J. Cieślak, *J. Antibiotics*, **34**, 282 (1981).
156. E. Ciszak, M. Gdaniec, M. Jaskólski and Z. Kosturkiewicz, *Acta Crystallogr.*, **C44**, 2144 (1988).
157. R. Norrestam, S. Mertz and I. Crossland, *Acta Crystallogr.*, **C39**, 1554 (1983).
158. F. Iwasaki and K.-Y. Akiba, *Acta Crystallogr.*, **B37**, 185 (1981).
159. W. Eul, G. Kiel and G. Gattow, *Z. Anorg. Allgem. Chem.*, **542**, 182 (1986).
160. F. Iwasaki and K.-Y. Akiba, *Acta Crystallogr.*, **B37**, 180 (1981).
161. J. P. Declercq, G. Germain, M. Van Meerssche, M. Van den Bril and R. Fuks, *Cryst. Struct. Commun.*, **9**, 1011 (1980).
162. J. Hvoslef, M. L. Tracy and C. P. Nash, *Acta Crystallogr.*, **C42**, 353 (1986).
163. K. Surma, M. Jaskólski, Z. Kosturkiewicz and J. Oszczapowicz, *Acta Crystallogr.*, **C44**, 1031 (1988).
164. U. Braun, R. Richter, J. Sieler, L. Beyer, I. Leban and L. Golič, *Acta Crystallogr.*, **C44**, 355 (1988).
165. R. A. Moss, J. Włostowska, W. Guo, M. Fedorynski, J. P. Springer and J. M. Hirshfield, *J. Org. Chem.*, **46**, 5048 (1981).
166. A. Gieren and B. Dederer, *Tetrahedron Lett.*, 1507 (1977); *Acta Crystallogr.*, **B33**, 3296 (1977).
167. J. D. Korp and I. Bernal, *Chem. Scr.*, **22**, 60 (1983).
168. N. W. Alcock, J. Barker and M. Kilner, *Acta Crystallogr.*, **C44**, 712 (1988).
169. U. Braun, J. Sieler, R. Richter, I. Leban and L. Golič, *Cryst. Res. Technol.*, **23**, 35 (1988).
170. R. L. Beddoes, R. J. Cernik, O. S. Mills and F. Stansfield, *J. Chem. Soc., Chem. Commun.*, 390 (1983).
171. J. Oszczapowicz, E. Tykarska, M. Jaskólski and Z. Kosturkiewicz, *Acta Crystallogr.*, **C42**, 1816 (1986).
172. E. Tykarska, M. Jaskólski and Z. Kosturkiewicz, *Acta Crystallogr.*, **C42**, 208 (1986).
173. N. G. Furmanova, *J. Struct. Chem.* (*Engl. Transl.*), **28**, 564 (1987).
174. G. L'abbé, D. Sorgeloos, S. Toppet, G. S. D. King and L. Van Meervelt, *Bull. Soc. Chim. Belges*, **90**, 63 (1981).
175. L. F. Chertanova, A. I. Yanovskii, Yu. T. Struchkov, V. F. Sopin, O. A. Rakitin, T. I. Godovikova and L. I. Khmel'nitskii, *J. Struct. Chem.*, **30**, 155 (1989).
176. A. F. Mishnev, Ya. Ya. Bleidelis, V. G. Andrianov and A. V. Eremeev, *J. Struct. Chem.* (*Engl. Transl.*), **26**, 119 (1985).
177. F. Bellucci, V. Bertolasi, V. Ferretti, and G. Gilli, *Acta Crystallogr.*, **C41**, 544 (1985).
178. K.-Y. Akiba, T. Tsuchiya, N. Inamoto, K.-I. Onuma, N. Nagashima and A. Nakamura, *Chem. Lett.*, 723 (1976).
179. R. Minkwitz, R. Kerbachi, R. Nass, D. Bernstein and H. Preut, *J. Fluorine Chem.*, **37**, 259 (1987).
180. W. Schuckmann, H. Fuess, O. Mösinger and W. Ried, *Acta Crystallogr.*, **B34**, 988 (1978).
181. H. A. Selling, A. B. Verweij, A. Piepenbroek and C. Th. Kiers, *Recl. Trav. Chem. Pays-Bas*, **96**, 263 (1977).
182. D. Petrović, B. Ribár, G. Argay, A. Kálmán and W. Nowacki, *Acta Crystallogr.*, **B33**, 106 (1977).
183. G. Argay, A. Kálmán, D. Lazar, B. Ribár and G. Tóth, *Acta Crystallogr.*, **B33**, 99 (1977).
184. A. Kálmán, G. Argay, B. Ribár and L. Toldy, *Tetrahedron Lett.*, 4241 (1977).

185. G. S. D. King, L. Van Meervelt and G. L'abbé, *Bull. Soc. Chim. Belges*, **91**, 729 (1982).
186. G. S. D. King, L. Van Meervelt and G. L'abbé, *Bull. Soc. Chim. Belges*, **92**, 495 (1983).
187. W. Ried and H. Dietschmann, *Ann. Chem.*, 1009 (1981).
188. G. Bellachioma, G. Cardaci and P. Zanazzi, *Inorg. Chem.*, **26**, 84 (1987).
189. P. Zanella, N. Brianese, U. Casellato, F. Ossola, M. Porcia, G. Rosetto and R. Graziani, *J. Chem. Soc., Dalton Trans.*, 2039 (1987).
190. J. S. McKennis and P. A. S. Smith, *J. Org. Chem.*, **37**, 4173 (1972).
191. R. C. Neuman, Jr. and V. Jonas, *J. Org. Chem.*, **39**, 929 (1974).
192. G. A. Olah and A. M. White, *J. Am. Chem. Soc.*, **90**, 6087 (1968).
193. C. Rabiller, J. P. Renou and G. J. Martin, *J. Chem. Soc., Perkin Trans. 2*, 536 (1977).
194. C. Rabiller, G. Ricolleau, M. L. Martin and G. J. Martin, *Nouv. J. Chim.*, **4**, 35 (1980).
195. R. J. F. M. Staps, J. W. Scheeren, F. W. Pijpers and R. J. F. Nivard, *Recl. Trav. Chim. Pays-Bas*, **98**, 445 (1979).
196. J. Daub, A. Hasenhündl, E. Salbeck, A. Gieren and T. Hübner, *Z. Naturforsch.*, **40B**, 1390 (1985).
197. N. O. Brace, *J. Fluorine Chem.*, **31**, 151 (1986).
198. P. Kollman, J. McKelvey and P. Gund, *J. Am. Chem. Soc.*, **97**, 1640 (1975).
199. T. Kozaki, K. Morihashi, and O. Kikuchi, *J. Mol. Struct.*, **168** (*Theochem.*, **45**), 265 (1988).
200. G. J. Martin and S. Poignant, *J. Chem. Soc., Perkin Trans. 2*, 642 (1974).
201. M. Caswell and G. L. Schmir, *J. Am. Chem. Soc.*, **101**, 7323 (1979).
202. P. A. Kollman, *Adv. Org. Chem.*, **9**, 1 (1976).
203. W. Walter and C. O. Meese, *Chem. Ber.*, **109**, 947 (1976).
204. M. E. Kletskii, R. M. Minyaev and V. I. Minkin, *J. Org. Chem. USSR* (*Engl. Transl.*), **16**, 601 (1980).
205. C. L. Perrin and T. J. Dwyer, *Chem. Rev.*, **90**, 935 (1990).
206. I. D. Cunningham and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 537 (1986).
207. A. Dondoni, L. Lunazzi, P. Giorgianni and D. Macciantelli, *J. Org. Chem.*, **40**, 2979 (1975).
208. A. Dondoni, L. Lunazzi, P. Giorgianni and D. Macciantelli, *J. Org. Chem.*, **46**, 4813 (1981).
209. V. G. Andrianov and A. V. Eremeev, *J. Org. Chem. USSR* (*Engl. Transl.*), **20**, 135 (1984).
210. J. E. Rowe and A. F. Hegarty, *J. Org. Chem.*, **49**, 3083 (1984).
211. J. E. Johnson, N. M. Silk, E. A. Nalley and M. Arfan, *J. Org. Chem.*, **46**, 546 (1981).
212. H.-O. Kalinowski and H. Kessler, *Top. Stereochem.*, **7**, 295 (1973).
213. K. Kanamori and J. D. Roberts, *J. Am. Chem. Soc.*, **105**, 4698 (1983).
214. R. L. Smith, D. W. Cochran, P. Gund and E. J. Cragoe, Jr., *J. Am. Chem. Soc.*, **101**, 191 (1979).
215. G. L. Kenyon, G. E. Struve, P. A. Kollman and T. I. Moder, *J. Am. Chem. Soc.*, **98**, 3695 (1976).
216. A. M. Sapse, G. Snyder and A. V. Santoro, *J. Phys. Chem.*, **85**, 662 (1981).
217. A. V. Santoro and G. Mickevicius, *J. Org. Chem.*, **44**, 117 (1979).
218. R. F. Dietrich, G. L. Kenyon, J. E. Douglas and P. A. Kollman, *J. Chem. Soc., Perkin Trans. 2*, 1592 (1980).
219. J. F. Capitani and L. Pedersen, *Chem. Phys. Lett.*, **54**, 547 (1978).
220. A. M. Sapse and L. J. Massa, *J. Org. Chem.*, **45**, 719 (1980).
221. L. Herzig, L. J. Massa, A. Santoro and A. M. Sapse, *J. Org. Chem.*, **46**, 2330 (1981).
222. A. M. Sapse, G. Snyder, A. V. Santoro and L. Herzig, *Int. J. Quantum Chem.*, **22**, 649 (1982).
223. P. Hanson and D. A. R. Williams, *J. Chem. Soc., Perkin Trans. 2*, 2162 (1973).
224. R. Kupfer, E.-U. Würthwein, M. Krestel and R. Allmann, *Chem. Ber.*, **119**, 3236 (1986).
225. E.-U. Würthwein, R. Kupfer, S. Meier, M. Krestel and R. Allmann, *Chem. Ber.*, **121**, 991 (1988).
226. G. Korber, P. Rademacher and R. Boese, *Acta Chem. Scand.*, **A42**, 571 (1988).
227. M. Michalik and R. Evers, *J. Prakt. Chem.*, **322**, 730 (1980).
228. K. Umemoto and K. Ouchi, *Proc. Indian Acad. Sci.* (*Chem. Sci.*), **94**, 1 (1985).
229. M. Zupan, V. Pirc, A. Pollak, B. Stanovnik and M. Tišler, *J. Heterocycl. Chem.*, **11**, 525 (1974).
230. M. L. Filleux, M. Naulet, J. P. Dorie, G. J. Martin, J. Pornet and L. Miginiac, *Tetrahedron Lett.*, 1435 (1974).
231. I. Wawer, *Pol. J. Chem.*, **62**, 223 (1988).
232. I. Wawer, *Magn. Reson. Chem.*, **25**, 514 (1987).
233. I. Wawer, *J. Mol. Liq.*, **38**, 1 (1988).
234. A. F. Hegarty and A. Chandler, *J. Chem. Soc., Chem. Commun.*, 130 (1980).
235. M. Drobnič-Košorok, S. Polanc, B. Stanovnik, M. Tišler and B. Verček, *J. Heterocycl. Chem.*, **15**, 1105 (1978).
236. I. Wawer, *Magn. Reson. Chem.*, **26**, 601 (1988).

237. H. Yoshida, T. Ogata and S. Inokawa, *Bull. Chem. Soc. Jpn.*, **52**, 1541 (1979).
238. G. Schwenker and H. Rosswag, *Tetrahedron Lett.*, 2691 (1968).
239. L. Lunazzi and A. Dondoni, *Tetrahedron Lett.*, 1079 (1977).
240. I. Wawer, *Magn. Reson. Chem.*, **27**, 1031 (1989).
241. D. J. Bertelli and J. T. Gerig, *Tetrahedron Lett.*, 2481 (1967).
242. J. P. Marsh, Jr. and L. Goodman, *Tetrahedron Lett.*, 683 (1967).
243. V. V. Negrebetskii, A. D. Sinitsa, V. I. Kal'chenko, L. I. Atamas' and L. N. Markovskii, *J. Gen. Chem. USSR (Engl. Transl.)*, **53**, 298 (1983).
244. J. Krechl, S. Smrčková, M. Ludwig and J. Kuthan, *Collect. Czech. Chem. Commun.*, **55**, 469 (1990).
245. J. Sandström and U. Sjöstrand, *Tetrahedron*, **34**, 371 (1978); U. Berg and U. Sjöstrand, *Org. Magn. Reson.*, **11**, 555 (1978); U. Berg, R. Isaksson, J. Sandström, U. Sjöstrand, A. Eiglsperger and A. Mannschreck, *Tetrahedron Lett.*, **23**, 4237 (1982); J. Sandström, *Top. Stereochem.*, **14**, 83 (1983); A. Z.-Q. Khan, R. Isaksson and J. Sandström, *J. Chem. Soc. Perkin Trans. 2*, 491 (1987).
246. J. M. Erhardt and J. D. Wuest, *J. Am. Chem. Soc.*, **102**, 6363 (1980).
247. R. T. Boeré, R. T. Oakley and R. W. Reed, *J. Organomet. Chem.*, **331**, 161 (1987).
248. B. J. Swanson, G. C. Crockett and T. H. Koch, *J. Org. Chem.*, **46**, 1082 (1981).
249. B. A. Arbuzov, A. V. Aganov, N. N. Zobova and O. V. Sofronova, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, **26**, 348 (1977).
250. V. V. Negrebetskii, L. Ya. Bogel'fer, A. D. Sinitsa and V. I. Kal'chenko, *J. Gen. Chem. USSR (Engl. Transl.)*, **51**, 1267 (1981).
251. B. A. Arbuzov, A. V. Aganov, N. N. Zobova and V. V. Klochkov, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, **30**, 544 (1981).
252. W. Walter and H. Weiss, *Tetrahedron Lett.*, 3009 (1974).
253. V. A. Khrustalev, K. N. Zelenin, S. M. Esakov and V. P. Sergutina, *J. Org. Chem. USSR (Engl. Transl.)*, **14**, 2167 (1978).
254. W. Ried and H. Woithe, *Helv. Chim. Acta*, **72**, 1860 (1989).
255. A. F. Grapov, V. N. Zontova, V. V. Negrebetskii, L. Ya. Bogel'fer and N. N. Mel'nikov, *J. Gen. Chem. USSR (Engl. Transl.)*, **53**, 1133 (1983).
256. R. Spitzner, J. Andersch and W. Schroth, *Ann. Chem.*, 931 (1989).
257. A. F. Hegarty and A. Chandler, *Tetrahedron Lett.*, **21**, 885 (1980).
258. L. Benati, P. C. Montevecchi and P. Spagnolo, *J. Chem. Soc., Chem. Commun.*, 1050 (1987).
259. G.-Q. Tang, J. MacInnis and M. Kasha, *J. Am. Chem. Soc.*, **109**, 2531 (1987).
260. J. Heldt, D. Gormin and M. Kasha, *J. Am. Chem. Soc.*, **110**, 8255 (1988).
261. H. Yoshida, K. Urushibata and T. Ogata, *Bull. Chem. Soc. Jpn.*, **56**, 1561 (1983).
262. B. L. Booth, R. D. Coster and M. F. J. R. P. Proença, *J. Chem. Soc., Perkin Trans. 1*, 1521 (1987).
263. G. L'abbé, L. Van Meervelt and G. S. D. King, *Bull. Soc. Chim. Belges*, **90**, 1185 (1981).
264. V. Riera, J. Ruiz, A. Tiripicchio and M. T. Camellini, *J. Organomet. Chem.*, **327**, C5 (1987).
265. R. F. Cunico and L. Bedell, *J. Organomet. Chem.*, **281**, 135 (1985).
266. K. K. Sharma and A. K. Aggarwal, *Indian J. Chem.*, **26A**, 906 (1987).
267. M. T. McCormack and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1701 (1976).
268. K. K. Sharma and A. K. Aggarwal, *Int. J. Quantum Chem.*, **30**, 213 (1986).
269. K. K. Sharma and A. K. Aggarwal, *Indian J. Chem.*, **28A**, 63 (1989).
270. R. J. Elliott and W. G. Richards, *J. Chem. Soc., Perkin Trans. 2*, 1005 (1982).
271. J. E. Johnson and S. C. Cornell, *J. Org. Chem.*, **45**, 4144 (1980).
272. D. G. McCarthy and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1080 (1977).
273. B. C. Challis, J. A. Challis and I. R. McDermott, *J. Chem. Soc., Perkin Trans. 2*, 634 (1979).
274. K. J. Dignam, A. F. Hegarty and P. L. Quain, *J. Org. Chem.*, **43**, 388 (1978).
275. J. E. Johnson, E. A. Nalley, C. Weidig and M. Arfan, *J. Org. Chem.*, **46**, 3623 (1981).
276. D. Sénéchal, M.-C. Sénéchal-Tocquer, D. Gentric, J.-Y. Le Bihan, B. Caro, M. Gruselle and G. Jaouen, *J. Chem. Soc., Chem. Commun.*, 632 (1987).
277. G. Aranda and B. Poiret, *Bioorg. Chem.*, **15**, 346 (1987).
278. G. Aranda, C. Gauvrit, M. Cesario, J. Guilhem, C. Pascard and M. E. Tran Huu Dau, *Phytochemistry*, **22**, 2431 (1983).
279. J. I. Seeman, *Chem. Rev.*, **83**, 83 (1983).
280. A. I. Meyers, *Aldrichimica Acta*, **18**, 59 (1985).
281. K. Gewald, H. Schäfer and K. Mauersberger, *Z. Chem.*, **17**, 223 (1977).
282. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).

283. P. A. Hunt, C. May and C. J. Moody, *Tetrahedron Lett.*, **29**, 3001 (1988).
284. V. Kvita, H. Sauter and B. Tuck, *Helv. Chim. Acta*, **71**, 1467 (1988).
285. E. Vilsmaier, G. Kristen and C. Tetzlaff, *J. Org. Chem.*, **53**, 1806 (1988).
286. P. Deslongchamps, *Tetrahedron*, **31**, 2463 (1975); P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Oxford, 1983.
287. J. D. Halliday and E. A. Symons, *Can. J. Chem.*, **56**, 1463 (1978).
288. A. Guggisberg, U. Kramer, C. Heidelberger, R. Charubala, E. Stephanou, M. Hesse and H. Schmid, *Helv. Chim. Acta*, **61**, 1050 (1978).
289. C. L. Perrin and G. M. L. Arrhenius, *J. Am. Chem. Soc.*, **104**, 2839 (1982).
290. C. L. Perrin and O. Nuñez, *J. Am. Chem. Soc.*, **108**, 5997 (1986).
291. A. J. Gutierrez, K. J. Shea and J. J. Svoboda, *J. Org. Chem.*, **54**, 4335 (1989).
292. A. Hassner, R. Fibiger and A. S. Amarasekara, *J. Org. Chem.*, **53**, 22 (1988).
293. H. Takahata, T. Takamatsu and T. Yamazaki, *J. Org. Chem.*, **54**, 4812 (1989).
294. R. C. Neuman, Jr. and G. S. Hammond, *J. Phys. Chem.*, **67**, 1659 (1963).
295. C. L. Perrin, *J. Am. Chem. Soc.*, **96**, 5631 (1974).
296. C. L. Perrin, E. R. Johnston and J. L. Ramírez, *J. Am. Chem. Soc.*, **102**, 6299 (1980).
297. C. L. Perrin, *J. Am. Chem. Soc.*, **108**, 6807 (1986).
298. C. L. Perrin and E. R. Johnston, *J. Am. Chem. Soc.*, **103**, 4697 (1981).
299. C. L. Perrin and E. R. Johnston, *Can. J. Chem.*, **59**, 2527 (1981).
300. P. Deslongchamps and R. J. Taillefer, *Can. J. Chem.*, **53**, 3029 (1975).
301. P. Deslongchamps, U. O. Cheriyan and R. J. Taillefer, *Can. J. Chem.*, **57**, 3262 (1979).
302. M. K. Kaloustian, M. I. A.-L. de Gutierrez and R. B. Nader, *J. Org. Chem.*, **44**, 666 (1979).
303. W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969, p. 526.
304. R. Huisgen and H. Ott, *Tetrahedron*, **6**, 253 (1959).
305. K. Burger, S. Penninger, M. Greisel and E. Daltrozzo, *J. Fluorine Chem.*, **15**, 1 (1980).
306. F. Grambal and J. Lasovský, *Collect. Czech. Chem. Commun.*, **50**, 2722 (1985).
307. A. F. Hegarty and M. Mullane, *J. Chem. Soc., Perkin Trans. 2*, 995 (1986).
308. K. S. Atwal, G. C. Rovnyak, B. C. O'Reilly and J. Schwartz, *J. Org. Chem.*, **54**, 5898 (1989).

CHAPTER 4

Detection and determination of imidic acid derivatives

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I. INTRODUCTION

Since the publication of the preceding volume on amidines and related compounds in this series in 1975, the chemistry of amidines has been developed considerably. It suffices to mention the discovery that new pharmaceuticals of improved properties can be obtained just by the modification of known ones via the introduction of an amidine group into a molecule. It was also found that amidoximes may selectively chelate some metal ions, thus opening new horizons for the recovery of rare elements. In consequence, noticeable effort was made to improve the methods of characterization and determination of imidic acid derivatives, because the question of the structure and purity of the compound is of interest in synthetic works, as well as in investigations concerned with physicochemical or pharmaceutical properties of the compound. Each of the methods applied for this purpose has some advantages and disadvantages with respect to a particular group of compounds. For example, UV spectra which are readily applied to steroids and generally to enones, and mass spectra which are very useful in structural studies of many natural products are of little use in the case of imidic acids derivatives.

In this chapter methods and applications of general use to problems encountered in amidines will be discussed, and problems requiring further research will be mentioned. Qualitative and quantitative determinations will not be separated as this would be a rather arbitrary division. The chapter is divided into sections according to the techniques applied.

II. CHROMATOGRAPHY

The earlier review on the detection and determination of amidines[1] included the statement: 'It should be noted that certain physicochemical methods, in particular all aspects of chromatography, have not been applied with any enthusiasm to the subject matter of this chapter'[1a], and further[1b]: 'Amidines have not been extensively investigated by chromatographic techniques and consequently ··· studies are worth more than passing interest'.

This has changed considerably in the last decade. The rapid development of chromatographic techniques, the application of amidino derivatives to gas-chromatographic analysis of various compounds containing an NH_2 group, as well as the results of investigations on structure–retention relations in amidines have resulted in the publication of several papers on the subject. It can be expected that chromatography will be widely applied in the future to analysis of amidines.

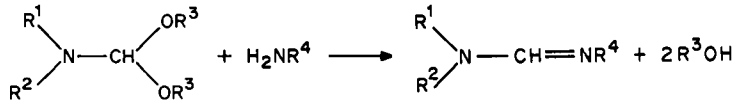
A. Gas Chromatography

Gas–liquid chromatography (GLC) is one of the most powerful and versatile analytical tools. It enables both qualitative and quantitative analysis of even very complex mixtures. As it is fast and requires minute amounts of the sample, it has now become one of the most popular routine analytical methods.

In the chemistry of amidines this technique is very useful in synthetic work as a tool for following the reaction course and as a method for purity determination. This is particularly important in the case of unsymmetrically *N,N'*-disubstituted amidines, since considerable amounts of the two symmetrically *N,N'*-disubstituted amidines are formed as by-products in their synthesis due to amino group exchange[2–5].

In spite of its advantages gas chromatography was not used until the last decade for analysis of amidines. The first attempts at such application are quite recent. It was shown in 1978 that amidines, even those which were considered thermally unstable, can be analysed by gas chromatography[6].

Amidines were proposed as very convenient derivatives for various NH_2-containing compounds. Derivatization is based on a known reaction of dialkyl acetals of *N,N'*-dialkylformamides with primary amines[7–10], carboxamides[7,10,11], sulphonamides[10,12,13] and other compounds[7,10,14–16].



(1) (2)

The most convenient reagent for derivatization seems to be *N,N*-dimethylformamide dimethyl acetal (1, $R^1 = R^2 = R^3 = Me$), widely known as the DMF–DMA reagent.

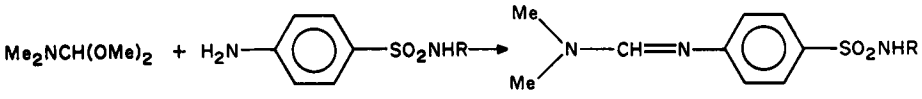
Some authors pointed out that these derivatives 'have excellent gas chromatographic and mass spectral characteristics'[12,16], and that 'their ease of preparation, even at submicrogram level, make them attractive for GLC studies'[12]. Thenot and Horning[16] showed that they are particularly convenient for GC analysis of aminoacids because, simultaneously with the formation of a dimethylaminomethylene ($Me_2N—CH=N—$) group from the NH_2 group, methylation of the carboxyl group also occurs, and the amidino derivatives obtained are thermally stable.

It should be emphasized that in any analytical work concerning derivatization of NH_2 groups by the DMF–DMA reagent the term 'amidine' is not even mentioned. The derivatives are called *N*-dimethylaminomethylene- or N-DMAM derivatives. Therefore, their GC data are scattered in the literature and are hardly found under the 'amidine' or 'amidino' entries.

Scoggins[17] derivatized mixtures of diastereomeric bis(4-aminocyclohexyl)methanes and 2,2-bis(4-aminocyclohexyl)propanes, and has found that these derivatives yield well-resolved peaks of the *cis–cis*, *cis–trans* and *trans–trans* isomers on a Poly A-103 column, whereas the free amines and the other three derivatives were not resolved satisfactorily. He then concluded that the simplicity of the reaction and the properties of the derivatives

'could make this procedure the method of choice in the analysis of amines with similar chemical and physical properties'.

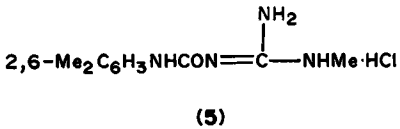
Vandenheuvel and Gruber[12] tested the applicability of these derivatives for analysis of the primary sulphonamides, *p*-ethylbenzenesulphonamide, *β*-naphtylsulphonamide and n-heptylsulphonamide on polar OV-17 column at 210 °C. They have found that this method can be applied in biological systems to detect sulphonamides in blood, and that the method has a detection limit of 25 ppb.



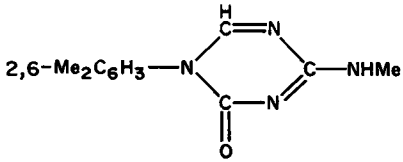
(3) (4)

Nose and coworkers[13] derivatized fourteen sulphonamides, determined their relative retentions (they called them 'retention indices') on three columns of different polarity (Table 1) and have shown that these sulpha drugs can be analysed simultaneously.

The DMF–DMA reagent was also applied for derivatization of lidamidine (5), which is referred to as amidinourea, but should be classified as a guanidino derivative. The resulting derivative of lidamidine, like the derivatives of other substituted guanidines, undergo further cyclization to form the triazine derivative 6, which is detected by gas chromatography[18].



(5)



(6)

The most commonly used parameter for the characterization of compounds by gas chromatography is the Kováts retention index[19,20], because under given gas-chromatographic conditions (i.e. column and temperature) there is only one definite retention index for a particular chemical structure and the probability of identical retention indices for two different compounds on three columns of various polarity is minimal. Therefore an unknown compound can be identified by gas chromatography only if its retention indices on a few (at least three) different stationary phases are known. This is not a problem if the retention indices of the compounds in question are reported in the

TABLE 1. Relative retentions[a] of *N,N'*-dimethylformamidines (4) derived from sulphonamides (3)[13]

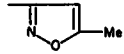
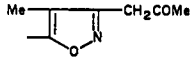
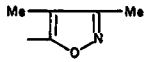
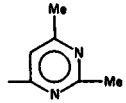
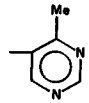
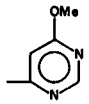
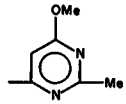
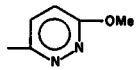
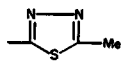
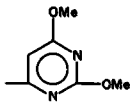
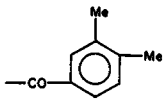
		Stationary phase		
Parent sulphonamide	R	OV-101 230 °C	OV-225 240 °C	XE-60 220 °C
Acetosulphamine	COMe	0.9	1.1	1.2
Sulphisomezole		2.3	3.3	3.9

TABLE 1. (*continued*)

Parent sulphonamide	R	Stationary phase		
		OV-101 230 °C	OV-225 240 °C	XE-60 220 °C
Acetylsulphisoxazole		2.4	3.7	4.2
Sulphisoxazole		2.4	3.8	4.2
Sulphathiazole		2.9	3.6	3.9
Sulphisomidine		3.1	3.0	3.7
Sulphamerazine		4.1	6.5	7.4
Sulphamonometoxine		4.3	4.8	5.7
Sulphamethomidine		4.4	4.3	5.4
Sulphamethoxypyridazine		4.8	8.1	9.0
Sulphamethizole		4.8	9.3	10.8
Sulphadimetoxine		7.2	10.7	13.2
Xylolylsulphamine		8.4	14.3	18.1
Sulphaphenazole		9.2	16.5	19.1

[a] Diethyldithiocarbamic acid 2-benzothiazolyl ester was taken as the internal standard.

literature, or if the samples are available for determination of their retentions. However, in investigations of unknown compounds, the lack of retention data is a real problem and, whenever possible, methods for the prediction of retention data are used for this purpose.

The most popular of these methods are additivity rules. According to them the retention index of a compound containing a given functional group is calculated by addition of an increment characteristic of this group to the retention index of the unsubstituted compound. However, if more than two functional groups have to be considered in the calculation of the retention index, the differences between the calculated and experimental values of retention indices are frequently much larger than the acceptable experimental errors.

Investigations on structure–retention relations, carried out on amidines, led to some general conclusions which are applicable also to other kinds of compounds[21]. Oszczapowicz and coworkers[21–29], in a search for some general rules for predicting retention parameters of any amidine, have determined Kováts retention indices of over 500 amidines on a non-polar GE SE-30 column.

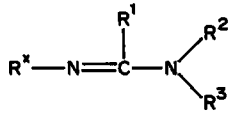
Oszczapowicz has pointed out[21,22] that the prediction of any parameter of a compound belonging to one group, based on the parameter of a compound belonging to another group, is a typical problem of correlation analysis, in which the parameters (P_1) of the compounds (x_i) of one series are expressed as a function, usually linear, of the parameters (P_2) of compounds (x_i) in another series (equation 1). Any additivity scheme is a very particular case of a linear equation (1), where the coefficient a is equal to unity by definition.

$$P_1(x_i) = aP_2(x_i) + b \tag{1}$$

It was found that Kováts retention indices (I) of amidines can be correlated with the retention indices of the corresponding simple compounds taken as the reference compounds (standards). The correlations are in the form

$$I(\text{amidine}) = aI(\text{standard}) + b \tag{2}$$

The trisubstituted amidines in the table below containing a variable substituent R^x in a series have been investigated.



Series	R^1	NR^2R^3	Series	R^1	NR^2R^3	Series	R^1	NR^2R^3
7	H	NMe_2	13	Me	NMe_2	20	Ph	NMe_2
8	H		15	Et	NMe_2	21	*p*-MeC_6H_4	NMe_2
9	H		17	*i*-Pr	NMe_2	22	*p*-$MeOC_6H_4$	NMe_2
10	H		18	*t*-Bu	NMe_2	23	*p*-ClC_6H_4	NMe_2
11	H		14	Me	N(Me)Ph	19	CH_2Ph	NMe_2
12	H	N(Me)Ph	16	Et	N(Me)Ph	24	NMe_2	NMe_2

Retention indices of selected representative amidines from each series are presented in Table 2. The indices of all the trisubstituted amidines studied were in the range 805–2578.

There are three sites in the amidine group to which various substituents can be attached, i.e. the functional carbon atom and the two nitrogen atoms.

In order to predict the retention indices of amidines of general formula $R^xN{=}CR^1{-}NR^2R^3$, where R^x is a variable substituent representing the substituted or unsubstituted alkyl or aryl group, the most appropriate correlation seemed to be with the retention indices of the corresponding substituted hydrocarbons R^xH. However, as shown in the case of these reference compounds[22–25] isomerism is not taken into account. Therefore, prediction of retention data for compounds containing these moieties in the molecule cannot yield accurate results. It was then assumed[22–26] that better results might be obtained by taking other simple compounds containing certain functional groups at the corresponding carbon atom as the standards. Consequently, the retention indices of the amidines were also correlated with those of the corresponding primary amines R^xNH_2 (Table 3 and 4).

It was found that the slopes of the correlation lines (parameter *a* in equation 2) are not the same when different types of compounds are taken as the reference series. Moreover, in certain cases the regression coefficient *a* is definitely different from unity. This shows convincingly that, at least for amidines, prediction of the retention indices cannot be based on the additivity rule, whereas a linear correlation may be successfully applied for the purpose.

It was also found that the *a* values depend on the series. This is particularly evident in the correlation with substituted hydrocarbons R^xH. These differences mean that some change of the substituent at a certain site of the molecule, e.g. at the amino nitrogen or the amidino carbon atom, may vary the parameter *a* concerning substitution at the other site, e.g. at the imino nitrogen atom.

Since for amidines substituted by alkyl substituents at the amino nitrogen atom (series **7**, **8**, **9** and **10**) the differences between the regression coefficients *a* are much below the

TABLE 2. Retention indices of representative amidines from various series on a non-polar column

			R^x					
Series	*t*(°C)	Ref.	Pr^n	Hex^n	Ph	CH_2Ph	$4\text{-}BrC_6H_4$	$4\text{-}O_2NC_6H_4$
7	240	22	864 ± 5	1166 ± 6	1385 ± 7	1408 ± 5	1732 ± 1	1969 ± 4
8	240	24	1202 ± 4	1501 ± 4	1733 ± 4	1751 ± 7	2060 ± 5	2295 ± 2
9	240	24	1273 ± 4	1577 ± 3	1798 ± 4	1821 ± 4	2126 ± 3	2363 ± 2
10	240	24	1378 ± 4	1668 ± 0	1898 ± 2	1918 ± 2	2239 ± 1	2475 ± 1
11	240	24	1255 ± 4	1551 ± 2	1792 ± 6	1792 ± 3	2122 ± 4	2487 ± 0
13	240	22	1001 ± 9	1284 ± 4	1452 ± 7	1441 ± 6	1780 ± 4	2009 ± 1
15	240	26	1065 ± 6	1366 ± 4	1510 ± 1	1617 ± 5	1826 ± 1	2076 ± 1
17	240	26	1065 ± 0	1374 ± 2	1541 ± 4	1561 ± 2	1856 ± 1	2107 ± 1
18	240	26	1093 ± 0	1393 ± 4	1539 ± 4	1607 ± 2	1843 ± 3	2120 ± 1
19	280	26	1605 ± 0	1881 ± 2	2056 ± 1	2148 ± 1	2374 ± 1	2630 ± 3
20	280	23	1498 ± 0	1689 ± 0	1842 ± 1	1943 ± 3	2160 ± 2	2415 ± 0
21	280	23	1583 ± 8	1767 ± 5	1909 ± 1	2023 ± 3	2208 ± 1	2454 ± 2
22	280	23	1734 ± 5	1915 ± 4	2059 ± 1	2169 ± 0	2360 ± 2	2610 ± 2
23	280	23	1687 ± 5	1870 ± 3	2013 ± 1	2121 ± 2	2321 ± 0	2578 ± 1
24	240	22	997 ± 4	1352 ± 5	1526 ± 3	1615 ± 3	1860 ± 6	2146 ± 0
12	280	28		1770 ± 11	1980 ± 6	1992 ± 0		2363 ± 5
14	280	29			1972 ± 0	1998 ± 5		
16	280	29			1985 ± 6	1998 ± 3		

TABLE 3. Parameters of the regression of retention indices of amidines vs retention indices of substituted hydrocarbons R^xH

Series	a^a	b^a	r^b	n^c	Ref.
7	1.28 ± 0.08	467	0.991	24	22
7	1.33 ± 0.10	275	0.990	19	24
8	1.31 ± 0.10	771	0.990	19	24
9	1.32 ± 0.09	838	0.990	19	24
10	1.32 ± 0.10	935	0.9989	19	24
11	1.44 ± 0.15	744	0.981	19	24
15	1.16 ± 0.08	599	0.989	22	26
13	1.20 ± 0.10	673	0.984	23	22
17	1.18 ± 0.10	679	0.984	23	26
18	1.15 ± 0.10	704	0.981	23	26
19	1.17 ± 0.12	1197	0.977	23	26
20	1.04 ± 0.12	1105	0.972	23	23
21	1.02 ± 0.10	1192	0.976	23	23
22	1.01 ± 0.11	1344	0.974	23	23
23	1.02 ± 0.11	1289	0.971	23	23
24	1.24 ± 0.09	641	0.987	22	22

[a] Parameters of equation 2.
[b] Correlation coefficient.
[c] Number of data points.

TABLE 4. Parameters of the regression of retention indices of amidines vs retention indices of primary amines R^xNH_2

Series	a^a	b^a	r^b	n^c	Ref.
7	1.11 ± 0.02	280	0.999	26	22
8	1.10 ± 0.04	615	0.998	20	24
9	1.10 ± 0.04	685	0.998	20	24
10	1.11 ± 0.03	780	0.998	20	24
11	1.20 ± 0.06	581	0.995	20	24
13	1.01 ± 0.03	450	0.998	24	22
15	0.98 ± 0.03	540	0.998	23	26
17	1.00 ± 0.04	544	0.997	23	26
18	0.97 ± 0.04	570	0.997	23	26
19	1.00 ± 0.04	1057	0.996	23	26
20	0.89 ± 0.05	980	0.992	23	23
21	0.86 ± 0.05	1074	0.991	23	23
22	0.86 ± 0.05	1225	0.991	23	23
23	0.87 ± 0.06	1167	0.990	23	23
24	1.03 ± 0.04	500	0.997	24	22
14	0.91 ± 0.09	1071	0.995	9	29
16	0.89 ± 0.05	1092	0.997	10	29

[a] Parameters of equation 2.
[b] Correlation coefficient.
[c] Number of data points.

confidence intervals, they can be regarded as practically identical. For formamidines (**11**) containing the oxo group in the alkyl substituent bonded to the amino nitrogen atom, the *a* value is considerably higher.

Similarly, the *a* values for all the series of N^1,N^1-dialkylamidines derived from the carboxylic acids (**13**, **15**, **17**, **18** and **19**) studied are indistinguishable within the confidence

intervals[26]. The same applies to various series of benzamidines (**20–23**), but in this case *a* has another value[23]. For tetramethylguanidines[22] (**24**) it is again different from that for the above-mentioned series. Thus, it was concluded that the structure of the alkyl substituent at the amino nitrogen of the amidine group has a noticeable influence on the regression coefficient *a* for substitution at the imino nitrogen atom, and that the *a* value depends mainly on the type of substituent (hydrogen atom, alkyl, aryl or amino group) at the other site and only to a negligible extent on its detailed structure.

It was also found[22–26] that for each series of amidines the correlation with retention indices of primary amines is of higher quality than that with substituted hydrocarbons. Although the former are therefore of a higher predictive value, the latter are still satisfactory.

1. *Dual parameter regressions*

On the basis of linear regressions it was assumed that when predicting retention indices for amidines, and in general for any type of compounds (Cpd), containing two substituents a linear regression (equation 3) can be applied:

$$I(\text{Cpd}) = a_1 I(\text{Std}_1) + a_2 I(\text{Std}_2) + b \tag{3}$$

For systems containing more than two substituents, a multiparameter linear regression (equation 4) is applicable:

$$I(\text{Cpd}) = \sum a_i(\text{Std}_i) + b \tag{4}$$

Secondary amines $(R^2)_2NH$ were used as the second standard series for the dual parameter regression (Table 5).

For dimethylbenzamidines (**20–23**), all the regression coefficients *a* were identical; thus, for prediction of their retention indices, the dual parameter regression (equation 3) can be applied. The same applies for N^1,N^1-dimethylamidine derivatives of aliphatic carboxylic acids (**7**, **13**, **15**, **17** and **19**).

When predicting retention indices of amidines with two variable substituents for

TABLE 5. Parameters of the multiple regression[a] of retention indices of amidines vs retention indices of standard compounds

Series	Std[b]		a_1	a_2	b	R[g]	n[h]	Ref.
	1	2						
c	PA	SA	1.12 ± 0.02	1.08 ± 0.04	−190	0.997	100	24
d	PA	SA	1.10 ± 0.02	1.09 ± 0.03	−174	0.998	80	24
e	PA	EtA	0.99 ± 0.03	0.93 ± 0.03	−115	0.992	115	26
e	PA	DMA	0.99 ± 0.04	0.79 ± 0.04	−186	0.987	115	26
f	PA	BS	0.87 ± 0.03	0.88 ± 0.07	389	0.991	92	23
f	PA	EtB	0.87 ± 0.03	0.88 ± 0.09	−36	0.986	92	23

[a] Equation 3.
[b] PA = primary amine R^aNH_2, SA = secondary amine R_2NH, EtA = ethyl esters of alkyl carboxylic acids, DMA = dimethylamides of carboxylic acids, BS = substituted benzene, EtB = ethyl benzoates.
[c] N^1,N^1-Dimethylformamidines.
[d] N^1,N^1-Dimethylformamidines, except those containing morpholine moiety.
[e] N^1,N^1-Dimethylacetamidines.
[f] N^1,N^1-Dimethylbenzamidines.
[g] Correlation coefficient.
[h] Number of data points.

substitution at the amidino carbon atom, two types of compound were tried as the second standard: ethyl esters and dimethylamides of the corresponding carboxylic acids. The latter seem to be more appropriate as their structure resembles more that of the N^1,N^1-dimethylamidines than that of esters. However, both the correlation coefficients R and the calculated confidence intervals for both parameters a_1 and a_2 indicate that the correlation wtih the esters is of slightly higher quality. The parameters a_1 for substitution at the imino nitrogen atom appeared, as expected, to be identical with those obtained in separate regressions with the retention indices of hydrocarbons. Dual parameter regression coefficients a_1 and a_2, calculated for all formamidines and for those excluding series **11**, are the same within the confidence intervals.

It can be concluded that for predictiting retention indices of trisubstituted amidines, the multi-parameter relation (equation 4 with three parameters) can be applied, providing substituents of only one type are present at each site.

2. *Chromatography on polar columns*

Oszczapowicz and coworkers[25] have also attempted to apply the correlation method in order to predict retention indices on polar phases. They have assumed that for series of compounds (Cpd^x) containing certain functional groups, the retention indices on a polar column $I^p(Cpd^x)$ can be related to their retention indices on a non-polar column $I^{np}(Cpd^x)$ by the correlation equation 5, where parameters a and b depend on both the nature of the stationary phase and the type of functional group:

$$I^p(Cpd^x) = aI^{np}(Cpd^x) + b \tag{5}$$

Alternatively, like on a non-polar phase, the $I^p(Cpd^x)$ values can be related to the retention indices of the corresponding simple model compounds (Std_x), measured on the same stationary phase (equation 6).

$$I^p(Cpd^x) = aI^p(Std^x) + b \tag{6}$$

Retention indices of two series of amidines were determined on a polar OV-225 stationary phase and correlated with retention indices on a non-polar GE SE-30 phase (Tables 6 and 7).

The attempts at correlations have shown that, for each of the series, at least two separate correlation lines are obtained: one for compounds in which R^x is alkyl, and the other for

TABLE 6. Parameters of the correlations of retention indices of amidines on a polar OV-225 column vs their retention indices on a non-polar GE SE-30 column[25]

Series	a^a	b^a	r^b	n^c
Alkyl derivatives				
7	1.05 ± 0.07	151	0.998	8
13	1.04 ± 0.06	559	0.998	8
Phenyl derivatives				
7	1.65 ± 0.17	−383	0.987	14
13	1.50 ± 0.14	−275	0.990	14

[a] Parameters of equation 5.
[b] Correlation coefficient.
[c] Number of data points.

TABLE 7. Parameters of the correlations of retention indices of amidines vs retention indices of standards both on a polar OV-225 stationary phase[25]

Series	Std[a]	a^b	b^b	r^c	n^d
Alkyl derivatives					
7	SH	1.10 ± 0.09	727	0.997	8
13	SH	1.00 ± 0.02	1291	0.9998	8
7	PA	1.03 ± 0.19	361	0.995	5
13	PA	1.00 ± 0.07	872	0.999	5
Phenyl derivatives					
7	SH	1.23 ± 0.15	866	0.983	14
13	SH	1.09 ± 0.15	969	0.977	14
7	PA	0.74 ± 0.08	919	0.984	14
13	PA	0.66 ± 0.10	1026	0.971	14

[a]PA = primary amines, SH = substituted hydrocarbons R^xH.
[b]Parameters of equation 8.
[c]Correlation coefficient.
[d]Number of data points.

those in which R^x is a substituted phenyl ring. It was also noted that the retention indices of *para*- and *meta*- nitrophenyl derivatives deviate considerably from the correlation lines. Thus, it was evident that for alkyl as well as phenyl derivatives separate correlations should be applied and that a separate correlation should perhaps be calculated for nitro derivatives.

Retention indices of compounds studied on polar phases were also correlated with those of simple model compounds taken as the standards, measured on the same stationary phase.

For both series of amidines the quality of the correlations with primary amines and those with hydrocarbons is comparable. It was concluded[25] that when predicting retention indices of N^1,N^1-dimethylformamidines (**7**), N^1,N^1-dimethylacetamidines (**13**) and perhaps other amidines as well, on a polar column, either equation 5 or equation 6 can be used, as both provide similar satisfactory results.

Recently, it was shown that even some tautomerizing amidines can be analysed by gas chromatography[27] (Table 8).

N,N'-Disubstituted amidines display tautomerism:

$$[XC_6H_4N{=}CH{-}NHC_6H_4Y \rightleftharpoons XC_6H_4NH{-}CH{=}NC_6H_4Y]$$
(25)

It is obvious that if the substituents X and Y are not identical, the tautomers will have different physical and chemical characteristics. It would therefore be expected that their retentions may also differ.

The parameters of the regression of retention indices of *N,N'*-diphenylformamidines (**25**) vs those of the corresponding anilines (equation 7) appeared to be very close to those calculated for the series of trisubstituted N^1,N^1-dialkyl-N^2-phenylformamidines (**7–10**). Thus it was concluded that *N,N'*-diphenylformamidines in the gas phase exist as monomeric species.

$$I(\text{amidine}) = (1.078 \pm 0.059) \cdot I(R^xNH_2) + (1.080 \pm 0.053) \cdot I(\text{RRNH}) - 127.7 \qquad (7)$$

The regression coefficients a_1 and a_2, obtained for *N,N'*-diphenylformamidines, are identical because the retentions of both tautomers are indistinguishable. Hence the

TABLE 8. Retention indices (I) of N,N'-diarylformamidines (**25**) on a non-polar column[27]

X	Y	I	X	Y	I
H	H	1933 ± 1	H	*m*-Cl	2200 ± 3
p-Me	*p*-Me	2199 ± 4	H	*m*-Br	2294 ± 2
p-OMe	*p*-OMe	2485 ± 3	*p*-Me	*p*-OMe	2326 ± 1
p-OEt	*p*-OEt	2169 ± 5	*p*-Me	*p*-OEt	2409 ± 3
p-Cl	*p*-Cl	2419 ± 2	*p*-Me	*p*-Cl	2304 ± 1
p-Br	*p*-Br	2366 ± 2	*p*-Me	*p*-Br	2406 ± 1
m-Me	*m*-Me	2180 ± 2	*p*-OMe	*p*-OEt	2539 ± 3
m-OMe	*m*-OMe	2477 ± 3	*p*-OMe	*p*-Cl	2443 ± 1
m-OEt	*m*-OEt	2586 ± 6	*p*-OMe	*p*-Br	2543 ± 1
m-Cl	*m*-Cl	2399 ± 2	*p*-OEt	*p*-Cl	2509 ± 5
m-Br	*m*-Br	2604 ± 6	*p*-Cl	*p*-Br	2535 ± 1
H	*p*-Me	2122 ± 3	*m*-Me	*m*-OMe	2315 ± 1
H	*p*-OMe	2266 ± 3	*m*-Me	*m*-OEt	2384 ± 4
H	*p*-OEt	2319 ± 3	*m*-Me	*m*-Cl	2296 ± 2
H	*p*-Cl	2215 ± 2	*m*-Me	*m*-Br	2404 ± 8
H	*p*-Br	2321 ± 4	*m*-OMe	*m*-OEt	2550 ± 3
H	*m*-Me	2095 ± 2	*m*-OMe	*m*-Cl	2458 ± 0
H	*m*-OMe	2230 ± 1	*m*-OEt	*m*-Cl	2509 ± 1
H	*m*-OEt	2291 ± 3	*m*-Cl	*m*-Br	2518 ± 1

equation for predicting the retention indices of N,N'-diphenylformamidines (**25**) takes the form of equation 8.

$$I(\mathbf{25}) = a[I(XC_6H_4NH_2) + I(YC_6H_4NH_2)] + b \tag{8}$$

This equation implies that the retention index of an unsymmetrically disubstituted formamidine is the mean of the retention indices of the two symmetrically disubstituted compounds, and that retention indices of symmetrically disubstituted amidines can be predicted on the basis of equation 9.

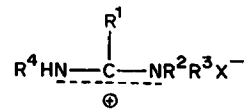
$$I(R^xN{=}CR{-}NHR^x) = 2aI(R^xNH_2) \tag{9}$$

General structure–retention relations for amidines are discussed elsewhere in a review article[21].

B. High-performance Liquid Chromatography

HPLC as an analytical tool has so many advantages with respect to other chromatographic techniques that, whenever applicable, it is now used as a routine method for the determination of various types of compounds even in very complex mixtures.

In the literature, however, only few reports on the applications of HPLC for analysis of amidines are found. The most noteworthy is that of Hanocq, Fuks and Lefebvre[30] in which various factors which influence separation of the salts of thirteen N,N-substituted amidines **26** by the HPLC method were discussed.



(**26**)

Analyses were performed at 50 °C on a μ-Bondapack C_{18} column, using as mobile phase a mixture of acetonitrile and a phosphoric acid–phosphate (20:80 v/v, pH 6.0) buffer containing 0.06 mM sodium salt of n-octyl sulphate; detector wavelength was 205 nm.

The effect of pH, the concentration of n-octyl sulphate and the percentage of acetonitrile on the capacity factors k' of the amidines are presented in Table 9. It is seen that these factors influence considerably the results of chromatography. The capacity factors increase with the pH value of the mobile phase, with the concentration of the counter-ion and with the decrease in the concentration of acetonitrile.

Optimal conditions were found to be 20% (v/v) of acetonitrile, 0.6 mM of sodium n-octyl sulphate and pH of mobile phase 2.5. The values of the capacity factors obtained under these conditions are summarized in Table 10.

It was concluded that this method can be applied for both qualitative as well as quantitative determination of amidines and impurities encountered in their synthesis.

Massil, Ezra and Grushka[31] analysed amidines by the reversed-phase ion-pair HPLC method. They have obtained very good separation of a mixture of acetamidine ($k' = 0.60$), isobutyramidine ($k' = 2.2$) and benzamidine ($k' = 8.6$). This method enabled them also to obtain a good resolution of amidines (e.g. isobutyramidine, $k' = 0.63$) and related impurities (isobutyronitrile, $k' = 0.25$ and isobutyramide, $k' = 2.25$). Separations were obtained on Phase-Sep S10 ODS column using 12.5/87.5 (v/v) methanol/water mixture as the mobile phase. The water component contained 1 mM of sodium heptasulphonate and 1% of KH_2PO_4. To obtain reasonable retention times addition of methanol to the mobile phase was required.

Quantitative determination of several manufacturing batches of technical grade isobutyramidine by the HPLC method were in very good agreement with the results obtained by titration, thus indicating that the method is precise, reproducible and without interference from the impurities.

An additional advantage of the method is that it enables one to determine the concentration of amidines either as solids or in aqueous solutions. As the authors concluded, 'the introduction of HPLC makes the determination of the amidines a routine task'[31].

The HPLC method appears to be very useful in analysis of drugs and cosmetic

TABLE 9. HPLC parameters for salts of amidines $[R^4NH—C(R^1)—NR^2R^3]^+X^-$ (26)[30]

	X	R^1	R^2	R^3	R^4	k'	σ^a	Detection limit (pg)
a	Cl	Me	3,4-$Cl_2C_6H_3$	H	*i*-Pr	6.85	0.06	71
b	Cl	Me	4-ClC_6H_4	H	*t*-Bu	4.29	0.04	47
c	Cl	Me	4-$EtO_2CC_6H_4$	H	*t*-Bu	5.90	0.05	88
d	Cl	CH_2=CH	2-$MeOC_6H_4$	H	*t*-Bu	3.71	0.03	82
e	Cl	CH_2=CMe	3-ClC_6H_4	H	*t*-Bu	7.81	0.02	166
f	Cl	CH_2=CMe	C_6H_5	H	*t*-Bu	3.77	0.04	101
g	Cl	CH_2=CMe	2-ClC_6H_4	H	*t*-Bu	5.96	0.06	119
h	ClO_4	CH_2=CMe	*i*-Pr	*i*-Pr	*t*-Bu	7.07	0.11	343
i	ClO_4	CH_2=CMe	4-$EtO_2CC_6H_4$	H	*t*-Bu	11.38	0.11	230
j	Cl	CH_2=CMe	4-ClC_6H_4	H	*t*-Bu	8.47	0.15	146
k	ClO_4	CH_2=CCl	Et	Et	*t*-Bu	4.59	0.04	343
l	Cl	CH_2=CCl	2-ClC_6H_4	H	*t*-Bu	9.57	0.12	238
m	Cl	CH_2=CCl	2-MeC_6H_4	H	*t*-Bu	5.83	0.05	166

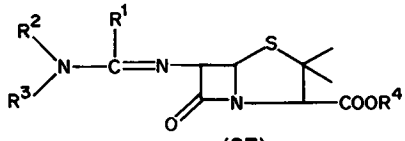
[a]Standard deviation.

TABLE 10. Influence of various parameters on capacity factors k' in HPLC of amidines **26**[30]

Parameter[a]		k' values[b]			
		26a	**26b**	**26c**	**26m**
acetonitrile	15	26.22	14.32	22.33	28.13
(v/v %)	18	14.07	8.03	11.33	16.19
	20	6.85	4.29	5.90	9.57
	22	6.25	3.99	5.15	8.36
n-octyl sulphate	0.4	6.09	3.80	5.26	8.69
sodium salt	0.5	6.52	4.07	5.56	9.32
(mM)	0.6	6.85	4.29	5.90	9.57
	0.8	7.98	4.78	6.47	10.44
pH	2.50	6.85	4.29	5.90	9.57
	2.65	11.46	6.55	10.05	15.29
	2.75	11.77	6.85	10.25	16.94
	3.00	12.00	6.89	10.32	24.55
	3.28	12.29	7.20	10.52	32.54

[a]The other component of the mobile phase is an aqueous phosphoric acid–phosphate buffer.
[b]Mean value from at least three measurements.

components containing the amidino group, as well as for determination of their degradation products. It was successfully used for the determination of amidinopenicillins such as mecillinam (**27a**) and pivmecillinam (**27b**)[32–34]. Amidinopenicillins undergo very easy degradation via different mechanisms, depending on the conditions, and thus various degradation products are formed. Among the fifteen known degradation products of mecillinam and pivmecillinam and among the manufacturing impurities there are several which contain intact amidino group.



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(a) mecillinam: $R^1=H$; $R^4=H$; $NR^2R^3=N$

(b) pivmecillinam: $R^1=H$; $R^4=Me_3CCOCH_2$; $NR^2R^3=N$

Determination of mecillinam was performed on a μ-Bondapack C_{18} column using a 220-nm UV detector. A series of eight mixtures of acetonitrile and aqueous 0.01 M sodium phosphate ranging from 25:75 to 0:100, respectively, were found to be useful for the HPLC analysis of mecillinam. The two systems which effectively separated all the compounds at reasonable times were mixtures A (15:85) and B (2.5:97.5).

Degradation products of mecillinam can be divided into two groups: the first contains compounds having a hexahydroazepine ring, and the second contains compounds which

do not have hexahydroazepine moiety. The two groups exhibit different chromatographic behaviour. Compounds of the first group are less polar, strongly retained, well separated by mobile phase A and are not eluted by mobile phase B. Compounds of the second group are more polar, weakly retained and are well separated by mobile phase B. Using these two phases the capacity factor k' of mecillinam is 2.83 and it is not eluted after 1 h, whereas the k' factors of the degradation products are 5.00–7.92 for group I which is not eluted after 1 h and 1.51–3.95 for group II.

Consequently mecillinam and its degradation products can be resolved satisfactorily, and mobile phase A yields better results for determination of mecillinam. This shows that the HPLC method is adequate for separation of mecillinam from impurities of both groups, and that it may be used for quantitative analysis of this drug and of its dosage form with acceptable accuracy and precision.

Comparison of the quantitative analysis of mecillinam by the HPLC method with the previously applied UV method has shown that the HPLC method is superior, because unidentified UV absorbing impurities may cause errors in determination by the UV analysis.

The HPLC method has also been applied for determination of pivmecillinam (pivaloyloxymethyl ester of mecillinam) and pivmecillinam capsules[33].

The previously described spectrophotometric procedure did not permit independent determination of pivmecillinam in the presence of its biologically active hydrolysis product, i.e. mecillinam. The products of degradation of **27a** and **27b** cannot be detected by spectrophotometric analysis[35].

The best results have been obtained on 5 μm Chromegabond X_8 column, using a mixture of acetonitrile and 0.01 M aqueous sodium phosphate buffer (60:40 v/v, pH 3.0) as a mobile phase, and a 220-nm UV detector, sensitivity 0.016 a.u.f.s. Under these conditions the k' values were: mecillinam—8.0, pivmecillinam—0.41, esterified degradation products—0.46, 0.92, 2.21, 10.92, and unesterified degradation products—0.12, 0.14, 0.26, 0.31, 0.34, 0.54, 1.04. These values indicate that the method enables separation of all the compounds mentioned. Hence, the HPLC method can be used for quantitative determination of pivmecillinam and the related compounds mentioned above. The accuracy of the method is comparable to the published spectroscopic assay, and the relative standard deviation of replicate assays is better than $\pm 0.7\%$[33].

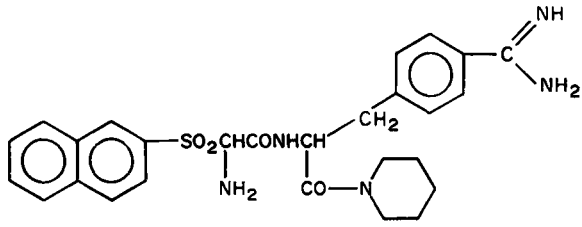
The HPLC method was also used for determination of mecillinam in urine after oral administration of pivmecillinam[34]. The latter is well absorbed from the gastrointestinal tract and its activity is due to its rapid biotransformation to mecillinam. For the HPLC method a 10-μg Chromegabond C_{18} column and mobile phase consisting of 15% of acetonitrile in 0.01 M potassium buffer (pH 5.0) were used, with a detection wavelength of 220 nm. The sensitivity limit of the HPLC assay is 50 μg per ml urine. The capacity factors k' were 2.5 for mecillinam and <0.5, 0.5, 0.8 and 2.75, respectively, for the urinary metabolites. These values show that the metabolites do not interfere with mecillinam, since they are eluted in the solvent front and are also weaker chromophores than **27a**[34].

The data on urinary excretion, obtained by the HPLC assay, are in good agreement with those obtained using microbiological assays following the parenteral administration of mecillinam or oral administration of pivmecillinam.

HPLC appeared to be a very suitable method for analysis of pharmacologically effective benzamidine derivatives which were previously determined only by a biological method.

The *N*α-(2-naphthylsulphonylglycyl)-4-amidinophenylalanine piperidide (**28**) was found to be a highly active selective inhibitor of trombin[36]. A Separon SIX C_{18} column and mixtures of acetonitrile–water–$HClO_4$ (320:180:0.4 and 180:320:0.4, respectively) as the mobile phase and UV 235-nm detection were used in its analysis.

The concentration of **28** in bile and in homogenates of rat liver was determined by



(28)

HPLC analysis. The sample of bile was simply diluted, while for the liver homogenation an extraction procedure was necessary. Satisfactory agreement between the concentrations of **28** determined biologically and by HPLC was obtained.

The recommended procedure for qualitative and quantitative determination of **28** and similar benzamidines substantially extends the scope of the method for the pharmacological characterization of new enzyme inhibitors.

Some amidines are used as preservatives in cosmetics and in pharmaceutical products due to their good antibacterial and antifungal activity[37]. A rapid HPLC method was developed for simultaneous determination of dibromopropanamidine, hexamidine and dibromohexamidine as diisethionates and chlorhexidine as dihydrochloride, which are used as preservatives in creams. The extraction step of these amidines, except for chlorhexidine, from creams before HPLC analysis is short and simple.

The optimized chromatographic parameters were: Erbasil C_{18} column; mobile phase: acetonitrile–water containing 0.05 M sodium perchlorate and 0.005 M of tetramethylammonium bromide (pH 3.0); detection UV 264 nm; detector sensitivity 0.64 a.u.f.s Under these conditions very good resolution of amidines with high precision in the quantitative assay was obtained. The k' values were 1.36 for dibromopropanamidine, 1.79 for hexamidine, 3.74 for dibromohexamidine and 5.25 for chlorhexidine.

On account of its simplicity the HPLC method was recommended for determination of amidines in cosmetic products.

C. Thin Layer Chromatography

Thin layer chromatography (TLC) is mainly applied to determine the number of components in a sample, or to detect given compounds in a mixture. Thus it was applied for purity determination and for identification of given amidines in a reaction mixture, while checking the reaction progress[5,38–48].

For characterization of a compound under given condition (stationary phase, solvent and temperature) the R_f values are used. It has to be kept in mind, however, that R_f values are less reproducible than retention values in gas chromatography, because the chromatography conditions are not as easily controlled as in gas chromatography. Therefore, the R_f values are reported in synthetic works only as a characterization of the compounds, whereas general structure–retention relations are not discussed. However, investigations of the influence of some structural parameters on the R_f values have been recently undertaken[49].

1. Amidines

The TLC method was applied in investigations on the amino group exchange in amidines[5].

$$XC_6H_4N{=}CH{-}NHC_6H_4X + NHR^1R^2 \rightleftharpoons XC_6H_4N{=}CH{-}NR^1R^2 + XC_6H_4NH_2$$

Trisubstituted and *N,N'*-disubstituted amidines were detected simultaneously in the reaction mixture and their relative concentrations were estimated by the spot sizes.

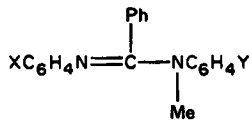
The TLC technique was also used for the determination of amidinopenicillins (**27**)[40,41]. Amidinopenicillins display a very strong activity against Gram-negative organisms, and some of them are commercially available and widely used. The β-lactam ring in amidinopenicillins undergoes easy cleavage, and a reliable and fast method for purity determination and detection of the degradation products is therefore necessary. It was found[42] that, under the conditions presented in Table 11, amidinopenicillins are well resolved from both the starting material and the degradation products.

Chlorhexidine, which is used as a common antiseptic in cosmetics (lotions) and in pharmaceutical preparations (ointments), was determined by the TLC method on Silicagel HF_{254} plates using n-butanol–acetic acid–water mixture (4:1:5; upper layer) as the developing system[43]. Visualization for detection was achieved by UV irradiation or by spraying with the iodoplatinate reagent prepared according to Stahl[50]. Chlorhexidine ($R_f = 0.5$) and its degradation products ($R_f = 0.3$, 0.4 and 0.8) are well resolved. For quantitative analysis, the silicagel plates were extracted with ethanol and the extracts determined by a spectroscopic method[43].

It was found[49] that, at least for some series of amidines, their R_f values on Silicagel plates correlate with their pK_a values, as expressed by equation 10.

$$R_f = a_0 - a_1 pK_a \tag{10}$$

For N^1-methyl-N^1,N^2-diaryl benzamidines **29**, the following parameters of equation 10 have been obtained: $a_0 = 2.97$, $a_1 = -(0.34 \pm 0.07)$, $r = 0.943$.



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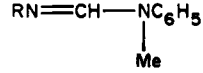


(**30**)

The differences between the experimental R_f values and the calculated values from equation 10 are within the limits of acceptable experimental error (Table 12). Better results

TABLE 11. R_f values for amidinopenicillins and 6-aminopenicillanic acid (6-APA)[42]

Compound	Developing system[a]		
	I	II	III
Mecillinam	0.55	0.20	0.37
Pivmecillinam	0.25	0.85	0.84
Other amidinopenicillins	0.42–0.65	0.15–0.30	0.30–0.45
6-APA	0.84	0.38	0.54
Degradation products of			
Mecillinam	—	0.05	0.05
Other amidinopenicillins		0.46	0.24
		0.92	
Pivmecillinam	—	0.02	0.02
		0.58	0.4
		0.65	

[a]On Silicagel GF_{254} plates. I: n-butanol–water–acetic acid 40:40:1.5 (lower layer); II: n-butanol–ethanol–acetone–water 4:1:4:1; III: methanol–acetone 1:1.

TABLE 12. R_f values for N^1-methyl-N^1,N^2-diaryl benzamidines (**29**) on a Silicagel plate[38]

	X	Y	pK_a	R_f	ΔR_f[a]
a	4-OMe	4-OMe	8.36	0.13	−0.02
b	4-OMe	H	7.96	0.17	−0.11
c	4-OMe	3-Cl	7.39	0.45	−0.02
d	4-Me	4-OMe	8.05	0.21	−0.04
e	4-Me	H	7.56	0.52	0.09
f	4-Me	3-Br	7.14	0.73	0.17
g	H	H	7.10	0.63	0.06
h	H	4-Br	6.68	0.81	0.10
i	3-OMe	4-OMe	7.21	0.44	−0.10
j	3-OMe	4-Br	6.72	0.62	−0.08
k	3-OMe	4-Br	6.30	0.78	−0.06
l	4-Br	4-OMe	6.86	0.76	0.11
m	4-Br	H	6.37	0.85	0.03
n	4-Br	4-Br	5.95	0.88	−0.08
o	3-Cl	H	6.10	0.87	−0.04

[a] $\Delta R_f = R_f(\text{exp.}) - R_f(\text{calc.})$.

are obtained if the substituent in the series is varied at only one site, and if all the R_f values are determined under the same, strictly controlled conditions[49].

The R_f values for N^1-methyl-N^1-phenylformamidines (**30**) on Silicagel plates were measured by using various developing systems (Table 13). It was found[49] that in each case good correlation was obtained (Table 14). However, the nature of the developing system considerably influences not only the R_f values, but also the parameters of equation 10.

TABLE 13. R_f values for N^1-methyl-N^1-phenylformamidines (**30**) on Silicagel plates in various developing systems[49]

	Developing system			
R	Acetone	Acetone/$CHCl_3$ 2:1	Methanol	pK_a of **30**
4-$O_2NC_6H_4$	0.66	0.64	0.71	3.54
3-ClC_6H_4	0.63	0.61	0.69	4.36
4-ClC_6H_4	0.66	0.62	0.69	4.68
3-$MeOC_6H_4$	0.60	0.57	0.63	5.14
C_6H_5	0.64	0.58	0.64	5.16
3-MeC_6H_4	0.63	0.57	0.66	5.51
4-MeC_6H_4	0.59	0.55	0.63	5.60
4-$MeOC_6H_4$	0.55	0.53	0.62	5.72
$PhCH_2$	0.15	0.39	0.45	8.20
CH_2=$CHCH_2$	0.26	0.43	0.42	8.41
n-Hex	0.14	0.40	0.43	8.72
n-Bu	0.28	0.40	0.40	8.88
i-Pr	0.16	0.40	0.43	8.98

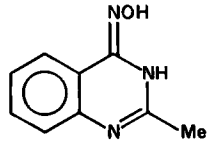
TABLE 14. Parameters of the regression of R_f values of N^1-methyl-N^1-phenylformamidines (30) vs their pK_a values (equation 10)[49]

System	a	b	r	ψ	ΔR_f[a] mean	ΔR_f[a] max
Acetone	-0.11 ± 0.02	1.12	0.953	0.331	0.05	0.11
Acetone/ $CHCl_3$ 1:1	-0.05 ± 0.01	0.82	0.987	0.176	0.01	0.04
Methanol	-0.06 ± 0.01	0.97	0.987	0.177	0.02	0.04

[a] $\Delta R_f = R_f$ (exp.) $- R_f$(calc.)

2. *Amidoximes*

The TLC method was applied in order to distinguish amidoxime **31** from the isomeric quinazoline oxide **32** formed as a by-product in its preparation[44]. Analysis was performed on Silicagel HF_{254} plates using two developing systems: methanol–ethyl acetate 1:4 (for **31** $R_f = 0.18$; for **32** $R_f = 0.61$) and methanol–ethyl acetate 2:3 (for **31** $R_f = 0.31$; for **32** $R_f = 0.83$).



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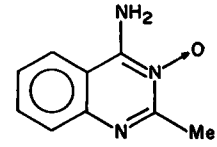

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As the R_f values of amidines correlate well with their pK_a values, it can be expected that similar relations should be obtained for other imidic acid derivatives. Unfortunately, in the papers where their R_f values are given for amidoximes, the pK_a values are not reported. However, it was recently found[49] that Hammett's σ values, being linearly related to the pK_a values, can be used instead. For *p*-substituted *N,N*-dimethylbenzamidoximes Me_2N—C(4-XC_6H_4)=NOH (Table 15) the following regression was obtained:

$$R_f = 0.40 + (0.32 \pm 0.09)\sigma, \quad r = 0.989$$

TABLE 15. R_f values for *p*-substituted *N,N*-dimethylbenzamidoximes [Me_2N—C(4-XC_6H_4)=NOH] on Silicagel plates

X	R_f[a]	σ[b]	ΔR_f[c]
OMe	0.29	−0.268	−0.03
Me	0.36	−0.170	0.01
H	0.41	0	0.01
Cl	0.50	0.227	0.02
NO_2	0.64	0.778	−0.01

[a] From Reference 51.
[b] From Reference 52.
[c] $\Delta R_f = R_f$(exp.) $- R_f$(calc.).

TABLE 16. R_f values of formazans **33** on a Silufol UV-254 plates

R^1	R^2	R^3	Developing system	R_f	Ref.
Ph	2-benzothiazolyl	4-MeC_6H_4	*a*	0.60	45
Ph	2-benzothiazolyl	4-$MeOC_6H_4$	*a*	0.61	45
Ph	2-benzothiazolyl	4-ClC_6H_4	*b*	0.55	45
Ph	2-benzothiazolyl	4-BrC_6H_4	*b*	0.75	45
Ph	2-benzothiazolyl	4-$HO_2CC_6H_4$	*b*	0.70	45
MeCO	2-thiazolyl	4-$MeOC_6H_4$	*c*	0.61	46
MeCO	2-thiazolyl	4-MeC_6H_4	*c*	0.75	46
MeCO	2-thiazolyl	C_6H_5	*c*	0.59	46
MeCO	2-thiazolyl	4-BrC_6H_4	*d*	0.60	46
MeCO	2-thiazolyl	4-$O_2NC_6H_4$	*d*	0.74	46
MeC=NOH	2-thiazolyl	2-thiazolyl	*d*	0.76	46
MeCO	2-thiazolyl	2-thiazolyl	*d*	0.28	46

[a]Ethanol–petroleum ether 1:1.
[b]Ethanol–chloroform 1:1.
[c]Ethyl acetate–chloroform 1:2.
[d]Ethyl acetate–heptane 1:1.

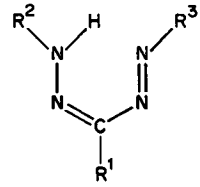
Again, the differences between the observed R_f values and the values calculated from regression are within acceptable experimental error.

3. *Amidrazones*

Purity checking of amidrazones on Silufol UV_{254} plates was described. Chromatograms were developed with chloroform or benzene, but the R_f values were not reported[53].

4. *Formazans*

The TLC method was applied for checking the purity as well as for characterization of various formazans **33**[45,46].



(33)

The R_f values are given in Table 16. Polar effects of substituents at the phenyl ring (in **33**, R^3 = Ar) are varied widely. However, neither correlations of the R_f values with substituent constants nor other general conclusions on the structure–retention relation are possible, because the R_f values of the compounds were measured under incomparable conditions.

III. MAGNETIC RESONANCE SPECTRA

Since the preceding review on detection and characterization of imidic acids derivatives[1] numerous NMR data for these compounds were published. It has to be kept in mind, however, that in that period of time spectacular developments of NMR techniques occurred, and versatile spectrometers for recording the magnetic resonance of various nuclei became commercially available. Many results, which at the time of their acquisition required sophisticated experimental methods, became easily accessible in just a few years.

The most striking example is the analysis of complex spin–spin systems of A_nB_m type in the proton NMR spectra, which now can be simplified by the increase in the spectrometer frequency and by the use of shift reagents. Other developments are assignments of groups of protons, or assignments of protons to carbon atoms by a two-dimensional NMR spectroscopy. Consequently, some results, which once attributed considerably to a better understanding of structural problems in amidines and related compounds, may seem now inadequate and deserve reinvestigation.

In the last decade ^{1}H NMR spectra became a routine characteristic for new compounds, and in synthetic reports they accompany other physical constants. For organic compounds they often replace elemental analysis because they provide more information about the compound without its destruction.

A. Structural Problems

NMR spectra were applied mainly for study of structural problems such as the structure of the predominant tautomeric form, the *cis–trans* (*E–Z*) isomerism of amidines and other imidic acid derivatives, and in conformational studies, including internal rotation around the C—N single bond.

Spectrometers for carbon magnetic resonance became commercially available several years later than those for proton resonance, thus it is no wonder that literature ^{13}C NMR data concerning amidines are much less numerous. Nevertheless, several relations between the structure and chemical shifts of amidines can be formulated on the basis of accessible data.

Carbon chemical shifts are much more sensitive than proton chemical shifts to steric interactions. Non-additive ^{13}C substituent effects, as a rule, indicate steric crowding of the carbon atoms involved[54]. ^{13}C NMR spectra are particularly useful in the study of isomerism and tautomerization. Structural changes can be slow on the NMR time scale, resulting in separate signals for each form (isomer or tautomer), or they are fast and averaged signals are observed. The latter case may provide quantitative information.

In the case of fast interchange between any two forms A and B of a molecule (isomers, tautomers or conformers) the averaged chemical shift $\delta_A(Z_i)$ of a given nucleus Z_i in the molecule (^{1}H, ^{13}C, ^{15}N, ^{31}P, etc.) depends on the chemical shifts of that nucleus in the individual forms $\delta_A(Z_i)$ and $\delta_B(Z_i)$ and on their molar fractions X_A and X_B, as expressed by equation 11[55,56].

$$\delta_{obs}(Z_i) = X_A\delta_A(Z_i) + X_B\delta_B(Z_i) \tag{11}$$

As, by definition, $X_B = 1 - X_A$, after substitution and rearrangement equation 12 is obtained.

$$X_A = \frac{\delta_{obs}(Z_i) - \delta_B(Z_i)}{\delta_A(Z_i) - \delta_B(Z_i)} \tag{12}$$

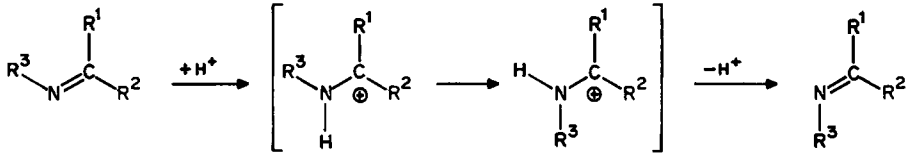
This relation may be applied to any nucleus as long as its chemical shifts in both forms are known and different. The precision of quantitative determinations depends on the ratio of

the difference between chemical shifts in the two forms to the error in the chemical shift determination. Thus it is evident that this method is much more precise than the one based on signal intensities in ^{1}H NMR spectra, especially since intensities may be affected by various effects. Moreover, if the relative concentration of one of the forms is about 5% or lower, the acceptable error in the determination of peak intensities results in a considerable error in the ratio of the two forms.

For configurational changes at the C=N bond in amidines, three possible mechanisms have been considered[57]:

1. A mechanism referred to as the 'lateral shift' mechanism which involves a linear transition state. It is generally considered to be more favourable than the second mechanism in isomerization of the RRC=NR moiety for all compounds containing the C=N double bond, except amidines.

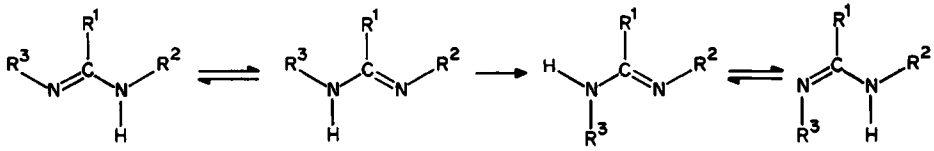
2- The second, termed the 'internal rotation' mechanism, involves a rotation about an axis going through the C and N atoms of the double bond. It is probably subject to acid catalysis, as demonstrated in the transformation **34a** → **34d**.



(34a) **(34b)** **(34c)** **(34d)**

It is believed that this mechanism is usually not taking place because NMR measurements of isomerization are carried out in a well-purified solvent[57]. However, experimental details given in some papers do not provide support for this belief.

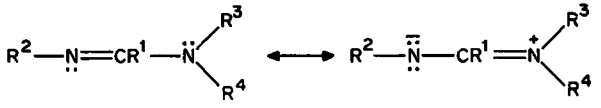
3. In monosubstituted and *N,N'*-disubstituted amidines a third tautomerization mechanism, referred to as the 'tautomeric rotation' mechanism[57], may exist. It involves prototropic tautomerization of an amidine **35a** to the other tautomeric form **35b**, rotation about the single C—N bond (**35b** → **35c**) and back tautomerization to the second geometrical isomer **35d**.



(35a) **(35b)** **(35c)** **(35d)**

It was generally assumed that for amidines the more favourable isomer has *E* configuration. However, it was shown recently[58] that the preferred configuration depends on the substituents R^1 and R^3 at the C=N double bond. In the case of bulky substituents, steric hindrance, which increase in the order Me, Et, *i*-Pr, *c*-Hex and *t*-Bu, increases the preference for the *Z* isomer. A phenyl ring does not cause sufficient steric hindrance and X-ray analysis has shown that N^2-phenylbenzamidines and N^2-phenylformamidines exist as the *E* isomers[59–64].

In amidines, strong conjugation between a lone electron pair at the amino nitrogen atom and the π-electrons of the C=N double bond is observed, as shown by the two mesomeric forms below.



X-ray data show that, due to this conjugation, the 'single' C—N bond always has some double-bond character[60]. On the basis of the IR data it was concluded that the amino nitrogen atom, often referred to as the 'sp^3 nitrogen' atom, is also in an sp^2 hybridization state[65]. The same conclusion was drawn from *ab initio* calculations for several amidines[66,67].

In this chapter only relevant chemical shifts are presented. Chemical shifts of nuclei which do not depend on the structure of the amidine group are not cited, even if they are reported in the literature.

B. ^{1}H and ^{13}C NMR Spectra

1. Chemical shift assignments

In all structural investigations proper assignment of chemical shifts is a crucial point. Chemical shifts of protons in the same group may differ to a considerable degree depending on whether they are bonded to the functional carbon atom or to the imino or amino nitrogen atom. Proper assignment of the signals (and thus determination of the structure) is not a problem in the case of simple compounds containing few carbon atoms, but if groups containing several atoms or aromatic rings are bonded to the three sites, assignments may become somehow confusing. In such cases various rules derived by regression analysis of accessible NMR data, which enable prediction of chemical shifts, are very helpful.

By analysing over 200 trisubstituted *trans* (*E*) amidines, Oszczapowicz and coworkers[68,69] derived additivity parameters for the calculation of ^{1}H and ^{13}C NMR chemical shifts for protons and carbon atoms of a phenyl ring, and for α and β protons and carbon atoms of alkyl groups bonded to either the nitrogen or carbon atoms of the amidino group.

a. ^{1}H NMR chemical shift calculations. The chemical shifts of a methylene group CH_2XY are usually calculated from Shoolery's rule[70] (equation 13), where δ_{eff} are the effective shielding constants of the substituents X and Y, respectively. The parameters calculated for amidines are summarized in Table 17.

$$\delta = 0.23 + \sum \delta_{eff} \tag{13}$$

Chemical shifts of protons in the $CHR^1R^2R^3$ group are calculated on the basis of the additivity rule[71], according to equation 14 where $T_0 = 0.824$, c_j is the number of identical substituents, and T_j are substituent constants. The parameter for the $RN{=}C(NMe_2)$— group is 1.096 ± 0.030, and for the RN=C(NMePh)— group 0.287 ± 0.012.

$$\delta = T_0 + \sum c_j T_j \tag{14}$$

Shoolery's rule may be treated as a particular case of equation 14, where one of the substituents R is a hydrogen atom. However, Shoolery's constants are better known and much more often used for chemical shift prediction. Moreover, they yield more precise chemical shift values since they are determined directly for a given substituent.

Chemical shifts of the protons in the phenyl ring are calculated by using equations 15–18[71].

For *para*-disubstituted derivatives

$$\delta_2 = 7.266 + d_o(R^1) + \gamma(R^1)d_m(R^4) \tag{15}$$

TABLE 17. Additivity parameters for calculation of chemical shifts of CH_2 groups linked to substituted aminomethyleneamino groups —N=CR'—NMe_2 (equation 13)[68]

R'	Additivity parameter
H	2.37 ± 0.03
Me	2.38 ± 0.04
i-Pr	2.46 ± 0.03
t-Bu	2.44 ± 0.02
Et	2.56 ± 0.08
p-$MeOC_6H_4$	2.19 ± 0.06
p-MeC_6H_4	2.14 ± 0.04
Ph	2.14 ± 0.02
p-ClC_6H_4	2.14 ± 0.09
p-$O_2NC_6H_4$	2.57 ± 0.06

and for *meta*-disubstituted derivatives

$$\delta_2 = 7.266 + d_o(R^1) + d_o(R^3) \tag{16}$$

$$\delta_4 = 7.266 + d_o(R^3) + d_p(R^1) \tag{17}$$

$$\delta_5 = 7.266 + d_m(R^1) + d_m(R^3) \tag{18}$$

where d_o, d_m and d_p are additivity parameters for calculating the chemical shifts of protons at positions *ortho*, *meta* or *para*, respectively, to the substituent R, and γ is a constant for substituent R^1.

The parameters of equations 15–18 for substituents at different sites of the amidino group are summarized in Tables 18 and 19. The derived parameters enable one to calculate fairly accurately chemical shifts of substituents at both nitrogen atoms and at the amidino carbon atom. In 90% of the cases the differences between the chemical shifts observed for amidines and those calculated on the basis of the parameters do not exceed 0.07 ppm. The highest differences are encountered in the case of a phenyl ring at the amidino carbon atom in benzamidines, but these still do not exceed 0.25 ppm[68,72].

It was found[68] that the ^1H NMR chemical shifts of substituents at the nitrogen atoms depend mainly on the structure of the substituent at the amidino carbon atom, and only to a certain degree on the type of substituent (i.e. alkyl or phenyl) at the second nitrogen atom. Thus, the chemical shifts of substituents at one of the nitrogen atoms for all amidines with the same substituent at the carbon atom (e.g. formamidines, acetamidines, benzamidines) and with the same type of substituent at the second nitrogen atom can be calculated using the same set of additivity parameters.

Only in the case of *p*-nitrobenzamidines does the set of additivity parameters differ from those for other benzamidines. It was assumed that this is due to a strong conjugation between the nitro group on the phenyl ring bonded to the amidino carbon atom and the phenyl ring on the nitrogen atom[68].

b. ^{13}C NMR chemical shift calculations. Chemical shifts of carbon atoms in a substituted phenyl ring are usually calculated by using additivity parameters (SCS, substituent-induced chemical shifts) and employing equation 19[73]:

$$\delta(C_i) = 128.5 + \sum \Delta\delta_{jk}(X_j) \tag{19}$$

where $\Delta\delta_{jk}$ is the additivity parameter (SCS) of substituent X_j being at position k ($C_{(1)}$, *o*, *m* or *p*) with respect to the C_i carbon atom.

TABLE 18. Additivity parameters of the substituted aminomethyleneamino group —N=CR^1—NR^{2}R^3 for calculation of chemical shifts of protons in a phenyl ring at the imino nitrogen atom (equations 15–18)[68]

R^1	R^2	R^3	d_o	d_m	d_p	γ
H	Me	Me	-0.35 ± 0.03	-0.09 ± 0.02	-0.33 ± 0.12	0.09 ± 0.02
H	—(CH$_2$)$_4$—		-0.35 ± 0.04	-0.10 ± 0.04	-0.34 ± 0.11	0.65 ± 0.46
H	—(CH$_2$)$_5$—		-0.35 ± 0.03	-0.09 ± 0.05	-0.37 ± 0.09	1.30 ± 0.92
H	—(CH$_2$)$_2$O(CH$_2$)$_2$—		-0.35 ± 0.04	-0.08 ± 0.13	-0.32 ± 0.08	0.58 ± 0.0
H[a]	Alkyl	Alkyl	-0.34 ± 0.02	-0.08 ± 0.02	-0.34 ± 0.03	0.63 ± 0.17
Me	Me	Ph	-0.44 ± 0.06	-0.02 ± 0.02	-0.29 ± 0.04	1.85 ± 1.81
Me	Me	Me	-0.60 ± 0.03	-0.10 ± 0.03	-0.36 ± 0.08	0.49 ± 0.12
i-Pr	Me	Me	-0.58 ± 0.02	-0.08 ± 0.03	-0.40 ± 0.08	0.77 ± 0.32
t-Bu	Me	Me	-0.65 ± 0.02	-0.14 ± 0.08	-0.49 ± 0.06	0.40 ± 0.12
Alk[b]	Alkyl	Alkyl	-0.62 ± 0.02	-0.10 ± 0.03	-0.44 ± 0.05	0.58 ± 0.18
C_6H_5	Me	Me	-0.69 ± 0.04	-0.32 ± 0.02	-0.50 ± 0.14	0.37 ± 0.11
4-MeC_6H_4	Me	Me	-0.73 ± 0.07	-0.33 ± 0.04	-0.48 ± 0.35	0.36 ± 0.11
4-$MeOC_6H_4$	Me	Me	-0.75 ± 0.07	-0.33 ± 0.06	-0.53 ± 0.09	0.62 ± 0.27
4-ClC_6H_4	Me	Me	-0.73 ± 0.05	-0.29 ± 0.09	-0.46 ± 0.06	0.49 ± 0.03
C_6H_5	—(CH$_2$)$_5$—		-0.77 ± 0.07	-0.37 ± 0.02	-0.67 ± 0.06	0.43 ± 0.67
XC_6H_4[c]	Alkyl	Alkyl	-0.75 ± 0.03	-0.33 ± 0.01	-0.51 ± 0.05	0.40 ± 0.24
4-$O_2NC_6H_4$	Me	Me	-0.59 ± 0.05	-0.14 ± 0.03	-0.47 ± 0.67	0.41 ± 0.0
C_6H_5	Me	Ph	-0.50 ± 0.08	-0.29 ± 0.05	-0.63 ± 0.15	2.97 ± 1.65

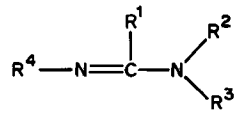
[a]Mean value for 34 compounds.
[b]Mean value for 28 compounds.
[c]Mean value for 24 compounds, not applicable to *p*-nitrophenyl derivatives.

TABLE 19. Additivity parameters of substituted amidino group $R^2N{=}C(NR^1_2)$— for calculation of chemical shifts of protons in a phenyl ring at the amidino carbon atom (equations 15–18)[68]

NR^1_2	R^2	d_o	d_m	γ
NMe_2	4-MeC_6H_4	-0.08 ± 0.12	0.02	2.60 ± 0.76
NMe_2	4-$MeOC_6H_4$	-0.08 ± 0.06	0.02	2.62 ± 0.42
NMe_2	4-ClC_6H_4	-0.08 ± 0.17	0.02	2.50 ± 0.38
NMe_2	4-$O_2NC_6H_4$	-0.08 ± 0.17	0.06	2.70 ± 1.08
NMe_2	3-$MeOC_6H_4$	-0.07 ± 0.10	0.00	2.34 ± 0.62
NMe_2	3-BrC_6H_4	-0.06 ± 0.07	0.02	2.49 ± 0.47
NMe_2	C_6H_5	-0.07 ± 0.04	0.01	2.44 ± 0.24
NMe_2	4-$MeC_4H_4CH_2$	-0.07 ± 0.10	0.02	2.29 ± 0.61
NMe_2	$C_6H_5CH_2$	-0.07 ± 0.12	0.02	2.35 ± 0.75
NMe_2	4-$ClC_6H_4CH_2$	-0.08 ± 0.06	0.02	2.38 ± 0.36
NMe_2	*n*-Hex	-0.05 ± 0.06	0.02	2.36 ± 0.37
NMe_2	*c*-Hex	-0.06 ± 0.04	0.06	2.42 ± 0.23
	4-ClC_6H_4	-0.14 ± 0.05	-0.09	1.19
	4-MeC_6H_4	-0.12 ± 0.03	-0.08	1.19

Oszczapowicz and coworkers derived additivity parameters for the calculation of chemical shifts of the phenyl ring at the three sites of the amidine group, i.e. at the imino nitrogen atom[69] (Table 20), at the amino nitrogen atom[74] (Table 21) and at the amidino carbon atom[74] (Table 22).

In addition to amidines mentioned in this chapter the following ones have been investigated (cf. Table 20):



Series	R^1	NR^2R^3
36	Me	
37	Me	
38	Me	

Series	R^1	NR^2R^3
39	Me	$N(Alk)_2$
40	H	N(Me)Ph
41	Me	N(Et)Ph
42	Me	N(Me)Ph

Chemical shifts of the carbon atoms in substituted alkyl groups RX are calculated on the basis of the chemical shifts of the corresponding reference hydrocarbons RH or RMe using either a regression (equation 20) or an additivity (equation 21) method:

$$\delta(C_i)_{Cpd} = a_x\delta(C_i)_{ref} + A_x \tag{20}$$

$$\delta(C_i)_{Cpd} = \delta(C_i)_{ref} + A'_x \tag{21}$$

TABLE 20. Additivity parameters of the aminomethyleneamino group $R^2R^3N—CR^1=N—$ for calculation of the ^{13}C NMR chemical shifts in the phenyl ring (equation 19)[69]

Series	$C_{(1)}$	*o*	*m*	*p*
7	23.5 ± 0.1	−7.4 ± 0.0	0.4 ± 0.0	−6.2 ± 0.1
9	23.6 ± 0.1	−7.5 ± 0.0	0.4 ± 0.0	−6.2 ± 0.0
10	24.0 ± 0.2	−7.3 ± 0.0	0.4 ± 0.0	−6.3 ± 0.0
11	22.9 ± 0.1	−7.4 ± 0.1	0.5 ± 0.0	−5.6 ± 0.2
40	22.9	−7.3	0.5	−5.2
13	23.7 ± 0.2	−6.0 ± 0.1	0.2 ± 0.1	−7.1 ± 0.1
36	23.6	−5.7	0.1	−7.2
37	23.6	−6.2	0.2	−7.2
38	22.9	−6.6	0.2	−7.5
41	23.4	−6.5	0.2	−7.0
42	23.2 ± 0.4	−6.3 ± 0.4	0.3 ± 0.0	−6.7 ± 0.2
39	24.1 ± 0.1	−6.3 ± 0.3	0.1 ± 0.0	−7.8 ± 0.4
24	23.3 ± 0.2	−6.7 ± 0.1	0.2 ± 0.0	−8.6 ± 0.5

TABLE 21. Additivity parameters of the aminomethyleneamino group $R^4N=CR^1—NR^2—$ for calculation of the ^{13}C NMR chemical shifts in the phenyl ring (equation 19)[74]

R^1	R^2	R^4	$C_{(1)}$	*o*	*m*	*p*
Me	Et	C_6H_5	16.05	0.19	0.75	−3.85
Me	Me	C_6H_5	17.70	−1.02	0.89	−2.02
Ph	Me	4-BrC_6H_4	17.44	−1.46	0.19	−3.37
Ph	Me	4-MeC_6H_4	17.78	−1.59	0.06	−3.76
Ph	Me	4-$MeOC_6H_4$	17.78	−1.50	0.06	−3.72

TABLE 22. Additivity parameters of the amidino group $R^4N=C(NMe_2)—$ for calculation of the ^{13}C NMR chemical shifts in the phenyl ring (equation 19)[74]

R^4	$C_{(1)}$	*o*	*m*	*p*
C_6H_5	5.35	0.32	−0.55	−0.20
4-MeC_6H_4	5.70	0.40	−0.50	−0.25
4-$MeOC_6H_4$	5.61	0.40	−0.42	−0.20
4-ClC_6H_4	5.04	0.23	−0.33	−0.06
4-$O_2NC_6H_4$	4.39	0.15	−0.05	−0.20
3-$MeOC_6H_4$	5.31	0.23	−0.46	−0.12
3-BrC_6H_4	4.87	0.15	−0.33	−0.37

where $\delta(C_i)_{Cpd}$ and $\delta(C_i)_{ref}$ are the chemical shifts of carbon atom *i* in a given compound (Cpd) and in a reference compound (ref), respectively.

It should be mentioned that, for certain substituents, some sources give additivity parameters, whereas other sources give regression parameters with differing values of the parameter A_x. As mentioned before (cf. Section II.A) the regression method should be regarded as the more reliable one, unless it is shown that the regression coefficient *a* is equal to unity, which means that regression 20 becomes additivity rule 21.

Recently, it was shown[75] that chemical shifts of carbon atoms of an alkyl group at the nitrogen atom of the amidino group can be predicted on the basis of the chemical shifts in a corresponding primary amine. The advantage of using an amine instead of a hydrocarbon as reference compound is that the amine, regardless of its structure, was used for the synthesis of a given amidine and thus its spectrum is available, whereas it can be sometimes difficult to find in the literature the spectrum of the corresponding hydrocarbon.

It was also found[75] that for alkyl substituents at the imino nitrogen atom in amidines excellent correlations ($r \geqslant 0.998$) with the chemical shifts in the corresponding primary amines are obtained, and that the regression coefficient a is practically equal to unity, and thus additivity parameters can be applied. These parameters are presented in Table 23.

TABLE 23. Additivity parameters of the aminomethyleneamino group $Me_2N—CR^1=N—$ for calculation of the ^{13}C NMR chemical shifts of α and β carbon atoms of alkyl groups (equation 21)[75a]

	Secondary C atom		Tertiary C atom	
R^1	A_α	A_β	A_α	A_β
H	13.03 ± 0.27	-1.17 ± 0.08	—	-1.1^b
H	14.04^b	-1.65^b	—	—
Me	7.73 ± 0.22	-1.57 ± 0.06	7.3^b	-0.8^b
Et	6.98 ± 0.57	-1.31 ± 0.09	5.9^b	-0.6^b
i-Pr	6.37 ± 0.19	-1.13 ± 0.51	6.8^b	
t-Bu	8.08 ± 0.11	-2.20 ± 0.29	7.2^b	-1.4^b
XC_6H_4	8.83 ± 0.53	-1.38 ± 0.12	—	—

[a]Based on chemical shifts of primary amines RNH_2.
[b]Insufficient data to calculate the confidence level.

TABLE 24. ^{13}C NMR chemical shifts of the amidino carbon atom in selected amidines $4\text{-}XC_6H_4N=CR^1—NR^2R^3$ in $CDCl_3$ solutions[a]

			X		
R^1	R^2	R^3	NO_2	H	Me
H	Me	Me	153.91	153.33	153.22
H	Me	Ph		156.78	156.82
H	—$(CH_2)_5$—		152.81	152.62	
H	—$(CH_2)_6$—			153.31	
Me	Me	Me	157.13	157.21	157.52
Me	Me	Ph		156.78	156.82
Et	Me	Me	161.11	161.58	161.80
i-Pr	Me	Me		163.19	163.48
t-Bu	Me	Me	167.42	167.87	168.00
CH_2Ph	Me	Me	157.33	157.55	157.91
Ph	Me	Me	161.32	160.94	161.97
Ph	H	XC_6H_4	153.13	154.43	
Ph	H	H	156.47	155.78	
$4\text{-}MeC_6H_4$	Me	Me	161.76	161.24	161.28

[a]From J. Oszczapowicz and coworkers, unpublished results.

Chemical shifts of the carbon atoms depend on the substituents at the three sites of the amidine group (Table 24); however, the relation with substituent parameters seems to be of a non-linear type[74].

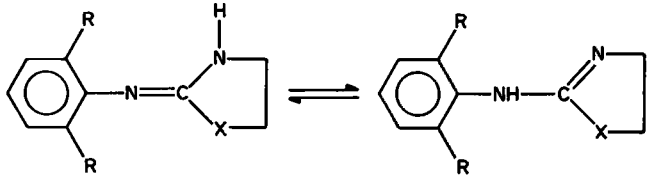
In trisubstituted amidines there are two substituents at the amino nitrogen atom. Their chemical shifts depend on whether or not rotation around the 'single' C—N bond is restricted. In the case of restricted rotation two separate signals for the protons at the carbon atom linked to the nitrogen are observed[69,72], one at a higher field (lower δ value) for the substituent in a *syn*-periplanar conformation with respect to the C=N double bond, and a second at a lower field for the proton in an *anti*-periplanar conformation. In the case of free rotation, only one signal and an averaged chemical shift are observed.

2. *Amidines*

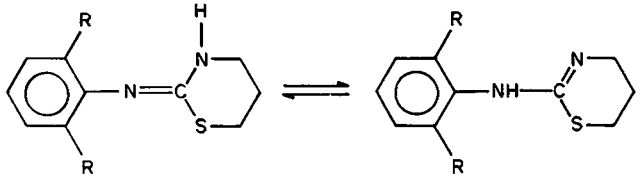
In 1972, NMR spectroscopy shed some new light on the problem of the protonation site of amidines.

Comparison of ^{1}H NMR spectra of protonated N^1-methyl-N^1,N^2-diarylformamidines (Table 25) with those of the free bases have shown that for both unsubstituted phenyl rings, at the imino and the amino nitrogen atoms the changes of the chemical shifts caused by protonation are exactly the same. All signals are shifted downfield, those of phenyl protons by 0.32 ppm and the signal of amidine CH by 0.60 ppm. In other amidines all the signals are also shifted downfield and the values for the corresponding protons are similar or approximately equal. This indicates that the positive charge is evenly distributed between both nitrogen atoms and its centre is on the amidino carbon atom. These results provided further evidence that protonation occurs at the imino nitrogen atom[76], as concluded earlier on the basis of the structure of quaternary amidinium salts.

Jackman and Jen[57] in 1975, using as examples some cyclic *N*-arylamidines and guanidines, have shown convincingly that ^{1}H NMR spectra can be applied for unambiguous determination of the predominant tautomeric form.



imino form (43) amino form



(44)

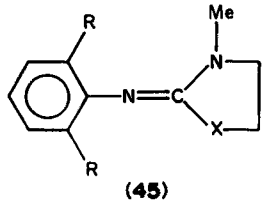
The spectra of tautomerizing compounds **43** and **44** were compared with those of the corresponding *N*-methylated derivatives **45**, **46** and **47**, where tautomerization is not possible and one or the other form, respectively, is 'fixed'.

In the spectra of the imino form of amidines (**43**, X = CH_2) and guanidines (**43**, X = NR)

TABLE 25. ^{1}H NMR chemical shifts (δ ppm) in trisubstituted formamidines 4-$R^1C_6H_4N{=}CH{-}N(C_6H_4R^2\text{-}4)Me$ (B) and their salts (BH^+)[76]

		CH		NCH_3		C=NAr				N(Me)Ar			
						$H_{(2,6)}$	$H_{(3,5)}$	$H_{(2,6)}$	$H_{(3,5)}$	$H_{(2,6)}$	$H_{(3,5)}$	$H_{(2,6)}$	$H_{(3,5)}$
R^1	R^2	B	BH^+	B	BH^+	B	B	BH^+	BH^+	B	B	BH^+	BH^+
H	H	8.20	8.80	3.41	3.83	7.20		7.52		7.20		7.52	
OMe	H	8.20	8.80	3.40	3.88	6.93[a]	7.33[a]	7.00[a]	7.60[a]	7.05		7.60	
H	OMe	8.07	8.55	3.40	3.88	7.07		7.65		7.05[a]	7.23[a]	7.05[a]	7.67[a]
NO_2	H	8.30	9.00	3.40	3.90	7.23	8.10	7.55	8.22	7.35		7.90	

[a]Assignment uncertain, $H_{(2,6)}$ and $H_{(3,5)}$ can be interchanged.



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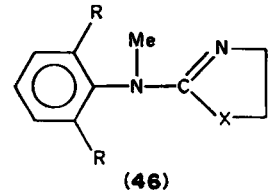

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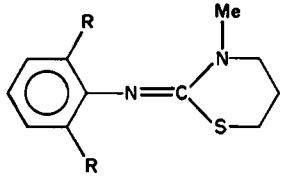

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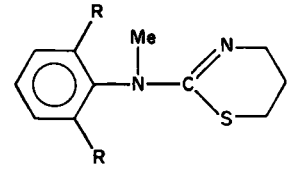


(48)

the *para* protons of the benzene ring are strongly shielded (*ca* 0.5 ppm) relative to the *meta* protons and to those of benzene itself.

The amino structure is characterized by considerable deshielding (*ca* 0.3 ppm) of the α protons (with respect to the nitrogen atom) in the heterocyclic ring ($H_{(3)}$ in **46** and $H_{(4)}$ in **48**) as compared with the imino form.

It was then shown[57] that in all the studied tautomerizing compounds the 'imino' form predominates (Tables 26 and 27). It was also shown that the relations observed between

TABLE 26. Characteristic ^1H NMR chemical shifts in cyclic amidines, and guanidines (**43**) and their *N*-methyl derivatives (**45** and **46**) in $CDCl_3$ solutions[57]

			Five-membered ring			Phenyl ring[a]	
	X	R	$H_{(3)}$	$H_{(4)}$	$H_{(5)}$	$H_{(m-)}$	$H_{(p-)}$
43a	CH_2	H	2.56	2.04	3.46		
43b	CH_2	Me	2.56[b]	2.05	3.35	6.97	6.81
43c	CH_2	Cl	(1.68–2.88)[c]		3.40	7.22	6.80
43d[d]	CH_2	Cl	2.50[f]	2.14	3.43		
43e[e]	CH_2	Cl	2.04	1.32	2.80		
43f	NH	Cl	—	3.45			
43g	NH	Me	—	3.41		7.00	6.83
43h	NH	Cl	—	3.49		7.23	6.80
43i	NMe	Cl	—	3.41		7.28	6.82
45a	CH_2	Cl	(1.58–2.44)[c]		3.43	7.25	6.78
45b	NMe	H		3.25		7.11[g]	6.78[g]
45c	NMe	Cl		3.34		7.20	6.76
46a	CH_2	Cl	(1.60–2.40)		3.76	7.42	7.24
46b	NH	H			3.64	7.20–7.53	

[a] Chemical shifts determined by AB_2 analysis.
[b] For the *E* isomer $\delta = 2.71$ at $-40\,°C$.
[c] Unresolved multiplet.
[d] In CD_3OD.
[e] In C_6D_6.
[f] For the *E* isomer $\delta = 2.71$ at $-40\,°C$.
[g] Determined at 300 MHz.

TABLE 27. ^{1}H NMR chemical shifts in cyclic amidines, derivatives of dihydro- and tetrahydro-1,3-thiazines (**44**) and their *N*-methyl derivatives (**47** and **48**) in $CDCl_3$ solution[57]

	R	$H_{(4)}$	$H_{(5)}$	$H_{(6)}$
44a	H	3.35	2.00	2.92
44a[a]	H	3.44	2.02	3.04
44b	Me	3.35	2.06	2.92
44b	Me	3.20	1.90	2.85
44c[b]	Cl	3.31	2.00	3.00
47a[b]	H	3.38	2.18	2.90
47a	H	3.38	2.17	2.87
47b[a]	Me	3.37	2.12	2.85
47c	Cl	3.43	2.15	2.92
48a	H	3.73	1.83	2.92
48b	Me	3.70	1.78	2.90
48c	Cl	3.70	1.80	2.96

[a]In CD_3OD.
[b]In DMSO-d_6.

the structure and the chemical shift can be applied to the spectra obtained in other solutions as well, because changes in the chemical shifts of the protons in question caused by solvent effects are much smaller than the differences between those of the two tautomeric forms (cf **44a** and **b**).

In the imino form, on account of steric effects of substituents R, the plane of the phenyl ring is expected to be almost perpendicular to the N=C—N plane. Thus, shielding effects of an aromatic ring on the CH_2 groups in a saturated heterocyclic ring may serve as an indication of the configuration (*E*, *Z*) of the C=N bond. However, since the rate of isomer interconversion at room temperature is comparable to the NMR time scale, only for compounds **43b** and **43d** is the second isomer detectable.

The structure of the predominant tautomer in cyclic *N*-arylamidines was also determined by ^{13}C NMR spectra[57]. For the corresponding *N*-methyl derivatives it was shown that in the *N*-aryl rings the chemical shifts of the *ortho* and *para* carbon atoms, and in the alicyclic ring the α carbon atom with respect to the ring nitrogen atom, are of good diagnostic values. In the aryl ring at the imino nitrogen the chemical shift is considerably lower than at the amino nitrogen atom (Table 28). The CH_2 carbon atom in the tautomer with an endocyclic double bond displays a signal at a higher field (allylic shift). Chemical shifts of other atoms in both rings are of lower diagnostic values.

By using this criterion it was shown that in all the studied amidines, as well as in cyclic guanidines, the imino tautomer predominates.

The first characterization of *E* and *Z* isomers of amidines by ^{13}C NMR spectra is due to Martin and coworkers[77]. For the crotonamidines (**49**: g, h and i, Table 29) two forms, i.e. *E* and *Z*, are observed in addition to the *cis* and *trans* isomers with respect to the C=C bond of the methylvinyl moiety.

Study on isomerization about the C=N double bond and rotation about the C—N single bond in N^1,N^1-dimethylamidines, carried by ^{1}H NMR spectroscopy[15], have shown that, upon addition of secondary amines to isocyanides in the presence of AgCl at low temperatures, unstable but isolable *Z* formamidines are stereospecifically formed. On heating them in an inert solvent, or on treatment with an acid at room temperature, they isomerize completely to the corresponding *E* isomers. In the stable *E* isomer of the N^2-(4-chlorophenyl) derivative, both NMe_2 groups give one signal at + 34 °C, but on cooling to

TABLE 28. Characteristic ^{13}C NMR chemical shifts in cyclic amidines **43–48**[57]

	R	X	Isomer		Phenyl ring				Heterocyclic ring	
					$C_{(1)}$	*o*	*m*	*p*	α	β
45	Cl	CH_2	imino		147.3	128.3	127.8	122.2	51.7	19.4
46	Cl	CH_2	amino		140.5	136.1	128.5	128.5	57.1	24.1
47	H	—	imino		150.0	122.8	128.5	122.5	27.6	24.6
48	H	—	amino		145.1	122.8[a]	128.3[a]	126.5	27.4	20.6
43	H	CH_2			149.0	121.2	129.0	122.0		
43	Me	CH_2		*E* + *Z*	147.8	129.3	127.9	122.3		
43	Cl	CH_2	imino	*E* + *Z*	146.1	128.3	128.9	122.8	28.4	21.9
43	Cl	CH_2	imino	*Z*[b]	145.9	128.6	127.9	122.7	28.7	21.6
43	Cl	CH_2	imino	*E*[b]	144.6	127.7	127.9	122.7	30.7	24.1
43	Me	$(CH_2)_2$	imino		—[c]	129.3	127.9	122.1	21.6[a]	23.3[a]
43	Cl	$(CH_2)_2$	imino		—[c]	128.5	128.0	122.7	22.7[a]	20.6[a]
43	Cl	$(CH_2)_2$	imino	*Z*[d]	144.5	128.5	127.9	122.6	22.2[a]	20.1[a]
43	Cl	$(CH_2)_2$	imino	*E*[d]	142.9	128.2	127.8	123.4	22.2[a]	20.6[a]
44	H	—			146.7	122.1	128.6	122.5	27.1	22.7
44	Me	—			145.5	130.8	127.5	122.7	26.9	23.5

[a]Assignment may be reversed.
[b]Determined at −60 °C.
[c]Unobservable, presumably because of exchange broadening.
[d]Determined at −70 °C.

TABLE 29. ^{13}C NMR chemical shifts in the *E* and *Z* isomers of trisubstituted amidines $PhN{=}CR^1{-}NR^2R^3$ (**49**)[77]

	R^1	R^2	R^3	Isomer	δ(ppm)					
					N—C=N	α	R^1 β	γ	R^2 α	R^3 α
a	H	Me	Me	*E*	153.0				39.8	34.1
b	H	Et	Et	*E*	152.0				43.4	37.0
c	H	Me	Ph	*E*	149.8				33.5	
d	Me	Me	Ph	*E*	155.2	16.2			38.8	
e	Et	Me	Me	*E*	160.5	19.9	11.1		37.6	37.2
f	n-Bu	Me	Me	*E*	160	27.1	29.6	22.6	37.95	37.4
g	CH=CHMe	Me	Me	*E*[a,b]	156.4	122.2	130.2	17.9	38.0	36.4
h	CH=CHMe	Me	Me	*Z*[c]	157.7	121.2	135.2	15.4	39.4	37.4
i	CH=CHMe	Me	Ph	*E*[a,b]	155.5	123.5	130.1	17.8	38.7	
j	CH=CHMe	Me	Ph	*Z*[c]	155.9	122.5	137.1	15.6	39.9	
k	CH=CHMe	H	H	*E*[b]	154.0	122.0	130.6	18.1		
l	CH=CHMe	H	H	*Z*[b]	157.0	120.8	134.4	18.1		
m	$CH{=}CMe_2$	Me	Me	*E*	157.7	118.1	138.9	24.2	38.2	36.6

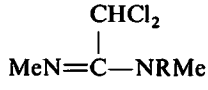
[a]*Z* form predominates (~60%).
[b]*trans*-CH=CHMe.
[c]*cis*-CH=CHMe.

−30 °C (in $CDCl_3$) separate signals for both groups are observed. The energy barrier, and thus the coalescence temperature, increase with the increased electron withdrawal of the substituent at the imino nitrogen atom.

The spectra of the *Z* isomers are quite different. The signal of the NMe_2 groups remains a singlet over the temperature range of +34 to −80 °C. It was assumed that this equivalence is due to a 'fixed' conformation (referred to as 'configuration') in which each of

the *N*-phenyl and NMe_2 planes is orthogonal to the amidino N=C—N group plane. Two separate signals obtained for the NMe_2 groups in the *ortho*-phenyl derivatives provide support for this assumption. No evidence was found for the isomerization of the amidines studied by nitrogen inversion. Rather, it occurs by the rotational mechanism.

Substantial differences between the spectra of *E* and *Z* isomers were observed[78] for phosphoryl derivatives [R = $(AlkO)_2PO$] of amidines **50–52**.



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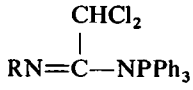

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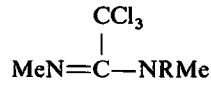
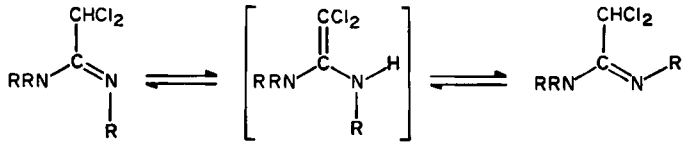


(52)

It was shown that for the two isomers different values of ^1H and ^{31}P chemical shifts and the ^{31}P–H coupling constants are observed. For **50** two separate ^{31}P signals are observed at room temperature, which at higher temperatures coalesce into one signal. In fresh solutions of **51** only signals of the *Z* isomer are observed at room temperature. The second isomer appears only after the temperature is increased to *ca* 50 °C, or after standing for a long time at room temperature. Evidence was provided in this case that the $Z \rightarrow E$ isomerization occurs by a free rotation around the C—N single bond in the tautomeric enamine **53**, rather than by a nitrogen inversion mechanism.

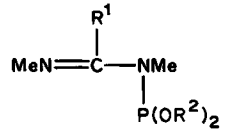


Z **(53)** *E*

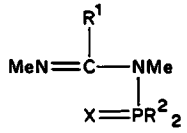
The enamine tautomer, however, was not detected either in the ^1H, or in the ^{13}C or in the ^{31}P NMR spectra of any of the compounds studied[78]. This was explained by the short lifetime of this isomer. Indirect evidence for the mechanism is the exchange of the $CHCl_2$ group protons in CD_3OD solutions, whose rates correlate with the activation energies of the $E \rightarrow Z$ isomerization[78]. Moreover, for compound **52**, where the enamine tautomer does not exist, the *E* form is not detected even in the temperature range of -40 to $+150$ °C. In amidine **51**, which contains a phenyl ring at the imino nitrogen, proton exchange in the $CHCl_2$ group does not occur even in boiling CD_3OD, and up to 200 °C it exists only as the *E* isomer.

^{13}C NMR spectra provided further evidence for $E \rightarrow Z$ isomerization in phosphorylated amidines[78] **50–52**. At room temperature separate signals for both isomers are observed. The J_{PC} coupling constants for both isomers are also different.

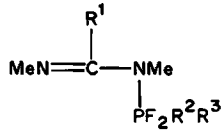
The migration of phosphorus-containing groups in **54**[79], **55**[79], **56**[80], **57**[81] and **58**[82] have been studied. ^{13}C NMR, ^1H NMR and ^{31}P NMR spectra were used in the study of the phosphotropic tautomerism[79–82] in these phosphorylated amidines. It was found that at



(54) R^1=Ph
(55) R^1=CF_3



(56)
X = O, NPh



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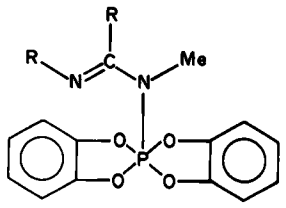
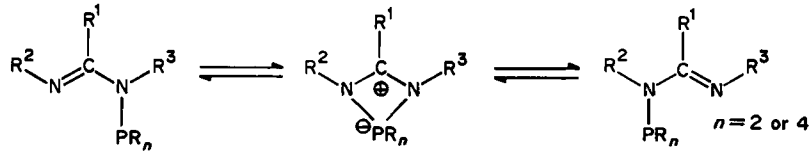


(58)

lower temperatures separate signals, and different $^{13}C-^{31}P$ coupling constants, are observed for the probe substituents.

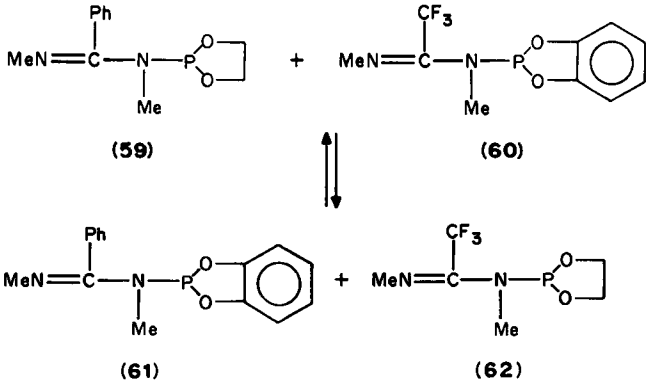
In the N—P^{III} phosphorylated N^1,N^2-dimethylbenzamidines (54) and trifluoroacetamidines (55) different chemical shifts for the methyl groups at the imino and amino nitrogens and different J_{PH} coupling constants are observed at room temperature. At higher temperatures an averaging of the chemical shifts and J_{PH} coupling constants occurs[79].

It was assumed that in amidines (58a) containing an N—P bond the group containing the P^{III} or P^V atom may undergo migration to the second nitrogen atom (phosphotropic tautomerism)[9,80] to give 58c via the four-membered intermediate 58b.



(58a) (58b) (58c)

^1H NMR spectra of equimolar mixtures of 59 with 60 or of 61 with 62 in benzene provide good evidence that such migration may indeed occur. When such mixtures are heated to 80 °C for 54 h, considerable amounts of the exchange products are formed.



(59) (60)

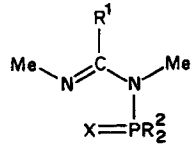
(61) (62)

Migrations of phosphoryl groups were studied also for N^1-methyl-N^2-alkylamidino fluorophosphonates[81] (57), and for N,N-dialkylamidino-bis(*o*-phenylenedioxa)phosphates[82] (58).

TABLE 30. Illustrative ^1H and ^{31}P chemical shifts in N^1-phosphonated N^1,N^2-dimethylamidines (63) in C_6D_6 solutions[80]

	X	R^1	R^2	T(°C)	Isomer	δ(ppm) N^1Me	δ(ppm) N^2Me	J^a_{PH} N^1Me $^3J_{PH}$	J^a_{PH} N^2Me $^5J_{PH}$	δ(ppm)[b,c] ^{31}P
a	O	Ph	OEt	30	E(81%)	3.32	2.92	8.1	0.6	−4.4
				30	Z(19%)	2.62	3.49	9.3	2.1	−2.1
				200	Z + E	3.03		6.1		
b	NPh	Ph	OEt	30	E(72%)	3.12	2.81	8.8	0.3	−3.3
				30	Z(28%)	2.66	3.32	9.4	2.0	−9.2
				200	Z + E	2.79		6 ± 1		
c	O	$CHCl_2$	OEt	30	E(50%)	2.84	3.59	7.3	1.2	−3.9
				30	Z(50%)	2.88	3.27	8.9	2.2	−1.4
				100	Z + E	2.90	3.49	8.1		

[a] ± 0.1 Hz.
[b] ± 0.5 Hz.
[c] 85% H_3PO_4 external standard



(63)

In the ^1H NMR spectra of N^1-phosphoryl-N^1,N^2-dimethylamidines **63**[80], both the *E* form and the less favourable *Z* form are observed.

An analogous mechanism was proposed also for the migration of a 2,4,6-tris(trifluoromethylsulphonyl)phenyl group in *N,N'*-di(*p*-tolyl)benzamidine[83].

The *E* isomers are characterized by lower values of J_{PH} and J_{PH} coupling constants and by a downfield shift in the ^{31}P NMR spectra compared with the *Z* isomers (Table 30). ^1H NMR spectra show that the amount of the *Z* isomer increases with increasing solvent polarity, and the *Z*:*E* ratios are 15:85 in benzene-d_6, 26:74 in *o*-dichlorobenzene and 37:63 in acetone-d_6. Data presented in Table 30 reveal another characteristic feature unnoticed in the original paper, that the *E*:*Z* ratio for C-alkylamidines is considerably higher than for benzamidines, because alkyl groups cause higher steric hindrance than the phenyl ring[58].

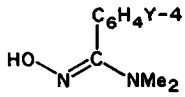
3. *Amidoximes*

Configuration and conformation of amidoximes became subjects of interest in the last two decades when very promising complexing properties of amidoximes were noticed.

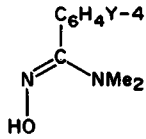
In 1971 an ASIS (aromatic solvent induced shift) method was applied in a study of the geometry of amidoximes[84]. For ten N^1-(substituted phenyl)benzamidoximes, differences in ^1H NMR chemical shifts between CS_2 and C_6D_6 solutions were discussed. The authors concluded that 'the two phenyl rings adopt a *trans* position', having in mind a conformation about the C—N single bond in which the *N*-phenyl ring is in a *syn*-periplanar position with respect to the imino nitrogen. However, the configuration of the C=N bond was not even discussed.

The question of *E*–*Z* isomerization of amidoximes was clarified by Gozlan and

coworkers[51]. In their work both *E* and *Z* isomers of *N,N*-dimethylbenzamidoxime (**64**) were first obtained and the structure of the *E* isomer was unambiguously determined by X-ray crystallography.



(*E*-64)

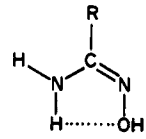


(*Z*-64)

It was then shown that ^{1}H NMR chemical shifts of the N—Me, NOH and *ortho* protons in the phenyl ring, as well as the ^{13}C NMR chemical shifts of the *N*-methyl groups are characteristic for a given isomer and hence may serve for configuration assignment. In both ^{1}H and ^{13}C NMR spectra, signals of the methyl groups of the *E* isomer are at a considerably lower field, and a similar relation was observed for protons of the oxime group, whereas an opposite relation is observed for *ortho* protons in the phenyl ring (Table 31).

The $E \rightarrow Z$ isomerization rate in various solvents and its mechanism were studied with the *p*-nitro derivative[51]. It was found that in aprotic solvents the rate constant increases with the solvent polarity, e.g. in acetonitrile it is about four times higher than in benzene, and the activation energy is about 0.8 kcal mol^{-1} lower. Consequently, it was concluded that in this case isomerization occurs by the rotational mechanism, although in most compounds containing the C=N moiety the inversion mechanism is more frequent due to the energy requirements. It was also found that in protic solvents the isomerization rate increases with the acidity of the reaction medium, also indicating that in this case the isomerization occurs by a rotational mechanism.

It was also concluded[51] that $E \rightarrow Z$ isomerization was not observed for unsubstituted and N-monosubstituted amidoximes because the *Z* configuration is stabilized by an intramolecular hydrogen bond, as shown by formula **65**, and thus much higher energy is required for isomerization.



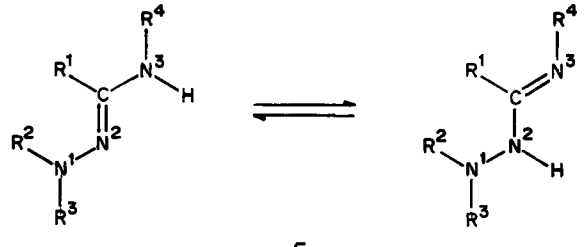
(65)

TABLE 31. ^{1}H and ^{13}C NMR chemical shifts in *E* and *Z* isomers of *p*-substituted *N,N*-dimethylbenzamidoximes **64**[51]

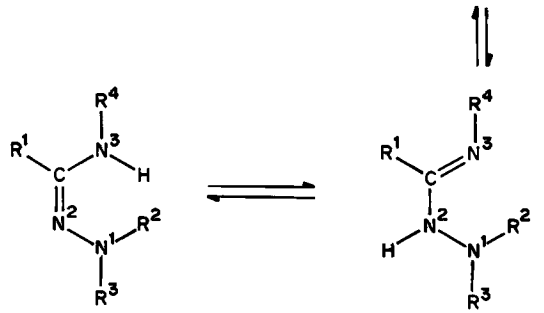
	^{1}H (δ ppm)						^{13}C (δ ppm)	
	NCH_3		H(*ortho*)		NOH		NCH_3	
Y	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*
Me	2.80	2.54	7.05	7.20	9.62	9.00	41.15	38.96
H	2.81	2.55	7.36	7.51	9.70	9.05	41.31	39.12
Cl	2.82	2.56	7.41	7.50	9.85	9.20	41.21	39.03
NO_2	2.84	2.60	8.20	8.28	10.20	9.40	41.29	39.29

4. Amidrazones

^{1}H NMR study of amidrazones provided further confirmation for previous findings[1c], that of the two tautomeric forms **66a** and **66b** only the one containing a C=N^2 double bond is found. For tautomer **66a** two geometric isomers *E* and *Z* are possible, and each one of them has two conformations for each of the groups N^{1}R^{2}R^3 and N^{3}HR^4.

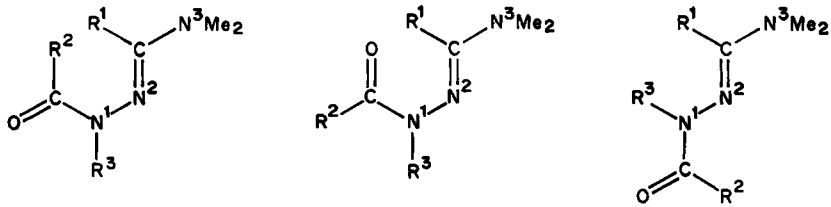


(66a) *E* (66b)



(66a') *Z* (66b')

Both ^{1}H and ^{13}C NMR spectra indicated that 1-acyl-1-alkyl-3,3-dimethylamidrazones **67** exist only in the *E* form. Conformational changes at room temperature are slow enough to give separate signals for substituents at the amidrazone carbon and at the N^1 nitrogen atom in the two conformers[85] (Table 32).



(67a) (67b) (67c)

It was claimed[85] that the observed separate signals are due to two conformations (**67a** and **67b**) obtained by rotation of the COR^2 acyl group. The assignments were based on the values of the coupling constants between the acyl carbon atom and the proton of the R^3 alkyl group, which were assumed to be 4.7 Hz for **67b** and < 2 Hz for **67a**.

It was shown that the ratios of the two conformers determined form ^{1}H NMR spectra

TABLE 32. ^1H and ^{13}C NMR chemical shifts[a] for *E* and *Z* 1-acyl-3,3-dimethylamidrazones (67)[85]

				^1H (δ ppm)				^{13}C (δ ppm)				
				R^1		R^2		C=O		C=N		
	R^1	R^2	R^3	*Z*	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*	%*E*
a	H	H	Me	7.86	7.58	7.97	8.11	156.1	159.7	158.2	150.1	77
b	H	H	Et	7.90	7.55	7.94	7.90	157.2	159.7	161.0	157.1	67
c	H	H	Pr	7.93	7.55	7.88	7.93	157.2	159.8	160.9	157.0	57
d	H	H	*i*-Pr	7.93	7.54	7.73	7.91	156.5	158.6	161.0	159.9	48
e	H	H	*t*-Bu	8.19[b]	7.59[c]	7.60	7.68[c]	155.5	—	161.2	—	< 5
f	H	H	Ph	8.30[b]	—	7.72	—	157.6	—	161.7	—	< 5
g	Me	Me	Pr	—	1.68	—	1.88	—	169.6	—	167.4	> 95
h	H	Me	Pr	—	7.45	—	1.90	—	169.1	—	156.5	> 95

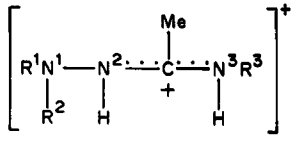
[a]For 10% solutions in CCl_4 at −30 °C.
[b]Broad.
[c]Measured at 0 °C.

correlate with Taft's steric constants E_s:

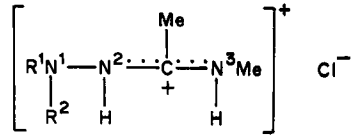
$$\lg(E'/Z') = 0.49 + 1.30E_s; \qquad r = 0.99$$

However, two signals were observed in the ^{13}C NMR spectra for the carbonyl carbon atom. This was not discussed in the paper and cannot be rationalized by two conformations of the acyl group. It seems that this discrepancy could be explained by conformational changes involving rotation around the $N^1—N^2$ bond (**67a** and **67c**), particularly because a high rotational barrier for this bond is expected by analogy to hydrazines[86]. The authors do not discuss this possibility, although they mention the high barrier for hydrazines on a different occasion. Consistency of the recorded chemical shifts and coupling constants with structures **67a** and **67c** could be obtained if the assignments of the C=O and $C=N^2$ signals (Table 32) in the ^{13}C NMR spectra were interchanged, and if it was assumed that the two conformations arise by rotation around the $N^1—N^2$ bond.

In the ^1H NMR spectra of amidrazone hydrochlorides (**68** and **69**) in DMSO-d_6 solutions at room temperature, each proton gives a separate signal. It means that proton exchange is slow, and rotation around the $N^1—N^2$ bond is hindered. The mobility of the N^2H protons increases with temperature and, at 50 °C, their signal is 'not localized'. Above 140 °C averaging of chemical shifts of all protons at nitrogen atoms occurs, and one common signals is observed[87].

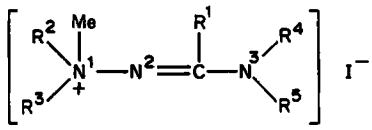


(68)



(69)

It was also shown[88] that, as a result of alkylation of amidrazones with methyl iodide, either N^1-methyl- or N^2-methyl-amidrazonium salts (**70** or **71**) can be formed, depending on the substituents at the N^1 nitrogen atom. The structures of thirteen products were determined by ^1H and ^{13}C NMR spectra.



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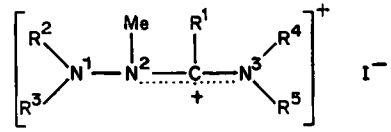
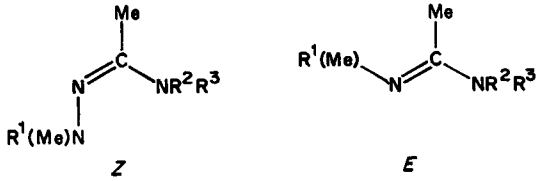


(71)

In 1986 Cunningham and Hegarty[89] synthesized four *Z*-acetamidrazones **72a–d** (called incorrectly amidines) and showed that two of them, **72a** and **72b**, can be stored indefinitely in the solid state at low temperature (−70 °C) without further reaction. **72b** was contaminated by a small quantity of the *E* isomer, whereas **72c** could not be isolated in a pure form as a single isomer; it was prepared *in situ* and subsequent isomerization was observed.



Z *E*

(72)

(a) R^1=2,4-$(O_2N)_2C_6H_3$ NR^2R^3=NMe_2
(b) R^1=4-$O_2NC_6H_4$ NR^2R^3=NMe_2
(c) R^1=Ph NR^2R^3=NMe_2
(d) R^1=2,4-$(O_2N)_2C_6H_3$ NR^2R^3=morpholino

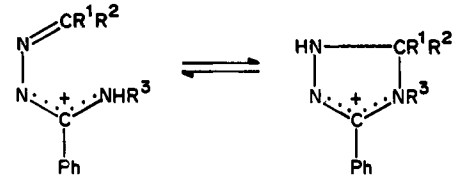
The chemical shifts of the methyl groups at the amidrazone carbon atom are well differentiated in the *E* and *Z* isomers and may serve as an indication of the structure of the isomer. Chemical shifts of the methyl groups at the nitrogen atoms of both isomers are much less differentiated (Table 33).

^{13}C NMR spectra were also applied to the study of ring–chain tautomerization in N^1-alkenylideneamidrazone salts (73a⇌73b)[90].

TABLE 33. ^1H NMR chemical shifts (δ ppm) for amidrazones **72** in $CDCl_3$ solutions[89]

		Methyl group			Phenyl ring		
		MeC=N	Me_2NC	MeNAr	$H_{(2,6)}$	$H_{(3)}$	$H_{(5)}$
a	*Z*	2.02	3.10	3.15	7.03	8.55	8.24
	E	3.02	3.15	3.15	7.04	8.55	8.17
b	*Z*	2.15	2.94	3.15	6.76	8.12	
	E	1.95	3.12	3.22	6.63	8.10	
c	*Z*	2.05	—[b]	3.20	——	7.0–8.4	——
	E	2.12	—[c]	3.18	——	6.9–8.6	——
d[a]	*E*	2.20	3.00	2.97	——	6.6–7.4	——

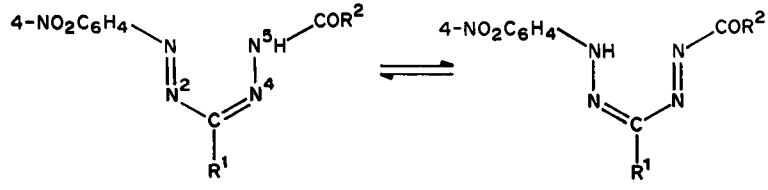
[a]The *Z* isomer isomerizes too fast and could not be isolated.
[b]Multiplets at 3.60–3.70 and 3.77–3.90 ppm.
[c]Multiplets at 3.30–3.60 and 3.70–3.90 ppm.



(73a) (73b)

5. Formazans

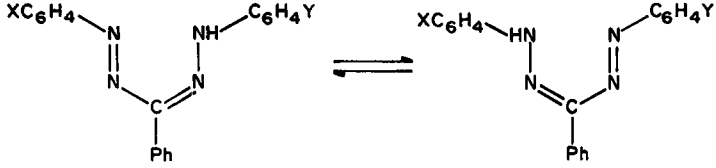
Comparison of the chemical shifts of the $H_{(2,6)}$ and $H_{(3,5)}$ protons of the *p*-nitrophenyl group in *N*-acylformazans (**74**) with those of corresponding model compounds indicated[91] that their structure is represented by the formula **74b**.



(74a) (74b)

Unsymmetrically 1,5-disubstituted formazans may exist in two tautomeric forms where the N^1 and N^5 nitrogen atoms may be termed azo (N^1) and hydrazo (N^5) nitrogen atoms.

In several papers on the tautomerism of formazans[46,92,93] their structure is related to that of a 1,3,5-triphenylformazan containing a nitro group at one of the terminal phenyl rings (**75**, X = *p*-NO_2, Y = H) which, according to Fischer, Kaul and Zollinger[94], exist practically only as the tautomer **75b**, where the *p*-nitrophenyl group is at the hydrazo nitrogen atom (NH group).



(75a) (75b)

These authors[94] recorded ^1H NMR spectra of three formazans (**75**, X = H, 4-OMe, 4-NO_2; Y = H) which contained a ^{15}N atom bonded to the unsubstituted (C_6H_4Y) phenyl ring, and those of the three unlabelled analogues. It was found that in labelled *N*-phenyl- and *N*-(*p*-methoxyphenyl)formazans the NH signal appeared as a doublet due to ^{15}N–^1H coupling (δ = 15.68 ppm, J = 45 Hz, and δ = 15.33 ppm, J = 86.5 Hz, respectively) whereas for the *p*-nitro derivative, similarly to the unlabelled compounds, the NH signal (δ = 14.68 ppm) appeared as a broad singlet. Thus it was concluded that, the phenyl and the *p*-methoxyphenyl derivatives, the proton is at the ^{15}N-labelled nitrogen, i.e. the substituted phenyl ring is at the azo (N^1) nitrogen atom. On this basis it was concluded that the *p*-nitrophenyl group is at the hydrazo (N^5) nitrogen atom.

It is noteworthy that this conclusion contradicts the general rules derived for

TABLE 34. Additivity parameters for calculation of ^{13}C NMR chemical shifts of the phenyl ring and the chemical shifts of the carbon atom in N^1,C^3,N^5-triphenylformazans (equation 19) in $CDCl_3$ solutions[93]

Phenyl at	$C_{(1)}$	$C_{(o)}$	$C_{(m)}$	$C_{(p)}$
Azo nitrogen atom	19.3	−9.8	0.8	−1.1
Hydrazo nitrogen atom	20.3	−9.8	0.8	−1.1
Carbon atom	8.8	−2.8	0.2	−1.0

amidines (cf. the chapter on basicity), where the electron-withdrawing substituent, such as a *p*-nitrophenyl group, is always at the double-bonded nitrogen atom.

There is no evidence, however, that the absence of the ^{15}N–H coupling in the NH group signal is not due to fast proton exchange in the chelate bridge between the N^1 and N^5 nitrogen atoms. Unambiguous evidence would be provided if the NH coupling in the ^1H NMR spectra of the ^{15}N-labelled formazan at the second phenyl ring were recorded, and temperature investigations were conducted.

Since this compound serves as the reference in determination of tautomeric structures of formazans, a structural reinvestigation by using other techniques would be useful.

For 1,3,5-triphenylformazans substituted in a phenyl ring at the nitrogen atom, all carbon atoms were assigned[93]. For all compounds studied only averaged chemical shifts are observed. Chemical shifts for individual tautomers were calculated on the assumption that in the case of symmetrically 1,5-disubstituted formazans (**75**, X = Y), the observed chemical shifts are the mean of the shifts in the two tautomeric forms **75a** and **75b** and that the *p*-nitrophenyl derivative exists practically only as the tautomer in which the *p*-nitrophenyl group is at the amino nitrogen[94]. On this basis the content of individual tautomers in the equilibrium mixtures have been calculated, probably by using equation 12. The same approach was used for another series of triphenylformazans[46,92].

On the basis of the literature data, additivity parameters (equation 19) for calculation of ^{13}C chemical shifts of the phenyl rings in formazans can be derived (Table 34).

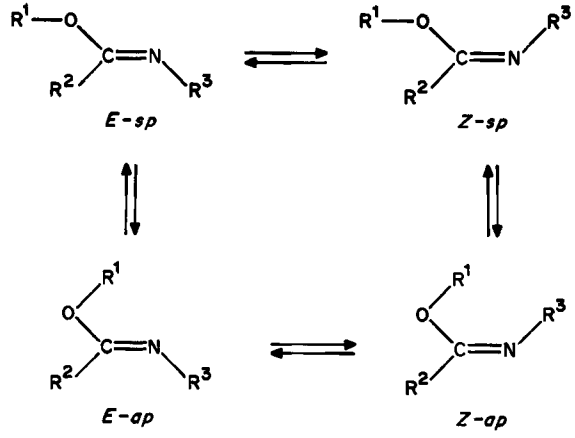
6. *Imidates*

The configuration and conformation of imidate esters were studied by using NOE difference spectra[95]. Imidates may exist as the two configurational isomers *E* and *Z* (**76**), each having two conformations, *sp* or *ap*, of the OR^1 group.

It was found that for imidates **76** only one configurational isomer is detectable in $CDCl_3$ and CD_2Cl_2 solutions both at room temperature and at low temperatures, although a 98:2 *E*:*Z* isomer ratio was earlier reported[96] for **76a** in $CDCl_3$ solutions.

Imidates **76c** and **76d** are substituted by a bulky *tert*-butyl group at the nitrogen atom. Steric repulsion between this group and the hydrogen atom in **76a** is too small to cause configurational changes, but in **76d**, which is substituted by a phenyl ring at the carbon of the C=N group, it is high enough to cause destabilization of the *E* isomer, and thus the compound at room temperature exists as rapidly interconverting *E* and *Z* isomers. At temperatures below −60 °C the signals of the two isomers of **76d** are clearly resolved, indicating an *E*:*Z* ratio of 64:36 in CD_2Cl_2 at −67 °C and 40:60 in $CDCl_3$ at −58 °C.

Low-temperature data for **76d** provided an instructive example of the application of the NOE technique for structure determination of imidates. For N–*t*-Bu Saturation there is 3.6% enhancement of the phenyl proton signals neighbouring the *tert*-butyl group in the *E*



(76)

(a) $R^1=R^3=Me, R^2=Ph$ (c) $R^1=Me, R^2=H, R^3=t\text{-}Bu$

(b) $R^1=R^2=R^3=Me$ (d) $R^1=Me, R^2=Ph, R^3=t\text{-}Bu$

isomer, and only 0.8% in the *Z* isomer. Thus configurational assignments can be made unequivocally on this basis. Considerable differences in the NOE enhancements are also observed for all other combinations of pairs of substituents in imidates **76a–d**.

For some imidoyl derivatives, additivity parameters for the calculation of chemical shifts in the phenyl ring have been derived[77] (Table 35).

Imidate anions $RN{=}CRO^{\ominus}$ formed *in situ* by treating the amide with NaH or KH in THF or Me_2SO_4 have been characterized by ^1H NMR spectra[97]. Indirect evidence was based on eliminating reasonable alternatives. The only direct evidence is a one four-bond coupling constant observed in one isomer of the *N*-benzylformimidate anion, which is significantly greater than the coupling observed in the parent amide.

Measurements of the kinetics of proton exchange in ethyl acetimidate[98] (referred to as imidate ester) in 46% H_2SO_4 show that the proton in the *cis* position with respect to the OR group exchanges faster than the proton in the *trans* position. In contrast, the *cis* proton of the protonated 2-iminotetrahydrofuran exchanges faster than the *trans* proton.

In addition to the ^1H NMR spectra discussed above, the literature also reports ^1H NMR spectra of the following imidic acids derivatives: amidines[99–103], amidinopenicillins[41,42,104–107], amidrazones[108,109] and formazans[110].

TABLE 35. Additivity parameters for calculation of ^{13}C NMR chemical shifts of the phenyl ring in imidoyl derivatives $C_6H_5N{=}CXY$ (equation 19)[77]

X	Y	$C_{(1)}$	$C_{(o)}$	$C_{(m)}$	$C_{(p)}$
H	OR	19.0	−7.4	0	−4.8
H	NMe_2	22.8	−7.8	0	−7.8
H	NEt_2	23.5	−7.9	−0.8	−6.9
R	NMe_2	23.1	−6.6	0	−7.8

C. ^{15}N NMR Spectra

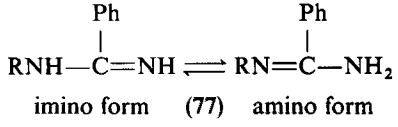
Widespread application of nitrogen magnetic resonance is indeed very recent. The first direct detection of the ^{15}N resonance signals at the natural abundance level was realized in 1964. The very low signal-to-noise ratio of 3–4 obtained for neat liquids was really discouraging. Low sensitivity of the ^{15}N resonance still remains the main disadvantage of the nitrogen NMR spectroscopy. However since, after carbon and hydrogen, nitrogen is the most important atom in organic and bioorganic molecules, considerable effort was expended in the last decades on improving NMR technology. The wide range displayed by ^{15}N chemical shifts, and the smaller number of nitrogen atoms in a molecule compared with carbon and hydrogen atoms which simplify the ^{15}N spectra, make nitrogen NMR spectroscopy attractive for investigation of organic molecules. Such spectra are particularly valuable as a means of distinguishing between isomeric structures, including tautomers.

A common reference and common scale are necessary in order to compare nitrogen chemical shifts in various molecules. The rapid development of ^{15}N spectroscopy resulted in the suggestion of at least thirteen different compounds in various solutions as standards for ^{15}N chemical shifts[111]. Two scales are encountered in the literature. One is the *screening constant scale*, which assigns plus sign to shifts to higher magnetic field at a constant frequency, or lower frequencies at constant magnetic field (σ constants). This scale is preferred by physicists and physical chemists because the screening constant is a quantity which appears in the equations of the general theory of chemical shifts.

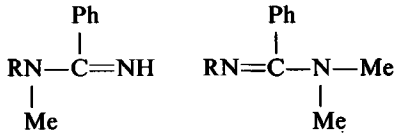
The second scale, the *frequency scale*, is based on preferences from ^{1}H and ^{13}C spectroscopy, and takes as positive all shifts to higher resonance frequencies at a constant magnetic field or to a lower magnetic field at a constant frequency (δ constants). In this scale the positive direction is that of increased energy of observed transitions, which are actually measured in any modern NMR spectrometers where the frequency sweep is used. This scale, analogous to those used in proton and carbon NMR spectroscopy, is preferred by organic chemists, and recommended by IUPAC[111,112]. Both scales have opposite signs and have different zero points, because two different standards are used to express chemical shifts. Therefore, prior to any comparison, one should find out what kind of standard was used. In this chapter, to avoid confusion, all chemical shifts are given according to the IUPAC recommendations in δ (ppm) units with respect to nitromethane. Chemical shifts were recalculated using conversion factors given on p. 53 in the monograph of Martin, Martin and Gouessnard[111].

1. Amidines

Tautomeric equilibria for monosubstituted benzamidines **77** were analysed by ^{15}N spectroscopy[113] using equation 12.



imino form (77) amino form

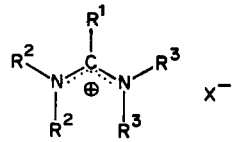


(78) (79)

The chemical shifts of the nitrogen atoms in individual tautomers were estimated from the chemical shifts in the corresponding, non-tautomerizing, methylated derivatives **78** and **79** (Table 36). For *N*-phenylbenzamidine (**77**, R = Ph) it was found that the tautomer substituted by R at the imino nitrogen predominates. The amount of the second tautomer was found to be 11% or 2%, depending upon which of the two nitrogen chemical shifts was taken for the calculations. This discrepancy arises since the chemical shift of one of the nitrogens depends to a certain degree on the substitution at the second one, and thus in the corresponding tautomer its value is not exactly identical with that in the methylated model derivative.

The authors estimated that the value of 11% is more reliable as it was based on the chemical shift of the unsubstituted nitrogen atom, because in model compound **78** there is only one methyl group whose influence on the chemical shift of the nitrogen atom was not taken into account.

Electronic delocalization in quaternary amidinium salts **80** was studied by the ^{15}N



(80)

TABLE 36. ^{15}N NMR chemical shifts[a] (δ ppm) for non-tautomerizing amidines $R^4N^2{=}CR^1{-}N^1R^2R^3$

R^1	R^2	R^3	R^4	N^1 amino	N^2 imino	Ref.
H	Me	Me	Ph	—[b]	−145.8	116
$Me_2C{=}CH$	Me	Me	Ph	—[b]	−135.5	116
Me_2N	Me	Me	Ph	—[b]	−171.7	116
H	Me	Me	Ph	−301.7	−153.5	117
H	Me	Me	4-MeC_6H_4	−302.0	−151.1	117
H	Me	Me	4-BrC_6H_4	−299.7	−151.8	117
H	—$(CH_2)_5$—		4-$MeOC_6H_4$	−280.5	−158.7	117
H	—$(CH_2)_5$—		4-MeC_6H_4	−279.9	−157.9	117
H	—$(CH_2)_5$—		4-BrC_6H_4	−277.4	−160.6	117
H	—$(CH_2)_5$—		3-$O_2NC_6H_4$	−274.1	−163.3	117
H	—$(CH_2)_5$—		4-$O_2NC_6H_4$	−269.2	−160.8	117
H	—$(CH_2)_6$—		4-ClC_6H_4	−274.5	−159.5	117
H	—$(CH_2)_6$—		4-BrC_6H_4	−274.4	−159.5	117
H	—$(CH_2)_6$—		4-$O_2NC_6H_4$	−274.3	−159.5	117
H	—$(CH_2)_2O(CH_2)_2$—		4-$MeOC_6H_4$	−289.6	−152.1	117
H	—$(CH_2)_2O(CH_2)_2$—		4-MeC_6H_4	−288.9	−151.2	117
H	—$(CH_2)_2O(CH_2)_2$—		Ph	−287.7	−150.9	117
H	—$(CH_2)_2O(CH_2)_2$—		4-ClC_6H_4	−286.6	−154.6	117
Ph	Me	Me	Me	−310.5[c]	−161.4[c]	113
Ph	Me	Me	H	−309.5[c]	−158.7[c]	113
Ph	Me	Me	Ph	−302.4[c]	−138.1[c]	113
Ph	Ph	Me	H	−283.5[c]	−143.7[c]	113

[a]Converted to the $MeNO_2$ scale.
[b]Not given.
Correction factor of −381.9 (p. 53 in Ref. 111) was used (liquid NH_3 external standard).

TABLE 37. ^{15}N NMR chemical shifts[a] for quaternary amidinium salts **80**[114]

				$\delta^{15}N$[b]		
R^1	R^2	R^3	X	NR^2	NR^3	$\delta^{13}C$
H	Me	Me	Cl	−275.9	−275.9	156.8
Me	Me	Me	$MeSO_4$	−273.3[b]	−273.3[b]	152.6
OMe	Me	Me	OSO_2F	−294.2	−294.2	164.3
SMe	Me	Me	OSO_2F	−269.1	−269.1	176.6
H	Et	Me	Cl	−275.6[c]	−250.6[c]	156.5
H	Et	Me	Cl	−275.6[c]	−250.6[c]	—
Cl	Me	Me	Cl	−269.0[c]	−269.0[c]	159
OMe	Et	Me	OSO_2F	−291.8	−272.1	164.8
OMe	Et	Me	OSO_2F	−291.8	−272.1	—
H	Et	Et	Cl	−249.7	−249.7	155.1
OMe	Et	Et	OSO_2F	−270.2	−270.2	164.7

[a]2 M solutions in CH_3CN.
[b]Correction factor −1.5, given in the paper.
[c]2 M solutions in CH_2Cl_2.

NMR spectroscopy[114]. It was found that for limited series of amidinium salts the ^{15}N chemical shifts are linearly correlated with the ^{13}C chemical shifts (Table 37) of the same N=C fragment by the relation

$$\delta^{15}N(\pm 1.3) = (78 \pm 11) - (2.25 \pm 0.11)\delta^{13}C$$

where $\delta^{15}N$ is expressed in ppm units using NO_3^- as a standard.

It was noted that the ^{13}C chemical shift decreases when the ^{15}N chemical shift and the electron delocalization increases. This was explained in terms of a push–pull mechanism governing the lone-pair density, which deshields the nitrogen atom and shields the sp^2 carbon atom[114].

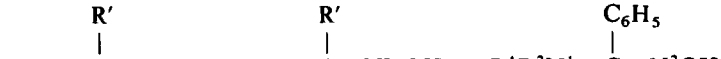
In order to discuss the chemical shifts of both NMe_2 and NEt_2 derivatives in terms of electron delocalization and steric effects, the value of the β-substituent effect was determined. It was found to be +11.1 ppm.

For series of similar compounds a good correlation was found between the activation parameter $E_a(\Delta E_T)$ for the rotation about the C—N bond and the chemical shift of the nitrogen atom[114].

Recently, it was found that the chemical shifts of both nitrogen atoms in formamidines $R^2N{=}CH{-}NR^1_2$ (Table 36) are related to the pK_a values of the corresponding primary (R^2NH_2) and secondary (HNR^1_2) amines related to the amidine molecule.

2. *Amidoximes*

For amidoximes, two tautomeric forms, the oxime form (**81a**) and the hydroxylamine form (**81b**), have been considered[115].



(81a) **(81b)** **(82)**

The ^{15}N NMR chemical shifts and $^1J^{15}_{NH}$ coupling constants of several benzamidoximes (**82**) have been determined[115] for the free bases and their HCl salts (Table 38). The

TABLE 38. ^{15}N NMR chemical shifts[a] (δ ppm) and coupling constants for benzamidoximes (**82**)[115]

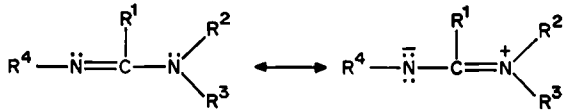
			$\delta^{15}N$		$^1J^{15}_{NH}$
R^1	R^2	Isomer	N^1	N^2	N^1—H
H	H	*Z*	−318.7	−94.2	87
H	H	*Z*	−318.1	−86.1	87.3
Ph	H	*Z*	−289.1	−73.2	91.6
Me	H	*Z*	−324.0	−92.9	87.9
—$(CH_2)_5$—		*Z*	−310.0	−72.8	—
—$(CH_2)_5$—		*E*	−303.2	−76.9	—
Me	Me	*E*	−326.3	−79.8	—
Ph	Me	*Z*	−304.8	−38.2	—
		HCl salts			
H	H		−280.0	−213.3	—[b]
Ph	H		−263.9	−193.9	—[b]

[a]Converted to the $MeNO_2$ scale.
[b]Not detected.

values of coupling constants indicate that the nitrogen atom bonded to substituent R has an sp^2 hybridization and thus that these amidoximes exist in the oxime form (**81a**) only. Coupling constants observed for salts have shown that protonation occurs at the imino (N^2) nitrogen atom.

D. Internal Rotation

The formal single C—N bond in amidines has in fact some double-bond character. By analogy to amides the two mesomeric forms **A** and **B** are considered in amidines.



(A) (B)

The partial double-bond character causes some restriction to rotation about the formal single bond. Obviously the higher the contribution of mesomeric form **B** to the structure of the amidine, the higher the rotational barrier. When a strongly electron-withdrawing substituent is at the imino nitrogen and electron-donating substituents are attached to the amino nitrogen, separate signals for the R^2 and R^3 groups for each of the two conformations are observed even at room temperature[69,74]. For other amidines, separate signals for the two conformers are observed at low temperatures.

A line-shape analysis of the ^1H as well as ^{13}C NMR spectra were applied for determination of the activation free energies for the internal rotation in several types of amidines in various solvents, such as chloroform, deuteriochloroform, benzene, methylene chloride, dichloroethylene and acetone[114,118–121]. The values of activation free energies as well as the coalescence temperatures (T_c, if reported) are given in Table 39.

It can be assumed that the conjugation in the amidine system, and thus the contribution of mesomeric form **B**, depend not only on the substituents at both nitrogen atoms, but also to a considerable extent on the substituent at the amidino carbon atom. The changes

TABLE 39. Activation free energies for internal rotation ($\Delta G^{\neq}_{Tc}$) and coalescence temperatures (T_c K) for amidines $R^4N{=}CR^1{-}NR^2R^3$

R^1	R^2	R^3	R^4	Method	Solvent	T_c(K)	$\Delta G^{\neq}_{Tc}$ (kJ mol^{-1})	Ref.
H	Me	Me	Ph	^{13}C	$CDCl_3$	318	35.6	118
H	Me	Me	Ph	^{1}H	$CDCl_3$	278	35.1	118
Et	Me	Me	Ph	^{13}C	CH_2Cl_2	213	26.3	118
Bu	Me	Me	Ph	^{13}C	$CDCl_3$	215	26.3	118
H	Et	Et	Ph	^{13}C	CH_2Cl_2	304	34.2	118
H	Et	Et	Ph	^{13}C	CH_2Cl_2	294	33.9	118
H	Et	Et	Ph	^{1}H	CH_2Cl_2	275	33.7	118
Ph	H	H	Ph	^{13}C	$CDCl_3$	261	30.6	118
Ph	H	H	Ph	^{1}H	$CDCl_3$	262	31.3	118
CH=CHMe	H	H	Ph	^{13}C	$CH_2{=}CCl_2$	233	28.2	118
CH=CHMe	H	H	Ph	^{13}C	$CH_2{=}CCl_2$	176	20.8	118
H	Me	Me	Ph	^{13}C	CD_3COCD_3	326	63.3	121
H	Me	Me	4-$ClC_6H_4CH_2$	^{13}C	CD_3COCD_3	275	52.8	121
H	Me	Me	$PhCH_2$	^{13}C	CD_3COCD_3	273	52.4	121
H	Me	Me	3-$MeOC_6H_4CH_2$	^{13}C	CD_3COCD_3	271	52.0	121
H	Me	Me	4-$MeC_6H_4CH_2$	^{13}C	CD_3COCD_3	270	51.8	121
H	Me	Me	n-Hex	^{13}C	CD_3COCD_3	263	50.4	121
H	Me	Me	n-Bu	^{13}C	CD_3COCD_3	264	50.6	121
H	Me	Me	*i*-Pr	^{13}C	CD_3COCD_3	264	50.6	121
H	Me	Me	n-Hex	^{13}C	CD_3COCD_3	<223	<40	121
H	Me	Me	c-Hex	^{13}C	CD_3COCD_3	<223	<40	121
H	Me	Me	Ph	^{13}C	CD_3COCD_3	256	51.9	121
H	Me	Me	Ph	^{13}C	CD_3COCD_3		63.3	121
Me	Me	Me	Ph	^{13}C	CD_3COCD_3		53.8	121
Et	Me	Me	Ph	^{13}C	$CDCl_3$		45.9	121
Bu	Me	Me	Ph	^{13}C	$CDCl_3$		45.9	121
i-Pr	Me	Me	Ph	^{13}C	CD_3COCD_3		~30	121
H	$(CH_2)_2O(CH_2)_2$		4-$O_2NC_6H_4$	^{13}C	CD_3COCD_3	328	63.0	120
H	$(CH_2)_2O(CH_2)_2$		3-$O_2NC_6H_4$	^{13}C	CD_3COCD_3	322	61.8	120
H	$(CH_2)_2O(CH_2)_2$		4-BrC_6H_4	^{13}C	CD_3COCD_3	311	59.6	120
H	$(CH_2)_2O(CH_2)_2$		3-BrC_6H_4	^{13}C	CD_3COCD_3	315	60.4	120
H	$(CH_2)_2O(CH_2)_2$		4-ClC_6H_4	^{13}C	CD_3COCD_3	306	58.6	120
H	$(CH_2)_2O(CH_2)_2$		Ph	^{13}C	CD_3COCD_3	298	57.0	120
H	$(CH_2)_2O(CH_2)_2$		4-MeC_6H_4	^{13}C	CD_3COCD_3	295	56.4	120
H	$(CH_2)_2O(CH_2)_2$		4-$EtOC_6H_4$	^{13}C	CD_3COCD_3	292	55.9	120
H	$(CH_2)_2O(CH_2)_2$		4-$MeOC_6H_4$	^{13}C	CD_3COCD_3	284	54.3	120
Me	Me	Me	4-$O_2NC_6H_4$	^{13}C	CD_3COCD_3	282	58.7	119
Me	Me	Me	3-$O_2NC_6H_4$	^{13}C	CD_3COCD_3	277	58.0	119
Me	Me	Me	3-BrC_6H_4	^{13}C	CD_3COCD_3	268	55.6	119
Me	Me	Me	4-BrC_6H_4	^{1}H	$CDCl_3$	223	50..0	119
Me	Me	Me	4-BrC_6H_4	^{13}C	CD_3COCD_3	266	55.4	119
Me	Me	Me	3-ClC_6H_4	^{1}H	CD_3COCD_3	223	50.1	119
Me	Me	Me	3-ClC_6H_4	^{13}C	CD_3COCD_3	268	55.8	119
Me	Me	Me	4-ClC_6H_6	^{1}H	CD_3COCD_3	217	49.0	119
Me	Me	Me	4-ClC_6H_4	^{13}C	CD_3COCD_3	261	54.0	119
Me	Me	Me	3-$EtOC_6H_4$	^{1}H	CD_3COCD_3	212	47.6	119
Me	Me	Me	3-$EtOC_6H_4$	^{13}C	CD_3COCD_3	256	53.0	119
Me	Me	Me	3-$MeOC_6H_4$	^{1}H	CD_3COCD_3	219	48.1	119
Me	Me	Me	3-$MeOC_6H_4$	^{13}C	CD_3COCD_3	254	52.5	119
Me	Me	Me	Ph	^{1}H	CD_3COCD_3	222	48.9	119
Me	Me	Me	Ph	^{13}C	CD_3COCD_3	256	53.0	119
Me	Me	Me	3-MeC_6H_4	^{1}H	CD_3COCD_3	231	49.3	119
Me	Me	Me	3-MeC_6H_4	^{13}C	CD_3COCD_3	252	52.1	119
Me	Me	Me	4-MeC_6H_4	^{1}H	CD_3COCD_3	219	48.1	119
Me	Me	Me	4-MeC_6H_4	^{13}C	CD_3COCD_3	252	52.1	119
Me	Me	Me	4-$EtOC_6H_4$	^{1}H	CD_3COCD_3	215	47.9	119
Me	Me	Me	4-$EtOC_6H_4$	^{13}C	CD_3COCD_3	248	51.2	119
Me	Me	Me	4-$MeOC_6H_4$	^{1}H	CD_3COCD_3	208	46.3	119
Me	Me	Me	4-$MeOC_6H_4$	^{13}C	CD_3COCD_3	248	51.2	119

observed in the ρ value of the Hammett equation in correlations of the pK_a values of amidines with the Hammett σ values at the imino nitrogen atom, following changes of the inductive effects of the substituent at the carbon atom[122,123], provide a certain support for this assumption. The results indicate that the conjugation increases with the increase of electron donation by the substituent at the amidino carbon atom.

Thus it can be expected that for the series of N^2-aryl amidines the values of the activation free energies will correlate with Hammett σ constants for substituents on the phenyl ring at the imino nitrogen atom, and that for each series differing by the substituent at the amidino carbon (e.g. formamidines and acetamidines) another ρ value will be obtained.

The activation free energies obtained for a series of formamidines (Table 39) were correlated with Taft's σ^* constants, but a rather poor correlation was obtained[121]. However, it should be mentioned that the choice of the substituent constant was not proper. The author assumed that 'the σ^* constants describe both the inductive and the resonance effects of the substituent', and did not even try to correlate the values of the activation free energies with other types of constants, such as σ or σ^0, which are those most commonly used in correlations for amidines containing a substituted phenyl ring at the imino nitrogen atom[122–124]. The activation energies for N^2-phenylacetamidines[119] appeared to be approximately 10 kJ lower than for the corresponding formamidines[121]. However, *ab initio* calculations by the same author and coworkers[125] indicated that the barrier height is nearly the same for formamidines and acetamidines. It was concluded that this 'should be explained as being mainly due to effects other than electron donation from C_FCH_3'.[125] It seems quite probable that this discrepancy is due to hydrogen bonding between the amidine and the water molecules present in a small quantity in the deutériated acetone, because in the experimental section of all the papers by the author[119–121] the problem of solvent purity was not even mentioned.

IV. INFRARED SPECTRA

A. Amidines

Analysis of IR spectra was the best method for investigating the structure of tautomers until the development of more convenient spectroscopic methods, such as ^{13}C and ^{15}N NMR spectroscopy. IR spectra were, and still are, particularly applicable to studies of tautomerism in monosubstituted amidines and to investigations of hydrogen bonding.

(83) (84)

In monosubstituted open-chain (**83**) and cyclic (**84**) amidines the two tautomeric forms are called imino form and amino form, depending on the bonding of the unsubstituted nitrogen atom. These two forms are well differentiated in the IR spectra.

Amidines are regarded as derivatives of amides, where the oxygen atom is replaced by nitrogen; thus in their IR spectroscopy similar terminology is applied. However, it must be mentioned that this terminology is not in general use and some small but confusing differences are encountered. Prevoršek[126,127] considered two bands as the Amidine I band: $\nu_{as}(N{=}C{-}N) \sim 1640\,cm^{-1}$ and $\nu(C{=}N) \sim 1615\,cm^{-1}$, whereas Sieveking and Lüttke[103] mentioned only the $\nu(C{=}N)$ band at 1680–1600 cm^{-1}.

The characteristic absorptions for open-chain amidines were assigned by analogy of structural fragments to primary and secondary amines and imines, and for cyclic amidines to lactams (Table 40 and 41).

The most informative parameter for determining the tautomeric structure of monosubstituted amidines are the NH stretching vibrations ν(NH), because for monomeric species each type of vibration occurs in a separate region not overlapping other vibrations. Thus, the absorptions are characteristic for a given tautomeric structure. The frequency of the Amidine I band (i.e. the C=N stretching vibration) ν(C=N) is not related in a straightforward manner to the structure of cyclic amidine, because it depends on two opposite effects. For the endocyclic C=N bond it is lower than for the exocyclic one, but on the other hand alkyl substitution on the ring nitrogen atom results in an increase of the C=N frequencies in the imino form and a decrease in those of the amino form.

TABLE 40. IR absorption regions (cm^{-1}) for monosubstituted amidines

	Range				
	open-chain amidines		cyclic amidines		
Vibration	amino form	imino form	imino form	amino form	associate
$\nu_{as}(NH_2)$	3515–3497	—	3540–3490	—	3490–3440 3360–3300
ν(NH sec.)	—	3450–3446		3400–3420	
ν(=NH imino)	—	3332–3305	—	3370–3250	
$\nu_s(NH_2)$	3415–3396[b]	—	3420–3390	—	3200–3000
ν(C=N), Amidine I	1615–1601[b]	—	1680–1600	1680–1600	1650–1630
ν_{as}(N=C—N)	1652–1640[a]	—			
$\delta_s(NH_2)$, Amidine II	1597–1589[c]	—	1610–1580	—	1670–1650 1630–1605
δ(>NH sec.), Amidine II	—	1525–1505[d]	—	1410–940[e]	1420–1385
ν(C—N), Amidine III	~1290		1450–1350	1310–1200	
δ(=NH, imino)	—		—	1450–1050	
$\gamma_{as}(NH_2)$, twisting			~1250?	—	
γ(=NH)	—		—	900–850	
$\delta_{as}(NH_2)$, ρ, rocking		—	~1100	~1100	990–965
$\gamma_s(NH_2)$, wagging		—	~600	—	

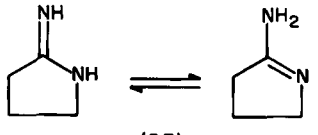
[a] 1656–1627 cm^{-1} in the solid state.
[b] 1610–1588 cm^{-1} in the solid state.
[c] 1610–1544 cm^{-1} in the solid state.
[d] 1571–1540 cm^{-1} in the solid state.
[e] uncertain

TABLE 41. IR absorption regions (cm^{-1}) for *N,N'*-disubstituted amidines[126,127,151]

Vibrations	In solution	In the solid state
ν(NH sec.)	3448–3350	3290–3115
ν(C=N), Amidine I	1655–1633	1647–1620
δ(>NH sec.), Amidine II	1519–1505	1550–1531
ν(C—N), Amidine III	1450–1350	
ν(N—R)	1210	1220
γ(NH)	900–600	

The Amidine II band, i.e. the in-plane bending vibrations, $\delta(NH_2)$, in a cyclic amidine is also not informative, because characteristic frequencies for the imino and amino form have not been found yet. The ranges of Amidine I and Amidine II bands are overlapping. The structure–frequency relations for the remaining amidine bands are not known well enough to be useful for the structure determinations[103].

Investigations into the IR spectra of cyclic amidines **85–88** have shown that these amidines exist in the solid state, as well as in solutions, in the amino form. However, the characteristic group frequencies depend strongly on the solvent and concentration, i.e. on the degree of association (cf Table 42).



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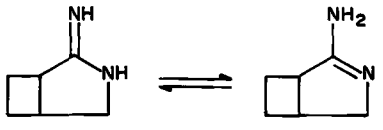

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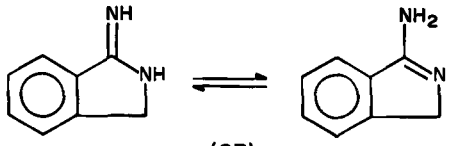

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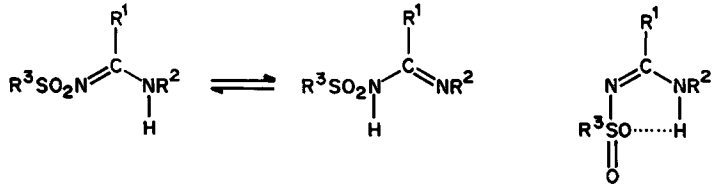
TABLE 42. Characteristic IR absorption bands (in cm^{-1}) for monomeric cyclic amidines[a] and their associates[b] with chloroform[103]

Compound	Solvent	$\nu_{as}(NH_2)$	$\nu_s(NH_2)$	ν(C=N)	$\delta_s(NH_2)$	ν(C—N)
85	C_2Cl_4	3507	3405	1661	1590	1383
85	$CHCl_3$	3513	3410	1655	1596	1392
86	C_2Cl_4	3504	3403	1648	1590	1384
86	$CHCl_3$	3513	3408	1643	1594	1393
87	C_2Cl_4	3503	3404	1632	1591	1407
87	$CHCl_3$	3508	3408	1633	1592	1412
88	C_2Cl_4	3496	3392	1673	1587	1380
88	$CHCl_3$	3506	3402	1667	1597	1384

[a]0.01 M solutions in 1,2-dichloroethene.
[b]0.01 M solutions in chloroform.

The spectra of the monodeuteriated amino group show that formation of the hydrogen bonds decreases the frequency by *ca* 400 cm^{-1} for CH and by *ca* 250 cm^{-1} for CD vibrations. Hydrogen bonding between the ring nitrogen atom and the hydrogen atom of chloroform causes a discernible shift of all bands characteristic for the amidines[103,128].

IR spectra of sulphonylbenzamidines[129] provided evidence for the predominance of the tautomer containing a sulphonyl group at the imino nitrogen atom **89a**.



(**89a**) (**89b**) (**89c**)

The NH stretching vibration region in the IR spectra of N-substituted *N'*-sulphonylbenzamidines in solution (with the exception of *N-tert*-butyl derivatives) showed one sharp weak band, and one broad strong band, which displayed only little changes of frequency or relative intensity upon dilution. The persistence of the broad band upon dilution indicated the presence of a strong intramolecular hydrogen bond, and provided evidence that these amidines exist predominantly as the *Z* isomers, since only this isomer is capable of such hydrogen-bond formation (cf. **89c**). Additional evidence for the *Z* configuration was provided by the cyclization capability of the iodomethyl derivative ($R^3 = CH_2I$). The weak absorption band is probably due to a low concentration of the *E* isomer.

The IR spectra of the *N-tert*-butyl derivatives, which for steric reasons cannot exist as the *Z* isomers, are markedly different in that the NH doublet observed for concentrated solutions collapsed to a sharp single band upon dilution, thus indicating that there is only intermolecular hydrogen bonding. It is noteworthy that, in addition, the *tert*-butyl derivatives are not capable of cyclization.

It seems obvious that in monosubstituted amidines the substituent at the nitrogen atom influences the tautomeric equilibrium. For monosubstituted *N*-arylbenzamidines this influence was studied by means of the IR spectra[130]. It was found that substituents like Me, OMe, OEt, NMe_2 and Cl in the *para*, *meta* and *ortho* position in the *N*-phenyl ring have little effect on the tautomeric equilibrium.

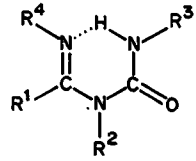
In the spectra of the amidines recorded in CCl_4 solutions, the following characteristic bands were observed: $\nu_{as}(NH_2)$ at 3525 cm^{-1}, $\nu_s(NH_2)$ at ~ 3410 cm^{-1} and ν(C=N) at ~ 1650 cm^{-1}. No absorption was observed in the $\nu(\geq NH)$ region at 3300–3005 cm^{-1}. This shows that *N*-arylbenzamidines exist in the amino form, i.e. that the aryl ring is at the imino nitrogen atom.

It is well known that amidines containing at least one hydrogen at the nitrogen atom, i.e. monosubstituted, *N,N'*-disubstituted and unsubstituted amidines, may form intermolecular or intramolecular hydrogen bonds[1]. IR spectroscopy is a very convenient tool for the detection of such hydrogen bonds. As a result of hydrogen-bond formation new bands appear at lower frequencies. Intramolecular and intermolecular hydrogen bonds are easily distinguished because the latter weaken or even disappear upon dilution with a solvent incapable of hydrogen-bond formation.

It is evident that substituents at both nitrogen atoms or at the amidino carbon atom that influence the basicity of the amidine also influence the strength of the hydrogen bond.

As the measure of an intramolecular hydrogen-bond strength in a series of carbamoylamidines **90**, the difference between the $\nu(\geq NH)$ frequency (3410 cm^{-1}) in an

amidine which cannot form an intramolecular hydrogen bond and amidine **90** was taken[131].



(90)

On the basis of these differences, amounting up to 700 cm^{-1} (Table 43), it was found that substituent R^1 at the amidino carbon atom exerts a very strong influence on the possibility of formation of an internal hydrogen-bonded bridge. Large substituents such as *t*-Bu and *i*-Pr cause the highest steric interference with neighbouring substituents R^2 and R^4, and in such cases intramolecular hydrogen bonding was not observed.

The influence of substituents R^2 and R^4 at the amidino nitrogen atoms is much smaller, because replacement of a methyl by a cyclohexyl group at either nitrogen of the amidino group (**90h** *vs* **90p** and **90q** *vs* **90w**; Table 43) or by a phenyl (**90q** *vs* **90v**) resulted in relatively small changes in the ν(NH) frequency.

Further conclusions can be drawn on the basis of these data. It seems obvious that the strength of the hydrogen bond depends mainly on the polar effects of the substituents at

TABLE 43. Changes in the ν(NH) frequency in amidines **90**[131]

	R^1	R^2	R^3	R^4	ν(NH) (cm^{-1})	Δν (cm^{-1})
a	Ph	Me	Me	Me	3472	+32
b	*t*-Bu	Me	4-ClC_6H_4	Me	3441	+1
c	*i*-Pr	Me	4-ClC_6H_4	Me	3440	0
d	H	Me	Me	Me	3200	−240
e	H	Me	Ph	Me	3040	−400
f	H	Me	4-ClC_6H_4	Me	3000	−440
g	H	Me	4-$O_2NC_6H_4$	Me	2940	−500
h	Me	Me	Me	Me	3100	−340
i	Me	Me	Ph	Me	2860	−580
j	Me	Me	4-ClC_6H_4	Me	2810	−630
k	Me	Me	4-$O_2NC_6H_4$	Me	2775	−665
l	Me	Me	C_6Cl_5	Me	2775	−665
m	Me	Me	$SO_2C_6H_5$	Me	2720	−720
n	Ph	Me	Me	Me	3145	−295
o	Ph	Me	Bu	Me	3140	−300
p	Ph	Me	c-Hex	Me	3140	−300
q	Ph	Me	Ph	Me	2880	−560
r	Ph	Me	1-Naph	Me	2860	−580
s	Ph	Me	4-ClC_6H_4	Me	2840	−600
t	Ph	Me	3-ClC_6H_4	Me	2830	−610
u	Ph	Me	4-$O_2NC_6H_4$	Me	2790	−650
v	Ph	Me	Ph	Ph	2980	−460
w	Ph	Me	Ph	c-Hex	2885	−585
x	Ph	c-Hex	Ph	c-Hex	2845	−595
y	Me	Et	Ph	Et	2820	−620
z	Et	Me	4-ClC_6H_4	Me	2800	−640

the proton-donating and proton-accepting sites. At the proton-accepting site, i.e. the imino nitrogen atom, the bond will be strengthened by electron-donating substituents which increase the basicity, and at the proton-donating site by electron-accepting substituents R^3 which increase the acidity of this proton (i.e. will strengthen the bond). Recently it was shown that polar effects of substituents at various sites of the amidine group can be enhanced or diminished by substituents at other sites[66,67,122–124,132]. The data in Table 43 provide good support for this reasoning.

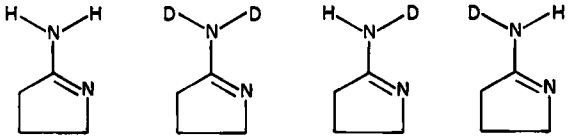
N-Acyl-formamidines (R^1 = H),-acetamidines (R^1 = Me) and -benzamidines (R^1 = Ph) can be regarded as a separate series. It is immediately seen that for each of these series the shift of the ν(NH) frequency, and thus the strength of the intramolecular hydrogen bond, increases with the increase in the electron-withdrawing ability properties of the substituent R^3 at the protonation site. Moreover, in each series four compounds with the same substituent R^3, namely Me, Ph, 4-ClC_6H_4 and 4-$O_2NC_6H_4$, were studied. These are: d, e, f, g for formamidines, h, i, j, k for acetamidines and n, o, p, q for benzamidines. It was found[133] that the Δ values for formamidines and benzamidines correlate very well with those for acetamidines, giving the following regression parameters:

$$\Delta\nu(\text{formamidines}) = 19.87 + (0.75 \pm 0.35)\Delta\nu(\text{acetamidines}) \qquad r = 0.998$$

$$\Delta\nu(\text{benzamidines}) = 71.60 + (1.08 \pm 0.13)\Delta\nu(\text{acetamidines}) \qquad r = 0.999$$

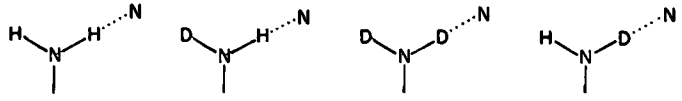
Although the regressions involve an insufficient number (only four) of experimental points, the differences between the calculated and experimental $\Delta\nu$ values, being $< 23\,cm^{-1}$ for a range of $260\,cm^{-1}$, indicate that the strength of a hydrogen bond indeed depends on polar effects of the substituent, and shows that polar effects of a substituent at one site depend on the substituent at another site of the amidino group.

For monodeuteriated cyclic amidines it was found[103] that the stretching frequency of the C—H or C—D bond depends on the *sp* or *ap* conformational orientation (in the work it was referred to as *cis* or *trans*) of this bond with respect to the ring nitrogen atom as shown below.



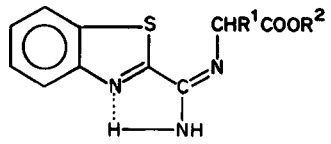
$\nu_{as}(cm^{-1})$: 3513	2688	*ap*: 3475	*sp*: 3450
$\nu_{as}(cm^{-1})$: 3410	2489	*sp*: 2535	*ap*: 2565

Monodeuteriation also influences the frequency of the hydrogen-bonded NH groups[103].

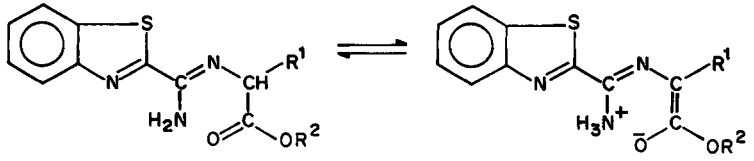


free (cm^{-1}): 3451	2567	2539	3445
H-bonded (cm^{-1}): 3050	3050	2280	2280

In general, IR spectra are not applicable for determination of the *syn vs anti* isomerism of amidines, but in specific cases they might provide indirect evidence on the existence of *E* or *Z* configuration. The IR spectra of 2-benzothiazolylamidines **91** are a good example of such specific application[102].



(91a) *E* isomer



(91b) *Z* isomer (91c)

The *E* isomer can form an intramolecular hydrogen bond between the amidino NH_2 group and the nitrogen atom of the benzothiazolyl moiety. As a result the ν(NH) frequencies observed (3260 and 3390 cm^{-1}) are lower than for other open-chain monosubstituted amidines (cf Table 40). The authors have found that the *Z* isomer exists in enolate form (91c), and that enolization of the *E* isomer is not detectable.

The protonation site in amidines was also studied by means of IR spectra[76]. Comparison of characteristic frequencies for trisubstituted formamidines $R^1N{=}CH{-}N(Me)R^2$ with those for their salts provided further evidence that protonation occurs at the imino nitrogen atom. The decrease of the C=N bond order, resulting from protonation at the imino nitrogen atom, causes considerable decrease of the ν_{as}(N=C—N) and ν(C=N) bands (40–70 and 14–31 cm^{-1}, respectively) as shown in Table 44.

A similar shift of the ν(C=N) band upon protonation was observed for N^1,N^1-dimethyl-N^2-(1-antraquinono)formamidines[134]. However, as a result of an intricate discussion of their IR and UV spectra the authors reached a rather surprising conclusion that in this case protonation occurs at the amino nitrogen.

Changes in the electron density and bond order in amidines resulting from substituents at the three sites of the amidino group cause not only variations in the ν(C=N) and ν(C—N) frequencies, but also in the pK_a values of amidines. Thus, attempts at a correlation of the ν(C=N) with the pK_a values for some trisubstituted formamidines and methacrylamidines have been made[135].

TABLE 44. Characteristic IR absorptions (in cm^{-1}) for trisubstituted formamidines $R^1C_6H_4N{=}CH{-}N(Me)R^2$ and their salts[76]

R^1	R^2	Base	Salt	Base	Salt
4-NO_2	Me	1635	1710	1576	1605
4-NO_2	Ph	1631	1685	1575	1600
H	4-$O_2NC_6H_4$	1639	1688	1588	1602
4-NO_2	4-$MeOC_6H_4$	1630	1668	1580	1598
4-OMe	4-$O_2NC_6H_4$	1630	1688	1592	1615
H	4-NCC_6H_4	1635	1685	1590	1605
4-CN	H	1636	1685	1584	1610

TABLE 45. Characteristic IR absorption of amidinopenicillins[a]

R^1	R^4	ν(C=N)	ν(C=O) β-lactam	ν(C=O) COOH	ν(C=O) COOX	Ref.
H	H	1695–1680	1770–1760	1610–1600	—	41
SO_2Y[b]	$CH_2OCOCMe_3$	1685–1675	1785–1775	—	1765–1740	104
Me	H	1685–1665	1775–1770	1620–1605	—	42
Ph	H	1675–1665	1775–1770	1620–1615	—	42
$PhCH_2$	H	1670–1660	1775–1765	1610–1605	—	42
$PhCH_2$	$CH_2OCOCMe_3$	1680	1780	—	1745	105
H	CH_2COMe	1620	1775	—	1740	107

[a]In KBr pellets.
[b]Y = Ph or 4-MeC_6H_4.

It was found that the ν(C=N) values (in cm^{-1}) recorded for the salts are related to the pK_a values by the following relations: Acetamidines (4 experimental points).

$$pK_a^T = 248.5 - 0.145\nu(C{=}N) \qquad r = 0.999$$

Methacrylamidines (6 experimental points),

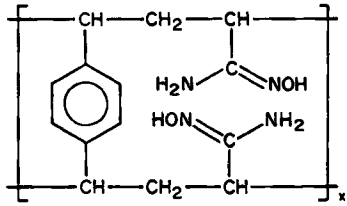
$$pK_a^T = 405.8 - 0.249\nu(C{=}N) \qquad r = 0.985$$

It was concluded that such relations can be applied for determination of pK_a values for insoluble amidines, and in this way the pK_a value for one methacrylamidine was calculated. However, it must be kept in mind that any vibration frequency depends to a considerable degree on the mass of the substituents[136]. For example, the mass of the substituent R^3 is varied by 45% only when phenyl is replaced by chlorophenyl, but by 90% when ethoxycarbonyl replaces phenyl. This probably contributes to the difference of 0.4 pK_a units between calculated and experimental pK_a values. Similar[72] and even higher deviations are encountered also for other series of amidines. Although such relations are of some theoretical value and require extensions, they are not recommended as a method of pK_a determination.

IR spectra have been regarded as the most convenient tool for routine analysis of amidinopenicillins[41,42,104,105,107]. These β-lactam antibiotics undergo degradation very easily and the β-lactam ν(C=O) band disappears whereas other frequencies are discernibly shifted. However, it was shown that the absorption regions of characteristic groups do not overlap (Table 45). Few other drugs containing the amidino group, such as lidamidine[18] and *N*-phenyl-*N'*-*tert*-butyl-3-propanamidine[100], were also characterized by IR spectra.

B. Amidoximes

Characteristic frequencies for the amidoxime group, exemplified by 3,5-disubstituted 4-isoxazolylamidoximes[137] and 2-pyridineamidoximes[138], are given in Table 46. The



(92)

TABLE 46. Characteristic IR absorptions (in cm^{-1}) of 4-isoxalylamidoximes and 2-pyridylamidoximes

Vibration	4-Isoxazolylamidoximes[137]	Pyridylamidoximes[138]
$\nu_{as}(NH_2)^a$	3390–3610	3356[b]
$\nu_s(NH_2)$	3190–3920	3356
ν(C=N)	1630–1660	1633
ν(N—OH)	900–950	950
δ(N—O)	790–795	—

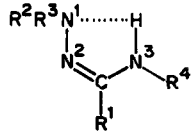
[a]For all other compounds the $\nu_{as}(NH_2)$ vibration is at a higher frequency than $\nu_s(NH_2)$; the reason why the assignments are reversed in this particular case is not discussed by the authors.
[b]Broad.

structure of a resin **92**, used for concentrating various metals present in aqueous solutions in trace amounts, was determined[139] by using IR spectroscopy.

In addition to the characteristic frequencies for other groups present in the resin, the following amidoxime frequencies were observed: $\nu(NH_2)$ at 3400 cm^{-1}, broad ν(OH) at 3325 cm^{-1}, broad ν(C=N) at 1650 cm^{-1} and broad ν(N—OH) at 900 cm^{-1}.

C. Amidrazones

For N^1,N^1-disubstituted and N^1,N^1,N^3-trisubstituted amidrazones **93** hydrogen bonding was observed in the IR spectra[1c,140]. In dilute CCl_4 solutions two absorption bands are observed in a range which depends on the substitution of the amidrazone group. When the substituent R^4 at N^3 is a hydrogen atom, and R^1, R^2 and R^3 are alkyl or aryl groups, the ν(NH) absorption bands appear in the region of 3493–3475 cm^{-1} and 3424–3375 cm^{-1}. When N^1 carries a hydrogen, the absorption bands are at 3475–3410 cm^{-1} and 3375–3297 cm^{-1}, respectively.



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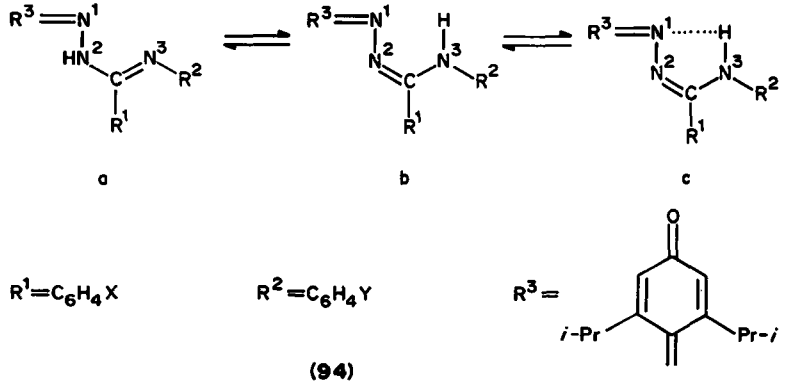


(94)

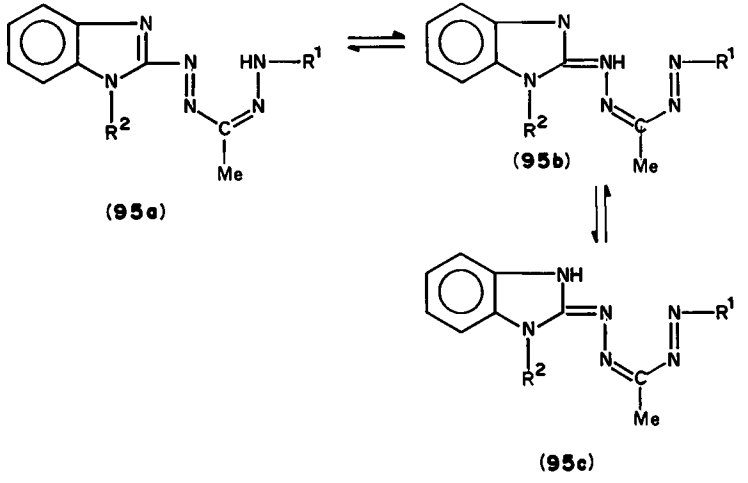
In the IR spectra of amidrazone derivatives of 2,6-diisopropyl-1,4-benzoquinone (**94**) three ν(NH) absorption bands are observed in the regions 3468–3411 cm^{-1}, 3368–3281 cm^{-1} and 3228–3215 cm^{-1}, respectively. The authors assumed[141] that the first region is due to form a, the second to form b and the third to form c having an intramolecular hydrogen bond.

In *E*-1,1,3,3-tetra-substituted amidrazones it was found[87] that the ν(C=N) band appears in the 1650–1660 cm^{-1} region.

D. Formazans

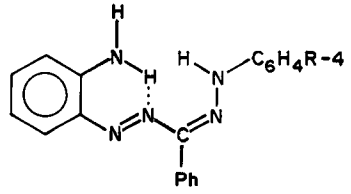
For formazans containing benzazolyl or pyrimidinyl groups it was shown[142–144] that the ν(NH) stretching vibrations are in the 3450–3420 cm^{-1} region for a free secondary amino group, and at 3360–3330 cm^{-1} for an intramolecular hydrogen bonded one. This band occurs at lower frequencies[46] if the nitrogen is substituted by an electron-withdrawing substituent. Such a frequency shift caused by substitution can be explained in the same way as for the case of hydrogen bonds in amidines (*vide supra*). It is obvious that the intramolecular hydrogen bond can be formed only if the compound has an appropriate configuration and conformation. Thus, in formazans containing bulky substituents at the nitrogen atoms of the amidrazone group, steric hindrance prevents the formation of a planar conformation and an intramolecular hydrogen bond in such cases is not observed[48].

In the case of *N*-(2-benzimidazolyl)formazans (**95**), in addition to the two usual tautomeric forms **95a** and **95b** a third one, called an 'imino form' by the authors, may exist.



In CCl_4 solutions only a ν(NH) absorption of a free secondary amino group in the region 3441–3427 cm^{-1} is observed. It was therefore concluded that these formazans exist in an 'imino form' **95c**. In $CHCl_3$ solutions, however, a weak band in the 3336–3286 cm^{-1} range also appears, and it was concluded that in this solvent intramolecular hydrogen bonding occurs. Consequently formazans exist in either of the two tautomeric forms **95a** and **95b**, because intramolecular hydrogen bonding is possible for these forms only[145]. Analogous results were obtained for other related formazans[108]. The reason why intramolecular hydrogen bonding occurs in $CHCl_3$ solutions but not in CCl_4 was not discussed.

In the IR spectra of *N*-(2-aminophenyl)-3-phenyl-*N'*-arylformazans (**96**) three ν(NH) bands of practically constant frequencies of mean values $3488.7 \pm 1.6\ cm^{-1}$, $3397.8 \pm 0.9\ cm^{-1}$ and $3302.8 \pm 0.6\ cm^{-1}$ were observed[92]. These bands were assigned respectively to the $\nu_s(NH_2)$, $\nu_{as}(NH_2)$ and ν(NH) vibrations of the hydrogen-bonded NH group. On this basis the authors concluded[92] that these formazans do not form intermolecular hydrogen bonds but exist in the form **96**. However, for compounds of structure **96** four absorption bands are expected, namely $\nu_s(NH_2)$, $\nu_{as}(NH_2)$, $\nu(N^5H)$ and a band for hydrogen-bonded NH_2. The reason why only three of them are observed was not discussed.



(96)

E. Complexes

The IR spectra of imidic acid derivatives reported in the literature can be divided in general into three groups depending on the type of the complex. The first group comprises collision complexes with proton-donating compounds. In such complexes, as a rule, a ν(X—H) frequency of the proton-donating compound is observed, and only little attention, if any, is paid to the characteristic frequencies of the imidic acid derivative itself. The second group includes complexes with various metal complexes, mainly metal carbonyls. In them attention is paid to the ν(C=O) frequencies, and the spectra are used mainly for analytical purposes. Sometimes the IR spectra of such complexes demonstrate that the CO groups have different spatial orientation. However, in some works the frequencies characteristic for the complexed amidine are given[137]. The third group includes boron complexes of amidines.

1. Complexes with proton-donating compounds

For complexes of N^1,N^1-dimethyl-N^2-arylformamidines with ethanol and substituted phenols it was found[146] that the ν(OH) frequencies depend on the polar effects of the substituents in the phenyl ring, and that the difference ($\Delta\nu$) between the frequencies in the complexed and uncomplexed molecule correlate with Hammett σ constants, as expressed by equation 22.

$$\Delta\nu(X—H) = a \cdot \sum\sigma + b \tag{22}$$

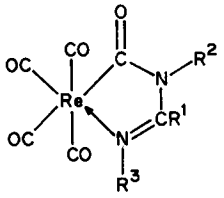
For ethanol $a = 53.7$ and $b = 300$ ($r = 0.96$).

Complexes of various series of amidines with $CDCl_3$ were studied by measuring the C—D stretching frequency. It was found[65] that in solutions of amidines in $CDCl_3$, in addition to the 1:1 complexes, other complexes containing more than one $CDCl_3$ molecule are formed. Recently it was found[128] that for $CDCl_3$ complexes with N^1,N^1-dimethyl-N^2-substituted phenylformamidines, the $\Delta\nu$(C—D) values correlate well with Hammett-type constants of substituents, and that the regression coefficient a depends to a considerable degree on the substitution at the amidino carbon atom. Preliminary results indicate that it increases on increasing the electron-donating properties of this substituent. It should be

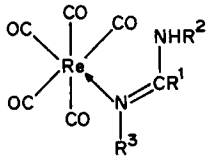
noted that these changes are similar to those observed for the σ values in correlations of the pK_a values of amidines with σ constants (cf the chapter on basicity).

2. Complexes with metal carbonyls

N,N'-Diphenylformamidines, acetamidines and benzamidines form with $Re(CO)_5X$ and $[Re(CO)_4X]_2$ two types of complexes, **97** and **98**, depending on the reaction conditions[147].



(97)

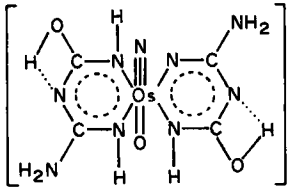


(98)

It was known that in complexes where the carbonyl ligand is bonded only to one metal atom (referred to as the terminal carbonyl group) the ν(C≡O) frequencies are in the 2100–1900 cm^{-1} region, depending on the metal and its substituents[148].

For complexes **97** a typical pattern of terminal C≡O groups is observed in the 2108–2020, 2022–1994, 1987–1967 and 1948–1913 cm^{-1} regions, in addition to the carbamoyl CO group at 1675–1650 cm^{-1}. The absorptions at 1583–1569 cm^{-1} assigned to ν_{as}(N—C—N) are approximately at 40–50 cm^{-1} lower frequencies than in the parent amidines. For complexes **98** four terminal CO bands are also observed, but a ν(NH) band at *ca* 3320 cm^{-1} also appears, indicating that the amidine is acting in the complex as a two-electron donor and is retaining the NH group.

Nitrido complexes of osmium of the type $[OOsN(L)_2]OH \cdot H_2O$, where L are various *N*-amidinoisoureas, have been investigated by means of IR spectroscopy[149]. In the free ligand the bands in the 3350–3180 cm^{-1} region are very broad, and they are assigned to the stretching vibrations of the free and hydrogen-bonded NH_2 and NH groups. In the complexes a discernible shift of one of these bands to *ca* 3145 cm^{-1} indicates coordination to the metal atom. The ν(N—C—N) band in a free ligand (1680 cm^{-1}) is shifted appreciably to lower frequencies (1650 cm^{-1}) and this shift was attributed by the authors to appreciable π-bonding between the metal and the ligand. The new band appearing in the 1260–1250 cm^{-1} range was assigned to the chelate ring vibrations. The absence of the band at 1340 cm^{-1} indicated that the amidinourea in a complex is completely enolized. Absorption bands at 1025 cm^{-1} and 900–800 cm^{-1} are assigned to the ν(Os≡N) and ν(Os=O) vibrations, respectively. On this basis structure **99** was suggested for the complex.

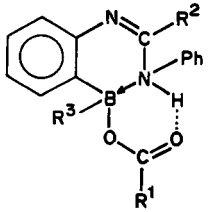


(99)

Complexes of the type $LZnCl_2$ (I) and L_2Zn (II), where L is a symmetrical 1,5-di-(1-alkylbenzimidazolyl-2)-3-alkyl formazan ligand, have been studied. In the complex the ν(NH) band (at 3840 cm^{-1} for the imino form) disappears and the ν(C=N) band (at 1670 cm^{-1}) is shifted to lower frequencies by about 40–50 cm^{-1} for type I and 75–80 cm^{-1} for type II complexes.

3. Boron complexes

In the complexes of acyloxyboranes with amidines **100**, five sharp bands at 3300, 3240, 3200, 3160 and 3135 cm^{-1} were observed[150] in the ν(NH) absorption region. Neither dilution nor heating of the sample up to 70–80 °C result in changes of the absorption pattern in this region. The appearance of the absorption in this region was attributed to Fermi resonance between the ν(NH) and δ(NH) overtones. In compounds **100** the ν(C=O) band of acylborane of 1680 cm^{-1} is shifted to the 1675–1650 cm^{-1} region, thus indicating the presence of a C=O···HN bonding.



(100)

V. ULTRAVIOLET AND VISIBLE SPECTRA

A. Amidines

In the electronic (UV-VIS) spectra of amidines, reported in the literature, the absorption is due to the aromatic moiety of the molecule and spectra are mainly given for characterization of the compound[76,130]. Only in a few cases were the UV-VIS spectra used in connection with the NMR or IR spectra as an additional tool for structure determination[134,152,153]. The ease of measurements and the sensitivity of the method make it a readily applicable method in quantitative determinations. It is noteworthy that changes in the UV spectra are used in pK_a determinations. For several amidines, UV absorption was applied for detection and quantitative determination in HPLC analysis[32,33]. In some cases UV spectroscopy was applied for investigations on $E \rightarrow Z$ isomerization, e.g. for N^1,N^1-dimethyl-N^2-phenylformamidine: in aqueous solutions at 305 nm the absorption of the Z isomer is much higher than that of the E isomer[15] enabling one to follow the reaction course. Similar investigation were carried out for amidoximes[154] and amidrazones[89].

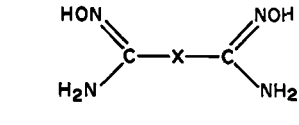
For trisubstituted amidines in acetonitrile solutions λ_{max} is in the region 246–378 nm with log ε in the range 4.22–4.34. For the hydrochloride salts a batochromic shift is observed, but if electron-donating substituents are attached to the nitrogen atoms this shift is about 10–20 nm, whereas in the case of electron-withdrawing substituents it is considerably higher, about 30–70 nm[76].

B. Amidoximes

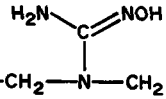
The influence of the pH value on the spectra of 3,5 disubstituted 4-isoxazolylamidoximes in water and water–ethanol mixtures has been investigated[137].

Although not much attention has been paid to the UV-VIS spectra of free amidoximes, the spectra of their complexes have been studied on account of their expected analytical and industrial applications. The spectra of complexes of ML_2X_2 type, where L is 2-pyridine-2 amidoxime, M is Cu^{+2}, Ni^{+2}, Co^{+2}, Fe^{+2} and Mn^{+2} whilst X = Cl, Br, NO_3, ClO_4 and OH have been studied and used for determining the structure of the complexes[138].

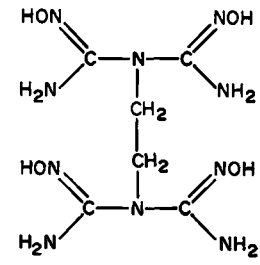
Numerous polyamidoxime–metal (mainly Cu^{2+}) complexes were studied. As polyamidoximes 3,3′-imino-, 3,3′-dioxy-, 3,3′-thiodipropionamidoxime, α,α′-azo-bis(isobutyramidoxime), nitrilotriacetamidoxime and ethylenediaminotetraacetamidoxime (**101** and **102**) were used.



(a) X = —$(CH_2)_2NH(CH_2)_2$—
(b) X = —$(CH_2)_2O(CH_2)_2$—
(c) X = —$(CH_2)_2S(CH_2)_2$—
(d) X = —$(Me)_2CN{=}NC(Me)_2$—



(101)



(102)

TABLE 47. UV-VIS absorption for complexes of amidoximes with some metals[155]

Metal	Amidoxime	λ_{max} (nm)	
Cu^{2+}	**101b**	740	
Cu^{2+}	**101a**	610	
Cu^{2+}	**101d**	605	
Cu^{2+}	**101c**	500	
Cu^{2+}	**101e**	710	
Cu^{2+}	**102**	690	
Fe^{2+}	**101b**	645	750[a]
Fe^{2+}	**101c**	615	770[a]
Fe^{2+}	**101e**	380[b]	
Fe^{2+}	**102**	580[b]	
Co^{2+}	**101d**	650[c]	500[c]
Co^{2+}	**101c**	520	
Co^{2+}	**102**	505	
Ni^{2+}	**101c**	575	
Ni^{2+}	**101e**	425	
Ni^{2+}	**102**	435	

[a]Shoulder.
[b]Low absorption.
[c]Not well defined.

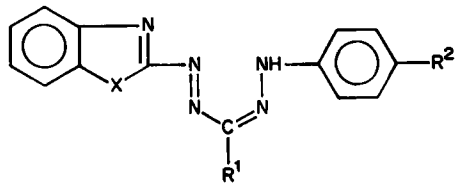
For all complexes the λ_{max} value depends mainly on the kind of metal and then on the heteroatom and on the substitution of the amidoxime[47,155] (Table 47).

C. Amidrazones

In the UV spectra of alkyl amidrazones $R^1R^2N^1N^2{=}C(Me)NR^3R^4$ (Table 48) an absorption band at 208–215 nm, $\lg \varepsilon = 3.33–3.51$, is observed. Substitution at the N^1 atom (hydrazine group) by a phenyl ring causes a bathochromic shift to 230–235 nm and an increase in molar absorption ($\lg \varepsilon = ca\ 3.90$). For hydrochlorides, a bathochromic shift of 12–20 nm with respect to the free bases and discernible decrease in the molar absorption is observed[87]. It is obvious that characteristic absorption bands for the phenyl ring also appear in the spectrum.

D. Formazans

Characteristic UV absorption of formazans **103** and their complexes with metals is summarized in Table 49. The λ_{max} value in the free base depends mainly on the type of substituents attached to the terminal nitrogen atoms[47,48,110,156]. In complexes it mainly depends on the type of metal atom[155].



(**103**) X=PhCH$_2$N,S,O

TABLE 48. Characteristic UV absorption of amidrazones $R^3R^4NC(CH_3){=}N^2N^1R^2R^1$ and their salts in water solutions[87]

				HCl salt		Free base	
R^1	R^2	R^3	R^4	λ_{max} (nm)	$\lg \varepsilon$	λ_{max} (nm)	$\lg \varepsilon$
H	H	H	H	209	3.51	223	3.51
Me	H	H	H	209	3.51	225	3.69
Et	H	H	H	208	3.42	226	3.58
n-Pr	H	H	H	208	3.33	225	3.72
i-Pr	H	H	H	210	3.52	224	3.74
t-Bu	H	H	H	208	3.51	224	3.72
Ph	H	H	H	228	3.96	234	3.82
				274	3.24	288	3.60
						309	3.50
Me	Me	H	H	207	3.47	225	3.49
Me	Ph	H	H	233	4.05	253	4.08
				272	3.24		
Me	Me	Ph	H	213	3.90	226	3.79
Me	Me	Me	Me	215	3.95	232	3.80
Me	Ph	Me	Me	235	4.14	222	4.24
				275	3.37	260	4.16

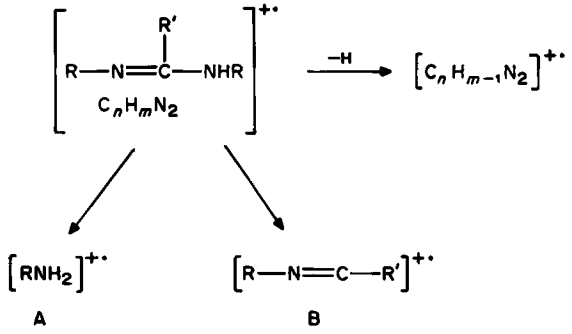
TABLE 49. UV–VIS absorption of formazans **103** and their complexes with metal ions[110]

			λ_{max} (nm)					
			Formazans		Complexes with metal ions			
X	R^1	R^2	Salt	base	Ni^{2+}	Zn^{2+}		Co^{2+}
NCH_2Ph	Ph	NO_2	554	628	678	666	680	710–760
NCH_2Ph	Ph	NMe_2	508	556	660	466	586	750–800
NCH_2Ph	Me	NO_2	522	628	674	568	422	700–750
NCH_2Ph	Me	NMe_2	510	548	652	520	584	750–800
S	Ph	NMe_2	586	608	676	668	670	690
S	Ph	NO_2	532	542	482	482	464	750–800
S	Me	NMe_2	510	510	546	486	550	670
S	Me	NO_2	500	554	670	528	610	750–800
O	Ph	NMe_2	472	574	660	640	560	670
O	Ph	NO_2	500	522	480	480	610	750–800
O	Me	NMe_2	456	566	640	516	540	655
O	Me	NO_2	476	526	640	640	596	750–800

VI. MASS SPECTRA

In the case of amidines and derivatives of imidic acids, which are usually synthetic or modified natural compounds, mass spectrometry is much less informative than other spectroscopic methods, and is not of much use for structure determination purposes. However, it is of some interest from the theoretical point of view. Therefore, the reports on mass spectra of amidines are not numerous.

The fragmentation pattern for eighteen unsubstituted and *N,N'*-disubstituted formamidines, acetamidines and pivalamidines have been studied[53]. From the fragmentation patterns presented for the *N,N'*-disubstituted amidines it can be concluded that the parent molecular ion undergoes initially a C—N bond cleavage, forming the ion radicals of the corresponding primary amine and imine (Scheme 1).



SCHEME 1. The initial fragmentation step for amidines

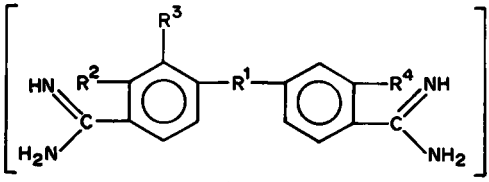
The most prominent peak in the spectrum for formamidines is the amine ion A, but for acetamidines and benzamidines the main peak is ion B formed by elimination of the amine

fragment. For all the amidines studied a prominent peak corresponding to the loss of one hydrogen atom was observed. Further fragmentation of the amine and imine ion radicals occurs according to the mechanisms presented in monographs on mass spectrometry. The fragmentations are further discussed in chapter 5.

VII. MISCELLANEOUS METHODS

A. Microchemical Methods

It was shown[157-161] that some drugs containing an unsubstituted amidino group can be identified as characteristic crystals formed on a microscale in reactions with reagents such as Reinecke salt, H_2PtCl_6, H_2PtCl_6 + NaBr, $HAuCl_4$, $HAuCl_4$ + NaBr, CdI_2 + HI, $NaHPO_4$, $K_3Fe(CN)_6$, $HgCl_2$, picric acid, 3,5-dinitrobenzoic acid, 5-nitrobarbituric acid or Dragendorf reagent. The method was applied to amidines used as antibacterial agents **104**, diuretical agents **105** and antihypertensive agents **106**. The microscope view and appearance of the crystal is given in detail by the authors.



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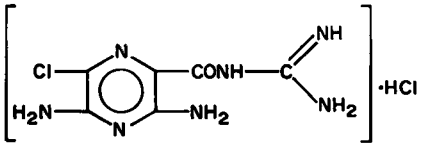

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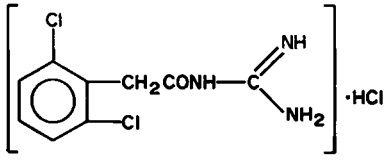

(106)

B. Microbiological Methods

A microbiological method for determination of amidinopenicillins using an agar plate diffusion technique was described. In this method Penassay agar[162] No 1, or impregnated discs[163], and the NCTC Esherichia coli 10418 as indicator organism were used. The method was standardized for determination of sensitivity level[164].

VII. ACKNOWLEDGEMENT

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IX. REFERENCES

1. W. H. Prichard, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, Chichester, 1975, pp. 157–185, (a) p. 159, (b) p. 165, (c) p. 171.
2. R. L. Shriner and F. W. Neumann, *Chem. Rev.*, **35**, 351 (1944).

3. J. Oszczapowicz, *Roczniki Chem.*, **44**, 453 (1970).
4. J. Oszczapowicz and R. Orliński, *Roczniki Chem.*, **44**, 2327 (1970).
5. J. Oszczapowicz and R. Orliński, *Roczniki Chem.*, **45**, 103 (1971).
6. J. Oszczapowicz, *Polish J. Chem.*, **52**, 1311 (1978).
7. H. Bredereck, F. Effenberger and A. Hoffmann, *Chem. Ber.*, **97**, 61 (1964).
8. M. Meerwein, W. Florian, N. Schonn and G. Stopp, *Justus Liebigs Ann. Chem.*, **641**, 1 (1961).
9. R. I. Fryer, J. W. Earley and L. M. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967).
10. H. E. Windberg, US Patent 3121064 (1964); *Chem. Abstr.*, **60**, 13197 (1964).
11. Yang I.-Ling and S. A. Lang jr., *J. Org. Chem.*, **44**, 4160 (1979).
12. W. J. A. Vandenheuvel and V. F. Gruber, *J. Chromatogr.*, **112**, 513 (1975).
13. N. Nose, S. Kobayashi, A. Hirose and A. Watanabe, *J. Chromatogr.*, **123**, 167 (1976).
14. H. Bredereck, F. Effenberger and H. Hajek, *Chem. Ber.*, **101**, 3062 (1968).
15. A. F. Hegarty and A, Chandler, *Chem. Commun.*, 130 (1980).
16. J. P. Thenot and E. C. Horning, *Anal. Lett.*, **5**, 519 (1977).
17. M. W. Scoggins, *J. Chromatogr. Sci.*, **13**, 146 (1975).
18. C. M. Won, J. J. Zalipsky, D. M. Patel and W. M. Grim, *J. Pharm. Sci*, **71**, 359 (1982).
19. E. Kováts, *Helv. Chim. Acta*, **41**, 1915 (1958).
20. L. S. Ettre, *Chromatographia*, **6**, 489 (1973).
21. J. Oszczapowicz, in *Similarity Models in Organic Chemistry, Biology and Related Fields*, Elsevier, Amsterdam (in press).
22. J. Oszczapowicz, J. Osek and E. Dolecka, *J. Chromatogr.*, **315**, 95 (1984).
23. J. Oszczapowicz, J. Osek, K. Ciszkowski, W. Krawczyk and M. Ostrowski, *J. Chromatogr.*, **330**, 79 (1985).
24. J. Osek, J. Oszczapowicz and W. Drzewiński, *J. Chromatogr.*, **351**, 177 (1986).
25. J. Oszczapowicz, J. Osek, W. Krawczyk and B. Kielak, *J. Chromatogr.*, **357**, 93 (1986).
26. J. Oszczapowicz, K. Ciszkowski and J. Osek, *J. Chromatogr.*, **362**, 383 (1986).
27. J. Osek, J. Jaroszewska-Manaj, W. Krawczyk and J. Oszczapowicz, *J. Chromatogr.*, **369**, 398 (1986).
28. J. Oszczapowicz, and M. Kumińska, in preparation.
29. J. Oszczapowicz, J. Jaroszewska-Manaj and B. Pojeć, in preparation.
30. M. Hanocq, R. Fuks and G. Lefebvre, *J. Pharm. Biomed. Anal.*, **1**, 211 (1983).
31. S. E. Massil, I. Ezra and E. Grushka, *J. Chromatogr.*, **439**, 476 (1988).
32. R. B. Hagel, E. H. Waysek and D. Humprey, *J. Chromatogr.*, **170**, 391 (1979).
33. R. B. Hagel and E. H. Waysek, *J. Chromatogr.*, **178**, 97 (1979).
34. N. Strojny and J. A. F. de Silva, *J. Chromatogr.*, **181**, 272 (1980).
35. C. Larsen and H. Bundgard, *Arch. Pharm. Chem. Sci. Ed.*, **5**, 1 (1977).
36. M. Paintz, M. Richter and J. Hauptmann, *Pharmazie*, **42**, 346 (1987).
37. B. Schönbach and E. M. Greenspan, *Medicine*, **27**, 327 (1948).
38. J. Oszczapowicz, E. Raczyńska and R. Orliński, *Polish J. Chem.*, **55**, 2031 (1981).
39. J. Oszczapowicz, E, Raczyńska and T. Pawlik, *Polish J. Chem.*, **58**, 117 (1984).
40. F. Lund and L. Tybring, *Nature*, **236**, 136 (1972).
41. I. Buśko-Oszczapowicz and J. Cieślak, *Acta Polon. Pharm.*, **30**, 43 (1973).
42. I. Buśko-Oszczapowicz, unpublished results.
43. E. Pawlak and Z. Gołucki, *Acta Polon. Pharm.*, **34**, 413 (1977).
44. H. Gonçalves F. Mathis and C. Foulcher, *Bull. Soc. Chim. France*, 2599 (1970).
45. N. A. Klyuyev, V. G. Zhil'nikov, C. G. Aleksandrov, I. I. Grandberg and G. N. Lipunova, *Zh. Org. Khim.*, **19**, 2615 (1983); *Chem. Abstr.*, **100**, 156139w (1984).
46. L. V. Shmelev, G. N. Lipunova, O. P. Sulim and N. P. Bednyagina, *Zh. Obshch. Khim.*, **56**, 2393 (1986).
47. T. I. Krivonogova, E. P. Darienko and G. N. Lipunova, *Zh. Obshch. Khim.*, **53**, 1163 (1983).
48. G. N. Lipunova, I. L. Sharova, E. C. Darienko, N. P. Bednyagina, G. N. Sigeikin and Yu. I. Aleksandrov, *Zh. Obshch. Khim.*, **53**, 178 (1983); *Chem. Absrt.* **98**, 198134 (1982).
49. J. Oszczapowicz, J. Jaroszewska-Manaj and I. Buśko-Oszczapowicz, in preparation.
50. E. Stahl, *Thin-Layer Chromatography*, Springer-Verlag, Berlin, 1969, p. 883.
51. H. Gozlan, R. Michelot, G. Riche and R. Rips, *Tetrahedron*, **33**, 2535 (1977).
52. D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
53. J. Barker, M. Jones and M. Kilner, *Org. Mass Spectrom.*, **20**, 619 (1985).
54. G. J. Martin, M. L. Martin and S. Odiot, *Org. Magn. Reson.*, 7, 2 (1975).

55. J. W. Emsley, J. Feeney and L. H. Sutcliffe, *High Resolution Nuclear Magnetic Resonance Spectroscopy*, Vol. 1, Chapter 9, Pergamon Press, Oxford, 1965.
56. F. W. Wehrli and T. Wirthlin, *Interpretation of Carbon-13 NMR Spectra*, Section 5, Heyden, London, Philadelphia, Rheine, 1978.
57. L. M. Jackman and T. Jen, *J. Am. Chem. Soc.*, **97**, 2811 (1975).
58. E. Ciszak, Doctoral Thesis, Adam Mickiewicz University, Poznań, Poland, 1988.
59. J. W. Krajewski, Z. Urbańczyk-Lipkowska, P. Gluziński, Ł. Lebioda, I. Buśko-Oszczapowicz and J. Cieślak, *J. Antibiotics*, **34**, 282 (1981).
60. J. W. Krajewski, Z. Urbańczyk-Lipkowska, P. Gluziński, I. Buśko-Oszczapowicz, J. Oszczapowicz, J. Bleidelis and A. Kemme, *Polish J. Chem.*, **55**, 1015 (1981).
61. J. Oszczapowicz, E. Tykarska, M. Jaskólski and Z. Kosturkiewicz, *Acta Crystallogr.*, **C42**, 1816 (1986).
62. K. Surma, M. Jaskólski, Z. Kosturkiewicz and J. Oszczapowicz, *Acta Crystallogr.*, **C44**, 1031 (1988).
63. A. Knychała, W. Rychlewska, Z. Kosturkiewicz and J. Oszczapowicz, *Acta Crystallogr.*, **C45**, 1047 (1989).
64. E. Ciszak, M. Gdaniec and Z. Kosturkiewicz, *Acta Crystallogr.*, **C43**, 1362 (1987).
65. R. Mierzecki, J. Oszczapowicz and G. Kozakowski, *Polish J. Chem.*, **53**, 1139 (1979).
66. J. Oszczapowicz, C. U. Regelmann and G. Häfelinger, *J. Chem. Soc., Perkin Trans. 2*, 1551 (1990).
67. G. Häfelinger, J. Oszczapowicz and F. K. H. Kuske, in preparation.
68. J. Oszczapowicz, W. Krawczyk, J. Osek and E. Raczyńska, *J. Chem. Res.* (*S*), 384; (*M*), 3975 (1985).
69. J. Oszczapowicz, E. Raczyńska and J. Osek, *Magn. Reson. Chem.*, **24**, 9 (1986).
70. J. N. Shoolery, Technical Information Bulletin, **2**, No 3, Varian Associates, Palo Alto, California, 1959.
71. A. Zschunke, *Kernmagnetische Resonanzspektroskopie in der Organische Chemie*, Akademie-Verlag, Berlin, 1972, (a) pp. 31–32, (b) pp. 35–36.
72. J. Oszczapowicz, unpublished results.
73. G. C. Levy and G. L. Nelson, *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*, Chapter 4, Wiley–Interscience, New York, 1972.
74. J. Oszczapowicz and I. Buśko-Oszczapowicz, in preparation.
75. J. Oszczapowicz and J. Jaroszewska-Manaj, in preparation.
76. Z. B. Kiro, Yu. A. Terenin, L. N. Nikolenko and B. I. Stepanov, *Zh. Org. Khim.*, **8**, 2573 (1972); *Chem. Abstr.*, **78**, 135210z (1973).
77. N. Naulet, M. L. Filleux, G. J. Martin and J. Pornet, *Org. Magn. Reson.*, **7**, 326 (1975).
78. V. V. Negrebetskii, L. Ya. Bogel'fer, A. D. Sinitsa, V. I. Kal'chenko and V. S. Krishtal', *Zh. Obshch. Khim.*, **51**, 1485 (1981); *Chem. Abstr.*, **95**, 186385 (1981).
79. V. V. Negrebetskii, L. Ya. Bogel'fer, A. D. Sinitsa, V. I. Kal'chenko, B. S. Krishtal' and L. N. Markovskii, *Zh. Obshch. Khim.*, **52**, 40 (1982); *Chem. Abstr.*, **96**, 162847 (1982).
80. V. V. Negrebetskii, L. Ya Bogel'fer, A. D. Sinitsa, V. I Kal'chenko, B. S. Krishtal' and L. N. Markovskii, *Zh. Obshch. Khim.*, **52**, 1496 (1982); *Chem. Abstr.*, **97**, 163118m (1982).
81. V. V. Negrebetskii, V. I. Kalchenko, R. B. Rudyi and L. N. Markovskii, *Zh. Obshch. Khim.*, **55**, 271 (1985); *Chem. Abstr.*, **103**, 37540x (1985).
82. V. V. Negrebetskii, V. I. Kal'chenko, R. B. Rudyi and L. N. Markovskii, *Zh. Obshch. Khim.*, **55**, 1982 (1985); *Chem. Abstr.*, **105**, 97559m (1986).
83. I. E. Mikhailov, V. I. Minkin, L. P. Olekhnovich, V. N. Boiko, V. N. Ignat'ev and L. M. Yagupol'skii, *Zh. Org. Khim.*, **20**, 454 (1984); *Chem. Abstr.* **101**, 71979r (1984).
84. N. E. Alexandrou and D. N. Nicolaides. *Org. Magn. Reson.*, **4**, 229 (1972).
85. V. A. Khrustalev, K. N. Zelenin, C. M. Isakov and V. P. Sergutina, *Zh. Org. Khim.*, **14**, 2350 (1978); *Chem. Abstr.*, **90**, 1376584 (1979).
86. Y. Shvo, in *The Chemistry of the hydrazo, Azo and Azoxy Group* (Ed. S. Patai), Wiley, Chichester, 1975, p. 1079.
87. V. A. Khrustalev, K. N. Zelenin and V. P. Sergutina, *Zh. Org. Khim.*, **15**, 2280 (1979).
88. V. A. Khrustalev, K. N. Zelenin and V. P. Sergutina, *Zh. Org. Khim.*, **15**, 2288 (1979).
89. I. D. Cunningham and F. A. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 537 (1986).
90. V. A. Khrustalev, V. P. Sergutina, K. N. Zelenin and V. V. Pinson, *Khim. Geterotsikl. Soedin.*, 1264 (1982); *Chem. Abstr.*, **98**, 16382k (1982).

91. B. I. Buzykin, L. P. Sysoeva, A. A. Espenbetov, Yu. T. Struchkov and Yu. P. Kitaev, *Zh. Org. Khim.*, **22**, 2277 (1986); *Chem. Abstr.*, **107**, 133786k (1987).
92. L. V. Shmelev, Yu. S., Ryabokobylko, A. V. Kessenikh and V. N. Ostrovskaya, *Zh. Obshch. Khim.*, **57**, 1637 (1987); *Chem. Abstr.*, **108**, 166892r (1988).
93. L. A. Fedorov, S. A. Sokolovskii, G. N. Lipunova, G. I. Sigeikin and L. I. Rusinova, *Izv. Akad.* Nauk SSSR, Ser. Khim., 691 (1987); *Chem. Abstr.*, **108**, 21274f (1988).
94. P. B. Fischer, L. B. Kaul and H. Zollinger, *Helv. Chim. Acta*, **51**, 1449 (1968).
95. D. E. Gallis and L. R. Crist, *Magn. Reson. Chem.*, **25** 480 (1987).
96. W. Walter and C. O. Meese, *Chem. Ber.*, **110**, 2463 (1977).
97. C. L. Perrin, C. P. Lollo and Chi-Sun Hahn, *J. Org. Chem.*, **50**, 1405 (1985).
98. C. L. Perrin and E. R. Johnston, *Can. J. Chem.*, **59**, 2527 (1981).
99. C. J. Shisoo, M. B. Devani, V. S. Bhadti, S. Ananthan and G. V. Ullas, *J. Chem. Res. (S)*, 375 (1985).
100. M. Van den Bril and R. Fuks, *Tetrahedron*, **37**, 2905 (1981).
101. T. V. Aleshnikova, A. F. Prokof'eva, V. V. Negrebetskii, A. F. Grapov and N. N. Melnikov, *Zh. Obshch. Khim.*, **56**, 2507 (1986). *Chem. Abstr.*, **108**, 75487w (1988).
102. P. Baudet and D. Rao, *Helv. Chim. Acta*, **53**, 1011 (1970).
103. H. W. Sieveking and W. Lüttke, *Justus Liebigs Ann. Chem.*, **2**, 189 (1977).
104. I. Buśko-Oszczapowicz and J. Cieślak, *Acta Polon. Pharm.*, **39**, 121 (1982).
105. I. Buśko-Oszczapowicz, J. Kazimierczak, T. Prussak, Z. Marchlewska, A. Kaluża, A. Cieniecka and J. Cieślak, *Acta Polon. Pharm.*, **33**, 191 (1976).
106. J. Cieślak, I. Buśko-Oszczapowicz, W. Rogowska, M. Stępniak, J. Sadowska, W. Kotula, A. Całk, T. Prussak-Więckowska and Z. Marchlewska, *Acta Polon. Pharm.*, **38**, 499 (1981).
107. J. Cieślak, I. Buśko-Oszczapowicz, A. Całka, W. Kotula, M. Wrociński, T. Prussak-Więckowska, Z. Marchlewska and M. Stepniak *Acta Polon. Pharm.*, **38**, 69 (1981).
108. R. F. Smith, D. S. Johnson, C. L. Hyde, T. C. Rosenthal and A. C. Bates, *J. Org. Chem.*, **36**, 1155 (1971).
109. R. F. Smith, D. S. Johnson, R. A. Abgott and M. J. Madden, *J. Org. Chem.*, **38**, 1344 (1973).
110. N. V. Serebryakova, G. N. Lipunova, N. P. Bednyagina and L. F. Lipatova, *Khim. Geterotsikl. Soed.*, 1403 (1970); *Chem. Abstr.*, **74**, 138178k (1971).
111. G. J. Martin, M. L. Martin and J-P. Gouessnard, *^{15}N NMR Spectroscopy*, Vol. 18 in series (Eds. P. Diehl, E. Fluck and R. Kosfeld), Springer-Verlag, Berlin, Heidelberg, New York, 1981.
112. IUPAC Recommendations for Nuclei Other than ^{1}H, *Pure Appl. Chem.*, **45**, 219 (1976).
113. B. Clement and T. Kämpchen, *Chem. Ber.*, **119**, 1101 (1986).
114. C. Rabiller, G. Ricoleau, M. L. Martin and G. J. Martin, *Nouv. J. Chem.*, **4**, 35 (1980).
115. B. Clement and T. Kämpchen, *Chem. Ber.*, **118**, 3481 (1985).
116. N. Naulet and G. J. Martin, *Tetrahedron Lett.*, 1493 (1979).
117. J. Oszczapowicz, I. Wawer, M. Dargatz and E. Kleinpeter, in preparation.
118. M. L. Filleux, N. Naulet, J. P. Doric, G. J. Martin, J. Pornet and L. Miginiac, *Tetrahedron Lett.*, 1435 (1974).
119. I. Wawer, *Magn. Reson. Chem.*, **26**, 601 (1988).
120. I. Wawer, *J. Mol. Liq.*, **38**, 1 (1988).
121. I. Wawer, *Magn. Reson. Chem.*, **27**, 577 (1989).
122. J. Oszczapowicz and W. Krawczyk, *J. Chem. Soc., Perkin Trans. 2*, 21 (1989).
123. J. Oszczapowicz and K. Ciszkowski, *J. Chem. Soc., Perkin Trans. 2*, 663 (1987).
124. J. Oszczapowicz and E. Raczyńska, *J. Chem. Soc., Perkin Trans. 2*, 1643 (1984).
125. W. Kinasiewicz, A. Leś and I. Wawer, *J. Mol. Struct. (Theochem.)*, **168**, 1 (1988).
126. D. C. Prevoršek, *J. Phys. Chem.*, **66**, 769 (1962).
127. D. C. Prevoršek, *J. Chim.-Phys., Phys. Chim. Biol.*, **55**, 840 (1958).
128. J. Oszczapowicz, J. Jaroszewska-Manaj, L. Skulski and K. Erbel, in preparation.
129. R. B. Tinkler, *J. Chem. Soc. B*, 1052 (1970).
130. B. V. Passet, G. N. Kul'bitskii, N. A. Kalashnikova and T. I. Voropaeva, *Zh. Org. Khim.*, **8**, 1246 (1972); *Chem. Abstr.*, **77**, 100964g (1972).
131. R. Kolb and G. Schwenker, *Chem. Ber.*, **106**, 105 (1973).
132. J. Oszczapowicz, W. Krawczyk and P. Łyżwiński, *J. Chem. Soc., Perkin Trans. 2*, 311 (1990).
133. I. Buśko-Oszczapowicz and J. Oszczapowicz, in preparation.
134. B. E. Zaitsev, L. B Krasnova, S. I. Popov and T. A. Mikhailova, *Zh. Org. Khim.*, **22**, 1743 (1986); *Chem. Abstr.*, **107**, 6907g (1987).

135. M. Hanocq, M. Van Damme and R. Fuks, *J. Pharm. Biomed. Anal.*, **31**, 29 (1985).
136. G. Varsanyi, *Assignments for Vibrational Spectra of 700 Benzene Derivatives*, Akademiai Kiado, Budapest, 1973.
137. J. L. Bernal, M. Pedrero, V. Cerdá and J. Cantallops, *Thermochim. Acta*, **98**, 19 (1986).
138. G. S. Sanyal, A. B. Modak and A. K. Mudi, *Indian J. Chem.*, **22A**, 307 (1983).
139. M. B. Colella, S. Siggia and R. M. Barnes, *Anal. Chem.*, **52**, 967 (1980).
140. W. Walter and H. Weiss, *Justus Liebigs Ann. Chem.*, **162**, 758 (1972).
141. K. S. Burmistrov, N. V. Toropin, S. J. Burmistrov and T. V. Gosteminskaya, *Zh. Org. Khim.*, **17**, 387 (1981); *Chem. Abstr.*, **95**, 42558 (1981).
142. E. S. Karavayeva, H. P. Bednyagina, T. A. Sharkova and J. J. Mudretsova, *Khim. Geterotsilol Soed.*, 1420 (1975); *Chem. Abstr.*, **84**, 59365k (1976).
143. I. I. Mudretsova and S. L. Mertsalov, *Khim. Geterotsikl. Soed.*, 1666 (1975).
144. I. A. Nasyr and W. M. Cherkasov, *Khim. Geterotsikl. Soed.*, 1409 (1976).
145. G. N. Tyruenkova, I. I. Mudretsova, S. L. Mertsalov and N. P. Bednyagina, *Khim. Geterotsikl. Soed.*, 818 (1980); *Chem. Abstr.*, **93**, 20374 (1980).
146. J. Vaes, F. Faubert and T. Zeegers-Huyskens, *Can. J. Chem.*, **53**, 604 (1975).
147. J. A. Clark and M. Kilner, *J. Chem. Soc., Dalton Trans.*, 2613 (1983).
148. L. A. Kazitsyna and B. Kupletska, *Applications of UV, IR and NMR Spectroscopy and Organic Chemistry*, Vyzshaya Shkola, Moscow, 1971 (Russian).
149. N. C. Ta and D. Sen, *J. Inorg. Nucl. Chem.*, **43**, 209 (1981).
150. V. A. Dorokhov, M. V. Bochkareva and O. O. Boldyreova, *Izv. Acad. Nauk SSSR, Ser. Khim.*, 411 (1979); *Chem. Abstr.*, **90**, 203057e (1979).
151. P. Sohár, *Acta Chim. Acad. Sci. Hung.*, **54**, 91 (1967).
152. A. P. de Jong and H. Van Dam, *J. Med. Chem.*, **23**, 889 (1980).
153. A. P. de Jong and H. Van Dam, *Pharmazie*, **36**, 349 (1981).
154. K. J. Dignam, A. F. Hegarty and P. L. Quaim, *J. Chem. Soc., Perkin Trans. 2*, 1457 (1979).
155. F. Borrull, J. Guasch, E. Casassas and V. Cerdá, *Polyhedron*, **5**, 1277 (1986).
156. O. M. Stashkevich, G. T. Pilyugin and W. W. Stashkevich, *Khim. Geterotsikl. Soed.*, 1104 (1970).
157. O. N. Yalçindag, *Sci. Pharm.*, **44**, 328 (1976).
158. O. N. Yalçindag and E. Onur, *Sci. Pharm.*, **45**, 318 (1977).
159. O. N. Yalçindag, *Sci. Pharm.*, **48**, 166 (1980).
160. O. N. Yalçindag, *Sci. Pharm.*, **48**, 391 (1980).
161. O. N. Yalçindag, *Sci. Pharm.*, **49**, 500 (1981).
162. J. D. Wiliams, J. Andrews, M. Mitchard and M. Kendall, *J. Antimicrob. Chemother.*, **2**, 61 (1976).
163. A. P. Ball, A. K. Viswan, M. Mitchard and R. Wise, *J. Antimicrob. Chemother.*, **4**, 241 (1978).
164. M. Zaremba, K. Zukowska-Nytko, A. Grala-Kaĺużna, A. Kacprazak-Wiatr, J. Piotrowski, J. Grygiel and J. Borowski, *Med. Dośw. Mikrobiol.*, **33**, 219 (1981); *Chem. Abstr.*, **98**, 31297e (1983).

CHAPTER 5

Mass spectra of amidines and related compounds

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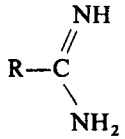
I. INTRODUCTION

The 1975 volume of the 'Chemistry of the Functional Groups' series on 'The Chemistry of Amidines and Imidates' included a discussion of the mass spectra of *N,N*-dimethyl-*N'*-arylformamidines as a section in the chapter on general and theoretical aspects of amidines by G. Häfelinger[1]. Since then, amidines and imidic acid derivatives have been the subject of relatively few mass spectrometric studies. Most of the scant literature data reported electron impact (EI) mass spectra recorded for analytical purposes. Only a minor fraction dealt with the characterization of ion structures or focused on the effect of substituents on the fragmentation pathways. Thus, the gas-phase ion chemistry of these compounds is virtually unknown.

The Chemistry of Amidines and Imidates, Volume 2
Edited by S. Patai and Z. Rappoport

II. MASS SPECTRA OF AMIDINES

Mass spectrometric data on amidines[2–10] are rather limited and mainly restricted to EI studies of formamidines with various N-substituents. Upon EI ionization, the fragmentation of amidines which are unsubstituted at nitrogen, e.g. **1a–e**, involved cleavage of the R—C bond to yield $[HNCNH]^{+\cdot}$ ions at *m/z* 42 and $[HNCNH_2]^+$ ions at *m/z* 43 as typically the base peaks, with the exception of **1e** whose base peak at *m/z* 104 was assigned to $[C_6H_5CNH]^+$ ions[2]. Amidines **1d** and **1e** showed also intense $[R]^+$ ions.

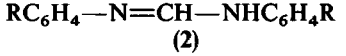


R = H (a) Cl (b) Me (c) *t*-Bu (d) Ph (e)

(1)

A. Formamidines

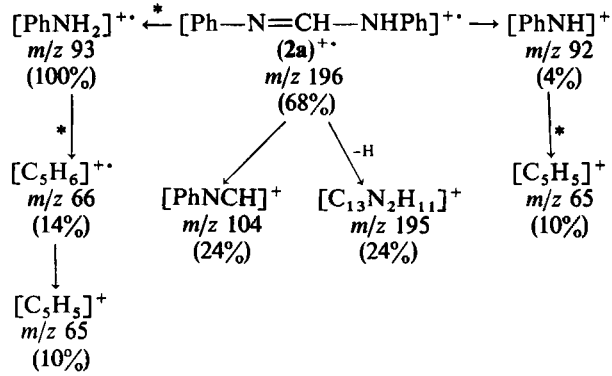
The mass spectrum of *N,N'*-diphenylformamidine **2a** has been reported by several



(2)

R = H (a) *o*-Me (b) *p*-Me (c) *m*-Cl (d) *p*-Cl (e) *p*-NMe_2 (f)

authors[3,4] and compared to the mass spectra of the corresponding acetamidine and benzamidine by Kilner and coworkers[2]. The proposed fragmentation scheme, shown in equation 1, was based on the presence of metastable ions (* symbol on the appropriate



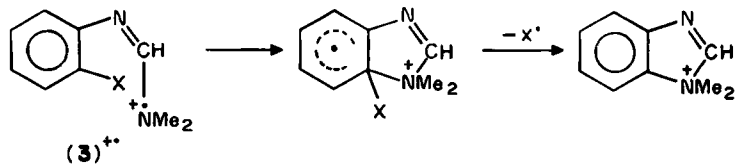
(1)

arrow) and accurate mass measurements[2]. The main fragmentation mode involved NH—CH bond rupture to afford the two fragment ions at *m/z* 92 and *m/z* 104. The base peak at *m/z* 93 was associated by a strong metastable transition to NH—CH bond cleavage with concomitant hydrogen migration to give, probably, the aniline radical cation.

The substituted *N,N'*-diarylformamidines **2b–f** have aniline-type ions as their base peaks[2–4]. Slight differences in the relative intensities of $[ArNH_2]^{+\cdot}$ and $[ArNH]^+$ ions were remarked in the case of the *ortho* (**2b**) and *para* (**2c**) tolyl isomers[2].

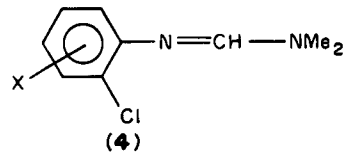
The mass spectrometric fragmentation pattern of *N,N*-dimethyl-*N'*-arylformamidines has been discussed[5,6] and reviewed[1]. The fragmentation process leading to significant

$[M-H]^+$ peaks, explained by the formation of benzimidazolium ions, has been further investigated by Kuschel and Grützmacher[7–9]. The loss of a chlorine atom gave rise to the most abundant $[M-Cl]^+$ ions in the mass spectra of *N,N*-dimethyl-*N'*-2-chlorophenylformamidine **3** (X = Cl), in contrast to the minor intensity of these fragments from the *meta*- and *para*-chloro-substituted analogues. This result was found to substantiate the postulated formation of benzimidazolium ions by a formal intramolecular aromatic substitution reaction on the radical cation of **3**, as shown in equation 2.



(2)

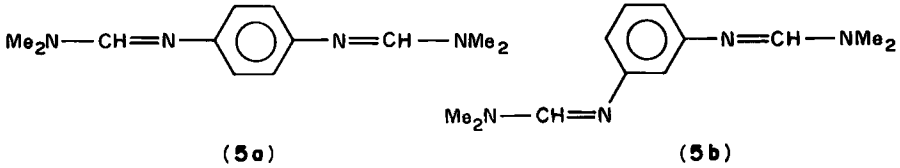
Further insight into the mechanism of the cyclization reaction outlined in equation 2 was sought by a study of the effect of substituents at the 2-chlorophenyl ring as in compounds **4a–n**, on the appearance potential (AP) and the intensity of $[M-Cl]^+$ ions



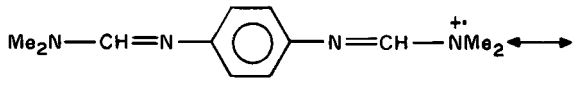
(4)

X =	H	4-NMe_2	4-MeO	4-Me	4-Cl	4-CN	4-NO_2	5-NMe_2	5-OMe
	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)
	5-Me	5-Cl	5-CN	5-NO_2	5-CF_3				
	(j)	(k)	(l)	(m)	(n)				

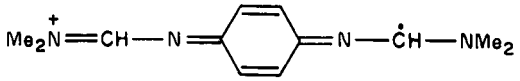
and on the ionization potential (IP) of the parent molecules[7]. While the IP values showed the expected decreasing trend with the increasing electron-donating ability of the X group and gave a linear correlation with the Hammett σ constants, the AP values did not exhibit any clear relationship. The intensity of the $[M-Cl]^+$ ions relative to the molecular ion intensity was reduced by 4- and 5-dimethylamino and 4-methoxy substituents, all other substituents displaying only minor effects. A similar effect had been observed in the mass spectra of *N,N*-dimethyl-*N'*-arylformamidines unsubstituted in the 2-position, where the relative intensity of the $[M-H]^+$ ions was reduced by *p*-hydroxy and *p*-methoxy substituents[1,6]. The formation of cyclic $[M-H]^+$ ions was strongly reduced from ionized **5a** with respect to **5b**[8]. These results have been interpreted by the contribution of resonance forms, e.g. distonic **5a''**, delocalizing the positive charge of the radical cation on the nitrogen atom as in **5a'**. Since the formal positive charge on the nitrogen atom was



(5a) **(5b)**



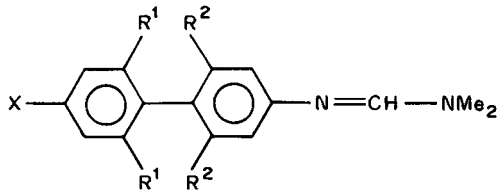
(5a')



(5a'')

thought to promote the cyclization to the benzimidazolium ions, their relative abundance was accordingly depleted by delocalizing the positive charge away from the attacking nitrogen atom.

To corroborate this mechanistic interpretation, the behavior of *N,N*-dimethyl-*N'*-biphenylylformamidines **6a–g** was examined[8]. In particular, a lower abundance of



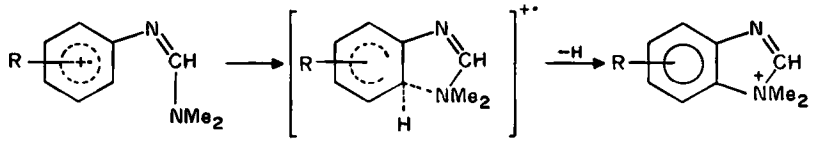
(6)

	X	R^1	R^2
(a)	H	H	H
(b)	NO_2	H	H
(c)	MeCO	H	H
(d)	MeO	H	H
(e)	$Me_2NCH{=}N-$	H	H
(f)	$Me_2NCH{=}N-$	Me	H
(g)	$Me_2NCH{=}N-$	Me	Me

$[M-H]^+$ ions was observed from ionized **6e** while compounds **6f** and **6g** showed the typical intensities of fragment ions, common to unsubstituted **6a**. Thus, methyl substitution in the 2,2' and 2,2',6,6' positions was suggested effectively to depress resonance interactions between X and the amidino group by steric hindrance to coplanarity. Further information on the mechanism of formation of cyclic benzimidazolium ions was provided by varying the *ortho* substituent X in compound **3** (equation 2), X = H, F, Cl, Br, I[9]. No simple relation was observed between the intensities of $[M-X]^+$ ions and the dissociation energies of the C—X bond, as might have been expected for a direct cleavage process. This observation, together with the trend of kinetic energy release in the fragment ions along the halogen series, substantiated a stepwise cyclization–elimination mechanism, as shown in equation 2, the first step being characterized by the highest activation energy.

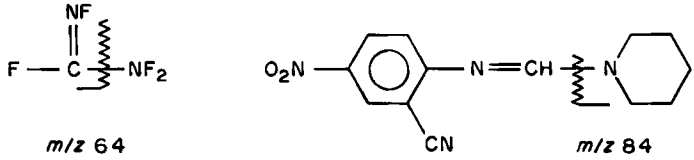
The problem concerning the fragmentation pathway leading to $[M-H]^+$ ions has been also addressed by Marsel and coworkers in their study on *m*- and *p*-substituted *N,N*-

dimethyl-*N'*-phenylformamidines[10]. They reported IP values and AP values for the formation of $[M - H]^+$ ions which varied within a larger range than previous data[6]. With the gross assumption that (AP – IP) values corresponded to approximate activation energies for the fragmentation process, a correlation of the (AP – IP) differences with Brown's σ^+ was attempted. Negative slopes were obtained for both *p*- and *m*-substituted isomers, which were interpreted according to a concerted cyclization–elimination process, initiated by nucleophilic attack of the nitrogen atom on a radical cationic aryl ring, as shown in equation 3. Clearly, the interpretation of mass spectrometric data on the origin of fragment ions from differently substituted compounds is debatable.



(3)

Tetrafluoroformamidine (**7**) has been obtained among the products of the direct fluorination of guanylurea and characterized by its mass spectrum, that displays a molecular ion of low intensity and a base peak at *m/z* 64[11]. The C—N single bond cleavage dominated also the mass spectrum of 1-[*N*-(2-cyano-4-nitrophenyl)formimidoyl] piperidine **8**, yielding the base peak at *m/z* 84[12].

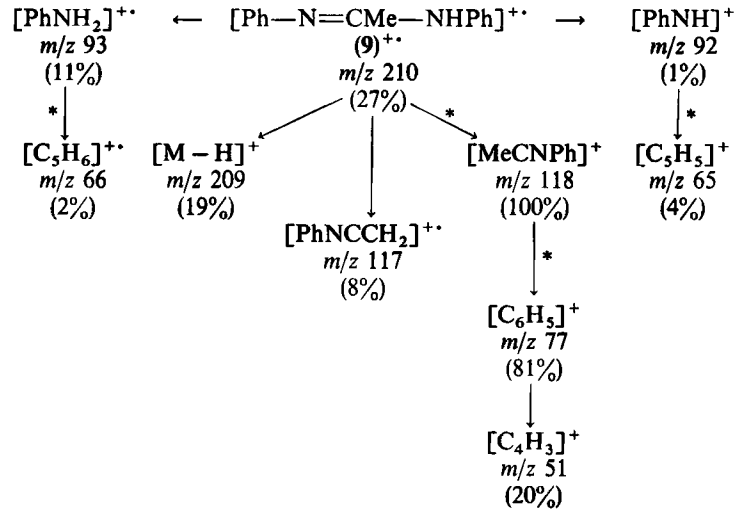


m/z 64 (**7**) *m/z* 84 (**8**)

B. Higher Amidines

The C—N single bond cleavage gave the most prominent ions in the mass spectra of nitrogen-substituted acetamidines and benzamidines of the general formula R'N= C(R)NHR', R = Me, Ph, studied by Kilner and coworkers[2]. A wide variety of relative ion intensities were found but the charge-retaining fragment from the C—N bond fission typically differentiated the mass spectra of acetamidines and benzamidines from the corresponding formamidines. Their general pattern is exemplified by the fragmentation schemes of *N,N'*-diphenylacetamidine **9** (equation 4) and *N,N'*-diphenylbenzamidine **10** (equation 5), which may be compared to equation 1 showing the fragmentation pattern of *N,N'*-diphenylformamidine. The positive charge was mainly retained by the $[RCNPh]^+$ fragment when R = Me, Ph, but by the $[PhNH_2]^{+\cdot}$ fragment when R = H.

A detailed study of the fragmentation pattern of bisamidine **11** using peak matching, direct analysis of daughter ions, defocusing and deuterium labelling has been reported by Schlunegger and coworkers[13].



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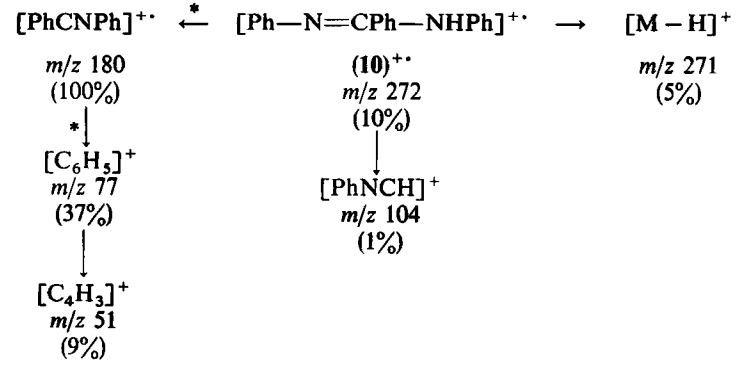

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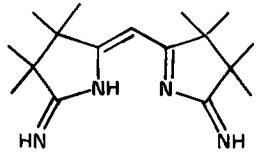
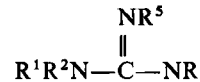


(11)

C. Guanidines

1. Guanidine and substituted guanidines

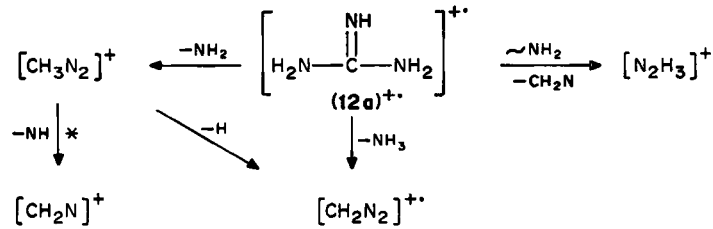
The fragmentation pathways upon EI of guanidine (**12a**) and some of its derivatives (**12b,c,f,i–o**) have been studied with metastable ion analysis and accurate mass measurements by peak matching[14].



(12)

	R^1	R^2	R^3	R^4	R^5
(a)	H	H	H	H	H
(b)	Me	H	H	H	H
(c)	Me	Me	H	H	H
(d)	Me	H	H	H	Me
(e)	Me	Me	H	H	Me
(f)	Me	Me	Me	Me	H
(g)	Me	Me	Me	H	Me
(h)	Me	Me	Me	Me	Me
(i)	c-C_6H_{11}	H	H	H	H
(j)	$PhCH_2$	H	H	H	H
(k)	Ph	Me	H	H	H
(l)	NH_2	H	H	H	H
(m)	CN	H	H	H	H
(n)	NO_2	H	H	H	H
(o)	NH_2CO	H	H	H	H
(p)	OH	H	H	H	H

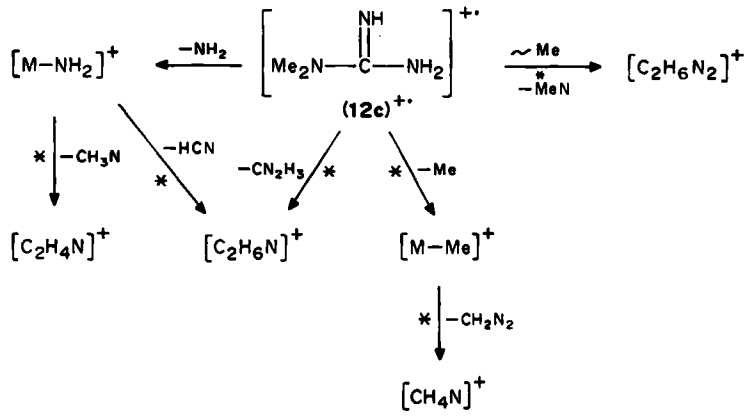
The carbon–amino nitrogen bond fission characterized the mass spectra of guanidine and of its methylated derivatives, all showing prominent molecular ions, though product ions were also found involving cleavage processes with rearrangement[14,15]. The base peak at m/z 43 in the mass spectrum of guanidine, **12a**, was due to loss of NH_2 from the molecular ion but an unexpected ion at m/z 31, $[N_2H_3]^+$, was thought to arise from migration of NH_2 to the imino nitrogen atom. Equation 6 summarizes the most significant

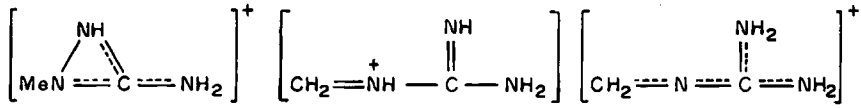


(6)

fragmentation pathways of ionized **12a** which may be compared to those assigned to the *N,N*-dimethyl derivative **12c** shown in equation 7.

Tentative ion structures have been proposed, founded only on reasonable guesses; e.g. the $[M - Me]^+$ ion in equation 7, produced from the molecular ion as a flat-topped metastable peak, was assigned a probable three-membered ring structure **13a** or a linear structure involving migration of a hydrogen atom **13b–c**. The ion corresponding to $[M - MeN]^+$ in equation 7 probably requiring migration of a methyl group to the imino nitrogen was a common feature in the mass spectra of all methylguanidines[14,15].





Upon EI, *N*-cyclohexylguanidine (**12i**) fragmented at the cycloalkyl group yielding the base peak at *m/z* 60 ($[CH_6N_3]^+$) and the $[M - C_3H_7]^+$ component to the peak at *m/z* 98. A second component to the peak at *m/z* 98 was due to $[M - CH_3N_2]^+$ ions. The latter fragment ions yielded the base peaks at *m/z* 106 in the mass spectra of the two isomers **12j–12k** which differed markedly in the molecular ion region. The molecular ion was the second most abundant ion in the case of **12j** but its intensity was weak compared to the intense $[M - H]^+$ ions from **12k**.

The nature of the substituent R^1 markedly influenced the fragmentation pattern of **12l–12o**; e.g. the molecular ions, base peak in the mass spectrum of **12l**, underwent cleavage of CH_2N_2 with hydrogen migration or stepwise loss of H and N_2H_2 to give abundant $[N_2H_4]^+$ ions at *m/z* 32 and $[CH_3N_2]^+$ ions at *m/z* 43. The molecular ions of **12m**, representing the base peak, competitively lost $[CHN_2]$ and NH_2 neutral fragments. $[M - NH_2]$ ions corresponded to the base peak in the mass spectrum of **12o** where loss of NH_2 from the urea group could occur.

In the 36 eV mass spectrum of *N*-hydroxyguanidine, **12p**, intense $[M]^{+\cdot}$ ions were accompanied by the most abundant $[CH_2N_2]^+$ and $[CH_3N_2]^+$ ions[16].

Pentafluoroguanidine has been characterized by its mass spectrum showing the two most intense peaks at *m/z* 97 ($[CF_3N_2]^+$) and *m/z* 78 ($[CF_2N_2]^+$)[11].

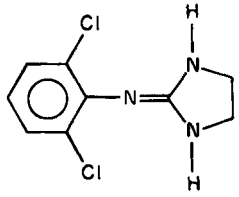
The ionization potentials of guanidine and methylguanidines **12b–h** have been reported[15] and reinterpreted[17]. The analysis of Baldwin and coworkers[17] suggested that the effect of methylation on the energy of the HOMO of (methyl)guanidines and related compounds is additive. Their quantitative estimates were found to agree with the difference of IP values between guanidine and pentamethylguanidine. However, the trend of the IP values for guanidine and *N,N*-dimethylguanidine was taken as indicative of ionization at different sites. It was argued that the IP of the imino nitrogen lone pair in guanidine itself was slightly below that of the amino nitrogen, but the situation was reversed upon dimethylation of the amino nitrogen as in **12c**. The whole discussion

appears in contrast with the notion that, in the presence of molecular orbitals lying close in energy to the HOMO, the EI ionization potential gives a weighted average of the IPs of all the orbitals concerned rather than the IP corresponding exclusively to the HOMO.

The gas-phase ion chemistry of guanidines or amidines in general do not appear to have ever been investigated. However, the computational determination of the proton affinity of guanidine may be mentioned. *Ab initio* calculations at the 4-31G level gave a proton affinity value of 263 kcal mol^{-1} [18] which would place guanidine as one of the strongest gaseous bases[19]. This was related to the exceptional stability of the guanidinium ion, owing to the Y-shaped delocalization of six π electrons.

2. *Biologically important guanidino compounds*

The mass spectrometric assay of the hypotensive drug 2-(2,6-dichlorophenylimino)-2-imidazolidine (**14**) (clonidine) and related compounds (**15–20**) has been developed,



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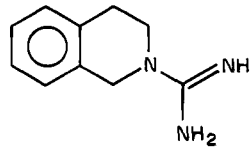

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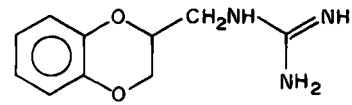

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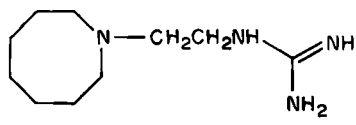

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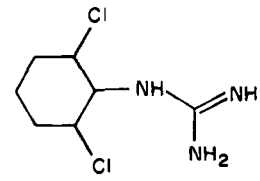

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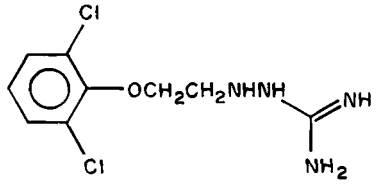

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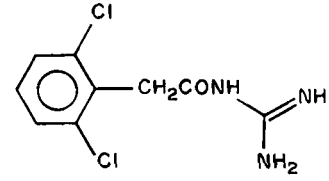
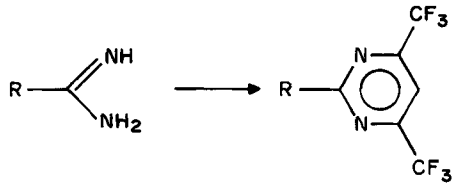


(20)

exploiting the high sensitivity and specificity of negative-ion chemical ionization by resonance electron capture[20]. To this end, suitable fluorinated derivatives were synthesized, the negative-ion mass spectrum of which contained abundant high mass ions undergoing little fragmentation.

Positive-ion CI and electron capture negative-ion CI mass spectra of compounds **15–20** have been recorded after conversion of the amidine group to a bis(trifluoromethyl) pyrimidine by reaction with hexafluoroacetylacetone (equation 8). With the exception



(8)

of **19**, $[M + H]^+$ ions represented the base peak in the positive-ion mass spectra, showing little or no fragmentation. In the negative-ion mass spectra, $[M]^{-\cdot}$ ions were the base peaks for all compounds except **18** and **19**. Intense negative-ion currents, compared to the positive-ion mode, allowed the detection of picogram amounts by selected ion monitoring.

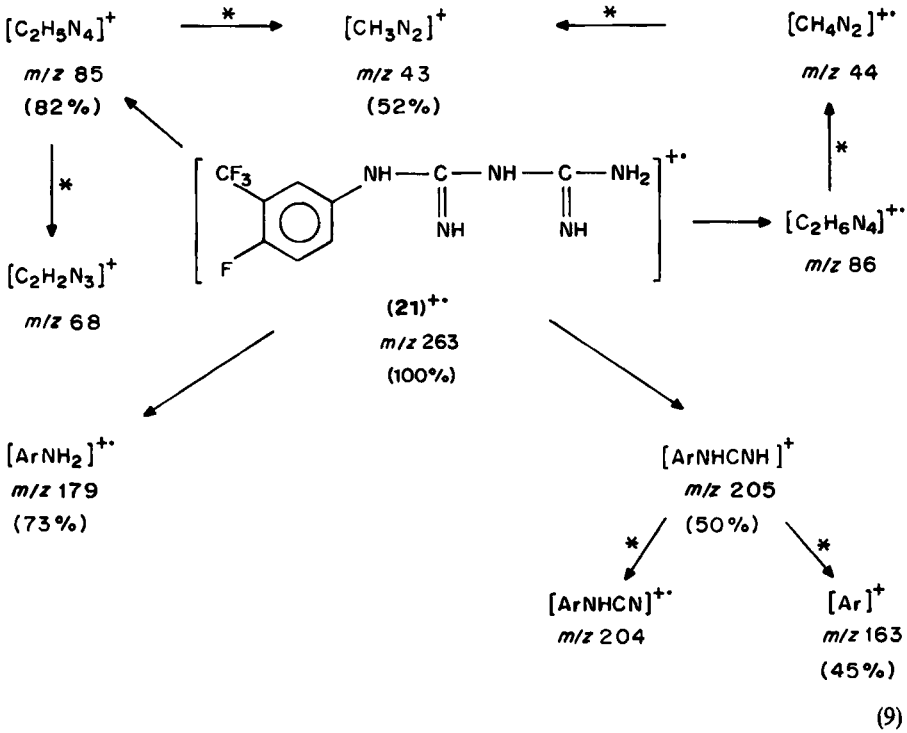
Similar results were obtained from clonidine, once converted to the disubstituted derivative upon reaction with 3,5-bis(trifluoromethyl)benzoyl chloride. The negative-ion mass spectrum of this derivative showed only a weak molecular anion but a characteristic base peak corresponding to $[M - HCl]^{-\cdot}$ ions which permitted the picogram detection of clonidine. Earlier attempts with the methyl, *p*-trifluoromethylbenzyl, pentafluorobenzyl and pentafluorobenzoyl derivatives of **14** met with poor success owing to the lack of intense characteristic high-mass negative ions, with chloride ions at *m/z* 35 and *m/z* 37 comprising a large fraction of the total ion current.

The desorption CI mass spectra of 21 biologically important guanidino compounds related to arginine $NH{=}C(NH_2)NH(CH_2)_3CH(NH_2)CO_2H$ have been reported[21]. The use of ammonia as the reagent gas provided the highest intensity of the analytically valuable $[M + H]^+$ ions which were missing, however, in the mass spectra of several compounds. In particular, the presence of an additional carboxylic acid group or alkyl branching at the methylene chain led to enhanced loss of water, with $[M + H - H_2O]^+$ ions as the base peaks.

Methylguanidine, arginine and related compounds could also be directly mass analyzed, without prior transformation into volatile derivatives, by using FAB ionization of their glycerol solution.[22] Both methylguanidine and arginine showed $[M + H]^+$ ions as the base peaks with little interference from dimer ions, $[2M + H^+]$, or glycerol (G) clusters, e.g. $[2G + H]^+$. In some cases the situation was reversed. Thus the FAB mass spectrum of arcaine, $NH{=}C(NH_2)NH(CH_2)_4NHC(NH_2) = NH$, examined as the sulfate, was dominated by the glycerol ions $[nG + H]^+$ and showed only weak $[M + H]^+$ and $[M + H + H_2SO_4]^+$ ions.

Several 1-arylbiguanidino compounds are endowed with pharmacological activity. Among them, the mass spectral features of compounds **21** and **22a–d** have been reported[23]. The 70 eV mass spectra, obtained by direct insertion at controlled temperature to avoid thermal decomposition, comprised some of the ions characteristic of guanidines[14]. The fragmentation pattern of **21** (equation 9) shows that the major fragment ions arise by ArNH—C bond fission to give $[C_2H_5N_4]^+$ ions at *m/z* 85 and $[ArNH_2]^{+\cdot}$ ions, involving hydrogen rearrangement, at *m/z* 179. In the case of the unsymmetrical 1,5-diaryl-substituted compound **22d** both possible arylamine ions and the corresponding ionic residues were formed.

The fungicide guanidino compound **23** has been characterized by its FAB positive-ion mass spectrum as the sulfate or acetate giving the monoprotonated base as the base



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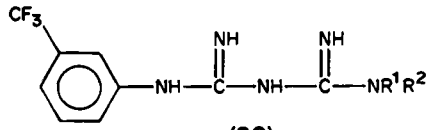
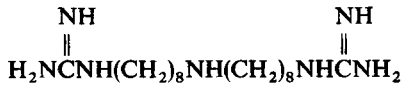


(22)

	(a)	(b)	(c)	(d)
R^1	Et	*i*-Pr	3-$CF_3C_6H_4$	8-Quinolyl
R^2	Et	H	H	H

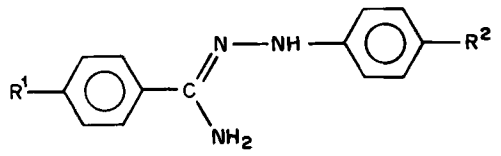


(23)

peak[24]. Fragmentation of $[M + H]^+$ ions occurred by loss of NH_3, CH_2N_2 and CH_5N_3 neutral molecules and by sequential cleavage at the methylene chain to give a series of prominent ions separated by 14 mass units.

D. Amidrazones

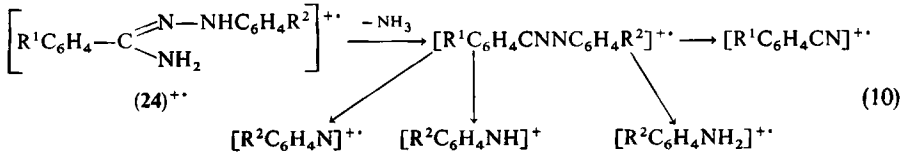
The amidrazones can be regarded as derivatives of amidines whose imino (or amino) nitrogen atom bears an amino substituent. The 70eV mass spectra of N^1-aryl benzamidrazones **24a–g** have been studied and the major ions were found to result from



(24)

	(a)	(b)	(c)	(d)	(e)	(f)	(g)
R^1	H	H	H	H	Br	Me	MeO
R^2	H	Br	Me	MeO	H	H	H

N—N bond cleavage[25]. The fragmentation pattern shown in equation 10 illustrates the possible origin of the most significant ions without implying the actual occurrence of any of the transitions involved.



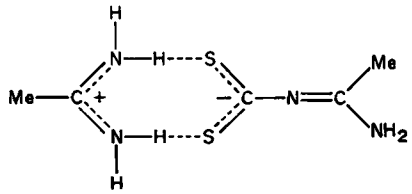
(10)

For all the compounds examined, distinct molecular ions were accompanied by base peaks corresponding to $[R^2C_6H_4N]^{+\cdot}$ ions except in the case of **24b**, which gave a mass spectrum dominated by equally intense $[R^2C_6H_4N]^{+\cdot}$ and $[R^2C_6H_4NH_2]^{+\cdot}$ ions. The process of formation of $[M - NH_3]^{+\cdot}$ ions at *m/z* 272 has been checked by using a labelled sample of **24b** in which all the hydrogen atoms attached to the nitrogen atoms had been replaced by deuterium atoms. The absence of any mass shift for the ions at *m/z* 272 was indicative that the hydrogen atoms lost with the ammonia neutral fragment originated exclusively from the amino nitrogen atoms.

E. Amidinium Salts

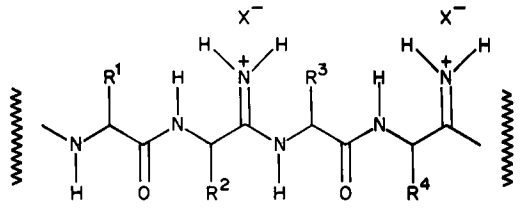
Many of the reported EI mass spectra of amidines and guanidines have been obtained from the corresponding amidinium or guanidinium salt which dissociated to the free base plus acid once introduced by the direct insertion probe[2,14]. In a few cases, compounds incorporating an amidinium group were directly mass analyzed.

The field desorption (FD) mass spectrum of acetamidinium *N*-acetimidoyldithiocarbamate, **25**, has been recorded at the probe temperature of 20 °C[27]. The molecular ion $[M]^{+\cdot}$ at *m/z* 192 corresponding to the whole cation–anion pair was accompanied by $[M + H]^+$ and $[M - H]^+$ ions. The base peak corresponded to $[M - 15]^+$ ions whose elemental composition was not determined.



(25)

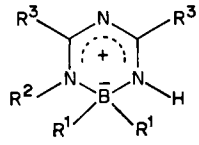
The preparation of poly(dipeptamidinium) salts of the general formula **26** has been described[27]. These compounds are polypeptide derivatives, in which the carbonyl oxygen of each second backbone amide group is replaced by a protonated imine nitrogen.



(26)

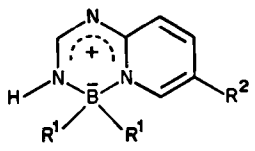
The FAB positive-ion mass spectra of monomeric and up to hexameric compounds with R = H, Me, $PhCH_2$ have been reported. Distinct molecular ion information was obtained, particulary when the terminal amino group was protected by *t*-butoxycarbonyl (BOC) group.

Conventional 70 eV EI mass spectra of compounds **27–29** have been reported[28]. The molecular ions were absent or gave peaks of low intensity. By far the most intense signal in the mass spectra was associated with $[M - R^1]^+$ ions and further fragmentations typically originated from the second R^1 group as exemplified by the fragmentation pattern of ionized **27a–d**, shown in equation 11. This behaviour was accounted for by the aromatic character imparted to $[M - R^1]^+$ ions by the 6π electrons delocalization.



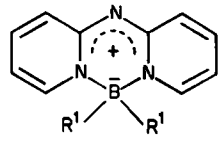
(27a–f)

	(a)	(b)	(c)	(d)	(e)	(f)
R^1	n-Pr	n-Bu	n-Pr	n-Pr	Ph	n-Bu
R^2	H	H	H	n-Pr	Me	H
R^3	Me	Et	Ph	Ph	Ph	Ph



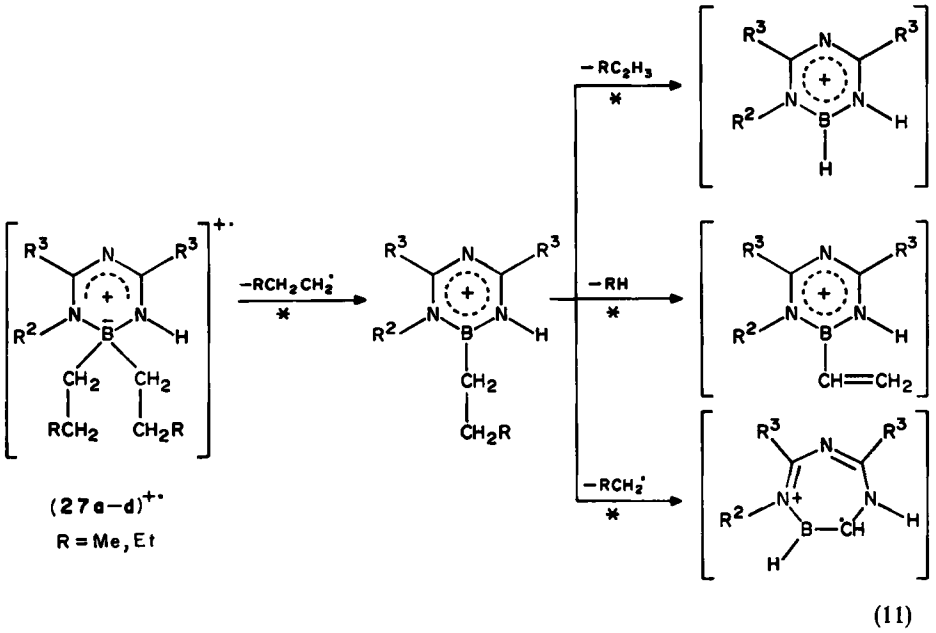
(28a–c)

	(a)	(b)	(c)
R^1	n-Pr	n-Bu	n-Bu
R^2	H	H	Cl

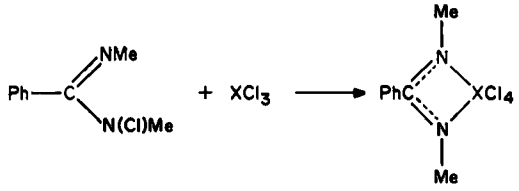


(29a–b)

	(a)	(b)
R^1	Et	n-Bu



(11)



(30)

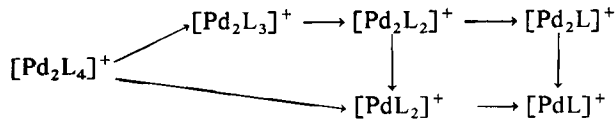
	(a)	(b)	(c)
X=	P	As	Sb

(12)

The [*N*,*N*′-dimethylbenzamidino]-*N*,*N*′-tetrachloroelement (V) (**30**), element = P, As, Sb, has been prepared according to reaction 12 and characterized by X-ray crystallography, NMR and mass spectrometry[29]. NMR data suggested that the electron distribution in the amino moiety of **30c** resembled that of amidinium cations. This relation was much less pronounced in the case of **30a** and **30b**. In the 70 and 20eV EI mass spectra, molecular ions were present only from **30c**, which was attributed to the high stability of the Sb—N bond. Similar fragment ions were present in the mass spectra of the three compounds, but with noticeable variation in relative abundances. $[M—Cl]^+$ ions gave the base peak in the mass spectrum of **30a** while the mass spectrum of **30b** showed only $[M—3Cl]^+$ ions of significant abundance. Other important fragment ions corresponded to $[PhC(NMe)_2]^+$ ions, fairly abundant in the mass spectrum of **30b**, probably originating from $[M—Cl]^+$ precursors, and $[PhCNMe]^+$ ions, base peaks in the mass spectra of **30a,b**, probable fragmentation product of $[M-3Cl]^+$ ions.

F. Amidino Complexes

Amidine and amidino groups are important ligands in transition metal chemistry. Amidino complexes have been studied extensively by Kilner and coworkers who used their 70eV mass spectra for characterization purposes[30]. Complexes of the general formula $\{M[R^2NC(R^1)NR^2]_2\}_n$ are involatile and were examined by direct insertion into the ion source at elevated temperature, which did not exclude the possible occurrence of thermolytic processes. Ions corresponding to dimeric complexes have been observed when M = Ni(II), Pd(II), Cu(II). Their fragmentation typically involved loss of amidino groups as exemplified by the fragmentation routes, most of them supported by metastable transitions, of bis(amidino) palladium(II) complexes, shown in equation 13[30b].

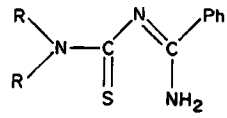


(13)

L = [RNC(Ph)CNR]
(R = *p*-FC_6H_4, *p*-$Pr^iC_6H_4$, Ph, *p*-MeC_6H_4, Me)

A second, least favoured, fragmentation pathway involved fragmentation of the ligand whilst it remained coordinated to the metal. Ions originating from the free ligand ion $[L]^+$ were the most intense and showed a fragmentation pattern very similar to that of the corresponding free amidine[2]. The mass spectra of the amidino complexes of copper(I) were very similar to those of the corresponding copper(II) compounds[30a]. At the highest *m/z* value, $[Cu_2L_2]^+$ ions were detected, which could represent either the molecular ions of dinuclear complexes or the thermolysis product of a possible tetranuclear complex.

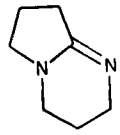
N-(*N*,*N*-Dialkylthiocarbamoyl)benzamidines (**31**) afforded, by deprotonation at the NH_2 group, bidentate ligands (L), via S and N donors, which were used to form new technetium(V) complexes[31].



(31)

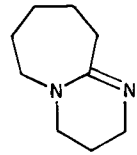
Nitrido complexes of the general formula $TcNL_2$ are neutral and their mass spectra were recorded with EI ionization. The molecular ions were accompanied by most fragment ions originating from the ligand. However, once $[M]^{+\cdot}$ ions were selected, their MIKE and CAD spectra yielded abundant metal-containing daughter ions. The ionic oxo complex $[TcOL_2]Cl$ (R = Et) was examined by FAB ionization. The ensuing mass spectrum showed both $[M]^{+\cdot}$ and $[M+H]^+$ ions and several metal-containing fragments involving loss of one oxygen or sulfur atom(s) and ligand elimination.

A FAB mass spectrometic study on complexes of difluoroboron cations $[BF_2]^+$ has been undertaken to ascertain the role of ion–molecule reactions in the high-pressure region just above the sample surface[32,33]. A divided FAB probe was loaded with the fluoroboron complex dissolved in a matrix of either 3-nitrobenzyl alcohol or tetramethylene sulfone on one half of the probe tip and with neat ligands of varying basic strength, from pyridine to strongly basic amidine ligands, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (**32**), 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (**33**) or 1,1,3,3-tetramethylguanidine, on the second half of the probe tip. FAB irradiation of



DBN

(32)



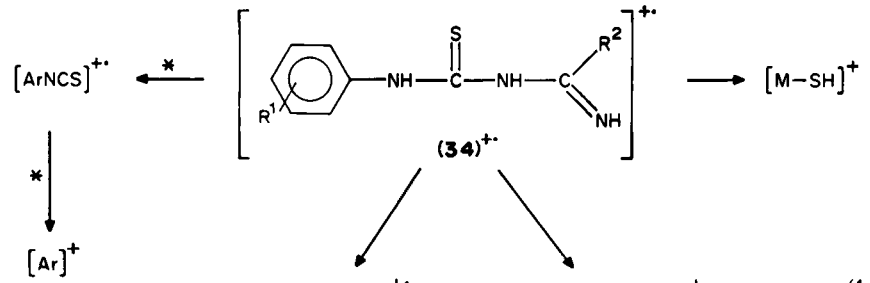
DBU

(33)

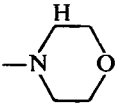
the dual target probe tip produced composite positive-ion FAB spectra with peaks arising from the difluoroboron cation salt (e.g. $[L_2BF_2]^+$, $[LBF_2]^+$) and from the basic ligand (e.g. $[DBN+H]^+$) in addition to mixed ions resulting from ligand displacement (e.g. $[L(DBN)BF_2]^+$, $[(DBN)_2BF_2]^+$). The relative ease of displacement of weaker ligand bases (L = pyridine, quinuclidine) by the strongly basic amidine ligands has been interpreted as due to gas-phase reactions which may render the interpretation of FAB spectra more difficult.

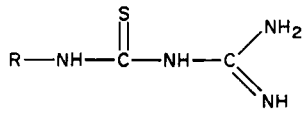
G. Miscellaneous Amidino Compounds

The EI mass spectra of several substituted amidinothioureas have been reported[34]. The unimolecular fragmentation pattern of ionized 1-arylthioureas (**34**) outlined in equation 14 was based on exact mass determinations and the presence of appropriate metastable peaks. The molecular ions always gave intense peaks. Loss of the guanidine moiety $NH_2C(NH)R^2$ gave rise to abundant ions, frequently base peaks, formally corresponding to ionized aryl isothiocyanates $[ArNCS]^{+\cdot}$, which fragmented further to aryl cations, except in the case of **34d**. Cleavage of the second NH—CS bond also yielded intense peaks due to $[ArNH_2]^{+\cdot}$ and $[M-ArNH]^+$ ions while the formation of $[M-SH]^+$ ions appeared less favored. $[M]^{+\cdot}$ and $[M-RNH]^+$ ions afforded the major peaks in the mass spectra of 1-alkyl-3-amidinothioureas **35** while $[RNH_2]^{+\cdot}$ ions were absent and $[RNCS]^{+\cdot}$ ions were usually negligible. Fragmentation of the alkyl group at the C—C bond in the α-position, accompanied by hydrogen migration, gave distinct ions at *m/z* 132 ($[C_3H_8N_4S]^+$) in the mass spectra of **35d–h**, i.e. in the presence of an alkyl chain longer than C_4.



(14)

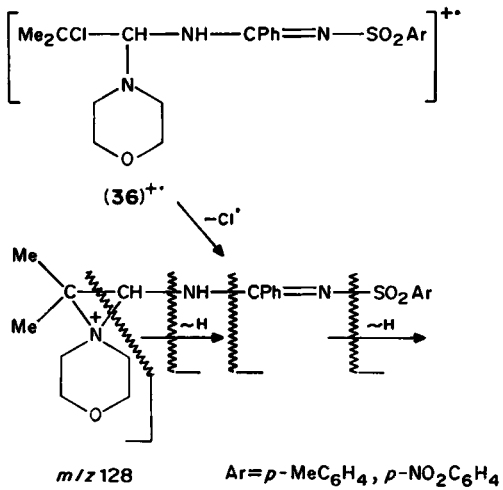
	(a)	(b)	(c)	(d)	(e)	(f)
R^1	H	*p*-Me	*p*-EtO	*o*-MeO	*p*-Cl	
R^2	NH_2	NH_2	NH_2	NH_2	NH_2	



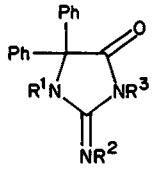
(35)

	(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)
R =	Me	Et	n-Pr	n-Bu	n-C_5H_{11}	n-C_6H_{13}	n-C_8H_{17}	n-$C_{10}H_{21}$

The structure of newly synthesized *N*-(arenesulfonyl)-*N'*-[(2-chloro-2-methyl-1-morpholino)-propyl]benzamidines **36** was probed also by their 70 eV mass spectra[35]. Molecular ions were absent but fast Cl loss led to $[M - Cl]^+$ ions which were assigned an aziridinium structure to account for the base peak at *m/z* 128.

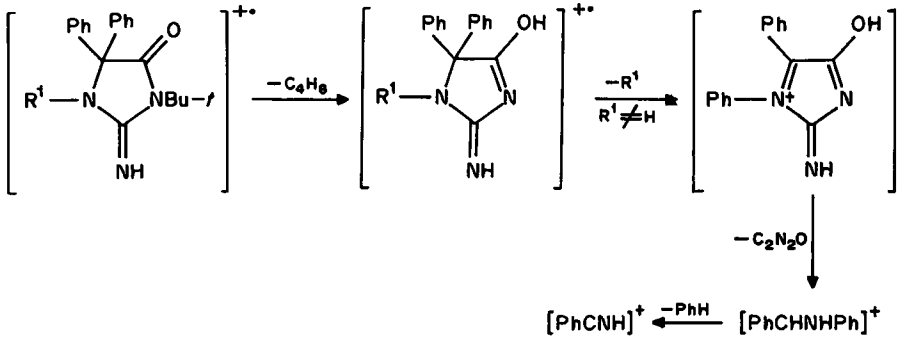


A study has been reported on the mass spectrometric behaviour of substituted glycocyamidine derivatives **37**, which may be regarded as incorporating the guanidine moiety $R^1R^2NC(NR^3)NR^4R^5$ into a five-membered ring[36].



(37)

The most representative fragmentation routes of ionized **37** bearing R^1 = H, Me, Et, $PhCH_2$, *t*-Bu; R^2 = H; R^3 = *t*-Bu as substituents, supported by first and second field free region metastable ions and exact mass measurements, are shown in equation 15. Ion



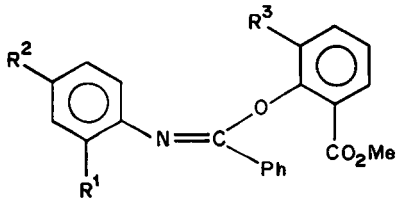
(15)

structures are only speculative and were suggested to result from a McLafferty-type rearrangement involved in the loss of C_4H_8 and from a phenyl migration process accompanying cleavage of the R^1 group.

Mass spectra of *N*-acetimidoyl dithiocarbamic acid, $H_2\overset{+}{N}{=}CMeNHCS_2^-$ (**38**)[37], and some of its salts[26] have been recorded for characterization purposes. The FD mass spectrum of **38** showed $[M]^{+\cdot}$ ions as base peak, $[M + H]^+$, $[M - H]^+$ and dimer ions. On the other hand, the 70 eV EI mass spectra of *N,N'*-diphenyl-*N*-formimidoyl dithiocarbamate salts M[PhN=CH—NPh—CS_2] did not yield significant information[38].

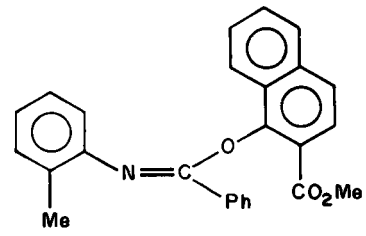
III. MASS SPECTRA OF IMIDIC ACID DERIVATIVES

Goldberg and Harris have reported a study on the EI mass spectra of some aryl *N*-arylbenzimidates (**39–42**) and their Chapman rearrangement products *N*-benzoyldiarylamines[39]. The mass spectra of compounds **39–42**, whose general formula may be written as $Ar^1N{=}CPh(OAr^2)$, typically showed a molecular ion of low intensity

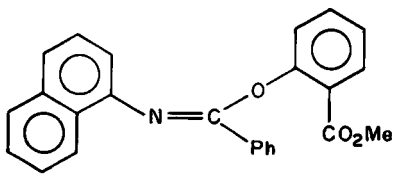


(39)

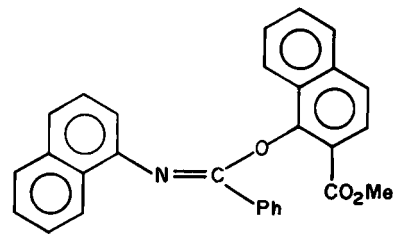
	R^1	R^2	R^3
(a)	H	Cl	H
(b)	Me	H	Me
(c)	Cl	H	Me



(40)

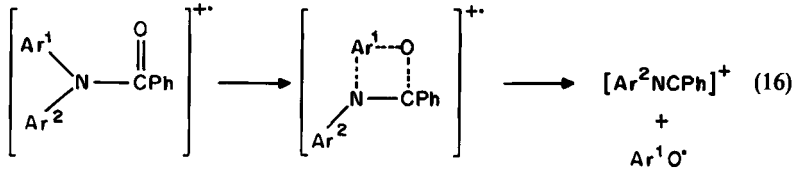


(41)



(42)

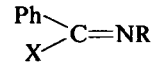
and a base peak corresponding to $[Ar^1NCPh]^+$ ions. The peak at *m/z* 105, $[PhCO]^+$, was most intense in the mass spectrum of **42** (41% relative to the base peak), a compound particularly prone to undergo Chapman rearrangement, and was ascribed to partial thermal conversion to the amide in the inlet system of the mass spectrometer. In the mass spectra of the corresponding amides, $Ar^1N(COPh)Ar^2$, the base peak ions at *m/z* 105 were accompanied by $[M—OAr^1]^+$ and $[M—OAr^2]^+$ ions. The latter ions could be traced to the possible occurrence of reverse Chapman rearrangement undergone by the ionized amides, as outlined in equation 16. The mass spectra of ethyl *N*-arylformimidates, ArN=



(16)

CH(OEt), exhibited major ion peaks corresponding to $[M]^{+\cdot}$, $[M-CO]^{+\cdot}$, $[M-EtO]^+$, which did not exclude extensive thermal conversion to formanilides[40].

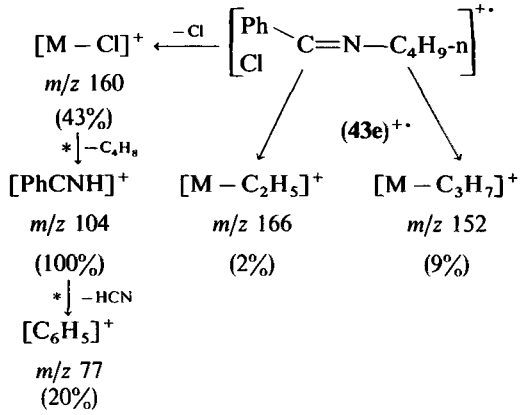
The mass spectral fragmentation pattern of benzimidoyl halides (**43**) has been discussed by Gal and coworkers[41]. Fast halogen loss prevented the detection of molecular ions,



(43)

	R	X
(a)	Me	Cl
(b)	Me	Br
(c)	Et	Cl
(d)	Et	Br
(e)	n-C_4H_9	Cl
(f)	$Br(CH_2)_5$	Br

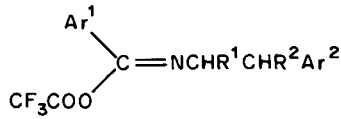
except in the case of **43a** and **43c**, although compound **43e** retained the chlorine atom in fragment ions of low intensity corresponding to $[M-C_2H_5]^+$ and $[M-C_3H_7]^+$ (equation 17). The base peaks in the mass spectra of **43c–f** ($R \neq Me$) formally



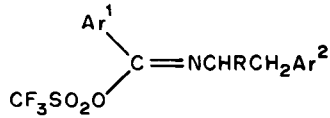
(17)

corresponded to the nitrilium ion $[PhCNH]^+$. The formation of this ion was unfavourable from ionized *N*-methylbenzimidoyl halides **43a** and **43b**, which displayed loss of the constituents of methyl halide forming $[PhCN]^{+\cdot}$ ions at *m/z* 103. Further fragmentation yielded $[C_6H_4]^{+\cdot}$ and $[C_6H_3]^+$ ions, also observed in the mass spectrum of benzonitrile.

The mass spectrometric behaviour of imidoyl trifluoroacetates (**44**) and imidoyl trifluoromethanesulfonates (**45**) has been investigated in the search for a fragmentation



(44)

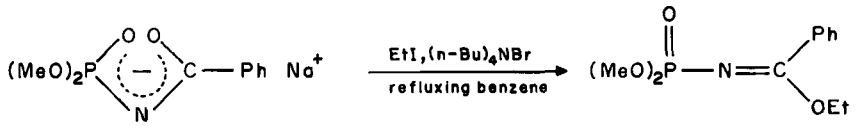


(45)

pattern resembling a retro-Ritter reaction[42]. Compounds **44** and **45**, formally mixed anhydrides, were obtained by the exclusive attack of trifluoroacetic anhydride and trifluoromethanesulfonic anhydride at the oxygen atom of the starting amide. The mass spectra of imidoyl trifluoroacetates **44** were characterized by ion peaks ω responding to $[M-CF_3CO_2]^+$, $[M-CF_3CO_2H]^{+\cdot}$, $[Ar^2CR^2CHR^1]^{+\cdot}$, $[Ar^1CN]^{+\cdot}$ and $[Ar^1CNH]^+$.

The origin of the latter was traced to a retro-Ritter process from the molecular ion, rather than to thermal decomposition in the probe tip. Imidoyl trifluoromethanesulfonates **45** displayed a similar fragment ion distribution.

Ethylation of the sodium salt of *N*-benzoyldimethylphosphoramidate with ethyl iodide in the presence of n-Bu_4NBr in refluxing benzene led to *E* and *Z* *O*-ethyl-*N*-(dimethylphosphoryl)benzimidate (**46a** and **46b**) (equation 18) characterized, *inter alia*, by

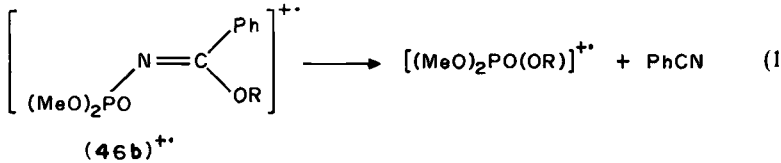


(46)

(a) *E* **isomer**

(b) *Z* **isomer** (18)

the detailed description of their mass spectra[43]. While the most important fragmentation pathways are common to the two geometrical isomers, the abundances of individual ions could be significantly different. A major fragmentation pathway involved loss of neutral $[C_2H_5O_3P]$ with hydrogen rearrangement, to yield formally the radical cation of ethylbenzimidate $[HNC(OEt)Ph]^{+\cdot}$, the base peak at *m/z* 105. The loss of PhCN from $[M]^{+\cdot}$ and $[M-H_2]^{+\cdot}$ ions was about twice more favourable in the case of the *Z* isomer **46b**. This finding was ascribed to the *cis* orientation of the *N*-dimethylphosphoryl group and the migrating OR group (R = Et, C_2H_3) as shown in equation 19.



(46b)$^{+\cdot}$ (19)

However, partial occurrence of *E*/*Z* isomerization of the neutral molecules, prior to ionization, at the ion source temperature used, could not be excluded.

IV. ACKNOWLEDGEMENTS

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V. REFERENCES

1. G. Häfelinger, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Chap. 1, Wiley, New York, 1975, p. 1.
2. J. Barker, M. Jones and M. Kilner, *Org. Mass Spectrom.*, **20**, 619 (1985).
3. A. A. H. Saeed and S. A. Selman, *Can. J. Spectrosc.*, **27**, 123 (1982).

4. N. G. Keats, J. E. Rockley and L. A. Summers, *Z. Naturforsch.*, **32b**, 1156 (1977).
5. A. K. Bose, I. Kugajevsky, P. T. Funke and K. G. Das, *Tetrahedron Lett.*, 3065 (1965).
6. H. F. Grützmacher and H. Kuschel, *Org. Mass Spectrom.*, **3**, 605 (1970).
7. H. Kuschel and H. F. Grützmacher, *Org. Mass Spectrom.*, **9**, 395 (1974).
8. H. Kuschel and H. F. Grützmacher, *Org. Mass Spectrom.*, **9**, 403 (1974).
9. H. Kuschel and H. F. Grützmacher, *Org. Mass Spectrom.*, **9**, 408 (1974).
10. M. Medved, S. Stavber, V. Kramer, L. Benčić and J. Marsel, *Croat. Chem. Acta*, **49**, 415 (1977).
11. R. J. Koshar, D. R. Husted and C. D. Wright, *J. Org. Chem.*, **32**, 3859 (1967).
12. M. F. G. Stevens and A. Kreutzberger, *Angew. Chem., Int. Ed. Engl.*, **8**, 142 (1969).
13. U. P. Schlunegger, S. Leutwyler, F. Friedli and R. Scheffold, *Helv. Chim. Acta*, **58**, 65 (1975).
14. J. H. Beynon, J. A. Hopkinson and A. E. Williams, *Org. Mass Spectrom.*, **1**, 169 (1968).
15. A. G. Loudon, A. Maccoll and K. S. Webb, *Adv. Mass Spectrom.*, **4**, 223 (1968).
16. G. Gattow and T. Kuhlmann, *Z. Anorg. Allg. Chem.*, **494**, 134 (1982).
17. M. A. Baldwin, A. G. Loudon, K. S. Webb and P. C. Cardnell, *Org. Mass Spectrom.*, **12**, 279 (1977).
18. T. Ohwada, A. Itai, T. Ohta and K. Shudo, *J. Am. Chem. Soc.*, **109**, 7036 (1987).
19. S. G. Lias, J. F. Liebman and R. D. Levin, *J. Phys. Chem. Ref. Data*, **13**, 695 (1984).
20. S. Murray and D. S. Davies, *Biomed. Mass Spectrom.*, **11**, 435 (1984).
21. E. L. Esmans, F. G. Alderweireldt, B. A. Marescau and A. A. Lowenthal, *Anal. Chem.*, **56**, 693 (1984).
22. A. Mori, Y. Watanabe, T. Aoyama and Y. Robin, *C. R. Seances Soc. Biol. Ses Fil.*, **178**, 659 (1984).
23. N. P. Buu-Hoi, P. Jacquignon, M. Mangane, S. Béranger and H. Pinhas, *J. Chem. Soc., Perkin Trans. 1*, 278 (1972).
24. H. R. Hudson, A. Lavorenti and M. Pianka, *Chem. Ind.*, 161 (1988).
25. Z. V. Bezuglaya, G. V. Avramenko, V. N. Bochkarev and B. I. Stepanov, *Zh. Obshch. Khim.*, **50**, 131 (1980).
26. W. Eul and G. Gattow, *Z. Anorg. Allg. Chem.*, **538**, 151 (1986).
27. H. Moser, A. Fliri, A. Steiger, G. Costello, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **69**, 1224 (1986).
28. B. M. Zolotarev, O. S. Chizhov, V. A. Dorokhov, L. I. Lavrinovich and B. M. Mikhailov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1312 (1978).
29. W. Höneise, W. Schwarz, G. Heckmann and A. Schmidt, *Z. Anorg. Allg. Chem.*, **533**, 55 (1986).
30. (a) M. Kilner and A. Pietrzykowski, *Polyhedron*, **2**, 1379 (1983).
(b) J. Barker, N. Cameron, M. Kilner, M. M. Mahoud and S. C. Wallwork, *J. Chem. Soc., Dalton Trans.*, 1359 (1986).
(c) J. Barker, M. Kilner and R. O. Gould, *J. Chem. Soc., Dalton Trans.*, 2687 (1987).
31. U. Abram, R. Muenze, J. Hartung, L. Beyer, R. Kirmse, K. Koehler, J. Stach, H. Behm and P. T. Beurskens, *Inorg. Chem.*, **28**, 834 (1989).
32. K. Balasanmugam, J. S. Hartman, J. M. Miller and Z. Yuan, *Can. J. Chem.*, **67**, 685 (1989).
33. For a recent discussion on the mechanism of formation of FAB mass spectra, see: J. Sunner, A. Morales and P. Kebarle, *Int. J. Mass Spectrom. Ion Processes*, **89**, 169 (1988).
34. T. Ueda, A. Takada, K. Takahashi and F. Ueda, *Chem. Pharm. Bull.*, **19**, 1990 (1971).
35. E. Rossi, R. Stradi and A. Benedusi, *Tetrahedron*, **43**, 4785 (1987).
36. J. Tamás, G. Czira, G. Simig and K. Lempert, *Org. Mass Spectrom.*, **10**, 390 (1975).
37. W. Eul and G. Gattow, *Z. Anorg. Allg. Chem.*, **543**, 81 (1986).
38. W. Eul and G. Gattow, *Z. Anorg. Allg. Chem.*, **535**, 159 (1986).
39. V. D. Goldberg and M. M. Harris, *J. Chem. Soc., Perkin Trans. 2*, 1303 (1973).
40. A. A. H. Saeed, S. A. Selman, A. W. A. Sultan and N. A. Abood, *Can. J. Spectrosc.*, **28**, 63 (1983).
41. J. Gal, B. A. Phillips and R. Smith, *Can. J. Chem.*, **51**, 132 (1973).
42. S. Nagubandi, *Org. Mass Spectrom.*, **15**, 535 (1980).
43. V. Mizrahi, T. Hendrickse and T. A. Modro, *Can. J. Chem.*, **61**, 118 (1983).

CHAPTER 6

Thermochemistry of amidines and related compounds

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I. INTRODUCTION

More than 15 years ago[1] Robert Shaw stated that it was embarrasing for a thermochemist to report the lack of experimental data on amidines and related compounds. The situation today is not much better. I will not repeat Shaw's estimates from 1975 but try to review some material related to the thermochemistry of amidines in some respect or another.

II. DIAZENES

Diazenes are a marginal group of compounds for this chapter. They have been included, however, to extend the scope of this review to their relatively abundant thermochemical data[2]. The data for diazenes (**1–10**), diphenyldiazene (**11**), cyclic diazenes (**12–16**) and diazene-*N*-oxides (**17–19**) collected in Table 1 were discussed earlier in Reference 2 (pp. 175–179 and 196) except those for **11** and **19**. Kirchner and his coworkers[6] estimated the dissociation enthalpy of the (N—O) bond [D(N—O) = 321.5 kJ mol^{-1}] in **19** as the

The Chemistry of Amidines and Imidates, Volume 2
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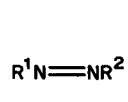

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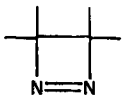

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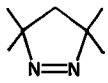

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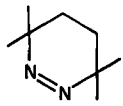

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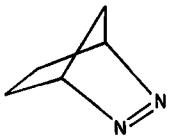

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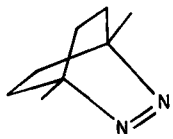


(16)

(17–19)

TABLE 1. Thermochemical data for dialkyl- and some cyclic diazenes and for three diazene *N*-oxides

	trans-Dialkyldiazenes					
	R^1	R^2	State	$\Delta_f H^\circ_m$(cr or l) (kJ mol^{-1})	$\Delta_f H^\circ_m$(g) (kJ mol^{-1})	References
1	Me	Me	—	—	148.6 ± 5.1[a]	2,3
2	Me	Et	—	—	92.2 ± 3.8[a]	2,3
3	Et	Et	—	—	120.4 ± 2.3[a]	2,3
4	Me	Bu	l	42.5 ± 2.2	78.9 ± 2.2	2
5	Pr	Pr	l	11.5 ± 3.5	51.3 ± 3.5	2
6	*i*-Pr	*i*-Pr	l	−0.3 ± 3.5	35.6 ± 3.6[b]	2
7	Bu	Bu	l	−40.1 ± 3.8	9.2 ± 3.8	2
8	*t*-Bu	*t*-Bu	l	−75.5 ± 2.7	−36.4 ± 2.75	2
9	*t*-Bu	1,1,3,3-Me_4-Bu	l	−172.9 ± 5.6	−119.3 ± 5.6	2
10	1,1,3,3-Me_4-Bu	1,1,3,3-Me_4-Bu	l	−263.3 ± 9.3	78.9 ± 2.2	2
11	Ph	Ph	cr	320.5 ± 1.7	414.3 ± 1.8	4,6
	Cyclic Diazenes					
12	3,3,4,4-Me_4-Δ^1-1,2-diazetine		cr	88.0 ± 2.7	150.3 ± 2.9	2
13	1,1,3,3-Me_4-trimethylenediazene		cr	−22.3 ± 3.5	39.3 ± 3.6	2
14	1,1,4,4-Me_4-tetramethylenediazene		l	−8.1 ± 4.6	42.0 ± 4.6	2
15	2,3-diazabicyclo[2.2.1]heptene-2		cr	152.1 ± 2.6	207.4 ± 2.7	2
16	1,4-Me_2-2,3-diazabicyclo-[2.2.2]octene-2		cr	20.4 ± 4.4	92.4 ± 4.4	2
	trans-*N*-Oxides					
17	Di-*n*-propyldiazene *N*-oxide		l	−82.7 ± 1.4	−31.0 ± 1.4	2,5
18	Di-*t*-butyldiazene *N*-oxide		l	−153.5 ± 2.1	−107.6 ± 2.1	2,5
19	Diphenyldiazene *N*-oxide		cr	243.4 ± 2.2	342.0 ± 2.4	6

[a]Estimated values.
[b]Estimated value only 28.9 kJ mol^{-1} (Reference 2).

TABLE 2. Strain energies (S) in compounds 12–16

Compound	$\Delta_f H^\circ_m$(g, obs) (kJ mol^{-1})	$\Delta_f H^\circ_m$(g, calc) (kJ mol^{-1})	S^a (kJ mol^{-1})	S^a/Ref. 7 (kJ mol^{-1})
12	150.3	47.8	102.5	—
13	39.3	27.0	12.3	11.3
14	42.0	6.2	35.8	34.7
15	207.4	134.3	73.1	64.4
16	92.4	48.4	44.0	42.3

[a] $S = \Delta_f H^\circ_m$(g, obs) − $\Delta_f H^\circ_m$(g, calc).

enthalpy of the reaction:

$$trans\text{-PhN=N(O)Ph(g)} = trans\text{-PhN=NPh(g)} + \text{O(g)} \quad (1)$$

where $\Delta_f H^\circ_m$(O, g) is 249.2 kJ mol^{-1} and the values for **19** and **11** are given in Table 1. Similarly, the D(N—O) values for **17** and **18** (331.5 and 320.4 kJ mol^{-1}, respectively) can be derived. The value of D(N—O) in **18** is about 11 kJ mol^{-1} less than in **17**, consistent with steric strain energy in the former[5a], in agreement with a molecular mechanics study[5b].

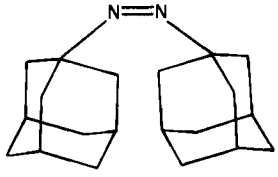
Engel[7] discussed the effect of strain energy on the thermal lability of cyclic diazenes (**13**–**16**) and estimated their strain energies using group contributions taken from the compilation of Benson and O'Neal[8]. We have complemented his data by estimating the strain energies of compounds **12**–**16** (Table 2) using Allen-type increments:

$$\Delta_f H^0_m(\text{g, calc}) = \sum \Delta_f H^\circ(\text{g, atoms}) - \sum E_b(\text{g}) - \alpha \quad (2)$$

where α, for instance, for 3,3,4,4-tetramethyl-Δ^1-1,2-diazetine (**12**) is $6\Gamma_{CCC} + 6\Gamma_{CCN_d} + 2\Delta_{CCC} + 6\Delta_{CCN_d} + \sum$(N=N). The values of the different parameters were taken from the compilation of Pihlaja[2] including Γ_{CCN_d} 18.7, Δ_{CCN_d} −7.7 and $\sum$(N=N) 1043.35 kJ mol^{-1}.

In general the present estimates (Table 2) are 1–2 kJ mol^{-1} higher than those of Engel[7] except that for 2,3-diazabicyclo[2.2.1]heptene-2 (**15**). One must, however, keep in mind that the experimental enthalpy of formation for *trans*-diisopropyldiazene (**6**) used as a model for **15** by Engel is obviously too positive by *ca* 7 kJ mol^{-1}.

Engel and his coworkers[9] also have discussed the energetics of the *cis–trans* isomerization and decomposition of several diazenes (e.g. **5**, **8**, **20** and **21**).



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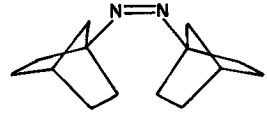


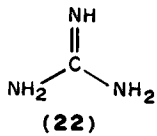
(21)

Foster and Beauchamp[10] studied the gas-phase ion chemistry of dimethyldiazene (**1**) and estimated its proton affinity at 887 ± 21 kJ mol^{-1}, in good agreement with their later estimate[11] of 875.3 ± 0.8 kJ mol^{-1}. In the latter report the ionization energy (8.45 ± 0.05 eV) for *trans*-dimethyldiazene (**1**) was also determined by photoionization mass spectrometry.

III. GUANIDINES

Despite the fact that guanidine and biguanide derivatives are often useful drugs and that the former is frequently incorporated in biologically important compounds, including many of the purines, surprisingly little thermochemical data are available even on this family of compounds.

Gund[12] estimated the delocalization energies of guanidine (**22**) and its cation (**23**) at 1.2β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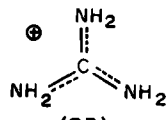
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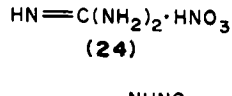
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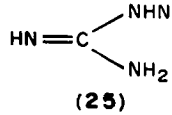
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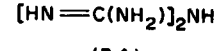

(34)

($83\,kJ\,mol^{-1}$) and 1.6β ($110\,kJ\,mol^{-1}$) stating that the filled orbitals of the 6π electron **23** resemble those of benzene. The loss of 0.6β on deprotonation of **23** is in agreement with Pauling's estimate[13] of 25–34 kJ mol^{-1}.

Lobanov and Karmanova[14] determined enthalpies of combustion and formation for guanidine nitrate [**24**: $\Delta_f H^\circ_m(cr) -405.0 \pm 4.6\,kJ\,mol^{-1}$) and nitroguanidine [**25**: $\Delta_f H^\circ_m(cr)$ -93.7 ± 1.7; for a melted crystal $-100.0 \pm 2.5\,kJ\,mol^{-1}$] but unfortunately they give only > 95% purity for the latter.

Cundall and coworkers[15] carried out vapour pressure measurements on several organic high explosives. In this context they also determined the standard enthalpy, entropy and Gibbs energy for sublimation of **25** at $142.7 \pm 2.0\,kJ\,mol^{-1}$, $116.8\,J\,mol^{-1}\,K^{-1}$ and $107.9 \pm 4.6\,kJ\,mol^{-1}$ respectively. This allows us to estimate $\Delta_f H^\circ_m(g, 25)$ at $(-93.7 \pm 142.7) = 49.0 \pm 5.5\,kJ\,mol^{-1}$ (the statistical error has been taken doubled to make some allowance for the impurity of the sample burnt in Reference 14).

Loudon and his colleagues[16] measured the electron impact (EI) ionization energies for guanidine (**22**) and several methyl substituted derivatives (**26–33**). These results were discussed later by Baldwin and coworkers[17] in relation to those for phosphoramides, formamides, acetamides, ureas and thioureas. In comparison with photoelectron spectra of formamides and acetamides[18] they found that the EI ionization energies did not give the ionization energy of the HOMO but values which were weighted averages of the ionization energies of all the orbitals concerned. The observations for **22** and **26–33** were best explained by assuming that the ionization energy of the imino nitrogen lone pair was a few tenths of an eV below that of the amino nitrogen lone pair (Table 3).

TABLE 3. The electron impact ionization energies [I(M)] for guanidine (**22**) and its methyl derivatives (**26–33**), $R^1C(=NR^3)NR^2$

Compound	R^1	R^2	R^3	I(M)(eV)
22	NH_2	NH_2	H	9.10
26	NHMe	NH_2	H	8.60
27	NHMe	NH_2	Me	8.40
28	NMe_2	NH_2	H	8.20
29	NHMe	NHMe	Me	8.15
30	NMe_2	NH_2	Me	8.05
31	NMe_2	NHMe	Me	7.95
32	NMe_2	NMe_2	H	8.10
33	NMe_2	NMe_2	Me	7.85

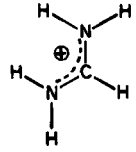
TABLE 4. Thermodynamic quantities in aqueous solution at 253 K for some neutralization processes

Process	$-\Delta H$ (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})	$-\Delta G$ (kJ mol^{-1})
$H^+ + OH^- = H_2O$	56	111	89
$H^+ + 22 = 23$	76	8	78
$H^+ + 34 = [34]H^+$	95	−71	74
$H^+ + [34]H^+ = [34]H_2^{2+}$	21	−13	17

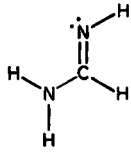
Fabbrizzi and his collaborators[19] showed that the protonation of guanidine (**22**) and biguanide (**34**) is 25 and 70‰, respectively, more exothermic than the neutralization of OH^-, the strongest base in aqueous solution. This effect is caused by the symmetrization of the mesomeric molecules during the process and the increased rigidity of the protonated base molecules is reflected by the unusual low and even negative entropy changes (Table 4).

IV. AMIDINES

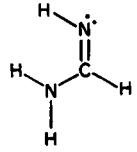
Zielinski and coworkers[20] performed *ab initio* SCF MO calculations for protonated (**35** A, H) neutral (**35**B,C) and deprotonated amidine (**35**F) using the 3-21G split valence basis set since amidine (**35**) is the simplest model, e.g. for the protonation and deprotonation of the N(3)–C(4)–NH_2 region in cytosine (**36**) and the N(1)–C(6)–NH_2 region of adenine (**37**).



(A) C_{2v}

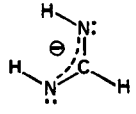


(B) C_s

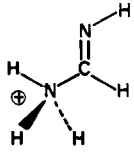


(C) C_s

(**35**)



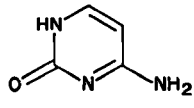
(F) C_{2v}



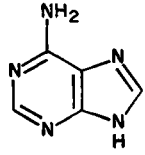
(H) C_s

A > H >> B ≈ C >> F

Ease of protonation



(**36**)

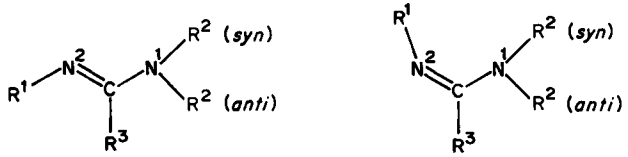


(**37**)

Protonation at the amidine (**35**) =NH site (planar form A) was calculated as being preferred over the $—NH_2$ site (form H) by 155 kJ mol^{-1}. Neutral amidine showed two, almost equally stable minima, B (rel. *E* 0.0 kJ mol^{-1}) and C (2.5 kJ mol^{-1}). The barriers to rotation about the C—N single bond were calculated at 49 and 40 kJ mol^{-1} for B and C, respectively. These can be compared with the rotational barriers about the exocylic C—N bond of cytosine (**36**), the double-bond character of which can be, however, somewhat increased due to conjugation with the heteroaromatic ring in **36**. The experimental activation energies for this rotation range from 36 to 74 kJ mol^{-1}, depending on the solvent and method used[21].

The minimum energy conformation for the anionic amidine is F. Its proton affinity is computed to be 1695 kJ mol^{-1} and it is very unstable compared to the neutral and cationic forms (by 2670 and 1700 kJ mol^{-1}, respectively).

Because of hindered rotation around the N(2)=C bond, substituted amidines can attain two configurations, one with the R^1 substituent *E* and the other with R^1 *Z* to the N(1). Two



(3)

conformations, with R^2 *syn*- or *anti*-periplanar to the N(2) nitrogen, are distinguishable when the rotation about the C—N(1) bond is slowed down sufficiently, and separate signals appear for the two R^2 groups in, e.g., ^{13}C NMR spectra. Waver has studied and reviewed the rotational barriers in substituted formamidines, acetamidines and butyramidines[22].

She found that electron-accepting substituents at the phenyl ring increase and electron-donating substituents decrease the barrier for rotation about the C—N(1) bond in *N*(1),*N*(1)-penta- (**38**) and -hexamethylene-*N*(2)-(*p*-substituted)phenylformamidines (**39**), which correlate linearly with the ^{13}C NMR chemical shift (δ) of the amidine carbon atom and with the Hammett σ constant[22a]:

$$\Delta G^{\neq}\,(\text{kJ mol}^{-1}) = -615.9 + 4.495\delta \text{ (for } \mathbf{38},\ r = 0.991)$$

$$\Delta G^{\neq}\,(\text{kJ mol}^{-1}) = -508.7 + 3.826\delta \text{ (for } \mathbf{39},\ r = 0.992)$$

$$\Delta G^{\neq}\,(\text{kJ mol}^{-1}) = 60.1 + 8.525\sigma \text{ (for } \mathbf{38},\ r = 0.992)$$

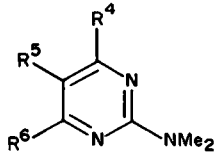
$$\Delta G^{\neq}\,(\text{kJ mol}^{-1}) = 69.6 + 8.331\sigma \text{ (for } \mathbf{39},\ r = 0.975)$$

When comparing *N*(1),*N*(1)-dimethyl-*N*(2)-(*m*-substituted)phenylformamidines (**40**) and -acetamidines (**41**; equation 3: R^3 = H or Me, respectively) with each other[22b] it was found that the barrier heights in **41** (51–59 kJ mol^{-1}) are in general about 10 kJ mol^{-1} lower than in **40**, mainly due to a steric interaction of the C—Me group with aromatic protons; this leads to non-planarity and a decrease in the conjugation. The barriers to rotation of **41** correlate again with the Hammett σ values ($\Delta G^{\neq} = 52.7 + 6.97\sigma$, $r = 0.968$).

The rotational barriers about the C—N(1) bond of *N*(1),*N*(1)-dimethyl- and *N*(1),*N*(1)-hexamethylene-*N*(2)-phenylformamidines did not show significant changes (usually less than 1 kJ mol^{-1} only) in different solvents[22b].

The low-temperature ^{13}C NMR spectra of ten formamidines (equation 3: $R^3 = H$) indicated that the barrier to rotation about the C—N(1) bond for R^1 = alkyl, benzyl and phenyl (cf. equation 3) is *ca* 51, 52 and 63 kJ mol^{-1}, respectively, and the height of the barrier is related to Taft substituent constants for R^1 (equation 3): $\Delta G^{\neq} = 49.25 + 8.08\sigma^* - 3.21E_s$. The barriers for rotation around the C—N(1) bond of alkyl substituted (R^1 = alkyl) acetamidines and (*m*-substituted)phenyl-substituted butyramidines (Bu derivatives preferred *Z* instead of *E* isomers; cf equation 3) were too low to be measured and phenylacetamidines (R^1 = Ph or substituted Ph) gave barriers similar to those of *N*(2)-alkylformamidines[22d,23].

For comparison one should mention that Riand and his coworkers[24] determined the free energies of activation ($\Delta G^{\neq}$) for hindered rotation around the exocyclic C—N bond in a series of 2- (**42**) and 4-(*N*,*N*-dimethylamino)pyrimidines (**43**) by ^1H and ^{13}C NMR lineshape analysis. The barrier heights varied from 38 to 60 kJ mol^{-1} for **42** and from 43 to 64 kJ mol^{-1} for **43**. The differences between these barriers for the corresponding



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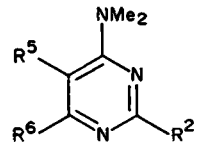


(43)

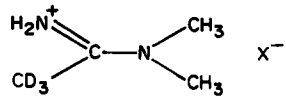
(a) $R^4 = NHNH_2$, $R^5 = R^6 = H$
(b) $R^4 = Cl$, $R^5 = H$, $R^6 = OCH_2Ph$
(c) R^4 = piperidin-1′-yl, $R^5 = H$, $R^6 = Cl$
(d) R^4 = 4′,6′-Cl_2-pyrimidin-2′-yl, $R^5 = R^6 = H$
(e) R^4 = 4′-NMe_2-6′-Cl-pyrimidin-2′-yl, $R^5 = R^6 = H$
(f) $R^4 = NMe_2$, $R^5 = Me$, $R^6 = H$
(g) $R^4 = NMe_2$, $R^5 = H$, $R^6 = Me$
(h) $R^4 = NMe_2$, $R^5 = NO_2$, $R^6 = H$
(i) $R^4 = NMe_2$, $R^5 = H$, $R^6 = Cl$
(j) $R^4 = OH$, $R^5 = R^6 = H$

(a) $R^2 = R^5 = R^6 = H$
(b) $R^2 = Cl$, $R^5 = R^6 = H$
(c) $R^2 = R^6 = Me$, $R^5 = H$
(d) $R^2 = Cl$, $R^5 = H$, $R^6 = Me$
(e) $R^2 = R^6 = Cl$, $R^5 = H$
(f) $R^2 = Cl$, $R^5 = H$, $R^6 = OCH_2Ph$
(g) $R^2 = NMe_2$, $R^5 = R^6 = H$
(h) $R^2 = NMe_2$, $R^5 = Me$, $R^6 = H$
(i) $R^2 = NMe_2$, $R^5 = H$, $R^6 = Me$
(j) $R^2 = NMe_2$, $R^5 = NO_2$, $R^6 = H$
(k) $R^2 = NMe_2$, $R^5 = H$, $R^6 = Cl$
(l) $R^2 = R^6 = Cl$, $R^5 = SMe$

symmetrical and unsymmetrical pyrimidines decrease with increasing electron-withdrawing power of the substituent, and substituent effects through the ring nitrogen atom were larger than through a ring carbon atom[24b]. Correlations of the ($\Delta G^{\neq}$) values with the $^1J_{C,H}$ coupling constant for the dimethylamino group and Hammett constants are discussed.

Neuman and Jonas[25] found it possible to obtain rotational barrier data with NMR lineshape analysis for the nitrate and chloride salts of *N*,*N*-dimethylacetamidinium-d_3 ion (**44a,b**) in 1,1,2,2-tetrachloroethane and DMSO at very low concentrations ($\Delta G^{\neq}$ = 92.5/90.0 for **44a** and 90.8/91.2 kJ mol^{-1} for **44b**, respectively). An attempt to relate these results to ion pairing and solute–solvent interactions was also made.

Thermodynamic data for proton ionization of several *N*(2)-substituted *N*(1),*N*(1)-dimethylacetamidinium ions in ethanol are reported[26] as well as the gas-phase basicities of a few *N*(1),*N*(1)-dimethyl-*N*(2)-(*p*-substituted)phenylformamidines[27].

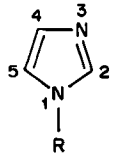


(44a) X = NO_3
(44b) X = Cl

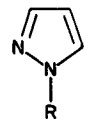
V. CYCLIC AMIDINES

A. Imidazoles

The importance of imidazole (**45**) has been emphasized[28]. Recently, the enthalpy of sublimation of imidazole has been determined by several groups of authors[29–31]. Effusion methods[29] seem to give the most reliable value (80.4–85.4 kJ mol^{-1}) whereas calorimetry appears to give a too small value (74.5 kJ mol^{-1} [30]). Jiménez and coworkers[29] redetermined the enthalpy of combustion for **45**, $\Delta_c H^\circ_m = -1801.9 \pm 0.5$ kJ mol^{-1}, which



(45 R = H)



(46)

deviates significantly from a previous value[32], -1810.6 ± 3.3 kJ mol^{-1}. Together with their enthalpy of fusion, 83.1 ± 0.2 kJ mol^{-1}, we can estimate the selected values for the enthalpies of formation of **45**, $\Delta_f H^\circ_m$ (cr and g) = 49.8 ± 0.6 and 132.9 ± 0.6 kJ mol^{-1}, respectively. Similarly, Jiménez and his group[29] determined $\Delta_f H^\circ_m$(cr) = 79.5 ± 1.5, $\Delta_{sub} H^\circ_m$ = 102.2 ± 0.4 and $\Delta_f H^\circ_m$(g) = 181.7 ± 1.4 kJ mol^{-1} for benzimidazole.

Guthrie and Pike[33] measured enthalpies of hydrolysis for three acylimidazole acetals [**45a,b,c**; R = $HC(OEt)_2$, $MeC(OEt)_2$ and $PhC(OMe)_2$, respectively] and used them to estimate their enthalpies of formation in the liquid and gaseous states (Table 5). In the same context they estimated the enthalpy of formation of **45** in the gas phase at 139.3 $\pm$ 1.9 kJ mol^{-1}. This is *ca* 6 kJ mol^{-1} more positive than the selected value[29] given above, which in turn is reflected in the values listed in Table 5.

The ionization energy[34] (8.96 eV) and proton affinity[35] (920.5 kJ mol^{-1}) for imidazole (**45**) have been reported.

Catalán and coworkers carried out INDO calculations of the protonation (ΔE_p) and lone pair orbital energies (ε_N) of twenty pyrazoles (**46**) and twenty imidazoles[36] with Me, CN, F, NH_2 and NO_2 substituents and observed a linear correlation between these

TABLE 5. Enthalpies of formation in the gaseous and liquid states and the Gibbs energies of formation for acylimidazole acetals (**45a–c**) in aqueous solution

Compound	$\Delta_f H^\circ_m$(l) (kJ mol^{-1})	$\Delta_f H^\circ_m$(g) (kJ mol^{-1})	$\Delta_f G^\circ_m$(aq) (kJ mol^{-1})
45a	-329.3 ± 2.8	-255.3 ± 3.0	-32.0 ± 4.9
45b	-368.9 ± 2.0	-296.8 ± 2.3	-40.6 ± 4.8
45c	-163.0 ± 3.6	-77.5 ± 3.7	142.6 ± 6.4

properties. Derivatives with a nitro substituent, however, gave a different linear correlation:

$$(\Delta E_p) = 679.6 + 675.9\varepsilon_N \quad (r = 0.981;\ \text{excluding } NO_2 \text{ compounds})$$

$$(\Delta E_p) = 765.3 + 819.7\varepsilon_N \quad (r = 0.991;\ NO_2 \text{ compounds})$$

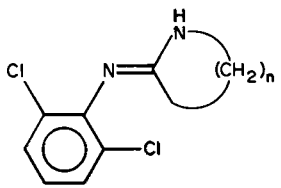
These correlations describe the modification of the reactivity centre by the polar substituents. In the case of the NO_2 substituents, the deviation from the common plot was stated to be due to some mixing of the orbitals on the nitrogen lone pair and on the nitro group.

B. Tautomerism

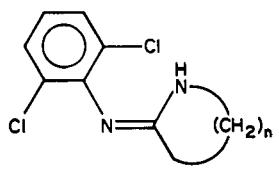
Several reports deal with the tautomerism in imidazole (ImH) and related systems. Jackman and Jen[37] discuss the use of ^1H and ^{13}C NMR chemical shifts to determine unambiguously the predominant tautomeric form of many aryl cyclic amidines and guanidines, 2-aminoimidazoles, 2-imino(amino)thiazines and related tautomeric systems like aryl acetamidines and aryl guanidines. Their results show that in all the potentially tautomeric systems studied the predominant tautomer was the aryl imino form [ArN=C(NHR)R'] rather than the amino form [ArNHC(=NR)R']. In some cases, e.g. for **47** and **48**, both *syn* and *anti* forms could be found at low temperatures. Gründeman and his group[37b] discuss qualitatively the prototropic processes at *N*(1),(3) and *N*(*exo*) in several *N*-acylated 2-aminobenzimidazoles.

Jiménez and his coworkers[38] studied the tautomeric equilibria of 4(5)-nitroimidazole (**49** and **50**) by MNDO and *ab initio* calculations and by dipole moment, solution and sublimation enthalpy measurements and MIKE and photoelectron spectra. The results showed that in the gas phase both tautomers are of similar energy but in water solution the 4-nitro tautomer (**49**) is stabilized by 12.6 kJ mol^{-1} due to its more effective solvation effect, which is probably due to the large difference in dipole moments (**49** 7.51*D* and **50** 3.87*D*, models 1-methyl-4-nitro- and 1-methyl-5-nitroimidazoles 7.36 and 4.07*D*, respectively).

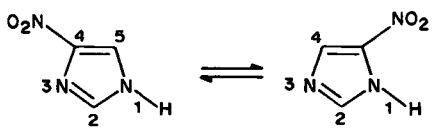
Munowitz and coworkers[39] have discussed the acid–base equilibria in the solid state using ^{15}N NMR spectroscopy of histidine (**51**). Bolton and McClelland[40] carried out *ab initio* calculations with the split-valence 3-21G basis set on imidazole nitrenium and carbenium ions, but these calculations are mainly of theoretical interest.



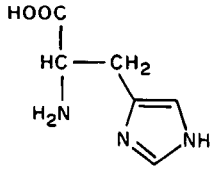
syn−**47** (n=2)
syn−**48** (n=3)



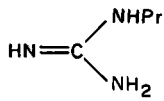
anti−**47** (n=2)
anti−**48** (n=3)



(49) **(50)**



(51)



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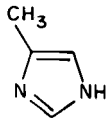


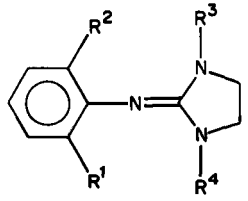
(53)

Recently, Scheraga and his group[41] improved a model for the free energy of hydration of conformationally flexible solute molecules by introducing an exact method for the calculation of the volume of the hydration shells and by improved selection of the numerical parameters. In this context they also compared the calculated and experimental free energies of hydration for propylguanidine (**52**) and 4-methylimidazole (**53**): -45.7 vs $-45.7\,kJ\,mol^{-1}$ for **52** and -43.6 vs $-42.9\,kJ\,mol^{-1}$ for **53**.

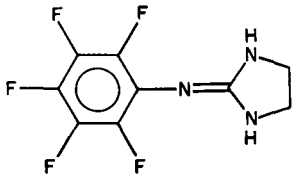
Solvent effects on the acidity and basicity of twelve azoles, including several imidazoles, have been calculated with fully optimized INDO geometries[42] in terms of protonation and deprotonation energies. Molar heat capacities of imidazole (**45**)[43,44] and benzimidazole[44] have been reported. The enthalpies of dissociation of ImH_2^+ and ImH have been measured at several temperatures and ionic strengths in water solution[45] and in aqueous methanol solvents[46]. Paiva and his group[47] discuss ionization of methyl derivatives of imidazole (**45**), histidine (**51**), thyreotropin releasing factor and related compounds in aqueous solutions. Jensen[48] studied the energetics of the complex formation between cadmium and **45** in aqueous solution and Sletten and Stögård[49] carried out SCF *ab initio* calculations for Li^+ and Cu^+ complexes of **45**.

C. Clonidine and Related Structures

Clonidine, 2-[(2,6-dichlorophenyl)imino]imidazolidine (**54**), is an antihypertensive drug widely used therapeutically. Therefore, even its energetic properties have been frequently discussed. de Jong and van Dam[50] employed UV photoelectron spectroscopy (UV PES) and CNDO/s molecular orbital calculations to investigate the electronic



	R^1	R^2	R^3	R^4
54	Cl	Cl	H	H
55	Cl	H	H	H
56	H	H	H	H
57	Me	H	H	H
58	Me	Me	H	H
59	Cl	Cl	Me	Me
60	F	F	H	H



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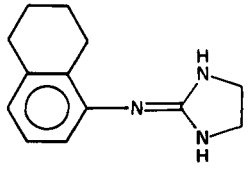


(62)

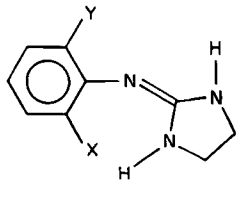
structure of clonidine and related 2-(arylimino)imidazolidines (**54–62**, Table 6). The assignment of the different bands (ionization energies) in the UV PE spectra was carried out by the CNDO/s calculations, substituent effects and differences in intensities between He(I) and He(II) spectra. The results showed that the phenyl and imidazolidine rings are perpendicular for all investigated 2-(arylimino)imidazolidines (Table 6). The first ionization energies of the pharmacologically active derivatives did not correlate with hypotensive activity[50].

TABLE 6. Ionization energies (eV) of **54–62** and their assignments[51]

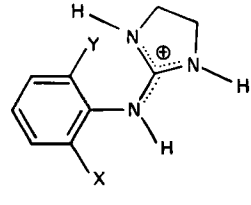
Compound	π_1	Ph_A	$\pi_{C=N}$	n_{N^-}	π_2
54	8.01	8.62	8.88	9.24	10.34
55	7.96	8.80	8.90	9.24	10.32
56	7.85	8.86	8.98	9.22	10.15
57	7.75	8.60	8.75	9.26	10.14
58	7.63	8.33	8.60	9.25	10.04
59	7.84	8.7	8.7	8.4	10.38
60	8.12	9.09	9.09	9.28	10.63
61	8.60	9.52	9.52	9.85	10.99
62	7.62	8.34	8.56	9.26	10.04

Pook and coworkers[51] applied ^1H and ^{13}C NMR spectroscopy to indicate with the aid of different model compounds, e.g. **59**, that **54** and **56** exist as 2-(arylimino)imidazolidine tautomers.

Timmermans and his group[52] established the ground state geometry of **54** (X = Y = H, interplanar angle $\theta = 34°$) and its protonated form **54H**$^+$ ($\theta = 40°$) by CNDO/2



(**54** X = Y = H)

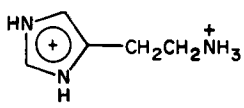


54H$^+$

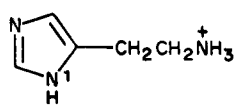
calculations. The preferred conformations of several free bases (**54** and related compounds) and their protonated forms were used as inputs for the semi-empirical calculation method used to obtain several quantum-mechanical parameters. The calculated parameters gave good correlations with the experimentally determined pK_a values of the molecules. Avbelj and Hadzi[53a] in turn concluded that the potential energy functions for 2-(arylimino)imidazolidines, e.g. **54**, indicate that the molecules assume any conformation within rather broad limits, and they derived equations connecting the conformational entropy with pK_i (K_i = dissociation constant) for [^3H]clonidine displacement[53b].

D. Histamines

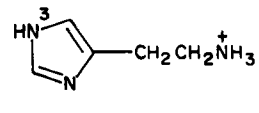
It is well known that histamine, β-(4-imidazolyl)ethylamine, interacts with two kinds of human receptors: the H_1 and H_2 receptors. The interaction with the former stimulates the smooth muscles, induces a strong depressive action and produces a



(63a)

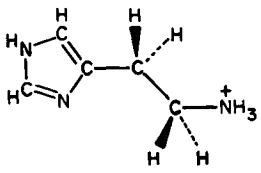


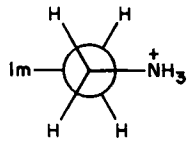
(63b)



(63c)

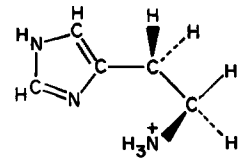
trans, $\theta_2 = 180°$

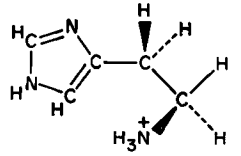


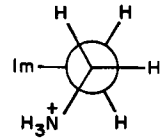


(63d)

gauche, $\theta_2 = 60°$ or $300°$







(63e)

characteristic clinical pattern of the allergic reactions. The interaction with the latter stimulates in turn the gastric secretions[54]. This is why histamine has been frequently studied both energetically and structurally.

Genellin and his coworkers[55a] applied molecular orbital calculations (EHT and CNDO method, Table 7) and ^{1}H NMR spectroscopy to determine the conformational energies of the histamine dication **63a** and of the two tautomeric forms of its monocation (**63b,c**) and to inspect the relative population of the *trans/gauche* rotamers (**63d,e**). The NMR data indicated that **63a** favoured slightly the *trans* form (**63d**, $x = 0.54$) and the monocation (**63b,c**) the *gauche* form (**63e**, $x = 0.55$). Methylation at the amino group of histamine increased the relative mole fraction (x) of the *trans* rotamer of the analogue of **63a** to 0.57 for $-{}^+NH_2Me$, to 0.72 for $-{}^+NHMe_2$ and to 0.92 for $-{}^+NMe_3$.

The *trans/gauche* conformer ratios for α- and β-methyl- and *N,N*-dimethylhistamines[55b] were predicted to be quite different (0.1, 0.02 and 4, respectively). However, none of these compounds showed significant biological selectivity. Despite the fact that 2- and 4-methylhistamines have very similar *trans/gauche* conformer populations, they showed a 1000-fold difference in their activity ratios. Although the side-chain rotamer preference did not appear to determine whether the conformationally mobile derivatives distinguish between H_1 and H_2 receptors, an altered rotamer preference was accompanied by reduced activity and the *trans* conformer appeared to be involved in both types of histamine receptor.

TABLE 7. Total energies by CNDO of minimum energy conformations for different histamine species

Species	*trans* ($\theta_2 = 180°$) θ_1 (deg)	*trans* ($\theta_2 = 180°$) E (au[a])	*gauche* ($\theta_2 = 300°$) θ_1 (deg)	*gauche* ($\theta_2 = 300°$) E (au[a])
63b	0	−78.2687	0	−78.2531
63c	0	−77.9065	60	−77.9125
63d	180	−77.9158	240	−77.9257

[a] 1 au = 27.2 eV = 2625.5 kJ mol^{-1}.

Later on Ganellin and his group[55c] calculated conformational energies of histamine and 4-methylhistamine monocations using the EHT molecular orbital procedure and expressed the results as potential energy surfaces. Their pre-assumption was that such a procedure provides a quantitative basis for comparison with other histamine derivatives. The general value of an approach of this type for studying relationships between conformation and biological activity (without parallel experimentation) is still open for argumentation. Ganellin[56] also returned to the question of imidazole geometry and histamine tautomerism and showed, using *ab initio* calculations, that histamine monocation favored N(3) tautomer (**63c**), whereas histamine base did not show a clear tautomer preference.

Topiol[57] carried out MNDO, MINDO/3 and *ab initio* calculations to study tautomerism in **63** and 2- and 4-methylhistamines. Despite some differences in the values of structural parameters, the changes in structure upon tautomerization and/or protonation predicted by the different methods were very similar. The MNDO method appeared to give a better quantitative agreement with the 3-21G and STO-3G results than the MINDO/3 method.

Jauregui and coworkers[58] carried out empirical atom–atom potential calculations for the above molecules and suggested that mobile *gauche* and *trans* conformations would be active with H_1 receptors whereas fairly rigid *gauche* conformations would be active with H_2 receptors.

Abraham and Birch[59] introduced the counter-ion into complete neglect of differential overlap (CNDO) calculations of conformations of **63a,b,c** and obtained results in good agreement with the conformations observed in aqueous solution.

According to Kang and Chou[60], *ab initio* and INDO molecular orbital calculations on histamine showed that the monocation (**63c**) favours the N(3) tautomer in agreement with the conclusion of Ganellin and his group[56]. In contrast to the opinion of the latter workers Kang and Chou were able to conclude that the neutral molecule favours the N(1) tautomer.

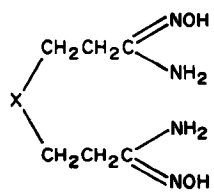
Xiao-Yuan and Shu-Jun[61] calculated energies of protonation (pE) and tautomerization for **63** and methylhistamines using the CNDO/2 method. The pE values showed the same trend as the pK_a values determined in aqueous solution. However, there was no apparent relation between the calculated pE and the biological activities. The relative stability of the N(1) and N(3) tautomers did reflect the H_2 receptor agonist activities: the smaller the energy of the former, the greater its activity.

Hernandez-Laguna and collaborators[54] calculated the charge distribution and conformational energy maps for **63** using (localized) CNDO/2 and *ab initio* STO-4G methods.

Sakurai and Takeshima[62] determined thermodynamic parameters for the acid dissociation of 2-mercaptohistamine, ergothioneine, 2-mercaptoimidazole, *N*-methyl-2-mercaptoimidazole and histamine dihydrochloride and compared them with literature data.

VI. AMIDOOXIMES

Cerdá and his group[63] studied the thermometric behaviour of three amidooximes (**64**–**66**) and evaluated thermodynamic quantities for their dissociation from the pK_a values and neutralization enthalpies (Table 8).



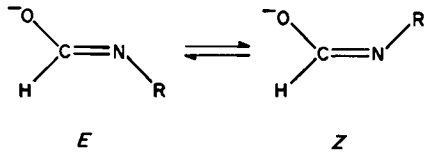
(**64**) X=NH
(**65**) X=O
(**66**) X=S

TABLE 8. Values of ΔG_i, ΔH_i and ΔS_i for **64–66**

Compound	i	pK(i)	ΔG_i (kJ mol^{-1})	ΔH_i (kJ mol^{-1})	ΔS_i (J mol^{-1} K^{-1})
64	1	3.54	20.2	30.0	32.8
	2	4.58	26.2	25.7	−1.4
	3	8.47	48.4	36.0	−41.0
65	1	4.61	26.3	32.9	22.0
	2	5.83	33.3	27.5	−19.4
66	1	4.95	28.2	31.3	10.2
		5.89	33.6	29.8	−12.8

VII. IMIDATES AND IMINIUM SALTS

Perrin and Thoburn[64] studied the kinetics of *E/Z* isomerization of *N*-arylformimidate anion, HC(O$^-$)=NAr (equation 4), in *N*-methylpropionamide solvent by an NMR saturation–transfer method. A Hammett plot of the rate constants gave a slope ρ of 2.3 or 2.1, which was very close to that observed in similar imine stereoisomerizations. Therefore, it can be concluded that *E/Z* isomerization of imidate anions proceeds by nitrogen inversion, despite a high-level MO calculation that favoured C—N rotation.



(4)

Two more reports are worth mentioning. Rabiller and coworkers[65] showed by dynamic ^{13}C NMR studies that the rotation about the C—N bond is generally slow and used relaxation time (T_1) measurements for a qualitative description of the molecular motion of iminium salts. Barr and his research group[66] carried out variable-temperature and variable-concentration ^{1}H and ^{7}Li NMR studies on hexameric iminolithium compounds, $(R^1R^2C{=}NLi)_6$, where (R^1, R^2) are (Me_2N, Ph), (Me_2N, Me_2N), (*t*-Bu, Ph) and (*t*-Bu, *t*-Bu).

VIII. MISCELLANEOUS

Due to the diffuse nature of this chapter there are several reports which deserve to be mentioned but do not fit under any other topic.

The enthalpy of sublimation (176 ± 10 kJ mol^{-1}) of cytosine has been determined and its enthalpy of formation in the gaseous state (−59.4 ± 10.0 kJ mol^{-1}) derived[67].

Benoit and Fréchette[68] studied calorimetrically solvent effects on the protonation of some purines, pyrimidines and related compounds.

A few reports deal with thermal decomposition (dec) and dissociation (dis) of guanidinium salts: nitrate (dec)[69a], acetate, carbonate, chloride, chromate, nitrate, sulphate and thiocyanate (dis)[69b] and nitroguanidine (dec)[69c]. Ratcliffe's NMR investigations on the molecular motion of guanidinium chloride, bromide and iodide should also be mentioned[70].

IX. CONCLUDING REMARKS

It is a pity that so little, strictly thermochemical material is available on amidines and related compounds. Obviously, working with them must be very difficult, which finds support in the strong theoretical orientation of many investigations quoted.

This author does not believe that we can ever replace the motivation and enjoyment of successful experimentation by a mere theoretical approach. Therefore, more empirical thermochemical investigations within this biologically and physiologically important category of compounds are very much needed. However, trying to compile something useful from so diffuse and limited sources of information has been a real learning experience. Nevertheless, I would not be willing to repeat it too often.

X. REFERENCES

1. R. Shaw, *Estimation of the Thermochemistry of Imidic Acid Derivatives*, Chap. 11 in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, Chichester, 1975.
2. K. Pihlaja, *Thermochemical Methods in the Structural Analysis of Organic Compounds*, Chap. 5 in *Molecular Structure and Energetics*, Vol. 2 (Eds. J. F. Liebman and A. Greenberg), VCH Publishers, Inc., New York, 1987.
3. F. D. Rossini and R. L. Montgomery, *J. Chem. Thermodyn.*, **10**, 465 (1978).
4. L. G. Cole and E. C. Gilbert, *J. Am. Chem. Soc.*, **73**, 5423 (1951).
5. (a) K. Byström, *J. Chem. Thermodyn.*, **13**, 139 (1981).
   (b) K. Byström, *J. Comput. Chem.*, **4**, 308 (1983).
6. J. J. Kirchner, W. E. Acree Jr., G. Pilcher and L. Shaofeng, *J. Chem. Thermodyn.*, **18**, 793 (1986).
7. P. S. Engel, *J. Am. Chem. Soc.*, **98**, 1972 (1976).
8. S. W. Benson and H. E. O'Neal, *Natl. Stand. Ref. Data Ser., Natl. Bur. Stand.*, **No. 21** (1970).
9. P. S. Engel, R. A. Melaugh, M. A. Page, S. Szilagyi and J. W. Timberlake, *J. Am. Chem. Soc.*, **98**, 1971 (1976) and references cited therein.
10. M. S. Foster and J. L. Beauchamp, *J. Am. Chem. Soc.*, **94**, 2425 (1972).
11. M. S. Foster, A. D. Williamson and J. L. Beauchamp, *Int. J. Mass Spectrom. Ion Phys.*, **15**, 429 (1974).
12. P. Gund, *J. Chem. Educ.*, **49**, 100 (1972).
13. L. Pauling, *The Nature of the Chemical Bond*, 3rd ed., Cornell University Press, Ithaca, New York, 1960, p. 286.
14. G. A. Lobanov and L. P. Karmanova, *Izv. Vyssh. Zaved., Khim. Khim. Tekhnol.*, **14**, 865 (1971).
15. R. B. Cundall, T. F. Palmer and C. E. C. Wood, *J. Chem. Soc., Faraday Trans. 1*, **74**, 1339 (1978).
16. A. G. Loudon, A. Maccoll and K. S. Webb, *Adv. Mass Spectrom.*, **4**, 223 (1968).
17. M. A. Baldwin, A. G. Loudon, K. S. Webb and P. C. Cardnell, *Org. Mass Spectrom.*, **12**, 279 (1977).
18. D. A. Sweigert and D. W. Turner, *J. Am. Chem. Soc.*, **94**, 5592 (1972).
19. L. Fabbrizzi, M. Micheloni, P. Paoletti and G. Schwarzenbach, *J. Am. Chem. Soc.*, **99**, 5574 (1977).
20. T. J. Zielinski, M. R. Peterson, I. G. Czismadia and R. Rein, *J. Comput. Chem.*, **3**, 62 (1982) and references cited therein.
21. J. S. Kwiatkowski and B. Pullman, *Adv. Heterocycl. Chem.*, **18**, 199 (1975).
22. (a) I. Waver, *Magn. Reson. Chem.*, **25**, 514 (1987) and references cited therein.
    (b) I. Waver, *Magn. Reson. Chem.*, **26**, 601 (1988) and references cited therein.
    (c) I. Waver, *Magn. Reson. Chem.*, **27**, 577 (1989).
    (d) I. Waver, *Magn. Reson. Chem.*, **27**, 1031 (1989) and references cited therein.
23. I. Waver, *J. Mol. Struct.*, **218**, 165 (1990).
24. (a) J. Riand, M.-Th. Chenon and N. Lumbroso-Bader, *J. Chem. Soc. Perkin Trans. 2*, 1248 (1979).
    (b) J. Riand, M.-Th. Chenon and N. Lumbroso-Bader, *J. Chem. Soc. Perkin Trans. 2*, 1551 (1987).
25. R. C. Neuman and V. Jonas, *J. Org. Chem.*, **39**, 929 (1974).
26. E. D. Raczynska, *J. Chem. Res. (S)*, 20 (1987).
27. M. Borgarello, R. Houriet, E. D. Raczynska and T. Drapala, *J. Org. Chem.*, **55**, 38 (1990).
28. C. A. Matuszak and A. J. Matuszak, *J. Chem. Educ.*, **53**, 280 (1976).
29. P. Jiménez, M. V. Roux, C. Turrión and F. Gomis, *J. Chem. Thermodyn.*, **19**, 985 (1987) and references cited therein.

30. R. Sabbah, *Thermochim. Acta*, **41**, 33 (1980).
31. H. G. M. DeWit, J. C. van Miltenburg and C. G. de Gruif, *J. Chem. Thermodyn.*, **15**, 651 (1983).
32. A. F. Bedford, P. B. Edmondson and C. T. Mortimer, *J. Chem. Soc.*, 2927 (1962).
33. J. P. Guthrie and D. C. Pike, *Can. J. Chem.*, **65**, 1951 (1987).
34. B. G. Ramsey, *J. Org. Chem.*, **44**, 2093 (1979).
35. S. G. Lias, J. F. Liebman and R. D. Levin, *J. Phys. Chem. Ref. Data*, **13**, 695 (1984).
36. J. Catalán, P. Pérez and J. Elguero, *Heterocycles*, **20**, 1717 (1983) and references cited therein.
37. (a) L. M. Jackman and T. Jen, *J. Am. Chem. Soc.*, **97**, 2811 (1975).
(b) E. Gründemann, H. Graubaum, D. Martin and E. Schiewald, *Magn. Reson. Chem.*, **24**, 21 (1986).
38. P. Jiménez, J. Laynes, R. M. Claramant, D. Sanz, J. P. Fayet, M. C. Vertut, J. Catalán, J. L. G. de Paz, G. Pfister-Guillouzo, C. Guimon, R. Flammang, A. Maquestiau and J. Elguero, *New J. Chem.*, **13**, 151 (1989).
39. M. Munowitz, W. W. Bachovchin, J. Herzfeld, C. M. Dobson and R. G. Griffin, *J. Am. Chem. Soc.*, **104**, 1192 (1982).
40. J. L. Bolton and R. A. McClelland, *J. Mol. Struct. (Theochem)*, **165**, 379 (1988).
41. Y. K. Kang, K. D. Gibson, G. Némethy and H. A. Scheraga, *J. Phys. Chem.*, **92**, 4739 (1988).
42. J. Catalán, M. Sanches-Cabezudo, J. L. G. de Paz and J. Elguero, *J. Mol. Struc. (Theochem)*, **166**, 415 (1988).
43. H. G. M. de Wit, J. C. A. Offringa, C. G. de Kruif and J. C. van Miltenburg, *Thermochim. Acta*, **65**, 43 (1983).
44. O. Enea, C. Jolicoeur and L. G. Hepler, *Can. J. Chem.*, **58**, 704 (1980).
45. V. P. Vasil'ev, L. A. Kochergina and V. Yu. Garavin, *Zh. Obshch. Khim.*, **55**, 1601 (1985).
46. Yu. S. Koryagin, V. A. Shormanov and G. A. Krestov, *Koord. Khim.*, **11**, 1046 (1985).
47. A. C. M. Paiva, L. Juliano and P. Boschcow, *J. Am. Chem. Soc.*, **98**, 7645 (1976).
48. J. B. Jensen, *Acta Chem. Scand*, **A29**, 250 (1975).
49. E. Sletten and Å. Stögård, *J. Mol. Struc. (Theochem)*, **153**, 289 (1987).
50. A. P. de Jong and H. van Dam, *J. Med. Chem.*, **23**, 889 (1980).
51. K.-H. Pook, H. Stähle and H. Daniel, *Chem. Ber.*, **107**, 2644 (1974).
52. P. B. M. W. M. Timmermans, P. A. van Zwieten, C. M. Meerman-van Benthem, K. van der Meer and J. J. C. Mulder, *Drug Res.*, **27(II)**, 2266 (1977) and references therein.
53. (a) F. Avbelj and D. Hadzi, *Mol. Pharmacol.*, **27**, 466 (1985) and references cited therein.
(b) A. P. De Jong and W. Saudijn, *Eur. J. Pharmacol.*, **69**, 175 (1981).
54. A. Hernandez-Laguna, F. J. Romero-Sanchyez and Y. G. Smeyers, *Ann. Quim.*, **81**, 247 (1985).
55. (a) C. R. Ganellin, E. S. Pepper, G. N. J. Port and W. G. Richards, *J. Med. Chem.*, **16**, 610 (1973);
(b) C. R. Ganellin, G. N. J. Port and W. G. Richards, *J. Med. Chem.*, **16**, 616 (1973).
(c) L. Farnell, W. G. Richards and C. R. Ganellin, *J. Med. Chem.*, **18**, 662 (1975).
56. W. G. Richards, J. Wallis and C. R. Ganellin, *Eur. J. Med. Chem.- Chim. Therapeutica*, **14**, 9 (1979).
57. S. Topiol, *J. Comput. Chem.*, **8**, 142 (1987).
58. E. A. Jauregui, M. R. Estrada, L. S. Mayorga and G. M. Ciuffo, *J. Mol. Struct.*, **54**, 257 (1979).
59. R. J. Abraham and D. Birch. *Mol. Pharmacol.*, **11**, 663 (1975).
60. S. Kang and D. Chou, *Chem. Phys. Lett*, **34**, 537 (1975).
61. F. Xiao-Yuan and S. Shu-Jun, *Int. J. Quantum Chem: Quantum Biol. Symp.*, **8**, 197 (1981).
62. H. Sakurai and S. Takeshima, *Talanta*, **24**, 531 (1977).
63. V. Cerdá, E. Casassas and F. Borrull, *Thermochim. Acta*, **57**, 195 (1982).
64. C. L. Perrin and J. D. Thoburn, *J. Org. Chem.*, **54**, 764 (1989).
65. C. Rabiller, J. P. Renou and G. J. Martin, *J. Chem. Soc. Perkin Trans. 2*, 536 (1977).
66. D. Barr, R. Snaith, R. E. Mulvey, K. Wade and D. Reed, *Magn. Reson. Chem.*, **24**, 713 (1986).
67. R. Sabbah, *Thermochim. Acta*, **35**, 73 (1980).
68. R. L. Benoit and M. Fréchette, *Thermochim. Acta*, **127**, 125 (1988).
69. (a) M. R. Udupa, *Thermochim. Acta*, **53**, 383 (1982);
(b) W. W. Wendlandt, M. Kasper and S. Bellamy, *Thermochim. Acta*, **75**, 239 (1984).
(c) P. P. Lee and M. H. Back, *Thermochim. Acta*, **127**, 89 (1988).
70. C. I. Ratcliffe, *Can. J. Chem.*, **63**, 1239 (1985).

CHAPTER 7

Recent advances in the synthesis of amidines

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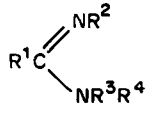
I. INTRODUCTION

In this chapter advances in the synthesis of amidines are reviewed. The term 'amidine' is restricted to compounds of Type **1**, where $R^1 = H$, alkyl, aryl or halogen and R^2–R^4 are usually hydrogen or organic radicals. Thus guanidines (**1**, $R^1 = NR^5R^6$), amidoximes (**1**, $R^2 = OH$) and amidrazones (**1**, $R^2 = NR^5R^6$) are excluded. Cyclic amidines, such as **2**, are mentioned occasionally but α-amino nitrogen heterocycles, which incorporate the



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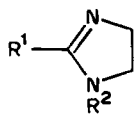


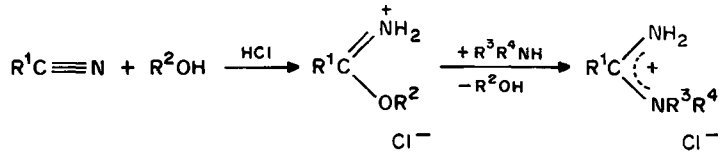
(2)

The Chemistry of Amidines and Imidates, Volume 2
Edited by S. Patai and Z. Rappoport

amidine structure, e.g. 2-aminopyridine, are beyond the scope of this review. Apart from the earlier account in this series[1], a Russian survey of the chemistry of amidines appeared in 1983[2].

II. PREPARATION FROM NITRILES

The classical Pinner synthesis[3–6], which proceeds in two steps (equation 1), is a reliable method for preparing a variety of amidines and is used extensively[7–10].



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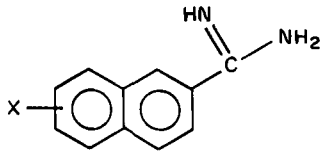

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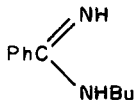
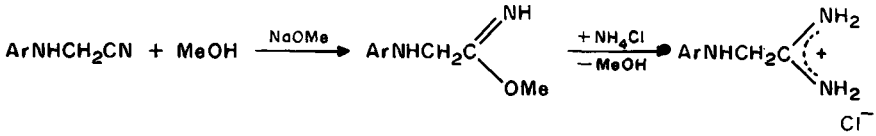
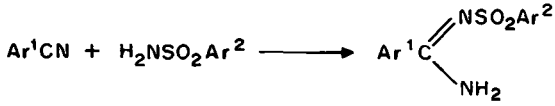


(4)

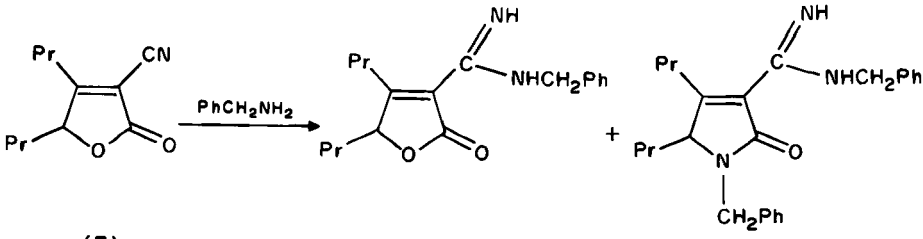
2-Cyanonaphthalenes give amidinonaphthalenes (3)[11] and 2- and 3-amidinofurans, -thiophens and -selenophens have been obtained from the corresponding cyano compounds[12]. Imidates may be formed by the base-catalysed addition of alcohols to nitriles; subsequent reaction with ammonium chloride produces amidine hydrochlorides[13]:



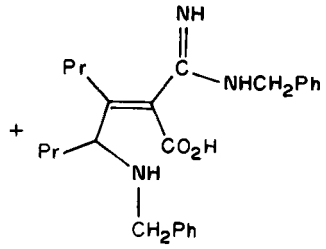
Heating a mixture of benzonitrile, butylamine and methanol under high pressure yields *N*-butylbenzamidine (4)[14]. Arenesulphonylamidines are obtained when aryl cyanides are heated with arenesulphonamides in the presence of an alkali metal salt of the sulphonamide[15]:



Treatment of the cyanobutenolide **5** with benzylamine results in a mixture of the corresponding amidine, the lactam amidine **6** as the major product and the amidino carboxylic acid **7**[16]:

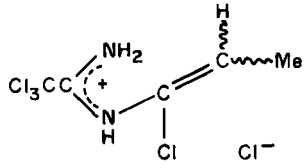


(5) (6)



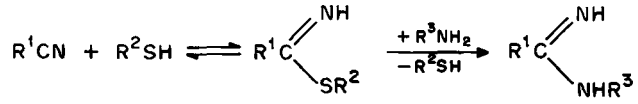
(7)

Both *E*- and *Z*-amidinium chlorides **8** are produced by the action of hydrogen chloride on a mixture of propionitrile and trichloroacetonitrile[17].



(8)

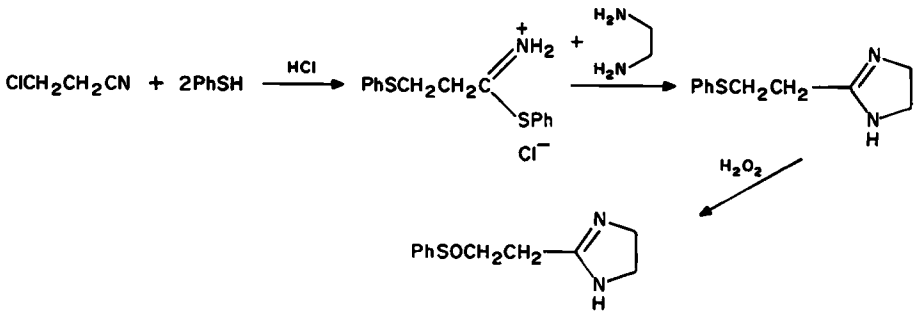
A modification of the Pinner synthesis involves thioimidates (equation 2).



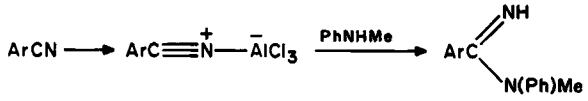
(2)

It has been shown that aromatic amines give good yields of amidines, but on adding the more basic aliphatic amines the first step is reversed and the nitriles are recovered. If, however, the reaction is conducted in a medium buffered with acetic acid, alkylated amidines are readily formed.[18]. Thioimidates were intermediates in the synthesis of various 1-amidinonaphthalenes[11] and of a phenylsulphinylamidine[19]:

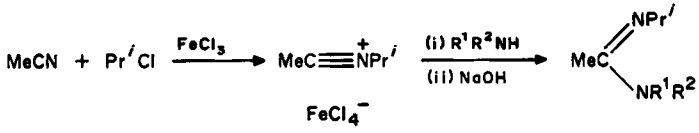
The action of primary amines on alkyl or aryl cyanides in the presence of tributylborane results in (dibutylboryl)amidines, which yield amidines on hydrolysis[20].



Nitrilium salts react with amines to give amidines. For example, the complexes of aryl cyanides with aluminium chloride afford disubstituted amidines by the action of *N*-methylaniline[21]:



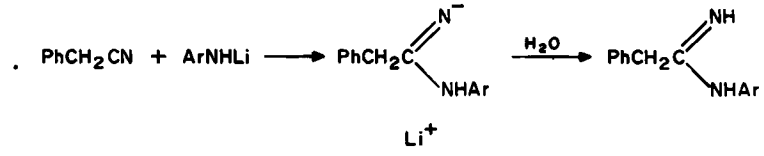
N-Substituted nitrilium salts are obtained by treating nitriles with iron(III) chloride and alkyl halides; subsequent addition of an amine or ammonia affords amidines in good yields[22]:



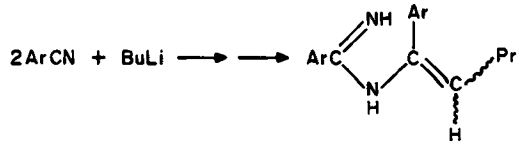
N-Ethylnitrilium tetrafluoroborates (**9**) and *N*-methylnitrilium fluorosulphonates (**10**) are readily formed from nitriles and triethyloxonium tetrafluoroborate, $Et_3O^+\ BF_4^-$, and methyl fluorosulphonate, respectively. These salts have been used to prepare a variety of amidines by treatment with aliphatic or aromatic amines[23–25].

$RC{\equiv}\overset{+}{N}Et\ \ BF_4^-$ (**9**) $\qquad$ $RC{\equiv}\overset{+}{N}Me\ \ FSO_3$ (**10**)

The formation of amidines from nitriles and organometallic compounds has been reported. Benzyl cyanide and the lithium derivatives of aromatic amines yield *N*-arylamidines[26]:

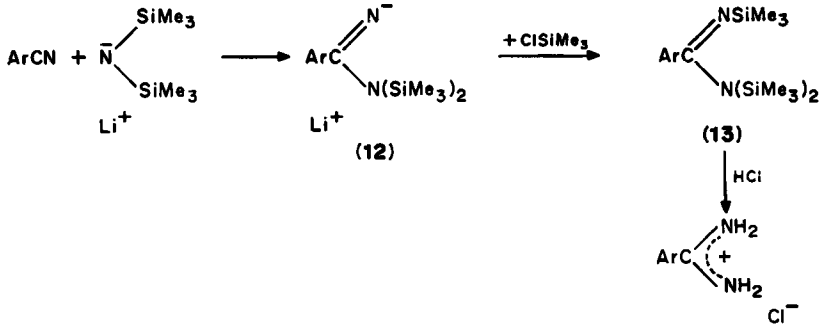


It is well known that the action of Grignard reagents or organolithium compounds on nitriles leads to ketones via intermediate imines. It has been found, however, that n-butyllithium reacts with two molecular equivalents of benzonitrile or *o*-chlorobenzonitrile to give, after hydrolysis, mainly the amidines **11** as mixtures of *E*- and *Z*-isomers[27,28]:

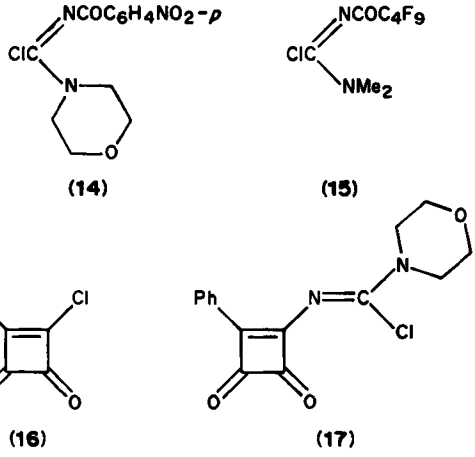


(11)

The action of lithium bis(trimethylsilyl)amide on aryl cyanides produces lithium salts **12**, which react with trimethylsilyl chloride to form the silylated amidines **13**[29]; the latter are readily hydrolysed to amidine hydrochlorides[30].

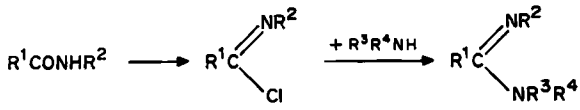


N,N-Dialkylcyanamides, R_2NCN, are sufficiently nucleophilic to add acyl chlorides possessing electron-withdrawing groups to yield acylated chloroformamidines. Thus, in the absence of a solvent, *N*-cyanomorpholine and *p*-nitrobenzoyl chloride give the amidine **14**[31], perfluoropentanoyl chloride and dimethylcyanamide afford compound **15**[32] and the chlorocyclobutenedione **16**, a vinylogous acyl chloride, and *N*-cyanomorpholine produce the analogue **17**[33]:

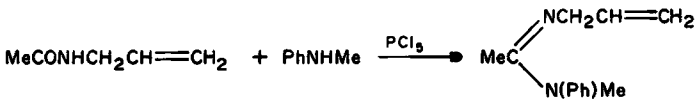


III. PREPARATION FROM AMIDES, THIOAMIDES AND LACTAMS

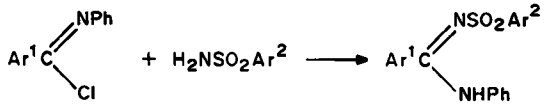
The synthesis of amidines from amides or thioamides requires activation of the latter by modification of the carbonyl or thiocarbonyl group. There are numerous ways of achieving this, of which the more important are described here. Imidoyl chlorides, prepared by the action of phosphorus pentachloride, phosphorus oxychloride or, preferably, thionyl chloride on secondary amides, react with ammonia or primary or secondary amines to yield amidines[34]:



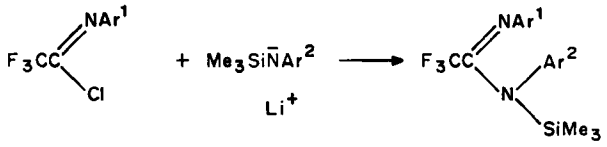
Recent examples illustrating this method are the formation of allylamidines from *N*-allylcarboxamides[35]:



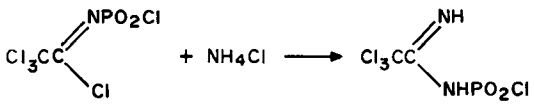
and of arenesulphonylamidines from imidoyl chlorides and arenesulphonamides[36]:



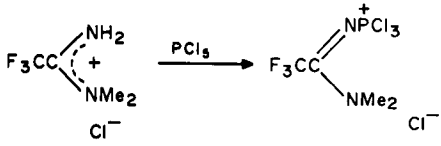
The reaction of *N*-aryltrifluoroacetimidoyl chlorides with lithium trimethylsilylarylamides gives silylated amidines[37]:



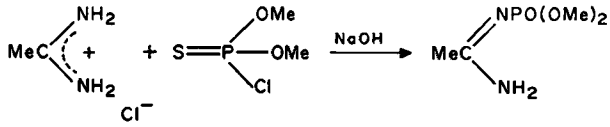
A phosphorylated amidine was obtained as shown[38]:



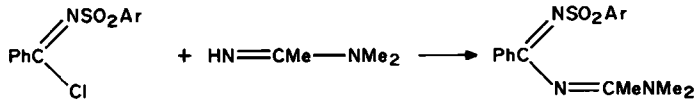
Phosphorylated amidines have also been prepared from amidinium salts by the action of phosphorus pentachloride[39]:



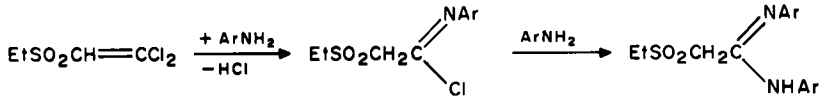
and other derivatives of pentavalent phosphorus[40]:



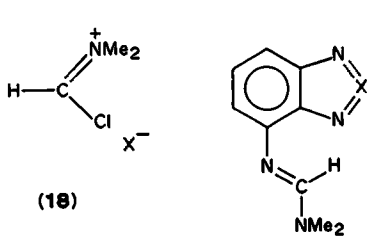
N-Arenesulphonylbenzimidoyl chlorides condense with amidines to yield imidoylamidines[41]:



Imidoyl chlorides are intermediates in the formation of amidines from dichlorovinyl sulphones and arylamines[42]:

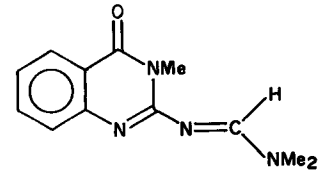


The activation of tertiary amides, especially dimethylformamide, with phosgene, thionyl chloride, oxalyl chloride or phosphorus oxychloride to yield Vilsmeier reagents, **18** (X = Cl or PO_2Cl_2), and the reactions of these salts with amines and other nucleophiles have received much attention[43]. The preparation of twenty-two formamidines from **18** and primary aliphatic or aromatic amines has been reported[44]. 4-Aminobenzo-2,1,3-



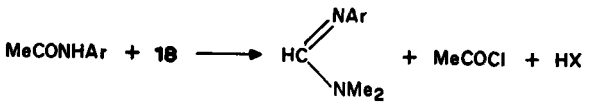
(18)

(19)

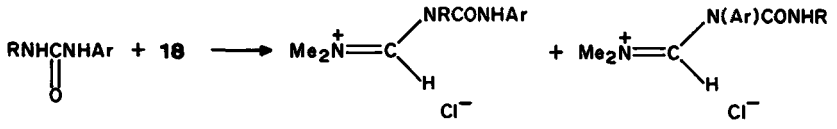


(20)

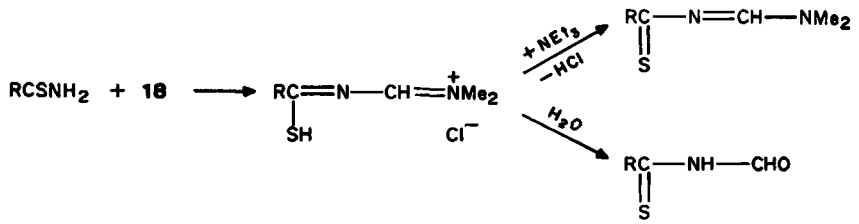
thiadiazole and its selenium analogue yield the formamidines **19** (X = S or Se) on treatment with **18**[45]; the quinazolinone derivative **20** was obtained similarly[46]. The action of Vilsmeier salts **18** on acetanilides results in formamidines with the elimination of acetyl chloride[47]:



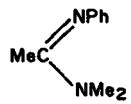
N-Alkyl-*N'*-arylureas react with **18** (X = Cl) to yield mixtures of amidinium salts[48]:



and with thioacetamide or thiobenzamide to form thioacylformamidinium salts, which can be deprotonated to thioacylformamidines or hydrolysed to *N*-thioacylformamides[49]:

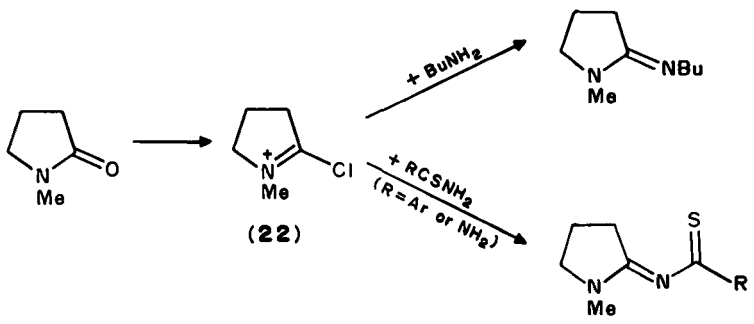


The Vilsmeier salt derived from dimethylacetamide reacts normally with aniline to give, after treatment with sodium hydroxide, the acetamidine **21**[50].

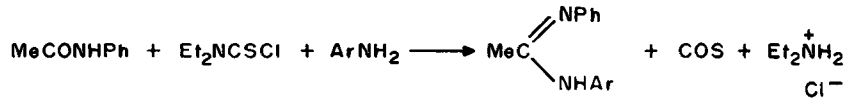


(21)

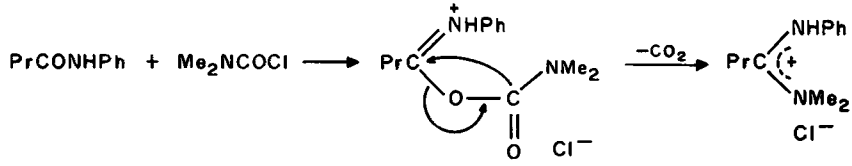
Lactams are activated by phosphorus oxychloride and similar reagents to yield salts, e.g. **22**[51], which react with amines[52] and thioamides, including thiourea[53], to afford amidines and thioacylamidines, respectively:



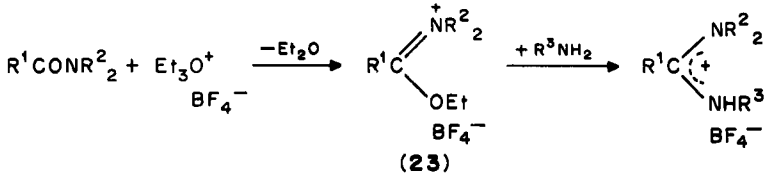
Amides react with amines in the presence of diethylthiocarbamoyl chloride to yield amidines[54]:



The formation of *N,N*-dimethylamidinium chlorides when secondary amides are heated with dimethylcarbamoyl chloride is a related reaction[55]:

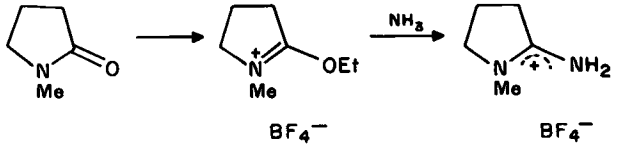


Treatment of amides with triethyloxonium tetrafluoroborate produces reactive salts **23**[56], which readily condense with amines to give amidinium salts[57]:

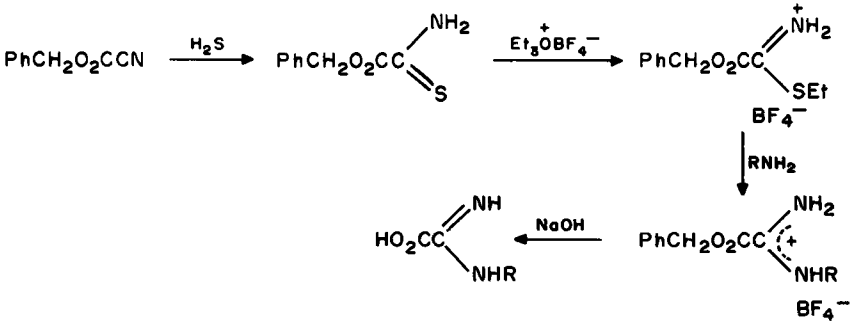


(23)

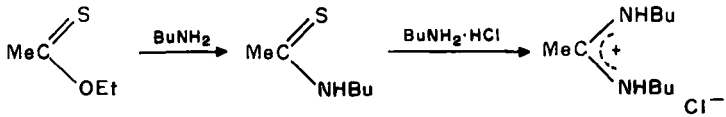
Lactams are similarly converted into amidinium tetrafluoroborates[51,57]:



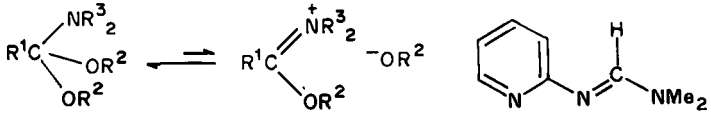
The method has been applied to the synthesis of amidino acids from benzyl cyanoformate[58]:



Under acidic conditions, thioamides are sufficiently electrophilic to react with amines to form amidines. It has been shown that the combined action of butylamine and butylamine hydrochloride on ethyl thioacetate produces *N,N*-dibutylacetamidinium chloride, presumably via *N*-butylthioacetamide[59]:

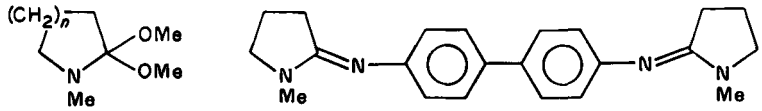


Closely related to the salts **23** are the 'amide acetals' **24**[60,61]. These compounds react with all types of primary amines to give amidines. Numerous heterocyclic formamidines have been prepared by the condensation of dimethylformamide acetals (**24**, $R^1 = H$, $R^2 = Me$ or Et, $R^3 = Me$) with 3-aminopyrazole[62], 2-aminopyridine (to yield **25**)[63], 2-aminopyrimidine[63], 2-aminopyrazine[64] and 6-aminopurine[65].



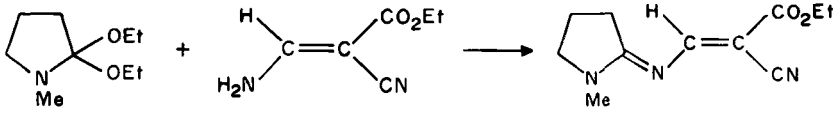
(24) **(25)**

The analogous lactam acetals **26** ($n = 1,2$ or 3) afford amidines by reaction with 2-aminobenzimidazole, 2-aminobenzothiazole, 2-aminopyridine and 2-aminopyrimidine. With diamines, such as ethylenediamine, 2,3-diaminopyridine and phenylenediamines, diamidines, e.g. **27**, are obtained[66].

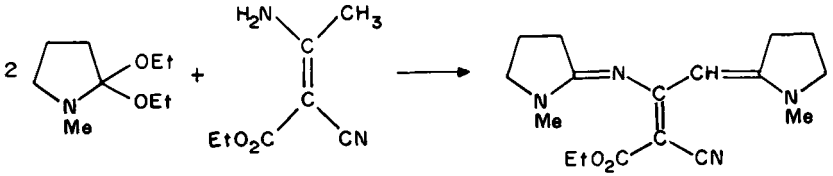


(26) **(27)**

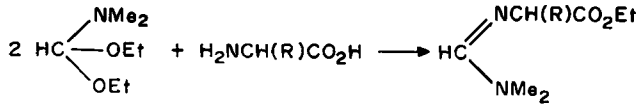
Primary enamines are attacked by amide acetals to yield enamidines[67]:



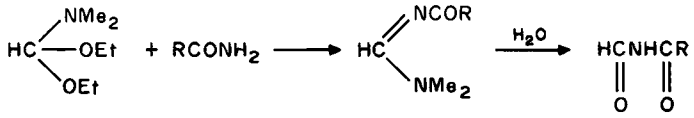
With ethyl β-amino-α-cyanocrotonate condensation occurs both with the amino and the activated methyl groups[68]:



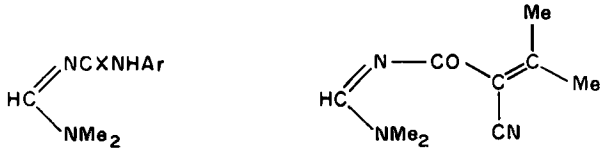
The reaction of dimethylformamide diethyl acetal with amino acids is accompanied by esterification, resulting in amidino esters[69]:



Primary amides or thioamides are converted into acylated amidines on treatment with dimethylformamide diethyl acetal; on hydrolysis with 70% aqueous acetic acid at room temperature the products give excellent yields of diacylamines[70,71]:

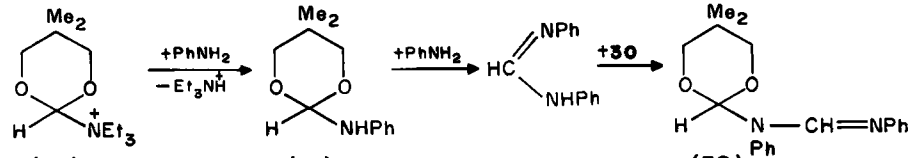


Arylureas and -thioureas similarly yield compounds **28** (X = O or S) by the action of dimethylformamide acetals[72,73]. With isopropylidenecyanoacetamide the amidine derivative **29** is obtained[74].



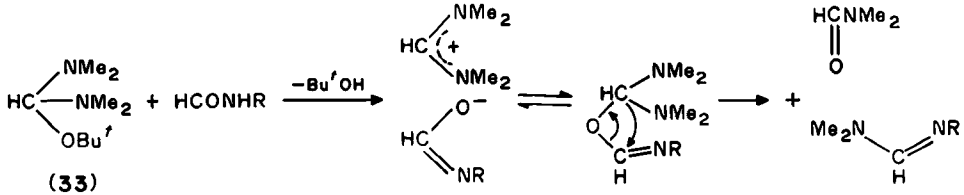
(28) **(29)**

The salt **30** is closely related to amide acetals. It reacts with aniline to give *N,N'*-diphenylformamidine via the acetal **31** of a secondary amide. The further reaction of diphenylformamidine with **30** yields the amidine **32**[75,76]:



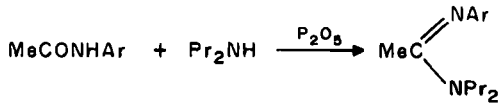
(30) **(31)** **(32)**

Another type of an activated amide is represented by the ester aminal **33**. This compound reacts with secondary amides to give amidines and dimethylformamide[69]:

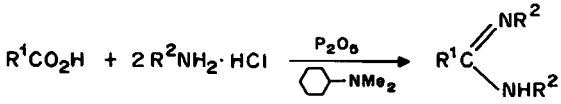


(33)

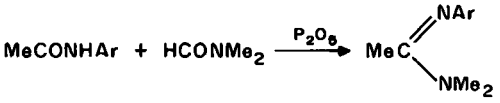
The action of amines on amides in the presence of various derivatives of phosphoric acid results in amidines. Heating a mixture of an anilide, a secondary aliphatic amine and phosphorus pentoxide furnishes a trisubstituted amidine[77]:



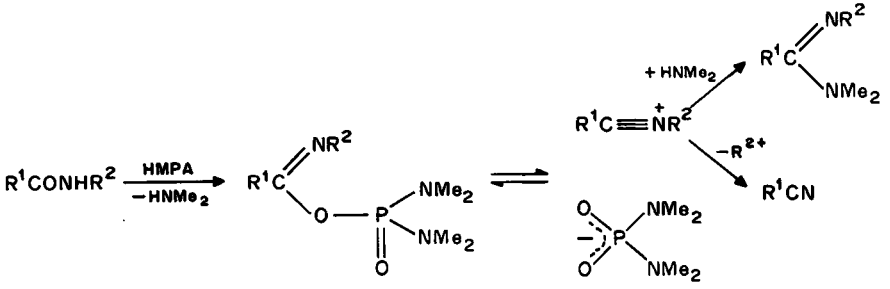
A modification of this method consists in heating a mixture of an aliphatic or aromatic acid, the hydrochloride of a primary aliphatic amine, *N*,*N*-dimethylcyclohexylamine and phosphorus pentoxide[78]:



A related reaction is that of dimethylformamide with secondary amides under the influence of phosphorus pentoxide to yield formamidines[79]:



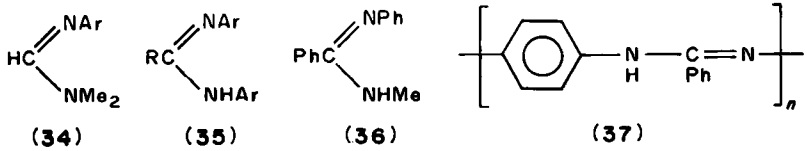
When secondary amides are heated with hexamethylphosphortriamide (HMPA) at *ca* 220 °C, mixtures of amidines and nitriles are produced, presumably via phosphorylated imidates (equation 3). If R^2 can exist as a relatively stable carbonium ion the formation of nitriles is favoured[80,81].



(3)

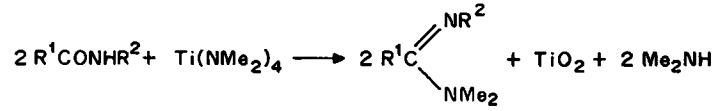
A similar reaction of formic acid with aromatic amines in the presence of HMPA yields formamidines **34**[82]. Polyphosphoric acid trimethylsilyl ester, which is readily obtained from hexamethyldisiloxane and phosphorus pentoxide[83], promotes the formation of symmetrically substituted amidines **35** from aliphatic or aromatic acids and arylamines-[84,85] and of unsymmetrically substituted amidines from secondary or tertiary amides and primary aliphatic or aromatic amines. Thus, heating the ester with *N*-methylbenzamide

and aniline at 160 °C yields compound **36**[85]. Polyamidines, e.g. **37**, are obtained from aromatic acids and aromatic diamines[86].

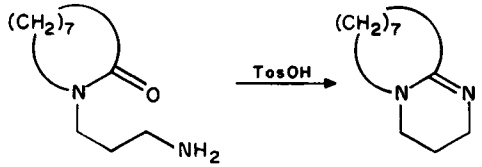


(34) **(35)** **(36)** **(37)**

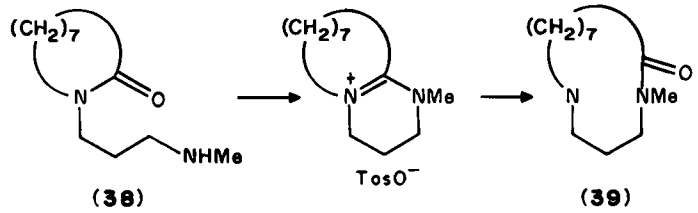
Tetrakis(dimethylamino)titanium reacts with all types of secondary amides: form anilide, *N*-methylacetamide, *t*-butylformamide, pyrrolidin-2-one etc. in refluxing tetrahydrofuran to give trisubstituted amidines[87]:



Bicyclic amidines are produced when *N*-(aminoalkyl)lactams are heated in xylene in the presence of *p*-toluenesulphonic acid:

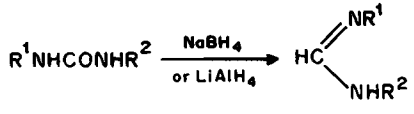


The *N*-methyl derivative **38** yields the transamidated macrocycle **39** via a bicyclic amidinium salt, traces of which can be isolated[88]:

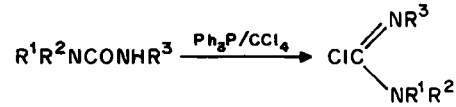


(38) **(39)**

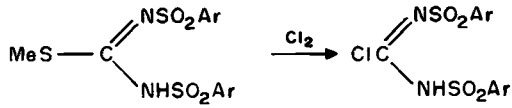
N,N'-Disubstituted ureas are reduced to formamidines by sodium borohydride[89] or lithium aluminium hydride[90]:



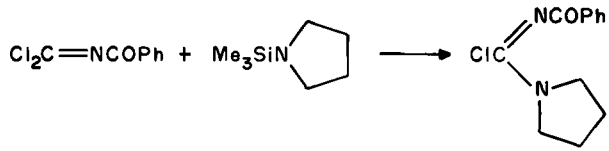
Chloroformamidines are produced by the combined action of carbon tetrachloride and triphenylphosphine on trisubstituted ureas[91]:



The chlorination of *N,N'*-diarenesulphonylpseudothioureas similarly leads to chloroformamidines[92]:



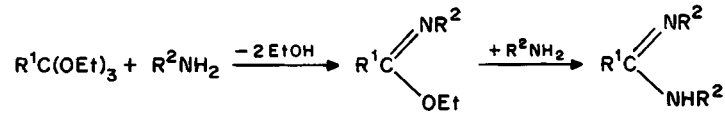
Aroylisocyanide dichlorides yield chloroformamidines on treatment with silylated amines[93]:



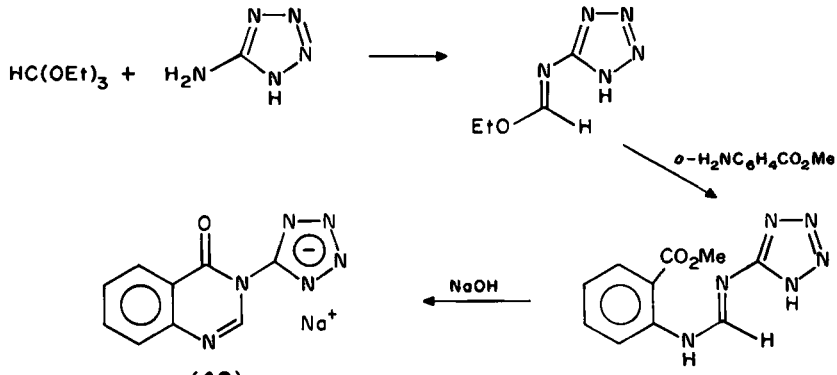
IV. MISCELLANEOUS SYNTHESES

A. From Orthoesters

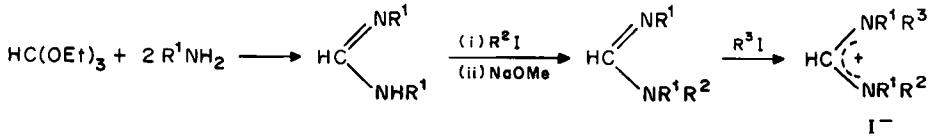
Primary amines react with orthoesters to give symmetrically disubstituted amidines by way of imidates. If catalytic amounts of acetic acid are added the imidates can be isolated[94,95]:



The method was used for the synthesis of the anti-allergic agent MDL-427 **40**[96]:

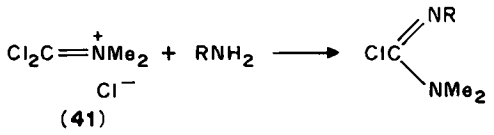


and for the preparation of unsymmetrically tetrasubstituted formamidinium salts by successive alkylations[97]:



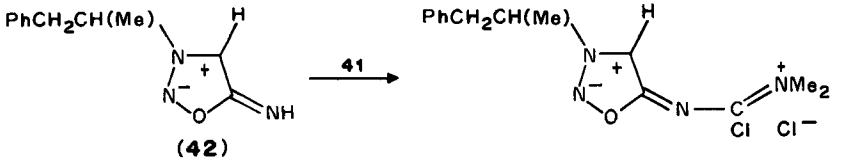
B. From *N*-Dichloromethylenedimethylammonium Chloride

N-Dichloromethylenedimethylammonium chloride ('phosgeneiminium chloride') **41** is related to the Vilsmeier salts **18** but it far surpasses them in reactivity[98,99]. It readily reacts with primary amines to afford chloroformamidines[100]:



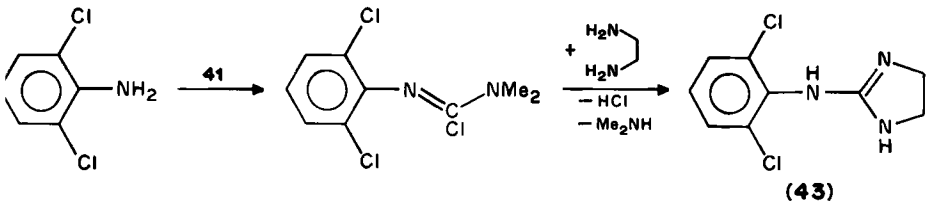
(41)

The sydnone imine **42** reacts analogously[101], as does 5-amino-4,6-dichloropyrimidine[102].



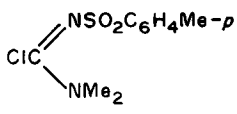
(42)

Successive treatment of 2,6-dichloroaniline with the phosgeneiminium salt and ethylenediamine yields Clophelin **43**[103]:



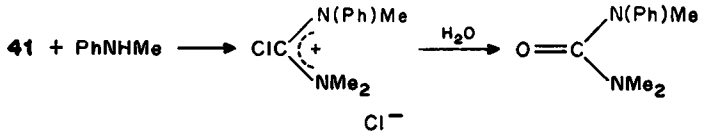
(43)

p-Toluenesulphonamide is converted into the sulphonylamidine **44** by the action of **41**[104,105]:

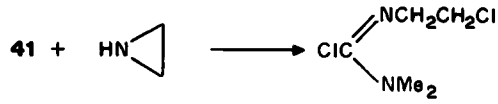


(44)

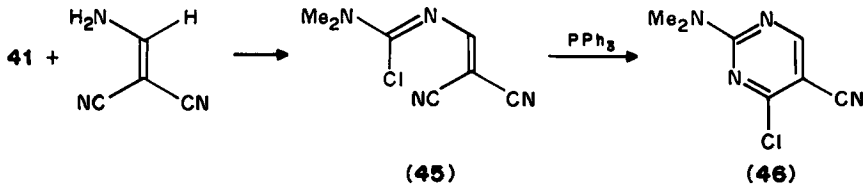
Secondary amines yield amidinium salts, which are hydrolysed to tetrasubstituted ureas[99]:



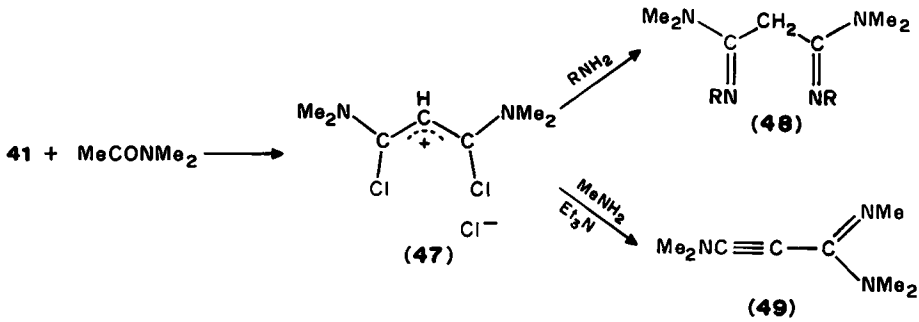
but aziridine suffers ring-fission[98]:



The action of phosgeneiminium chloride on 2,2-dicyanovinylamine leads to the amidine **45**, which cyclizes to the pyrimidine **46** under the influence of triphenylphosphine[106]:

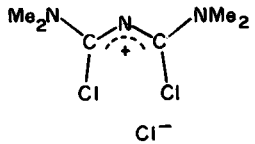


N,N-Dimethylacetamide reacts with **41** to give the propenylium salt **47**, which forms diamidines **48** on treatment with primary amines; treatment with methylamine in the presence of triethylamine yields the ynamine amidine **49**[107]:

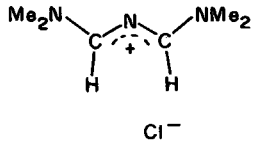


The 1,3-dichloro-2-azapropenylium salt **50**, a useful reagent for the synthesis of various heterocycles[108], is obtained from **41** and dimethylcyanamide[109].

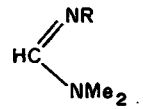
The related azapropenylium salt **51** is prepared by the action of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) on dimethylformamide[110]; it reacts with primary amines RNH_2 or primary amides $RCONH_2$ to yield formamidines **52** and acylated formamidines **53**, respectively[111].



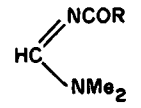
(50)



(51)



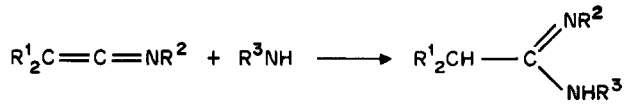
(52)

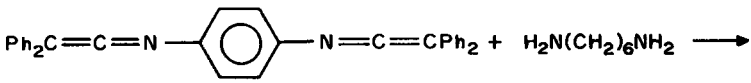


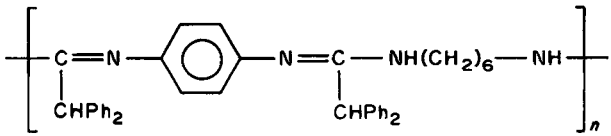
(53)

C. From Compounds with Cumulated Double Bonds

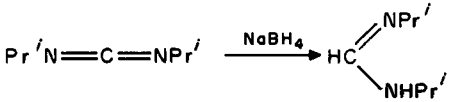
A number of amidine syntheses proceed from compounds possessing cumulated double bonds. A reaction of this type is the addition of amines to ketenimines which has been used to prepare polyamidines[112]:



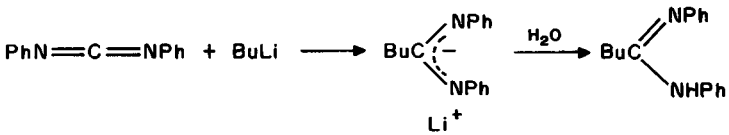




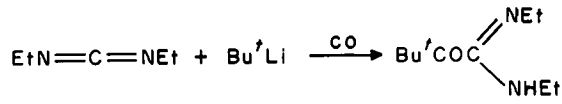
Carbodiimides are reduced to formamidines by sodium borohydride[113]:



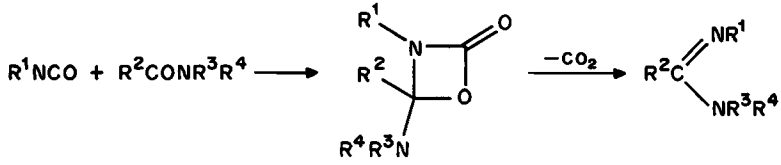
and they add Grignard reagents or organolithium compounds to yield metal derivatives, which afford amidines on hydrolysis[114]:

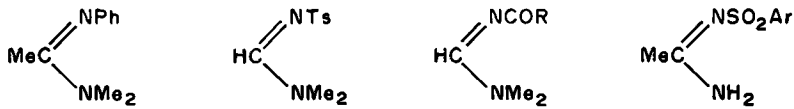


The combined action of t-butyllithium and carbon monoxide on carbodiimides leads via Bu'COLi to thermally unstable α-oxoamidines[115]:



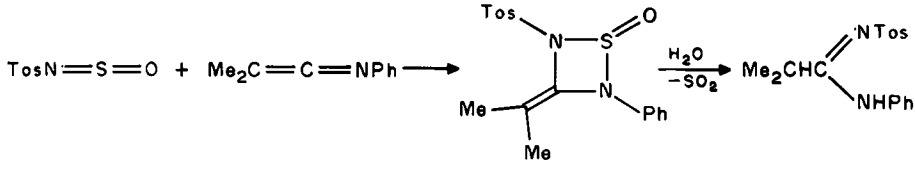
The [2 + 2] cycloaddition of isocyanates to amides yields unstable four-membered ring compounds, which decompose spontaneously into carbon dioxide and amidines:





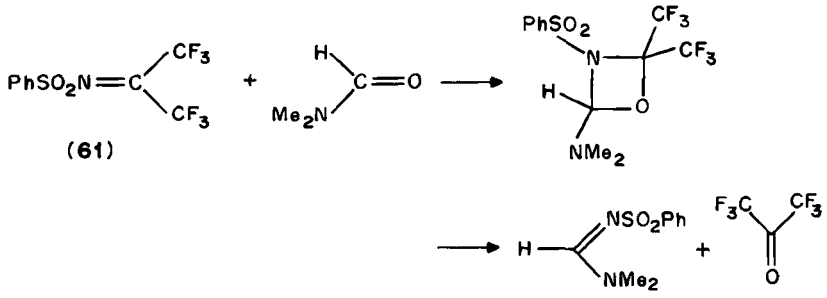
(54) (55) (56) (57)

Thus, heating phenyl isocynate with benzamide at 200 °C gives *N*-phenylbenzamidine[116], phenyl isocyanate and dimethylacetamide afford the acetamidine **54**[117], and the *p*-toluenesulphonylformamidine **55** is formed from *p*-toluenesulphonyl isocyanate and dimethylformamide[118]. The reaction has been extended to the preparation of numerous formamidines from aryl isocyanates and dimethylformamide[119]. *N*-Acylformamidines **56** are produced by heating mixtures of acyl chlorides (ArCOCl or Cl_3CCOCl), sodium cyanate, dimethylformamide and lithium chloride[120]. Thioacetamide and arenesulphonyl isocyanates give the amidines **57** with loss of carbon oxysulphide[121]. The *N*-sulphinylsulphonamide **58** reacts with dimethylketene *N*-phenylimine to give the cycloadduct **59**, which is hydrolysed to sulphur dioxide and the amidine **60**; when other ketenimines were used the intermediates could not be isolated[122].



(58) (59) (60)

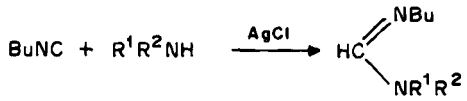
The formation of *N*-benzenesulphonyl-*N'N'*-dimethylformamidine from the imine **61** and dimethylformamide is though to involve an intermediate oxazetidinone[123]:



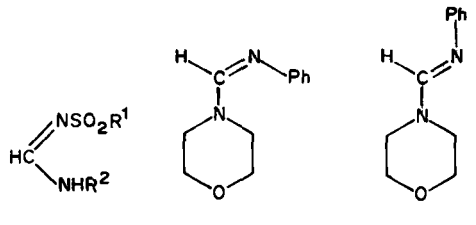
(61)

D. From Isocyanides

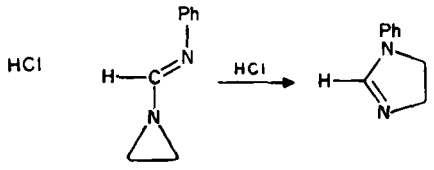
The reaction of aryl isocyanides with amines to form formamidines has been known for a century[124] but alkyl isocyanides did not react. It was found that under catalysis by silver chloride and other salts of metals of Groups IB and IIB aliphatic isocyanides add all kinds of primary and secondary amines[125–127]:



The method has been applied to the preparation of *N*-sulphonylformamidines **62** from various isocyanides and methanesulphonamide or arenesulphonamides; the ^{13}C NMR spectra of the products show that they exist in solution in the tautomeric form shown[128]. A number of glycosylformamidines have been obtained from sugar isocyanides and various amines in the presence of silver chloride[129]. The catalysed addition of morpholine to phenyl isocyanide leads to the *Z*-isomer **63**, which rearranges to the stable *E*-isomer **64** at room temperature. The corresponding aziridine derivative **65** undergoes ring-expansion on treatment with hydrogen chloride to yield *N*-phenylimidazoline[130,131].



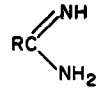
(62) (63) (64)



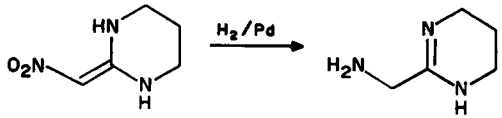
(65)

E. Formation of Amidines by Addition Reactions

Aliphatic aldehydes react with sodamide in liquid ammonia to yield amidines **66** [132]. Catalytic hydrogenation of the nitro compound **67** leads to a cyclic amidine[133].

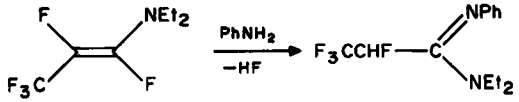


(66)

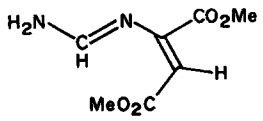


(67)

The electrophilic enamine **68** reacts with aniline to give an amidine[134]. The enamidine **69** is formed by the addition of formamidine to dimethyl acetylenedicarboxylate at $-10\,°C$[135].

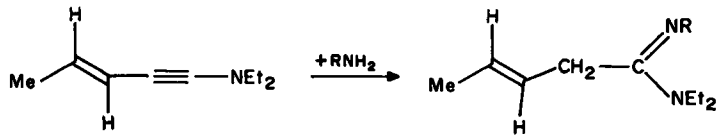


(68)



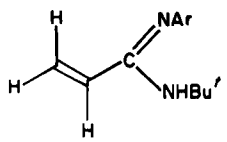
(69)

Primary amines add to the enynamine **70** at the triple bond to yield olefinic amidines[136].

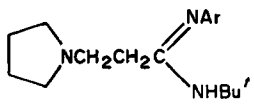


(70)

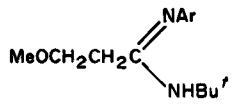
N,N'-Disubstituted propenamidines **71** (Ar = 2-ClC_6H_4 or 2-$O_2NC_6H_4$) react with amines[137], alcohols[138], thiols[139] and malononitrile[140] to afford the respective adducts, e.g. **72–75**.



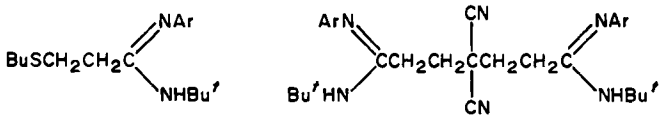
(71)



(72)



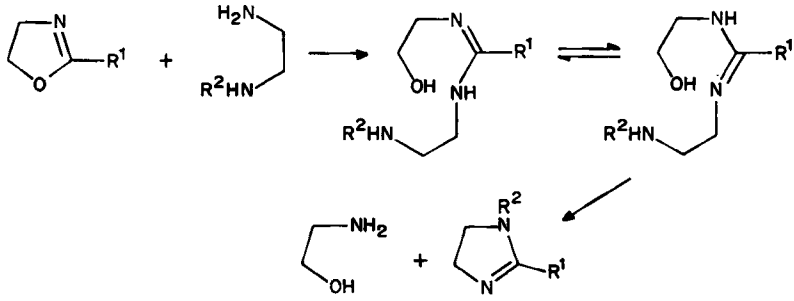
(73)



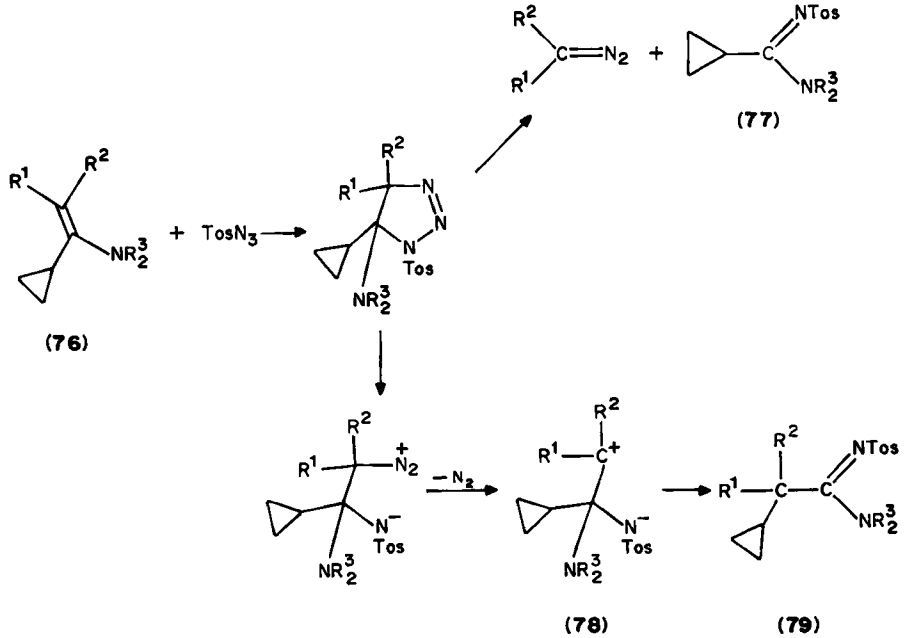
(74) (75)

F. From Heterocyclic Compounds

2-Alkyl-2-oxazolines react with ethylene diamine or *N*-alkylethylene diamines to yield cyclic amidines with the elimination of ethanolamine[141]:



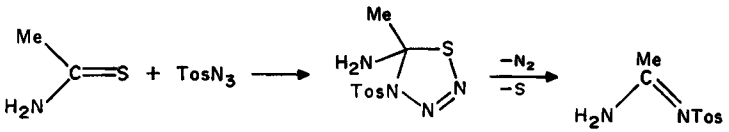
The 1,3-dipolar cycloaddition of tosyl azide to α-cyclopropylenamines **76** (NR^3_2 = morpholino) results in triazolines, which decompose by two pathways (see Scheme 1).



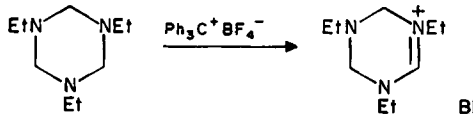
SCHEME 1

In the first, diazoalkanes and amidines **77** are produced, while the second leads to rearranged amidines **79**. Increasing alkyl substitution in the enamine favours the formation of the rearranged products, presumably by stabilizing the intermediate carbenium ions **78**. Thus, with compound **76** ($R^1 = R^2 = H$) the ratio of amidines **77**:**79** is 25:75; for **76** ($R^1 = R^2 = Me$) this ratio is reversed[142].

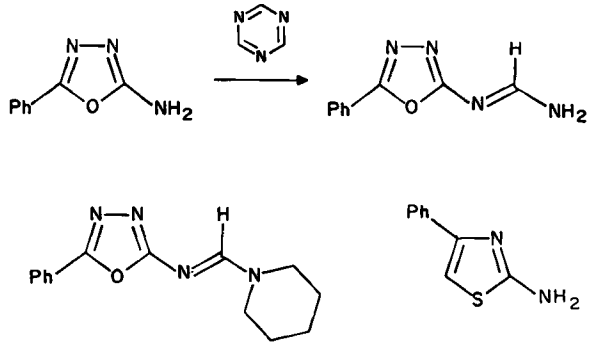
A thiatriazoline is thought to be the intermediate in the formation of tosylamidines from thioamides and tosyl azide[143]:



Dehydrogenation of 1,3,5-triethylhexahydro-1,3,5-triazine with triphenylmethyl tetrafluoroborate affords the corresponding amidinium salt[144]:

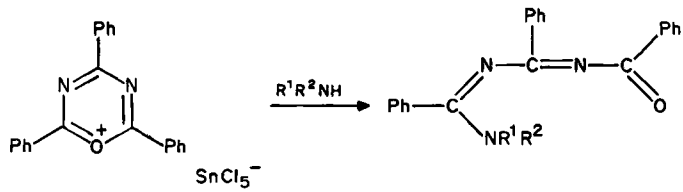


1,3,5-Triazine is a source of formamide in its reaction with 2-amino-5-phenyl-1,3,4-oxadiazole to yield the corresponding formamidine; in the presence of piperidine, compound **80** is obtained[145]. The aminothiazole **81** behaves analogously[146].



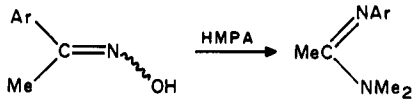
(80) **(81)**

2,4,6-Triphenyl-1,3,5-oxadiazinium pentachlorostannate is transformed into derivatives of benzamidine by the action of primary or secondary amines[147]:

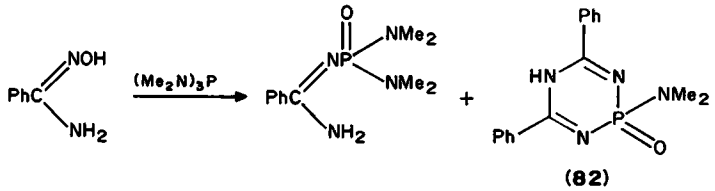


G. Other Reactions

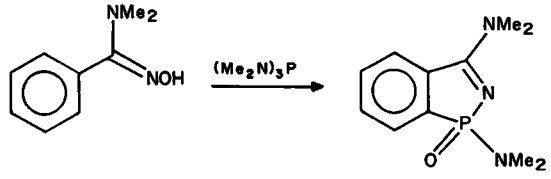
Amidines are produced by a type of Beckmann rearrangement when ketoximes are heated with hexamethylphosphortriamide[148]:



The action of tris(dimethylamino)phosphine on amide oximes yields mixtures of amidines and 2,5-dihydro-1,3,5,2-triazaphosphorin 2-oxides **82**[149]; *N*,*N*-dialkylamidoximes give 1*H*-2,1-benzazaphosphole 2-oxides **83** in this reaction.

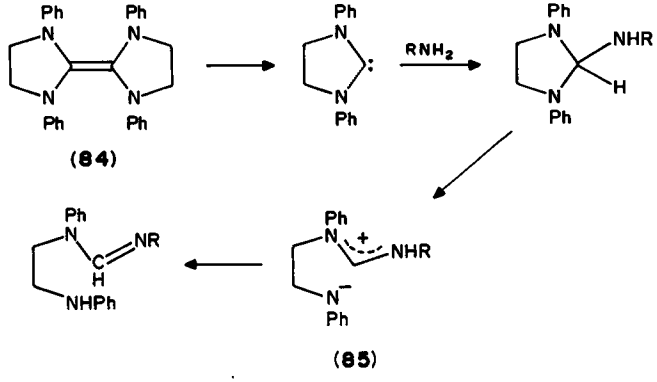


(82)



(83)

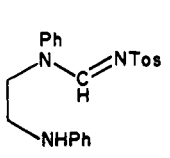
The action of primary aliphatic or aromatic amines on the imidazolidine derivative **84** results in *N*-(anilinoethyl)formamidines. The authors consider the zwitterion **85** as a possible intermediate (Scheme 2)[150].



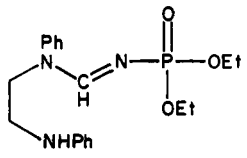
(84) **(85)**

SCHEME 2

Analogous reactions of **84** with *p*-toluenesulphonamide and the phosphoramide $H_2NP(O)(OEt)_2$ afford the formamidine derivatives **86** and **87**, respectively[151].

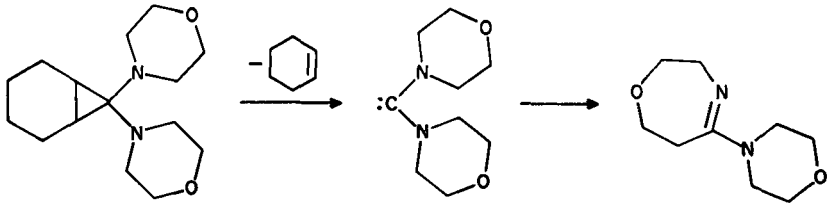


(86)



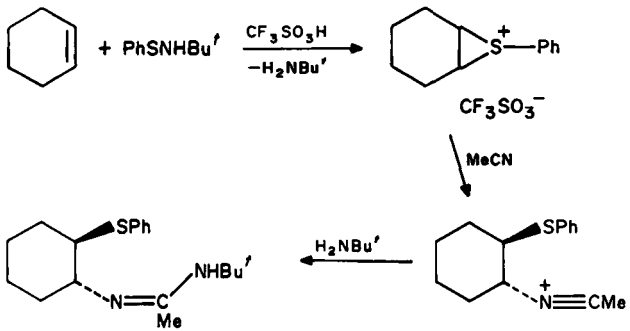
(87)

Flash-vacuum pyrolysis of various diaminobicyclo[*n*.1.0]alkanes results in cycloalkenes and amidines, possibly via carbene intermediates. Dimorpholinobicyclo[4.1.0]heptane, for example, gave cyclohexene and the cyclic amidine **88**[152].

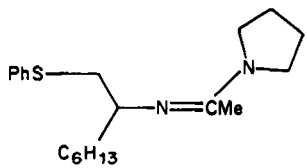


(88)

The combined action of nitriles and olefins on phenylsulphenamides in the presence of trifluoromethanesulphonic acid leads to amidines by way of episulphonium salts:

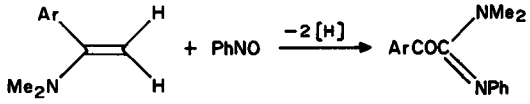


1-Octene, *N*-(phenylsulphenyl)pyrrolidine and acetonitrile gave solely compound **89** in this reaction[153].



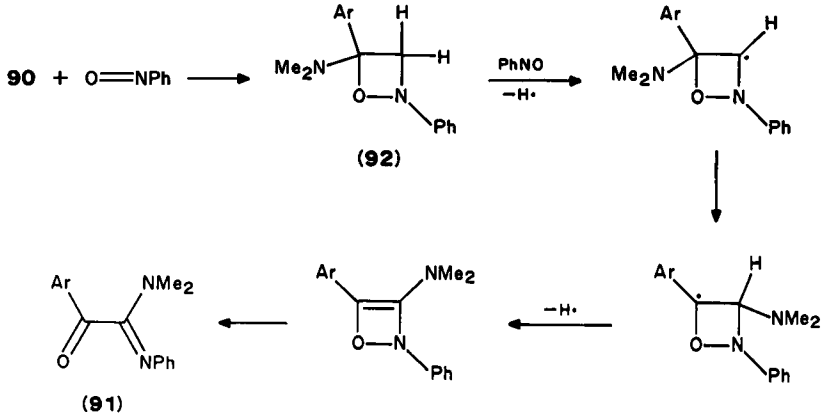
(89)

Treatment of the enamines **90** with nitrosobenzene surprisingly produces rearranged amidines **91**, together with azoxybenzene and other reduction products of nitrosobenzene[154]:



(90) **(91)**

The authors suggest the intermediate formation of 1,2-oxazetidines **92**, which rearrange by a radical mechanism and then open to yield the products (Scheme 3)[155].



SCHEME 3

V. REFERENCES

1. J. A. Gautier, M. Miocque and C. C. Farnoux, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, New York, 1975, p. 283.
2. V. G. Granik, *Usp. Khim.*, **52**, 669 (1983); *Russ. Chem. Rev.*, **52**, 377 (1983).
3. A. Pinner and F. Klein, *Chem. Ber.*, **10**, 1889 (1877).
4. A. Pinner, *Die Iminoäther und ihre Derivate*, Oppenheim, Berlin, 1892.
5. Reference 1, p. 292.
6. R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).
7. G. Wagner and J. Wunderlich, *Pharmazie*, **31**, 766 (1976).
8. G. Wagner, B. Voigt, D. Danicke and T. Liebermann, *Pharmazie*, **31**, 528 (1976).
9. R. R. Tidwell, L. L. Fox and J. D. Geratz, *Biochim. Biophys. Acta*, **445**, 729 (1976).
10. T. Pantev and R. Georgieva, *Farmatsiya (Sofia)*, **29**, 1 (1979).
11. G. Wagner and B. Voigt, *Pharmazie*, **33**, 568 (1979).
12. B. Decroix and P. Pastour, *J. Chem. Res. (S)*, 132 (1978).
13. C. Soula, A. Marsura and C. Luu-Duc, *J. Pharm. Belg.*, **42**, 293 (1987).
14. Japan, Patent, 7,392,301 (1973); *Chem. Abstr.*, **80**, 145 849 (1974).
15. USSR Patent, 910,611 (1982); *Chem. Abstr.*, **97**, 91 965 (1982).
16. A. A. Avetisyan, S. Kh. Karagez, M. T. Dangvan and D. L. Gezalyan, *Arm. Khim. Zh.* **32**, 389 (1979); *Chem. Abstr.*, **92**, 215 023 (1980).

17. Japan, Patent, 77,131,521 (1977); *Chem. Abstr.*, **88**, 120 625 (1978).
18. R. C. Schnur, *J. Org. Chem.*, **44**, 3726 (1979).
19. Brit. Patent, 1,519,353 (1978); *Chem. Abstr.*, **90**, 121 204 (1979).
20. V. A. Dorokhov, A. R. Amamchyan, V. S. Bogdanov and T. R. Shchegoleva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2622 (1987).
21. J. I. Ogonor, *Tetrahedron*, **37**, 2909 (1981).
22. R. Fuks, *Tetrahedron*, **29**, 2147 (1973).
23. Belg. Patent, 831,934 (1976); *Chem. Abstr.*, **85**, 116 917 (1976).
24. Brit. Patent, 1,466,047 (1977); *Chem. Abstr.*, **87**, 117 663 (1977).
25. M. Strebelle and R. Fuks, *Bull. Soc. Chim. Belg.*, **87**, 717 (1978).
26. B. V. Passet, G. N. Kulbitskii, N. A. Kalashnikova and T. I. Voropaeva, *Zh. Org. Khim.*, **8**, 1246 (1972).
27. L. S. Cook and B. J. Wakefield, *Tetrahedron Lett.*, 147 (1976).
28. L. S. Cook and B. J. Wakefield, *J. Chem. Soc., Perkin Trans. 1*, 2392 (1980).
29. R. T. Boere, R. T. Oakley and R. W. Reed, *J. Organomet. Chem.*, **331**, 161 (1987).
30. A. R. Sanger, *Inorg. Nucl. Chem. Lett.*, **9**, 231 (1967).
31. W. Ried, H. Dietschmann and H. E. Erle, *Synthesis*, 619 (1980).
32. V. N. Lebedev, V. V. Yurechko and T. P. Vishnyakova, *Zh. Vses. Khim. Ova.*, **26**, 465 (1981); *Chem. Abstr.*, **95**, 168 502 (1981).
33. W. Ried and H. Dietschmann, *Ann. Chem.*, 1009 (1981).
34. Reference 1, p. 296.
35. J. I. Ogonor, *Acta Pol. Pharm.*, **43**, 191 (1986).
36. V. L. Dubina, L. N. Shchebitchenko, I. Yu. Kozak and N. V. Dubina, *Zh. Org. Khim.*, **22**, 2590 (1986).
37. W. Maringgele and A. Meller, *Z. Anorg. Allg. Chem.*, **445**, 107 (1978).
38. V. P. Kukhar and T. N. Kasheva, *Zh. Obshch. Khim.*, **46**, 1462 (1976).
39. A. D. Sinitsa and V. I. Kalchenko, *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol., Khim. Biol. Nauki*, 1007 (1977); *Chem. Abstr.*, **88**, 89 765 (1978).
40. N. M. Mironovskaya, S. F. Dymova, I. L. Vladimirova and N. N. Melnikov, *Zh. Obshch. Khim.*, **48**, 2465 (1978).
41. V. L. Dubina, V. P. Pedan and I. K. Dembinskii, *Zh. Org. Khim.*, **12**, 64 (1976).
42. A. V. Martynov, A. N. Mirskova, I. D. Kalikhman, P. V. Makerov and M. G. Voronkov, *Zh. Org. Khim.*, **15**, 427 (1979).
43. C. Jutz, in *Iminium Salts in Organic Chemistry*, Part 1 (Eds. H. Böhme and H. G. Viehe), Wiley, New York, 1976, p. 225.
44. D. Dzharov, *Farmatsiya (Sofia)*, **27**, 1 (1977).
45. E. K. Dyachenko, V. G. Posin, A. A. Smirnova, A. I. Kapitan, N. D. Rozhkova and M. P. Papirnik, *Zh. Org. Khim.*, **23**, 2456 (1987).
46. L. M. Yun, S. A. Makhmudov, Kh. M. Shakhidoyatov, Ch. Sh. Kadyrov and S. S. Kasymova, *Khim. Prir. Soedin.*, 680 (1980); *Chem. Abstr.*, **94**, 175 039 (1981).
47. J. Besan, L. Kulcsar and M. Kovacs, *Synthesis*, 883 (1980).
48. I. Bitter, E. Karpati-Adam and L. Toke, *Acta Chim. Acad. Sci. Hung.*, **102**, 235 (1979).
49. J. Liebscher, *Synthesis*, 1084 (1982).
50. U. S. Patent, 4,353,830 (1982); *Chem. Abstr.*, **98**, 534 344 (1983).
51. R. G. Glushkov and V. G. Granik, *Usp. Khim.*, **38**, 1989 (1969); *Russ. Chem. Rev.*, **38**, 913 (1969).
52. U. S. Patent 4, 321, 202 (1982); *Chem. Abstr.*, **96**, 217 693 (1982).
53. J. Liebscher, M. Paetzel and U. Bechstein, *Z. Chem.*, **26**, 289 (1986).
54. M. Ogata and H. Matsumoto, *Heterocycles*, **11**, 139 (1978).
55. E. Haug, W. Kantlehner, P. Speh and H. J. Bräuner, *Synthesis*, 35 (1983).
56. W. Kantlehner, in *Iminium Salts in Organic Chemistry*, Part 2 (Eds. H. Böhme and H. G. Viehe), Wiley, New York, 1979, p. 181.
57. T. Kato, A. Takada and T. Ueda, *Chem. Pharm. Bull.*, **20**, 901 (1972).
58. Y. Nii, K. Okano, S. Kobayashi and M. Ohto, *Tetrahedron Lett.*, 2517 (1979).
59. P. Reynaud, J. D. Brion and G. Menara, *Bull. Soc. Chim. Fr.*, 301 (1976).
60. J. Gloede, L. Haase and H. Gross, *Z. Chem.*, **9**, 201 (1969).
61. R. F. Abdulla and R. S. Brinkmeyer, *Tetrahedron*, **35**, 1675 (1979).
62. V. G. Granik, E. O. Sochneva and I. V. Persianova, *Khim. Geterotsikl. Soedin.*, 379(1978); *Chem. Abstr.*, **89**, 43 228 (1978).

63. H. Junek, M. Mittelbach and B. Thierrichter, *Monatsh. Chem.*, **110**, 1279 (1979).
64. E. C. Taylor and D. J. Dumas, *J. Org. Chem.*, **45**, 2485 (1980).
65. R. S. Kosmane and N. J. Leonard, *J. Org. Chem.*, **46**, 1457 (1981).
66. P. Ahuja, J. Singh, M. B. Nigam, V. Sardana, K. Kar and N. Anand, *Indian J. Chem., Sect. B*, **21B**, 849 (1982).
67. V. G. Granik, N. B. Marchenko, E. O. Sochneva, R. G. Glushkov, T. F. Vlasova and Yu. N. Sheinker, *Khim. Geterotsikl. Soedin.*, 805 (1976); *Chem. Abstr.*, **85**, 108 568 (1976).
68. V. G. Granik, N. B. Marchenko, E. O. Sochneva, T. F. Vlasova, A. B. Grigorev, M. K. Polievktov and R. G. Glushkov, *Khim. Geterotsikl. Soedin.*, 1505 (1976); *Chem. Abstr.*, **86**, 139 814 (1977).
69. W. Kantlehner, F. Wagner and H. Bredereck, *Ann. Chem.*, 344 (1980).
70. Y. Lin, S. A. Lang, Jr., M. F. Lovell and N. A. Perkinson, *J. Org. Chem.*, **44**, 4160 (1979).
71. Y. Lin and S. A. Lang, Jr., *Synthesis*, 119 (1980).
72. Y. Lin, S. A. Lang, Jr. and S. P. Petty, *J. Org. Chem.*, **45**, 3750 (1980).
73. S. I. Kaimanakova, E. F. Kuleshova, N. P. Soloveva and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1553 (1982); *Chem. Abstr.*, **98**, 89 306 (1983).
74. N. I. Smetskaya, N. A. Mukhina and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 799 (1984); *Chem. Abstr.*, **101**, 230 309 (1984).
75. W. Tritschler and S. Kabusz, *Synthesis*, 32 (1972).
76. W. Tritschler and S. Kabusz, *Synthesis*, 423 (1973).
77. B. W. Hansen and E. B. Pedersen, *Acta Chem. Scand.*, **B34**, 369 (1980).
78. E. B. Pedersen and D. Carlsen, *Chem. Scr.*, **23**, 123 (1984).
79. E. B. Pedersen, *Synthesis*, 546 (1979).
80. E. B. Pedersen, N. O. Vesterager and S. O. Lawesson, *Synthesis*, 547 (1972).
81. E. B. Pedersen and S. O. Lawesson, *Tetrahedron*, **29**, 4205 (1973).
82. E. B. Pedersen, *Acta Chem. Scand.*, **B31**, 261 (1977).
83. T. Imamoto, T. Matsumoto, H. Yokoyama, M. Yokoyama and K. Yamaguchi, *J. Org. Chem.*, **49**, 1105 (1984).
84. M. Kakimoto, S. Ogata, A. Mochizuki and Y. Imai, *Chem. Lett.*, 821 (1984).
85. S. Ogata, A. Mochizuki, M. Kakimoto and Y. Imai, *Bull. Chem. Soc. Jpn.*, **59**, 2171 (1986).
86. S. Ogata, M. Kakimoto and Y.Imai, *Makromol. Chem., Rapid Commun.*, **6**, 835 (1985).
87. J. D. Wilson, J. S. Wager and H. Weingarten, *J. Org. Chem.*, **36**, 1613 (1971).
88. C. Heidelberger, A. Guggisberg, E. Stephanou and M. Hesse, *Helv. Chem. Acta*, **64**, 399 (1981).
89. Y. Kikugawa, S. Yamada, H. Nagashima and K. Kaji, *Tetrahedron Lett.*, 699 (1969).
90. G. Lettieri, A. Larizza, G. Brancaccio and P. Monforte, *Atti Soc. Peloritana Sci. Fis., Mat. Nat.*, **24**, 77 (1978); *Chem. Abstr.*, **92**, 94 028 (1980).
91. W. Ried and R. Christ, *Ann. Chem.*, 693 (1980).
92. E. A. Abrazhanova, V. N. Sevastyanov and A. F. Pronskii, *Zh. Org. Khim.*, **11**, 2243 (1975).
93. German (East) Patent 258, 223 (1989); *Chem. Abstr.*, **110**, 134 895 (1989).
94. R. M. Roberts and R. H. de Wolfe, *J. Am. Chem. Soc.*, **76**, 2411 (1954).
95. E. C. Taylor and W. A. Ehrhart, *J. Org. Chem.*, **28**, 1108 (1963).
96. A. P. Vinogradoff and N. P. Peet, *J. Heterocycl. Chem.*, **26**, 97 (1989).
97. S. C. Wicherink, J. W. Scheeren and R. J. F. Nivard, *Synthesis*, 273 (1977).
98. H. G. Viehe and Z. Janousek, *Angew. Chem., Int. Ed. Engl.*, **12**, 806 (1973).
99. Z. Janousek and H. G. Viehe, Reference 43, p. 343.
100. H. G. Viehe and Z. Janousek, *Angew. Chem., Int. Ed. Engl.*, **10**, 573 (1971).
101. R. G. Glushkov, L. I. Dronova, L. A. Nikolaeva, B. A. Medvedev, M. D. Mashkovskii, N. P. Soloveva, K. F. Turchin and I. V. Persianova, *Khim. Farm. Zh.*, **12**, 59 (1978); *Chem. Abstr.*, **89**, 109 286 (1978).
102. R. G. Glushkov, L. I. Dronova, L. A. Nikolaeva, B. A. Medvedev and M. D. Mashkovskii, *Khim. Farm. Zh.*, **15**, 39 (1981); *Chem. Abstr.*, **95**, 132 801 (1981).
103. R. G. Glushkov, L. I. Dronova, L. A. Nikolaeva and Yu. I. Kostikova, *Khim. Farm. Zh.*, **12**, 93 (1978); *Chem. Abstr.*, **88**, 190 679 (1978).
104. V. P. Kukhar, A. M. Pinchuk and M. V. Shevchenko, *Zh. Org. Khim.*, **9**, 43 (1973).
105. V. P. Kukhar, V. I. Pasternak and A. V. Kirsanov, *Zh. Org. Khim.*, **2**, 1309 (1966).
106. N. G. Pavlenko and V. P. Kukhar, *Ukr. Khim. Zh. (Russ. Ed.)*, **48**, 395 (1982); *Chem. Abstr.*, **97**, 23 735 (1982).

107. B. Caillaux, P. George, F. Tataruch, Z. Janousek and H. G. Viehe, *Chimia (Switz.)*, **30**, 387 (1976).
108. A. Antus-Ercsenyi and I. Bitter, *Acta Chim. Acad. Sci. Hung.*, **99**, 29 (1979).
109. Z. Janousek and H. G. Viehe, *Angew. Chem., Int. Ed. Engl.*, **12**, 74 (1973).
110. H. Gold, *Angew Chem.*, **72**, 956 (1960).
111. J. T. Gupton, C. Colon, C. R. Harrison, M. J. Lizzi and D. E. Polk, *J. Org. Chem.*, **45**, 4522 (1980).
112. K. Kurita, Y. Kusayama and Y. Iwakura, *J. Polym. Sci., Polym. Chem. Ed.*, **15**, 2163 (1977).
113. K. Kaji, H. Matsubara, H. Nagashima, Y. Kikugawa and S. Yamada, *Chem. Pharm. Bull.*, **26**, 2246 (1978).
114. J. Pornet and L. Miginiac, *Bull. Soc. Chim. Fr.*, 994 (1974).
115. D. Seyferth and R. C. Hui, *J. Org. Chem.*, **50**, 1985 (1985).
116. P. F. Wiley, *J. Am. Chem. Soc.*, **81**, 3746 (1949).
117. M. L. Weiner, *J. Org. Chem.*, **25**, 2245 (1960).
118. C. King, *J. Org. Chem.*, **25**, 352 (1960).
119. J. L. Neymeyer, *J. Pharm. Sci.*, **53**, 1539 (1964).
120. German Patent 3, 125, 438 (1983); *Chem. Abstr.*, **99**, 122 071 (1983).
121. K. Burger and E. Hoess, *Chem.-Ztg.*, **112**, 349 (1988).
122. T. Minami, F. Takimoto and T. Agawa, *Bull. Chem. Soc. Jpn.*, **48**, 3259 (1975).
123. A. V. Fokin, N. D. Chkanikov, V. L. Vershinin and A. F. Kolomiets, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 949 (1984).
124. J. U. Nef, *Ann. Chem.*, **270**, 267 (1892).
125. T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota and H. Yoshioka, *Bull. Chem. Soc. Jpn.*, **42**, 3310 (1969).
126. T. Saegusa and Y. Ito, *Synthesis*, 291 (1975).
127. T. Saegusa and Y. Ito, in *Isonitrile Chemistry* (Ed. I. Ugi), Academic Press, London, 1971, p. 65.
128. P. Jakobsen and S. Treppendahl, *Tetrahedron*, **33**, 3137 (1977).
129. D. Marmet, P. Boullanger and G. Descotes, *Tetrahedron Lett.*, **21**, 1459 (1980).
130. A. F. Hegarty and A. Chandler, *J. Chem. Soc., Chem. Commun.*, 130 (1980).
131. A. F. Hegarty and A. Chandler, *Tetrahedron Lett.*, **21**, 885 (1980).
132. Japan. Patent 7,512,408 (1975); *Chem. Abstr.*, **83**, 178 370 (1975).
133. S. Rajappa and R. Srinivasan, *Indian J. Chem.*, **178**, 339 (1979).
134. Japan. Patent 5,857,357 (1983); *Chem. Abstr.*, **99**, 121 842 (1983).
135. L. P. Prikazchikova, L. I. Rybchenko and V. M. Cherkasov, *Khim. Geterotsikl. Soedin.*, 831 (1977); *Chem. Abstr.*, **87**, 184 452 (1977).
136. S. E. Tolchinskii, I. A. Maretina and A. A. Petrov. *Zh. Org. Khim.*, **17**, 1807 (1981).
137. R. Fuks and M. Van Den Bril, *Tetrahedron*, **37**, 2895 (1981).
138. M. Van Den Bril and R. Fuks, *Tetrahedron*, **37**, 2905 (1981).
139. R. Fuks and M. Van Den Bril, *Synthesis*, 121 (1980).
140. M. Van Den Bril and R. Fuks, *Synthesis*, 893 (1980).
141. K. H. Magosch, *Synthesis*, 37 (1972).
142. D. Pocar and P. Trimarco, *J. Chem. Soc., Perkin Trans. 1*, 622 (1976).
143. O. V. Zelenskaya, V. A. Kozinskii, A. V. Nazarenko and A. P. Ranskii, *Zh. Prikl. Khim. (Leningrad)*, **57**, 1155 (1984); *Chem. Abstr.*, **102**, 5 853 (1985).
144. H. Möhrle and U. Scharf, *Arch. Pharm.*, **307**, 51 (1974).
145. P. Henklein and G. Westphal, *Z. Chem.*, **13**, 429 (1973).
146. A. Kreutzberger and M. U. Uzbek, *Angew. Chem., Int. Ed. Engl.*, **11**, 144 (1972).
147. R. Fuks, M. Strebelle and A. Wenders, *Synthesis*, 788 (1977).
148. J. T. Gupton, J. P. Idoux, R. Leonard and G. DeCrescenzo, *Synth. Commun.*, **13**, 1083 (1983).
149. L. Lopez and J. Barrans, *J. Chem. Soc., Perkin Trans. 1*, 1806 (1977).
150. J. Hocker and R. Merten, *Chem. Ber.*, **105**, 1651 (1972).
151. J. Hocker and R. Merten, *Ann. Chem.*, 16 (1978).
152. E. Vilsmaier, G. Kristen and C. Tetzlaff, *J. Org. Chem.*, **53**, 1806 (1988).
153. P. Brownbridge, *Tetrahedron Lett.*, **25**, 3759 (1984).
154. L. N. Koikov, P. B. Terentev and Yu. G. Bundel, *Zh. Org. Khim.*, **18**, 669 (1982).
155. L. N. Koikov, P. B. Terentev, D. S. Yufit, Yu. T. Struchkov and V. E. Zubarev, *Zh. Org. Khim.*, **21**, 1820 (1985).

CHAPTER 8

Reactions and synthetic uses of amidines

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I. INTRODUCTION

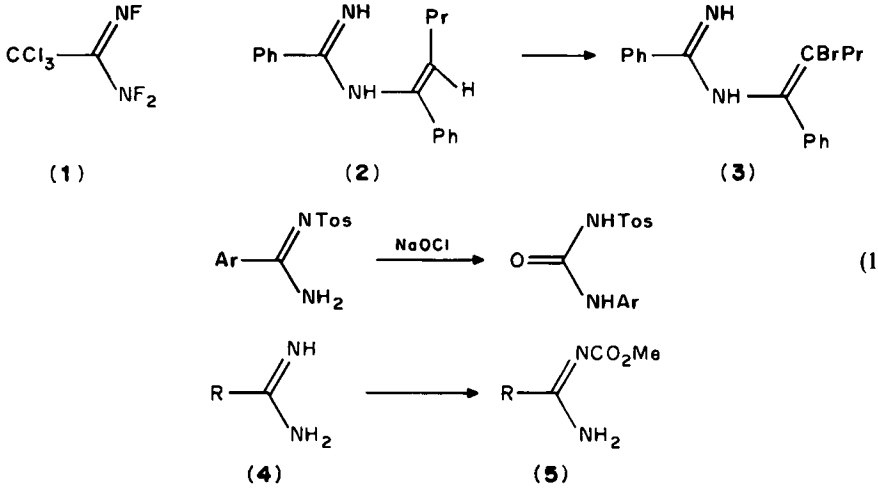
In this chapter reactions and synthetic uses of amidines are discussed. By far the larger part deals with the preparation of heterocyclic compounds. A headings such as 'pyridines' means the formation of a six-membered ring containing one nitrogen atom; thus pyridines, partially or completely hydrogenated pyridines, pyridones and annelated pyridines, e.g. quinolines, are included in this section. Apart from the earlier account in this series[1] there has been a very general review of the chemistry of amidines[2], as well as a more specialized survey of syntheses with heterocyclic amidines[3] and a review of the use of amidine-protected nucleosides for the synthesis of oligodeoxynucleotides[4].

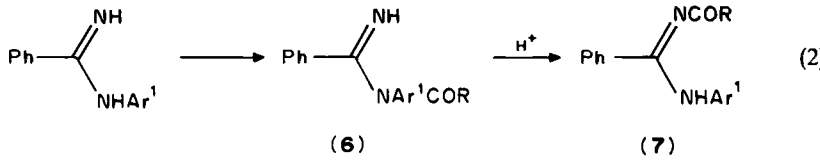
The Chemistry of Amidines and Imidates, Volume 2
Edited by S. Patai and Z. Rappoport

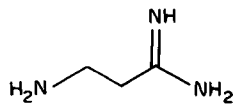
II. REACTIONS OF AMIDINES

A. With Electrophiles

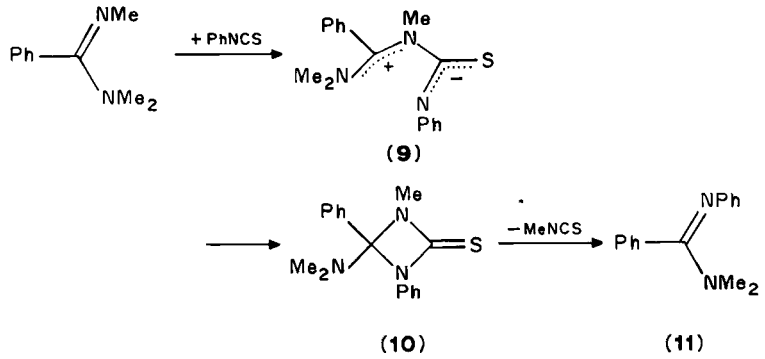
Fluorination of trichloroacetamidine hydrochloride with fluorine in the presence of sodium fluoride and nickel filings at low temperatures results in the trifluoroamidine **1**[5]. Bromination of the enamidine **2** yields the bromo derivative **3** by an addition–elimination mechanism[6]. *N*-Tosylamidines form ureas on treatment with sodium hypochlorite by a Hofmann rearrangement (equation 1)[7]. Simple amidines **4** (R = H, Me or Ar) are converted into *N*-methoxycarbonyl derivatives **5** by the action of methyl chloroformate[8]. Acylation of *N*-arylamidines occurs at the substituted nitrogen atom to yield the amidines **6** (R = Me or Ar[2])[9]; the products readily rearrange to the isomers **7** under the influence of a trace of hydrochloric acid (equation 2)[10]. The site of acylation of aminoalkylamidines, e.g. **8**, has been investigated[11].





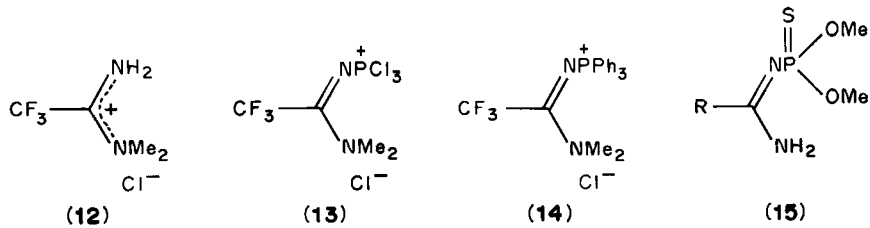


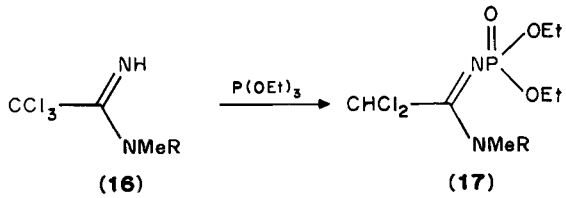
Treatment of *N*,*N*,*N*′-trimethylbenzamidine with phenyl isothiocyanate results in the amidine **11** and methyl isothiocyanate. The kinetics of this exchange reaction point to the intermediacy of the betaine **9** and the 1,3-diazetidinethione **10** (Scheme 1)[12].



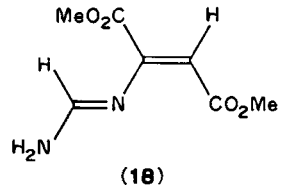
SCHEME 1

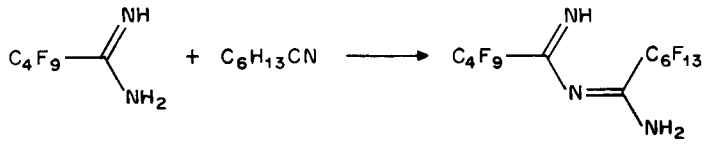
A number of phosphorylated amidines has been obtained by Russian workers. *N,N*-Dimethyltrifluoroacetamidine hydrochloride (**12**) reacts with phosphorus pentachloride to yield the salt **13**; with triphenylphosphine–carbon tetrachloride the triphenyl analogue **14** is formed[13]. Acetamidine and benzamidine react with $SP(OMe)_2Cl$ to yield compounds **15** (R = Me or Ph)[14]. The action of triethyl phosphite on the trichloroacetamidines **16** (R = H or Me) is accompanied by reduction, giving derivatives **17** of dichloroacetamidine[15,16].





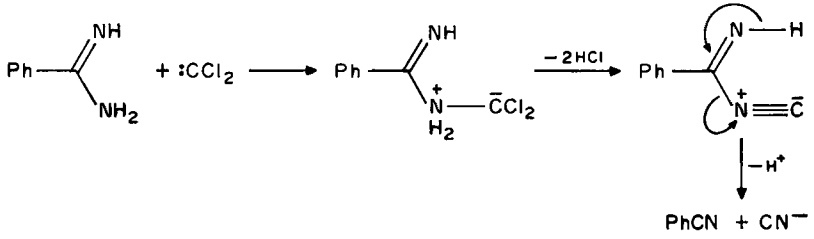
The adduct **18** of formamidine to dimethyl acetylenedicarboxylate has been described[17]. The kinetics of the addition reactions of amidines to fluorinated nitriles, e.g. equation 3, have been determined[18].





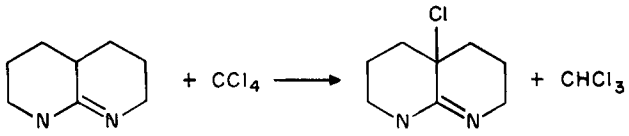
(3)

The action of dichlorocarbene, generated from chloroform and sodium hydroxide under phase-transfer conditions, on benzamidine results in benzonitrile and sodium cyanide, possibly as depicted in Scheme 2[19].

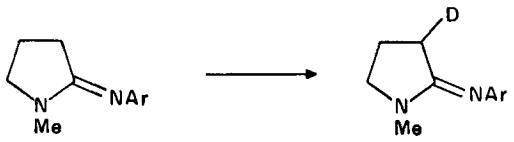


SCHEME 2

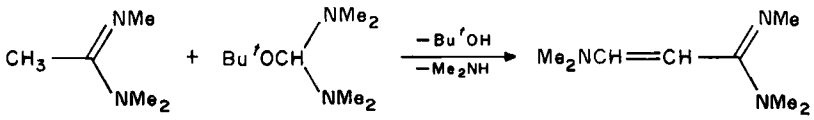
Bicyclic amidines are chlorinated at the α-carbon atom by carbon tetrachloride in the absence of light and oxygen (equation 4)[20]. Another type of reaction at the α-carbon atom of amidines is hydrogen–deuterium exchange, e.g. equation 5[21], and condensation (equation 6)[22]. The activation of the α-methylene group of amidines is attributed to the existence of amidine–enediamine tautomerism (equation 7); it is an important feature of ring-forming reactions of amidines (see equations 68, 69, 72, 77, 78, 83 and 87 and Schemes 9 and 12 below).



(4)



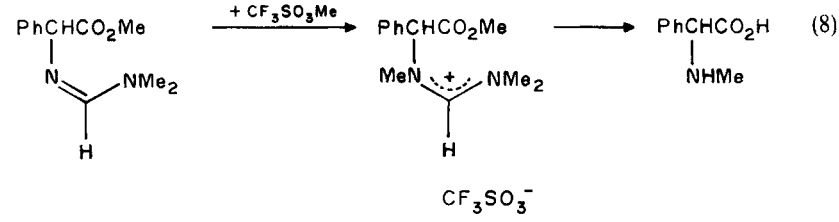
(5)



(6)

(7)

N,N-Dimethylformamidines derived from esters of α-amino acids are alkylated at the other nitrogen atom; subsequent hydrolysis yields *N*-alkylamino acids with almost complete retention of configuration (equation 8)[23]. *C*-Alkylation of compounds of type **19** can be accomplished by prior conversion into the lithium derivatives **20**. The reaction sequence has been used to prepare a great variety of *C*-substituted α-amino acids (equation 9)[24]. Meyers and his coworkers have put lithiated formamidines akin to **20** to impressive use. Treatment of pyrrolidine with *N'*-*t*-butyl-*N,N*-dimethylformamidine yields **21**, which was converted into α-alkylpyrrolidinylformamidines **22** by way of its lithio derivative. The formamido group was then removed by alkaline hydrolysis or by treatment with hydrazine, yielding 2-alkylpyrrolidines **23**. Lithiation of **22**, followed by alkylation and hydrazinolysis, gave 2,5-dialkylpyrrolidines **24** as mixtures of diastereomers (equation 10). The sequence was used for the synthesis of the fire ant venom 2-ethyl-5-heptylpyrrolidine. The formamidino derivative **25** of tetrahydropyridine affords solely the rearranged 4-methyl derivative **26**[26]. Successive treatment of the tetrahydro-β-carboline **27** with potassium hydride and *t*-butyllithium yields the metalated derivative **28**, which forms 1-alkyl-tetrahydro-β-carbolines **29** (R = Me or Bu). When 1-bromo-3-chloropropane is used as the alkylating agent the tetracyclic compound **30** is obtained (equation 11)[26]. Alkylated tetrahydropyridines have been prepared, starting with the piperidine derivative **31**, via the phenylselenyl compound **32**, which is hydrolysed to the 2,3-dehydro compound **33**. The latter on successive lithiation and alkylation yields **34**. Hydrazinolysis of **34** gives 2-alkyl-1,2-dehydropiperidines **35**, while further lithiation, alkylation and hydrazinolysis affords 2,6-dialkyl-1,2-dehydropiperidines **36**. The latter sequence was used for the synthesis of solenopsin A (*trans*-2-methyl-6-undecylpiperidine)



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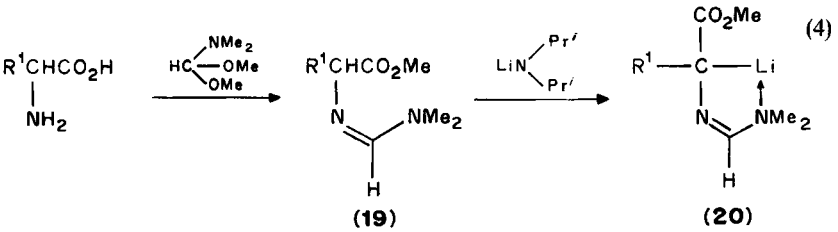

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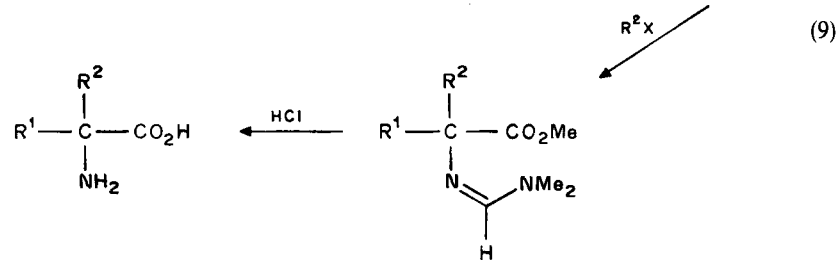

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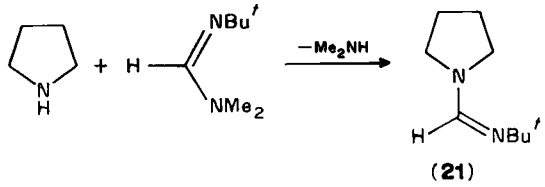

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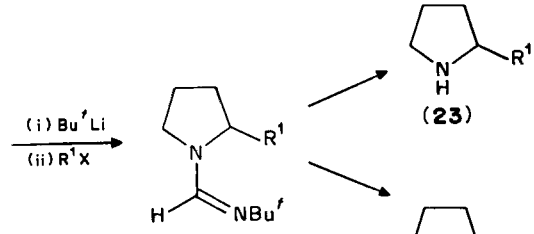
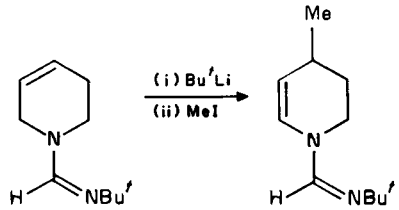


(22) (23) (24) (10)



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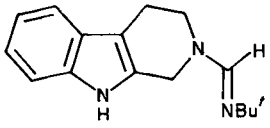

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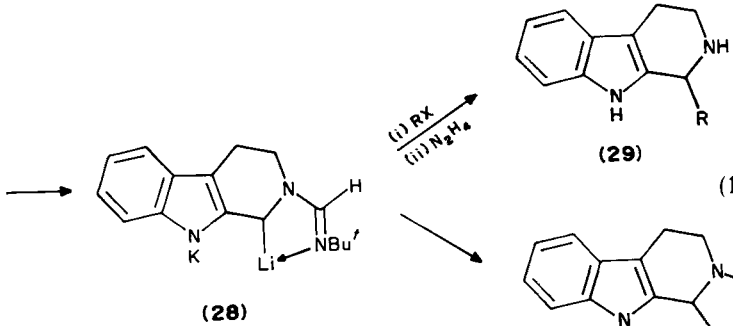
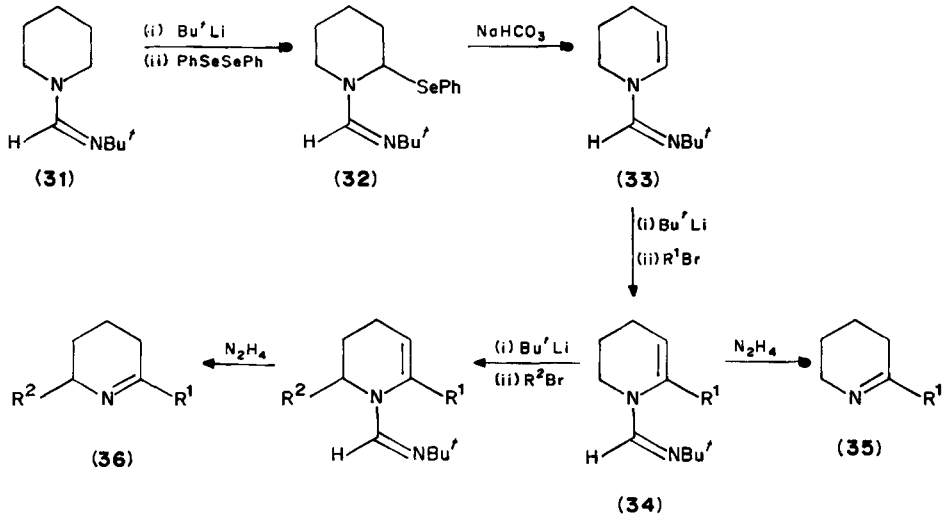
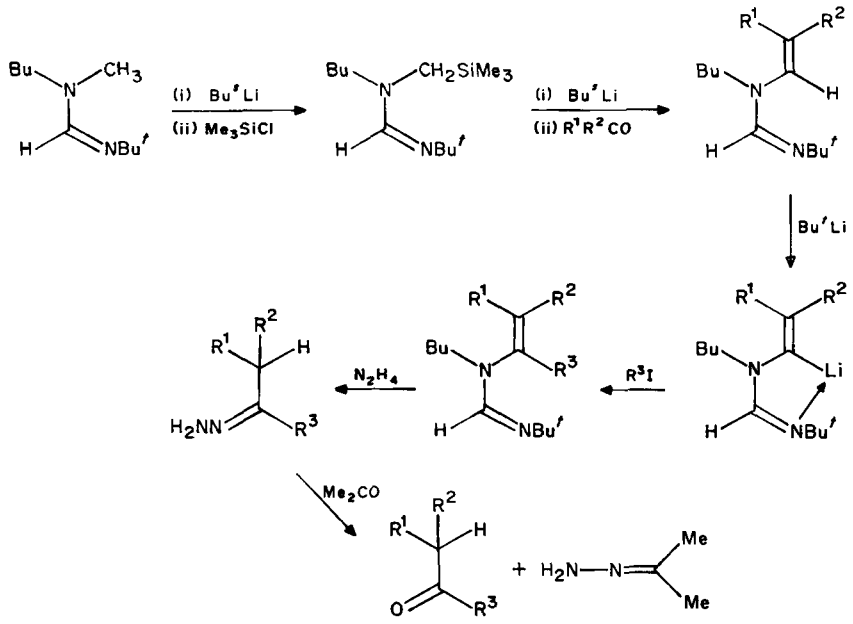


(28) (29) (30) (11)

by reducing **36** ($R^1 = C_{11}H_{23}$, R^2 = Me) with lithium aluminium hydride (Scheme 3)[27]. A method for the homologation of carbonyl compounds is shown in Scheme 4.[27] Thus, from benzophenone and butyl iodide the ketone **37** is obtained, cyclohexanone and butyl iodide give **38**, and piperonal and methyl iodide yield the ketone **39**. Chiral formamidines have

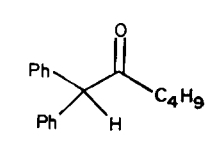


SCHEME 3



SCHEME 4

been employed for the synthesis of optically active 1-alkyltetrahydroisoquinolines. Treatment of *N*-formyltetrahydroisoquinoline with triethyloxonium fluoroborate, followed by disilylated (1*S*, 2*S*)-1-phenyl-2-amino-1,3-propanediol gave the formamidine **40**, which was converted into various alkyltetrahydroisoquinolines **41** (R = Me, Bu, Bu^t, $PhCH_2$ or $PhCH_2CH_2$) by successive lithiation, alkylation and hydrazinolysis (equation 12). All products had the *S*-configuration and in each case the enantiomeric excess was better than 90%[28]. Among other chiral auxiliaries evaluated, the *t*-butyl ether of valinol proved to be particularly advantageous[29]. The derived formamidine **42** afforded (−)-salsolidine (**43**) of nearly complete optical purity[30].



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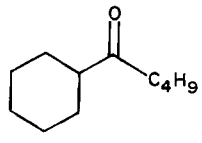

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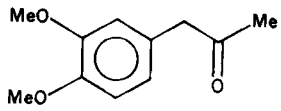

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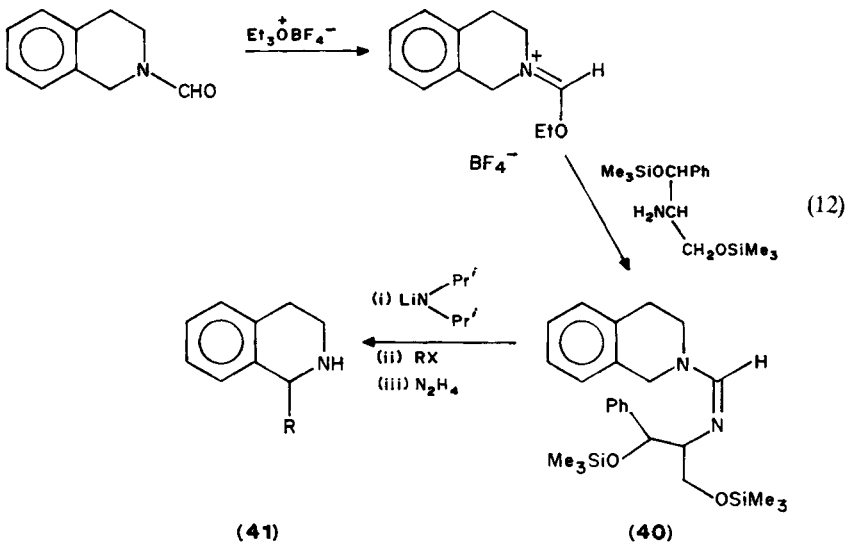
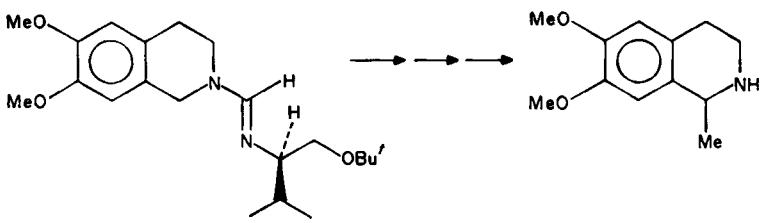


(12)

(41)

(40)

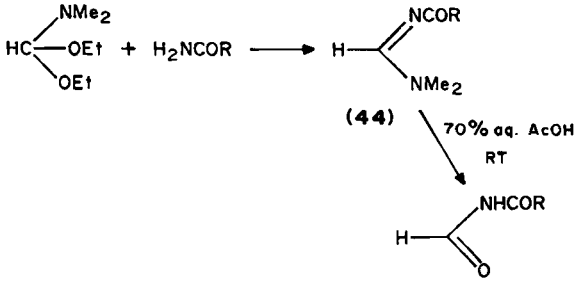


(42)

(43)

B. With Nucleophiles

Mild hydrolysis of acylamidines **44**, obtained by the condensation of primary amides with dimethylformamide diethyl acetal, gives diacylamines in excellent yields (equation 13)[31]. A method for converting ketones $R^1R^2CHCOR^3$ into acids $R^1R^2R^3CCO_2H$ is illustrated in equation 14. The ketone is transformed into the pyrrolidine enamine **45**, which reacts with the phosphoryl azide $(PhO)_2P(O)N_3$ to give a rearranged amidine. Alkaline hydrolysis gives the substituted acid[32]. The selective removal of the methoxycarbonyl group in the formamidinopyrazine *N*-oxide **46** was brought about by treatment with lithium iodide in hot wet dimethylformamide; the formamidino group was then split off by leaving the compound in methanol containing triethyl orthoformate and toluene-*p*-sulphonic acid, giving the protected aminoaldehyde **47**, a useful intermediate for pteridine synthesis (equation 15)[33].



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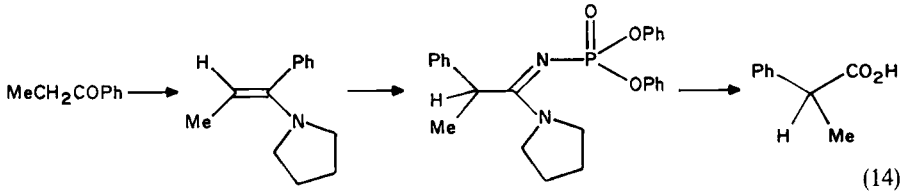

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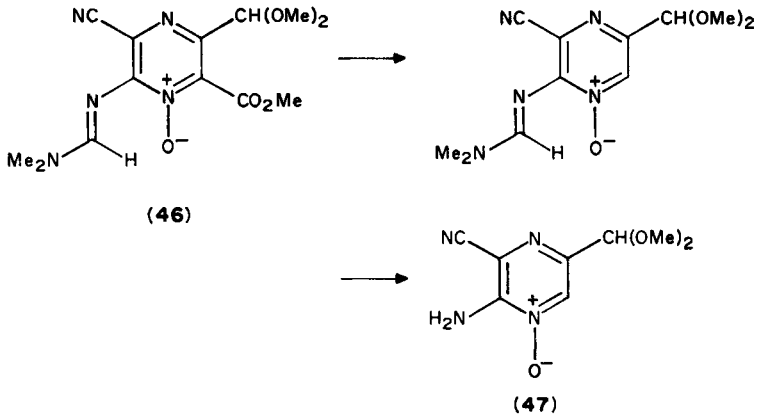
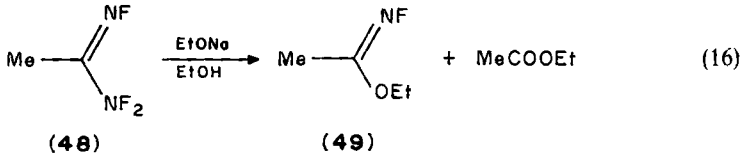
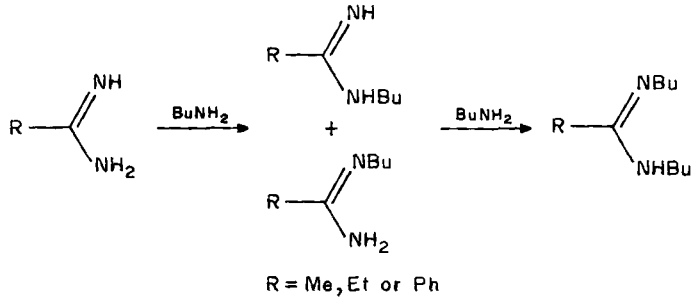


(15)

N,N,N'-Trifluoroacetamidine (**48**) reacts with ethanolic sodium ethoxide to give a mixture of the imidate **49** and ethyl acetate (equation 16)[34]. The exchange reaction of simple amidines with butylamine produces mixtures of tautomeric amidines, which react further with butylamine to yield *N,N'*-dibutylamidines (equation 17)[35]. Hydrazinolysis of acetamidine hydrochlorides with hydrazine or substituted hydrazines in ethanol affords high yields of hydrazidines (equation 18)[36]; the reaction also proceeds well under high pressure[37]. *N,N'*-Dibenzylformamidine exchanges one of its benzylamino groups for morpholine when it is heated with the morpholine enamine derivative of isopropyl methyl ketone (equation 19)[38]. The *N,N*-dimethylformamidino group in compound **50** is readily exchanged on treatment with secondary amines (equation 20)[39]. A more complex exchange reaction is shown in equation 21[40]. The amidine **51** exchanges one of its methoxy groups for cyanide when it is heated with trimethylsilyl cyanide (equation 22)[41].



(48) (49) (16)



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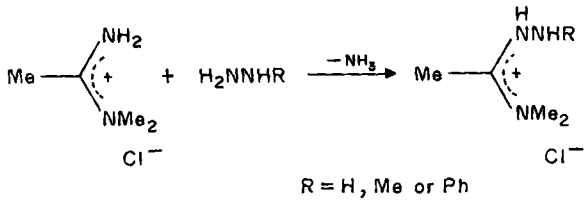

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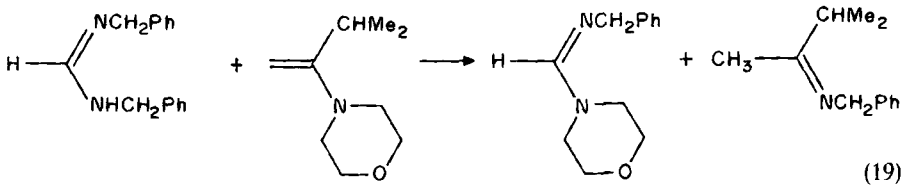

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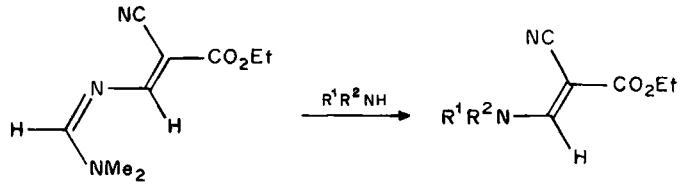
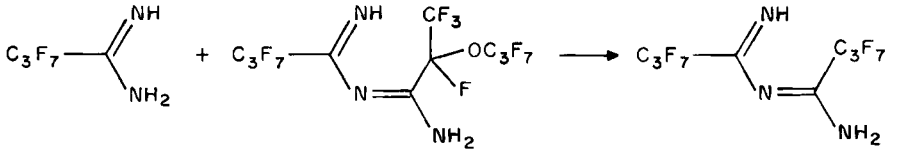


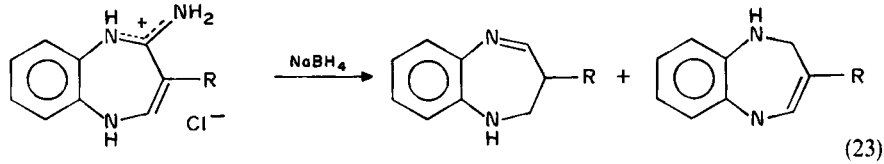
(50) (20)



(21)

(51) (22)

The amidinium salts **52** (R = CN or CO_2Et) suffer deamination on treatment with sodium borohydride (equation 23)[42]. Cyclic amidines are cleaved by the action of lithium diisobutylaluminium hydride. Thus compound **53**, prepared[43] from *N*-isopropyl-1,3-diaminopropane and ethyl acetoacetate, gives *N*-ethyl-*N'*-isopropyl-1,3-diaminopropane (equation 24) and DBU is reduced to 1,5-diazacycloundecane (equation 25). The reaction has been used as a method for the monoalkylation of polyamines. For example, 1,8-diaminonaphthalene yields the heptyl derivative (equation 26) and 1,3-diaminopropane has been converted into spermine (**54**) by treatment of its tosylate with succinonitrile, followed by hexamethyldisilazane and reduction of the resulting bis(trimethylsilyl) derivative (equation 27)[44].



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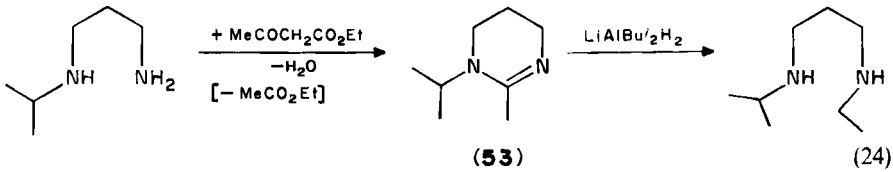
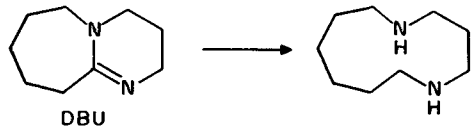


(53) (24)



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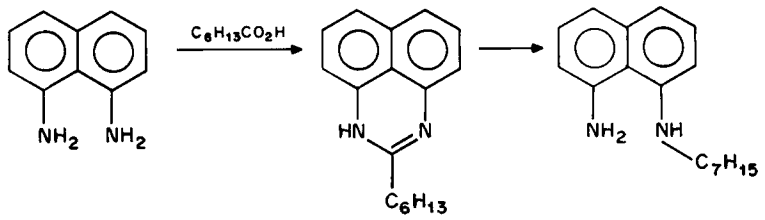

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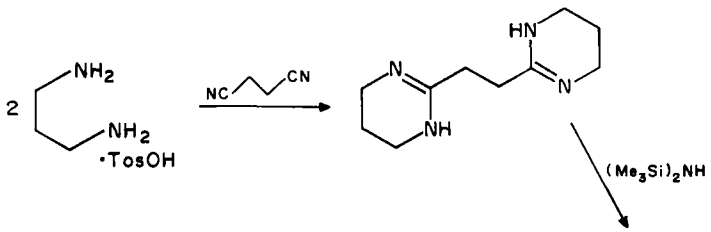

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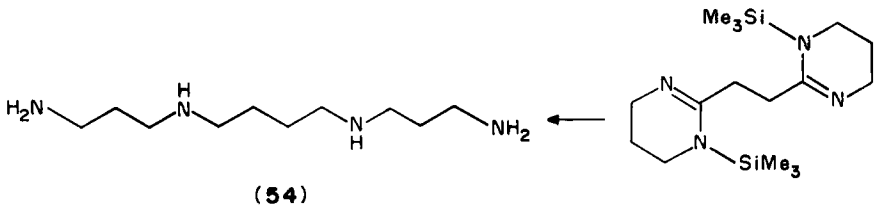
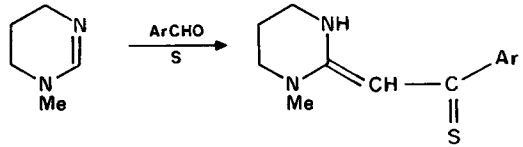


(54)

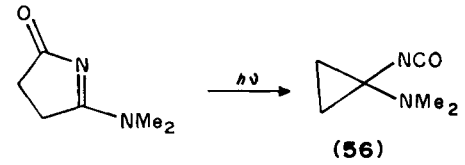
C. Miscellaneous Reactions

The cyclic amidine **55** is converted into thioacylketene aminals by the combined action of aromatic aldehydes and sulphur in a process akin to the Willgerodt–Kindler reaction (equation 28)[45]. 2-Dimethylamino-1-pyrrolin-5-one undergoes a remarkable ring-contraction on irradiation, yielding the cyclopropyl isocyanate **56** (equation 29)[46]. The pesticidal amidine **57** undergoes photolysis in water to afford mainly the hydrolysis product **58**, together with a little of the ether **59** (equation 30)[47]. The thiazetidine *S*-oxide **60** extrudes sulphur monoxide on flash-vacuum pyrolysis to yield the enamidine **61** (equation 31)[48].



(55)

(28)



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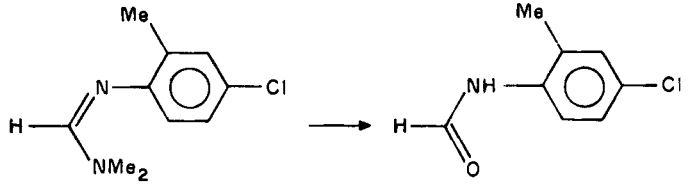
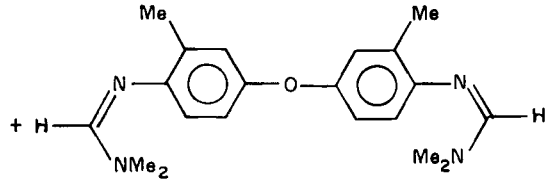
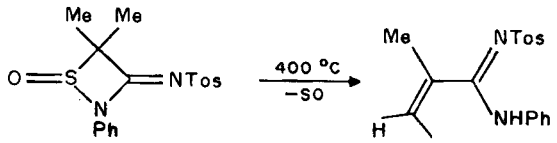


(57) (58)

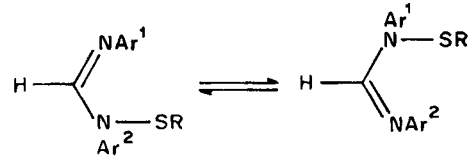


(59) (30)



(60) (61) (31)

The 1,3-migration of groups from one nitrogen atom to the other has been observed for a number of amidines. The migrating group may be sulphenyl (equation 32)[49], chlorine, Ph_2S^+, Ph_3P^+ or Ph_3As^+ (e.g. equation 33)[50] or nitroso (equation 34)[51]. A degenerate [3,3] sigmatropic shift (equation 35) has been reported[51].



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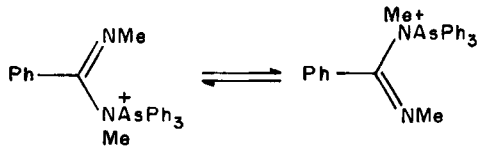

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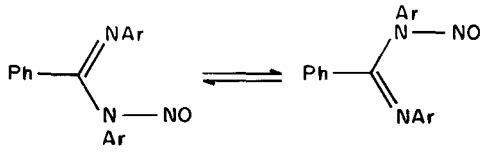
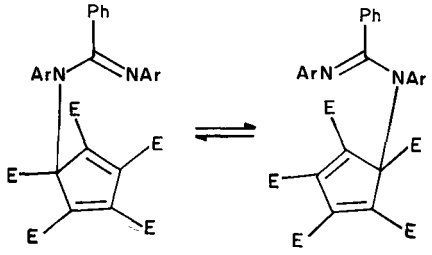


(34)

A = *p*-Tol

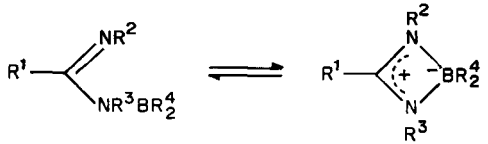


(35)

Ar = *p*-Tol, E = CO_2Me

III. SYNTHESIS OF HETEROCYCLIC COMPOUNDS FROM AMIDINES

A review on amidinoboranes, which exist as equilibrium mixtures with four-membered boron nitrogen heterocycles (equation 36), has appeared[52].



(36)

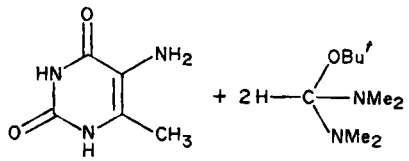
A. Five-membered Rings

1. Pyrroles

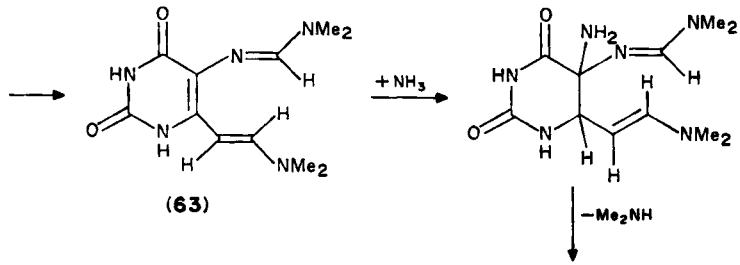
5-Amino-6-methyluracil condenses with the ester aminal **62** on heating to give the amidine **63**, which in turn yields the annelated pyrrole **64** on treatment with ammonia (equation 37)[53]. The action of *N*,*N*-dimethylbenzamidine on diphenylcyclopropenone results in the pyrrolinone **65** (equation 38)[54]. Lithiation of the formamidine **31** (see Scheme 3) with *t*-butyllithium, followed by reaction with pentynylcopper, gives the copper derivative **66**, which on treatment with 1-chloro-3-iodopropane and subsequent hydrolysis furnishes the azabicyclo[4.3.0]nonane **67** (equation 39)[55].

2. Imidazoles

The amidine **69**, formed from *o*-phenylenediamine and the nitrile **68**, cyclizes spontaneously to benzimidazole (equation 40)[56]; a similar reaction of 2,3-diaminopyridine is shown in equation 41[57]. *o*-Fluoronitrobenzene readily condenses with *N*,*N'*-dimethylbenzamidine; the product yields the benzimidazazolium nitrite **70** on heating (equation 42)[58]. Thermal cyclization of the complex cyclohexylamidine **71** (as the formate)



(62)



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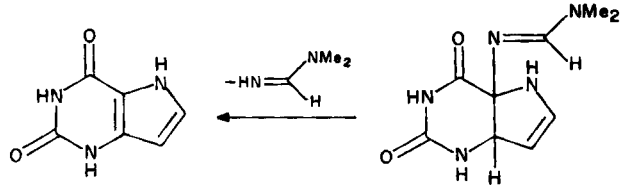
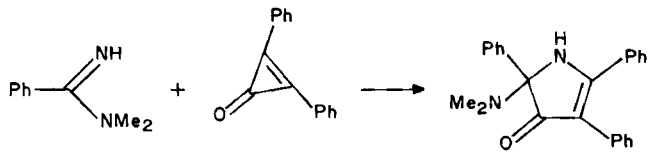


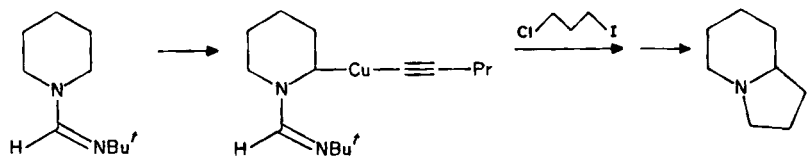
(64)

(37)



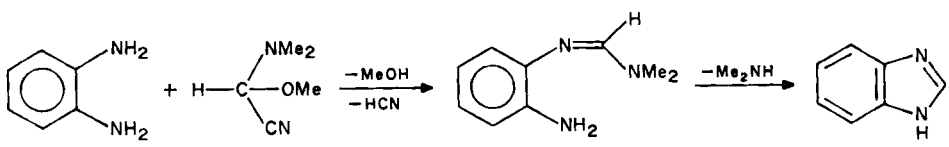
(65)

(38)



(31) (66) (67)

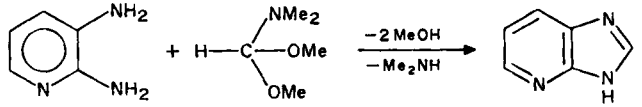
(39)



(68) (69)

(40)

gives the imidazole **72**, accompanied by a trace of the isomer **73** (equation 43)[59]. The reduced imidazoquinoxaline **74** is formed by the action of *N*-methylbenzamidine on 1-methylquinoxalinium iodide (equation 44)[60]. Heating the formamidinophenylazouracil **75** yields 8-dimethylaminotheophylline (**77**), which is formed by way of the isolable *N*-anilino compound **76** (equation 45)[61]. The iminoimidazoline **79** results from the reaction of benzamidine with α-acetamido-β,β-dichloroacrylonitrile (**78**) (equation 46)[62]. Bromination of the *N*-allylbenzamidine **80** yields the imidazoline hydrobromide **81** (equation 47); in contrast, the cinnamyl analogue **82** forms the tetrahydropyrimidine **83** (equation 48)[63].



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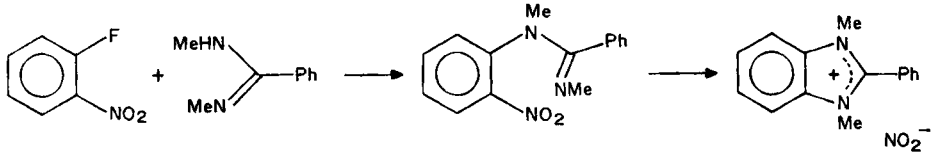
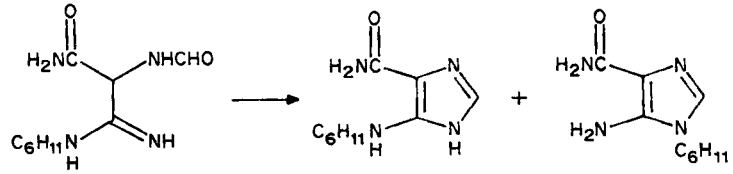
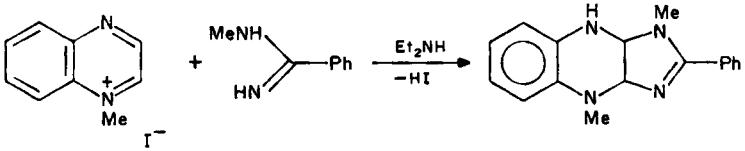


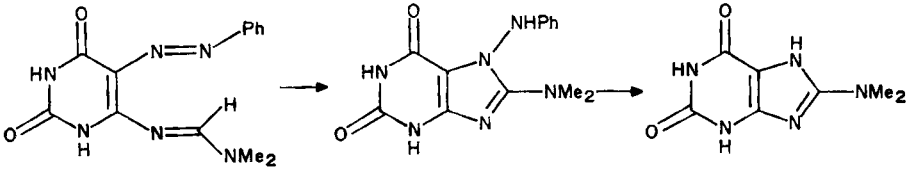
(70) (42)



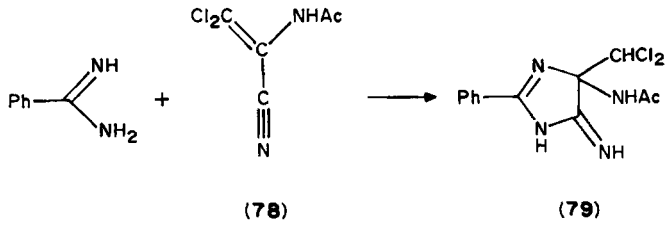
(71) (72) (73) (43)



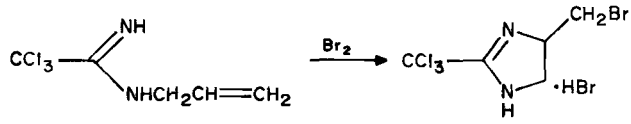
(74) (44)



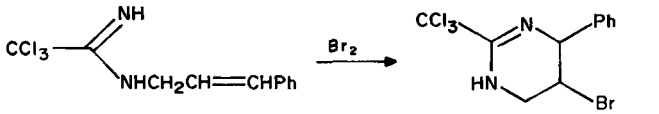
(75) (76) (77) (45)



(78) (79) (46)

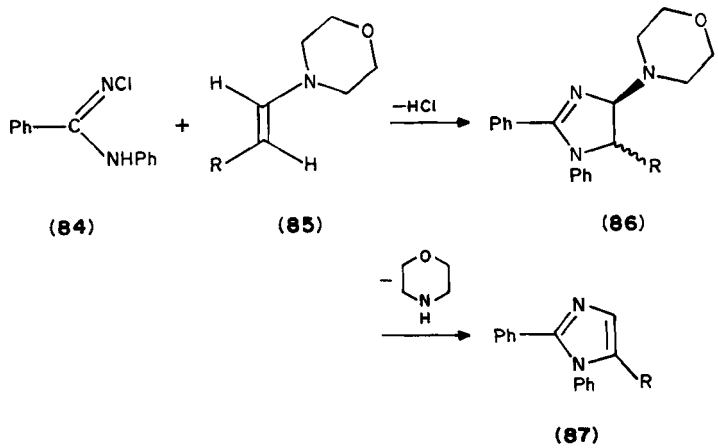


(80) (81) (47)

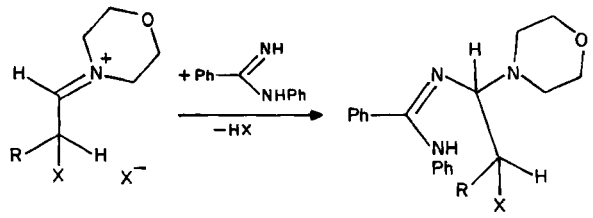


(82) (83) (48)

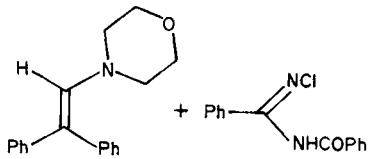
N-Chloro-*N'*-phenylbenzamidine **84**, obtained by the action of *N*-chlorosuccinimide on *N*-phenylbenzamidine, reacts with enamines **85** (R = alkyl or aryl) to yield unstable 4-dialkylaminoimidazolines **86**, which readily eliminate a secondary amine to form imidazoles **87** (equation 49)[64]. The same result is obtained when mixtures of *N*-phenylbenzamidine and enamines **85** are treated with bromine[65]. It has been suggested that both reactions proceed via a halogenoimmonium salt **88** (X = Cl or Br), which adds *N*-phenylbenzamidine to yield **89** (equation 50). *N*-Benzoyl-*N'*-chlorobenzamidine and the enamine **90** gave a mixture of the imidazoline **92** and the amidine **93**; the latter is thought to be formed by rearrangement of the common intermediate **91** (equation 51)[66]. A



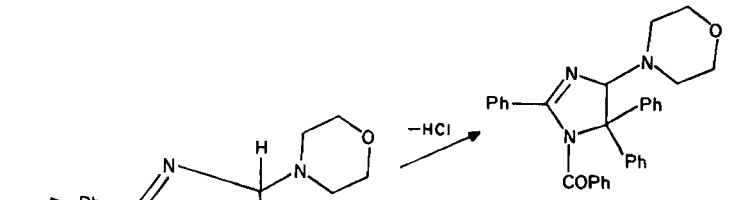
(84) (85) (86) (87) (49)



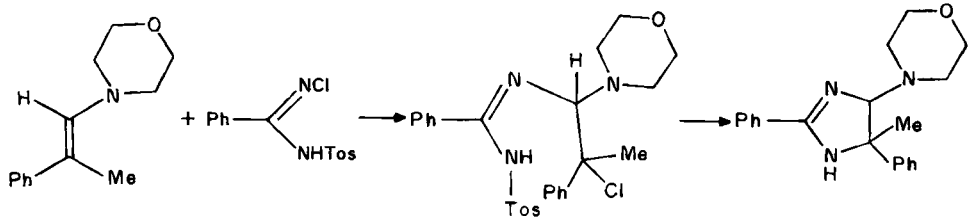
(88) (89) **86** (50)



(90)

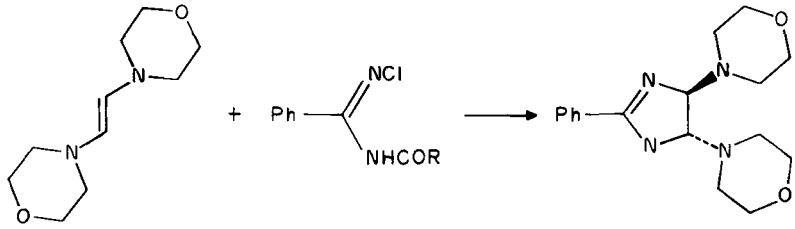


(91) (92) (93) (51)



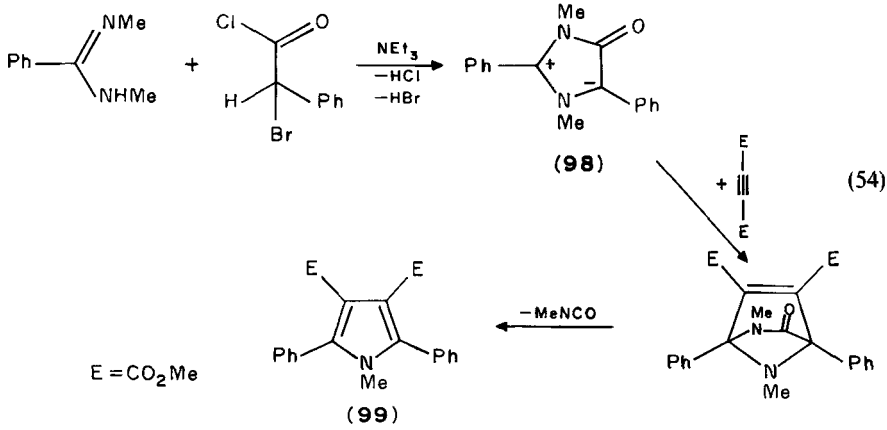
(94) (95) (96) (52)

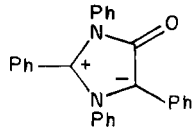
compound of the same type as **89** and **91**, namely the tosyl derivative **95**, was isolated from the reaction of *N*-chloro-*N'*-tosylbenzamidine with the enamine **94** in chloroform; cyclization to the imidazoline **96** occurred readily (equation 52)[67]. The imidazolines **97** are produced from *N*-acyl-*N'*-chlorobenzamidines and *trans*-1,2-dimorpholinoethene (equation 53)[68].



(97)

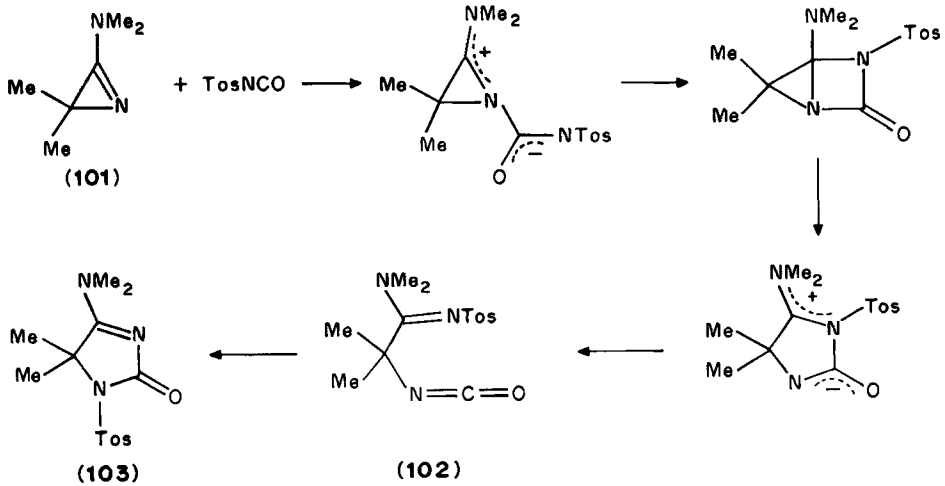
The action of α-bromophenylacetyl chloride on *N,N'*-dimethylbenzamidine results in the unstable mesoionic *anhydro*-4-hydroxyimidazolium hydroxide **98**, which can be trapped as the pyrrole **99** by an *in situ* reaction with dimethyl acetylenedicarboxylate (equation 54)[69]. The tetraphenyl analogue **100**, prepared similarly from *N,N'*-diphenylbenzamidine, can be isolated[70].



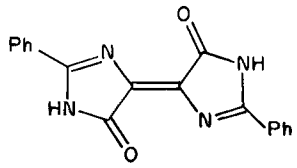


(100)

The isocyanatoamidine **102** is obtained when the azirine **101** is treated with tosyl isocyanate. The reaction is thought to proceed by way of two dipolar intermediates. Compound **102** readily rearranges to the imidazolinone **103** (Scheme 5)[71]. It has been claimed that benzamidine reacts with dimethyl acetylenedicarboxylate in boiling methanol to yield the biimidazolinone **104**[72] (cf. equation 93, below).



SCHEME 5



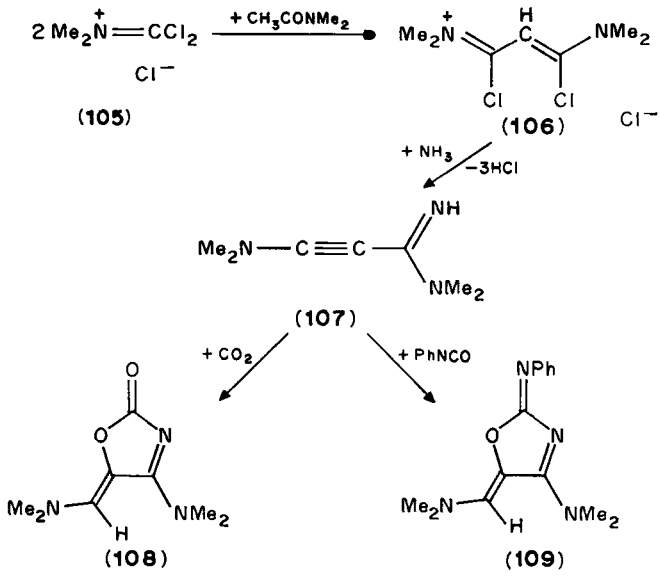
3. *Oxazoles and thiazoles*

'Phosgeneiminium chloride' (Viehe's salt, **105**) and dimethylacetamide yield the salt **106**, which reacts with ammonia to give the ynamine-amidine **107**. The latter is converted into the oxazolines **108** and **109** by the action of carbon dioxide and phenyl isocyanate, respectively (Scheme 6)[73].

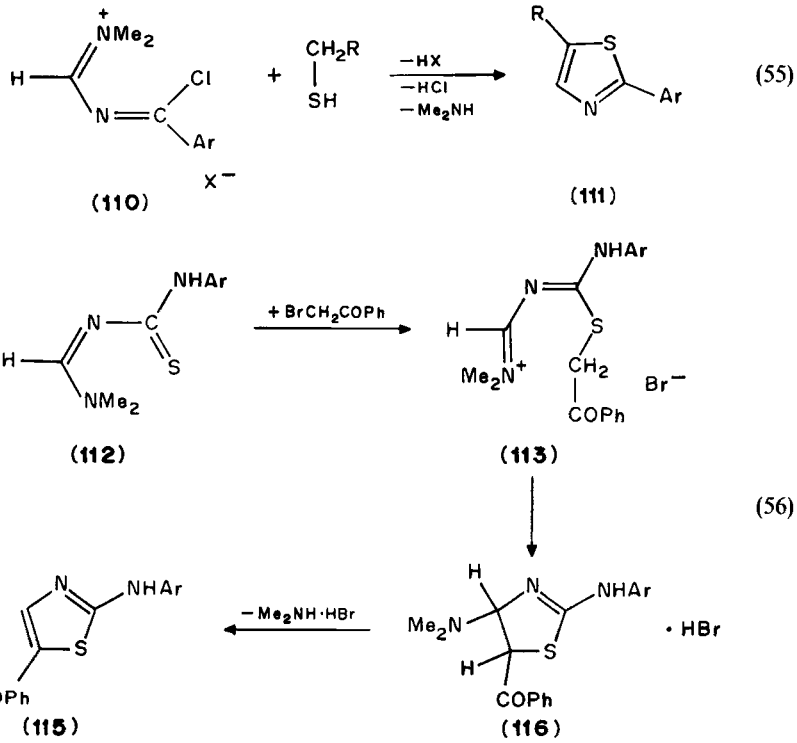
Thiazoles **111** (Ar = *p*-$MeOC_6H_4$; R = CO_2Me, Ac or Bz) are formed from the amidine **110** and the appropriate thiols (equation 55)[74]. The amidines **112**, obtained from dimethylformamide dimethylacetal and *N*-arylthioureas, react with phenacyl bromide to yield thiazoles **115** via the isolable intermediates **113** and **114** (equation 56)[75].

4. *Systems containing three heteroatoms*

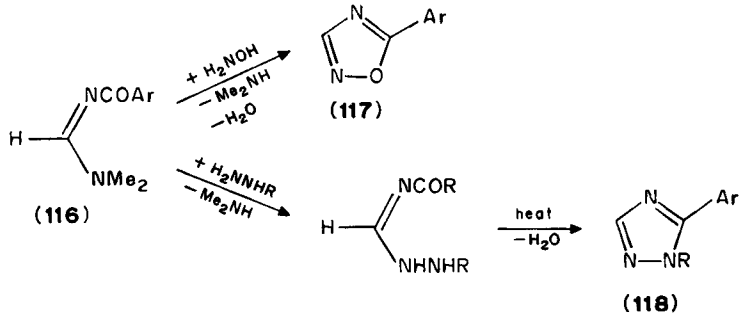
Acylamidines **116** are converted into 1,2,4-oxadiazoles **117** and 1,2,4-triazoles **118** (R = H or Me) by treatment with hydroxylamine and hydrazines, respectively. In the latter case intermediate hydrazidines are isolated (Scheme 7)[76]. The 3-amino-1,2,4-oxadiazole **120** (R = 2,6-dichlorobenzyl) is produced from the *N*-cyanoamidine **119** and hydroxylamine, as shown in equation 57[77]. The formamidinopteridine 3-oxide **121** is cleaved on treatment with hydroxylamine; the resulting diamidoxime **122** cyclizes to the oxadiazole **123** in hydrochloric acid (equation 58)[78]. The formamidinopyridine **124** is converted into *s*-triazolo[1,5-*a*]pyridine (**125**) by the action of hydroxylamine-*O*-sulphonic acid



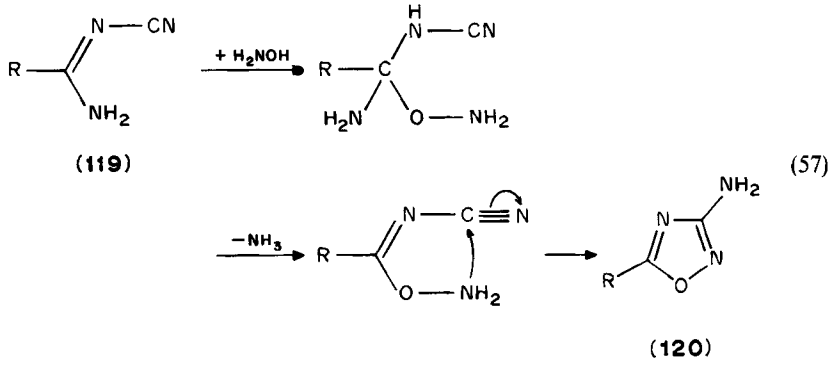
SCHEME 6



(equation 59)[79]. This reagent transforms the amidine **126** into the 1,2,4-thiadiazole **127** (equation 60)[80].



SCHEME 7



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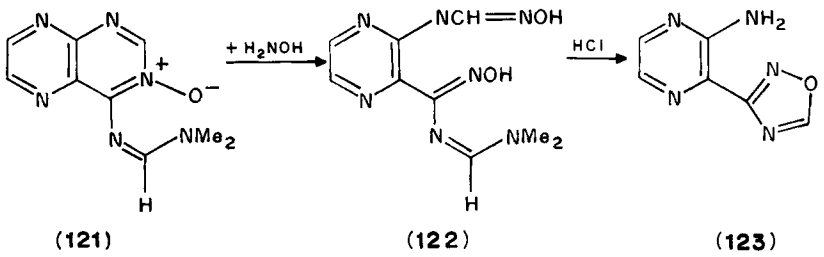
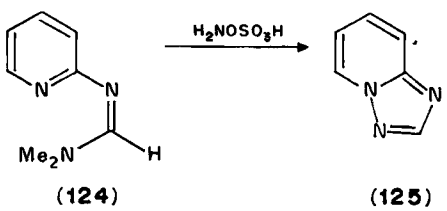


(58)



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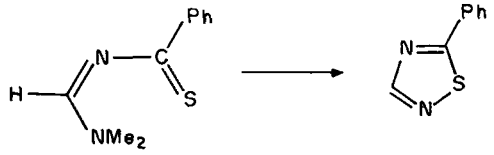
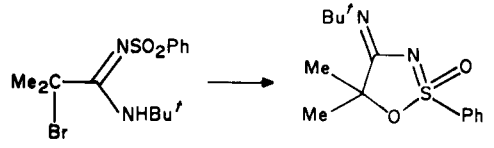


(126) (127) (60)

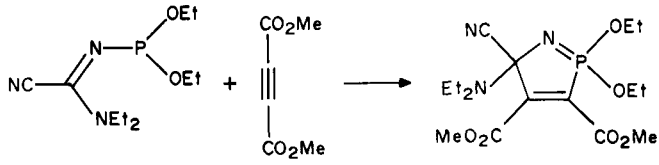
The 4-imino-4,5-dihydro-1,2λ^6,3-oxathiazol-2-one **129** is formed in the reaction of potassium *t*-butoxide with the amidine **128** (equation 61)[81].



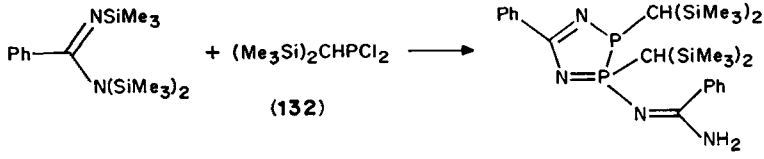
(128) (129) (61)

5. Systems containing nitrogen and phosphorus or boron

The phosphorylated amidine **130** adds dimethyl acetylenedicarboxylate to form the azaphosphole **131** (equation 62)[82]. The reaction of *N,N,N'*-tris(trimethylsilyl)-benzamidine with the phosphine **132** unexpectedly yielded the 1,4-diaza-2,3-diphospholene **133** (equation 63)[83]. The amidine **134**, formed from *N,N*-dimethylbenzamidoxime and tris(dimethylamino)phosphine, cyclizes to 1,3-bis(dimethylamino)-1*H*-2,1-benzazaphosphole 1-oxide (**135**) by the radical mechanism outlined in equation 64[84].

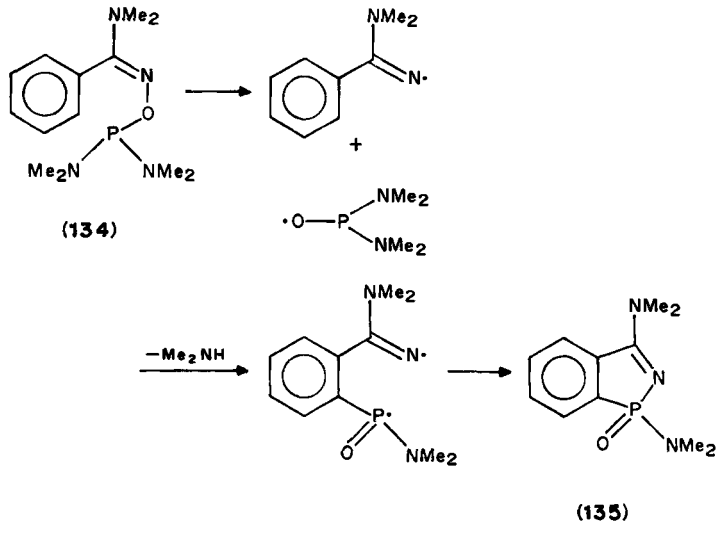


(130) (131) (62)



(132) (133) (63)

Amidines add 1,2-dicarbonyl compounds to form unstable products **136**, which rapidly decompose to intractable mixtures. When the addition is carried out in the presence of bis(diphenylboron) oxide, stable crystalline boron heterocycles **137** (R^1 = Me or Ph; R^2, R^3 = H, Me or Ph) are isolated (equation 65)[85].



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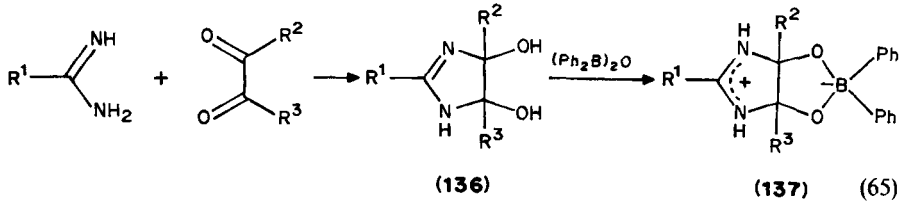
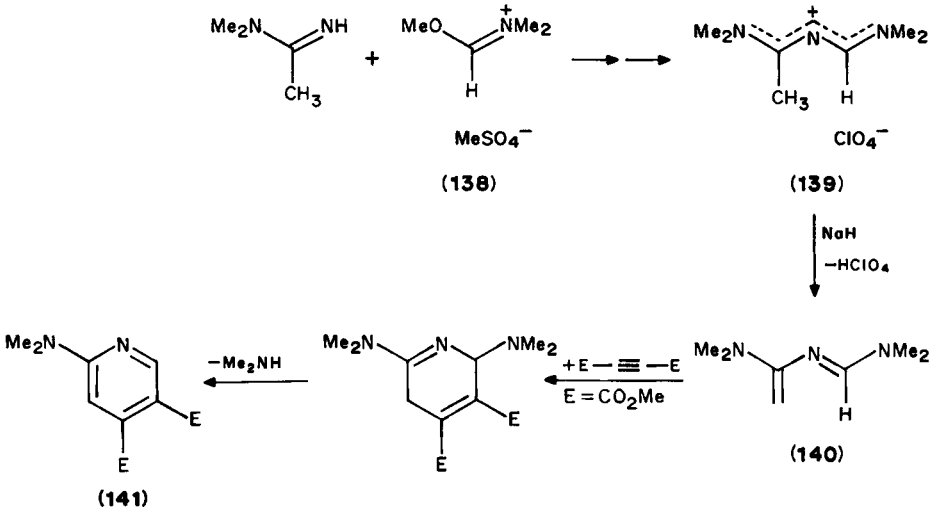


(65)

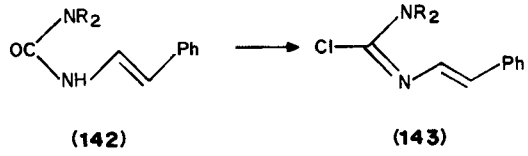
B. Six-membered Rings

1. Pyridines

N,N-Dimethylacetamidine condenses with the dimethylformamide–dimethyl sulphate adduct **138** to yield an amidinium salt, isolated as the perchlorate **139**. Deprotonation generates the unstable 2-azabutadiene **140**, which reacts *in situ* with dimethyl acetylenedicarboxylate to form the pyridine **141** (Scheme 8)[86]. The urea **142** is converted into the chloroformamidine **143** by the combined action of carbon tetrachloride and triphenylphosphine; successive treatment with lithium phenylacetylide and polyphosphoric acid yields 2-morpholino-4,5-diphenylpyridine (**144**) (equation 66)[87]. The dimer (**145**) of malononitrile reacts with formamidine acetate to afford the pyridine **146** (equation 67)[88]. Condensation of ethyl β-aminocrotonate with dimethylacetamide dimethylacetal affords the amidine **147**, which cyclizes to the γ-pyridone **148** when heated (equation 68)[89]. This reaction illustrates the reactivity of α-methylene groups of amidines discussed previously (see equation 7). Another example of this phenomenon is the thermal ring-closure of the acetamidine derivative **149** to the α-pyridone **150** (equation 69)[90]. The amidine **151**, prepared from isopropylidenecyanoacetamide and dimethylformamide diethylacetal, yields 3-cyano-4-methyl-α-pyridone (**152**) on heating (equation 70)[91]. The bicyclic α-pyridone **153** is formed by a similar reaction (equation 71)[92].

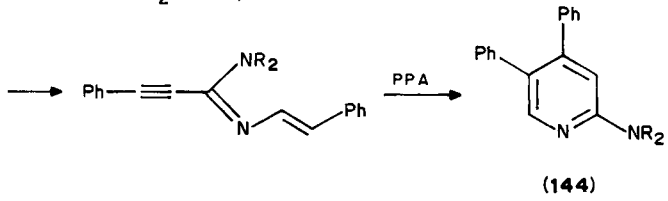


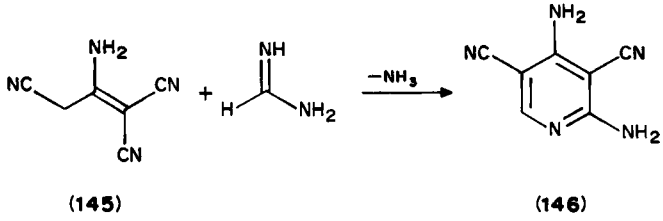
SCHEME 8



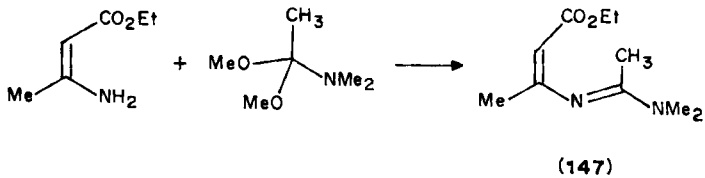
(66)

R_2N = morpholino

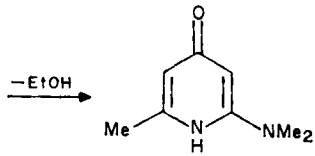




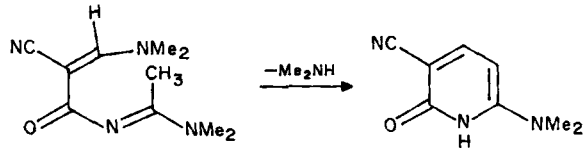
(67)



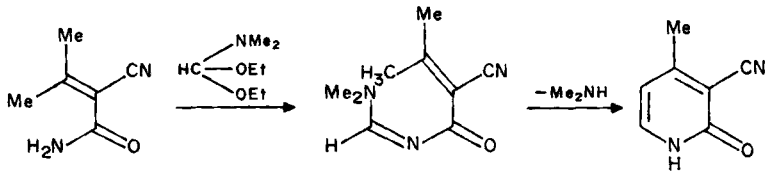
(147)



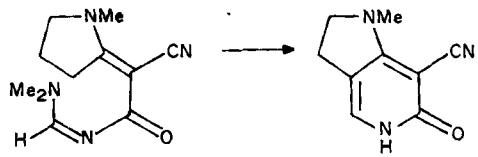
(148) (68)



(149) (150) (69)

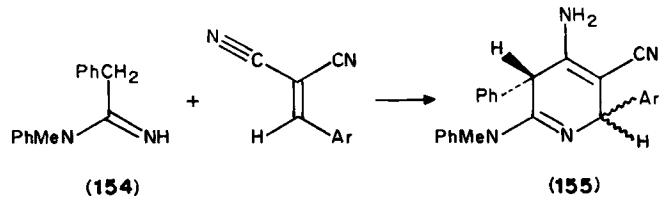


(151) (152) (70)

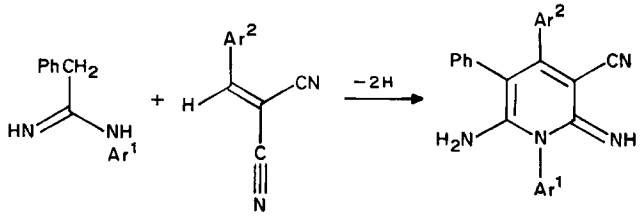


(153) (71)

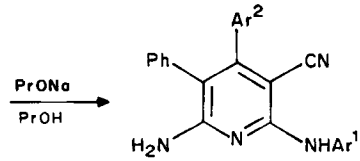
The formation of heterocyclic compounds from amidines and ylidenemalononitriles (1,1-dicyanoethenes) has been extensively investigated by Robev[93]. Treatment of *N*-methyl-*N*-phenyl-phenylacetamidine (**154**) with arylidenemalononitriles at room temperature affords the adducts **155** as separable mixtures of *cis*- and *trans*-isomers (equation 72)[94]. When monosubstituted phenylacetamidines are employed in this reaction, adducts of a different type are formed, which undergo spontaneous dehydrogenation to the imines **156**. The latter are converted into the pyridines **157** by a Dimroth rearrangement (equation 73)[95].



(154) (155) (72)

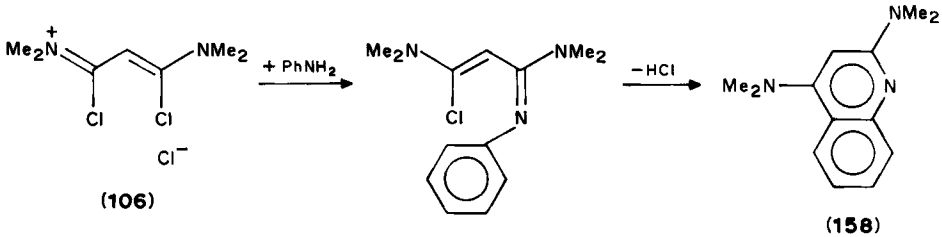


(156)

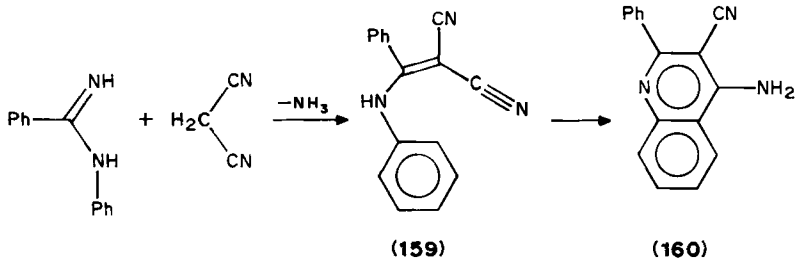


(157) (73)

The propenylium salt **106** reacts with aniline under conditions of high dilution to give 2,4-bis(dimethylamino)quinoline (**158**) (equation 74)[96]. The condensation product **159** of *N*-phenylbenzamidine with malononitrile cyclizes to the quinoline **160** under acid catalysis (equation 75)[97]. Treatment of the chloroformamidine **161** with acetylenic

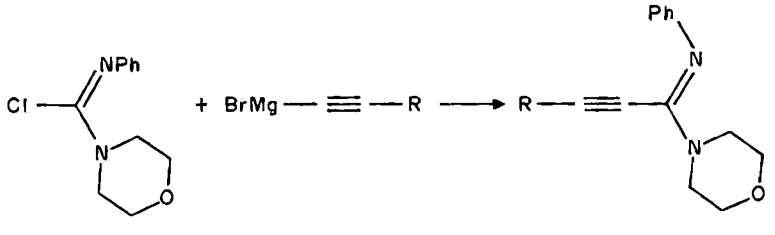


(106) (158) (74)

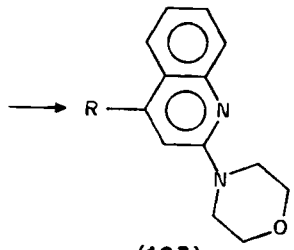


(159) (160) (75)

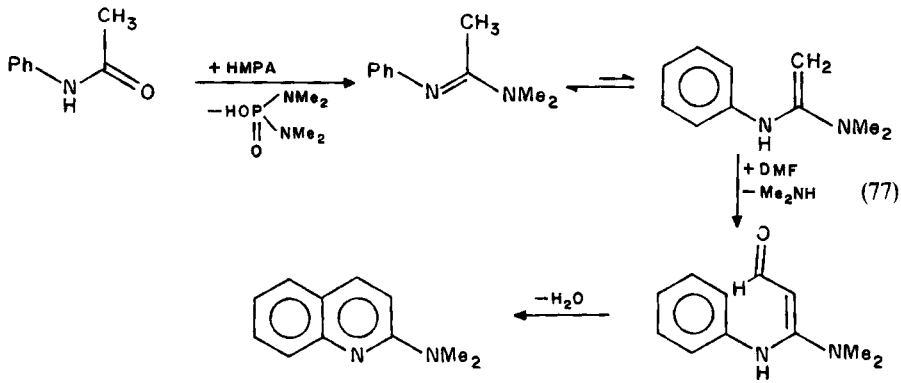
Grignard reagents yields the amidines **162** (R = H, Ph or cyclohexyl), which form the quinolines **163** under the influence of polyphosphoric acid (equation 76)[98]. Heating acetanilide in turn with HMPA and DMF gives 2-dimethylaminoquinoline, as shown in equation 77[99]. The formation of the quinolone **165** from the amidine **164** proceeds by a similar mechanism (equation 78)[100,101]. Other syntheses of quinolones etc. are shown in equations 79[102] and 80[103].



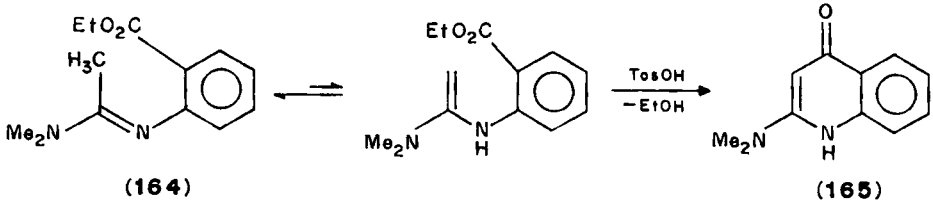
(161) (162)



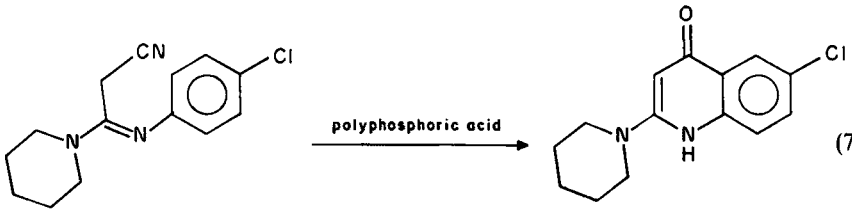
(163) (76)



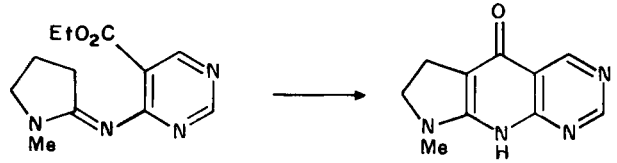
(77)



(164) (165) (78)

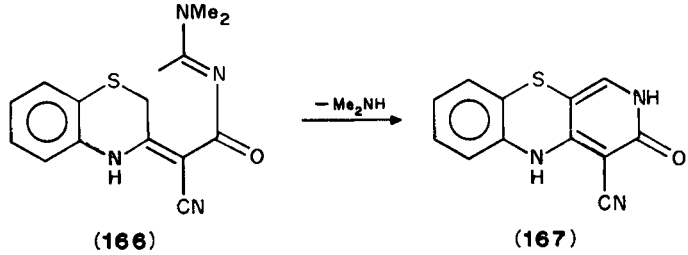


(79)



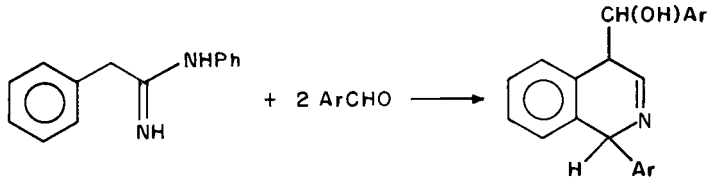
(80)

4-Cyano-2,3-dihydro-3-oxo-5*H*-pyrido[1,4-*b*][1,4]benzothiazine (**167**) results from the thermal ring-closure of the amidine **166** (equation 81)[104]. *N*-Phenylphenylacetamidine reacts with two molecules of aromatic aldehydes to give 1,4-dihydroisoquinolines (equation 82)[105].



(166) (167)

(81)

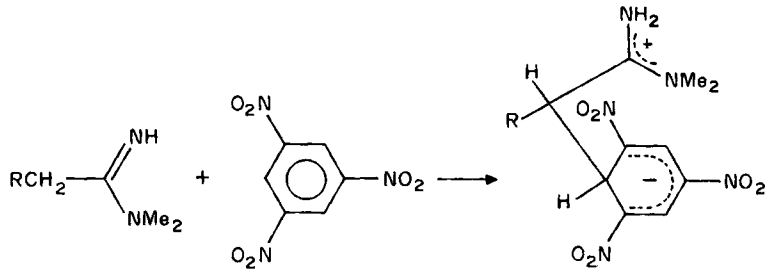


(82)

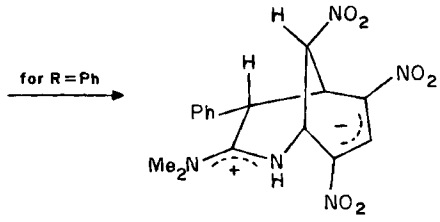
N,*N*-Dimethylacetamidine forms the crystalline Meisenheimer complex **168** (R = H) with 1,3,5-trinitrobenzene. When *N*,*N*-dimethylphenylacetamidine is used, the resulting complex at once cyclizes to the bridged betaine **169** (equation 83)[106]. 1,3,5-Trinitrobenzene and the bicyclic amidine **170** yield an analogous bridged dipolar compound **171** as a mixture of two stereoisomers; on the other hand, 1,3-dinitronaphthalene forms the Meisenheimer complex **172**, which has no tendency to cyclize[107].

2. *Pyridazines and pyrazines*

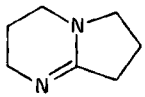
The action of the acetamidine **173** on 3-phenyl-6-α-pyridyl-1,2,4,5-tetrazine (**175**, R = α-pyridyl) leads to a mixture of the isomeric pyridazines **176** and **177**. The process represents a Diels–Alder reaction with inverse electron demand of the electron-rich dienophile, the



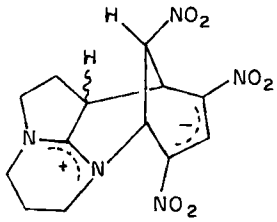
(168) (83)



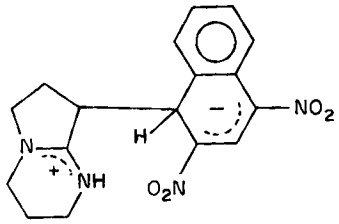
(169)



(170)



(171)

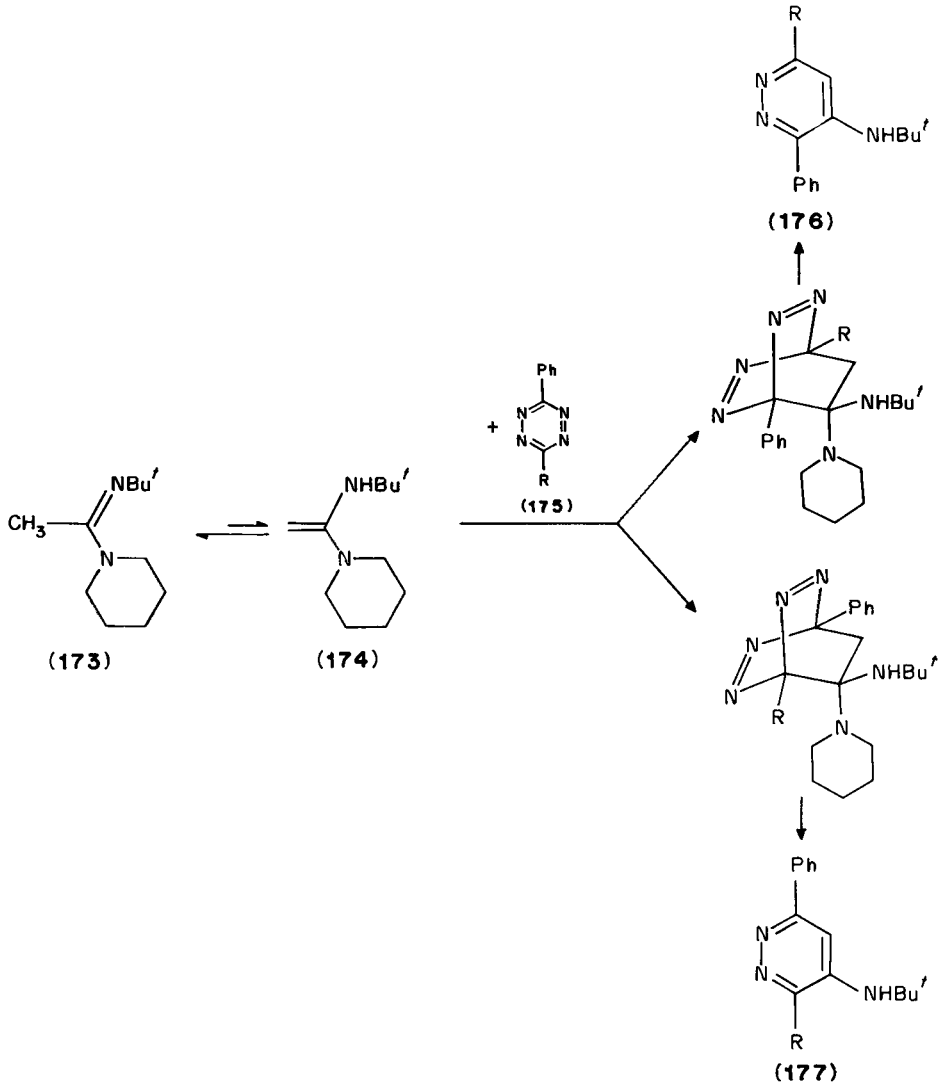


(172)

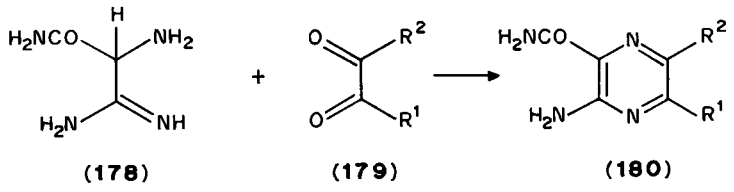
tautomeric ketene aminal **174** (see equation 7), with the electron-poor diene, the tetrazine. Two regioisomeric adducts are formed, which give the products by sequential loss of nitrogen and piperidine (Scheme 9)[108].

2-Amidino-2-aminoacetamide (**178**) condenses with numerous 1,2-dicarbonyl compounds **179** (R^1, R^2 = H, Me, Ph, etc.) to yield 2-aminopyrazine-3-carboxamides **180**, which are useful precursors of pteridines (equation 84)[109]. Phenylglyoxal reacts with **178** at pH 8–9 to give the pyrazine **180** (R^1 = H, R^2 = Ph)[109], whereas at pH 4–5 the isomer **180** (R^1 = Ph, R^2 = H) is obtained[110]. Treatment of the benzyl derivatives **181** with formic acid–acetic anhydride yields 1-benzylpteridin-4(1*H*)-ones **182** (equation 85)[111].

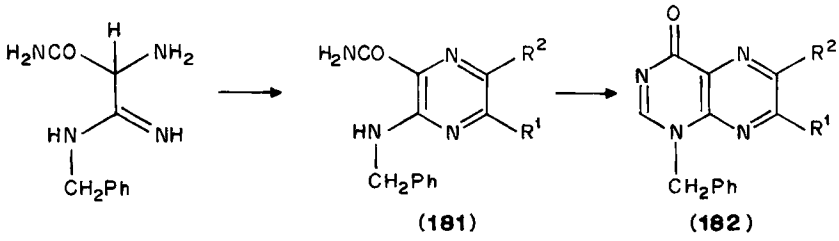
The amidinouracils **183** cyclize on heating to the pteridinediones **184** (equation 86)[112]. The *N*-oxide **187** is formed from 4-chloro-5-nitro-6-pyrrolidinopyrimidine (**185**) and the cyclic amidine **186** (equation 87)[113]; 1-fluoro-2,4-dinitrobenzene undergoes an analogous reaction with the amidine[114].


R
N
N
NHBu'
Ph
(176)
N
N
R
N
N
NHBu'
Ph
N
Ph
N
N
N
R
(175)
NBu'
CH3
N
(173)
NHBu'
N
(174)
N
N
Ph
N
NHBu'
N
R
N
Ph
N
N
NHBu'
R
(177)

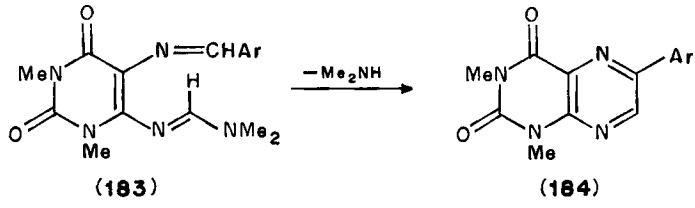
SCHEME 9


H
H2NCO
NH2
H2N
NH
(178)
+
O
R2
O
R1
(179)
H2NCO
N
R2
H2N
N
R1
(180)

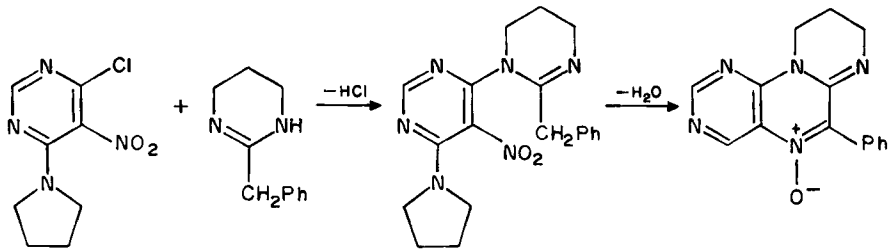
(84)



(85)



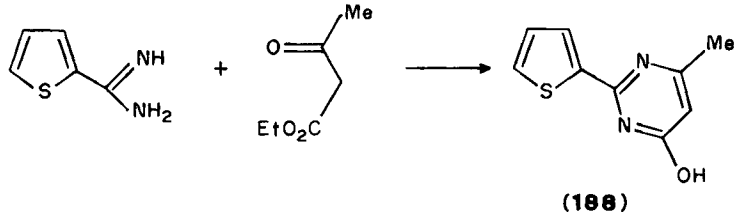
(86)



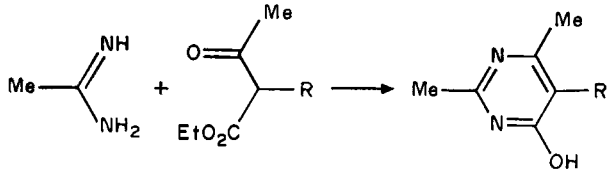
(87)

3. Pyrimidines

The classical Pinner synthesis[115] of 4-hydroxypyrimidines from amidines and β-keto esters and related compounds is exemplified by the formation of the thienyl derivative **188** from 2-amidinothiophen and ethyl acetoacetate (equation 88)[116] and of compound **189** (R = 3,4-dimethoxybenzyl) (equation 89)[117]. Cycloheptanone-, cyclooctanone- and cyclododecanone-carboxylic esters have been condensed with numerous amidines to give the corresponding pyrimidines (equation 90)[118]. The reaction of ethyl cyclohexanone-2-carboxylate with the amidine **190** takes an abnormal course, resulting in the pyridone **191** (equation 91)[119]. Numerous dihydropyrimidine-4,6-diones **193** have been prepared from aliphatic and aromatic amidines and the malonic esters **192** (R^2 = H, Me, Pr or Ph) (equation 92)[120].

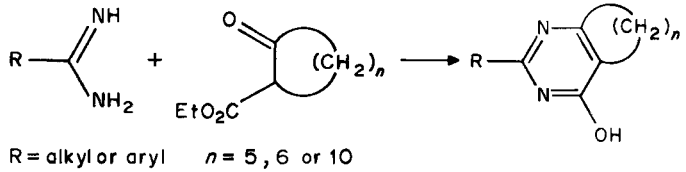


(88)

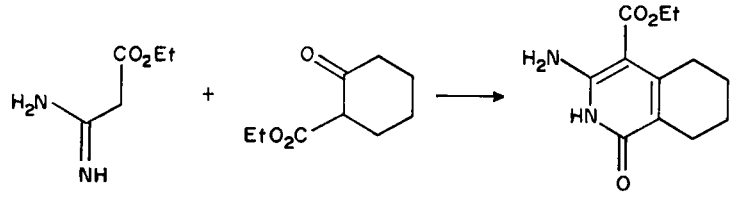


(89)

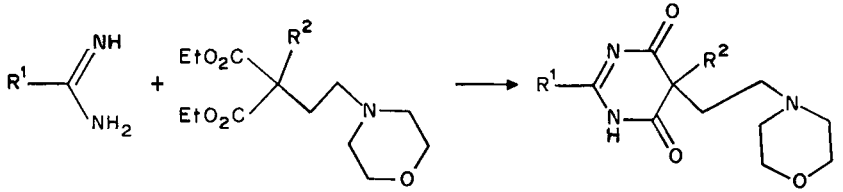
(189)



R = alkyl or aryl $n = 5, 6$ or 10 (90)

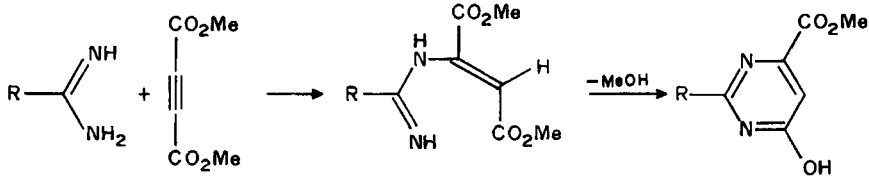


(190) (191) (91)

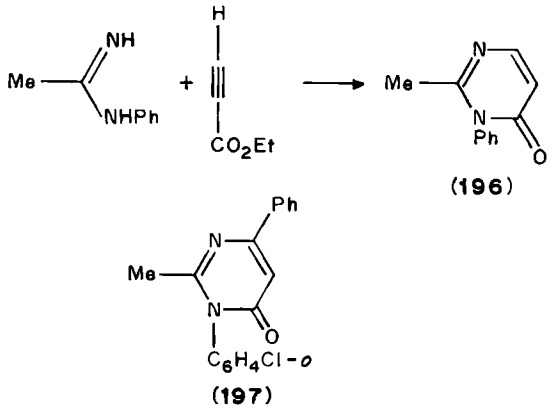


(192) (193) (92)

Acetamidine and trichloroacetamidine react with dimethyl acetylenedicarboxylate in boiling methanol in the presence of sodium methoxide to give low yields of 4-hydroxypyrimidine-6-carboxylic esters **195** (R = Me or Cl_3C) via the isolable intermediate adducts **194** (equation 93)[121]. *N*-Phenylacetamidine and ethyl propiolate similarly furnish the pyrimidone **196** (equation 94)[122]; the pyrimidone **197** was prepared analogously from *N*-*o*-chlorophenylbenzamidine and ethyl phenylpropiolate[123].

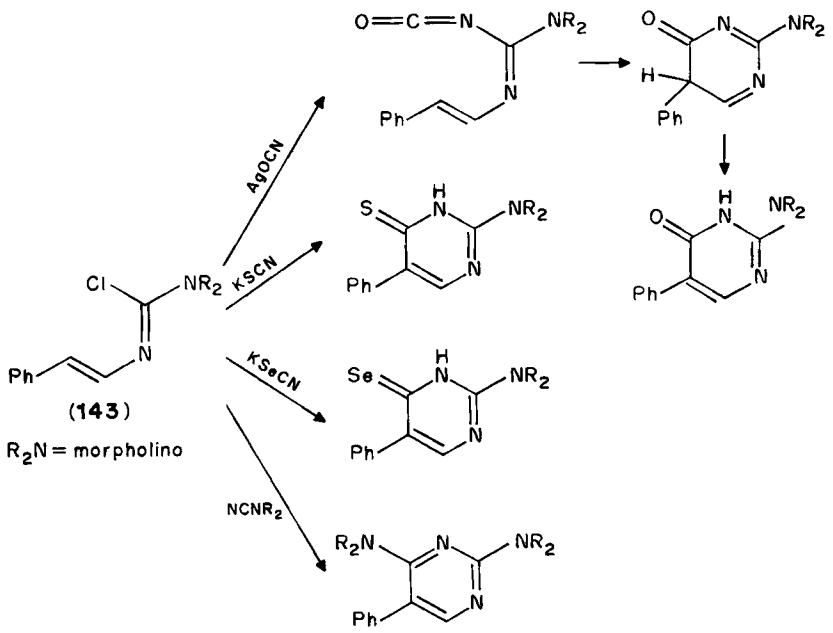


(194) (195) (93)



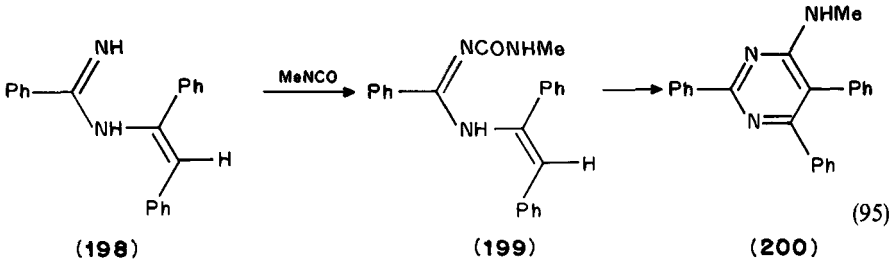
(94)

A number of pyrimidine syntheses from eneamidines have been reported. The chloroformamidine **143** reacts with silver cyanate, potassium thiocyanate and potassium selenocyanate to yield 2-morpholino-5-phenyl-4-pyrimidone and its sulphur and selenium analogues, respectively. With *N*-cyanomorpholine 2,4-dimorpholino-5-phenylpyrimidine is obtained (Scheme 10)[87]. The unsaturated amidine **198** adds methyl isocyanate to give the urea derivative **199**, which cyclizes to the pyrimidine **200** under the influence of tosyl chloride and pyridine (equation 95)[124]. Ethoxymethylenemalononitrile reacts with *N*-phenylbenzamidine in hot ethanolic potassium hydroxide to yield the pyrimidine **202**, which is formed by a Dimroth rearrangement of the intermediate imine **201**

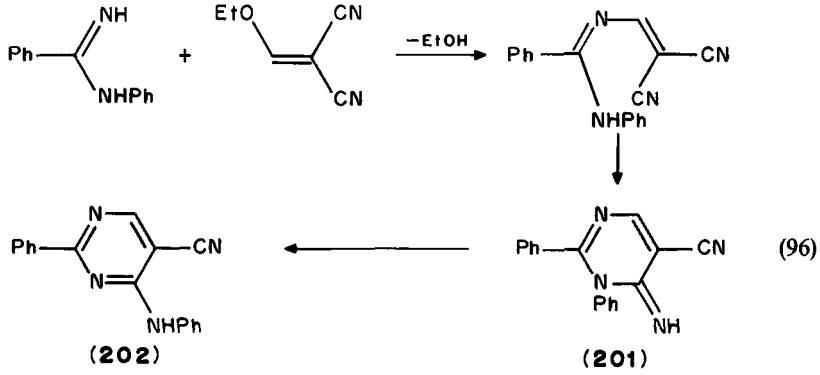


SCHEME 10

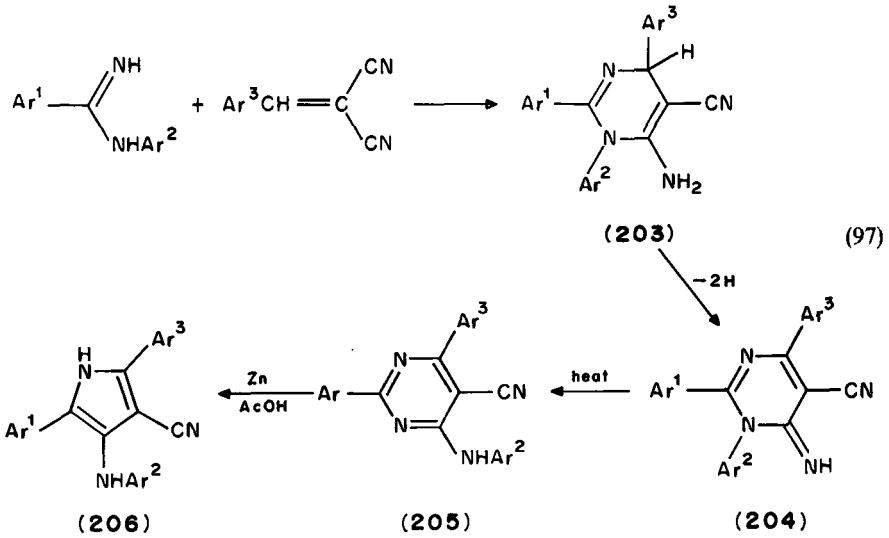
(equation 96)[125]. Arylmethylenemalononitriles and *N*-arylamidines give the imines **204** by spontaneous dehydrogenation of the initial adducts **203**. The imines rearrange to the pyrimidines **205** on heating (equation 97). Fifty compounds of this type were reported[126]. The pyrimidines **205** undergo a remarkable ring-contraction to the pyrroles **206** under the influence of zinc and acetic acid (equation 97)[127]. The dieneamidine **208**, obtained by the



(95)

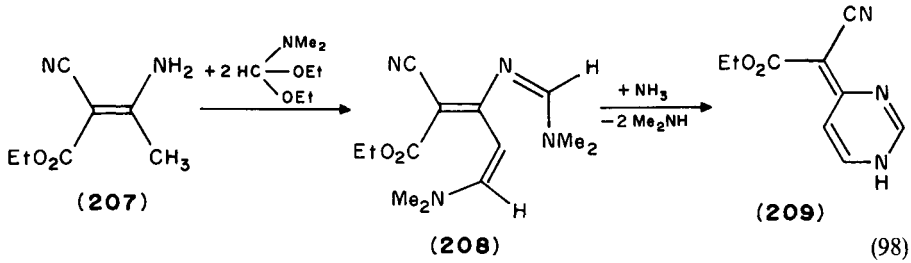


(96)

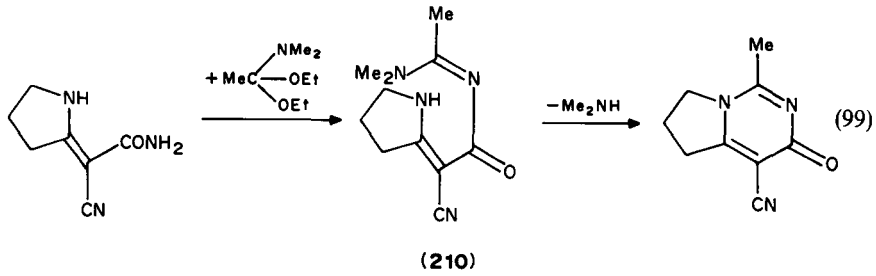


(97)

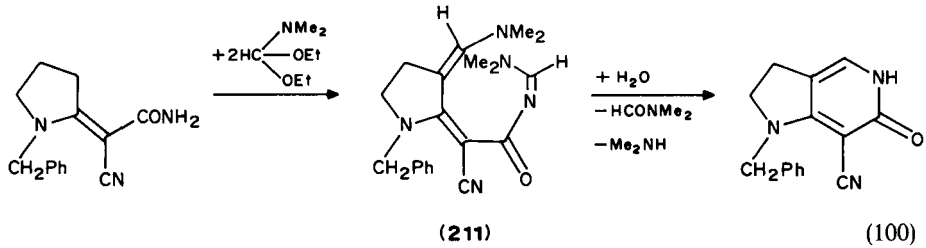
action of dimethylformamide diethylacetal on ethyl β-amino-α-cyanocrotonate (**207**) yields the dihydropyrimidine **209** on treatment with ammonia (equation 98)[128]. Pyrimidines and pyridines fused to a five-membered ring have been prepared by the thermal cyclization of the acylamidine **210** (equation 99)[129], by boiling compound **211** with water (equation 100)[130] and by the reaction of the urethane **212** with ammonia (equation 101)[131]. The action of trifluoroacetamidine on the ylidenemalononitrile **213** affords the aminopyrimidine **214** (equation 102)[132]. Aminomethylenemalononitrile reacts with Viehe's salt **105** to yield the chloroformamidine **215**, which is transformed into the



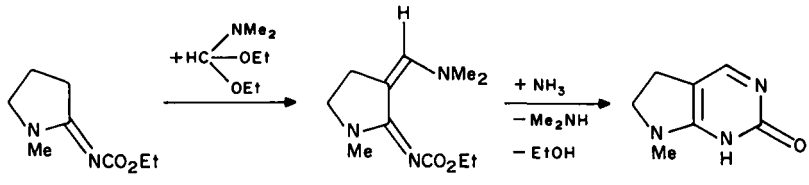
(98)



(99)

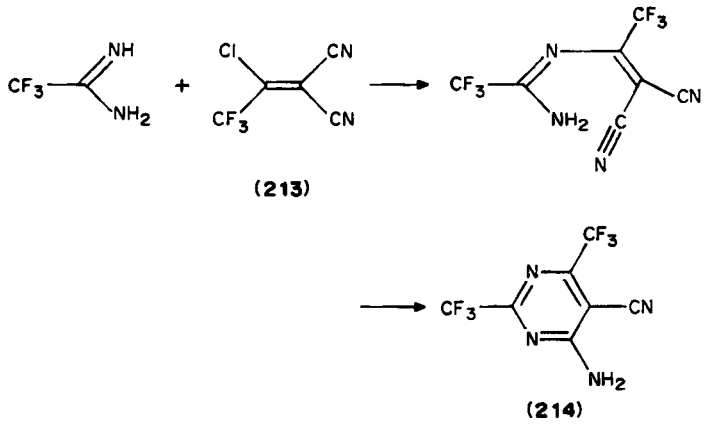


(100)

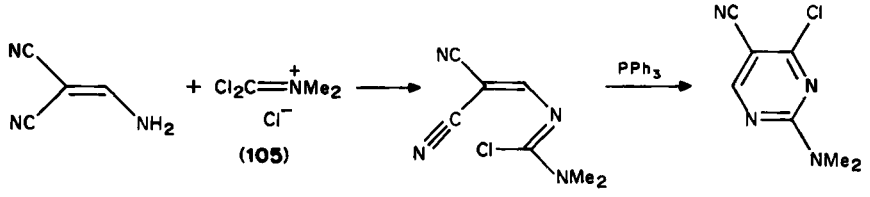


(101)

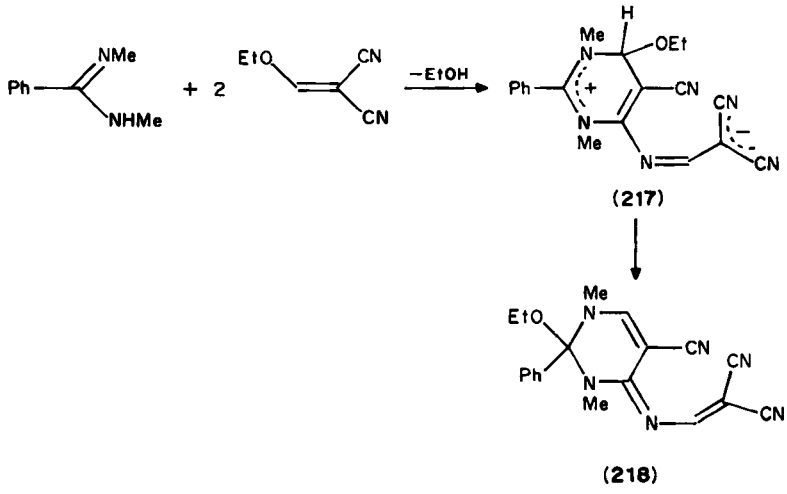
pyrimidine **216** by the action of triphenylphosphine (equation 103)[133]. Treatment of *N,N'*-dimethylbenzamidine with ethoxymethyl enemalononitrile gives the betaine **217**, which rearranges to the tetrahydropyrimidine **218** in boiling ethanol (equation 104)[134]. The adduct **219** of acrolein to benzamidine (equation 105) has been fully characterized by IR, UV and ^{1}H NMR spectroscopy and X-ray diffraction[135].



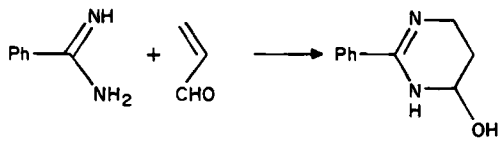
(213) (214) (102)



(105) (215) (216) (103)



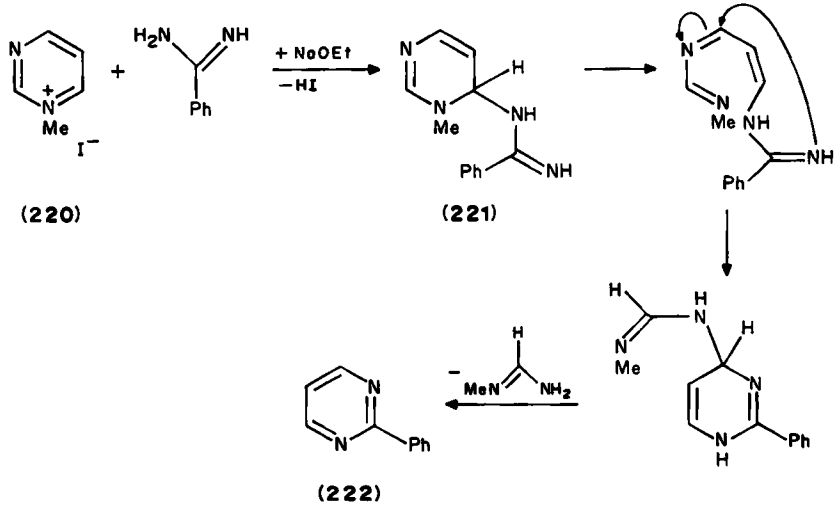
(217) (218) (104)



(105)

(219)

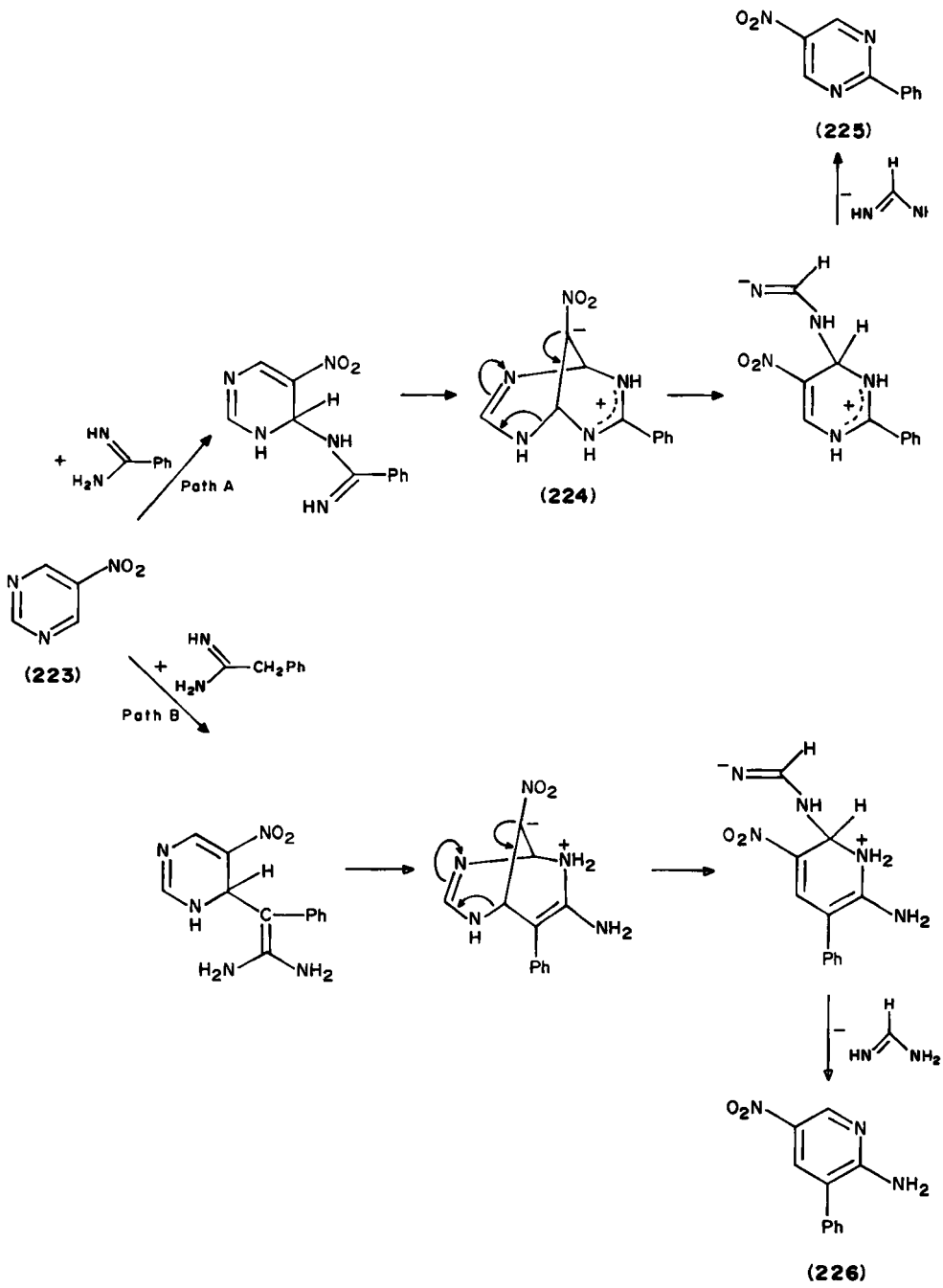
Some remarkable transformations of pyrimidines, induced by amidines, have been reported by Van der Plas and his coworkers. *N*-Methylpyrimidinium iodide (**220**) reacts with benzamidine in ethanolic sodium ethoxide to produce 2-phenylpyrimidine (**222**). It is proposed that the reaction is initiated by attack of the amidine at position 6 of the pyrimidine ring to give the adduct **221**, which opens and then recyclizes in an alternative way, as shown in Scheme 11. Elimination of *N*-methylformamidine yields the product. The mechanism is supported by the findings that *N*-methylpyrimidinium iodide enriched with ^{15}N at both nitrogen atoms gives an unlabelled product[136]. 5-Nitropyrimidine (**223**) and benzamidine yield 5-nitro-2-phenylpyrimidine (**225**), whereas with phenylacetamidine the aminopyridine **226** is obtained. To account for these diverse products the authors suggest (Scheme 12) that in the former case the reaction is initiated by nucleophilic attack of a nitrogen atom of the amidine (Path A) to form the bridged intermediate **224**, which gives the product by ring-opening, followed by elimination of formamidine, while in the latter case it is the α-carbon atom of the amidine which becomes attached to C-6 of the pyrimidine (Path B); subsequent cyclization, ring-opening and loss of formamidine yield **226**. Propionamidine (**227**) reacts with 5-nitropyrimidine in both senses to afford a mixture of the pyrimidine **228** and the pyridine **229** (equation 106)[137].



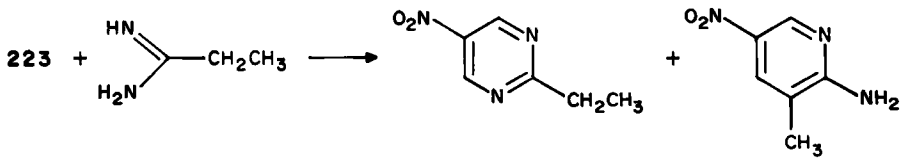
(220) (221) (222)

SCHEME 11

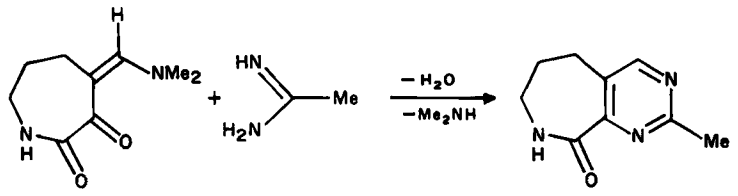
The bicyclic pyrimidine **231** is obtained from the keto lactam **230** and acetamidine (equation 107)[138]. The formamidinopyridine **232** reacts with benzylamine to yield the pyridopyrimidine **233** (equation 108)[139]. Treatment of the imido ester hydrochloride **234** with cyanamide yields the *N*-cyano derivative **235**, which is converted into the



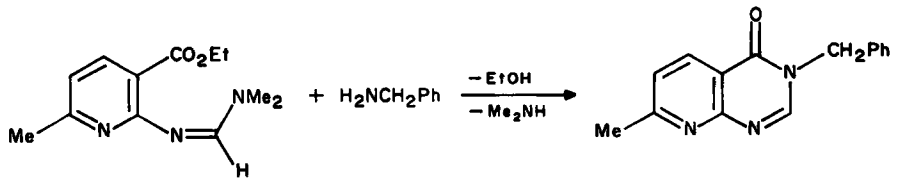
SCHEME 12



(227) (228) (229) (106)

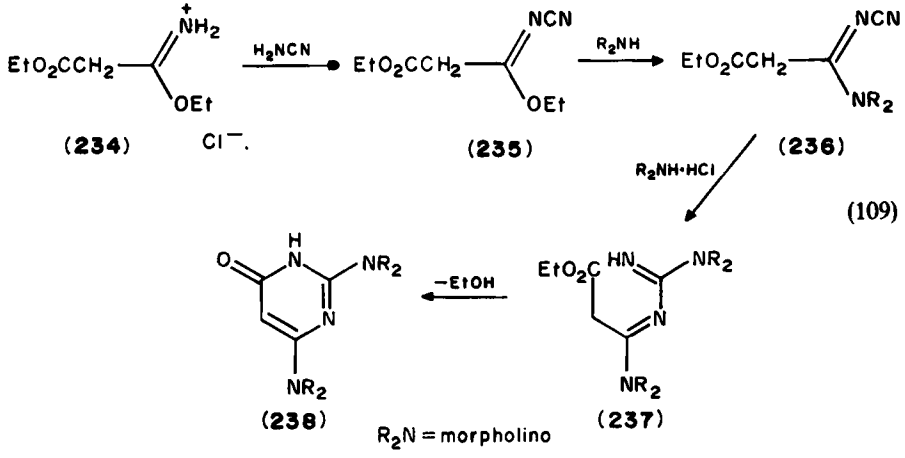


(230) (231) (107)



(232) (233) (108)

cyanoamidine **236** by the action of morpholine. A subsequent reaction with morpholine gives the guanidine **237**, which readily cyclizes to the pyrimidine **238** (equation 109)[140]. Successive treatment of 5-aminotetrazole with triethyl orthoformate and methyl anthranilate yields the tetrazolylformamidine **239**, which in the presence of sodium hydroxide undergoes ring-closure to the anti-allergic agent 'MDL-427' **240** (equation 110)[141]. Viehe's salt **105** reacts with dimethylcyanamide to give the azapropenylium salt **241**, which

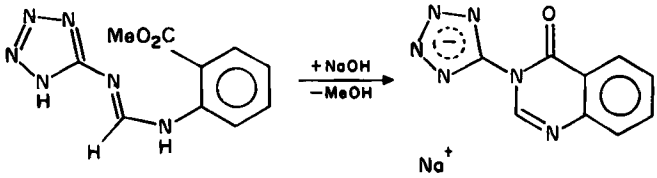


(234) (235) (236) (109)

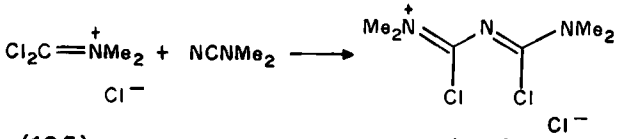
(238) (237)

R_2N = morpholino

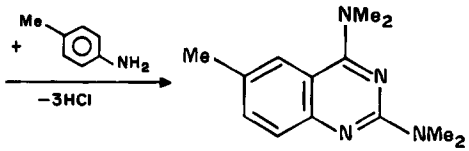
is converted into 6-methyl-2,4-bis(dimethylamino)quinazoline by the action of *p*-toluidine (equation 111)[142]. A similar reaction of the propenylium salt **106** with α-aminopyridine yields the pyridopyrimidinium salt **242** (equation 112)[142].



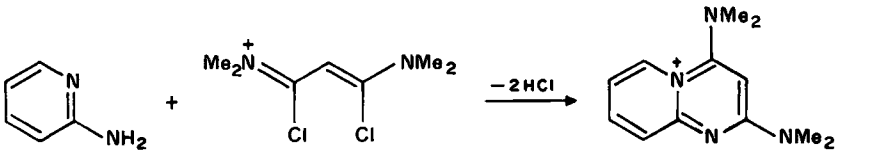
(239) (240) (110)



(105) (241) (111)

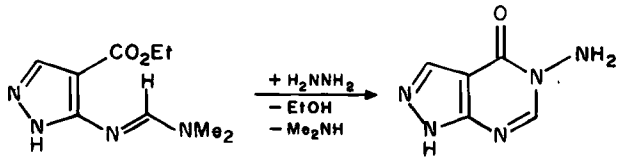


(111)

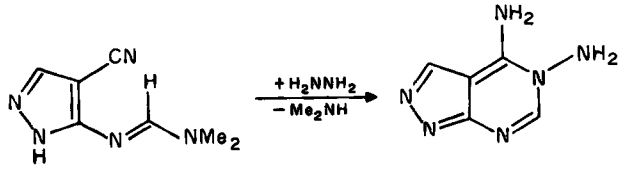


(106) (242) (112)

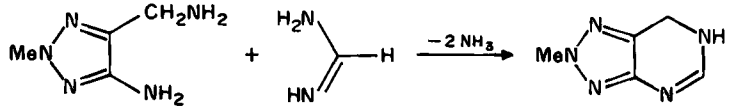
The *N*-aminopyrazolopyrimidone **244** results from the action of hydrazine on the formamidinopyrazole **243** (equation 113)[143]; the nitrile **245** reacts in an analogous fashion (equation 114)[143]. 4-Amino-5-(aminomethyl)triazoles condense with formamidine acetate to afford 1,6-dihydro-8-azapurines (equations 115 and 116)[144]. A derivative of the same ring system was obtained from the aminotriazolecarboxamide **246** and acetamidine (equation 117)[145].



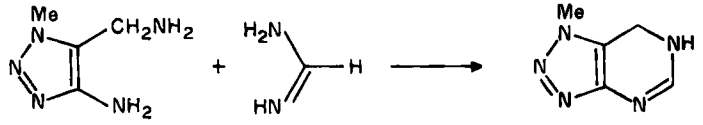
(243) (244) (113)



(245) (114)



(115)



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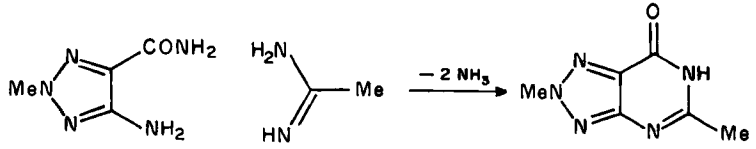
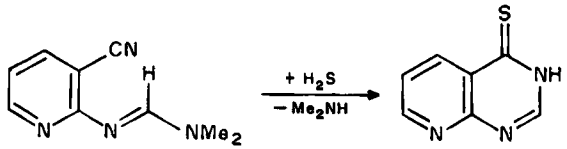
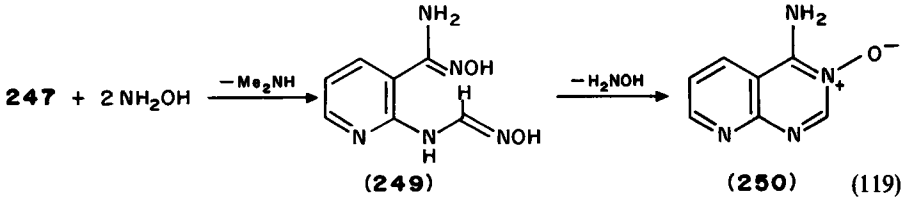


(246) (117)

The 2-formamidinonicotinonitrile **247** is converted into the pyridopyrimidinethione **248** by the action of hydrogen sulphide (equation 118)[146]. Hydroxylamine transforms compound **247** into the diamidoxime **249**, which cyclizes to the *N*-oxide **250** on heating (equation 119)[147]. 6-Chloro-5-ethoxycarbonyl-3-methylthio-1,2,4-triazine (**251**) condenses with benzamidine to yield the acylated amidine **252**, which undergoes ring-closure to the 7-azapteridine derivative **253** (equation 120)[148]. *N*-1-Naphthylbenzamidine (**254**) reacts with trimethyl orthoacetate to yield the benzo[*h*]quinazoline **255** (equation 121)[149]; the urea **256** undergoes a similar cyclization in hot dimethylformamide (equation 122)[150]. 2-Acetyl-3,6-dianilino-1,4-benzoquinone reacts with amidines in hot ethanol to afford quinazolinequinones **257** (equation 123)[151]. The anthrapyrimidine **259** is produced by the action of ammonium acetate on the formamidinoanthraquinone **258** (equation 124)[152]. 3-Aminoindole reacts with dimethylformamide–phosphorus oxychloride to yield the amidine-aldehyde **260**, which is converted into pyrimido[5,4-*b*]indole (**261**) by ammonia (equation 125)[153]. Derivatives **263** of the isomeric pyrimido[4,5-*b*]indole ring system are produced by the action of amidines on 3-arylmethyleneindolin-2-ones **262** (equation 126)[154].



(247) (248) (118)



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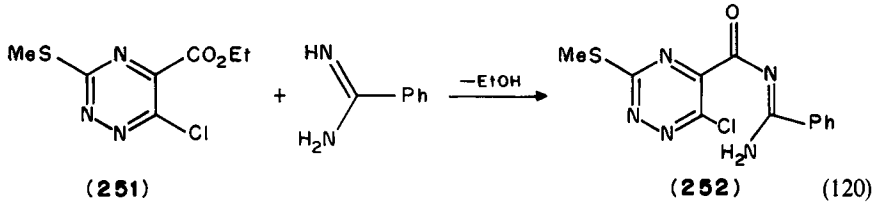

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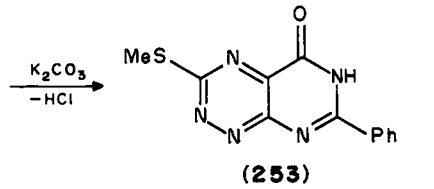

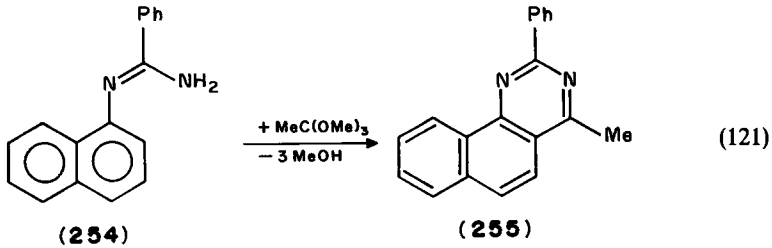

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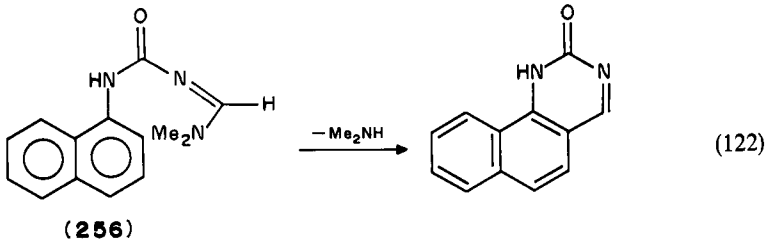

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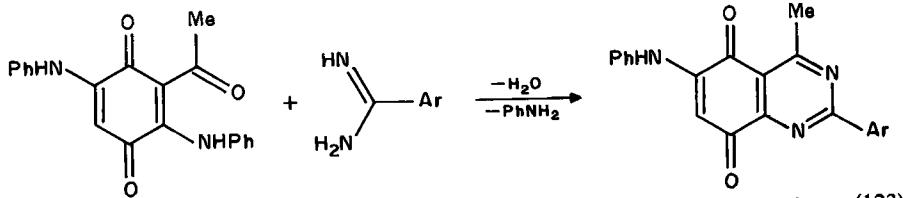

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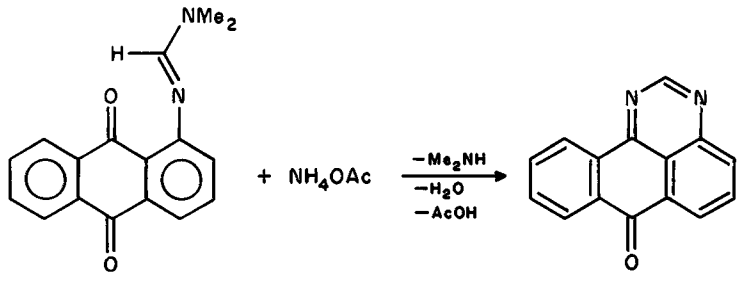
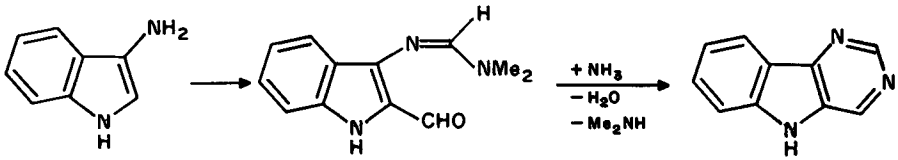
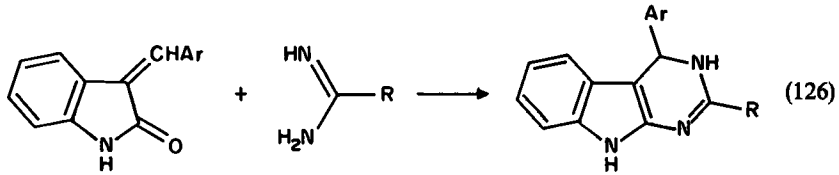


(258) (259) (124)



(260) (261) (125)

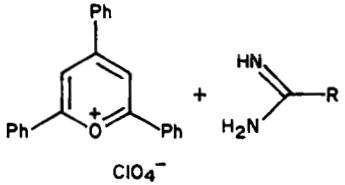


(262) (263) (126)

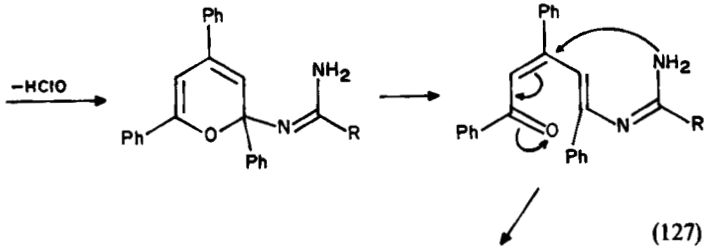
A number of oxygen heterocycles react with amidines to form pyrimidines with concomitant opening of the oxygen-containing ring. 2,4,6-Triphenylpyrylium perchlorate (**264**) and amidines yield, in a four-stage reaction, 2-substituted 4,6-diphenylpyrimidines **265** (equation 127)[155]. The action of acetamidine on the dihydrofuran **266** leads to the aminopyrimidone **267** (equation 128)[156]. The 4-thiazolylisoflavone **268** and formamidine yield the pyrimidine **269** (equation 129)[157]; the isoflavone **270** is similarly transformed into the pyrimidine aldehyde **271**, which exists as the hemiacetal **272** (equation 130)[158,159].

4. *Triazines*

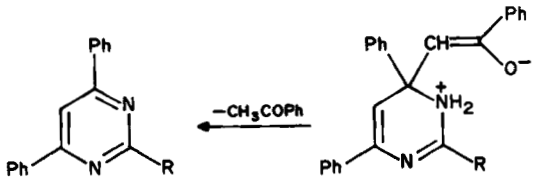
Vilsmeier salts **273** react with *N*-cyanoamidines at room temperature to yield 2-chloro-1,3,5-triazines **274** (equation 131)[160]. The action of hexafluoroacetone imine (**275**) on trifluoroacetamidine leads to the dihydrotriazine **276** (equation 132)[161]. The dihydrotriazine **281** is formed from the morpholinoenamine **277** and *N*-chlorobenzamidine. The authors propose that the process is initiated by a transfer of chlorine (cf. equation 50) to yield the ions **278** and **279**, which combine; the product undergoes a 1,2-shift of the morpholino group and then reacts with a second molecule of benzamidine anion to give the diamidine **280**. Cyclization and loss of ammonia complete the process (Scheme 13)[162]. The tetracyclic triazine **284** is produced by the action of pyridine on the cyclic chloroformamidine **282**, presumably via the salt **283** (equation 133)[163]. Heating



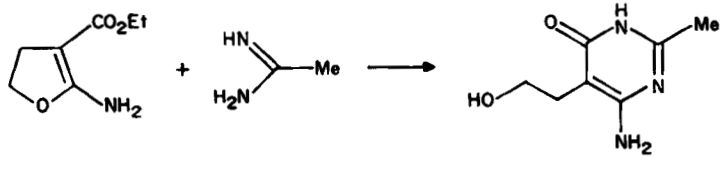
(264)



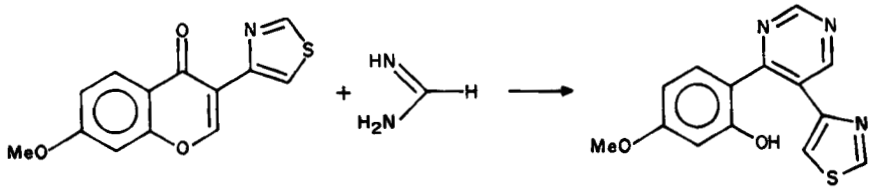
(127)



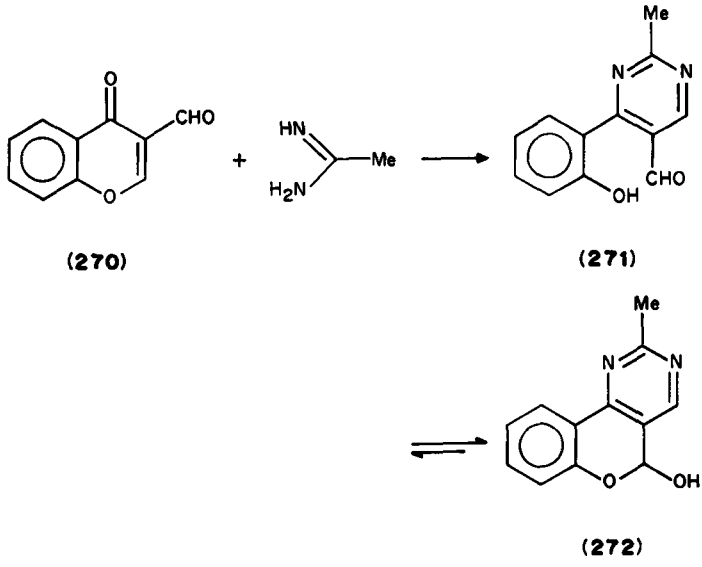
(265)



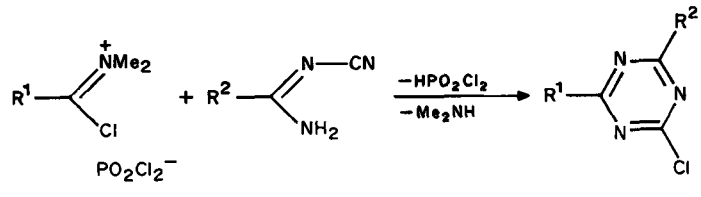
(266) (267) (128)



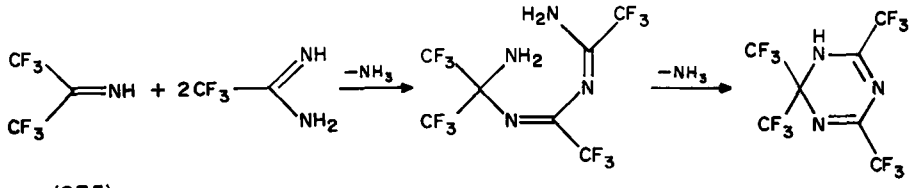
(268) (269) (129)



(270) (271) (272) (130)



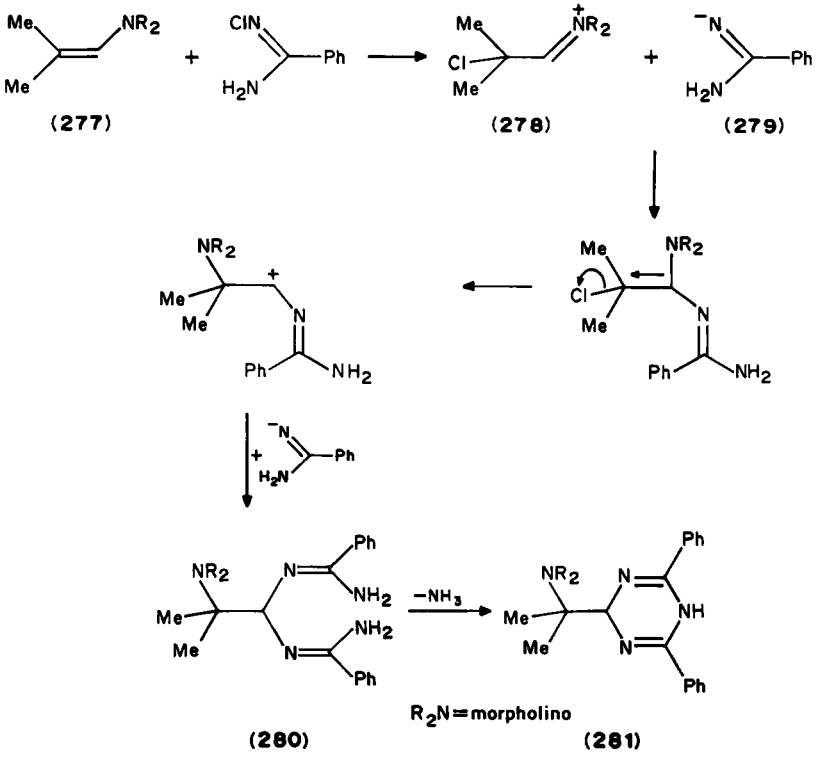
(273) (274) (131)



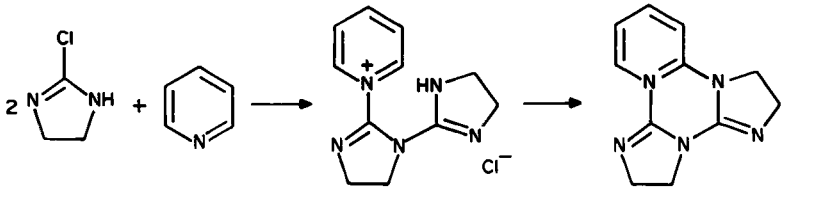
(275) (276) (132)

the complex amidine derivative **285** to 120 °C yields the trimethyltriazinedione **286**, whereas at 200 °C the dimethyltriazinedione **287** is formed (equation 134)[164].

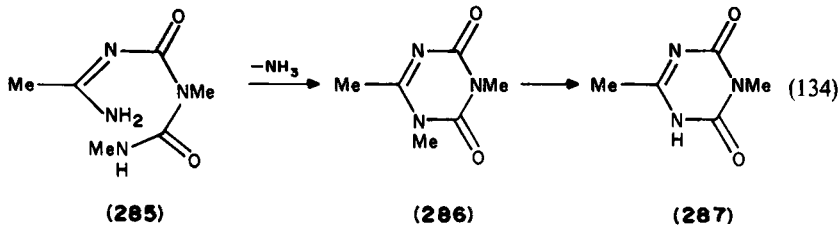
Several reports on the reactions of amidines with isocyanates and isothiocyanates have appeared[165]. *N*-Arylbenzimidoyl isothiocyanates **288** and acetamidine yield the triazinethione **289**; similarly, with *N*-phenylacetamidine the *N*-phenyl derivative **290** is obtained (equation 135)[166,167]



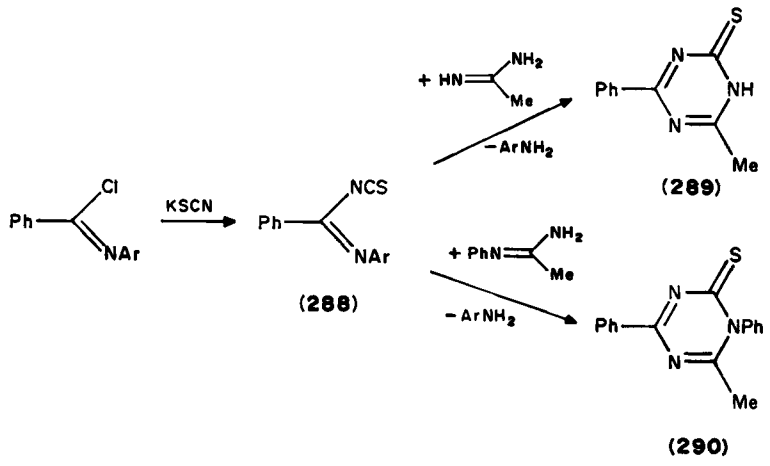
SCHEME 13



(133)

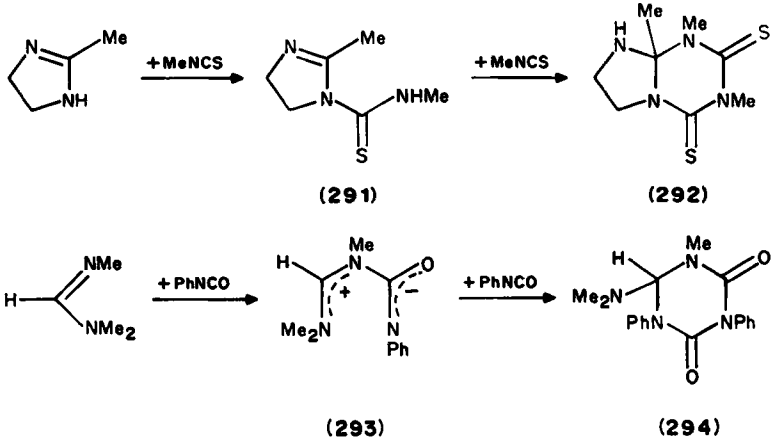


(134)



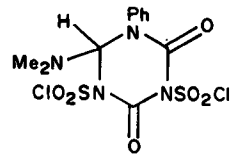
(135)

Methyl isothiocyanate adds to 2-methyl-1-imidazoline to give the thiourea **291**, which forms the hexahydrotriazinedithione **292** on treatment with further methyl isothiocyanate (equation 136)[168]. *N,N,N'*-Trimethylformamidine reacts directly with two molecules of phenyl isocyanate to afford the 1:2 adduct **294** via the postulated 1,4-dipolar intermediate **293** (equation 137)[169]. The analogue **295** is obtained from *N,N*-dimethyl-*N'*-phenylformamidine and chlorosulphonyl isocyanate[170]. *N,N'*-Dimethylbenzamidine and phenylsulphonyl isocyanate yield either the 1:2 adduct **296** or the 2:1 adduct **297** according to the proportions of the reagents (equation 138)[171]. The action of phenyl isocyanate on the α-formamidinopyridine **298** at room temperature results in the diazetidinone **299**; at higher temperatures the pyridotriazinedione **300** is obtained. The latter is formed by the combination of phenyl isocyanate with α-pyridyl isocyanate, which arises from the decomposition of the diazetidinone (Scheme 14)[172]. The pyridazine analogue **302** is similarly produced from phenyl isocyanate and the amidine **301** (equation 139)[173]. The formamidinothiazoline **303** and phenyl isocyanate afford the 1:1 adduct **304**; with an excess of phenyl isocyanate the 1:2 adduct **305** is obtained. Heating a mixture of **303** and an excess of phenyl isocyanate at 240 °C yields compound **306**, an analogue of **300** (equation 140)[174].

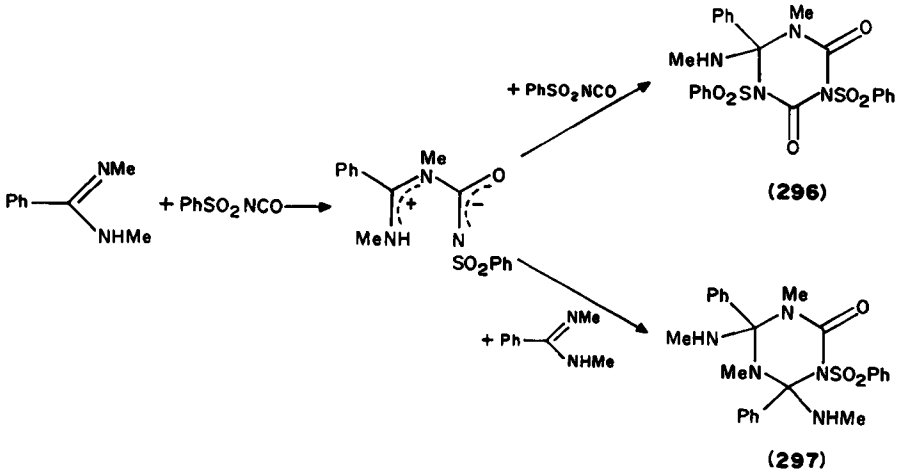


(136)

(137)



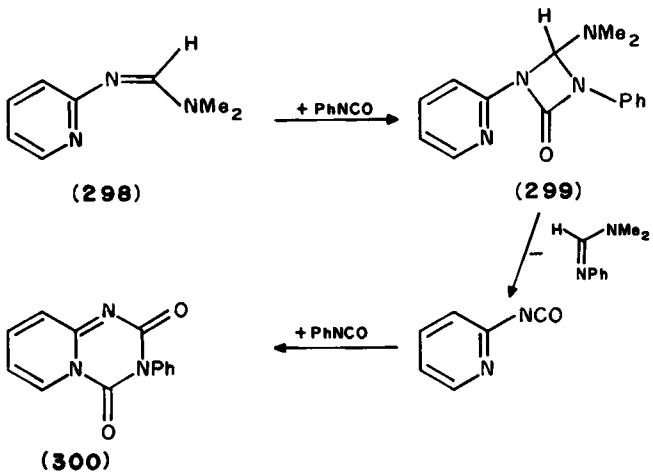
(295)



(296)

(297)

(138)

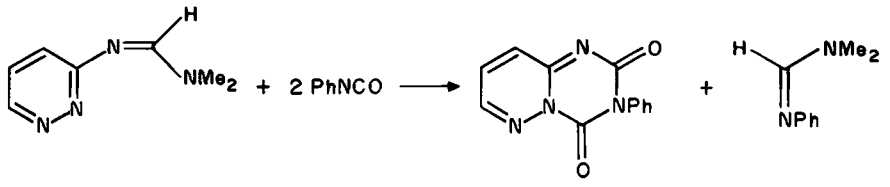


(298)

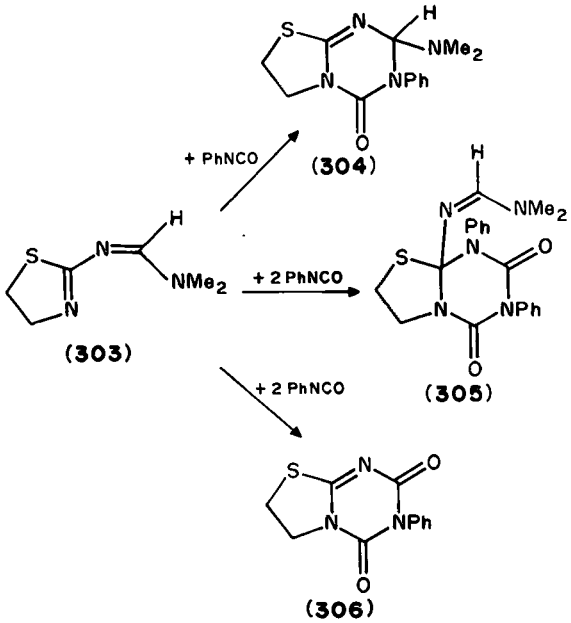
(299)

(300)

SCHEME 14



(301) (302) (139)



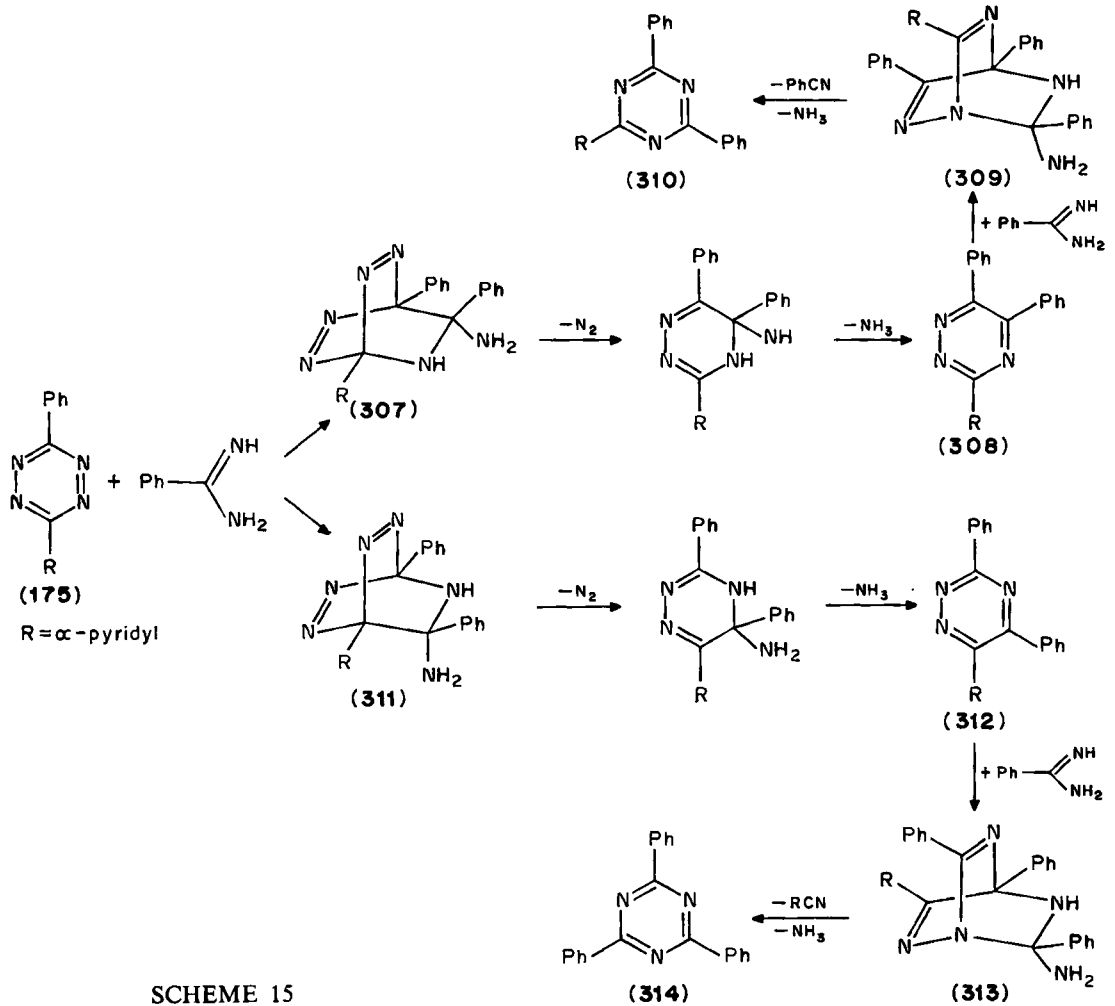
(140)

Heating the 1,2,4,5-tetrazine **175** with benzamidine yields a mixture of four products: two 1,2,4-triazines **308** and **312**, and two 1,3,5-triazines **310** and **314**. The two former arise from the isomeric Diels–Alder adducts **307** and **311** by extrusion of nitrogen, followed by elimination of ammonia. The 1,3,5-triazines are formed from the 1,2,4-triazines by a second Diels–Alder reaction of benzamidine at N-2 and C-5. The resulting adducts **309** and **313** then loss benzonitrile and α-cyanopyridine, respectively, followed by ammonia (Scheme 15)[175].

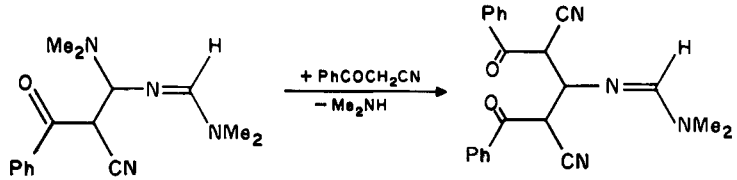
5. *Other ring systems*

The amidine **315** condenses with α-cyanoacetophenone to yield compound **316**, which readily cyclizes to the pyran **317** (equation 141)[176].

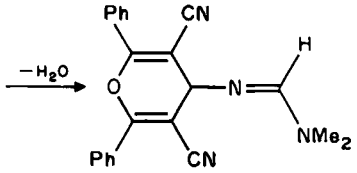
The 1,2-thiazine *S*-oxide **319** is formed by Diels–Alder addition of the sulphinylamidine **318** to isoprene (equation 142)[177]. Thioaroylformamidines **320** react with ketene to give 1,3-thiazin-6-ones **321** (equation 143)[178]. 1-Chloro-3-phenyl-1,2,4-benzothiadiazine (**322**) is produced by the action of sulphur dichloride on *N*-phenyl-*N'*-chlorobenzamidine (equation 144)[179]. The analogous reaction with *N*-phenyltrichloroacetamidine results in


(175)
R=α-pyridyl
(307)
(311)
(308)
(312)
(309)
(310)
(313)
(314)
−N2
−NH3
−PhCN
−RCN
+ Ph
NH
NH2

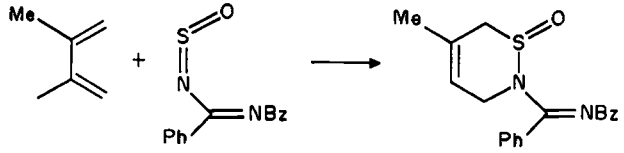
SCHEME 15



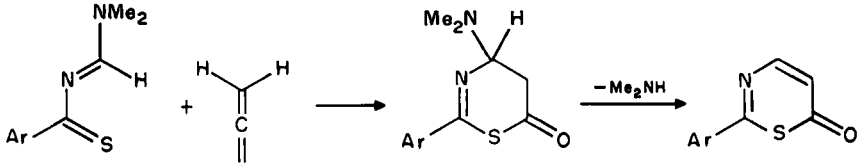
(315) (316) (141)



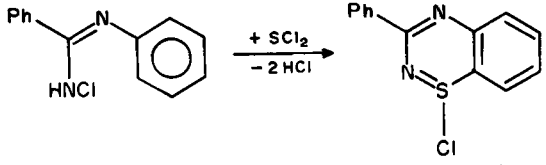
(317)



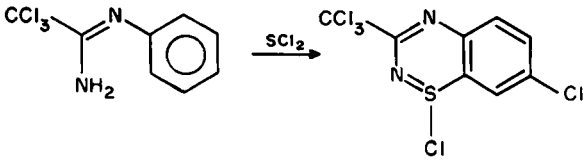
(318) (319) (142)



(320) (321) (143)

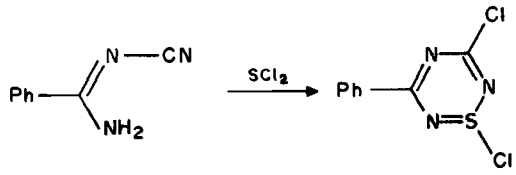


(322) (144)

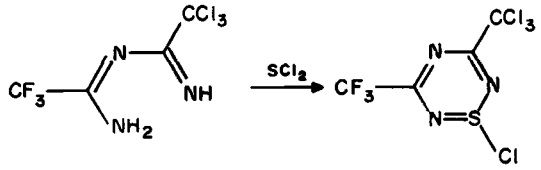


(323) (145)

the 7-chlorobenzothiadiazine **323** (equation 145)[180]. 1,2,4,6-Thiatriazines are obtained from *N*-cyanoamidines (equation 146)[181] or imidoylamidines (equation 147)[182].

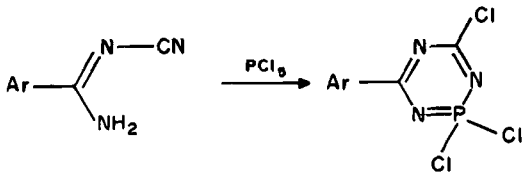


(146)

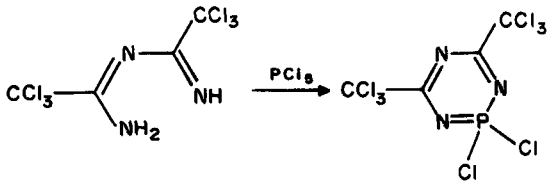


(147)

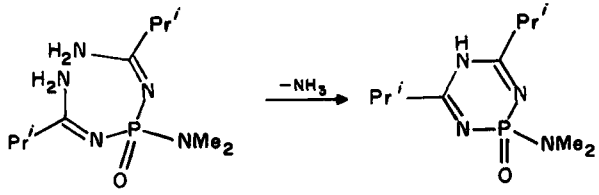
1,1-Dichloro-1,2,4,6-phosphatriazines result from the reaction of phosphorus pentachloride with *N*-cyanoamidines (equation 148)[183] or imidoylamidines (equation 149)[184]. The dihydrophosphatriazine 2-oxide **325** is formed by cyclization of the diamidine **324** (equation 150)[184]. 1,3,2,4,6-Diphosphatriazines **326** have been prepared from amidines as shown in equation 151[185].



(148)

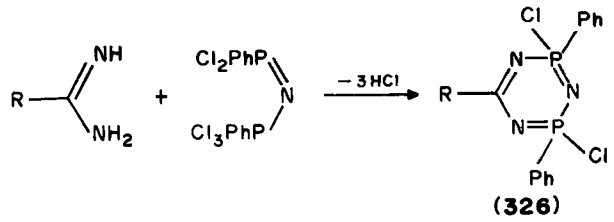


(149)



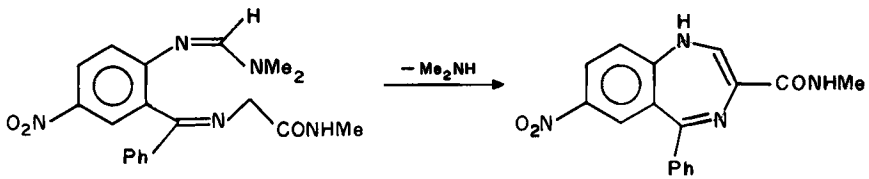
(150)

(324) **(325)**



(326) (151)

Thermal cyclization of the complex amidine **327** yields the benzodiazepine **328** (equation 152)[186].



(327) (328) (152)

IV. REFERENCES

1. J. A. Gautier, M. Miocque and C. C. Farnoux, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, London, 1975, p. 283.
2. V. G. Granik, *Usp. Khim.*, **52**, 669 (1983); *Russ. Chem. Rev.*, **52**, 377 (1983).
3. M. Tišler, *Heterocycles*, **20**, 1591 (1983).
4. M. H. Caruthers, L. J. McBride, L. P. Bracco and J. W. Dubendorff, *Nucleosides Nucleotides*, **4**, 95 (1985).
5. A. V. Fokin, V. P. Stolyarov, V. A. Komarov and A. T. Uzun, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2139 (1977); *Chem. Abstr.*, **88**, 22 104 (1978).
6. L. S. Cook, N. D. Venayak and B. J. Wakefield, *J. Chem. Res. (S)*, 199 (1983).
7. USSR Patent 533, 591 (1976); *Chem. Abstr.*, **86**, 121 013 (1977).
8. German Patent 3,134,144 (1983); *Chem. Abstr.*, **99**, 5 226 (1983).
9. French Patent 2,081,556 (1972); *Chem. Abstr.*, 77, 61 615 (1972).
10. E. P. Navarrete, C. H. Rodriguez, A. H. Pavez and V. A. Marquez, *Bol. Soc. Chil. Quim.*, **27**, 227 (1982); *Chem. Abstr.*, **97**, 23 411 (1982).
11. P. L. Barker, P. L. Gendler and H. Rappoport, *J. Org. Chem.*, **46**, 2455 (1981).
12. R. Kolb and G. Schwenker, *Tetrahedron Lett.*, 4699 (1972).
13. A. D. Sinitsa and V. I. Kalchenko, *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol., Khim. Biol. Nauk*, 1007 (1977); *Chem. Abstr.*, **88**, 89 765 (1978).
14. N. M. Mironovskaya, S. F. Dymova, I. L. Vladimirova and N. N. Melnikov, *Zh. Obshch. Khim.*, **48**, 2465 (1978); *Chem. Abstr.*, **90**, 86 907 (1979).
15. V. I. Shevchenko, V. I. Kalchenko and A. D. Sinitsa, *Zh. Obshch. Khim.*, **47**, 2157 (1977); *Chem. Abstr.*, **88**, 22 103 (1978).
16. A. D. Sinitsa, V. S. Krishtal, V. I. Kalchenko and L. N. Markovskii, *Zh. Obshch. Khim.*, **50**, 2409 (1980); *Chem. Abstr.*, **95**, 24 191 (1981).
17. L. P. Prikazchikova, L. I. Rybchenko and V. M. Cherkasov, *Khim. Geterotsikl. Soedin.*, 831 (1977); *Chem. Abstr.*, **87**, 184 452 (1977).
18. G. M. Tolmacheva, S. P. Krukovskii, E. L. Berman and V. A. Ponomarenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1963 (1976); *Chem. Abstr.*, **86**, 88 663 (1977).
19. J. Graefe, *Z. Chem.*, **15**, 301 (1975).
20. S. Löfås and P. Ahlberg, *J. Chem. Soc., Chem. Commun.*, 998 (1981).
21. V. G. Granik, A. M. Zhidkova, T. F. Vlasova, R. G. Glushkov and Yu. N. Sheinker, *Khim. Geterotsikl. Soedin.*, 533 (1974); *Chem. Abstr.*, **81**, 62 725 (1974).

22. W. Kantlehner, F. Wagner and H. Bredereck, *Ann. Chem.*, 344 (1980).
23. M. J. O'Donnell, W. A. Bruder, B. W. Daughterty, D. Liu and K. Wojciechowski, *Tetrahedron Lett.*, **25**, 3651 (1984).
24. J. J. Fitt and H. W. Gschwend, *J. Org. Chem.*, **42**, 2639 (1977).
25. A. I. Meyers, P. D. Edwards, W. F. Reiker and T. R. Bailey, *J. Am. Chem. Soc.*, **106**, 3270 (1984).
26. A. I. Meyers and M. F. Loewe, *Tetrahedron Lett.*, **25**, 2641 (1984).
27. A. I. Meyers, P. D. Edwards, T. R. Bailey and G. E. Jagdmann, Jr., *J. Org. Chem.*, **50**, 1019 (1985).
28. A. I. Meyers and L. M. Fuentes, *J. Am. Chem. Soc.*, **105**, 117 (1983).
29. A. I. Meyers, L. M. Fuentes and Y. Kubota, *Tetrahedron*, **40**, 1361 (1984).
30. A. I. Meyers, M. Boes and D. A. Dickman, *Angew. Chem., Int. Ed. Engl.*, **23**, 458 (1984).
31. Y. Lin and S. A. Long, Jr., *Synthesis*, 119 (1980).
32. Jap. Patent 7,959,238 (1979); *Chem. Abstr.*, **91**, 156 827 (1979).
33. E. C. Taylor and D. J. Dumas, *J. Org. Chem.*, **45**, 2485 (1980).
34. A. V. Fokin, V. P. Stolyarov, A. M. Gukov, A. T. Uzun and V. A. Komarov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2802 (1978); *Chem. Abstr.*, **90**, 120 979 (1979).
35. P. Reynaud, J. D. Brion and G. Menard, *Bull. Soc. Chim. Fr.*, 449 (1978).
36. V. A. Khrustalev, K. N. Zelenin and V. P. Sergutina, *Zh. Org. Khim.*, **15**, 2280 (1979); *Chem. Abstr.*, **92**, 180 607 (1980).
37. German Patent 3,126,388 (1983); *Chem. Abstr.*, **98**, 160 259 (1983).
38. P. Ahlberg and M. Ek, *Chem. Scr.*, **10**, 47 (1976).
39. V. G. Granik, E. O. Sochneva, N. P. Soloveva, G. Ya. Shvarts, R. D. Syubaev and M. D. Mashkovskii, *Khim.-Farm. Zh.*, **14**, 36 (1980); *Chem. Abstr.*, **93**, 220 653 (1980).
40. M. M. Davtyan, A. V. Ignatenko, S. P. Kukovskii and V. A. Ponomarenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2775 (1977); *Chem. Abstr.*, **88**, 120 546 (1978).
41. W. Kantlehner, E. Haug, P. Speh and H. J. Bräuner, *Chem.-Ztg.*, **109**, 433 (1985).
42. Y. Okamoto and T. Kinoshita, *Chem. Pharm. Bull.*, **29**, 1165 (1981).
43. H. Baganz and S. Rabe, *Chem. Ber.*, **98**, 3652 (1965).
44. H. Yamamoto and K. Maruoka, *J. Am. Chem. Soc.*, **103**, 4186 (1981).
45. S. Rajappa, M. D. Nair, R. Sreenivasan and B. G. Advan, *Tetrahedron*, **38**, 1673 (1982).
46. B. J. Swanson, G. C. Crockett and T. H. Koch, *J. Org. Chem.*, **46**, 1082 (1981).
47. G. C. C. Su and M. J. Zabic, *J. Agric. Food Chem.*, **20**, 320 (1972).
48. G. L'abbé, A. Van Asch, J. P. Dekerk and T. Minami, *Tetrahedron Lett.*, **22**, 583 (1981).
49. L. P. Olekhnovich, I. E. Mikhailov, N. M. Ivanchenko, Yu. A. Zhdanov and V. I. Minkin, *Zh. Org. Khim.*, **15**, 1355 (1979); *Chem. Abstr.*, **91**, 210 648 (1979).
50. K. Hartke and H. M. Wolff, *Chem. Ber.*, **113**, 1394 (1980).
51. V. I. Minkin, I. E. Mikhailov and G. A. Dushenko, *J. Chem. Soc., Chem. Commun.*, 1181 (1988).
52. B. M. Mikhailov, *Pure Appl. Chem.*, **49**, 749 (1977).
53. R. S. Klein, M. I. Lim, S. Y. K. Tam and J. J. Fox, *J. Org. Chem.*, **43**, 2536 (1978).
54. T. Eicher, F. Abdesaken, G. Franke and J. L. Weber, *Tetrahedron Lett.*, 3915 (1975).
55. P. D. Edwards and A. I. Meyers, *Tetrahedron Lett.*, **25**, 939 (1984).
56. H. Bredereck, G. Simchen and W. Kantlehner, *Chem. Ber.*, **104**, 932 (1971).
57. B. Stanovnik and M. Tišler, *Synthesis*, 121 (1974).
58. H. M. Wolff and K. Hartke, *Arch. Pharm. (Weinheim, Ger.)*, **313**, 266 (1980).
59. W. F. Keir and H. C. S. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1847 (1976).
60. L. M. Naumova, V. N. Charushin, O. N. Chupakhin and G. G. Izmailova, *Khim. Geterotsikl. Soedin.*, 390 (1985); *Chem. Abstr.*, **104**, 50 846 (1986).
61. F. Yoneda, M. Higuchi and T. Nagamatsu, *J. Am. Chem. Soc.*, **96**, 5607 (1974).
62. T. K. Vinogradova, G. N. Miskevich and B. S. Drach, *Zh. Org. Chim.*, **16**, 1869 (1980); *Chem. Abstr.*, **94**, 84 010 (1981).
63. I. I. Ershova, Yu. I. Gevaza and V. I. Staninets, *Ukr. Khim. Zh. (Russ. Ed.)*, **43**, 884 (1977); *Chem. Abstr.*, **87**, 201 457 (1977).
64. L. Citerio, D. Pocar, R. Stradi and B. Gioia, *J. Chem. Soc., Perkin Trans. 1*, 309 (1978).
65. M. Gobbini, P. Giacconi and R. Stradi, *Synthesis*, 940 (1983).
66. L. Citerio, D. Pocar, M. L. Saccarello and R. Stradi, *Tetrahedron*, **35**, 2453 (1979).
67. E. Rossi, R. Stradi and A. Benedusi, *Tetrahedron*, **43**, 4785 (1987).
68. L. Citerio, M. L. Saccarello, R. Stradi and B. Gioia, *J. Chem. Res. (S)*, 347 (1979).
69. M. Hamaguchi and T. Ubata, *Chem. Lett.*, 169 (1975).
70. K. T. Potts and S. J. Chen, *J. Org. Chem.*, **42**, 1639 (1977).

71. E. Schaumann and S. Grabley, *Chem. Ber.*, **113**, 934 (1980).
72. L. P. Prikazchikova, L. I. Rybchenko and V. M. Cherkasov, *Ukr. Khim. Zh. (Russ. Ed.)*, **46**, 70 (1980); *Chem. Abstr.*, **92**, 215 339 (1980).
73. B. Caillaux, P. George, F. Tataruch, Z. Janousek and H. G. Viehe, *Chimia (Switz.)*, **30**, 387 (1976).
74. East German Patent 123,093 (1976); *Chem. Abstr.*, **87**, 117 845 (1977).
75. Y. Lin, C. M. Seifert, S. M. Kang, J. P. Dusza and S. A. Lang, Jr., *J. Heterocycl. Chem.*, **16**, 1377 (1979).
76. Y. Lin, S. A. Lang, Jr., M. F. Lovell and N. A. Perkinson, *J. Org. Chem.*, **44**, 4160 (1979).
77. M. J. Dimsdale, *J. Heterocycl. Chem.*, **18**, 37 (1981).
78. M. Kocevar, B. Stanovnik and M. Tišler, *Tetrahedron*, **39**, 823 (1983).
79. Y. Lin and S. A. Lang, Jr., *J. Org. Chem.*, **46**, 3123 (1981).
80. Y. Lin, S. A. Lang, Jr. and S. P. Petty, *J. Org. Chem.*, **45**, 3750 (1980).
81. G. L'abbé and A. Verbruggen, *Tetrahedron Lett.*, 49 (1979).
82. V. I. Shevchenko, A. D. Sinitsa and V. I. Kalchenko, *Zh. Obshch. Khim.*, **46**, 541 (1976); *Chem. Abstr.*, **85**, 21 545 (1976).
83. J. P. Majoral, C. Roques, M. R. Mazieres, J. Jaud and M. Sanchez, *J. Chem. Soc., Chem. Commun.*, 1496 (1989).
84. L. Lopez and J. Barrans, *J. Chem. Soc., Perkin Trans. 1*, 1806 (1977).
85. W. Kliegel and H. W. Motzkus, *Chem. Ber.*, **121**, 1865 (1988).
86. R. Gompper and U. Heinemann, *Angew. Chem., Int. Ed. Engl.*, **19**, 217 (1980).
87. W. Ried and H. E. Erle, *Chem. Ber.*, **112**, 640 (1979).
88. H. Junek, M. Mittelbach and B. Thierrichter, *Monatsh. Chem.*, **110**, 1279 (1979).
89. V. G. Granik, N. B. Marchenko, E. O. Sochneva, R. G. Glushkov, T. F. Vlasova and Yu. N. Sheinker, *Khim. Geterotsikl. Soedin.*, 805 (1976); *Chem. Abstr.*, **85**, 108 568 (1976).
90. V. G. Granik, O. Ya. Belyaeva, R. G. Glushkov, T. F. Vlasova and O. S. Anisimova, *Khim. Geterotsikl. Soedin.*, 1106 (1977); *Chem. Abstr.*, **88**, 6 779 (1978).
91. N. I. Smetskaya, N. A. Mukhina and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 799 (1984); *Chem. Abstr.*, **101**, 230 309 (1984).
92. V. G. Granik, N. B. Marchenko, T. F. Vlasova and R. G. Glushkov, *Khim. Geterotsikl. Soedin.*, 1509 (1976); *Chem. Abstr.*, **86**, 139 783 (1977).
93. S. K. Robev, *Khim. Geterotsikl. Soedin.*, 1587 (1981); *Chem. Abstr.*, **96**, 68 853 (1982).
94. S. K. Robev, *Tetrahedron Lett.*, **21**, 2097 (1980).
95. S. K. Robev, *Heterocycles*, **14**, 461 (1980).
96. H. G. Viehe and G. J. de Voghel, *Chimia (Switz.)*, **30**, 189 (1976).
97. S. K. Robev, *Dokl. Bolg. Akad. Nauk*, **31**, 865 (1978); *Chem. Abstr.*, **90**, 186 898 (1979).
98. W. Ried and P. Weidemann, *Chem. Ber.*, **104**, 3329 (1971).
99. E. B. Pedersen and S. O. Lawesson, *Acta Chem. Scand.*, **28B**, 1045 (1974).
100. N. B. Marchenko, V. G. Granik, T. F. Vlasova, O. S. Anisimova and R. G. Glushkov, *Khim. Geterotsikl. Soedin.*, 665 (1976); *Chem. Abstr.*, **85**, 78 075 (1976).
101. V. G. Granik, A. M. Zhidkova, S. S. Kiselev, R. G. Glushkov, A. I. Polezhaeva and M. D. Mashkovskii, *Khim.-Farm. Zh.*, **12**, 66 (1978); *Chem. Abstr.*, **89**, 163 465 (1978).
102. D. R. Tatke, S. Seshadri, A. Das and M.R.R. Rao, *Indian J. Chem., Sect. B*, **17B**, 491 (1979).
103. V. G. Granik, N. B. Marchenko and R. G. Glushkov, *Khim. Geterotsikl. Soedin.*, 1549 (1978); *Chem. Abstr.*, **90**, 121 529 (1979).
104. R. J. Chorvat and S. E. Radak, *Tetrahedron Lett.*, **21**, 421 (1980).
105. S. K. Robev, *Dokl. Bolg. Akad. Nauk*, **41**, 69 (1988); *Chem. Abstr.*, **111**, 39 317 (1989).
106. R. R. Bard and M. J. Strauss, *J. Am. Chem. Soc.*, **97**, 3789 (1975).
107. D. C. Palmer and M. J. Strauss, *Tetrahedron Lett.*, 1431 (1976).
108. H. P. Figeys, A. Mathy and A. Dralants, *Synth. Commun.*, 655 (1981).
109. O. Vogl and E. C. Taylor, *J. Am. Chem. Soc.*, **81**, 2472 (1959).
110. W. F. Keir, A. H. Mac Lennan and H. C. S. Wood, *J. Chem. Soc., Perkin Trans. 1*, 1002 (1978).
111. W. F. Keir, A. H. Mac Lennan and H. C. S Wood, *J. Chem. Soc., Perkin Trans. 1*, 1321 (1977).
112. F. Yoneda and M. Higuchi, (*a*) *Heterocycles*, **4**, 1659 (1976); (*b*) *J. Chem. Soc., Perkin Trans. 1*, 1336 (1977).
113. P. C. Parthasarathy, S. Iyer, M. Hendi, D. K. Ray and V. B. Srivastava, *Indian J. Chem., Sect. B*, **22B**, 1233 (1983).

114. P. C. Parthasarathy, B. S. Joshi, M. R. Chaphekar, D. H. Gawad, L. Anandan, M. A. Likhate, M. Hendi, S. Mudaliar and S. Iyer, *Indian J. Chem., Sect. B*, **22B**, 1250 (1983).
115. Reference 1, p. 325.
116. B. Decroix and P. Pastour, *J. Chem. Res. (S)*, 132 (1978).
117. A. A. Aroyan, M. S. Kramer and A. G. Saakyan, *Arm. Khim. Zh.*, **28**, 150 (1975); *Chem. Abstr.*, **83**, 79 185 (1975).
118. G. Bernath, J. Lazar, L. Gera, G. Gondos and Z. Ecsery, *Acta Chim. Hung.*, **115**, 231 (1984).
119. M. Suesse and S. Johne, *Z. Chem.*, **27**, 69 (1987).
120. I. Gagauzov and A. Poryazov, *Probl. Farm.*, **3**, 51 (1975); *Chem. Abstr.*, **87**, 23 199 (1977).
121. L. P. Prikazchikova, L. I. Rybchenko and V. M. Cherkasov, *Khim. Geterotsikl. Soedin.*, 831 (1977); *Chem. Abstr.*, **87**, 184 452 (1977).
122. K. A. Gupta, A. K. Saxena and P. C. Jain, *Synthesis*, 905 (1981).
123. Indian Patent 158,084 (1986); *Chem. Abstr.*, **107**, 59 051 (1987).
124. N. D. Venayak and B. J. Wakefield, *J. Chem. Res. (S)*, 200 (1983).
125. S. K. Robev, *Dokl. Bolg. Akad. Nauk*, **33**, 635 (1980); *Chem. Abstr.*, **94**, 83 735 (1981).
126. S. K. Robev, *Dokl. Bolg. Akad. Nauk*, **30**, 719 (1977); *Chem. Abstr.*, **87**, 167 970 (1977).
127. S. K. Robev, *Tetrahedron Lett.*, 1163 (1978).
128. E. N. Dozorova, N. P. Soloveva and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1109 (1988); *Chem. Abstr.*, **110**, 192 759 (1989).
129. V. G. Granik, E. O. Sochneva, N. P. Soloveva, E. F. Kuleshova and O. S. Anisimova, *Khim. Geterotsikl. Soedin.*, 1120 (1980); *Chem. Abstr.*, **94**, 192 250 (1981).
130. V. A. Azimov, N. N. Bychikhina and L. N. Yakhontov, *Khim. Geterotsikl. Soedin.*, 1283 (1981); *Chem. Abstr.*, **95**, 219 982 (1981).
131. E. F. Kaimanakova, E. F. Kuleshova, N. P. Soloveva and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1553 (1982); *Chem. Abstr.*, **98**, 89 306 (1983).
132. A. Ya. Ilchenko, V. I. Krokhtyak and L. M. Yagupolskii, *Khim. Geterotsikl. Soedin.*, 1680 (1981); *Chem. Abstr.*, **96**, 85 512 (1982).
133. N. G. Paulenko and V. P. Kukhar, *Ukr. Khim. Zh. (Russ. Ed.)*, **48**, 395 (1982); *Chem. Abstr.*, **97**, 23 735 (1982).
134. K. Hartke and H. M. Wolff, *Arch. Pharm. (Weinheim, Ger.)*, **313**, 208 (1980).
135. A. L. Weis and D. Zamir, *J. Org. Chem.*, **52**, 3421 (1987).
136. E. A. Oostveen, H. C. Van der Plas and H. Jongejan, *Recl. Trav. Chim. Pays-Bas*, **95**, 209 (1976).
137. P. Barczynski and H. C. Van der Plas, *J. Org. Chem.*, **47**, 1077 (1982).
138. R. G. Glushkov, O. Ya, Belyaeva, V. G. Granik, M. K. Polievktov, A. B. Girgorev, V. E. Serokhvostova and T. F. Vlasova, *Khim. Geterotsikl. Soedin.*, 1640 (1976); *Chem. Abstr.*, **86**, 121 287 (1977).
139. E. O. Sochneva, N. P. Soloveva and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1671 (1978); *Chem. Abstr.*, **90**, 121 530 (1979).
140. J. M. McCall, B. V. Kamdar and D. Kloosterman, *Synthesis*, 123 (1980).
141. A. P. Vinogradoff and N. P. Peet, *J. Heterocycl. Chem.*, **26**, 97 (1989).
142. A. Antus-Ercsenyi and I. Bitter, *Acta Chim. Acad. Sci. Hung.*, **99**, 29 (1979).
143. M. Tišler, B. Stanovnik and Z. Zrimsek, *Heterocycles*, **17**, 405 (1982).
144. A. Albert, *J. Chem. Soc., Perkin Trans. 1*, 291 (1976).
145. A. Albert and A. M. Trotter, *J. Chem. Soc., Perkin Trans. 1*, 922 (1979).
146. M. Tišler, B. Stanovnik and Z. Zrimsek, *Synthesis*, 299 (1981).
147. B. Vercek, I. Leban, B. Stanovnik and M. Tišler, *J. Org. Chem.*, **44**, 1695 (1979).
148. J. J. Huang, *J. Org. Chem.*, **50**, 2293 (1985).
149. S. K. Robev, *Dokl. Bolg. Akad. Nauk*, **36**, 1551 (1983); *Chem. Abstr.*, **101**, 110 858 (1984).
150. S. K. Robev, *Dokl. Bolg. Akad. Nauk*, **40**, 41 (1987); *Chem. Abstr.*, **109**, 128 942 (1988).
151. W. Schaefer and C. Falkner, *Ann. Chem.*, 1809 (1976).
152. L. B. Krasnova, S. I. Popov and N. S. Dokunikhin, *Zh. Org. Khim.*, **9**, 1494 (1973); *Chem. Abstr.*, **79**, 91 826 (1973).
153. N. N. Suvorov, V. A. Chernov, V. S. Velezheva, Yu. A. Ershova, S. V. Simakov and V. P. Sevodin, *Khim.-Farm. Zh.*, **15**, 27 (1981); *Chem. Abstr.*, **96**, 85 492 (1982).
154. V. P. Borovik, L. Yu. Ivanovskaya and V. P. Mamaev, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 110 (1977); *Chem. Abstr.*, **88**, 152 548 (1978).
155. M. P. Zhdanova, E. A. Zvezdina and G. N. Dorofenko, *Khim. Geterotsikl. Soedin.*, 456 (1978); *Chem. Abstr.*, **89**, 43 321 (1978).

156. H. Wamhoff and C. Materne, *Ann. Chem.*, **754**, 113 (1971).
157. V. P. Khilya, G. M. Golubushina, E. N. Meita and M. Yu. Kornilov, *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol., Khim. Biol. Nauki*, 55 (1980); *Chem. Abstr.*, **93**, 95 175 (1980).
158. U. Peterson and H. Heitzer, *Ann. Chem.*, 1663 (1976).
159. W. Löwe, *Ann. Chem.*, 1050 (1977).
160. R. L. N. Harris, *Synthesis*, 841 (1980).
161. N. A. Kapran, Yu. L. Yagupolskii and V. M. Cherkasov, *Zh. Org. Khim.*, **19**, 1192 (1983); *Chem. Abstr.* **99**, 139 910 (1983).
162. L. Citerio, D. Pocar, R. Stradi and B. Gioia, *Tetrahedron*, **35**, 69 (1979).
163. F. Saczewski and H. Foks, *Synthesis*, 154 (1981).
164. A. Etienne, G. Lonchambon, J. Roques, B. Lemmens and F. Pintard, *C.R. Acad. Sci. Paris, Ser. C*, **287**, 285 (1978).
165. Reference 1, p. 335.
166. J. Neuffer and J. Goerdeler, *Chem. Ber.*, **104**, 3498 (1971).
167. G. Barnikow and H. Ebeling, *Z. Chem.*, **13**, 424 (1978).
168. A. C. Veronese, C. Di Bello, F. Filira and F. D'Angeli, *Gazz. Chim. Ital.*, **101**, 569 (1971).
169. K. Seckinger, *Helv. Chim. Acta*, **56**, 776 (1973).
170. H. Suschitzky, R. E. Walrond and R. Hull. *J. Chem. Soc., Perkin Trans. 1*, 47 (1977).
171. G. Schwenker and R. Kolb, *Chem. Ber.*, **108**, 1142 (1975).
172. M. Tišler and B. Stanovnik, *J. Chem. Soc., Chem. Commun.*, 313 (1980).
173. M. Zupan, B. Stanovnik and M. Tišler, *J. Org. Chem.*, **37**, 2960 (1972).
174. D. Richter and H. Ulrich, *Chem. Ber.*, **103**, 3525 (1970).
175. H. P. Figeys and A. Mathy, *Tetrahedron Lett.*, **22**, 1393 (1981).
176. S. Morimura, *Heterocycles*, **14**, 1449 (1980).
177. G. S. Borovikova, E. S. Levchenko, E. I. Borovik and E. A. Darmokhval, *Zh. Org. Khim.*, **20**, 190 (1984); *Chem. Abstr.*, **100**, 209 279 (1984).
178. J. C. Meslin and H. Quiniou, (*a*) *Synthesis*, 298 (1974); (*b*) *Tetrahedron*, **31**, 3055 (1975).
179. E. S. Levchenko, G. S. Borovikova, E. I. Borovik and V. N. Kalinin, *Zh. Org. Khim.*, **20**, 196 (1984); *Chem. Abstr.*, **100**, 191 836 (1984).
180. L. N. Markovskii, E. A. Darmokhval and E. S. Levchenko, *Zh. Org. Khim.*, **9**, 2038 (1973); *Chem. Abstr.*, **80**, 27 220 (1974).
181. P. P. Kornuta, L. I. Derii and E. A. Romanenko, *Khim. Geterotsikl. Soedin.*, 273 (1978); *Chem. Abstr.*, **88**, 152 576 (1978).
182. P. P. Kornuta, L. I. Derii and L. N. Markovskii, *Zh. Org. Khim.*, **16**, 1308 (1980); *Chem. Abstr.*, **93**, 204 600 (1980).
183. P. P. Kornuta, N. V. Kolotilo and L. N. Markovskii, *Zh. Obshch. Khim.*, **47**, 342 (1977); *Chem. Abstr.*, **87**, 23 223 (1977).
184. P. P. Kornuta and N. V. Kolotilo, *Zh. Obshch. Khim.*, **48**, 1181 (1978); *Chem. Abstr.*, **89**, 109 392 (1978).
185. K. L. Paciorek, J. H. Nakahara, D. H. Harris, M. E. Smythe and R. H. Kratzer, Report 1985, SN-2007-F, AFOSR-TR-85-0500; *Chem. Abstr.*, **106**, 102 400 (1987).
186. R. I. Fryer, J. V. Earley and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967).

CHAPTER 9

Imidates including cyclic imidates

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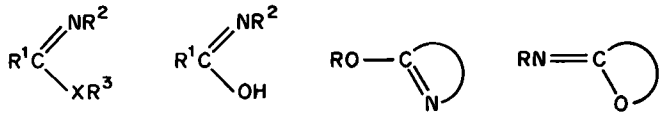
The Chemistry of Amidines and Imidates, Volume 2
Edited by S. Patai and Z. Rappoport

I. INTRODUCTION AND SCOPE

Imidates (**1**, X = O), the esters of imidic acids or iso-amides (**2**) and their thio-analogues (**1**, X = S) are in the main well-defined chemical compounds. This review will cover the



(1) (2) (3) (4)

chemistry of compounds of type **1** as well as, where appropriate, that of compounds of type **3** and **4** (although these latter compounds could more appropriately appear in reviews of heterocyclic compounds) as it has developed since the author's earlier review[1]. Readers should, therefore, refer to the earlier work[1] in conjunction with this review to gain an overall picture of imidate chemistry. More recently (1979) Böhme and Viehe[2] published a wide-ranging review which contains references to imidate chemistry. Other short reviews on specific topics will be referred to where appropriate in the text.

Imidates appear as useful synthetic intermediates in numerous papers dealing with a very wide range of chemical topics, hence this review can in no way be exhaustive but will attempt to map out some of the more important developments of recent years.

II. NOMENCLATURE

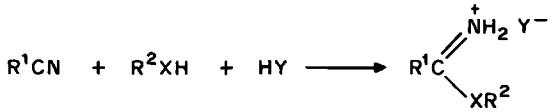
The nomenclature of compounds of type **1** has changed over the years. From time to time the older names, imino ether, imido or imidic ester and imidoate, are still to be found even in recent scientific papers. The most modern nomenclature would term compound **5**, methyl ethanimidate, and compound **6**, ethyl *N*-methylbenzenecarboximidate. However, for consistency over the author's reviews[1] it is proposed to retain the name methyl acetimidate for species **5** and ethyl *N*-methylbenzimidate for compound **6**—these names still being widely found in recent publications.

(5) (6)

III. SYNTHESIS

A. The Pinner Synthesis

The Pinner synthesis, extensively covered in the earlier review[1], continues to be a common synthetic route leading to imidate salts. A useful one pot synthesis involves the generation of hydrogen chloride *in situ* by dropping acetyl chloride (1.05 mole) diluted with, e.g., ethyl acetate into ethanol (2.05 mole) in the presence of a nitrile (1 mole) at temperatures below 5 °C. The mixture is stirred during the addition and kept for 12–48 h,

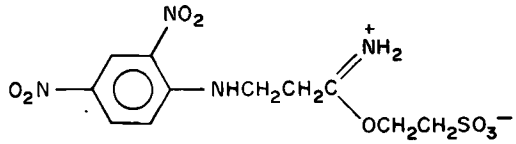


X = O, S; Y = Cl, Br

dry ether then being added if necessary to precipitate the product. The method has also been applied to cyanohydrins, e.g. mandelonitriles[3].

In the case of hindered benzonitriles[1], 2-azidobenzonitrile[4] has been successfully converted into an imidate via the Pinner method whereas 2,4,6-trihydroxybenzonitrile[5] and 4-azido-2-hydroxybenzonitrile[6] failed to react under such conditions. Hindered nitriles possessing tertiary α-centres have been successfully used to prepare imidate intermediates for conversion into esters and amides[7].

Studies on biological systems have involved the Pinner synthesis of labelled imidates and deuterium[8] and tritium[9,10] labelled acetonitrile as well as ^{14}C labelled hydrogen cyanide[10,11], acetonitrile[9,12,13], adiponitrile[14], suberonitrile[15], 4-azidobenzonitrile[16], and 4,4′-dithio-bisbutyronitrile[15] have been used in this way. Moreover, radioactive halogen has been used to label 4-hydroxy-3,5-diiodobenzonitrile used in a Pinner synthesis[17]. Imidate (7) which has been synthesized in a radioactive form (^3H) is an interesting example



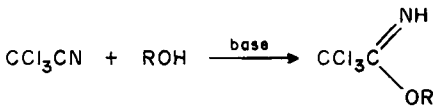
(7)

where both alcohol and acid functionalities are on the same moiety (isethionic acid, $HOCH_2CH_2SO_3H$[18]).

Although the Pinner reaction leads to *N*-unsubstituted imidates, related reactions, e.g. the addition of alcohols, phenols or thiophenols to *N*-methylnitrilium triflates, produce *N*-methylimidate salts in very good yields[19,20]. Trimethylsilylmethyl triflate salts of nitriles have also been employed[21]. An imidate-like intermediate has also been recognized in the reaction of benzonitrile, propan-2-ol and boron trifluoride[22].

B. Base Catalysed Reactions of Nitriles with Alcohols

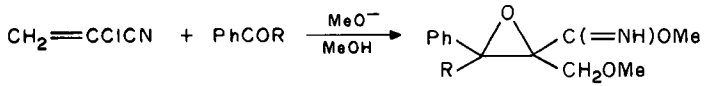
This route[1] has come to the fore in recent years with much interest being shown in the synthesis of allylic[23], propargylic[23] and sugar[24] imidates derived from trichloroacetonitrile (see Section IV.O for further references). In the case of secondary and tertiary alcohols—the latter failing to react in the Pinner procedure—best results are reported from the addition of the alcohol/alkoxide to an ether solution of trichloroacetonitrile, i.e. the reverse of the addition procedure in the primary alcohol case[25]. Interest in compounds of type **8** centres on their ability to alkylate hydroxy groups[26] (see Section IV.O) to give, e.g., *t*-butyl esters and ethers.



(8)

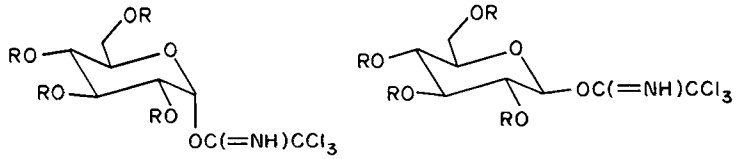
Heterocyclic compounds having a cyano group alpha to a hetero atom (usually N or O) form imidates with alcohols in the presence of bases such as sodium borohydride[27,28], potassium carbonate[29] or traces of concentrated ammonia[30] and 3,5-dinitrobenzonitrile

reacts similarly with methanol/methoxide ion[31]. The glycol[32], $HOCH_2CH{=}CHCH_2OH$, and thiophenols[33] have been utilized in related syntheses and the nitrile **9** in the presence of benzaldehyde or benzophenone has been converted directly into the glycidic imidate **10** (R = H or Ph)[34].



(9) (10)

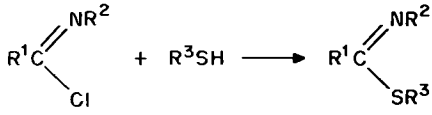
In carbohydrate chemistry protected (e.g. benzylated) sugars with free anomeric hydroxy groups have been converted into stable *O*-glycosyl trichloroacetimidates under base catalysis[24,35]. The synthetic pathway is illustrated by the use of 2,3,4,6-tetra-benzylglucose but related sugars give analogous results. When sodium hydride is the base catalyst of choice, the *O*-α-glucopyranosyl trichloroacetimidate **11** is obtained as the thermodynamic product in very high yield but the use of potassium carbonate permits the isolation of the β-anomer **12** in good yield as it brings about rapid formation of the kinetic product **12**[24,35,36].



(11) (R = $PhCH_2$) (12)

C. Reaction of Imidoyl Halides with Alkoxides and Phenoxides

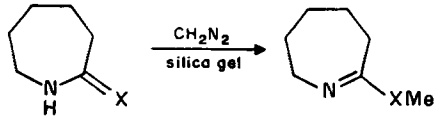
Phase transfer catalysts such as tetrabutylammonium bromide[37] have found use in imidate synthesis using imidoyl halides and phenols[1] or their thio analogues in dichloromethane/water under basic conditions. Unsaturated alcohols[38], e.g. cyclohex-2-



en-1-ol, have also been employed in this reaction using potassium hydride as base in THF[39], as has *t*-butylmercaptan in the presence of pyridine[40]. However, 4-aminophenol furnishes amidines rather than imidates[41] in related reactions.

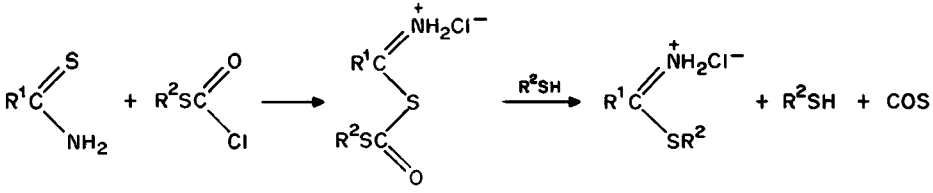
D. Conversion of Amides and Thioamides into Imidates

Various reagents have been utilized to alkylate amides and their thio-analogues[1] and improvements in technique have been reported in some instances, e.g. the reaction of amides, lactams and thiolactams with diazomethane, although not a universally applicable reaction, is much accelerated in the presence of neutral silica gel[42]. Labelling,

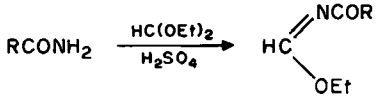


(X=O,S)

and competitive studies involving added thiols, have shown that the interaction of thioamides with thiochloroformate esters takes the following pathway[43] and this synthesis has been extended to include thiolactams[44].



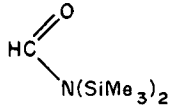
It has been noted that in the interaction of amides with triethyl orthoformate, increasing yields of *N*-acyl-imidate are realized as the electronegativity of the R-group of the amide **13** increases[45].



(13)

Trimethyloxonium fluoroborate is a useful reagent for the synthesis of α,β-unsaturated imidates from the corresponding amides, the synthetic route being superior to earlier published methods[46]. Imidates not available via the Pinner procedure can be prepared in this way[46,47]. Diketopiperazines have been successfully converted into diimidates by this method[48].

The silylation of amides[49–52] is of current interest because some imidate derivatives such as *N*,*O*-bis(trimethylsilyl)trifluoroacetamide are silylating agents in their own right[53–55] (see Section IV.P) or can act as nitrile precursors in the presence of Lewis acids[56]. Studies, including ^{13}C NMR, point to lactams undergoing *N*-silylation, hetero-aromatic amides such as 2-hydroxypyridines being silylated on oxygen and acetanilides yielding mixtures of *N*- and *O*-silylated products[49,51], with *O*-silylation being favoured by increasing the electronegative substitution pattern of the aryl group[49]. In addition, although the formamide **14** has the *N*,*N*-disubstituted structure shown, higher members of the homologous series exist as the *N*,*O*-substituted species **15**[50]. Trimethylsilyl triflate has



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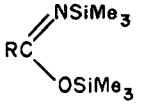
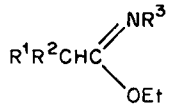


(15)

been used to prepare, from amides, imidates which act as intermediates in the synthesis of α-amino-β-hydroxycarboxylic acids[57].

Whereas alkylation of arylacetamides gives imidates (**16**; $R^1 = Ar$) exclusively, the use of cyanoacetamides gives rise to mixtures of imidates (**16**; $R^1 = CN$) and enamine ethers (**17**; $R^1 = CN$), the equilibrium being dependent on temperature and solvent[58].



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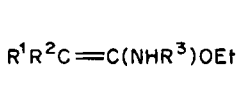
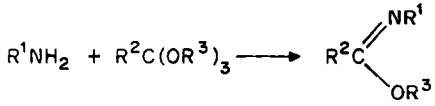


(17)

A novel synthesis leading finally to 1,3,4-oxadiazoles involves the interaction of benzotrichloride with an acid hydrazide in the presence of an alcohol[59].

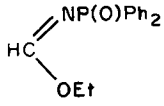
E. Imidates from the Reaction of Amino Compounds and Ortho Esters

Aromatic amines including hindered amines, e.g. those possessing 2-bromo[60] or 2,5-dimethyl[61] substitution patterns, yield *N*-substituted imidates on treatment with ortho esters[1]. Unlike most aliphatic amines, aminoacetonitrile forms an imidate on interaction



with triethyl orthoformate but the catalytic conditions (concentrated sulphuric acid) are fairly critical as imidazole derivatives are produced in the presence of other catalysts[62].

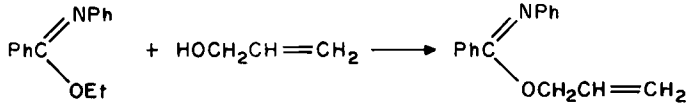
Amides react similarly[45] to give *N*-acyl-imidates (see Section IV.L) and $Ph_2P(O)NH_2$ has been converted into the imidate **18**[63].



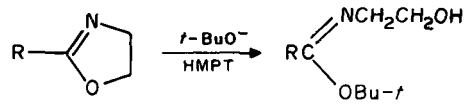
(18)

F. Transesterification of Imidates

Allylic imidates have been produced from ethyl imidates by transesterification[23,64].



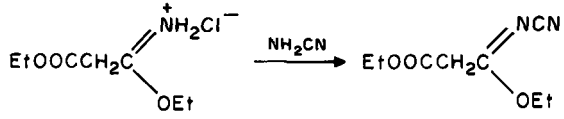
Oxazolines may be converted into open chain imidates by the action in HMPT of *t*-butoxide ion[65].



G. Preparation of *N*-Substituted Imidates from Simpler Imidates

The reactions between imidates and amino acid derivatives[1] such as peptides, leading either to *N*-substituted imidates or amidines, are discussed in Section IV.H.7.

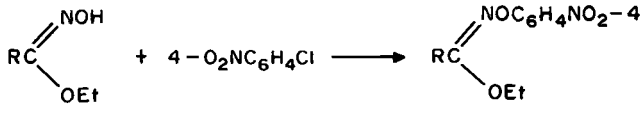
Cyanamide[66] reacts selectively with the imino group of the imidate **19** to yield the *N*-cyano derivative **20** and imidates of the type **21**[67] and **22**[68] have been prepared by the action of the appropriate chloroformic acid derivative on the corresponding *N*-unsubstituted imidates.



(19) **(20)**

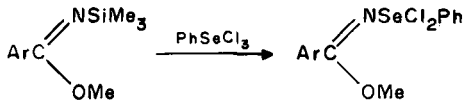
(21) **(22)**

Aryl halides with appropriate activating groups have been shown to react with *N*-hydroxy-imidates to yield compounds of the type **23**, which are useful intermediates in the synthesis of *O*-arylhydroxylamines[68–70].



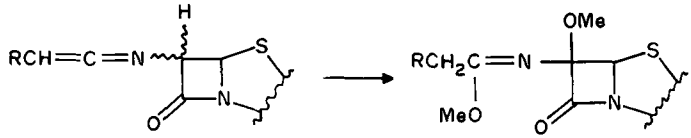
(23)

N-Trimethylsilyl-imidates can be converted into *N*-selenyl-substituted analogues[71] and related reactions have been carried out with compounds of type Ph_2BCl[72].



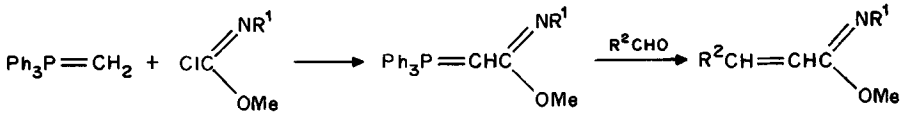
H. Imidates from Unsaturated Systems

Ketenimine derivatives of cephalosphorins (**24**) react with bromine followed by lithium methoxide to yield imidates[73,74].



(24) (25)

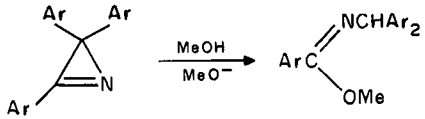
Reaction of a phosphorus ylide (**26**) with chloroformimidates of type **27** opens up a pathway to α,β-unsaturated imidates[75]. Imidates have also been recorded as products



(26) (27)

from the reaction of isocyanides with perfluorinated acetylenes in protic solvents[76], and from the reactions[77] of isocyanates with alkenes of the type $R^1O(Me_2N)C{=}CR^2_2$.

Azirines (**28**) can undergo ring opening reactions with alkoxides to yield imidates (**29**)[78].



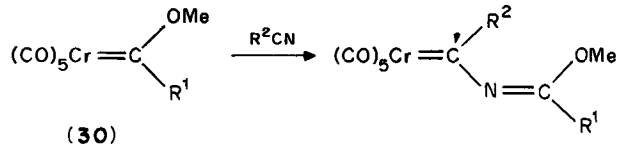
(28) (29)

I. Imidates from Metal Complexes and Organometallic Compounds

Reference is made in this section both to preparations from which free imidates may be derived and to those in which suitable ligands are converted into imidates which then remain within the complexes. The reader is also referred to further references in Reference 79.

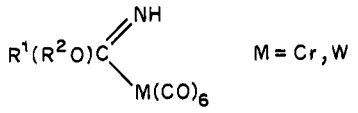
1. Chromium and tungsten complexes

Imidate complexes of chromium[80] can be formed by the action of alkyl or aryl nitriles on carbene complexes of type **30**; related work involves the insertion of the C≡N moiety of

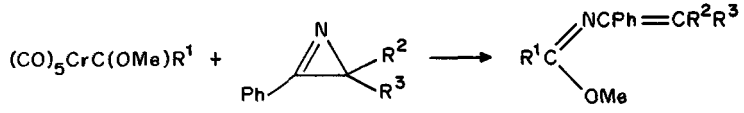


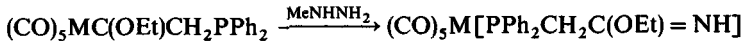
(30)

Me_2NCN into a chromium or tungsten carbene carbon bond[81]. Alkoxyorganocarbene metal complexes of chromium or tungsten[82] also yield imidate complexes (**31**) on treatment with $Ph_2S{=}NH$ and chromium carbene complexes react with 1-azirines to give *N*-vinylimidates[83]. Chromium or tungsten complexes of type **32** (M = Cr or W) on



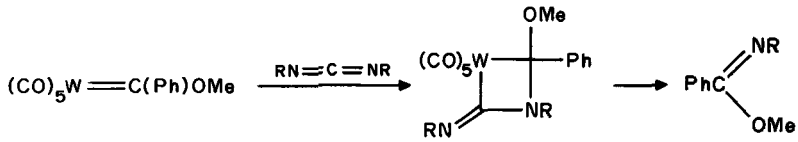
(31)





(32) (33)

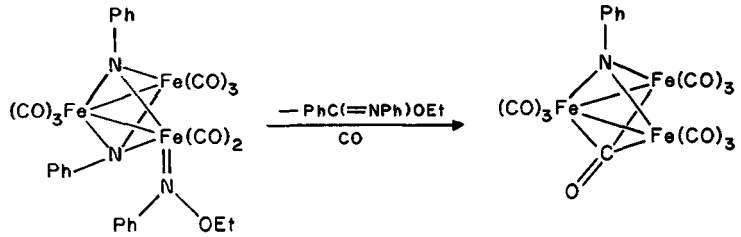
treatment with methylhydrazine[84] yield the imidate complexes (33). The cyclic species (35) derived from interaction of a carbodiimide and the tungsten complex (34) decompose with loss of an imidate moiety[85]. The nitrile $Ph_2PCH_2CH_2CN$ yields phosphine imidate complexes of tungsten, $W(CO)_4L$, but the reaction conditions can also lead to amine complexes[86].



(34) (35)

2. Iron complexes

Iron complexes (36) possessing carbene and nitrene ligands have been prepared from the corresponding carbonyl compounds by interaction with EtOTf and have been found to eliminate imidate, e.g. on exposure to carbon monoxide[87,88].



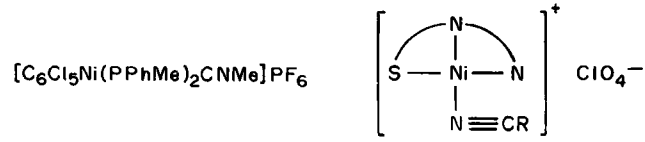
(36)

3. Cobalt and nickel complexes

The complex [Co(4-CNpy)$(Hdmg)_2$Cl] (Hdmg = dimethylglyoximate monoanion) has been converted into an imidate complex in which the imidate was shown by ^{1}H NMR to

have a 4:1 ratio of the *E*/*Z* arrangements in $CDCl_3$ but to be exclusively of the *E* configuration in the solid state[89].

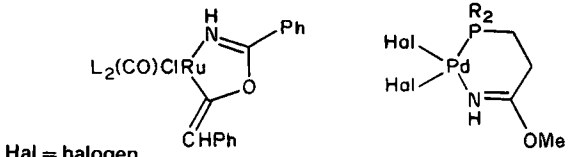
Carbene complexes[90] of pentachlorophenylnickel(II) (**37**) and nitrile complexes[71,91], e.g. of type **38**, also react with alcohols to give imidate complexes. In the case of compound **38** the alcohol is required to be dry, otherwise a nitrile-to-amide conversion takes place[79].



(**37**) (**38**)

4. Ruthenium and palladium complexes

The structure of a ruthenium complex of type **39** has been confirmed by X-ray studies[92]. Palladium(II) nitrile complexes have been studied[93–95] and complexes of type **40** have

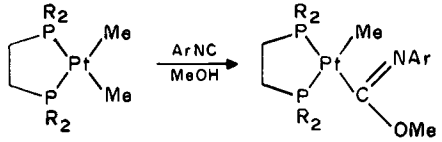


(**39**) (**40**)

been derived from them by the action of alcohols or thiols. However, the action of a thiophenol on *cis*$[Pd(2\text{-}MeC_6H_4CN)(PPh_3)_2]_2(BF_4)_2$ causes loss of the nitrile ligand with formation of $[Pd(SAr)(PPh_3)_2]_2(BF_4)_2$ in place of formation of an imidate complex[93].

5. Platinum complexes

Platinum complexes of the type **41** react in methanol with aryl isocyanides to give imidates (**42**) of proven *Z*-stereochemistry[96] and related species have been synthesized



(**41**) (**42**)

with an ethylene linkage between the phosphorus ligands[97]. *o*-Cyanobenzylbis(diphenylphosphine)ethyleneplatinum(II) tetrafluoroborate similarly gives complexes by nucleophilic attack of alcohols[98] and complexes of the type $[Ph_2PCH_2]_2Pt[C(OMe)=NR]_2$ have been shown to act as bidentate ligands (L) forming complexes of the type MX_2L where M = Cd, Hg, Zn and X = halogen[99].

6. Gold complexes

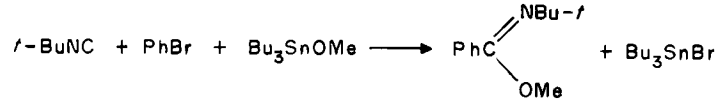
Trigold(I) imidate complexes are known[100,101] and have been studied by Mössbauer spectroscopy[102]; ligands (L), e.g. triphenylphosphine[100], react with trigold complexes (**43**) to give gold complexes of type **44**.

$$[AuC(OR^1)=NR^2]_3 + L \longrightarrow LAuC(OR^1)=NR^2$$

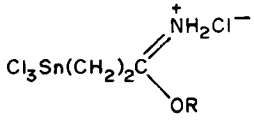
(**43**) (**44**)

7. Organotin compounds

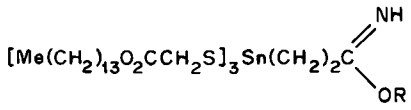
The following reaction yielding imidate as product takes place at 120 °C in the presence of $(Ph_3P)_4Pd$ as catalyst[103].



The introduction of stannous chloride into a Pinner synthesis involving acrylonitrile[104] resulted in formation of the organotin compound (**45**) in which the halogen ligands can be replaced by sulphur ligands (**46**).



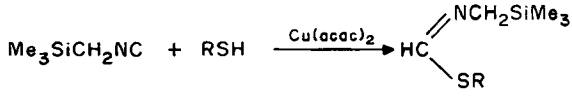
(**45**)



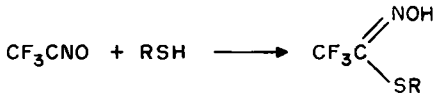
(**46**)

J. Miscellaneous Preparations of Imidates

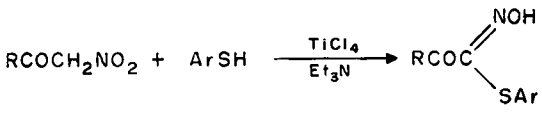
Isocyanides of type **47** react readily with thiols or thiophenols in the presence of $Cu(acac)_2$ to give thioimidates, although alcohols fail to react in this way[105–108]. Trifluoromethyl cyanate[109] also reacts with thiols or thiophenols to yield thioimidates (**48**) and α-nitroketones[110] can similarly be converted into aryl thioimidates.



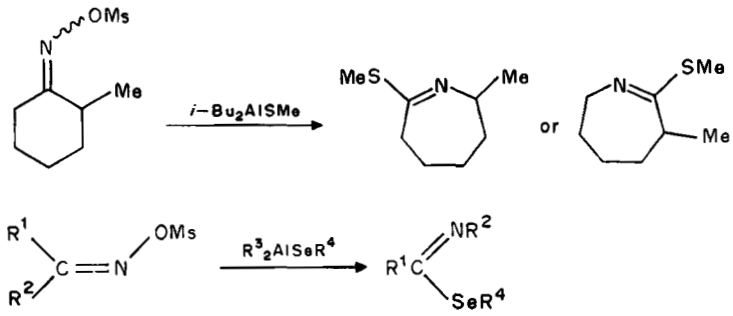
(**47**)



(**48**)



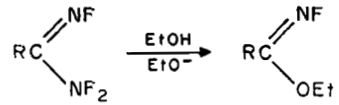
Various imines have proved to be useful starting materials for imidate syntheses, e.g. organoaluminium compounds have been used to carry out the following reactions leading to thio and selenyl imidates[111,112].



Favorskii-type rearrangements of α-chloroketimines in the presence of methoxide ion can give either imidates or amides[113] and the dinitrile **49** with one equivalent of ethoxide ion as base yields imidate **50**—higher base concentrations leading to other products[114].

(49) **(50)**

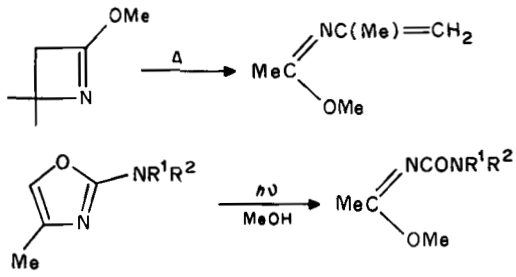
Ketimine *N,S*-acetals have also found use as starting materials in imidate synthesis[115] and the alkyl amidines (**51**) form imidates (**52**) on treatment with base[116].



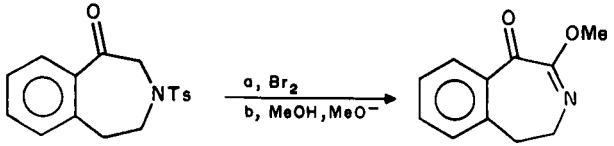
(51) **(52)**

Gas phase thermolysis and photolysis of α-azidoethers produces imidates[117], and the migrating aptitudes of various groups under these different conditions have been studied.

Individual imidates have also appeared as products in reactions involving the ring opening reactions of a variety of heterocyclic compounds such as 1-azetines[118], 1-

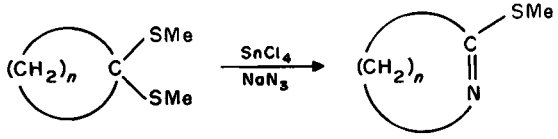


azirines[78,83], oxazoles[119], oxazolines[65], 1,2,4-triazines[120] and 1,2,3-triazolines[121], and removal of a 4-toluenesulphonyl group from sulphonamides[122] of type **53** has given rise to the cyclic imidate **54**.

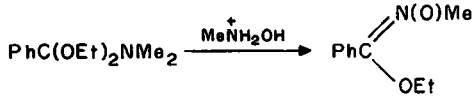


(53) **(54)**

Cyclic thioimidates including steroidal imidates have been synthesized from thioketals on interaction with azide ion in the presence of stannic chloride[123].



Imidate and thioimidate *N*-oxides are also known[124,125], see equation (1).



(1)

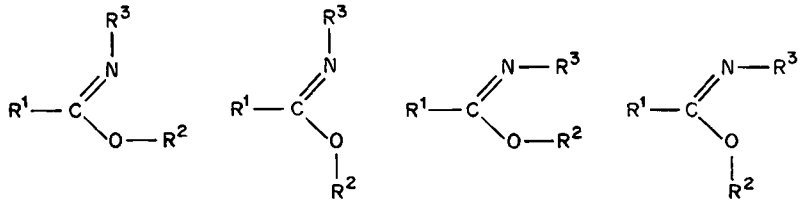
IV. PROPERTIES OF IMIDATES

A. General Properties

Simple aliphatic imidate salts tend to be hygroscopic[1] undergoing hydrolysis (see Section IV.E) while aromatic imidate salts or compounds of higher molecular weight are in general more stable but are best stored under anhydrous conditions. Other unstable imidate salts include aliphatic compounds with strong electronegative groups, e.g. $CCl_3C(OR)=NH_2Cl$. Such compounds lose alkyl halides and form amides very readily, however they are stable as their bases (see Section IV.D).

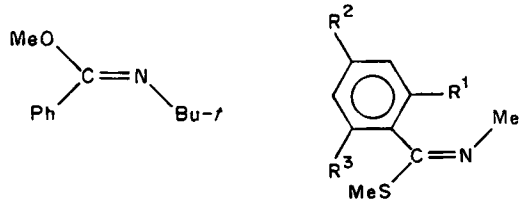
B. Isomerism and Imidate Conformations

Non-cyclic imidates possess four possible planar configurations (**55a, b, c, d**) due (i) to the presence of the C=N moiety and (ii) to the partial double-bond character of the C—O bond. These structures (**55a–d**) are designated as *E* and *Z* by relating the remoteness or nearness, respectively, of the R^3 and OR^2 groups and additionally as *cis* or *trans* depending on the relative positions of the R^1 and OR^2 groups (see References 1, 126, and 127 and references cited therein). An alternative nomenclature relates the geometric configuration of the OR^2 group and the nitrogen substituent (R^3) in terms of *syn* and *anti*, leaving *cis* and *trans* to indicate the conformation of R^2 on oxygen with respect to the nitrogen substituent R^3 (see Reference 127 and references cited therein and also Perrin's chapter in this volume). Compound **55a** is thus *anti-cis* and compound **55d**, *syn-trans*. Although some earlier work based on ^1H NMR and dipole moment measurements on *O*-imidates gave conflicting results relating to configurations[1,126,127], spin–spin coupling ^1H NMR



E-trans (55a) *E-cis* (55b) *Z-trans* (55c) *Z-cis* (55d)

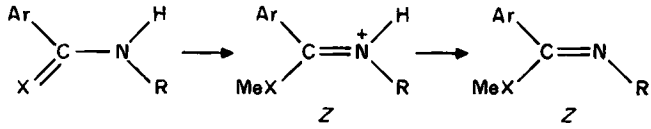
studies of C-alkyl and N-alkyl protons of imidates undertaken by Walter and coworkers[128] and utilizing shift reagents in CCl_4 or CD_3OD highlighted the presence of *E*-imidates either exclusively or in very high percentages. Subsequently aryl imidates (**55**; R^1 = aryl) have also been shown by NMR NOE studies to have high *E*/*Z* ratios[129] or to be exclusively *E*. However, if bulky groups are present, as in compound **56**, steric factors become increasingly important and, at −67 °C, the ^1H NMR spectrum of the imidate can be resolved into peaks characteristic of both *E* and *Z* isomers and hence imidate **56** is undergoing rapid isomerization of configurations at room temperature[130].



(56) (57)

In the case of thiobenzimidates, e.g. of type **57**, the *E* and *Z* forms have been isolated chromatographically and the *E*/*Z* ratios and barriers to isomerization determined by NMR[131,132]. The predominance of the *E*-isomer is not so marked for *S*-imidates as it is for *O*-imidates[129,132].

Conversion of a series of amides (**58**, X = O) by alkylation led to imidate salts (**59**, X = O)

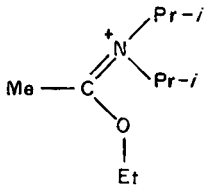


(58) (59) (60)

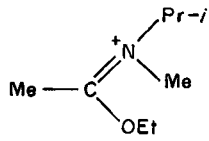
possessing the *Z*-configuration from which the thermodynamically unstable *Z*-imidates (**60**, X = O) could be formed by treatment with pyridine at low temperatures, and related studies have been carried out on thioimidates (**59**, X = S) where higher percentages of the *Z*-forms exist normally[129]. The rate of isomerization of protonated imidates varies widely, methyl *N*-methylacetimidate undergoing $Z \rightleftharpoons E$ equilibrium only very slowly even at elevated temperatures whereas methyl *N*-phenylbenzimidate equilibrates more readily. Protonated imidates or their thio analogues can undergo isomerization by rotation about

the C=N moiety in acid solution, whereas the free bases isomerize via planar inversion pathways or imine–enamine procedures (see Reference 133 and references cited therein; see also the chapter by Perrin in this volume).

In the case of *N*,*N*-disubstituted imidates there can be serious steric interactions, e.g. in compound **61** between an *N*-isopropyl group and the *O*-ethyl group[133], and this causes the molecule to adopt the arrangement shown (**61**). The *N*-methyl-*N*-isopropylimidate (**62**),



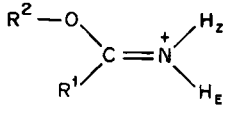
(**61**)



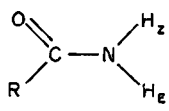
(**62**)

prepared by alkylation of ethyl *N*-isopropylacetimidate, is formed in a 1:1 ratio of *E*:*Z* isomers from which the pure *E*-isomer may be isolated by crystallization[133]. Basic conditions permit $E \rightleftharpoons Z$ interconversions in compound **61**, the mechanism involving an enamine route as seen by deuterium incorporation in the *C*-methyl group. Such interconversions do not take place in acid solution[133].

Comparisons between proton exchange in strong acid have been made for imidates and amides using NMR techniques[134]. For the imidate (**63**; R^1 = Me, R^2 = Et), H_Z exchanges appreciably faster than H_E whereas in the case of primary amides (**64**), H_E exchanges faster, pointing to different mechanistic pathways for exchange[134].

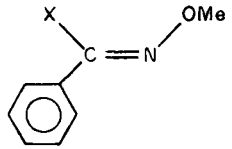


(**63**)

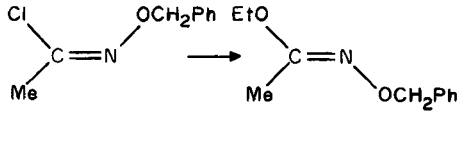


(**64**)

The stereochemical outcome of the reaction of hydroximoyl chlorides with alkoxides appears to be dependent on the conditions of the reaction, the structure of the chloride and its configuration (*Z*/*E*)[135–137]. Thus the *Z*-hydroximoyl chloride (**65**; X = Cl) when treated with methoxide ion in methanol/dimethyl sulphoxide gives exclusively the *Z*-imidate (**65**; X = OMe) whereas the *E*-halide is much less stereospecific in reaction, although the principal imidate product still exhibits stereochemical retention[136]. However a *Z*-hydroximoyl halide (**66**) reacted with sodium ethoxide[137] to yield the *E*-hydroximidate **67**. In each case the stereochemistry was checked by independent synthesis[136,137]. Isomeriz-



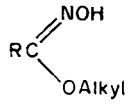
(**65**)



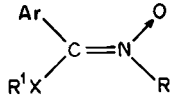
(**66**) (**67**)

ation ($Z \rightleftharpoons E$) rates for compounds of type **65** (X = OMe) have also been investigated[138].

Some alkyl hydroximidates (**68**) exist exclusively in the *E* form[139] and imidate *N*-oxides[124] and their thio analogues[125] (**69**; X = O,S) have been identified in both *E* and *Z* forms with pure *Z*-isomers being obtained by crystallization in the case of the thio compound (**69**; X = S). The corresponding oxygen compounds (**69**; X = O), although separable by flash chromatography, quickly re-equilibrate[124].

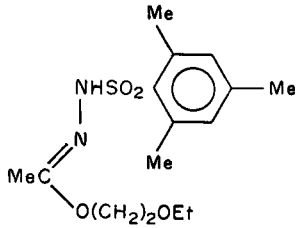


(**68**)

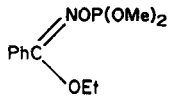


(**69**)

X-ray analysis[140] has proved that the hydrazimidate **70** exists in the *E* form allowing further correlations to be carried out using NMR data, and the imidate **71** exists in *Z* and *E* forms separable by chromatography[141]. The structures of perfluorinated imidates and thioimidates have also been studied using ^{19}F NMR[142].

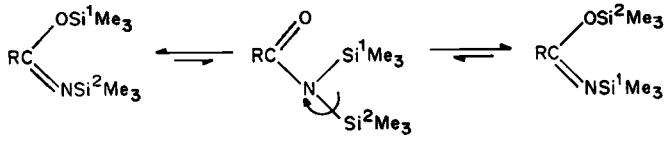


(**70**)



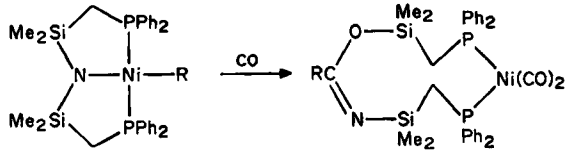
(**71**)

Imidate–amide tautomerism is exhibited by bis(trimethylsilyl)amides (**72**). Except for $HCON(SiMe_3)_2$ these compounds exist mainly as the *N,O*-disilylimidate tautomers (**73a** and **b**) which undergo reversible intramolecular exchange of the trimethylsilyl groups between nitrogen and oxygen, brought about by rapid free rotation of the carbon–nitrogen bond of the amide tautomer (**72**)[143–146].



(**73a**) (**72**) (**73b**)

The nickel(0) complex **74** has been shown by X-ray analysis, variable temperature ^1H and ^{29}Si NMR and ^{15}N labelling experiments to have predominantly the imidate structure **74** both in the solid state and in solution[147].



(74)

C. Spectra of Imidates

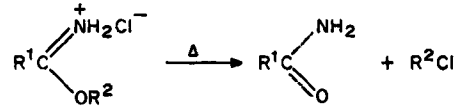
The spectra (IR, Raman, UV, NMR, and mass spectra) associated with a wide variety of imidate types have been reviewed[1,148] and the preceding section of this chapter (Section IV.B) details the use of NMR techniques, e.g. ^{13}C data[131], ^{1}H data[128,130], ^{19}F studies[142] and NOE experiments[129], to determine the *E*/*Z* configuration of imidates[149]. The position of silylation[49] of lactams, 2-hydroxypyridines and acetanilides has also been investigated by ^{13}C NMR and the imidate⇌amide tautomerism (72⇌73) for imidates of type 73 has been studied by looking at ^{15}N spectra[145].

Imidates and their salts are subject to rearrangement and to hydrolysis reactions[1] and hence care must be taken in the interpretation of spectroscopic data, e.g. mass spectra studies on *N*-arylformimidates showed that these compounds underwent Chapman rearrangements[1,150] prior to fragmentation[151].

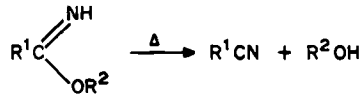
D. Thermal Decomposition of Imidates

1. *N*-Unsubstituted imidates

Whereas *N*-unsubstituted imidate salts normally decompose on heating to give amides and alkyl halides, their bases are stable to heat when, for compound 75, R^1 = alkyl, or

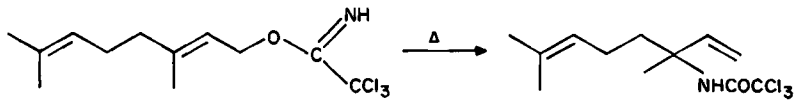


decompose to nitrile and alcohol when R^1 = aryl (species 75).



(75)

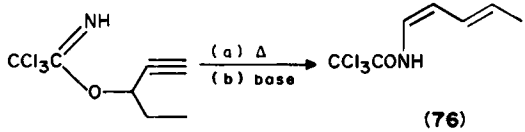
Extensive studies on allyl trichloroacetimidates have shown that these compounds undergo, on heating, concerted [3,3]-sigmatropic rearrangements to give allylically transposed trichloroacetamides (equation 2)[152]; see Overman[23] and references cited therein.



(2)

The rearrangements are totally regiospecific and highly stereoselective[23], the transformation to amide occurring suprafacially with virtually complete transfer of chirality[153]. In some instances much milder rearrangement conditions have been made possible by the use of mercury(II) or palladium(II) salts as catalysts[23,154], the rearrangements taking place most readily with imidates prepared from tertiary alcohols. The reactions, now known as Overman or Overman–Claisen rearrangements (equation 2)[155–157], are of synthetic significance because of the ease of removal of the trichloroacetyl group; e.g. use has been made of this reaction in the synthesis of the isomers of polyoxamic acid[157], amino acids[155], 3-amino-1,2-diols[158], 4-amino-2,5-hexadienoic acid[156], aminosugars[159] and (±)-acivicin[160].

1-*N*-Trichloroacetylamino-1,3-dienes can be prepared by thermal rerrangement of the corresponding propargylic imidates, usually in the presence of a free radical inhibitor[23,161,162] (see especially references cited in Reference 23). The reaction (equation 3)



(3)

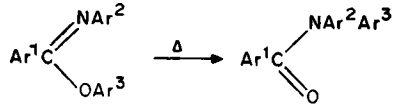
(76)

proceeds via the intermediacy of a 1,2-diene, 1-trichloroacetylaminopenta-1,2-diene, in the example cited[161]. Although the kinetic product is favoured in this [3,3]-sigmatropic rearrangement, the thermodynamic diene (76) is available by base catalysed equilibration.

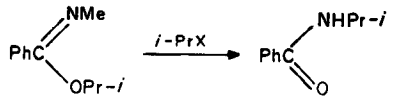
2. *N-Substituted imidates*

The thermal decomposition of *N*-substituted imidate salts is often complex[1], but use has been made of the reaction to prepare *N*-(α-methoxyallyl)amides[163].

The thermal, intramolecular 1,3-shift of an aryl group from oxygen to nitrogen in aryl *N*-aryl arylimidates has become known as the Chapman rearrangement and extensive reviews are available (References 1 and 150 and references cited therein). A recent application of the reaction involves the synthesis of arylaminocoumarins[164].

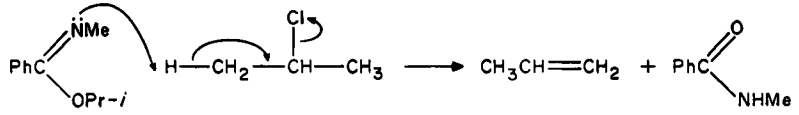


Rearrangement pathways of *O*-alkyl arylimidates depend on the nature of the alkyl group and are subject to catalysis by alkyl halides[1,149,150]. Studies by Challis and Frenkel[149] have shown the catalysed reaction (equation 4) to follow the equation,



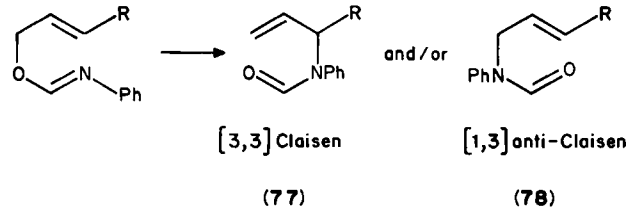
(4)

rate = k [imidate] [alkyl halide] and they invoke a two-step mechanism involving a benzimidonium intermediate. However, if isopropyl halide is used as catalyst, a concomitant E2 elimination takes place[149] (equation 5).



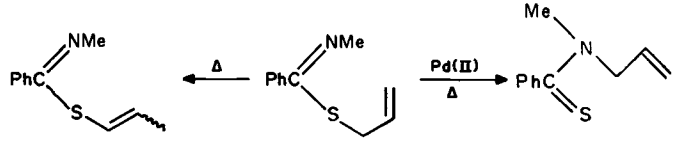
(5)

Metal catalysts[165,166] have been utilized to good effect in the Claisen rearrangement of allyl *N*-substituted imidates (see Reference 166 and references cited therein) allowing many reactions to be carried out at 25 °C instead of the 200 °C required for the thermal process[166]. Product and mechanistic studies showed palladium(0) catalysts to give *ca* 1:1 ratio of products **77** and **78**, palladium (II) catalysts to form exclusively the Claisen product



(77) (78)

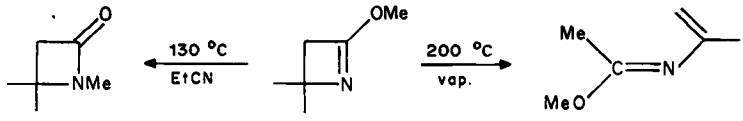
(77), whereas rhodium (I) and iridium (I) yielded predominantly the anti-Claisen product **(78)** with only the palladium (II) catalyst giving high stereoselectivity in addition to regioselectivity[166]. *S*-Allyl thioimidates also rearrange on heating[150,167,168], giving the isomerized product **79**, but the thioamide **80** when palladium (II) salts are present. The



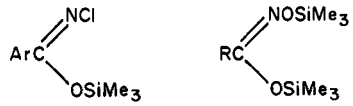
(79) (80)

palladium(II) reaction has also been applied to cyclic thioimidates, for example, to synthesize *N*-alkyl-thio-ε-caprolactam[167].

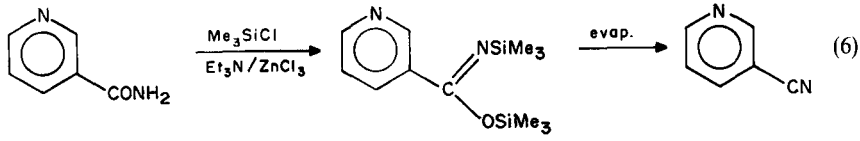
Pyrolysis of 2-alkoxyazetines gives different products in the liquid and vapour phases[118] (compounds **81** and **82** respectively). Isocyanates may be obtained by heating imidates of type **83**[169] or type **84** (R = perfluoroalkyl)[170] and reaction 6 is a useful route to nitriles[56].



(81) (82)



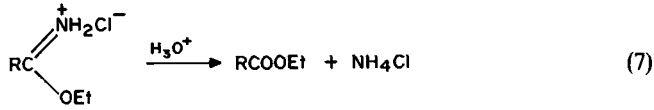
(83) (84)



(6)

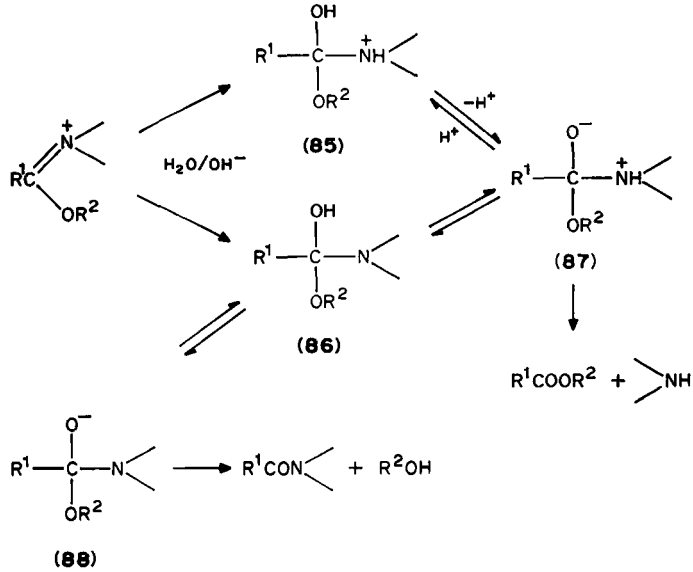
E. Hydrolysis of Imidates

Imidate salts are extensively subject to hydrolysis, especially under acid conditions when the hydrolysis products normally are as shown in equation 7.



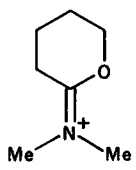
(7)

Following on from extensive work already reported in the earlier review[1], more recent studies[171] have come, in the main, from groups led by Schmir[172–176] and Deslongchamps[177–181]. It has been proposed that Scheme 1 represents the mechanism of hydrolysis of imidate salts in basic media with the rate-determining steps being the

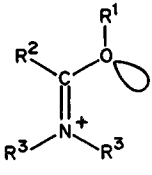


SCHEME 1

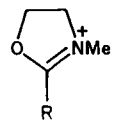
interaction of an imidate with water or hydroxide ion to give cationic (**85**) or neutral (**86**) intermediates of tetrahedral structure—thereafter the breakdown pathways of the intermediates depend very much on the imidate structure[172–176]. It is known that all the intermediates (**85–88**) are formed[180,181] and that C—O or C—N bond cleavage can be concomitant with protonation or deprotonation in some instances[173,174]. Except for imidates derived from weakly basic amines[1,175], e.g. ethyl *N*-4-nitrophenylformimidate, neutral or cationic species in general furnish amines whereas amides and alcohols arise from breakdown of anionic intermediates. Normally amide and alcohol are the thermodynamic products, ester and amine being the result of kinetic control. Although factors such as the pK_A of the conjugate acid of the leaving group or the ability of any remaining heteroatoms to confer stability on the incipient carbocation may play a part in determining the reaction pathway, Deslongchamps[179] in a review paper presents evidence that cleavage of the tetrahedral intermediates is under stereoelectronic control and hence is heavily dependent on conformation and, in particular, on the orientation of the lone-pair orbitals of the hetero atoms. Thus antiperiplanar arrangements of lone-pair orbitals relative to the leaving group assist in the cleavage of an N—C or O—C bond. To test this theory cyclic imidates were used to lock molecules in *syn* (**89**) and *anti* (**91**) arrangements corresponding to the *syn* (**90**) and *anti* (**92**) conformations (in stereoelectronic terms, see above) of acyclic imidates. The products predicted on stereoelectronic grounds from rigid *anti*-imidate salts under conditions of kinetic control are exclusively ester/amine and those were confirmed experimentally. In the case of acyclic imidates, imidate **90** (R^1 = Et, R^2 = H, R^3 = Me) shown by NOE to have a *syn* conformation gives mixtures of ester/amine and amide/alcohol products in accord with stereoelectronic theory whereas



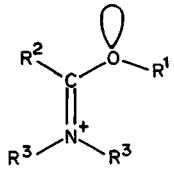
(**89**)



(**90**)



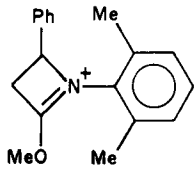
(**91**)



(**92**)

imidate **92** (R^1 = Et, R^2 = t-Bu, R^3 = Me) locked into an *anti* arrangement by the bulky R^2 substituent gives ester/amine products exclusively under alkaline hydrolysis and kinetic control[179].

In comparison with the above hydrolysis, in acidic conditions ester/amine products arise from the hydrolysis of both *anti* (**92**) and *syn* (**90**) imidate salts[177,178,180,181]. It has been noted that for cleavage of a C—N bond the nitrogen of any tetrahedral intermediate must either be protonated under acidic conditions or hydrogen bonded with solvent in basic media[179–181]. Hence in the case of any imidate, e.g. compound **93** which is highly

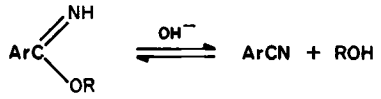


(**93**)

hindered to protonation, base hydrolysis proceeds to yield a lactam althouh at pH values below 4 ester/amine products appear[181].

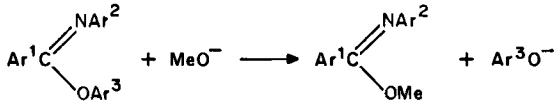
Other studies[182,183] include comparison of hydrolysis of benzimidates and benzamides in sulphuric acid solutions[184] and Hammett relationships in the alkaline hydrolysis of aryl *N*-aryl arlyimidates[185,186].

Benzimidates under basic conditions may also yield nitriles (equation 8) and this



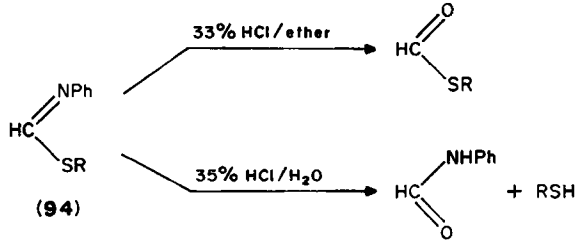
(8)

elimination has been shown to follow an ElcB mechanism[187]. Hammett plots for the displacement reaction 9 have also been reported[188].



(9)

Less work has been carried out on thioimidates but the thioformimidate **94** hydrolyses[189] as shown in equation 10 and the thioimidate *N*-oxide **95** is hydrolysed[125] in accord with equation 11.



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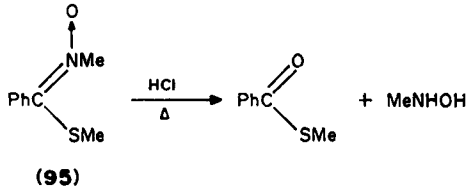
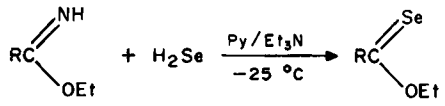


(11)

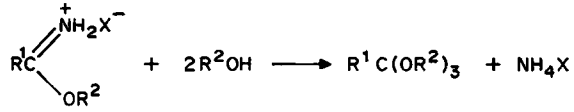
F. Action of Imidates with Hydrogen Sulphide and Hydrogen Selenide

Further examples of the preparation of thionesters[190] from imidates and of dithioesters from imidates[191] and thioimidates[192] by interaction with hydrogen sulphide have been published and an improved method[193,194] for the synthesis of selenoesters has been evolved.



G. Alcoholysis of Imidate Salts—Preparation of *Ortho* Esters

Studies on the alcoholysis of imidate salts to give *ortho* esters were reviewed extensively[1] and little new work has appeared, although the method has been used to prepare bicyclic bis-ortho esters[195].

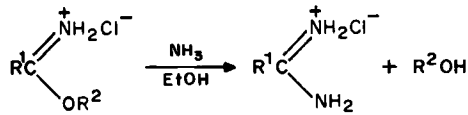


H. The Reaction of Imidates with Ammonia and its Derivatives

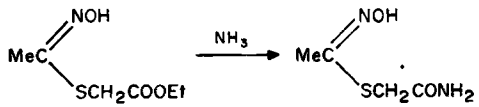
1. Reactions with ammonia

The reaction between imidates and ammonia (equation 12) to give amidines is well documented[1,196] with the mechanism of the reaction having been elucidated by Hand and Jencks[197], and the reader is referred to these earlier reviews.

Selective attack by ammonia[198] on the thioimidate (**96**) leads to amide (**97**) rather than amidine.



(12)

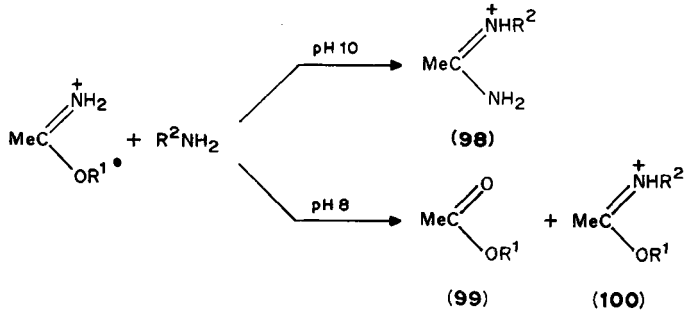


(**96**) (**97**)

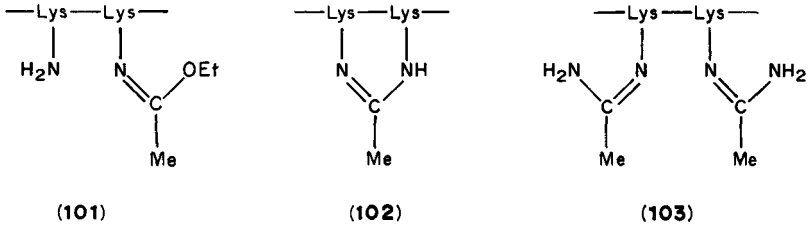
2. Reactions with primary amines

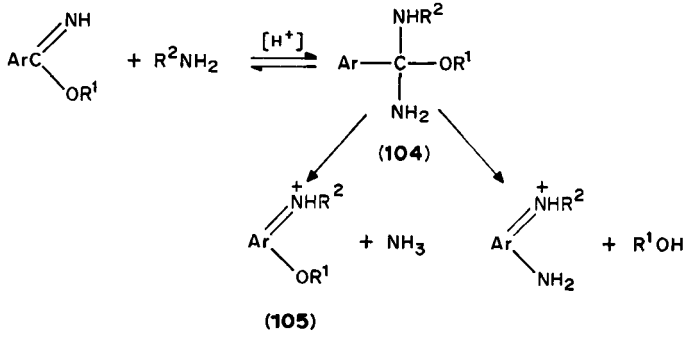
Due to the growing interest in the interaction of proteins and related smaller molecules with both mono- and di-imidates[1] (see also Section IV.H.7) the study of the mechanism of the interaction between primary amines and imidates has become of increasing importance. Hence Browne and Kent[199,200] studied the reaction of acetimidates with primary amines under conditions analogous to those used in protein condensations and found that amidines (**98**) were rapidly and cleanly formed at pH values of *ca* 19 whereas at lower pH (e.g. *ca* 8) competing reactions[201] gave rise to esters (**99**) and *N*-substituted imidates (**100**).

Studies on the amidination of acetimidates with horse liver alcohol dehydrogenase[200] (LADH) and cytochrome C[202] also suggest that yields of amidines are maximized at pH 10, e.g. LADH has 28 out of 30 lysine ε-amino groups per subunit modified at pH

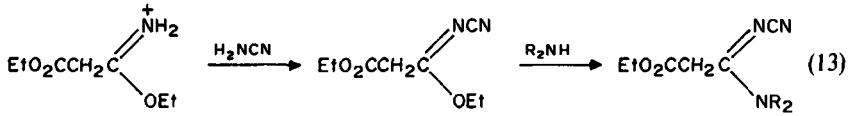


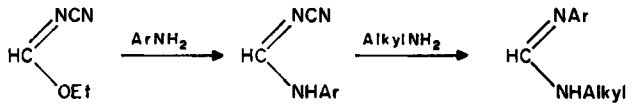
10 with overall retention of basic charge. It is very likely that some earlier work requires to be reassessed in the light of these findings as at lower pH values —Lys—Lys— subunits may form amidines of type **102** rather than of type **103** due to the initial formation of imidates of type **101**. Gilbert and Jencks[203], in a study of the aminolysis of alkyl benzimidates, have shown that at alkaline pH values formation of a tetrahedral intermediate **104** is rate determining, but at acidic pH values expulsion of alcohol from the same intermediate is rate determining and hence there is marked exchange of amine for ammonia to give product **105**.





Choice of appropriate conditions has led to the following reactions[66,204] (equations 13 and 14) and to the synthesis of pirbenicillin[205], and clavulanic acid derivatives[206] among other compounds potentially useful as drugs[207–209].



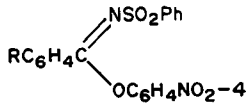


(14)

Despite the fact that thiols are better nucleophiles and also better leaving groups than the corresponding alcohols, thioimidates have found less use in amidine synthesis because, particularly with more basic amines, reversal with nitrile formation occurs although weakly basic amines react successfully to give amidines. Schnur[210] has found, however, that amidines can be formed in good yields by the action of an amine in an acetic acid/acetate buffer in $CHCl_3$ on a thioimidate salt at room temperature.

3. *Reactions with secondary amines*

N,N-Disubstituted amidines have been prepared from pyrrolidines[211] and piperidines[212] and Hammett relationships[213] have been derived for the action of Et_2NH on imidates of type **106**.



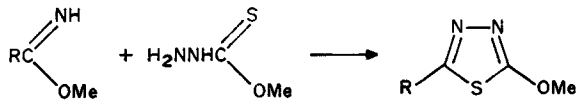
(106)

4. *Reaction with tertiary amines*

Tertiary amines may be used to prepare imidate bases from their salts[1].

5. *Reaction of Imidates with hydrazine and its derivatives*

The reactions of hydrazine and substituted hydrazines with imidates and thioimidates is well documented[1,214] and much recent work[215–219] has followed similar patterns (see also Section IV.I.10 relating to 1,2,4-triazoles). However, a series of *N*-sulphonylformamidrazones has been prepared to investigate their amide/hydrazone structures[220]. Other novel syntheses include the preparation of 1,2,4-thiadiazoles[221] (equation 15) and of the fused pyrazole system **107**[222]; see also Section IV.I.4.



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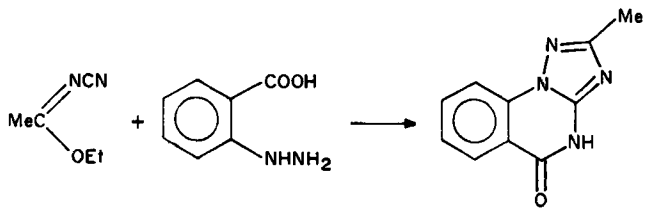
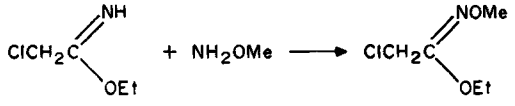


(107)

6. Reaction of imidates with hydroxylamines

The imino group of an imidate or thioimidate can be replaced by the oximino group of hydroxylamine[1]. Use has also recently been made of *O*-alkyl-hydroxylamines in synthesis[223,224] (equations 16 and 17). Compounds of type **108** have potential use as pesticides[225,226] and compounds of type **109** can reactivate pyrophosphate inhibited cholinesterase[227,228], but these imidates are often synthesized by other routes.



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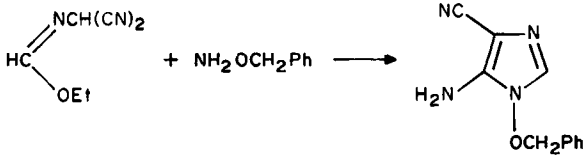

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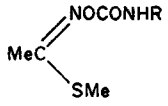

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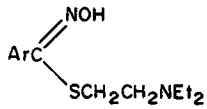
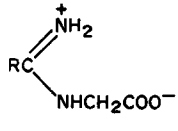


(109)

7. Reaction of imidates with α-amino acid derivatives including peptides and proteins

Depending on the reaction conditions, imidates react with α-amino acids and their simple derivatives[1] to form either imino-peptides (**110**), imidazolones (**111**) or *N*-substituted imidates (**112**). However, chiral oxazolines have been prepared by the condensation of imidates with β-hydroxy-α-amino-acid esters[229,230] and a series of polydipeptamidinium salts (**113**) has been obtained by the action of thioimidates on amidinopeptides[231].



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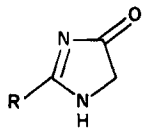

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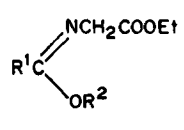

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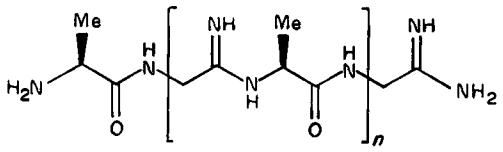
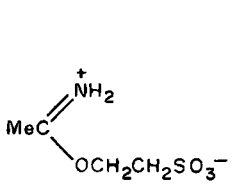


(113)

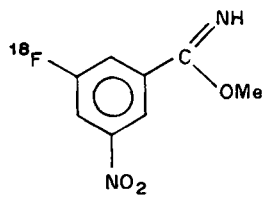
Imidates react with free amino groups, e.g. the ε-amino groups of lysine in peptides and proteins[1], and the new work that has appeared in this biological/biochemical area merits an up-to-date review of these aspects which lie outside this chemical review. As explained in Section IV.H.2, amidination of proteins with mono-imidates such as acetimidates is best carried out at *ca* pH 10 in order to retain overall basic charge of the protein by maximizing amidine formation (cf compound **103**). At lower pH values secondary products such as *N*-substituted imidates (**101**) and cyclic amidines (**102**) appear. The amidine moiety may be removed by the use of methylamine buffers of *ca* pH 11.4 without serious disruption of the protein[202].

Methyl thioacetimidate[232], ethyl bromoacetimidate[233], methyl [^3H]-acetimidate which has a higher specific radioactivity than methyl [^{14}C]-acetimidate[9] in addition to ethyl and methyl acetimidates have all been used in reactions with proteins[202,217,234–243]. Whereas ethyl and methyl acetimidates are reagents permeant to lipid biolayers[241], the related isothionyl acetimidate (**114**) is impermeant to such membranes[236,241,244,245].

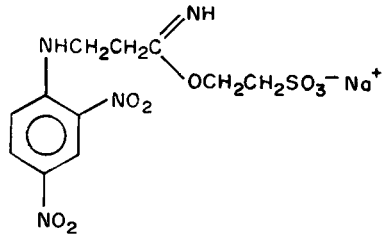
Crosslinking of proteins is also of biological interest and has been carried out using methyl 3-mercaptopropionimidate[246], methyl 4-mercaptobutyrimidate[239,246–249] and their dimeric analogues dimethyl 3,3′-dithiobispropionimidate[248,250–253] and 4,4′-dithiobisbutyrimidate[254]. Other work on crosslinking has utilized diethyl malondiimidate[238],



(**114**)



(**115**)



(**116**)

dimethyl adipimidate[238,250,255], dimethyl suberimidate[235,238,250,253,255,256] including a ^{14}C labelled form[254], among others[257].

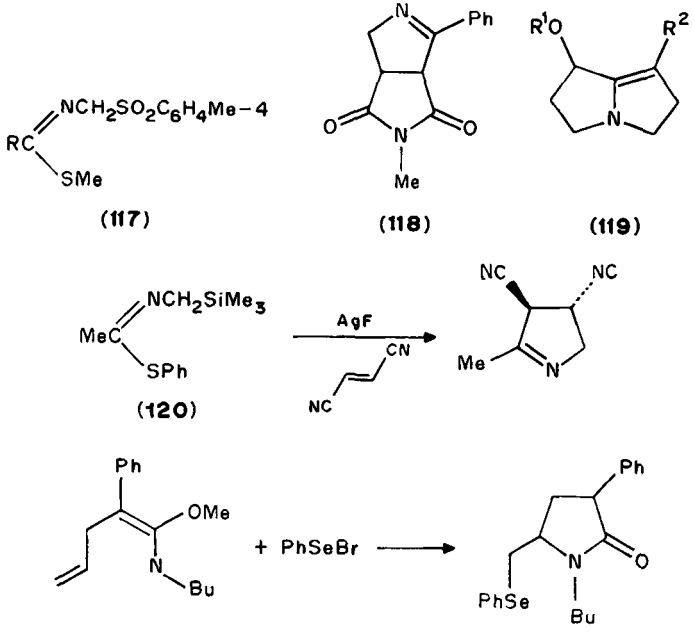
Several aromatic imidates[258] have also proved useful in protein coupling experiments, e.g. methyl 4-hydroxybenzimidate (Wood reagent)[239,259–264] allows incorporation of ^{125}I after condensation, e.g. with cell wall surface proteins. Methyl and ethyl 4-azidobenzimidates[16,265–268] are photoactivatable cross-linking agents. Other reagents include compounds **115** and **116**[18,75].

I. Preparation of Heterocyclic Compounds

1. Preparation of pyrroles and their reduced derivatives

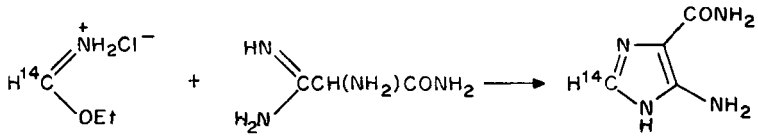
2,3,4-Trisubstituted pyrroles, which were otherwise difficult to obtain[269], have been synthesized by the condensation of electron-deficient alkenes with imidates of type **117** in base. Methylides prepared from thioimidates of type **120** also condense with alkenes but yield pyrrolidines[21,270], and related reactions[271,272] have led to the fused systems **118** and **119**.

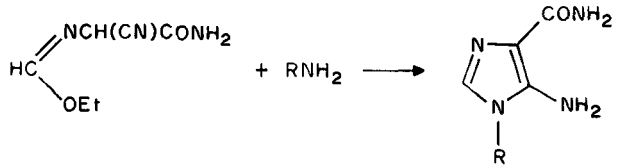
Pyrrolidine-2-ones are available from the cyclization reactions of γ-unsaturated imidates[273] and thioimidates[274], e.g. equation 18, and pyrrolidines from the condensation of *N*-acyl formimidate methylides and alkenes[105].

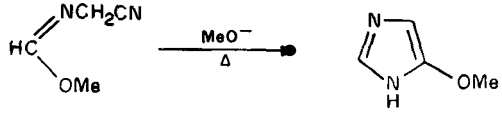


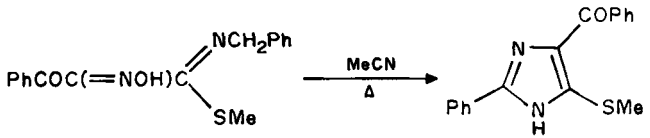
2. *Formation of imidazoles, imidazolines and benzimidazoles*

Much work on the synthesis of imidazoles via imidates has centred on obtaining the imidazoles with substituents suitable for further synthesis, e.g. of purines. Aminomalonic acid derivatives are useful in this respect, acting directly with imidates to give imidazoles[11,275,276] (equation 19) or by formation of *N*-substituted imidates which are subsequently cyclized with amines[223,277] (equation 20). Nucleosides have been derived in this way from amino-sugars[278] or sugar imidates[279]. Other suitably substituted imidates can also be cyclized to imidazoles[62,280,281] (equation 21 and 22).









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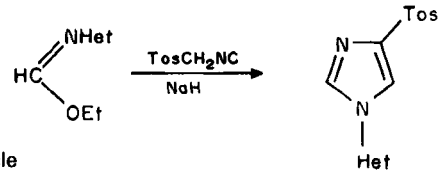


Het = heterocycle

(121)

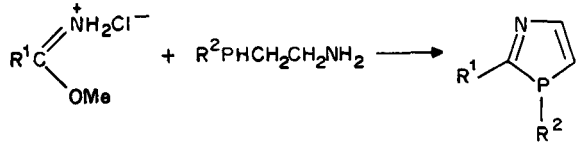
Other compounds prepared via imidates include the tosyl derivative[282] **121**, imidazolyl-4-methanols[283] and 2,2'-biimidazole[284] among others[285].

Imidazolines are available by the action of 1,2-diaminoalkanes on imidates or their derivatives[1,286] and use has been made of this reaction to prepare optically labile imidazolines for the asymmetric transformation of alanine[287].

Benzimidazoles arise from the condensation of imidates and 1,2-diaminobenzene[1,288] and 4,5,6-triaminopyridine has been used analogously[289].

3. *Formation of 1,3-azaphospholines and 1,3-benzazaphospholes*

1,3-Azaphospholines[290] and 1,3-benzazaphospholes[291,292] can be prepared by reactions 23 and 24, respectively.



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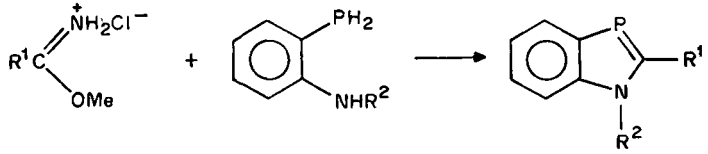
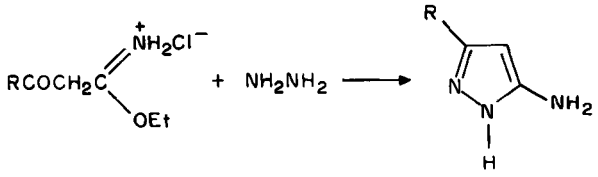


(24)

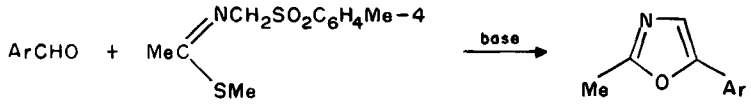
4. *Preparation of pyrazoles and their benzo derivatives*

Pyrazoles can be formed by the action of hydrazines on β-ketoimidates[293,294]. Thermolysis of 2-azidobenzimidate gives rise to 3-ethoxybenzopyrazole[4].

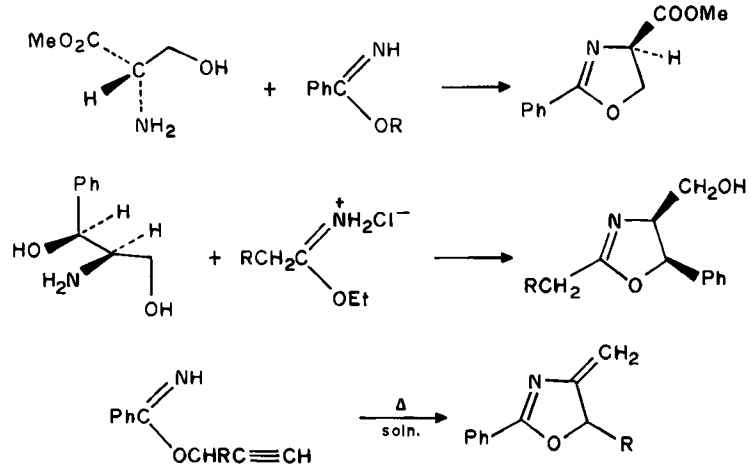


5. Preparation of oxazoles, benzoxazoles and their reduced derivatives

Oxazoles have previously been synthesized by the action of aryl aldehydes on dithiodiimidates[1] and 2,5-disubstituted oxazoles[295] have more recently been prepared by an adaptation of that reaction.



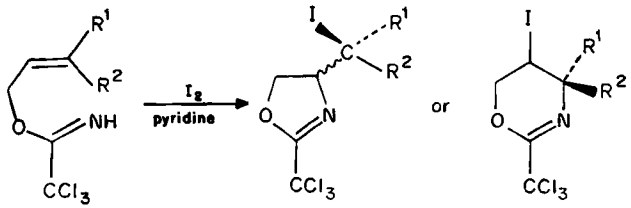
It has been found that ω-hydroxy-*N*-substituted amidines (and not, as previously suggested, *N*-substituted imidates[1]) are the intermediates in the formation of 2-oxazolines from the reaction between 1,2-aminoalcohols and imidates[296]. However, the recent main thrust of the work on oxazolines derived from imidates has been in the synthesis of chiral oxazolines capable of being exploited for asymmetric syntheses with much of this work coming from Meyers' group[47,229,297,298] among others[230,299]. For this purpose the imidates are condensed with optically active β-hydroxy-α-amino acid esters or their reduced derivatives, and then, e.g., the resultant oxazolines are subjected to lithiation and alkylation. Other syntheses of oxazolines include the formation of 4-methyleneoxazolines[300] from imidates of type **122** and the use of oxazolines in the preparation of the antibiotic (*S*)-3-fluoroalanine-2-d[301], the siderophore agrobactin[302] and a chiral peptide analogue[303].



(122)

Cyclization reactions of *O*-allyl trichloroacetimidates in the presence of iodine/pyridine or *N*-iodosuccinimide in chloroform have been shown to give 4,5-dihydrooxazoles (**123**) by 5-exo ring closure[304] of *Z*-allyl imidates[305–307] whereas the *E*-allyl analogues give 6-endo ring closure[304] with resultant formation of 4,5-dihydro-1,3-oxazines (**124**) (*E* and *Z* here refer to the allylic group stereochemistry and not to that of the imidate). Use has been made of this reaction in the synthesis of daunosamine[308].

α-Hydroxyimidate bases react with oxalyl chloride to yield oxazolidine-2,4-diones and, as their salts, with *N*,*N*-dicyclohexylcarbodiimide to form 2-cyclohexyliminoxazolidin-4-ones[309].

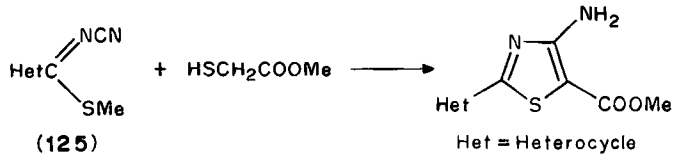


(123) (124)

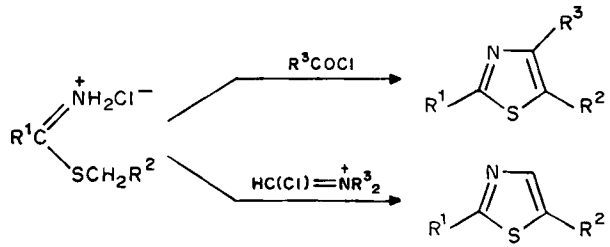
Benzoxazoles, including the anti-inflammatory drug Benoxaprofen[310], are made by reacting imidates with *o*-aminophenols[1].

6. *Preparation of thiazoles and benzothiazoles*

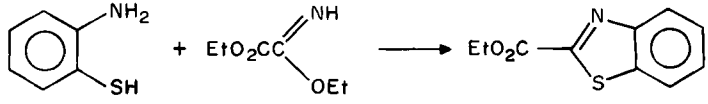
Thiazoles have been derived from the action of *β*-mercapto esters or amides[311] on thioimidates of type **125** and also from the action of acyl chlorides or imino chlorides on thioimidates[312].



(125) Het = Heterocycle



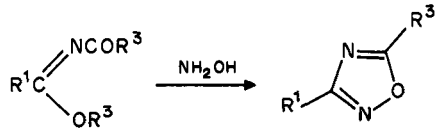
2-Carboethoxybenzothiazole (**127**) is the major product[313] of the reaction of *o*-aminothiophenol and imidate **126**.



(126) (127)

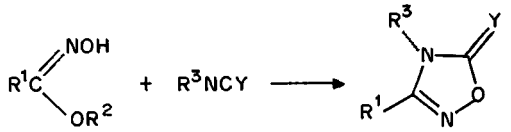
7. *Preparation of oxadiazoles*

1,2,4-Oxadiazoles[1] (**128**) are found as products in the reaction between hydroxylamine and *N*-acylimidates[314] and are also reported to be formed by the action of imidates on amidoximes[315]. Nitrile oxides also yield 3,5-disubstituted-1,2,4-oxadiazoles by reaction



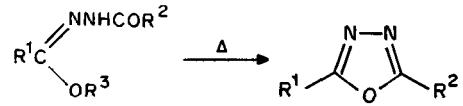
(128)

with imidates[316] and *N*-hydroxyimidates react with isocyanates or isothiocyanates (**129**; Y = O or S) to form 1,2,4-oxadiazol-5-ones or -thiones[317].



(129)

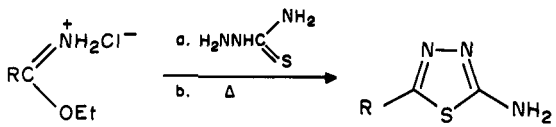
1,3,4-Oxadiazoles[1,59] are obtained by cyclization of imidates of type **130**.



(130)

8. Preparation of thiadiazoles and dithiazoles

Further examples[221,318] of 1,3,4-thiadiazoles derived from imidates[1] have been reported and 2-amino-1,3,4-thiadiazoles[319] have been isolated from the cyclization reaction 25. The fused system **132** arises by the action of P_2S_5 on the thioimidate **131**[320].



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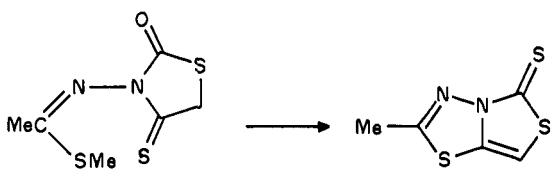
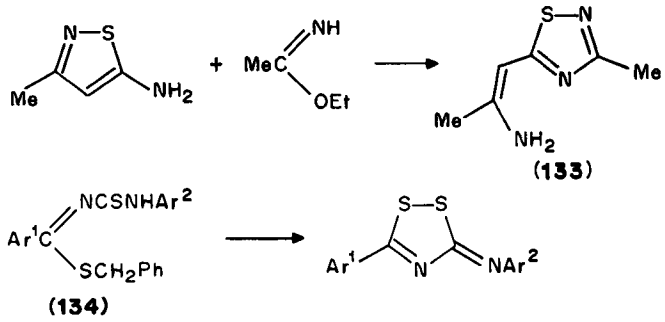


(131) (132)

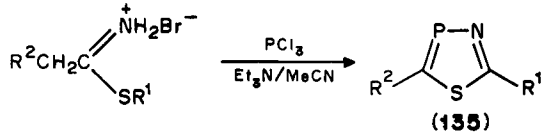
The 1,2,4-thiadiazole[321] **133** has been prepared by reaction 26 and 3-arylimino-1,2,4-dithiazoles are prepared by the reaction of bromine in chloroform on thioimidates of type **134**[322,323].



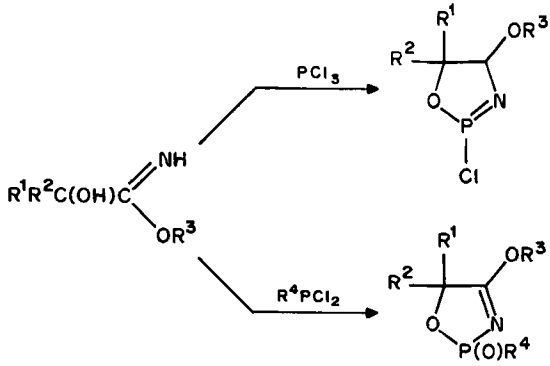
(26)

9. Preparation of 1,3,4-thiazaphospholes, 1,3,2-oxazaphospholines and related species

1,3,4-Thiazaphospholes (**135**) have been prepared from thioimidates. The reaction is believed to proceed via a four-membered cyclic intermediate[324].

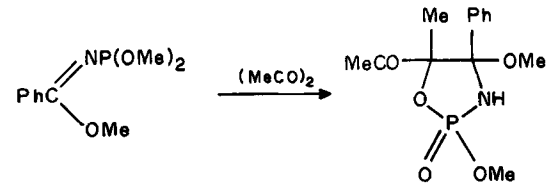


α-Hydroxyimidates react with phosphorus trichloride to give 1,3,2-oxazaphospholines[325] (equation 27) and with phosphorus dichlorides to give related compounds containing pentavalent phosphorus[326] (equation 28). Biacetyl has also found use in the preparation of oxazaphospholidines[327] (equation 29) and cyclic phosphates[328] arise from the condensation of $MeOP(O)F_2$ and *N,O*-bistrimethylsilylfluoroacetamide.



(27)

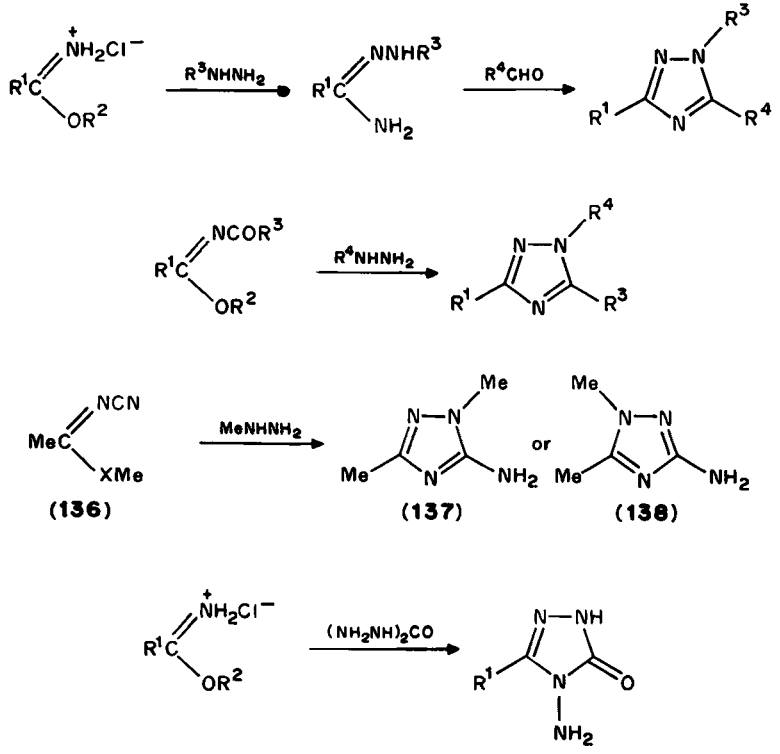
(28)



(29)

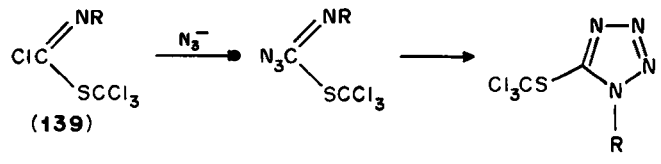
10. Preparation of 1,2,4-triazoles

1,2,4-Triazoles are often synthesized from imidates via amidrazone intermediates which may or may not be isolated[1,145,214,329–332] but are also available from the action of hydrazines on *N*-acyl imidates[1,314,333,334] and *N*-cyanoimidates[335,336]. In this latter case[336] there is high selectivity with compound **136** (X = O) yielding the 5-aminotriazole **137** whereas the thioimidate **136** (X = S) yielded the 3-amino derivative **138**. 1,2,4-Triazolin-5-ones[332,337] have been prepared by related reactions and fused systems involving the triazole ring formed from imidates include 1,2,4-triazolo[4,3-*a*]-pyrazines[338], pyrazolo[1,5-*b*]-1,2,4-triazoles[339] and 1,2,4-triazolo[1,5-*a*]-pyrimidines[340,341].

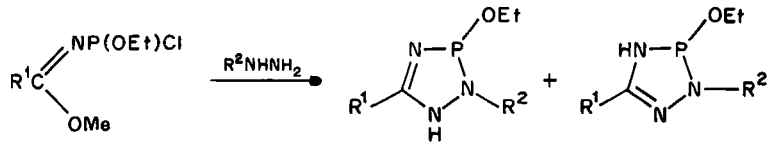


11. Preparation of tetrazoles and triazaphospholes

Tetrazoles can be synthesized from imidates via amidrazone intermediates[1,214] or directly using hydrazoic acid[1] or, in the case of imidate **139**, azide anion[342].



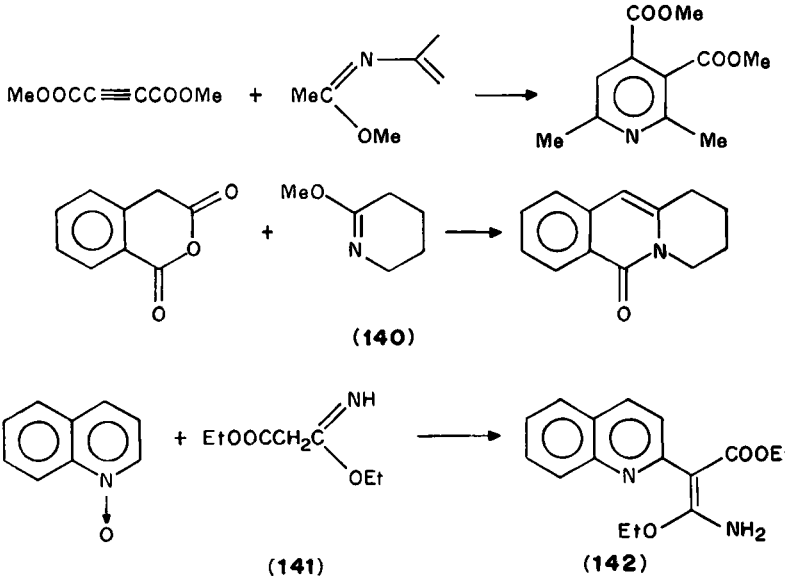
Closely related 1,2,4,3-triazaphospholes[343] are available via reaction 30.



(30)

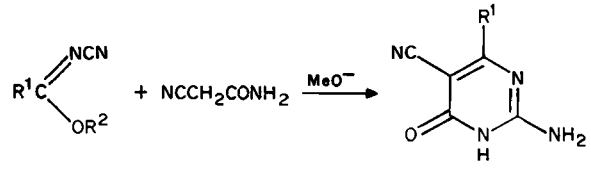
12. Preparation of azines

a. Pyridines and their fused derivatives. Aue and Thomas[118,344] have condensed acetylenedicarboxylic acid esters with imidates to yield pyridines. However, the main thrust of work in this area has been in the preparation of isoquinolines[345] and related fused systems[346,347] from imidates including cyclic imidates (**140**) and homophthalic anhydride and of quinolines[348–350] from suitably *N*-substituted imidates. Quinoline or isoquinoline *N*-oxides[351] condense with imidates of type **141** to produce substituted ethylenes (**142**).



Intramolecular amidoselenation of *N*-alkenyl imidates yields piperidines[352].

b. Pyrimidines and their fused systems. This biologically important class of compounds has been extensively synthesized from imidates either directly or via amidine derivatives[1]. Recently pyrimidines[353] and their derivatives have been synthesized by the action of *N*-cyano-imidates[354] usually with malonic acid derivatives[355–358] (equation 31) and from



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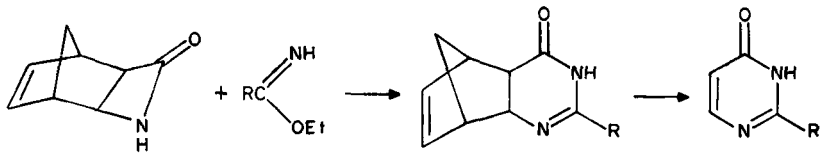
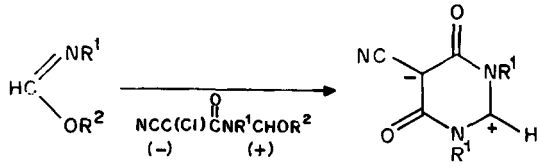


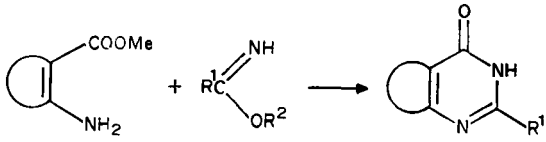
(32)

imidate/lactam condensations[359,360] (equation 32). Mesoionic species (**143**) have been derived by the action of 1,4-dipolar zwitterions on imidates[361].



(143)

Two main routes lead to pyrimidines which are part of fused systems: (a) intermolecular condensation of an imidate with a ring compound having adjacent amino and carboxylic acid groups and (b) intramolecular condensation of a carboxylic acid derivative with an adjacent imidate group normally formed by the action of an ortho ester on the amino function (equations 33 and 34). In this latter case (equation 34) the product can depend on the nature and molecular ratio of the ortho ester to hydrazide[362–364]. The reactions 33 and 34 are highly versatile and, in addition to quinazolin-4-ones[313,362–366] and their saturated derivatives[367–369], pyrimidine nuclei fused to furan[370], benzofuran[371], oxazole[372], isoquinoline[373], thiazole[374,375], indole[376], 1,2,4-triazole[222], 1,4-thiazine[377], as well as imidazole[372,378,379] rings have been prepared. Fused systems have also been generated from the action of ketenes[380] and aryl isocyanates[381] on imidates.



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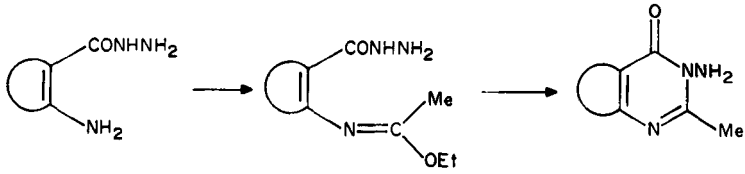
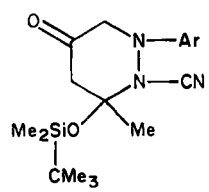


(34)

c. Pyridazines. Diels–Alder addition of compounds of type ArN=NCN with *N*-unsaturated imidates acting as dienes[382] yields compounds of type **144**, and there is a report that methyl *N*-allylacetimidate yields a 4-aminopyridazine by Diels–Alder addition to a 1,2,4,5-tetrazine[383], but see also Section IV.I.12.f.

d. 1,2,4-Triazines. 1,2,4-Triazines (**145**) are available from Diels–Alder condensation reactions of imidates or thioimidates and *s*-tetrazines acting as dienes[1,384] (but see also the

section above), and from the interaction of α-keto acid hydrazones and imidates[385], e.g. compound **146**, but these compounds are more usually obtained from amidrazones with 1,2-diketo compounds[1,214].



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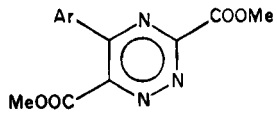

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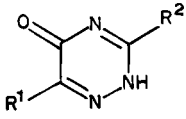
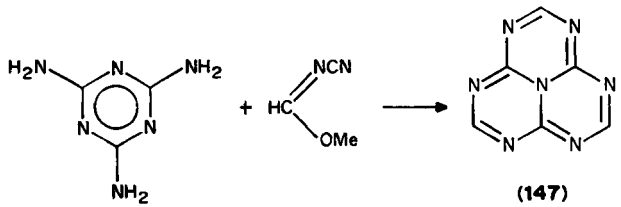


(146)

e. 1,3,5-Triazines and their derivatives. Further examples of both symmetrically[386,387] and unsymmetrically substituted[388,389] 1,3,5-triazines arising from imidate trimerization reactions have been noted since the earlier review[1]. However, many interesting triazines including the fused systems 5-azaadenine[390], pyrazolo- and 1,2,3-triazolo[1,5-*a*] triazines[391,392] and azacycl[3,3,3]azines[393,394] (**147**) among others[395,396] have been derived from the action of *N*-cyanoimidates on amidines[1,397] including cyclic amidines or cyanamide[398]. Exceptionally under these conditions 5-amino-1*H*-tetrazole gives 2-amino-4-azido-1,3,5-triazine rather than a fused cyclic product[399].



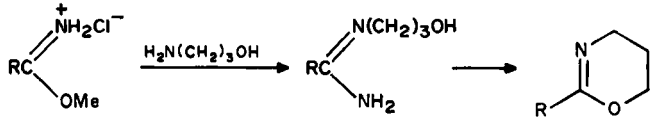
(147)

1,3,5-Triazin-2,4-diones can arise from the interaction of imidates and isocyanates[400,401].

f. 1,2,4,5-Tetrazines. Symmetrically[1,402,403] and unsymmetrically[1,28] 3,6-disubstituted-1,2,4,5-tetrazines are formed in the reaction of hydrazine, usually as its hydrate on imidates or imidate/amidine mixtures.

13. Preparation of 1,3- and 1,4-oxazines

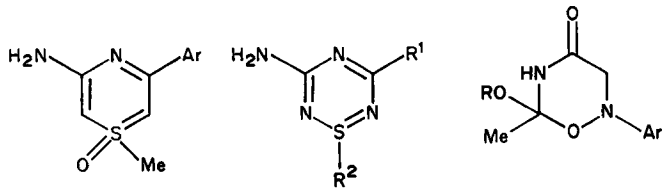
Amidines have been recognised as the intermediates[296,404] in the condensation of imidates and propanolamines to give dihydro-1,3-oxazines[368,405,406]. Related compounds are available from the treatment of allyl trichloroacetimidates with *N*-iodosuccinimide[306,307] (see Section IV.I.5) and 2*H*-1,3-oxazin-2-ones and thiones[407] from the action of phosgene or thiophosgene on 2-hydroxybenzimidates.



Morpholine-2,3,5-triones result from the interaction of oxalyl chloride and α-hydroxyimidate salts, the free imidates yielding oxazolidine-2,4-diones[309].

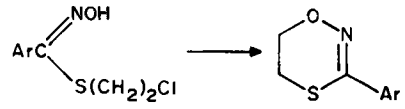
14. Preparation of other six-membered heterocyclic systems

Compounds of types **148** and **149** have been prepared from *N*-cyanoimidates and the appropriate sulphur compounds[408,409], the oxadiazin-4-one **150** from arylnitroso species



(148) **(149)** **(150)**

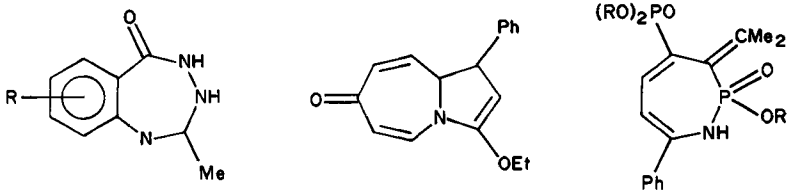
and imidates[382], and 1,4,2-oxathiazines by ring closure[410] of thioimidates of type **151**.



(151)

15. Preparation of azepines and azaphosphenins

The synthesis of azepines and their fused derivatives has been reviewed[1,411,412]. 2-Aminobenzoic acid hydrazides with ortho esters can yield triazepines **152** but more usually give quinazolin-4-ones[362–364], and the azepine **153** has been isolated from the intramolecular cyclization of ethyl *N*-2-methoxyphenylphenylpropiolimidate[413].

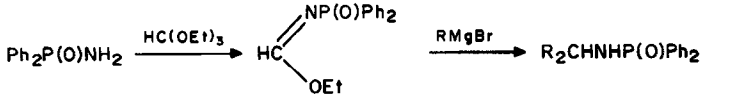


(152) **(153)** **(154)**

The azaphosphenin **154** has been synthesized[414] via the intermediacy of the imidate $PhC(OEt)=NP(OR)_2$.

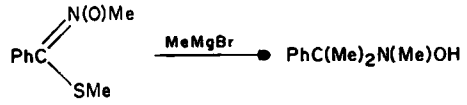
J. Reaction of Imidates with Grignard Reagents and Metal Alkyls

Primary amines are available from both sulphonamides[1] and phosphorus amides[63] via imidate intermediates (equation 35).



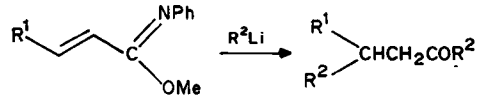
(35)

Thioimidate *N*-oxides (**155**) react with alkyl Grignard reagents[125] to yield substituted hydroxylamines (**156**).

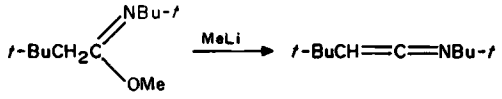


(**155**) (**156**)

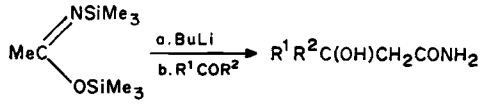
Both Grignard and alkyl lithium reagents react with imidate **157**, the latter reagent yielding ketones[415]. Keteneimines[416] are synthesized by the action of methyl lithium on imidate **158** and imidate **159** can be converted into β-hydroxy acid amides[417] via reaction sequence 36.



(**157**)

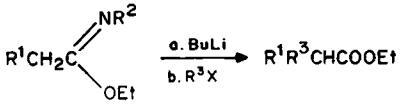


(**158**)

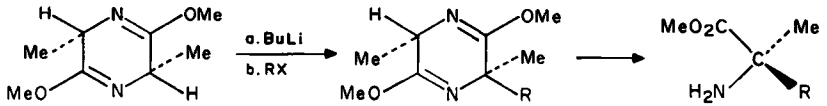


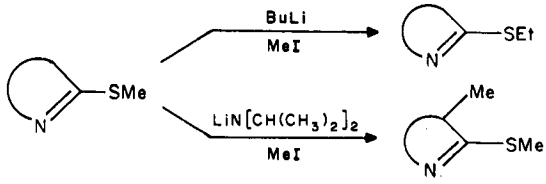
(**159**) (36)

In recent times imidates have proved to be useful intermediates in asymmetric syntheses[48,418–420]. The products, often obtained in high enantiomeric excess, include carboxylic acid esters[420] and non-proteinogenic α-amino acid esters[48,418] among others[419]. Reaction 37a illustrates the kinetic product of alkylation of a cyclic thioimidate and reaction 37b the thermodynamic product of the reaction[123]. Related sulphenylation reactions have been studied[421].



(R^2 chiral)





(37a)

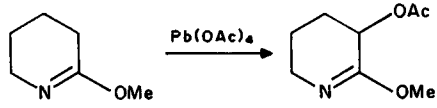
(37b)

K. Oxidation and Reduction of Imidates

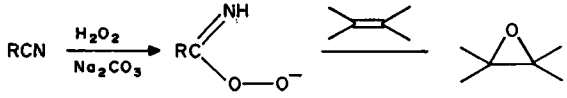
1. Oxidation

Alkoxyoxiridines and hydroxylamine derivatives by subsequent hydrolysis[422] are the normal products of oxidation of *N*-substituted imidates with peracids[1,130], but nitroso dimers have also been identified[423].

Lead tetraacetate oxidizes both *N*-substituted imidates and cyclic imidates at the α-position[423].



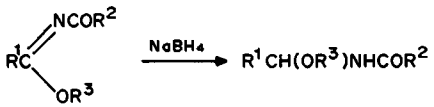
Perimidic acid salts (**160**) have themselves proved to be useful oxidizing agents[424–426] yielding oxiranes with alkenes.



(160)

2. Reduction

Imidates are reduced to amines[1,427–429] by sodium borohydride or cyanoborohydride, although yields tend to be lower with this latter reagent[428]. *N*-Acylimidates similarly yield *N*-(α-alkoxyalkyl)amides[163,430,431].



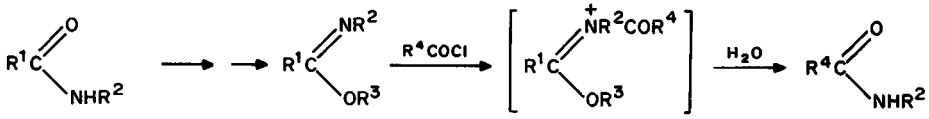
Hydrogen over palladium reduces the nitro group of ethyl 2-hydroxy-4-nitrobenzimidate but appears to be without effect on the imidate moiety[6].

L. *N*-Acyl and *N*-Sulphonyl Imidates

Improved methods[432,433] have been developed for the acylation of imidates[1] but *N*-acyl imidates may also be prepared directly[434,435] as shown in equation 38. A hindered base, e.g. 2,4,6-trimethylpyridine, has been found useful in the condensation of imidates and methyl chloroformate[436] to give *N*-carbomethoxyimidates.

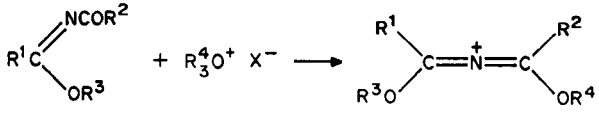
(38)

Transacylation reactions have also been studied—reaction sequence 39—and such reactions have proved useful for exchanging the substitution pattern of the lactam ring of penicillins and cephalosporins[437,438].



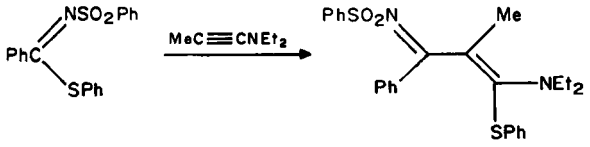
(39)

1,3-Dialkoxy-2-azapropenylium salts (**161**) have been derived from *N*-acyl imidates[439] which can also be useful intermediates in the synthesis of a wide range of heterocyclic compounds such as oxadiazoles[314], pyrrolidines[105], thiazoles[312] and 1,2,4-triazoles[314,333,334] and the reader is referred to the appropriate sections of this review.



(161)

N-Sulphonyl-1-azabuta-1,3-dienes (**162**) have been prepared from *N*-sulphonyl imidates and alkynes[440] or alkenes[441], and the aminating agent (**164**), useful in preparing aziridines from alkenes[442], is available from *N*-hydroxyimidates (**163**).



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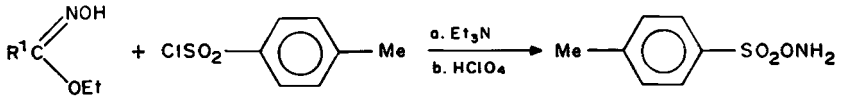
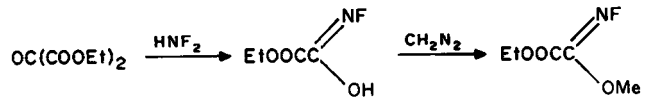


(163) (164)

M. Reactions of *N*-Halo Imidates

Little new work has been oberved in this area[1] but the *N*-fluoroimidate **165** has been prepared[443] and *N*-chloroimidates give products of type **166** on reaction with sulphur[444].



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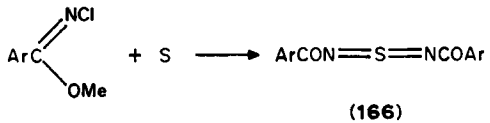
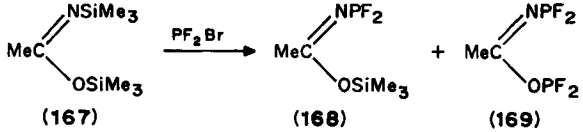


(166)

N. Phosphorus Derivatives of Imidates

Imidate **167** reacts with bromodifluorophosphine at −80 °C to yield the imidate **168** or subsequently the product **169** with excess reagent[445] and imidates of type $Ph_3P^+N{=}CRSMe$ arise from the alkylation[446] of $Ph_3P(SCN)_2$. Todd–Atherton phosphorylation[447] of imidates gives high yields of product **170** and Wittig reactions have been used to prepare α,β-unsaturated imidates[75,448,449] as well as alkenes[450] from cyclic imidates of type **4**.



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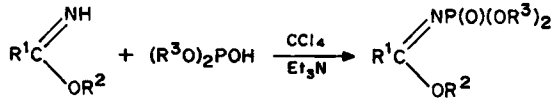
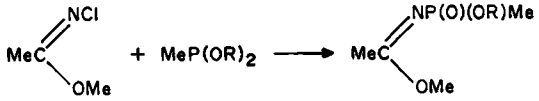
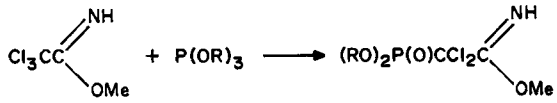
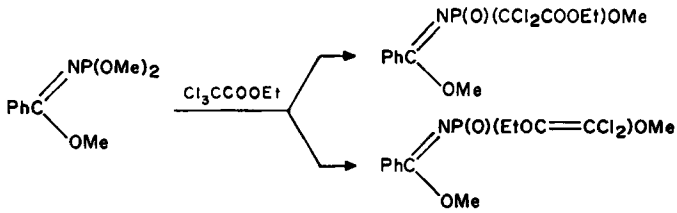


(170)

Imidates having replaceable halogen atoms react with phosphorus compounds to yield a variety of products[451,452] and imidates with *N*-phosphorus groups[453,454] undergo Arbuzov and Perkov type reactions[455].







The *E*/*Z* forms of $PhC(OEt){=}NP(O)(OMe)_2$ have been separated chromatographically[141] and pK_a values have been measured[456] for imidates of type $R^1R^2P(O)XC(=NH)OEt$ where R^1,R^2 = alkyl or alkoxy and X = CH_2, OCH_2 and CH_2CH_2.

Thioimidates are normally made by alkylation of the appropriate *N*-phosphorus thioamide[1], e.g. with monochloroacetic acid derivatives[457].

Heterocyclic systems containing phosphorus atoms in the ring[458] are described in the main in Sections IV.I.3, IV.I.9 and IV.I.11.

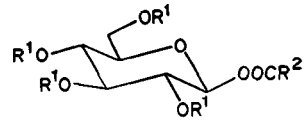
O. Trichloroacetimidates

The preparation of trichloroacetimidates (**8**,**11**,**12**), a series of highly versatile reagents, is discussed in Section III.B.

O-Allyl trichloroacetimidates undergo ring closure reactions to yield 4,5-dihydrooxazoles or 4,5-dihydro-1,3-oxazines[158,304–308,459–461] (see Section IV.I.5) and allylic and propargyllic trichloroacetimidates are subject to thermal rearrangement[23,152–162] (see Section IV.D.1).

In addition, the imidates **8** are useful alkylating agents, e.g. compound **8** (R = CH_2Ph) acts as a benzylating agent towards both primary and secondary hydroxy groups under mild conditions which do not normally upset other acid or base sensitive protecting groups[462–466]. Moreover, imidate **8** (R = *t*-Bu) offers a convenient route to *t*-butyl esters and ethers which are otherwise difficult to synthesize[26]. With chiral substrates no racemization has been observed[465].

Trichloroacetimidate derivatives of sugars[24,35,36], e.g. compounds **11** and **12**, are useful intermediates undergoing attack by a wide range of O-, S-, N- and C-nucleophiles to give good yields of products with high degrees of anomeric specificity which are not often found in other methods of synthesis. The reader is referred to Reference 24 and references cited therein for detailed discussion. Acids, such as carboxylic acids[35,467], hydrazoic acid[467] and dibenzylphosphate[468], react directly with the α-anomer **11** to yield the β-products **171a,b,c** respectively. Nucleophiles other than acids, e.g. thiols[36], alcohols[26,462–467], sugars (see below) or some heterocycles[469], require the presence of an acid catalyst such as boron trifluoride etherate[24,35] for reaction. Carbon nucleophiles[470] based on silyl enol ethers, allyl trimethylsilanes or trimethylsilyl cyanide react to form *C*-glycosides, e.g. compound **172** and electron-rich heterocycles[469] such as furans give product **173**.



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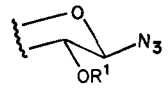
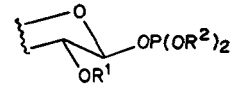
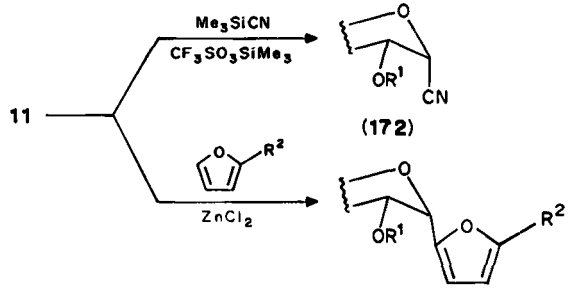


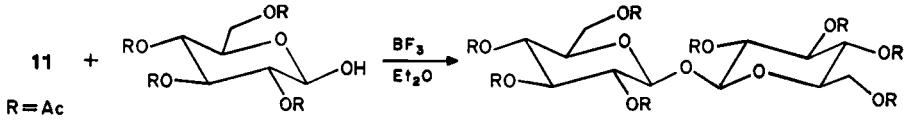
(171b)



(171c)



O-Glycosyl trichloroacetimidates have also found wide application in the linking of carbohydrates to give di-, tri- and tetra-saccharides[24], the method being superior to the older Koenigs–Knorr synthesis in terms of both yield and stereochemistry. The stereochemical outcome of the reaction depends on the nature of the protecting groups. Thus perbenzylated (non-participating) α-trichloroacetimidate of D-glucose (**11**; R = CH_2Ph) reacts with inversion at the anomeric site in the presence of boron trifluoride etherate as catalyst to give β-glycosides whereas its peracetylated counterpart (**11**, R = CH_3CO) reacts with neighbouring group participation. Stronger catalysts such as trimethylsilyl triflate yield the α-glycoside which is thermodynamically more stable[24]. The method involving neighbouring group participation[471] is illustrated by the synthesis of the β,β-linked trehalose **174**.



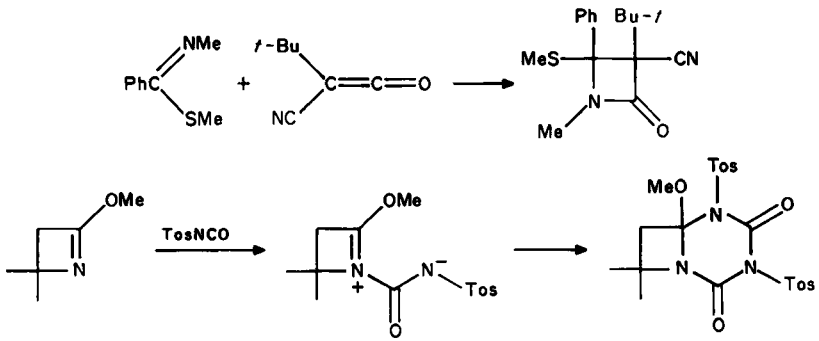
Examples of the application of trichloroacetimidates in the synthesis of pharmacologically and biologically important species include the synthesis of a glucuronide of the antidepressant mianserin[472], glucosides of digitoxigenin[473] and of dipalmitin[474], further examples being found in reviews by Schmidt[24] and Williams[475].

Trichloroacetimidates have also proved to be useful intermediates in the synthesis of D-*erythro*-sphingosine[476], isoxazolines of antitumour interest[32,160] and amino sugars[159,459,460].

P. Miscellaneous Reactions of Imidates

1. 1,4-Dipolar addition reactions

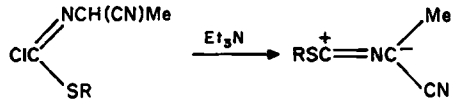
Imidates and thioimidates[477–481] undergo cycloaddition reactions with ketenes and related compounds and the reaction has been extensively studied by Aue and Thomas[344,400,482] among others[478] who extended the work by the introduction of cyclic imidates showing the mechanism to involve 1,4-dipolar cycloaddition pathways by isolation of an intermediate **175** in one case[400]. However, not all imidates react in this way[483].



(175)

2. Imidate and thioimidate methylides

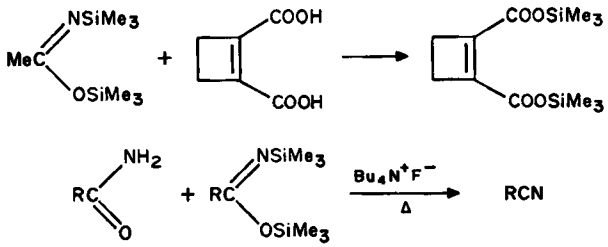
Imidate methylides based on imidates of type **120** have been discussed in Section IV.I.1 dealing with pyrrole and pyrrolidine syntheses[21,105–108,269–272] and use of these and related 1,3-dipoles (**176**) has been extended to give 4*H*-imidazoles[484] by interaction with EtOOCCN and oxazoles by addition to ketones[485].



(176)

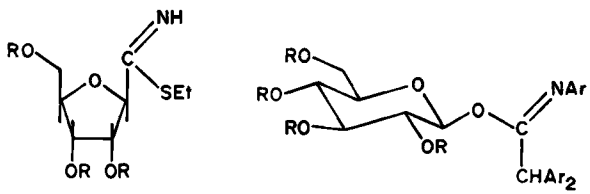
3. Silylation via imidates

N,O-Disilylamides (**15**) are useful silylating agents forming both silyl ethers and esters[54,55,486–488]. In addition, thermal decomposition of *N,O*-disilyl compounds yields nitriles opening up a convenient route from amides to nitriles[56].



4. Sugar imidates

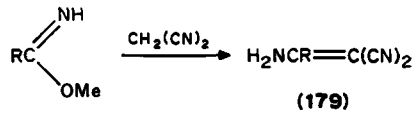
The chemistry of imidates derived from sugars in which the saccharide acts as an alcohol (e.g. compounds **11** and **12**) is extensively reviewed in Section III.B. However, sugar derivatives in which the saccharide is attached to the carbon atom of the imidate or thioimidate moiety (**177**) are also known and have been used in the main to prepare nucleosides[279,489–492]. The imidate **178** has also been synthesized[469] and found to undergo attack by electron-rich heterocycles to form derivatives such as compound **173**. Sugar amidines derived from imido-lactones have also been noted in a study of the cyanohydrin synthesis of sugars[493].



(177) R=CH_2Ph **(178)**

5. Sundry reactions of imidates

β-Enaminoesters[494] and enaminodinitriles[495] (**179**) have been derived from imidates as have *N*-(alkylamino)alkyl, alkyl and aryl ketones[496] (**180**), unsaturated aldehydes[497] and α-hydroxy-amines[498].



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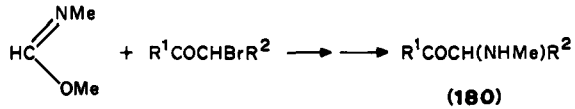
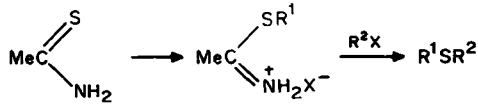
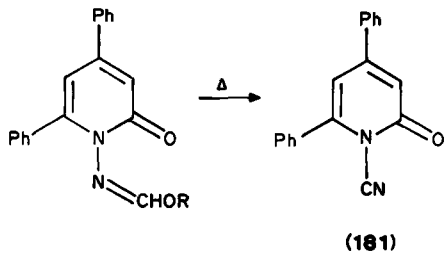


(180)

Use of liquid–liquid phase transfer catalysts permits the synthesis of unsymmetrical sulphides without recourse to odoriferous thiols[499].



Other reactions include the synthesis of DL-canaline[500] [$H_2NOCH_2CH_2CH(NH_2)$-COOH] by the addition of acrolein to the imidate MeC(=NOH)OEt, the formation[501] of the *N*-cyanopyridone **181** and the addition of $TeCl_4$ to allylic imidates[502].



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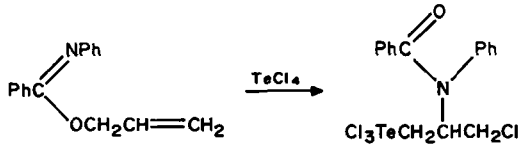
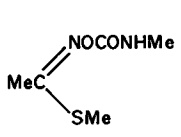


Q. Uses of Imidates

Imidates have found extensive use in modifying and cross-linking peptides and proteins and this important area of biological chemistry is reviewed in Section IV.H.7.

However, the study of the industrial potential of imidates has increased enormously in recent years and many hundreds of references are to be found in *Chemical Abstracts*, particularly in relation to plant and food protection products, and this subject area would merit a review of its own. Pesticides, bactericides and fungicides[40] are often based on *N*-hydroxythioimidates[198,224,226–228,503], e.g. methomyl (**182**), thiodical (**183**) and oxamyl (**184**), although other systems (**185** and **186**) have also been studied[504–506].



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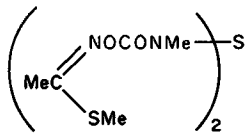

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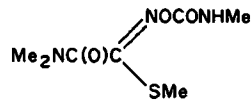

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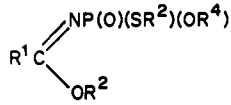

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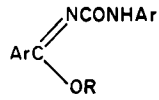

(186)

Other uses include imidates as stabilizing agents[507] for CH_3CCl_3.

V. ACKNOWLEDGEMENTS

The author gratefully acknowledges useful comments and help from Dr. Daniel Hunter in preparing the manuscript and from Mrs. D. G. Neilson in collating references.

VI. REFERENCES

1. D. G. Neilson, in *The Chemistry of Amidines and Imidates* (*The Chemistry of The Functional Groups*) (Ed. S. Patai), Wiley–Interscience, London, 1975, pp. 387–489.
2. H. Böhme and H. G. Viehe, *Iminium Salts in Organic Chemistry* (*Advances in Organic Chemistry, Methods and Results*, Vol. 9, Pt. 2), Interscience, New York, 1979.
3. D. Hunter and D. G. Neilson, unpublished results.
4. A. A. Manoucher, R. K. Smalley and R. H. Smith, *J. Chem. Soc., Perkin Trans., 1*, 2501 (1983).
5. W. D. Guither, M. D. Coburn and R. N. Castle, *Heterocycles*, **12**, 745 (1979).
6. R. J. Bergeron, J. B. Dionis and M. J. Ingeno, *J. Org. Chem.*, **52**, 144 (1987).
7. A. N. Mandal, S. R. Raychaudhuri and A. Chatterjee, *Synthesis*, 727 (1983).
8. M. T. H. Liu, N. H. Chrishti, C. D. Burkholder, W. E. Jones and J. S. Wasson, *J. Org. Chem.*, **45**, 4515 (1980).
9. J. Armstrong, P. F. Leadlay and R. N. Perham, *Anal. Biochem.*, **109**, 410 (1980).
10. T. Y. Toribara, *Int. J. Appl. Radiat. Isot.*, **29**, 597 (1978); *Chem. Abstr.*, **90**, 83190 (1979).
11. E. Koltai, D. Banfi, I. Szatmari, M. Hornyak-Hamori, J. Schawartz and T. Szuts, *J. Labelled Compd. Radiopharm.*, **16**, 777 (1979); *Chem. Abstr.*, **92**, 181078 (1980).
12. D. W. Repke and J. E. Zull, *J. Biol. Chem.*, **247**, 2189 (1972).
13. D. L. Bates, R. W. Perham and J. R. Coggins, *Anal. Biochem.*, **68**, 175 (1975).
14. W. C. Mentzer, G. K. H. Lam, B. H. Lubin, A. Greenquist, S. L. Schrier and W. Lande, *J. Supramol. Struct.*, **9**, 275 (1978); *Chem. Abstr.*, **91**, 155545 (1979).
15. W. Stoffel and K. Preissner, *Hoppe-Seyler's Z. Physiol. Chem.*, **360**, 691 (1979).
16. G. Klein, M. Satre, A. C. Dianoux and P. V. Vignais, *Biochemistry*, **20**, 1339 (1981).
17. S. Nishimura and H. Akimoto, European Patent Appl., EP **75**, 881 (1983); *Chem. Abstr.*, **99**, 70481 (1983).
18. J. B. Denny and R. M. Roberts, *J. Biol. Chem.*, **257**, 2460 (1982).
19. B. L. Booth, K. O. Jibodu and M. F. Proenca, *J. Chem. Soc, Chem. Commun.*, 1151 (1980).
20. B. L. Booth, K. O. Jibodu, M. Fernanda and J. R. P. Proenca, *J. chem. Soc., Perkin Trans, 1*, 1067 (1983).
21. N. J. Turro, Y. Cha, I. R. Gould, A. Padwa, J. R. Gasdaska and M. Thomas, *J. Org. Chem.*, **50**, 4415 (1985).
22. J. L. Fry and R. A. Ott, *J. Org. Chem.*, **46**, 3333 (1981).
23. L. E. Overman, *Acc. Chem. Res*, 218 (1980).

24. R. R. Schmidt, *Angew. Chem., Int. Ed. Engl.*, **25**, 212 (1986).
25. L. E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976).
26. A. Armstrong, I. Brackenridge, R. F. W. Jackson and J. M. Kirk, *Tetrahedron Lett.*, **29**, 2483 (1988).
27. H. Watanabe, Y. Kigeegawa and S. Yamada, *Chem. Pharm. Bull.*, **21**, 465 (1973).
28. S. A. Lang, Jr., B. D. Johnson and E. Cohen, *J. Heterocycl. Chem.*, **12**, 1143 (1975).
29. H. Moeller, H. Bellinger and G. Koppensteiner, German Patent, 2,024,052 (1971); *Chem. Abstr.*, **76**, 72506 (1972).
30. A. J. Floyd, R. G. Kinsman, Y. Roshan-Ali and D. W. Brown, *Tetrahedron*, **39**, 3881 (1983).
31. T. Abe, *Bull. Chem. Soc. Jpn.*, **56**, 1206 (1983).
32. D. M. Vyas, T. M. Doyle and Y. Chiang, US Patent 4, 692, 538 (1987); *Chem. Abstr.*, **108**, 21877 (1988).
33. .V. I. Gorbatenko, M. N. Gertsyuk and L. I. Samarai, *Zh. Org. Khim.*, **15**, 2047 (1979).
34. R. Scheffold, P. Geisser and R. Boss, *Chimia*, **29**, 461 (1975).
35. R. R. Schmidt and J. Michel, *Angew. Chem., Int. Ed. Engl.*, **19**, 731 (1980).
36. R. R. Schmidt and M. Stumpp. *Ann. Chem.*, 1249 (1983).
37. J. E. Rowe, *Synthesis*, 114 (1980).
38. K. Hartke, W. Richter, W. Massa and G. Baum, *Tetrahedron Lett.*, **27**, 2743 (1986).
39. S. Knapp and D. V. Patel, *Tetrahedron Lett.*, **23**, 3539 (1982).
40. W. Eckhardt, H. Zondler and R. Nyfeler, European Patent Appl., EP 207,000 (1986); *Chem. Abstr.*, **106**, 84,653 (1987).
41. J. R. Shroff, B. Elpern, S. Kobrin and P. Cervoni, *J. Med. Chem.*, **25**, 359 (1982).
42. H. Nishiyama, H. Nagase and K. Ohno, *Tetrahedron Lett.*, 4671 (1979).
43. D. Anderson, P. Zinke and S. L. Razniak, *J. Org. Chem.*, **48**, 1544 (1983).
44. E. Mohacsi and E. M. Gordon, *Synth. Commun.*, **14**, 1159 (1984).
45. S. Treppendahl and P. Jakobsen, *Acta Chem. Scand., Ser. B*, **B32**, 778 (1978).
46. K. Sato, O. Miyamoto, S. Inoue and T. Ota, *Synthesis*, 137 (1982).
47. A. I. Meyers, M. A. Hanagan, L. M. Trefonas and R. J. Baker, *Tetrahedron*, **39**, 1991 (1983).
48. U. Schöllkopf, *Tetrahedron*, **39**, 2085 (1983).
49. S. A. Matlin, P. G. Sammes and R. M. Uptom, *J. Chem. Soc., Perkin Trans. 1*, 2478 (1979).
50. C. H. Yoder, W. C. Copenhafer and B. DuBeshter, *J. Am. Chem. Soc.*, **96**, 4283 (1974).
51. G. Snatzke and J. Vlahov, *Ann. Chem.*, 439 (1985).
52. B. Dejak, Z. Lasocki and H. Jancke, *Bull. Pol. Acad. Sci., Chem.*, **33**, 275 (1985).
53. G. Michael, *Z. Chem.*, **25**, 19 (1985).
54. E. Martinez and E. Gelpi, *Adv. Chromatogr. (Houston) 14th.*, 677 (1979); *Chem. Abstr.*, **92**, 106661 (1980).
55. P. Dowd and K. Kang, *Synth. Commun.*, **4**, 151 (1974).
56. B. Rigo, C. Lespagnol and M. Pauly, *Tetrahedron Lett.*, **27**, 347 (1986).
57. T. Oesterle and G. Simchen, *Synthesis*, 403 (1985).
58. H. Ahlbrecht and C. Vonderheid, *Chem. Ber.*, **106**, 2009 (1973).
59. M. Golfier and R. Milcent, *Synthesis*, 946 (1979).
60. H. Theobold, B. Wuerzer and K. Kuhs, *German Patent* 2, 821, 809 (1979); *Chem. Abstr.*, **92**, 163987 (1980).
61. R. Trave, L. G. Aranti and G. Zecchi, *J. Chem. Soc., Perkin Trans. 1*, 1533 (1987).
62. R. S. Hosmane, F. N. Burnett and M. S. Albert, *J. Org. Chem.*, **49**, 1212 (1984).
63. A. Zwierzak and E. Slusarska, *Synthesis*, 691 (1979).
64. O. Suzuki and S. Inoue, *Bull. Chem. Soc. Jpn.*, **62**, 239 (1989).
65. G. Schmitt and W. Ebertz, *Angew. Chem.*, **94**, 650 (1982).
66. J. M. McCall, B. V. Kamdar and D. Kloosterman, *Synthesis*, 123 (1980).
67. R. Allmann, M. Krestel, R. Kupfer and E. U. Wuerthwein, *Chem. Ber.*, **119**, 2444 (1986).
68. G. Zinner and E. Ketz, *Synthesis*, 165 (1973).
69. Y. Tamura, J. Minamikawa and M. Ikeda, *Synthesis*, 1 (1977).
70. A. J. Castellino and H. Rapoport, *J. Org. Chem.*, **49**, 1348 (1984).
71. N. Y. Derkach and T. V. Lyapina, *Zh. Org. Khim.*, **17**, 529 (1981).
72. W. Maringgele and A. Meller, *Z. Anorg. Allg. Chem.*, **443**, 148 (1978).
73. T. Saito, Y. Sugimura, Y. Iwano, K. Iino and T. Hiraoka, *J. Chem. Soc., Chem. Commun.*, 516 (1976).
74. Y. Sugimura, K. Iino, Y. Iwano, T. Saito and T. Hiraoka, *Tetrahedron Lett.*, 1307 (1976).

75. H. Yoshida, T. Ogata and S. Inokawa, *Synthesis*, 627 (1977).
76. T. R. Oakes and D. J. Donavan, *J. Org. Chem.*, **38**, 1319 (1973).
77. E. Schaumann, S. S. Sieveking and W. Walter, *Chem. Ber.*, **107**, 3589 (1974).
78. A. H. Schulthess and H. J. Hansen, *Helv. Chim. Acta*, **64**, 1322 (1981).
79. P. Paul and K. Nag, *Inorg. Chem.*, **26**, 1586 (1987).
80. D. C. Yang, V. Dragisich, W. D. Wulff and J. C. Huffman, *J. Am. Chem. Soc.*, **110**, 307 (1988).
81. H. Fischer and U. Schubert, *Angew. Chem.*, **93**, 482 (1981).
82. H. G. Raubenheimer, G. J. Kruger, F. Scott and R. Otte, *Organometallics*, **6**, 1789 (1987).
83. L. S. Hegedus, A. Kramer and C. Yijun, *Organometallics*, **4**, 1747 (1985).
84. H. G. Raubenheimer, G. J. Kruger, H. W. Viljoen and S. Lotz, *J. Organomet. Chem.*, **314**, 281 (1986).
85. K. Weiss and P. Kindi, *Angew. Chem.*, **96**, 616 (1984).
86. S. Akhavan, C. S. Kim and B. N. Storhoff, *Inorg. Chim. Acta*, **115**, 173 (1986).
87. G. D. Williams, R. R. Whittle, G. L. Geoffroy and A. L. Reingold, *J. Am. Chem. Soc.*, **109**, 3936 (1987).
88. G. D. Williams, G. L. Geoffroy, R. R. Whittle and A. L. Reingold, *J. Am. Chem. Soc.*, **107**, 729 (1985).
89. L. G. Marzilli, M. F. Summers, J. H. Ramsden Jr., N. Bresciani-Pahor and L. Randaccio, *J. Chem. Soc., Dalton Trans.*, 511 (1984).
90. M. Wada, S. Kanai, R. Maeda, M. Kinoshita and K. Oguro, *Inorg. Chem.*, **18**, 417 (1979).
91. M. Wada and T. Shimohigashi, *Inorg. Chem.*, **15**, 954 (1976).
92. A. Romero, A. Santos and A. Vegas, *Organometallics*, **6**, 1584 (1987).
93. A. Ros, R. A. Michelin, T. Boschi and R. Roulet, *Inorg. Chim. Acta*, **35**, 43 (1979).
94. S. Komorita and S. Yamada, *Synth. React. Inorg. Met.-Org. Chem.*, **14**, 485 (1984).
95. M. Habir, H. Trujillo, C. A. Alexander and B. N. Storhoff, *Inorg. Chem.*, **24**, 2344 (1985).
96. N. W. Alcock, J. M. Brown and T. D. Maclean, *J. Chem. Soc., Chem. Commun.*, 1689 (1984).
97. R. A. Michelin and R. Ros, *J. Organomet. Chem.*, **169**, C42 (1979).
98. D. Schwarzenbach, A. Pinkerton, G. Chapius, J. Wenger, R. Ros and R. Roulet, *Inorg. Chim. Acta*, **25**, 255 (1977).
99. G. Banditelli, A. L. Bandini, G. Minghetti and F. Bonati, *Synth. React. Inorg. Met. Met.-Org. Chem.*, **9**, 539 (1979).
100. G. Banditelli, F. Bonati and G. Minghetti, *Gazz. Chim. Ital.*, **110**, 317 (1980).
101. C. M. Tiripicchio and G. Minghetti, *J. Organomet. Chem.*, **171**, 399 (1979).
102. G. Banditelli, F. Bonati, S. Calogero, G. Valle, F. E. Wagner and R. Wordel, *Organometallics*, **5**, 1346 (1986).
103. M. Kosugi, T. Ogata, H. Tamura, H. Sano and T. Migita, *Chem. Lett.*, 1197 (1986).
104. W. Wehner and A. Gero, German Patent 3,005,019; *Chem. Abstr.*, **94**, 65842 (1981).
105. T. Livinghouse and R. Smith, *J. Chem. Soc., Chem. Commun.*, 210 (1983).
106. R. Smith and T. Livinghouse, *J. Org. Chem.*, **48**, 1554 (1983).
107. R. Smith and T. Livinghouse, *Synth. Commun.*, **14**, 639 (1984).
108. R. Smith and T. Livinghouse, *Tetrahedron*, **41**, 3559 (1985).
109. W. J. Middleton, *J. Org. Chem.*, **49**, 919 (1984).
110. M. E. Jung, D. D. Grove and S. I. Khan, *J. Org. Chem.*, **52**, 4570 (1987).
111. M. E. Jung, P. A. Blair and J. A. Lowe, *Tetrahedron Lett.*, 1439 (1976).
112. A. P. Kozikowski and A. Ames, *J. Org. Chem.*, **43**, 2735 (1978).
113. N. DeKimpe, P. Sulmon, L. Moëns, N. Schamp, J. Declercq and M. Van Meerssche, *J. Org. Chem.*, **51**, 3839 (1986).
114. J. Perchais and J. P. Fleury, *Tetrahedron*, **30**, 999 (1974).
115. H. Boehme and G. Braun, *Arch. Pharm.*, **317**, 408 (1984).
116. A. V. Fokin, V. P. Stolyarov, A. M. Gukov, A. T. Uzan and V. A. Komarov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2802 (1978); *Chem. Abstr.*, **90**, 120979 (1979).
117. A. Hassner, R. Fibiger and A. S. Amarasekara, *J. Org. Chem.*, **53**, 22 (1988).
118. D. H. Aue and D. Thomas, *J. Org. Chem.*, **40**, 1349 (1975).
119. R. G. Harrison, D. M. Rackham and W. J. Ross, *J. Org. Chem.*, **44**, 3572 (1979).
120. S. Konno, M. Yokoyama and H. Yamanaka, *Heterocycles*, **19**, 1865 (1982).
121. G. A. Lanovaya and V. F. Mishchenko, *Zh. Org. Khim.*, **15**, 2203 (1979).
122. W. R. McKay and G. R. Proctor, *J. Chem. Soc., Perkin Trans. 1*, 2435 (1981).
123. B. M. Trost, M. Vaultier and M. L. Santiago, *J. Am. Chem. Soc.*, **102**, 7932 (1980).

124. S. Ashburner and R. M. Coates, *J. Org. Chem.*, **50**, 3076 (1985).
125. R. M. Coates and S. J. Firsan, *J. Org. Chem.*, **51**, 5198 (1986).
126. G. Häfelinger, in *The Chemistry of Amidines and Imidates* (*The Chemistry of The Functional Groups*) (Ed. S. Patai), Wiley–Interscience, London, 1975, pp. 11 and 84.
127. G. Fodor and B. A. Phillips, in *The Chemistry of Amidines and Imidates* (*The Chemistry of The Functional Groups*) (Ed. S. Patai), Wiley–Interscience, London, 1975, p. 132.
128. C. O. Meese, W. Walter and M. Berger, *J. Am. Chem. Soc.*, **96**, 2259 (1974).
129. W. Walter and C. O. Meese, *Chem. Ber.*, **110**, 2463 (1977).
130. C. O. Gonzalez, D. E. Gallis and D. R. Crist, *J. Org. Chem.*, **51**, 3266 (1986).
131. W. Walter, W. Ruback and C. O. Meese, *Org. Magn. Reson.*, **11**, 612 (1978).
132. W. Walter, W. Ruback and C. O. Meese, *Chem. Ber.*, **113**, 171 (1980).
133. M. Caswell and G. L. Schmir, *J. Am. Chem. Soc.*, **101**, 7323 (1979).
134. C. L. Perrin and E. R. Johnston, *Can. J. Chem.*, **59**, 2527 (1981).
135. J. E. Johnson and S. C. Cornell, *J. Org. Chem.*, **45**, 4144 (1980).
136. J. E. Johnson, E. A. Nalley, C. Weidig and M. Afran, *J. Org. Chem.*, **46**, 3623 (1981).
137. J. E. Johnson, A. Ghafouripour, Y. K. Haug, A. W. Cordes, W. T. Pennington and O. Exner, *J. Org. Chem.*, **50**, 993 (1985).
138. J. E. Johnson, N. M. Silk and M. Arfan, *J. Org. Chem.*, **47**, 1958 (1982).
139. L. Brion, P. Reynauld and S. Kirkiacharian, *Synthesis*, 220 (1983).
140. P. G. Williard and L. A. Grab, *Tetrahedron Lett.*, **22**, 2731 (1981).
141. V. Mizrahi, T. Hendrickse and T. A. Modro, *Can. J. Chem.*, **61**, 118 (1983).
142. K. E. Peterman and J. M. Shreeve, *Inorg. Chem.*, **14**, 1106 (1975).
143. K. Itoh, M. Katsuda and Y. Ishii, *J. Chem. Soc. (B)*, 302 (1970).
144. A. Komoriya and C. H. Yoder, *J. Am. Chem. Soc.*, **94**, 5285 (1972).
145. W. C. Copenhafer, B. DuBeshter and C. H. Yoder, *J. Am. Chem. Soc.*, **96**, 4283 (1974).
146. B. Dejak and Z. Lasocki, *J. Organomet. Chem.*, **246**, 151 (1983).
147. M. D. Fryzuk and P. A. MacNeil, *J. Am. Chem. Soc.*, **106**, 6993 (1984).
148. W. H. Pritchard in *The Chemistry of Amidines and Imidates* (*The Chemistry of The Functional Groups*) (Ed. S. Patai), Wiley–Interscience, London, 1975, p. 177.
149. B. C. Challis and A. D. Frenkel, *J. Chem. Soc., Perkin Trans. 2*, 192 (1978).
150. C. G. McCarty and L. A. Garner, in *The Chemistry of Amidines and Imidates* (*The Chemistry of The Functional Groups*) (Ed. S. Patai), Wiley–Interscience, London, 1975, pp. 189–240.
151. A. A. H. Saeed, S. A. Selman, A. W. A. Sultan and N. A. Abood, *Can. J. Spectrosc.*, **28**, 63 (1983).
152. A. Clizbe and L. E. Overman, *Org. Synth.*, **58**, 4 (1978).
153. Y. Yamamoto, H. Shimoda, J. Oda and Y. Inouye, *Bull. Chem. Soc. Jpn.*, **49**, 3247 (1976).
154. L. E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976).
155. S. Takano, M. Akiyama and K. Ogasawara, *Chem. Commun.*, 770 (1984).
156. P. Bey, F. Gerhart and M. Jung, *J. Org. Chem.*, **51**, 2835 (1986).
157. A. K. Saksena, R. G. Lovey, V. M. Girijavallabhan, A. K. Ganguly and A. T. McPhail, *J. Org. Chem.*, **51**, 5024 (1986).
158. G. Cardillo, M. Orena and S. Sandri, *Chem. Commun.*, 1489 (1983).
159. I. Dyong, H. Merten and J. Thiem, *Tetrahedron Lett.*, **25**, 277 (1984).
160. D. M. Vyas, Y. Chiang and T. M. Doyle, *Tetrahedron Lett.*, **25**, 487 (1984).
161. L. E. Overman, C. K. Marlowe and L. A. Clizbe, *Tetrahedron Lett.*, 599 (1979).
162. A. L. Campbell and G. R. Lenz, *Synthesis*, 423 (1987).
163. J. P. Lokensgard, J. W. Fischer, W. J. Bartz and J. Meinwald, *J. Org. Chem.*, **50**, 5609 (1985).
164. M. D. Bhavsar and D. J. Bhaisa, *Man-Made Text., India*, **29**, 63 (1986); *Chem. Abstr.*, **106**, 49967 (1987).
165. T. Ikariya, Y. Ishikawa, K. Hirai and S. Yoshikawa, *Chem. Lett.*, **11**, 1815 (1982).
166. T. G. Schenck and B. Bosnich, *J. Am. Chem. Soc.*, **107**, 2058 (1985).
167. Y. Tamura, M. Kagotani and Z. Yoshida, *J. Org. Chem.*, **45**, 5221 (1980).
168. Y. Tamura, M. Kagotani and Z. Yoshida, *Tetrahedron Lett.*, **22**, 4245 (1981).
169. B. V. Burger, L. Birkofer, H. Dickopp and G. Schmidtberg, *S. Afr. J. Chem.*, **32**, 41 (1984); *Chem. Abstr.*, **101**, 72814 (1984).
170. W. J. Middleton, *J. Org. Chem.*, **49**, 4541 (1984).
171. Y. Pocker, M. W. Beug and K. L. Stephens, *J. Am. Chem. Soc.*, **96**, 174 (1974).
172. V. F. Smith and G. L. Schmir, *J. Am. Chem. Soc.*, **97**, 3171 (1975).
173. Y. Lee and G. L. Schmir, *J. Am. Chem. Soc.*, **100**, 6700 (1978).

174. Y. Lee and G. L. Schmir, *J. Am. Chem. Soc.*, **101**, 3026 (1979).
175. Y. Lee and G. L. Schmir, *J. Am. Chem. Soc.*, **101**, 6277 (1979).
176. M. Caswell and G. L. Schmir, *J. Am. Chem. Soc.*, **101**, 7323 (1979).
177. P. Deslongchamps, S. Dubé, C. Lebreux, D. R. Patterson and R. J. Taillefer, *Can. J. Chem.*, **53**, 2791 (1975).
178. P. Deslongchamps and R. J. Taillefer, *Can. J. Chem.*, **53**, 3029 (1975).
179. P. Deslongchamps, *Tetrahedron*, **31**, 2463 (1975).
180. P. Deslongchamps, U. O. Cheriyan and R. J. Taillefer, *Can. J. Chem.*, **57**, 3262 (1979).
181. P. Deslongchamps and M. Caron, *Can. J. Chem.*, **58**, 2061 (1980).
182. C. L. Perrin and E. R. Johnston, *Can. J. Chem.*, **59**, 2527 (1981).
183. J. Kavelvek, L. Hejtmankova, S. Ludmila and V. Sterba, *Collect. Czech. Chem. Commun.*, **52**, 1285 (1987).
184. R. A. Cox and K. Yates, *Can. J. Chem.*, **59**, 2853 (1981).
185. A. P. Prudchenko, L. P. Drizhd and V. A. Savelova, *Zh. Org. Khim.*, **22**, 1029 (1986).
186. A. P. Prudchenko, L. P. Drizhd and V. A. Savelova, *Zh. Org. Khim.*, **22**, 1909 (1986).
187. H. F. Gilbert and W. P. Jencks, *J. Am. Chem. Soc.*, **101**, 5774 (1979).
188. J. E. Rowe, *Aust. J. Chem.*, **36**, 1259 (1983).
189. Y. Mastubara, T. Nakamura, M. Yoshihara and T. Maeshima, *Chem. Pharm. Bull.*, **30**, 3389 (1982).
190. H. Moeller, C. Gloxhuber and H. Schnegelberger, German Patent 2, 164, 851 (1973); *Chem. Abstr.*, **79**, 92199 (1973).
191. B. Glatz, G. Helmechen, H. Muxfelot, H. Porcher, R. Prewo, J. Senn. J. J. Stezowski, R. J. Stojda and D. R. White, *J. Am. Chem. Soc.*, **101**, 2171 (1979).
192. G. Levesque, J. Gressier and M. Proust, *Synthesis*, 963 (1981).
193. V. I. Cohen, *J. Org. Chem.*, **42**, 2645 (1977).
194. A. Couture, P. Grandclaudon and E. Huguerre, *Synthesis*, 363 (1987).
195. O. B. Chalova, E. A. Kantor, T. K. Kiladze, N. E. Maksimova and D. L. Rakhmankulov, USSR Patent SU 925, 959 (1982); *Chem. Abstr.*, **97**, 216199 (1982).
196. J. A. Gautier, M. Miocque and C. C. Farnoux, in *The Chemistry of Amidines and Imidates* (*The Chemistry of The Functional Groups*) (Ed. S. Patai), Wiley–Interscience, London, 1975, pp. 292–296.
197. E. S. Hand and W. P. Jencks, *J. Am. Chem. Soc.*, **84**, 3505 (1962).
198. J. A. Durden, Jr., US Patent 4, 454, 134 (1984); *Chem. Abstr.*, **101**, 130, 252 (1984).
199. D. T. Browne and S. B. H. Kent, *Biochem. Biophys. Res. Commun.*, **67**, 126 (1975).
200. D. T. Browne and S. B. H. Kent, *Biochem. Biophys. Res. Commun.*, **67**, 133 (1975).
201. A. J. Makoff and A. D. B. Malcolm, *Biochem. J.*, **193**, 245 (1981).
202. C. J. A. Wallace and D. E. Harris, *Biochem. J.*, **217**, 589 (1984).
203. H. F. Gilbert and W. P. Jencks, *J. Am. Chem. Soc.*, **104**, 6769 (1982).
204. E. Cereda, E. Bellora and A. Donetti, *Synthesis*, 289 (1986).
205. E. S. Hamanaka and J. G. Stam, South African Patent 74,00509 (1973); *Chem. Abstr.*, **83**, 58808 (1975).
206. M. L. Gilpin, European Patent Appl., EP 46,349 (1982); *Chem. Abstr.*, **97**, 23,534 (1982).
207. W. J. Leanza, K. J. Wildonger, T. W. Miller and B. G. Christesen, *J. Med. Chem.*, **22**, 1435 (1979).
208. A. Buschauer, K. Wegner and W. Schunack, *Eur. J. Med. Chem. Chim. Ther.*, **17**, 505 (1982); *Chem. Abstr.*, **98**, 89269 (1983).
209. C. B. Chapleo, P. L. Myers, A. C. B. Smith, M. R. Stillings, L. A. Tulloch and D. S. Walter, *J. Med. Chem.*, **31**, 7 (1988).
210. R. C. Schnur, *J. Org. Chem.*, **44**, 3726 (1979).
211. H. Meyer, *Ann. Chem.*, 1291 (1979).
212. M. Scott and C. Rasmussen, German Patent 2,912,026 (1979); *Chem. Abstr.*, **92**, 110861 (1980).
213. L. P. Drizhd, A. V. Skrypka and V. A. Savelova, *Ukr. Khim. Zh.*, **52**, 1072 (1986); *Chem. Abstr.*, **107**, 133658 (1987).
214. K. M. Watson and D. G. Neilson, in *The Chemistry of Amidines and Imidates* (*The Chemistry of The Functional Groups*) (Ed. S. Patai), Wiley–Interscience, London, 1975, pp. 491–544.
215. V. A. Khrustalev, K. N. Zelinin and V. P. Sergutira, *Zh. Org. Khim.*, **5**, 2280 (1979).
216. E. K. Mikitenko and N. N. Romanov, USSR Patent 827, 487 (1981); *Chem. Abstr.*, **95**, 134388 (1981).
217. E. F. Rothgery and L. E. Katz, US Patent 4, 282, 169 (1981); *Chem. Abstr.*, **96**, 68627 (1982).

218. K. N. Zelinin, V. A, Khrustalev, V. P. Sergutina and V. V. Pinson, *Zh. Org. Khim.*, **17**, 1825 (1981).
219. K. N. Zelinin, V. V. Pinson and V. A. Khrustalev, *Zh. Org. Khim.*, **18**, 1613 (1982).
220. P. Jakobsen and S. Treppendahl, *Tetrahedron*, **38**, 369 (1982).
221. H. Kristinsson and T. Winkler, *Helv. Chim. Acta*, **65**, 2606 (1982).
222. P. Heckendorn and T. Winkler, *Helv. Chim. Acta*, **63**, 1 (1980).
223. A. A. Watson, *J. Org. Chem.*, **42**, 1610 (1977).
224. J. Stetter, W. Fuehrer and W. Brandes, European Patent Appl, EP 56, 161 (1982); *Chem. Abstr.*, **97**, 215788 (1982).
225. J. Drabek and M. Boeger, European Patent Appl., EP 49, 684 (1982); *Chem. Abstr.*, **97**, 91977 (1982).
226. M. E. Jung, D. D. Grove and S. I. Khan, *J. Org. Chem.*, **52**, 4570 (1987).
227. B. A. Korolev and V. E. Krivenchuk, *Veterinariya (Moscow)*, 58 (1983); *Chem. Abstr.*, **99**, 65550 (1983).
228. B. P. Pant and D. K. Daiswal, *Indian J. Chem., Sect. B*, **22B**, 51 (1983); *Chem. Abstr.*, **99**, 38136 (1983).
229. A. I. Meyers, R. K. Smith and C. E. Whitten, *J. Org. Chem.*, **44**, 2250 (1979).
230. K. Mori and Y. Funaki, *Tetrahedron*, **41**, 2379 (1985).
231. H. Moser, A. Fliri, A. Steiger, G. Costello, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **69**, 1224 (1986).
232. C. J. Stoeckert Jr, M. Beer, J. M. Wiggins and J. C. Wierman, *J. Mol. Biol.*, **177**, 483 (1984).
233. J. Diopoh and M. Olomucki, *Hoppe-Seyler's Z. Physiol. Chem.*, **360**, 1257 (1979).
234. M. S. Davies and R. Virden, *Biochem. Soc. Trans.*, **6**, 1222 (1978).
235. H. M. Tinberg and L. Packer, *Methods Enzymol.*, **56G**, 622 (1979).
236. A. Shaw and G. V. Martinetti, *Chem. Phys. Lipids.*, **27**, 329 (1980); *Chem. Abstr.*, **94**, 11382 (1981).
237. K. C. Flanders, D. H. Mar, R. J. Folz, R. D. England, S. A. Coolican, D. E. Harris, A. D. Floyd and R. S. Gurd, *Biochemistry*, **21**, 4244 (1982).
238. G. Galella and D. B. Smith, *Can. J. Biochem.*, **60**, 71 (1982).
239. J. A. Weare, *Biochem. Biophys. Res. Commun.*, **104**, 1319 (1982).
240. T. L. Chad, M. R. Berenfeld and T. G. Gabuzda, *Biochem. Biophys. Acta*, **771**, 183 (1984).
241. T. N. Davis and J. E. Cronan, Jr., *J. Biol. Chem.*, **260**, 663 (1985).
242. R. A. Jue and R. F. Doolittle, *Biochemistry*, **24**, 182 (1985).
243. C. Longstaff, R. D. Calhoon and R. R. Rando, *Biochemistry*, **25**, 6311 (1986).
244. P. P. Nemes, G. P. Miljanich and E. A. Dratz, *Methods Enzymol.*, **81**, 275 (1982).
245. S. F. Greenhut and M. A. Roseman, *Biochemistry*, **24**, 1252 (1985).
246. K. Peters and F. M. Richards, *Ann. Rev. Biochem.*, **46**, 523 (1977).
247. M. E. Birnbaumer, W. T. Schrader and B. W. O.'Malley, *Biochem. J.*, **181**, 201 (1979).
248. P. D. Bragg and G. Hou, *Eur. J. Biochem.*, **106**, 495 (1980).
249. B. Bizzini, *FEMS Symp.*, **24**, 427 (1984); *Chem. Abstr.*, **102**, 19251 (1985).
250. R. Y. F. Schweinberger, *Z. Pflanzenphysiol.*, **94**, 135 (1979); *Chem. Abstr.*, **91**, 52992 (1979).
251. G. F. Dancey, J. Culter and B. D. Schwartz, *J. Immunol.*, **123**, 870 (1979).
252. C. Valtersson, *Acta Chem. Scand., Ser. B.*, **B36**, 406 (1982).
253. M. Pinilla, J. Luque and K. F. Tipton, *Biochim. Biophys. Acta*, **702**, 254 (1982).
254. W. Stoffel and K. Preissner, *Hoppe-Seyler's Z. Physiol. Chem.*, **360**, 691 (1979).
255. Z. Shaked and S. N. Wolfe, European Patent Appl., EP 175, 582 (1986); *Chem. Abstr.*, **105**, 113620 (1986).
256. A. Monneron and J.d'Alayer, *FEBS Lett.*, **122**, 241 (1980); *Chem. Abstr.*, **94**, 150951 (1981).
257. R. Siuta-Mangano and H. Edelstein, US Patent 4,793,993 (1988); *Chem. Abstr.*, **110**, 198920 (1989).
258. R. C. Reba, *J. Radioanal Chem.*, **57**, 553 (1980); *Chem. Abstr.*, **94**, 30308 (1981).
259. D. R. Tolan, J. M. Lambert, G. Boileau, T. G. Fanning, J. W. Kenny, A. Vaslos and R. R. Traut, *Anal Biochem.*, **103**, 101 (1980).
260. J. J. Langone, *Methods Enzymol.*, **70**, 221 (1980).
261. M. Praissman, L. Praissman, S. B. H. Kent and J. M. Berkowitz, *Anal. Biochem.*, **115**, 287 (1981).
262. M. Praissman, R. S. Izzo and J. K. Berkowitz, *Anal. Biochem.*, **121**, 190 (1982).
263. G. R. Bright and B. S. Spooner, *Anal. Biochem.*, **131**, 301 (1983).
264. K. A. Wall and F. W. Fitch, *J. Immunol. Methods*, **77**, 1 (1985); *Chem. Abstr.*, **102**, 164935 (1985).
265. J. Mueller and G. Pfleiderer, *J. Appl. Biochem.*, **1**, 301 (1979).

266. W. Burgermeister, M. Hekman and E. J. Helmreich, *J. Biol. Chem.*, **257**, 5306 (1982).
267. C. C. Chen, J. S. Her and Y. C. Chen, *J. Chim. Biochem. Soc.*, **12**, 80 (1983); *Chem. Abstr.*, **102**, 44167 (1985).
268. C. A. Lingwood, *J. Lipid Res.*, **25**, 1010 (1984).
269. H. A. Houwing and A. M. Van Leusen, *J. Heterocycl. Chem.*, **18**, 1127 (1981).
270. A. Padwa, J. R. Gasdaska, G. Hoffmanns and H. Rebello, *J. Org. Chem.*, **52**, 1027 (1987).
271. E. Vedejs and G. R. Martinez, *J. Am. Chem. Soc.*, **102**, 7993 (1980).
272. O. Tsuge, S. Kanemasa, T. Yamada and K. Matsuda, *Heterocycles*, **23**, 2489 (1985).
273. A. Toshimitsu, K. Terao and S. Uemura, *J. Chem. Soc., Chem. Commun.*, 530 (1986).
274. H. Takahata, *J. Chem. Soc., Chem. Commun.*, 1627 (1987).
275. T. Atsumi, Y. Tarumi and N. Yoshida, German Patent 2, 838, 892 (1979); *Chem. Abstr.*, **90**, 204102 (1979).
276. K. A.M. El-Bayouki, M. Hammad, S. A. Osman and W. M. Basyouni, *Orient. J. Chem.*, **2**, 45 (1986); *Chem. Abstr.*, **106**, 196367 (1987).
277. N. J. Cusack, G. Shaw and F. I. Logemann, *J. Chem. Soc. Perkin Trans. 1*, 2316 (1980).
278. P. Goya and A. Martinez, *Heterocycles*, **24**, 3451 (1986).
279. M. T. Garcia-López, R. Herranz and J. I. Andrés, *J. Chem. Soc., Perkin Trans. 1*, 2303 (1983).
280. Azizur-Rahman, H. Ila and H. Junjappa, *J. Chem. Soc., Chem. Commun.*, 430 (1984).
281. R. S. Hosmane, *Tetrahedron Lett.*, **25**, 363 (1984).
282. E. C. Taylor, J. L. LaMattina and C. Tseng, *J. Org. Chem.*, **47**, 2043 (1982).
283. P. Dziuron and W. Schunak, *Arch. Pharm.*, **307**, 470 (1974).
284. D. P. Matthews, J. P. Whitten and J. R. McCarthy, *Synthesis*, 336 (1986).
285. C. Avendano, T. Ramos and E. Gomez-Molinero, *J. Heterocycl. Chem.*, **22**, 537 (1985).
286. G. Levesque, J. Gressier and H. Proust, *Synthesis*, 963 (1981).
287. S. Shibata, H. Matsushita, K. Kato, M. Noguchi, M. Saburi and S. Yoshikawa, *Bull. Chem. Soc. Jpn.*, **52**, 2938 (1979).
288. G. Tennant, in *Heterocyclic Compounds*, Vol. 40, Pt. 1, *Benzimidazoles and Congeneric Tricyclic Compounds* (Ed. P. N. Preston), Wiley–Interscience, London, 1980, p. 13.
289. K. L. Kurilenko and V. M. Cherkasov, *Ukr. Khim. Zh.*, **45**, 760 (1979); *Chem. Abstr.*, **91**, 175305 (1979).
290. J. Heinicke and A. Tzschach, *Z. Chem.*, **26**, 407 (1986).
291. K. Issleib and R. Vollmer, *Z. Anorg. Allg. Chem.*, **481**, 22 (1981).
292. J. Heinicke and A. Tzschach, *Tetrahedron Lett.*, **23**, 3643 (1982).
293. R. Neidlein and U. Askani, *Synthesis*, 48 (1975).
294. H. Ishikawa, S. Nakagawa, S. Kida, Y. Kawashima and N. Nakayama, Japanese Patent, JP 61,236,768 (1986); *Chem. Abstr.*, **106**, 102281 (1987).
295. H. A. Houwing, J. Wildeman and A.M. Van Leusen, *J. Heterocylc. Chem.*, **18**, 1139 (1981).
296. M. I. Butt, D. G. Neilson, K. M. Watson and Z. Ullah, *J. Chem. Soc., Perkin Trans. 1*, 2328 (1977).
297. A. I. Meyers, G. Knaus, K. Kamata and M. E. Ford, *J. Am. Chem. Soc.*, **98**, 567 (1976).
298. A. I. Meyers and N. R. Natale, *Heterocycles*, **18**, 13 (1982).
299. S. Shibata, H. Matsushita, H. Kaneko, M. Noguchi, M. Saburi and S. Yoshikawa, *Bull. Chem. Soc. Jpn.*, **55**, 3546 (1982).
300. L. E. Overman, S. Tsuboi and S. Angle, *J. Org. Chem.*, **44**, 2323 (1979).
301. P. J. Reider, R. S. Eichenconn, P. Davis, V. J. Grenda, A. J. Zambito and E. J. J. Grabowski, *J. Org. Chem.*, **52**, 3326 (1987).
302. R. J. Bergeron, J. S. McManis, J. Dionis and J. R. Garlich, *J. Org. Chem.*, **50**, 2780 (1985).
303. R. E. Hermes and L. J. Mathias, *J. Polym. Sci., Part C, Polym. Lett.*, **25**, 161 (1987).
304. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).
305. G. Cardillo, M. Orena, G. Porzi and S. Sandri, *J. Chem. Soc., Chem. Commun.*, 1308 (1982).
306. A. Bongini, G. Cardillo, M. Orena, S. Sandri and C. Tomasini, *J. Org. Chem.*, **51**, 4905 (1986).
307. A. Bongini, G. Cardillo, M. Orena, S. Sandri and C. Tomasini, *J. Chem. Soc., Perkin Trans. 1*, 1339, 1345 (1986).
308. H. W. Pauls and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1031 (1983).
309. M. I. Butt, D. G. Neilson and K. M. Watson, *J. Chem. Soc., Perkin Trans.* **1**, 542 (1976).
310. H. M. Hugel, *Synth. Commun.*, **15**, 1075 (1985).
311. W. Ried and D. Kuhnt, *Ann. Chem.*, 780 (1986).

312. J. Liebscher and J. Mitzner, *Synthesis*, 414 (1985).
313. A. McKillop, A. Henderson, P. S. Ray, C. Avendano and E.G. Molinero, *Tetrahedron Lett.*, **23**, 3357 (1982).
314. M. A. Perez, C. A. Dorado and J. L. Soto, *Synthesis*, 483 (1983).
315. G. A. Shvekhgeimer, V. I. Kelarev and L. A. Dyankova, *Khim. Geterotsikl Soedin*, 1609 (1984); *Chem. Abstr.*, **102**, 149193 (1985).
316. P. Rajopalan, *Tetrahedron Lett.*, 311 (1969).
317. A. B. H. Amor and B. Baccar, *J. Soc. Chim., Tunis*, **2**, 9 (1986); *Chem. Abstr.*, **107**, 39709 (1987).
318. H. R. Mueller and H. Bollinger, Swiss Patent 612,191 (1979); *Chem. Abstr.*, **91**, 175362 (1979).
319. E. Ayca, A. A. Ikizler and R. Aslan, *Chim Acta Turc.*, **12**, 305 (1984); *Chem. Abstr.*, **106**, 84495 (1987).
320. E. K. Mikitenko and N. N. Romanov, *Khim. Geterotsikl. Soedin*, 199 (1981); *Chem. Abstr.*, **95**, 7130 (1981).
321. K. Akiba, A. Noda, K. Ohkata, T. Akiyama, Y. Murata and Y. Yamamoto, *Heterocycles*, **15**, 1155 (1981).
322. M. R. Ali, R. Singh and V. K. Verma, *J. Indian Chem. Soc.*, **59**, 663 (1982); *Chem. Abstr.*, **97**, 163897 (1982).
323. R. Rai and K. Verma, *Indian J. Chem., Sect. B*, **18B**, 284 (1979); *Chem. Abstr.*, **92**, 94310 (1980).
324. A. Schmidpeter, K. Karaghiosoff, C. Cleve and D. Schomburg, *Angew. Chem.*, **97**, 125 (1985).
325. Y. E. Shishkin and Y. M. Yukhno, *J. Gen. Chem.*, **46**, 1603 (1976).
326. M. I. Butt and D. G. Neilson, unpublished results.
327. I. V. Konovalova, R. D. Gareen, M. V. Cherkina, E. G. Yarkova, L. A. Burneava and A. N. Pudovik, *Zh. Obshch. Khim.*, **52**, 1962 (1982).
328. R. Schwarz and I. Ugi, *Angew. Chem.*, **93**, 836 (1981).
329. T. Vanek, J. Farkas and J. Gut, *Collect. Czech. Chem. Commun.*, **44**, 1334 (1979).
330. A. Omodei-Sale, P. Consonni and G. Galliani, *J. Med. Chem.*, **26**, 1187 (1983).
331. A. Ikizler, *Doga Seri A*, **1**, 25 (1983); *Chem Abstr.*, **99**, 105182 (1983).
332. N. Nihon, Japanese Patent JP 58,225,070 (1983); *Chem. Abstr.*, **100**, 209881 (1984).
333. R. R. Schmidt, W. Guilliard, D. Heermann and M. Hoffmann, *J. Heterocycl. Chem.*, **20**, 1447 (1983).
334. C. Luethy and R. Zurflueh, European Patent Appl., EP 185, 256 (1986); *Chem. Abstr.*, **105**, 133896 (1986).
335. J. Svetlik, *Heterocycles*, **20**, 1495 (1983).
336. H. Kristinsson and T. Winkler, *Helv. Chim. Acta*, **66**, 1129 (1983).
337. A. Ikizler, *Doga Kim. Ser.*, **10**, 34 (1986); *Chem. Abstr.*, **106**, 138338 (1987).
338. S. W. Schneller, J. L. May and E. DeClercq, *Croat. Chem. Acta*, **59**, 307 (1986); *Chem. Abstr.*, **107**, 7490 (1987).
339. T. Sato, T. Kawagishi and N. Koyakata, Japanese Patent, JP 68, 215, 687 (1985); *Chem. Abstr.*, **104**, 188170 (1986).
340. Y. Lin and S. A. Lang, Jr., *J. Org. Chem.*, **46**, 3123 (1981).
341. M. Bonanomi and L. Baiocchi, *J. Heterocycl. Chem.*, **20**, 1657 (1983).
342. R. Galli, O. Palla and F. Gozzo, *J. Chem. Soc., Perkin Trans. 1*, 2813 (1982).
343. Y. Charbonnel and J. Barrans, *C. R. Acad. Sci. Paris, Ser. C*, **272** 1675 (1971).
344. D. H. Aue and D. Thomas, *J Org. Chem.*, **40**, 2360 (1975).
345. E. Stanoeva, M. Haimova and V. I. Ognyanov, *Ann. Chem.*, 389 (1984).
346. M. Haimova, V. I. Ognyanov and N. M. Mollov, *Synthesis*, 845 (1980).
347. G. M. Coppola, *J. Heterocycl. Chem.*, **18**, 767 (1981).
348. N. D. Harris, *Synthesis*, 826 (1976).
349. J. Y. Merour and F. Tatibouët, *Synthesis*, 698 (1978).
350. L. G. Qiang and N. H. Baine, *Tetrahedron Lett.*, **29**, 3517 (1988).
351. H. Yamanaka, M. Komatsu, S. Ogawa and S. Konno, *Chem. Pharm. Bull.*, **27**, 806 (1979).
352. K. Terao, A. Toshimitsu and S. Uemura, *J. Chem. Soc., Perkin Trans. 1*, 1837 (1986).
353. D. J. Brown and K. Ienega, *J. Chem. Soc., Perkin Trans., 1*, 372 (1974).
354. A. Edenhofer, H. Speigelberg and W. E. Oberhaensli, *Helv. Chim. Acta*, **58**, 1230 (1975).
355. H. Kristinsson, *J. Chem. Soc., Chem. Commun.*, 350 (1974).
356. H. Uchida, A. Chinone and M. Ohta, *Bull. Chem. Soc. Jpn.*, **47**, 1720 (1974).
357. D. J. Brown and K. Ienaga, *Aust. J. Chem.*, **28**, 119 (1975).

358. M. A. Pérez, J. L. Soto and J. R. Carrillo, *Synthesis*, 402 (1983).
359. G. Stájer, E. A. Szabó, G. Bernáth and P. Sohár, *Magy. Kem. Foly.*, **92**, 234 (1986); *Chem. Abstr.*, **106**, 84543 (1987).
360. G. Stájer, A. E. Szabó, G. Bernath and P. Sohár, *Synthesis*, 290 (1987).
361. F. Mercer, L. Hermandez, Jr. and H. W. Moore, *Heterocycles*, **12**, 45 (1979).
362. N. P. Peet and S. Sunder, *J. Heterocycl. Chem.*, **21**, 1807 (1984).
363. R. W. Leiby, *J. Heterocycl. Chem.*, **21**, 1825 (1984).
364. R. W. Leiby, *J. Org. Chem.*, **50**, 2926 (1985).
365. E. Honkanen, A. Pippuri, P. Kairisalo, P. Nore, H. Karppanen and I. Paakkari, *J. Med. Chem.*, **26**, 1433 (1983).
366. I. Ganjian and I. Lalezari, *Synth. Commun.*, **14**, 33 (1984).
367. T. Hara, Y. Kayama and T. Sunami, *J. Org. Chem.*, **43**, 4865 (1978).
368. G. Bernáth, G. Stájer, A. E. Szabó, F. Fulop and P. Sohár, *Tetrahedron*, **41**, 1353 (1985).
369. G. Stájer, A. E. Szabó, F. Fulop, G. Bernáth and P. Sohár, *Chem. Ber.*, **120**, 259 (1987).
370. F. Johannsen, A. Joergensen, K. A. M. El-Bayouki and E. B. Pedersen, *Chem. Ser.*, **26**, 337 (1986); *Chem. Abstr.*, **106**, 67249 (1987).
371. V. P. Makoveskii, Y. M. Volovenko and A. A. Svishchuk, *Ukr. Khim. Zh.*, **51**, 528 (1985); *Chem. Abstr.*, **104**, 5836 (1986).
372. Y. Otsuka, Japanese Patent 72 21434 (1972); *Chem. Abstr.*, **77**, 101650 (1972).
373. J. Kobor, F. Fulop, M. S. El-Gharib and G. Bernáth, *J. Heterocycl. Chem.*, **21**, 149 (1984).
374. A. Singh and A. S. Uppal, *J. Indian Chem. Soc.*, **55**, 1040 (1978).
375. A. Singh, A. S. Uppal, T. K. Bindal and M. Singh, *Indian J. Chem., Sect. B*, **19B**, 37 (1980).
376. H. Wamhoff and B. Wehling, *Chem. Ber.*, **108**, 2107 (1975).
377. W. Ried and D. Kuhnt, *Ann. Chem.*, 551 (1987).
378. B. Hajjem, M. T. Kaddachi and B. Baccar, *J. Soc. Chim., Tunis*, **2**, 15 (1985); *Chem. Abstr.*, **106**, 119529 (1987).
379. R. S. Hosmane, B. B. Lim and F. Burnett, *J. Org. Chem.*, **53**, 382 (1988).
380. N. Katagiri, R. Njwa and T. Kato, *Heterocycles*, **20**, 597 (1983).
381. U. Kraatz, *Tetrahedron Lett.*, 1219 (1973).
382. W. Ried, U. Reiher and J. Bats, *Helv. Chim. Acta*, **70**, 1255 (1987).
383. G. Seitz and W. Overheu, *Arch. Pharm. (Weinheim)*, **310**, 936 (1977); **312**, 452 (1979).
384. D. L. Boger and J. S. Panek, *Tetrahedron Lett.*, **24**, 4511 (1983).
385. J. Daunis, R. Jacquier and C. Pigiere, *Tetrahedron*, **30**, 3171 (1974).
386. V. I. Kelarev, D. Ammar, A. F. Lunin, R. L. Ushakova, A. I. Mikaya, N. V. Petrova and S. H. Shvekhgeimer, *Zh. Org. Khim.*, **19**, 2401 (1983).
387. V. I. Keralev, F. L. Yahia, R. A. Karahanov, A. F. Lunin and O. V. Malova, *Khim. Geterotsikl Soedin*, 107 (1986); *Chem. Abstr.*, **106**, 4982 (1987).
388. W. M. Koppes and H. G. Adolph, *J. Org. Chem.*, **46**, 406 (1981).
389. Y. A. Lin, T. L. Fields, V. L. Lee nd S.A. Lang, Jr., *J. Heterocycl. Chem.*, **19**, 613 (1982).
390. I. Lalezari and S. Nabahi, *J. Heterocycl. Chem.*, **17**, 1121 (1980).
391. T. Strohmeyer, D. R. Sliskovic, S. A. Lang, Jr and Y. Lin, *J. Heterocycl. Chem.*, **22**, 7 (1985).
392. F. T. Oakes and N. J. Leonard, *J. Org. Chem.*, **50**, 4986 (1985).
393. R. S. Hosmane, M. A. Rossman and N. J. Leonard, *J. Am. Chem. Soc.*, **104**, 5497 (1982).
394. M. A. Rossman, N. J. Leonard, S. Urano and P. R. LeBreton, *J. Am. Chem. Soc.*, **107**, 3884 (1985).
395. N. J. Leonard, R. S. Hosmane, Y. S. Agasimundin, L. J. Kostuba and F. T. Oakes, *J. Am. Chem. Soc.*, **106**, 6847 (1984).
396. Y. S. Agasimundin, F. T. Oakes and N. J. Leonard, *J. Org. Chem.*, **50**, 2474 (1985).
397. S. Weiss and H. Krommer, German Patent 3, 411, 202 (1985); *Chem. Abstr.*, **104**, 68890 (1986).
398. M. A. Perez and J. L. Soto, *Heterocycles*, **20**, 463 (1983).
399. W. Ried, G. Beller, B. Kuembel and D. Kuhnt, *Synthesis*, 311 (1985).
400. D. H. Aue and D. Thomas, *J. Org. Chem.*, **40**, 2356 (1975).
401. W. Kantlehner, P. Fischer, W. Kugel, E. Moehring and H. Bredereck, *Ann. Chem.*, 512 (1978).
402. D. G. Neilson, K. M. Watson and T. J. R. Weakley, *J. Chem. Soc., Perkin Trans. 1*, 333 (1979).
403. D. Hunter and D. G. Neilson, *J. Chem. Soc., Perkin Trans. 1*, 1371 (1981); 1601 (1983).
404. G. Bernáth, F. Fulop, L. Gera, L. Hackler, A. Kalman, G. Argay and P. Sohár, *Tetrahedron*, **35**, 799 (1979).
405. P. Sohár, G. Stájer and G. Bernáth, *Org. Magn. Reson.*, **21**, 512 (1983).

406. G. Stájer, A. E. Szabó, F. Fulop, G. Bernáth and P. Sohár, *J. Heterocycl. Chem.*, **21**, 1373 (1984).
407. P. Stoss, *Chem. Ber.*, **111**, 314 (1978).
408. W. Ried and D. Kuhnt, *Ann. Chem.*, 1648 (1986).
409. W. Ried and M. A. Jacobi, *Chem. Ber.*, **121**, 383 (1988).
410. W. G. Brouwer, A. R. Blem, A. R. Bell and R. A. Davis, European Patent Appl., EP 104, 940 (1984); *Chem. Abstr.*, **101**, 38485 (1984).
411. B. Renfroe and C. Harrington, in *Heterocyclic Compounds*, Vol. 43, Pt. 1, Wiley–Interscience, London, pp. 234, 235, 237, 244, 247, 251.
412. J. W. H. Watthey and J. Stanton, in *Heterocyclic Compounds*, Vol. 43, Pt. 2, Wiley–Interscience, London, pp. 90, 96.
413. M. Barreau and G. Ponsinet, *Synthesis*, 262 (1987).
414. Z. A. Bredikhina, N. G. Khusainova, Y. Y. Efremov, R. L. Korshunov and A. N. Pudovik, *Zh. Obshch. Khim.* **55**, 1710 (1985).
415. S. Inoue, O. Suzuki and K. Sato, *J. Chem. Soc., Chem. Commun.*, 1773 (1985).
416. W. Adam, O. DeLucchi, H. Quast, R. Recktenwald, Y. Rautgundis and F. Yany, *Angew. Chem.*, **91**, 855 (1979).
417. T. Morwick, *Tetrahedron Lett.*, **21**, 3227 (1980).
418. U. Schöllkopf, W. Hartwig, K. H. Pospischil and H. Kehne, *Synthesis*, 966 (1981).
419. Y. Nakahara, K. Beppu and T. Ogawa, *Tetrahedron Lett.*, **22**, 3197 (1981).
420. C. Gluchowski, T. Tiner-Harding, J. K. Smith, D. Bergbreiter and M. Newcomb, *J. Org. Chem.*, **49**, 2650 (1984).
421. P. A. Zoretic, P. Soja and N. D. Sinha, *J. Org. Chem.*, **43**, 1379 (1978).
422. D. H. Aue and D. Thomas, *J. Org. Chem.*, **39**, 3855 (1974).
423. A. J. Biloski and B. Ganem, *J. Org. Chem.*, **48**, 3118 (1983).
424. G. B. Payne, *Tetrahedron* **18**, 763 (1962).
425. A. L. Arias, S. Adkins, C. J. Nagel and R. D. Bach, *J. Org. Chem.*, **48**, 888 (1983).
426. S. Szakacs and F. Nagy, *Magy. Kem. Foly.*, **88**, 193 (1982); *Chem. Abstr.*, **97**, 182250 (1982).
427. Y. Tsuda, T. Sano and H. Watanabe, *Synthesis*, 652 (1977).
428. R. J. Sundberg, C. P. Walters and J. D. Bloom, *J. Org. Chem.*, **46**, 3730 (1981).
429. S. Nagarajan and B. Ganen, *J. Org. Chem.*, **51**, 4856 (1986).
430. T. Matsumoto, M. Yanagiya, K. Tsuzuki, T. Watanabe and Y. Nakajima, Japanese Patent 79, 145, 609 (1979); *Chem. Abstr.*, **92**, 146456 (1980).
431. F. Matsuda, M. Yanagiya and T. Matsumoto, *Tetrahedron Lett.*, **23**, 4043 (1982).
432. M. A. Perez, C. A. Dorado and J. L. Soto, *Synthesis*, 483 (1983).
433. R. Kupfer, M. Nagel, E. U. Wuerthwein and R. Allmann, *Chem. Ber.*, **118**, 3089 (1985).
434. B. A. Gostevskli, O. A. Vyazankina, I. D. Kalikhman, O. B. Bannikova and N. S. Vyazankin, *Zh. Obshch. Khim.*, **53**, 2051 (1983).
435. L. I. Belousoya, I. D. Kalikhman, O. A. Vyazankina, E. L. Brodskaya and N. S. Vyazankin, *Zh. Obshch. Khim.*, **57**, 1199 (1987).
436. F. J. Cuadrado, M. A. Perez and J. L. Soto, *J. Chem. Soc., Perkin Trans. 1*, 2447 (1984).
437. A. Koda, K. Takanobu, I. Isaka, T. Kashiwagi, K. Takahashi, S. Kawahara and M. Murakami, *J. Pharm. Soc. Jpn.*, **92**, 459 (1972).
438. T. Saito, K. Nishihata and S. Fukatsu, *J. Chem. Soc., Perkin Trans. 1*, 1058 (1981).
439. E. U. Wuerthwein and R. Kupfer, *Chem. Ber.*, **119**, 1557 (1986).
440. R. A. Abramovitch, B. Mavunkel, J. R. Stowers, M. Wegrzyn and C. Riche, *J. Chem. Soc., Chem. Commun.*, 845 (1985).
441. R. Neidlein and U. J. Klotz, *Chem. Ber.*, **118**, 3217 (1985).
442. J. C. Bottard, *J. Chem. Soc., Chem. Commun.*, 560 (1980).
443. A. V. Folkin, Y. N. Studnev, I. Timofeenko and V. P. Stolyarov, *Izv. Akad. Nauk SSSR, Ser. Kim.*, 2622 (1981).
444. G. S. Borovikova, E. S. Levchenko and E. I. Borovik, *Zh. Org. Khim.*, **15**, 2313 (1979).
445. E. E. V. Ebsworth, D. W. H. Rankin, W. Steger and J. G. Wright, *J. Chem. Soc., Dalton Trans.*, 1768 (1980).
446. Y. Tamura, T. Kawasaki, M. Adichi and Y. Kita, *Synthesis*, 887 (1979).
447. B. I. No, V. E. Shishkin, Y. M. Yukhno, E. V. Mednikov, S. V. Ufimtsev and S. I. Maikov, *Zh. Obshch. Khim.*, **56**, 1192 (1986).
448. H. Yoshida, T. Ogata and S. Inokawa, *Synthesis*, 626 (1977).
449. H. Yoshida, T. Ogata and S. Inokawa, *Bull. Chem. Soc. Jpn.*, **50**, 3315 (1977).

450. S. M. Clift and J. Schwartz, *J. Am. Chem. Soc.*, **106**, 8300 (1984).
451. V. P. Kukhar and E. I. Sagina, *Zh. Obshch. Khim.*, **49**, 1025 (1979).
452. J. A. Muller and H. S. Aaron, *Phosphorus Sulphur*, **25**, 339 (1985).
453. I. V. Konovalova, L. A. Burnaeva, R. D. Gareev, T. M. Moshkina and A. N. Pudovik, *Zh. Obshch. Khim.*, **54**, 2203 (1984).
454. I. V. Konovalova, R. D. Gareev, E. G. Yarkova, L. Burnaeva, M. V. Cherkina, N. M. Aleksanina and A. N. Pudovik, *Zh. Obshch. Khim.*, **52**, 1491 (1982).
455. I. V. Konovalova, L. A. Burnaeva, R. D. Gareev, A. S. Lyakhova, T. M. Moshkina and A. N. Pudovik, *Zh. Obshch. Khim.*, **53**, 1471 (1983).
456. V. E. Shishkin, E. V. Mednikov, B. I. No and N. V. Shishkina, *Zh. Obshch. Khim.*, **49**, 2720 (1979).
457. N. G. Zabirov, R. A. Cherkasov and A. N. Pudovik, *Zh. Obshch. Khim.*, **56**, 1237 (1986).
458. N. G. Khusainova, Z. A. Bredikhina and A. N. Pudovik, *Zh. Obshch. Khim.*, **52**, 1296 (1982).
459. P. G. Sammes and D. Thetford, *J. Chem. Soc., Chem. Commun.*, 352 (1985).
460. R. M. Guiliano, T. W. Deisenroth and W. C. Frank, *J. Org. Chem.*, **51**, 2304 (1986).
461. G. Cardillo, M. Orena, S. Sandri and C. Tomasini, *Tetrahedron*, **42**, 917 (1986).
462. T. Iversen and D. R. Bundle, *J. Chem. Soc., Chem. Commun.*, 1240 (1981).
463. H. P. Wessel, T. Iversen and D. R. Bundle, *J. Chem. Soc., Perkin Trans. 1*, 2247 (1985).
464. H. Takaku, T. Ito and K. Imai, *Chem. Lett.*, 1005 (1986).
465. U. Widmer, *Synthesis*, 568 (1987).
466. P. Barbier and F. Schneider, *J. Org. Chem.*, **53**, 1218 (1988).
467. R. R. Schmidt and J. Michel, *J. Carbohydr. Chem.*, **4**, 141 (1985).
468. R. R. Schmidt and M. Stumpp, *Ann. Chem.*, 680 (1984).
469. R. R. Schmidt and G. Effenberger, *Ann. Chem.*, 825 (1987).
470. M. G. Hoffmann and R. R. Schmidt, *Ann. Chem.*, 2403 (1985).
471. S. J. Cook, R. Khan and J. M. Brown, *J. Carbohydr. Chem.*, **3**, 343 (1984).
472. C. A. A. Van Boechel, L. P. C. Delbressine and F. M. Kaspersen, *Recl. Trav. Chim, Pays-Bas*, **104**, 259 (1985).
473. H. Rathore, A. H. L. From, K. Ahmed and D. S. Fullerton, *J. Med. Chem.*, **29**, 1945 (1986).
474. I. I. Bityukova, L. V. Volkova and R. P. Evstigneeva, *Zh. Obshch. Khim.*, **55**, 2807 (1985).
475. N. R. Williams, *Carbohydr. Chem., Part 1*, **20**, 19 (1988); **21**, 18 (1989).
476. B. Bernet and A. Vasella, *Tetrahedron Lett.*, **24**, 5491 (1983).
477. E. Schaumann, H. Mrotzek and F. Assmann, *Ann. Chem.*, 334 (1979).
478. H. W. Moore, L. J. Hernandez and R. Chambers, *J. Am. Chem. Soc.*, **100**, 2245 (1978).
479. W. R. McKay and G. R. Proctor, *J. Chem. Soc., Perkin Trans. 1*, 2443 (1981).
480. N. Katagiri, R. Niwa and T. Kato, *Chem. Pharm. Bull.*, **31**, 2899 (1983).
481. I. Antonini, M. Cardellini, F. Claudi and F. M. Moracci, *Synthesis*, 379 (1986).
482. D. H. Aue and D. Thomas, *J. Org. Chem.*, **40**, 2552 (1975).
483. A. Etienne, G. Lonchambon, J. Roques, B. Lemmens and F. Pintard, *C. R. Hebd. Seances Acad. Sci., Ser. C.*, **287**, 285 (1978).
484. R. Bossio, S. Marcaccini and R. Pepino, *Tetrahedron Lett.*, **27**, 4643 (1986).
485. O. Tsuge, S. Kanemasa, T. Yamada and K. Matsuda, *J. Org. Chem.*, **52**, 2523 (1987).
486. T. P. Mawhinney and M. A. Madson, *J. Org. Chem.*, **47**, 3336 (1982).
487. S. D. Young, C. T. Buse and C. H. Heathcock, *Org. Synthesis*, **63**, 79 (1985).
488. G. Bauer and W. Vogt, *Anal. Chem.*, **53**, 917 (1981).
489. T. Huynh-Dinh, A. Kolb, C. Goyuette and J. Igolen, *J. Heterocycl. Chem.*, **12**, 111 (1975).
490. T. Vanek, J. Farkas and J. Gut, *Collect. Czech. Chem. Commun.*, **44**, 1334 (1979).
491. F. Freeman, *Synthesis*, 935 (1981).
492. H. S. El Khadem and J. Kawai, *Carbohydr. Res.*, **153**, 271 (1986).
493. A. S. Serianni, H. A. Nunez and R. Baker, *J. Org. Chem.*, **45**, 3329 (1980).
494. J. Célérier, E. Deloisy, P. Kapron, G. Lhommet and P. Maitte, *Synthesis*, 130 (1981).
495. R. W. H. Berry, P. C. Drewry and H. F. Hodson, *J. Chem. Res. (S)*, 87 (1988).
496. A. Guzman, J. M. Muchowski and N. T. Naal, *J. Org. Chem.*, **46**, 1224 (1981).
497. M. K. Tay, E. E. Aboujaoude, N. Collignon and P. Savignac, *Tetrahedron Lett.*, **28**, 1263 (1987).
498. P. G. Sammes and D. Thetford, *Tetrahedron Lett.*, **27**, 2275 (1986).
499. T. Takido and K. Itabashi, *Synthesis*, 817 (1987).
500. G. A. Rosenthal and D. Thomas, *Anal. Biochem.*, **140**, 246 (1984).

501. A. R. Katritzky and P. Molina-Buendia, *J. Chem. Soc., Perkin Trans. 1*, 1957 (1979).
502. L. Engham, *J. Am. Chem. Soc.*, **106**, 3977 (1984).
503. J. Drabek and M. Boeger, US Patent 4, 364, 959 (1982); *Chem. Abstr.*, **98**, 215201 (1983).
504. T. Kume, S. Tsuboi and K. Isono, *Japanese Patent*, JP 61, 260, 089; *Chem. Abstr.*, **106**, 176661 (1987).
505. R. K. Huff, D. D. Evans and N. H. Anderson, European Patent Appl., 5944 (1979); *Chem. Abstr.*, **93**, 150018 (1980).
506. S. J. Nelson, US Patent 4, 431, 667 (1984); *Chem. Abstr.*, **100**, 191600 (1984).
507. J. Sasaoka, H. Udagawa and K. Mizushiro, Japanese Patent 79, 132, 509 (1979); *Chem. Abstr.*, **93**, 146246 (1980).

CHAPTER 10

Synthesis and chemistry of guanidine derivatives

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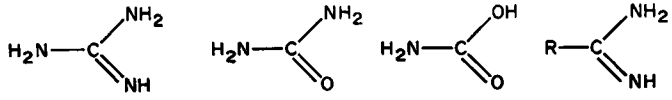
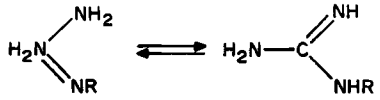
I. INTRODUCTION

Guanidine (**1**) is the imide of urea (**2**), or the amidine of carbamic acid (**3**). The chemistry of guanidines, however, is closely related to that of amidines (**4**) which were reviewed in a previous volume in this series[1], and which are also the subjects of the present supplementary volume. In this chapter, in Section II, the methods of synthesis of guanidines and substituted guanidines will be surveyed. Typical and recent methods have been selected from the vast number of reported methods.



(**1**) (**2**) (**3**) (**4**)

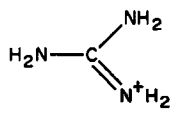
Section III discusses the tautomers of substituted guanidines (**5A** and **5B**). Much confusion in representing the tautomers is found in the literature even now, but recent structural studies, especially by X-ray crystallography, have shown that the tautomer **5A** is generally preferred when the substituent R is an electron-withdrawing group.



(**5A**) (**5B**)

Guanidine is one of the strongest organic bases, and the basicity of some substituted guanidines has been investigated systematically. The results will be described in Section IV.

The C—N bonds in guanidines and guanidinium ions (**6**) are partial double bonds with single-bond character. Introduction of a substituent into guanidine and/or a guanidinium ion changes the character of all of the C—N bonds. In that respect the barriers of isomerization about the C—N bonds have attracted interest and will also be discussed in Section V, along with mechanistic investigations of the isomerization in guanidines and guanidinium ions.



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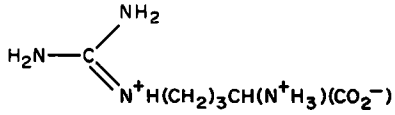


(7)

Suggested coordination of the guanidine (or guanidinium) group of arginine (**7**) with an anion or a metal *in vivo* has prompted several recent model studies. These results will be briefly mentioned in Section VI. In addition, coordination of guanidinium ions with crown ethers will also be described.

Guanidines have been used as starting materials for the synthesis of useful drugs and other preparations. Recent reports of reactions of guanidines will be surveyed in Section VII.

Guanidine and its derivatives have been known to show various biological properties and thus have been studied in the field of pharmacology in recent years. In practical medicine, they have been applied to chemotherapy of illnesses such as hypertension and diabetes.

Although some of the earlier preparative methods have been given in *Rodd's Chemistry of Carbon Compounds*[2], and industrial methods have been mentioned in short reviews[3,4], general reviews on the physicochemical properties, reactions and coordination have not been published. Thus it is our intention in this review to focus on these points.

II. PREPARATION OF GUANIDINES

A survey of methods of preparation of guanidines is described in this section. The discussion is divided into four parts: (A) Synthesis of Guanidine; (B) Synthesis of Carbon-Substituted Guanidines; (C) Synthesis of Nitrogen-Substituted Guanidines; (D) Synthesis of Miscellaneous Guanidines. Commercially available guanidines are listed in Table 1 with suppliers and approximate prices.

A. Synthesis of Guanidine

Guanidine has been obtained as its salts (**6**) by the following reactions: (1) addition of ammonium salts to cyanoguanidine (dicyandiamide) (**8**); (2) addition of ammonium salts to cyanamide (**10**); (3) reaction of thiourea with ammonium salts in the presence of lead(II) chloride. Method (1) is most common in the industrial preparation of guanidinium salts[3–5], but the laboratory synthesis of guanidinium nitrate by method (1)[6,7] is not recommendable due to potential danger[8].

Free guanidine (**1**) is strongly basic ($pK_a = 13.6$, Section IV), very hygroscopic and crystalline (mp 48–49 °C[10]). It also absorbs carbon dioxide. It has been isolated by treating an alcoholic solution of guanidinium perchlorate with potassium hydroxide[9,10].

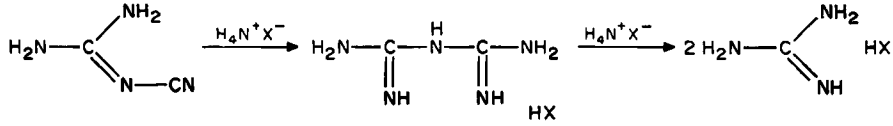
TABLE 1. Typical commercially available guanidines

Compounds[a]	Suppliers A[b]	F[c]	S[d]	Price[e]
4-Aminobutylguanidine (Agmatine) sulfate	−	−	+	$$$
D-Arginine free base, hydrochloride	+	+	+	$$$
L-Arginine free base, hydrochloride	+	+	+	$
methyl ester	−	+	+	$$
phosphate	−	−	+	$$$$
L-Canavanine sulfate	+	+	+	$$$
Creatine anhydrous or hydrate	+	+	+	$
Creatinine free base	+	+	+	$
Cyanoguanidine (Dicyandiamide)	+	+	+	$
[(2,6-Dichlorobenzylidene)amino]guanidine (Guanabenz)	−	−	+	$$$$
Ethylguanidine hydrochloride	+	−	−	$$
1-Ethyl-3-nitro-1-nitrosoguanidine	+	−	+	$$
Guanidine acetate	−	+	−	$
carbonate	+	+	+	$
hydrochloride	+	+	+	$
nitrate	+	+	+	$
sulfate	+	+	−	$
thiocyanate	+	+	+	$
Guanidinoacetic acid	+	+	+	$
4-Guanidinobenzoic acid hydrochloride	−	+	+	$$$
4-Guanidinobutyric acid	−	+	+	$$$
3-Guanidinopropionic acid	−	−	+	$$$
Guanidinosuccinic acid	−	−	+	$$$
Methylguanidine hydrochloride	+	−	+	$$
1-Methyl-3-nitroguanidine	+	−	−	$
1-Methyl-3-nitro-1-nitrosoguanidine	+	+	+	$$
Nitroguanidine	+	+	−	$
1-Propyl-3-nitro-1-nitrosoguanidine	+	−	+	$$
1,1,3,3-Tetramethylguanidine	+	+	+	$

[a]Trivial name is given in parentheses.
[b]Aldrich 1990–1991.
[c]Fluka 1990–1991.
[d]Sigma 1990.
[e]$: *ca* $20 or less/100 g, $$: *ca* $20–90/25 g, $$$: *ca* $10–50/1 g, $$$$: *ca* $20 or more/100 mg.

1. *Addition of ammonium salts to cyanoguanidine (8)*

Guanidinium salts (2) have been obtained directly from cyanoguanidine (8) by fusion (at 160 °C for nitrate, at 260 °C for benzenesulfonate) with 2 equiv of ammonium salts[6,7,11] in 80–95% yield. Again it should be noted that the preparation of guanidinium nitrate by this procedure is reported to be dangerous[8]. By use of an equimolecular mixture

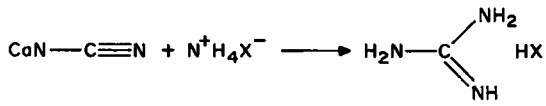


(8) (9) (6)

of **8** and ammonium salts, biguanide (diguanide) (**9**) can be isolated[11], which undergoes further reaction with a second molecule of the ammonium salt to give **6**.

*2. Addition of ammonium salts to cyanamide (**10**)*

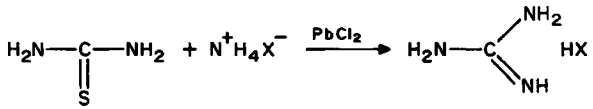
The fusion of calcium cyanamide and three moles of ammonium salt (at 100 °C for nitrate) gives guanidinium salt **6** (in 75% yield for nitrate[12]). The advantage of this method is that it avoids the isolation of pure cyanamide, which is generated *in situ* under the reaction condition.



(10) **(6)**

*3. Reaction of thiourea (**11**) with ammonium salts in the presence of lead(II) chloride*

Thiourea (**11**) reacts with a large excess of ammonium salts (*ca* 20 equiv) in the presence of 1 equiv. of $PbCl_2$ at 300 °C in 95% yield[13]. Unfortunately, the process requires the use of a large excess of ammonium salts and heating in an autoclave.



(11) **(6)**

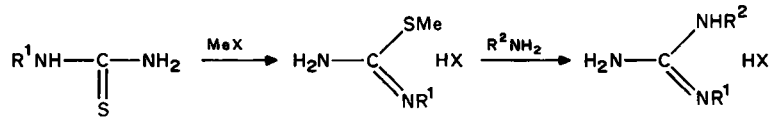
B. Synthesis of Carbon-substituted Guanidines

Various methods of preparing alkyl- and arylguanidines from thiourea, urea, carbodiimide, cyanamide, and cyanoguanidine are described, as well as alkylation and arylation of guanidine and syntheses of biguanides (**9**), cyanoguanidines (**8**), guanidine, derived acids, guanylurea, guanylthiourea, and acylguanidines.

1. Synthesis from thiourea

In practice two types of activation of thioureas are used for the reaction with amines: (a) conversion to *S*-methylisothiourea (**12**); (b) conversion to aminoiminomethanesulfonic acids (**16**).

*a. Conversion to S-methylisothiourea (**12**).* Addition of methyl iodide or dimethyl sulfate to thiourea gives almost quantitative yields of the *S*-methylisothiuronium salt (**12**), which can be isolated. The salt is converted into alkl- and arylguanidinium salt (**13**) with

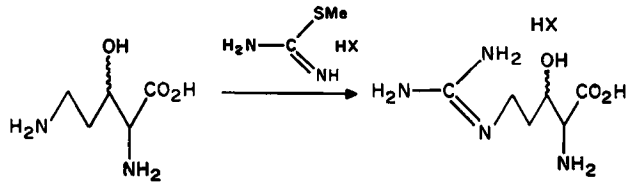


(12) **(13)**

amines at 60–80 °C (Rathke procedure)[14–16,20]. This is one of the most useful methods for preparation of various guanidines (*vide infra*); the yields are generally good to excellent.

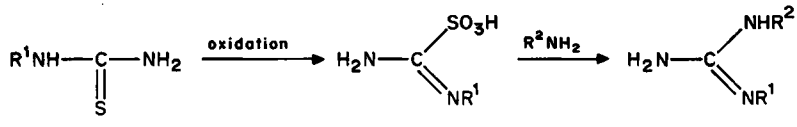
All of the eight possible methyl-substituted guanidines have been prepared by this method by use of *S*-methylisothioureas in 40–50% yields after crystallization[17,18].

3(*R*)- and 3(*S*)-hydroxy-(2*S*)-arginines (**14**) have been obtained recently from the corresponding *β*-hydroxyornithines (**15**) in 57 and 60% yield by this method[19].

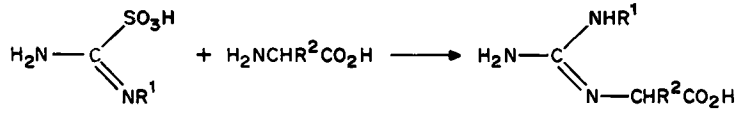


(**15**) (**14**)

b. Conversion to aminoiminomethanesulfonic acids (16). Oxidation of thioureas by peracids gives aminoiminomethanesulfonic acids (**16**), some of which (unsubstituted and phenylated **16**) can be isolated in 50–80% yield and react with amines at room temperature to give substituted guanidines (**17**)[21,22]. The method is relatively new, and amino acids react better with **16** than with the *S*-methylisothiuronium salt (**12**) to give guanidino acids (**18**)[21]. The yield in the reaction of unsubstituted **16** with glycine is 80%. Aminoiminomethanesulfinic acids give **18** in much poorer yields than the corresponding aminoiminomethanesulfonic acids[21].



(**16**) (**17**)



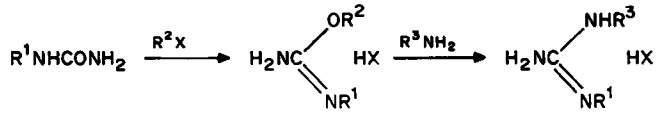
(**16**) (**18**)

2. Synthesis from urea

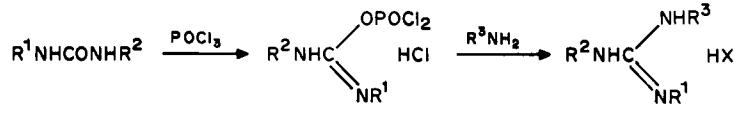
Three types of activation of urea are used for the reaction with amines: (a) conversion to *O*-alkylisourea; (b) activation by phosphoryl chloride; (c) activation by phosgene.

a. Conversion to O-alkylisourea (19). Alkylation of urea gives *O*-alkylisouronium salts (**19**), which react with amines to afford substituted guanidines (**17**)[22,23]. The reaction is the extension of the well-known Pinner method for the preparation of amidines[24], and has also been a method for the preparation of various guanidines.

b. Activation by phosphoryl chloride. Reaction of urea with $POCl_3$ gives complex **20**, the structure of which has not been confirmed. The latter reacts *in situ* with amines to give trisubstituted guanidines (**17a**)[25].



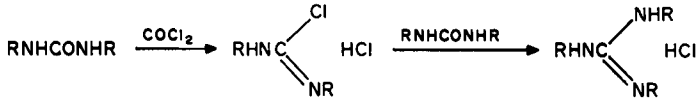
(19) (17)



(20) (17a)

A series of 2-(substituted phenyl)-1,1,3,3-tetramethylguanidines has been prepared by this method[26].

c. Activation by phosgene. *N,N'*-Disubstituted ureas react with phosgene to give *N,N',N''*-trisubstituted guanidinium chloride (**17a**), directly[27]. The initial product is considered to be chloroformamidinium chloride (**21**), which reacts with a second molecule of the urea and breaks down to a trisubstituted guanidine and isocyanate[27]. The reaction may be useful for the preparation of symmetrical *N,N',N''*-trialkylguanidinium salts[28], but unsymmetrical ureas may give mixtures of guanidines[27].

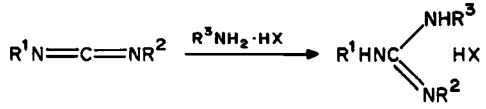


(21) (17a)

3. Synthesis from carbodiimide

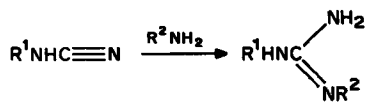
Carbodiimide by reaction with alcohol in the presence of alkoxides[29] gives *O*-alkylisourea, from which substituted guanidines may be prepared (see previous section).

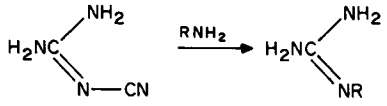
The reaction of an amine salt with carbodiimide gives a guanidinium salt directly[30].



4. Synthesis from cyanamide and cyanoguanidine

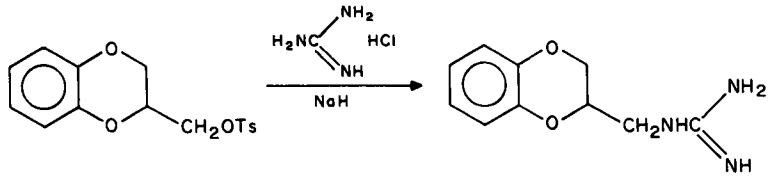
The method is the extension of those previously described for the preparation of guanidine, and reaction of an amine with cyanamide[3,31,32] at room temperature has been used widely for preparation of substituted guanidines. The yield from an anilinium salt with cyanamide is around 70%[31]. Reaction of an alkylamine with cyanoguanidine may give a mixture of products via formation of biguanide[11].





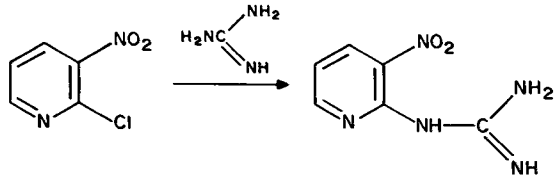
5. Alkylation and arylation of guanidine

Alkylation of guanidine by simple alkyl halides often leads to mixtures of products. However, a sterically hindered tosylate (**22**) reacts with free guanidine to give a monosubstituted adduct (**23**)[33].



(**22**) (**23**)

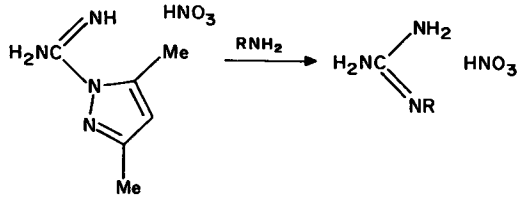
Arylation of guanidines is also limited, but a strongly electrophilic pyridine (**24**) reacts with free guanidine to give adduct **25**[34].



(**24**) (**25**)

6. Miscellaneous methods

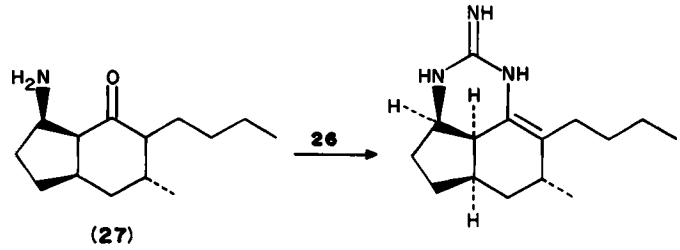
Substituted guanidinium salts are obtained[35] by reaction of amines with 3,5-dimethyl-1-guanylpyrazole nitrate (**26**), which is obtained by reaction of acetylacetone with aminoguanidine nitrate[36].



(**26**)

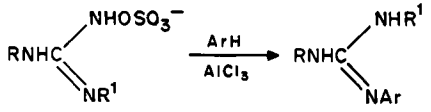
This method has been used in the final step of the synthesis of (–)-ptilocaulin. Reaction of β-aminoketone (**27**) with **26** gives (–)-ptilocaulin in 58–65% yield after 6 h at 145–155 °C[37].

A guanidino group is introduced electrophilically into aromatic hydrocarbons by the reaction of hydroxyguanidine-*O*-sulfonic acid (**28**) with aluminum chloride[38].



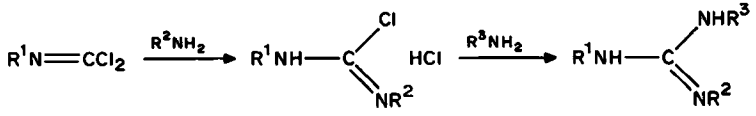
(27)

(−)-ptilocaulin



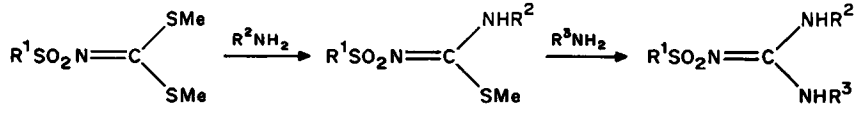
(28)

Isocyanide dichlorides (29) have been used for the preparation of tri-, tetra- and penta-substituted guanidines[39]. Some of the intermediate chlorides (30) can be isolated and reacted with another amine.



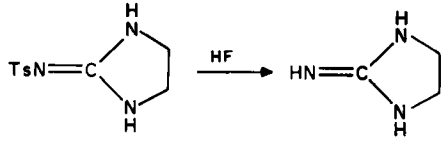
(29) (30)

Reaction of amines with *S,S*-dimethyl-*N*-sulfonyliminodithiocarbonimidates (31), which are easily prepared from the reaction of sulfonylamide with carbon disulfide in the presence of alkali followed by quenching with MeI, gives *N*-sulfonylisothioureas (32)[40] in 50–80% yield. Compound 31 affords *N*-sulfonylguanidines (33) by reaction with amines as described in Section II.B.1.a.



(31) (32) (33)

The cyclic tosylguanidine (34) prepared from the corresponding diamine by this procedure is detosylated by the reaction of anhydrous hydrogen fluoride[41].

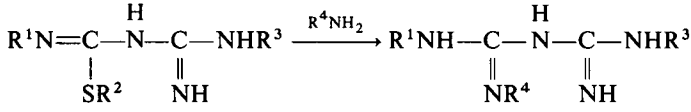


(34)

7. Synthesis of biguanide

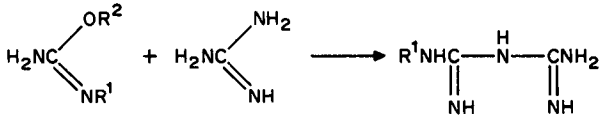
Synthetic methods for biguanide derivatives have been reviewed[42]. These are essentially extensions of the methods for guanidines and carbon-substituted guanidines:

a. Reaction of amines with N^1,N^5-disubstituted guanyl-S-alkylisothioureas (35)[43]. Compound **35** prepared from guanylthiourea reacts with amines to give N^1,N^5-disubstituted biguanides.

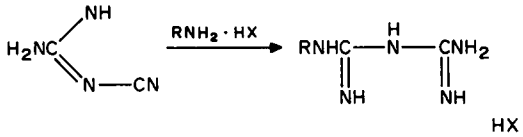


(35)

b. Reaction of guanidine with O-alkylisourea[44]. *O*-Alkylisourea prepared from urea reacts with guanidine to give substituted biguanide.

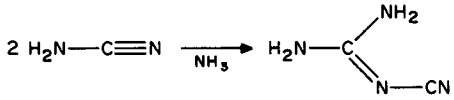


c. Reaction of cyanoguanidine with amine salts[11,45]. Alkyl- or arylamine reacts with cyanoguanidine to give substituted biguanide.

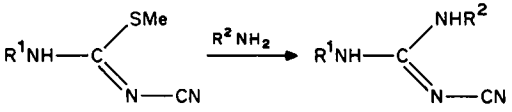


8. Synthesis of cyanoguanidine

Cyanoguanidine is commercially available (Table 1) and has been prepared by dimerization of cyanamide[46].



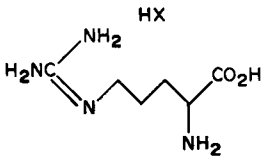
Substituted cyanoguanidines have been obtained by the reaction of ammonia or substituted amines with cyanoisourea (**36**), which is synthesized from the reaction of sodium cyanamide with isothiocyanate followed by methylation of the resulting adduct[47,48].



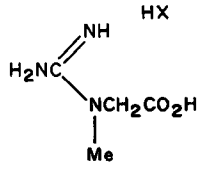
(36)

9. Synthesis of guanidine-derived acids

Arginine (7) and creatine (methylguanidinoacetic acid, 37) are typical compounds in this group.



(7)



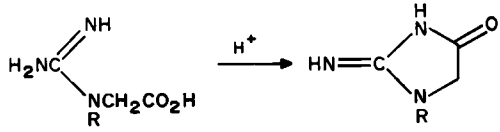
(37)

The isothiourea method (Section II.B.1.a) and the aminoiminomethanesulfonic acid method (Section II.B.1.b) for the preparation of carbon-substituted guanidine are most common for the synthesis of guanidino acids.

Guanidinoacetic acid (glycocyamine)[21,49], creatine[50], hydroxyarginines[19], 4-guanidinobutanoic acid[21] and other guanidine derivatives have been prepared by these methods.

L-Arginine has been obtained from gelatine conveniently[51]. Cyclization of α-guanidinoacetic acids occurs on heating with acids to give imidazoline derivatives (38, 39)[52,53].

Glycocyamidines have also been prepared by the reaction of guanidine with glyoxals[54].



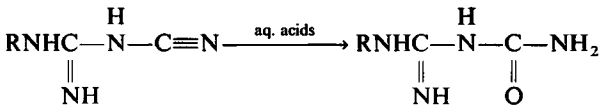
R=H glycocyamine — glycocyamidine (38)

R=Me creatine — creatinine (39)

10. Synthesis of guanylurea and guanylthiourea

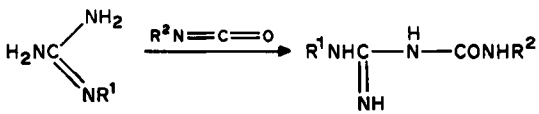
Methods of preparation of these compounds have already been reviewed[42]. The most common methods for guanylureas include:

a. Acid hydrolysis of cyanoguanidine[55]. Cyanoguanidines are hydrolyzed under acidic conditions to give guanylureas (40).



(40)

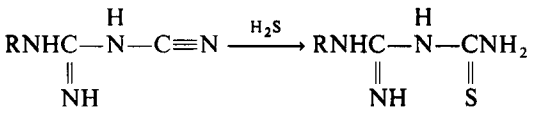
b. Reaction of isocyanate with guanidine[56]. Isocyanate reacts easily with guanidine to form guanylurea (40).



(40)

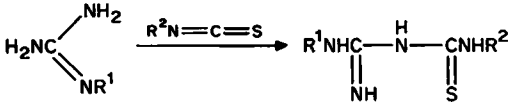
Similarly, the most common methods for guanylthioureas include:

a. Addition of hydrogen sulfide to cyanoguanidine[57]. Cyanoguanidines react with hydrogen sulfide to give guanylthioureas (**41**).



(**41**)

b. Reaction of isothiocyanate with guanidine[58]. Isothiocyanates react with guanidine to afford guanylthioureas (**41**).

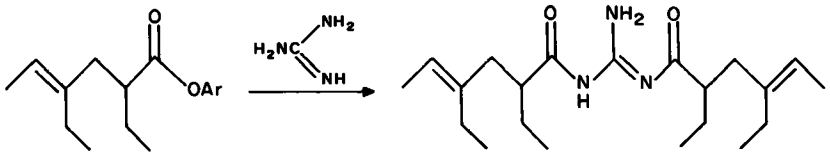


(**41**)

11. Synthesis of acylguanidines

Monoacylguanidines have been synthesized by the following methods:

a. Acylation of guanidine with acid anhydride[59] *or ester*[60]. Guanidine is easily acylated by acid anhydrides or esters. A diacylguanidine (triophamine, **42**) was synthesized by the reaction of ester (**43**) with guanidine in 48% yield[61].



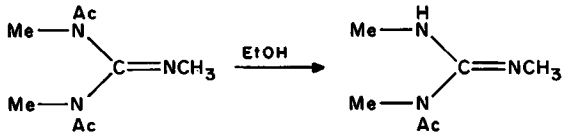
(**43**)

Ar= *p*-$NO_2C_6H_4$

(**42**)

triophamine

b. Controlled deacylation of di- or triacetyl guanidine[62]. Acetyl-*N*,*N*′,*N*″-trimethylguanidine (**44**) is prepared from the corresponding diacetyl compound (**45**) in 41% yield by use of absolute ethanol at 75 °C for 1.5 h[63].



(**45**) (**44**)

Cyclization products of α-guanidino acids as described in Section II.B.9 may be considered to be (cyclic) acylguanidines.

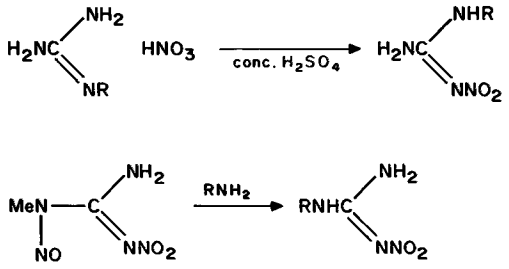
Alkoxycarbonylguanidines have been obtained from guanylureas by treatment with alcoholic hydrogen chloride[64].

C. Synthesis of Nitrogen-substituted Guanidines

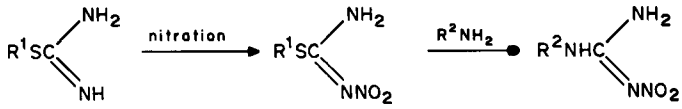
In this section the syntheses of nitroguanidines, nitrosoguanidines and aminoguanidines are surveyed.

1. *Synthesis of nitroguanidines*

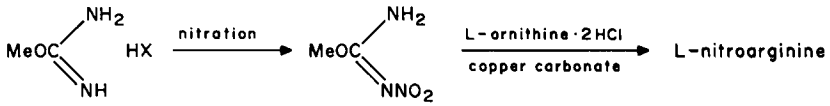
The chemistry of nitroguanidines was reviewed in 1952[65]. At that time nitration of guanidines was the only common method for preparing nitroguanidines[66–68], although several nitroguanidines had been prepared by treatment of *N*-methyl-*N*-nitroso-*N'*-nitroguanidines (*vide infra*) with amines[69,70].



The isothiourea method has been used for the preparation of nitroguanidines since 1954[71]. Amines react with nitroisothiourea, which is obtained from isothiourea by nitration.



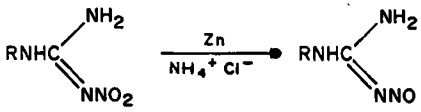
The isourea method has also been reported to be useful for the preparation of nitroguanidino acids, such as nitroarginine[72]. Nitroisoureas have been obtained by nitration of isoureas.



2. *Synthesis of nitrosoguanidines*

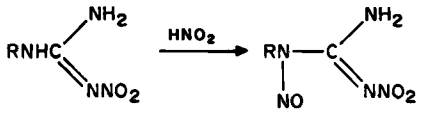
Nitrosoguanidines have been synthesized by the methods given below.

a. Controlled reduction of nitroguanidines. Nitrosoguanidines (**46**) have been obtained in 45–52% yield from nitroguanidines (**47**) with zinc dust in the presence of aqueous ammonium chloride below 20–25 °C[73].



(47) (46)

b. Nitrosation of guanidines. Nitrosation has been carried out with nitrous acid[70] or nitrosyl chloride[74]. *N*-Alkyl-*N*-nitroso-*N'*-nitroguanidines (**48**), which are among the important precursors for diazoalkanes[75], have been obtained from *N*-alkyl-*N'*-nitroguanidines (**49**) by nitrosation[70].

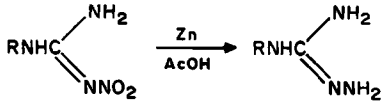


(49) (48)

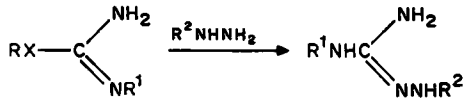
3. Synthesis of aminoguanidines

The chemistry of aminoguanidines was reviewed in 1939[76] and 1962[77]. The most common synthetic methods for aminoguanidines are given below.

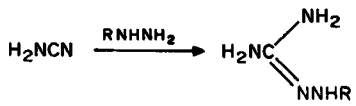
a. Reduction of nitroguanidine. Aminoguanidines have been obtained from nitroguanidines with zinc and acetic acid at 40 °C[78].



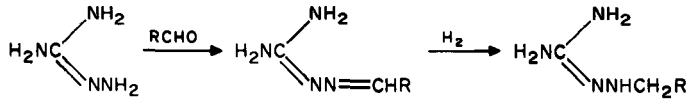
b. Reaction of hydrazine with isothiourea[79]*, isourea*[80] *and cyanamide*[81]. These are the extensions of the previously described methods for carbon-substituted guanidines, in which amines are used instead of hydrazines.



X=O or S



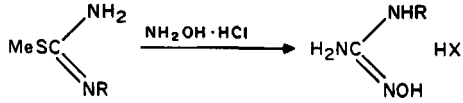
Catalytic hydrogenation of guanyl hydrazones, which have been prepared by condensation of aminoguanidine with aldehydes or ketones, gives 1-(alkylamino) guanidines[82].

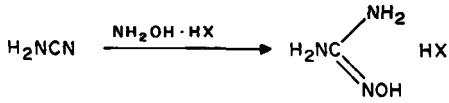


D. Synthesis of Miscellaneous Guanidines

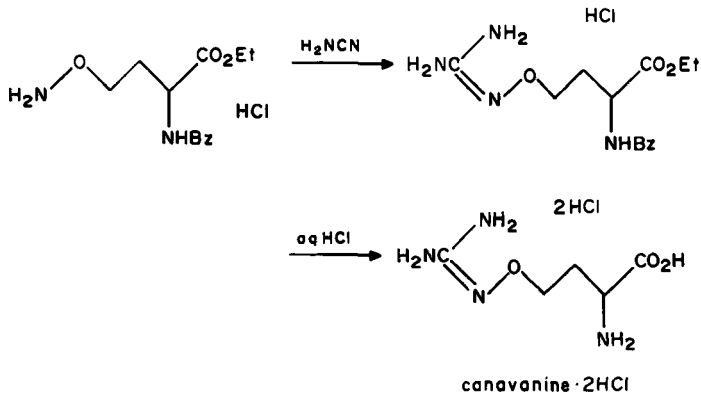
1. *Synthesis of oxygen-substituted guanidines*

N-Hydroxyguanidinium salts have been prepared by the reaction of hydroxylamine with *S*-methylisothiourea[83] or cyanamide[84].





Canavanine (**50**) has been synthesized in 80% yield by the cyanamide method[85], in contrast to the isothiourea or isourea[86] method which gives much lower yields of **50**.



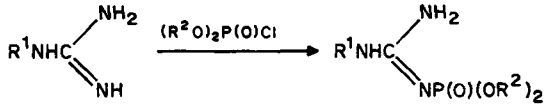
canavanine·2HCl

(50)

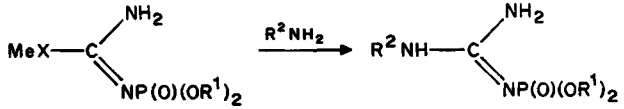
2. *Synthesis of phosphorylguanidine*

N-Phosphorylguanidines have been prepared by the following methods.

a. Phosphorylation of guanidines with $POCl_3$[87] *or* $(RO)_2P(O)Cl$[88]. Phosphocreatine has been prepared by phosphorylation.



b. Reaction of amines with phosphorylisourea[89] *or phosphorylisothiourea*[90]. Phosphorylisoureas and phosphorylisothioureas are prepared by phosphorylation from isoureas or isothioureas, respectively. Phosphoarginine has been synthesized by the use of phosphorylisourea.

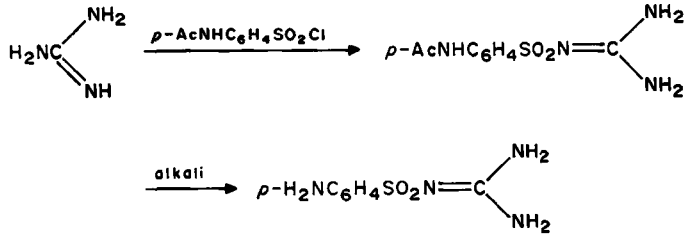


X=O or S

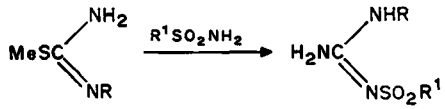
3. Synthesis of sulfonylguanidine

N-Sulfonylguanidines have been prepared by the methods given below.

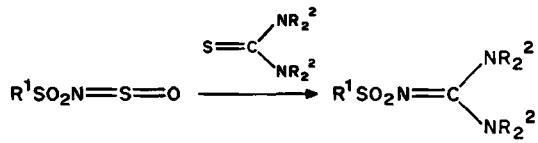
a. Sulfonylation of guanidines with $ArSO_2Cl$[3,17,91]. The useful drug sulfaguanidine has been prepared by sulfonylation of guanidine with *p*-acetylaminosulfonyl chloride followed by hydrolysis.



b. Reaction of sulfonamides with isothiourea[92].

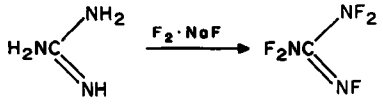


c. Reaction of thiourea with N-sulfinylsulfonamide[92].



4. Synthesis of halogenated guanidines

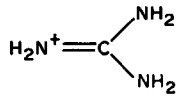
N-Haloguanidines, which are usually explosive on heating, have been prepared by halogenation of guanidines with NaOCl[93], NaOBr[94], Cl_2[95], Br_2[95] and F_2[96]. Perfluoroguanidine has been prepared from guanidinium hydrochloride with F_2[96].



III. STRUCTURE OF GUANIDINES

A. Structure of Guanidinium Ions

Determination of the crystal structure of guanidinium chloride has revealed that the three nitrogen atoms are nearly equivalent and lie in almost the same plane as the carbon atom[97]. The structure is slightly distorted by crystal packing forces to the C_{3v} symmetry. The carbon–nitrogen bond lengths (1.318, 1.325, 1.325 Å) are halfway between the normal C—N single bond length (1.47 Å) and the pure double bond length (1.24 Å)[98]. These data confirm that the structure of the guanidinium ion is a resonance hybrid of three equivalent forms, one of which is shown below.



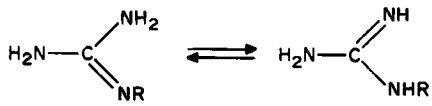
The infrared spectrum of guanidinium chloride and iodide and their perdeutero derivatives have been obtained, and assignments for the fundamental vibration are consistent with the symmetrical D_{3h} structure[99].

In the crystal structures of 4-guanidinobutanoic acid hydrochloride[100] and 3-guanidinopropionic acid[101], the three C—N bond lengths are reported to be 1.32, 1.32 and 1.34 Å, and 1.32, 1.32 and 1.33 Å, respectively.

These results indicate that the structures of carbon-substituted guanidinium ions do not differ from that of the parent guanidinium ion, suggesting that the contribution of the three resonance structures is comparable.

B. Structure of Substituted Guanidines

A neutral monosubstituted guanidine can exist in two forms, which have conventionally been referred to as the amino (**a**) and imino (**b**) form. Unfortunately, the strong basicity of the guanidino group in simple alkyl- and arylguanidines has precluded the X-ray diffraction studies of these compounds.



amino form (a) imino form (b)

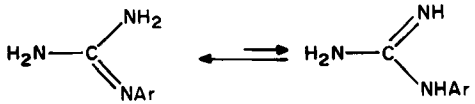
Recently ^{15}N NMR has been employed to investigate the amino-to-imino equilibrium constant of L-arginine (**51**)[102] and of arylguanidines (**52**)[103] in solutions of pH 14 by comparison of the chemical shifts for these compounds and related model compounds such as tetramethylguanidine and pentamethylguanidine. The estimated equilibrium constant for L-arginine is about 1.8, hence the imino form (**51b**) is slightly favored. The preferred tautomer in arylguanidines is, in contrast, the amino form (**52a**).

amino form 36%

(**51a**)

imino form 64%

(**51b**)



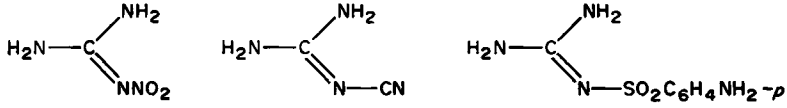
(**52a**) (**52b**)

Guanidino groups remain uncharged under neutral conditions in guanidines with electron-withdrawing substituents such as nitroguanidine (**53**), cyanoguanidine (**54**), sulfaguanidine (**55**), L-canavanine (**56**) and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (**57**; MNNG). The industrial and biological importance of these compounds, in addition to the ease of their isolation, have made them widely studied molecules. Interestingly, many of them were originally proposed to exist in the wrong form [imino (**b**)].

For nitroguanidine, the imino form (**53b**) was favored[104] until McKay cast doubt on this, based on the chemical studies[105]. The amino form (**53a**) has been supported by work on the ^1H NMR[106] of crystalline nitroguanidine, and by the acidity[107] and the dipole moment[108] measurements of nitroguanidines. Finally, a crystal structure study by X-ray diffraction has established the amino form (**53a**)[109].

In the case of cyanoguanidine, the originally suggested imino form (**54b**)[110] was corrected when X-ray crystallographic analysis pointed to the amino form (**54a**) in 1940[111]. IR spectra[112] and *ab initio* STO-3G calculations[113] have also supported the amino form (**54a**).

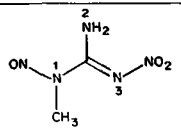
Crystallographic studies of sulfaguanidine hydrate (**55**)[114], L-canavanine (**56**)[115] and

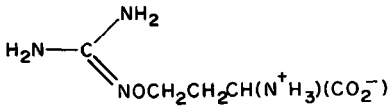


nitroguanidine cyanoguanidine sulfaguanidine hydrate

(**53a**) (**54a**) (**55a**)

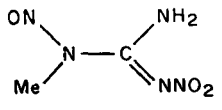
TABLE 2. Structural parameters of compounds containing the guanidino group as determined by X-ray diffraction

Compound	R	C—N bond lengths (Å)			NCN bond angles (deg)			Reference
		C—N^1	C—N^2	C—N^3	N^1CN^2	N^2CN^3	N^1CN^3	
Nitroguanidine (53)	NO_2	1.34	1.34	1.35	118	129	112	109
Cyanoguanidine (54)	CN	1.333	1.339	1.341	118.7	123.8	117.5	117
Sulfaguanidine hydrate (55)	$SO_2C_6H_4NH_2$	1.329	1.334	1.348	118.1	126.0	115.8	114
L-Canavanine (56)	$O(CH_2)_2CH(CO_2^-)NH_3^+$	1.361	1.347	1.302	116.4	125.2	118.4	115
N-Methyl-*N'*-nitro-*N*-nitrosoguanidine (57)		1.391	1.307	1.346	119.3	129.1	111.7	116



L-canavanine

(56a)



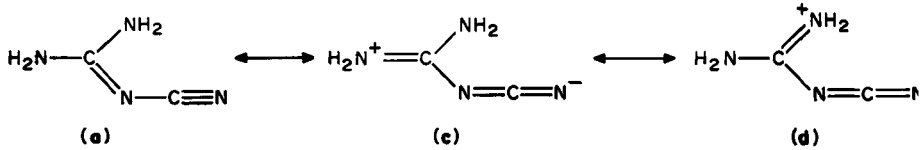
N-methyl-*N'*-nitro-*N*-nitrosoguanidine

(MNNG)

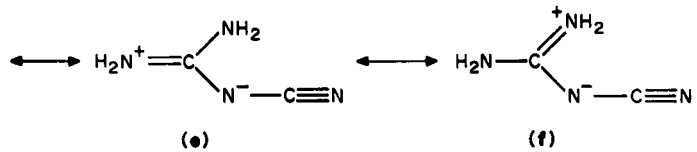
(57a)

MNNG (57)[116], and an ^{15}N NMR study of sulfaguanidine[117] have also been accomplished in recent years. All of them suggest the amino structure (a) as illustrated above. Some bond lengths and bond angles in these compounds are listed in Table 2.

The similarity in C—N bond lengths around the central carbon in the guanidino group has been explained by the presence of zwitterionic resonance hybrid structures, for example **a**, **c**, **d** for cyanoguanidine[111]. Support for this explanation has been acquired by a low-temperature X-ray measurement of cyanoguanidine, which has revealed the charge deformation density. The importance of the two additional resonance structures **e** and **f** has been suggested[117].

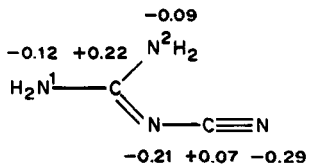


(a) (c) (d)



(e) (f)

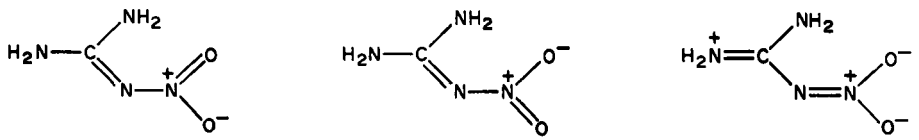
The calculated charge distribution of cyanoguanidine (54) is shown below[118].

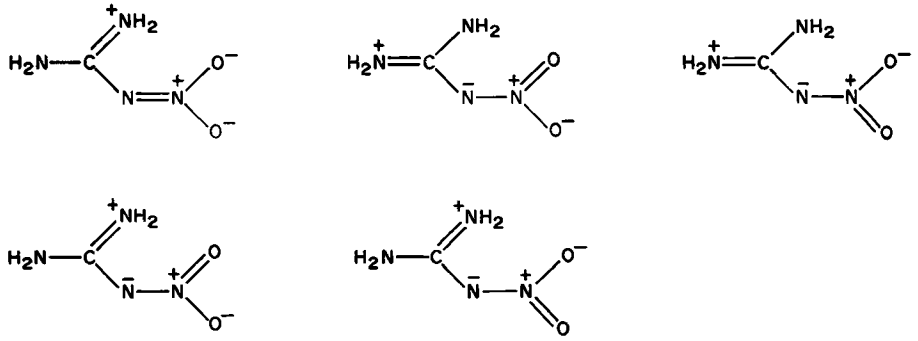


+0.21(total) for *H*,*H* of N^2H_2

+0.18(total) for *H*,*H* of N^1H_2

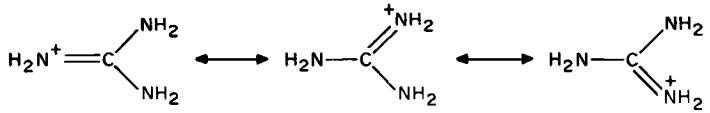
The VESCF(BJ)CI MO calculation for nitroguanidine has also indicated a highly delocalized electronic structure[119], which is a resonance hybrid of the eight forms shown below.





IV. BASICITY OF GUANIDINES

Guanidine is a monoacid base of strength comparable to sodium hydroxide. The remarkable stability of the guanidinium ion, which is inert to boiling water, has sometimes been discussed based on 'Y-delocalization (or Y-aromaticity)'[120–123], but it has also been explained well by resonance among three structures that are all equivalent[124].



The pK_a value of the parent guanidinium salt has been determined by potentiometric titration to be 13.6[125] in water at 25 °C.

A. Basicity of Methyl-substituted Guanidines

The pK_a values of all the possible methyl-substituted guanidines have been reported[17]. The results are cited in Table 3, indicating that the values are only slightly affected by methyl substitution. A small base-weakening effect is observed by introduction of a methyl group into guanidine because the substitution destroys the equivalence of the three

TABLE 3. pK_a values for methyl-substituted guanidinium salts in water at 25 °C. Reproduced by permission of the Royal Society of Chemistry from Ref. 17

Compound	pK_a
Guanidinium sulfate	13.6
N-Methylguanidinium sulfate	13.4
N,N-Dimethylguanidinium sulfate	13.4
N,N'-Dimethylguanidinium iodide	13.6
N,N,N'-Trimethylguanidinium iodide	13.6
N,N',N''-Trimethylguanidinium sulfate	13.9
N,N,N',N'-Tetramethylguanidinium iodide	13.6
N,N,N',N''-Tetramethylguanidinium iodide	13.9
Pentamethylguanidinium iodide	13.8

nitrogens. The combined electronic base-strengthening effect of the methyl groups compensates for the nonequivalence effect, but among isomers with the same number of methyl substituents the ones with the more even distribution of methyl groups are stronger bases.

B. Basicity of Monosubstituted Guanidines

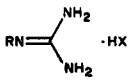
A correlation equation for the pK_a values of monosubstituted guanidinium salts (16 compounds—see Table 4) with the Hammett σ_I value has been proposed[125]:

$$pK_a = 14.18(\pm 0.25) - 22.58(\pm 0.78)\sigma_I$$

This is a revision of the equation proposed by Charton[126] derived from eight compounds, namely by $pK_a = 14.20 - 24.09\sigma_I$.

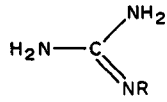
In these equations, the pK_a values of guanidine and methylguanidine are recalculated based on statistical factors to provide a common basis for the correlation. The dissociation constants are multiplied by the statistical factors of 6 and 5, respectively, for the number of protons that can dissociate. Thus it should be noted that the pK_a values of these compounds in Table 4 are larger than those in Table 3 by log 6 (guanidine) or log 5

TABLE 4. pK_a values for monosubstituted guanidinium salts in water at 25 °C. Reproduced by permission of the Royal Society of Chemistry from Ref. 125.

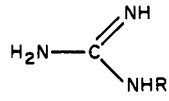
Compound 	pK_a[a]	σ_I[b]	ΔpK_a[c]
Me	**14.1**[d,e]	−0.01	−0.31
H	**14.38**[d,e]	0.00	+0.20
Ph	**10.77**[d,f]	0.12	−0.70
NH_2	**11.04**[d]	0.17	+0.70
4-$O_2NC_6H_4$	**9.13** ± 0.02	0.23	+0.14
OH	**7.96** ± 0.04	0.24	−0.80
NHCOPh	**7.94** ± 0.06	0.28	+0.08
$CONH_2$	**8.11** ± 0.05	0.28	+0.25
COMe	**8.20** ± 0.05	0.30	+0.79
COPh	**6.98** ± 0.05	0.30	−0.43
CO_2Et	**7.03** ± 0.05	0.30	−0.38
NHPh	**8.26** ± 0.06	0.30	+0.85
OMe	**7.46**[f]	0.30	+0.05
$OCH_2CO_2^-$	7.51[g]	0.32	+0.56
$CSNH_2$	**5.56** ± 0.02	0.38	−0.04
SO_2NH_2	**1.83** ± 0.02	0.53	−0.28
CN	−0.85 ± 0.05[g]	0.57	−2.16
NO_2	**−0.98** ± 0.02	0.67	−0.03

[a] pK_a values in bold type are those used in the correlation described in the text.
[b] σ_I values are from M. Charton, *Prog. Phys. Org. Chem.*, **13**, 119 (1981).
[c] ΔpK_a is the deviation of the observed from the calculated pK_a value according to the equation in the text.
[d] From D. D. Perrin, *Dissociation Constants of Bases in Aqueous Solution*, Butterworths, London, 1972.
[e] With statistical corrections, × 5 applied to methylguanidine and × 6 to guanidine.
[f] Reference 126.
[g] Not included in the correlation.

(methylguanidine). The authors assume that the amino tautomer (**a**) predominates when R is an electron acceptor and the imino tautomer (**b**) is considered predominant or the two isomers are present in comparable amounts when R is an electron donor.



amino form (a)



imino form (b)

$$pK_a = 14.0 - 3.60\sigma^*$$

Perrin also has proposed an equation[127], however he did not present any details.

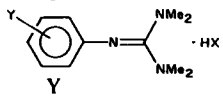
C. Basicity of Substituted 2-Phenyl-1,1,3,3-tetramethylguanidines

A number of pK_a values of substituted 2-phenyl-1,1,3,3-tetramethylguanidines in water[26] and in acetonitrile[128] have been reported. Several data are listed in Table 5. A good relation of the pK_a values in water with the Hammett's $\sigma_{m,p}$ values is found:

$$pK_a(\text{in water}) = (12.12 \pm 0.02) - (1.84 \pm 0.05)\sigma_{m,p}$$

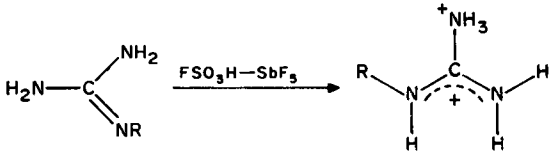
The difference in pK_a in acetonitrile (AN) and water, ΔpK^{AN-H_2O}, is fairly constant: $\Delta pK_a^{AN-H_2O} = 8.1 \pm 0.5$.

TABLE 5. pK_a values for substituted 2-phenyl-1,1,3,3-tetramethylguanidinium salts in water and in acetonitrile (AN) at 25 °C. Reproduced by permission of the National Research Council of Canada from Ref. 128

Compound  Y	pK_a^{AN}	$pK_a^{H_2O}$	$\Delta pK_a^{AN-H_2O}$
H	20.6 ± 0.1	12.18 ± 0.02	8.4 ± 0.1
4-NO_2	17.82 ± 0.07	9.78 ± 0.09	8.0 ± 0.1
4-CN	18.37 ± 0.08	10.95 ± 0.05	7.42 ± 0.09
4-CF_3	19.00 ± 0.09	11.36 ± 0.04	7.6 ± 0.1
4-Cl	19.68 ± 0.10	11.70 ± 0.02	8.0 ± 0.1
4-Br	19.6 ± 0.1	11.60 ± 0.10	8.0 ± 0.1
4-Me	20.9 ± 0.1	12.37 ± 0.01	8.5 ± 0.1
4-OMe	21.0 ± 0.1	12.57 ± 0.03	8.4 ± 0.1
3-CF_3	19.09 ± 0.09	—	—
3-Cl	19.30 ± 0.09	11.47 ± 0.09	7.8 ± 0.2
3-Me	20.8 ± 0.1	12.25 ± 0.04	8.5 ± 0.1
3-OMe	20.4 ± 0.1	11.96 ± 0.04	8.4 ± 0.1
2-CF_3	17.70 ± 0.08	—	—
2-Cl	18.80 ± 0.09	11.2 ± 0.1	7.6 ± 0.1
2-Me	20.5 ± 0.1	12.28 ± 0.03	8.2 ± 0.1
2-OMe	21.0 ± 0.1	12.19 ± 0.04	8.8 ± 0.1

D. Miscellaneous Acid and Base Properties of Guanidines

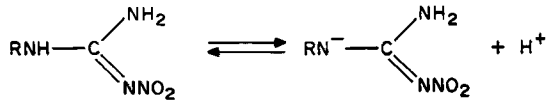
Diprotonated guanidines have been observed by ^1H NMR in the FSO_3H–SbF_5(magic acid) system[129].



The NMR spectrum of the diprotonated guanidine at $-80\,°C$ consists of an N^+H_3 group at δ 8.68 and two protons at δ 8.07 and 7.85.

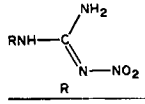
In methylguanidine, the second protonation is at one of the primary amine groups.

The acidity of 1-substituted 3-nitroguanidines has been reported[126]. In the nitroguanidines, the corresponding anions are fairly stable. Values of pK_a are given in Table 6.



The lithium derivative, $[(Me_2N)_2C{=}NLi]_2$, has been isolated by the reaction of *N,N,N′,N′*-tetramethylguanidine and methyllithium[130]. The lithium compound has been determined by cryoscopy to be dimeric in benzene.

TABLE 6. pK_a values for 1-substituted 3-nitroguanidines in water at 24 °C. Reprinted with permission from Charton, *J. Org. Chem.*, **30**, 970. Copyright (1969) American Chemical Society[126]

Compound 	pK_a
H	12.80
EtO_2CCH_2	11.20
NH_2	10.60
$NCCH_2$	9.30
PhCO	8.10
H_2NCO	7.50
Ph	10.50

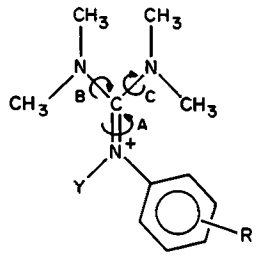
V. BARRIERS TO ISOMERIZATION ABOUT GUANIDINE AND GUANIDINIUM CARBON–NITROGEN BONDS

A. Barriers to Isomerization about Guanidinium Carbon–Nitrogen Bonds

Temperature-dependent NMR studies have been the general method to determine rates of carbon–carbon (or carbon–nitrogen) double bond isomerization[131].

For the parent guanidinium ion, since the six N—H protons are chemically equivalent, standard NMR studies using isotropic conditions have been precluded. However, proton NMR studies in an anisotropic nematic liquid crystalline solution have deduced an upper limit of $\Delta G^{\neq} \leqslant 13$ kcal mol^{-1} for the free energy of activation for bond rotation[132].

The restricted rotation of 2-aryl-1,1,3,3-tetramethylguanidinium trifluoroacetate has been investigated by Kessler and coworkers[133]. Two mechanisms have been considered, one being rotation about the C—N bond and the other deprotonation to the corresponding free guanidine followed by inversion and protonation. The rotation mechanism is more likely for two reasons. First, in 2-alkyl-1,1,3,3-tetramethylguanidinium salts the ^{1}H NMR signals of the α protons of the alkyl group are coupled with the NH protons while the signals of dimethylamino protons appear as singlets. Secondly, a similar free energy of activation has been observed for pentamethylarylguanidinium iodide[134]. Three rotational barriers have been observed in the former salt and two processes can be measured in the latter. Thus the rotation about the C—N bonds in γ position with respect to the aryl ring (processes B and C) and the C—N bond β to aryl (process A) has been observed as illustrated below.



(Y=H or CH_3)

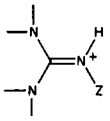
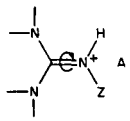
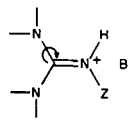
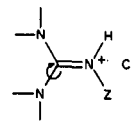
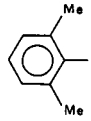
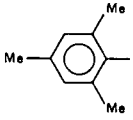
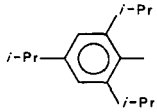
The activation energies ($\Delta G^{\neq}$) and coalescence temperatures (T_c) for these processes in these salts are listed in Tables 7 and 8, respectively.

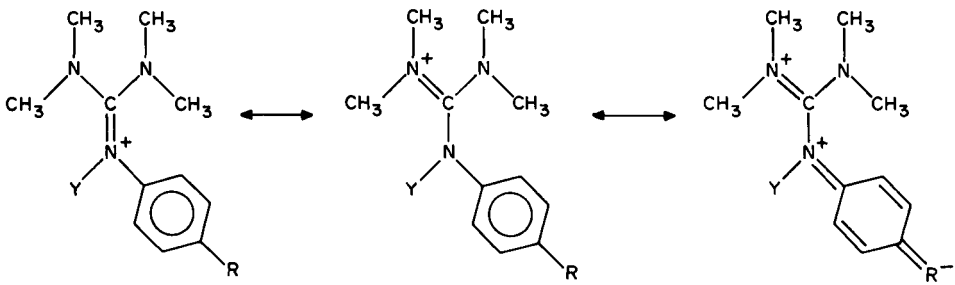
The rotational barriers are correlated linearly with the Hammett σ_p^- constants of *p*-substituents in the aryl group, especially in the pentamethylarylguanidinium salts. In the system, ρ is -1.00 for process B (or C), and ρ is $+1.09$ for process A. Thus, electron-withdrawing groups inhibit the rotation about the C—N bond γ to the aryl group and facilitate the C=N$^+$ rotation (bond β to the aryl ring). These results suggest the importance of resonance structures **58** and **59**.

Large groups in *ortho* positions stabilize the C=N bond against rotation. A similar steric effect has also been observed for rotation about the C=C bond in *o*-substituted stilbenes[135] (see p. 511).

Temperature-dependent NMR of —N(CH_2Ar)$_2$ and —NMe_2 resonances in 2,2-dibenzyl-1,1,3,3-tetramethylguanidinium chloride have shown that the free energy of activation of rotation about the C—NMe_2 bonds and the C—N(CH_2Ph)$_2$ bond is 14.6 $\pm$ 0.2(+3 °C) and 13.8 $\pm$ 0.2(+17 °C) kcal mol^{-1}, respectively[136]. A nonplanar structure

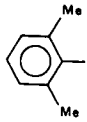
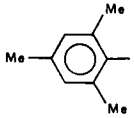
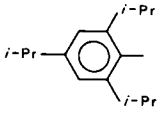
TABLE 7. Rotational barriers for 2-aryl-1,1,3,3-tetramethylguanidinium trifluoroacetates[133] in $CDCl_3$–CF_3CO_2H. Reprinted with permission from Ref. 133. Copyright (1969) Pergamon Press PLC

Compound						
						
Z	T_c (°C)	$\Delta G_c^{\neq}$ (kcal mol^{-1})	T_c (°C)	$\Delta G_c^{\neq}$ (kcal mol^{-1})	T_c (°C)	$\Delta G_c^{\neq}$ (kcal mol^{-1})
p-$Me_2NC_6H_4$—	−18	12.9	−30.5	12.6	−60.5	10.5
p-$MeOC_6H_4$—	−16	13.0	−32.5	12.6	−62	10.4
p-MeC_6H_4—	−21	12.7	−28.5	12.7	−52.5	11.0
Ph—	−25	12.5	−25	12.9	−48	11.2
p-FC_6H_4	−24	12.6	−25	12.9	−58	10.6
p-ClC_6H_4	−28	12.4	−27	12.8	−48	11.2
p-$CH_3COC_6H_4$—	−38	11.9	−38	12.3	−38	11.7
p-NCC_6H_4—	−37	11.9	−43	12	—	—
p-$O_2NC_6H_4$—	−44	11.6	−40	12.1	—	—
	+24	14.9	−44	11.8	−61	10.4
	+34	15.4	−51.5	11.3	−53	10.8
	+56	16.5	−56	11.0	−63	10.3

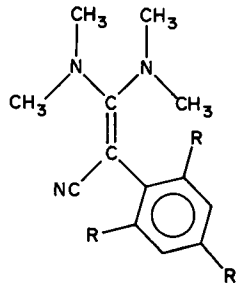


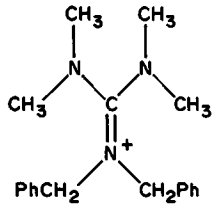
(58) (59)

TABLE 8. Rotational barriers for 2-aryl-1,1,2,3,3-pentamethylguanidinium iodides. Reproduced by permission of VCH Verlagsgesellschaft mbH from Ref. 134.

Compound Z	T_c (°C)	$\Delta G_c^{\neq}$ (kcal mol^{-1})	T_c (°C)	$\Delta G_c^{\neq}$ (kcal mol^{-1})
p-$Me_2NC_6H_4$—	−21	12.4[a]	9	14.55[b]
p-$MeOC_6H_4$—	−32	11.8[a]	18	15.0[b]
p-MeC_6H_4—	−42	11.3[a]	23	15.2[b]
Ph—	−46	11.1[a]	28	15.5[b]
p-FC_6H_4—	−43	11.2[a]	25	15.4[b]
p-ClC_6H_4—	−54	10.7[a]	31.5	15.7[b]
p-$CH_3COC_6H_4$—	−66	10.1[a]	50	16.6[b]
p-NCC_6H_4—	−70	9.9[a]	52	16.7[b]
p-$O_2NC_6H_4$	−80	9.4[a]	58	17.0[b]
	12	14.2[b]	12	14.2[b]
	144	21.2[c]	14	14.3[a]
	195	24.0[c]	8	14.1[a]

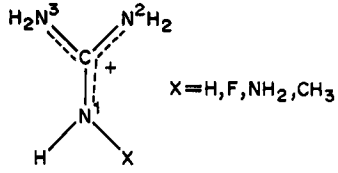
[a]Dichloromethane is used as solvent.
[b]Nitromethane-d_3 is used as solvent.
[c]Formamide is used as solvent.





is proposed for the highly substituted guanidinium salt based on the nonequivalence of the benzyl hydrogens at low temperatures.

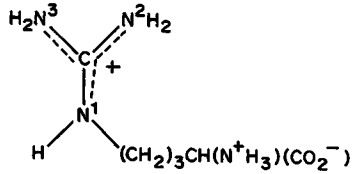
Ab initio calculations have been carried out for the parent guanidinium ion[137], and monosubstituted (F, NH_2, CH_3) guanidinium ions[138] using GAUSSIAN-70 with an STO-6-31G basis set.



The calculated barrier of rotation for the parent ion is 14.73 kcal mol^{-1} and those about C—N^1, C—N^2, C—N^3, for the fluoro substituted ion are 19.7, 19.3, and 11.5 kcal mol^{-1}, respectively.

^{15}N NMR has been employed to investigate the barrier to rotation about the C—N^1 bond in the guanidinium group of L-arginine by line-shape analyses of the N^2 and N^3 resonances[102].

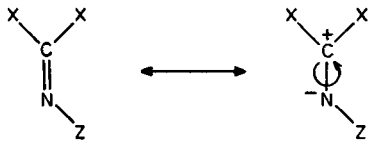
The $\Delta G^{\neq}$ value obtained is 12.9 kcal mol^{-1} (at 8 °C) which is close to $\Delta G^{\neq}$ for other guanidinium ions as described.



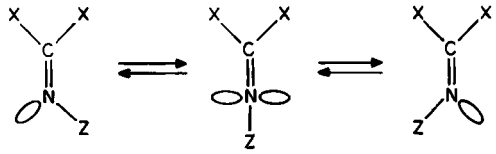
B. Barriers to Isomerization about Free Guanidine Carbon–Nitrogen Bonds

In principle there are two possibilities for the *syn–anti* isomerization about a carbon–nitrogen double bond in free guanidine:

(a) Rotation of the N substituent out of the plane of the molecule. The sp^2 hybridization of the nitrogen atom, and hence the bond angle (C–N–Z), is retained.

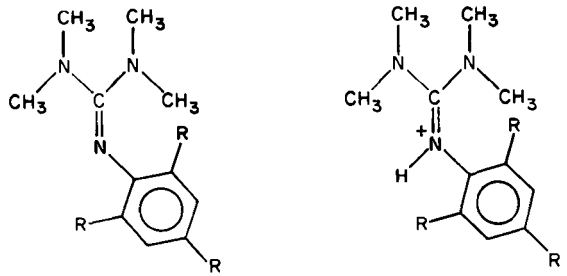


(b) Inversion of the N substituent by an in-plane 'lateral shift' via a transition state with sp hybridization at nitrogen. The bond angle (C–N–Z) increases to 180° in the transition state.



The mechanism which has been supported has been the inversion mechanism, although an intermediate mechanism with both components has been proposed for some imines[139,140].

Two main arguments have been adduced in support of the inversion mechanism. In the first place, the effect of polarity of the solvent on the rate of isomerization of tetramethylphenylguanidine is small [$\Delta G^{\neq} = 12.0$ kcal mol^{-1} in CD_3CN (− 38 °C), $\Delta G^{\neq} = 12.1$ kcal mol^{-1} in CS_2 (− 35 °C)][141]. A polar solvent should facilitate isomerization by rotation, because the transition state in rotation should be substantially charge separated. Secondly, the influence of substituents in the *o*-position in 2-aryl-1,1,3,3-tetramethylguanidines[142] on the rates of isomerization is totally different from that in the corresponding guanidinium salts. Thus, the barrier is lowered as the size of R increases in the free guanidines as shown in Table 9; in contrast, the barrier is heightened by the substituents R in the guanidinium salts as described in the previous section.

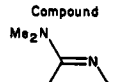
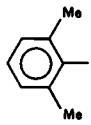
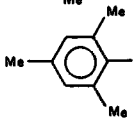
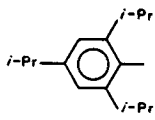


The electronic effect of *p*-substituents in the aryl group in the free guanidines is similar to that in the guanidinium salts[142]. $\Delta G^{\neq}$ and T_c for the guanidines are listed in Table 9. In the system ρ is + 2.95 (± 0.30) (at − 50 °C) against σ_p^-. Also, in the aliphatic derivatives of tetramethylguanidines similar electronic effects have been observed as shown in Table 10.

Generally, in carbon–nitrogen double-bonded compounds $X_2C{=}NZ$, the isomerization rate increases very rapidly as the substituent Z is varied in the order: RO ≈ R_2N < halogen < alkyl < aryl < acyl[131,142]. Substituents X on the imino carbon also increase the inversion rate, the order being quinone ring < alkyl < acetyl < alkoxycarbonyl < aryl < methoxy < alkylthio < dialkylamino[131,142].

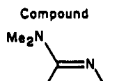
Recently, a $\Delta G^{\neq}$ value (at − 14 °C) of 10.4 kcal mol^{-1} for isomerization of the guanidino group of L-arginine has been obtained by ^{15}N NMR[102]. The value is much smaller than the value 18.7 kcal mol^{-1} (at 73 °C) for pentamethylguanidine. The low barrier may be due to the contributions from tautomers **B** and **C**, which should have lower barriers for rotation about the C—N^2 bond.

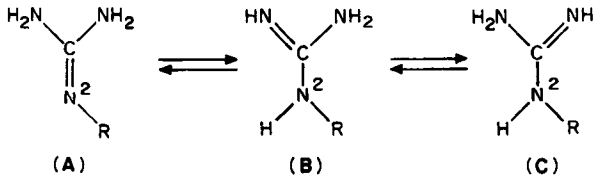
TABLE 9. Rotational barriers for 2-aryl-1,1,3,3-tetramethylguanidines. Reprinted with permission from Ref. 142. Copyright (1970) Pergamon Press PLC

Compound  Z	T_c[a] (°C)	$\Delta G_c^{\neq}$ (kcal mol^{-1})
p-$Me_2NC_6H_4$—	−5	13.7
p-$MeOC_6H_4$—	−8	13.5
p-MeC_6H_4—	−24	12.65
Ph—	−35	12.1
p-FC_6H_4—	−26	12.6
p-ClC_6H_4—	−41	11.8
p-$CH_3COC_6H_4$—	−85	9.4
p-NCC_6H_4—	−84	9.45
p-$O_2NC_6H_4$—	−100	8.5
	−36	12.0(11.0)[b]
	−24	12.6(11.1)[b]
	−46.5	11.4(10.2)[b]

[a]The $CS_2/CDCl_3$ solvent system is used.
[b]Electronic effect of the alkyl groups (0.5 kcal mol^{-1} for one CH_3 group, 0.4 kcal mol^{-1} for one *i*-Pr group) is subtracted from the experimental $\Delta G^{\neq}_{exp}$ value. The corrected values are listed in parentheses.

TABLE 10. Rotational barriers for aliphatic tetramethylguanidines. Reprinted with permission from Ref. 142. Copyright (1970) Pergamon Press PLC

Compound  Z	Solvent	T_c (°C)	$\Delta G_c^{\neq}$ (kcal mol^{-1})
NMe_2	Diphenyl ether	> 200	> 25
OMe		> 200	> 25
H	$CDCl_3$	< −80	< 10
CH_3		73	18.7
Et		65	18.2
i-Pr		53	17.5
SO_2Ph	$CS_2/CDCl_3$	−120	7.85
COMe		−100	8.95
CN		−95	9.2
NO_2		−65	10.9



VI. COORDINATION OF GUANIDINES AND GUANIDINIUM IONS WITH METALS, ANIONS AND CROWN ETHERS

The guanidinium group of arginine has been shown to act as an anion recognition site in many metalloenzymes[143]. For example, in the iron protein, transferrin, the arginine residue has been known to play an important role in the coordination with a synergistic anion (bicarbonate or carbonate) for strong binding of Fe^{3+} or other metal ions to the transferrin[144,145]. Such properties have promoted the study of the coordination chemistry of guanidinium ions and guanidines.

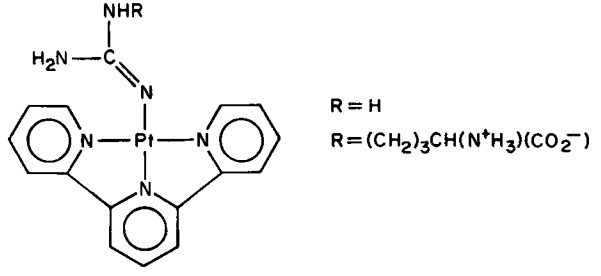
A. Coordination of Guanidines with Metal Ions

Guanidine forms three types of complexes with metals[146]: (a) cationic complexes (in which the guanidium cation is formed by taking up a proton); (b) adducts with neutral molecules or coordination products with ionic salts; (c) substitution products.

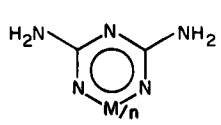
Cationic complexes have been studied as those with rare earth elements such as La[146]. Substitution products such as $(Me_2N)_2C{=}NLi$ (Section IV.D) are not common.

A number of complexes of tetramethylguanidine with main group elements such as R_3Al[147], and transition metals Co^{II}, Cu^{II}, Zn^{II}, Pd^{II}, Ni^{II} and Cr^{III} have indicated[148] the imino nitrogen to be the donor site.

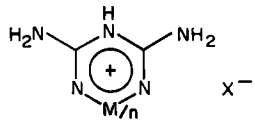
Recently, $[Pt(trpy)Cl]^+$ (trpy = tripyridine) has been used for the complexation with guanidinium salts and arginine under slightly basic (pH 8.5–10.5) conditions[149]. The study is related to the binding of Pt(II) to L-arginine (Arg) in the tuna cytochrome *c*, in which Arg 91 reacts with Pt(II) even at pH 7.0. The high reactivity of Arg 91 has been explained by the structural environment in cytochrome *c*.



Biguanides form deeply colored chelate complexes with many metals[146], and have stabilized a number of usually high oxidation states of the metals. These complexes can be classified into two groups: (a) uncharged metal biguanides $[M(big)_n]$ (**60**); (b) charged metal biguanides $[M(big\ H)_n]X_n$ (**61**).



(60)



(61)

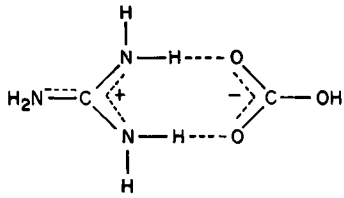
The structures illustrated above have been confirmed by X-ray crystallography for $Cr(big)_3$[150] and $Co(big\ H)_3Cl_3$[151], respectively.

B. Coordination of Guanidinium Ions with Anions

Models studies of the anion recognition of arginines described above have appeared recently.

Ab initio calculations of the guanidinium-formate and guanidine–formic acid pairs have been carried out[152]. The potential curves of these complexes cross at a C–C distance of about 4 Å with the charged (guanidinium–formate) state being more stable at shorter distances.

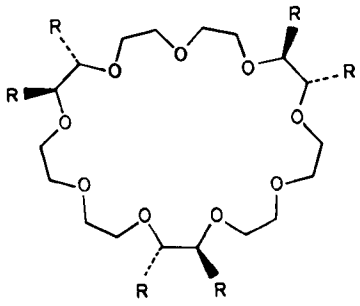
The X-ray crystallographic study of guanidinium bicarbonate indicates that the guanidinium cation forms two hydrogen bonds (average N—H···O distance 2.87 Å) with the same bicarbonate anion, and is thus well suited for anion binding[153].



C. Coordination of Guanidinium Ions with Crown Ethers

The existence of interaction between dibenzo-18-crown-6 and guanidinium salts has been demonstrated by Pedersen[154] by the use of UV spectroscopy. Later a crystalline complex between guanidinium nitrate and 18-crown-6 ether was obtained and the structural analysis by X-ray diffraction was carried out[155]. As it turns out the stoichiometry is 1:2 (18-crown-6: guanidinium nitrate) and the two guanidinium cations are each hydrogen bonded to one face of the 18-crown-6 ether with just one hydrogen bond. This result indicates that the crown ether cavity is too small for the guanidinium ions, which may fit into bigger crown ethers in an encapsulated form. In this context, guanidinium salts are compared with other cations (K^+ and n-Bu_4N^+) for their ability to act as templates in the formation of benzo-27-crown-9 and to complex the cyclic polyethers once formed[156,157]. The following order has been observed for the ability to serve as templates for the benzo-27-crown-9: K^+ > guanidinium ion > tetrabutylammonium ion > tetramethylammonium ion. The complexation of guanidinium ions with the crown ether has been implied by the fact that the crown ether solubilizes *ca* 1 mol (per mol of host) of the otherwise insoluble crystalline guanidinium tetraphenylborate[156].

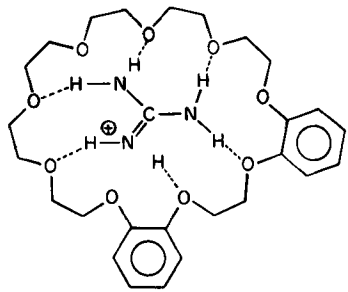
Stability constants K_s of guanidinium complexes of the hexacarboxylate 27-crown-9 have been shown to be very large ($K_s = 9000 \pm 7001\,mol^{-1}$)[158]. But the stability of the complexes decreases markedly as the number and bulk of the substituents on the guanidinium ion increases (methylguanidinium, $K_s = 451 \pm 40$; *N,N'*-diethylguanidinium,



$R = CO_2^- \ HN^+(CH_2CH_2OH)_3$

$K_s < 10$ l mol^{-1}). The steric effect suggests that inclusion of guanidino groups into the macrocyclic cavity occurs, making the crown ether a guanidinium receptor molecule.

A systematic study has been carried out on X-ray structures and kinetic stabilities of 1:1 complexes of guanidinium perchlorate with benzo-27-crown-9, dibenzo-27-crown-9 and dibenzo-30-crown-10[159]. From the X-ray analysis of these complexes two points have become clear: (a) all the hydrogen atoms of the guanidinium cation are used in hydrogen bonds linking it to the macrocyclic host in these encapsulated complexes; (b) the electrostatic interaction and hydrogen-bonding scheme in the 30-membered ring are not as ideal as those in the 27-membered ring. This, however, is not reflected in the kinetic stability of the complexes. The activation energies of decomplexation have been given by temperature-dependent NMR to be 11.4 (at -33 °C), 11.2 (at -40 °C) and 12.0 (at -33 °C) kcal mol^{-1} for the complexes with benzo-27-crown-9, dibenzo-27-crown-9 and dibenzo-30-crown-10, respectively.



VII. REACTIONS OF GUANIDINES

A. Hydrolysis of Guanidines

In aqueous solution guanidine is hydrolyzed very slowly, first to urea and eventually to carbon dioxide and ammonia.

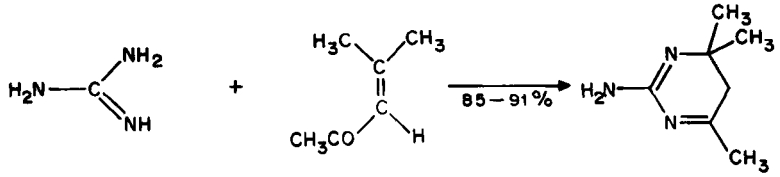
In the presence of alkali, the rate of hydrolysis increases. About 34% of guanidine (1.3 mol l^{-1} of solution) is hydrolyzed to form urea at room temperature after 41 days in the presence of 1 equiv of NaOH; in contrast about 19% is hydrolyzed after 31 days without NaOH[160]. The hydrolysis is reversible and, in fact, formation of guanidine from urea and ammonia has been reported[161] although the yield based on urea does not exceed 30%.

B. Condensation of Guanidines with Carbonyl Compounds to Synthesize Five- or Six-membered Rings

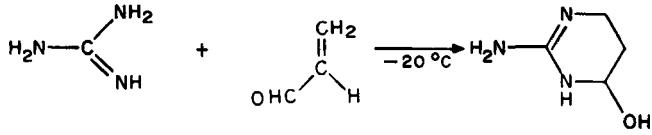
Cyclization is one of the most important reactions of guanidines, and especially the synthesis of pyrimidines has been studied extensively[162–164].

1. *Synthesis of pyrimidines and other six-membered heterocycles*

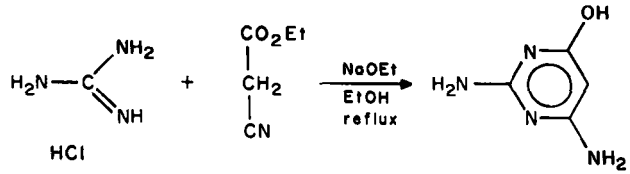
The reaction of α,β-unsaturated ketones or aldehydes with amidines[165] or guanidines has been used since 1899, when Traube reported the condensation of mesityl oxide with guanidine as shown below[166].



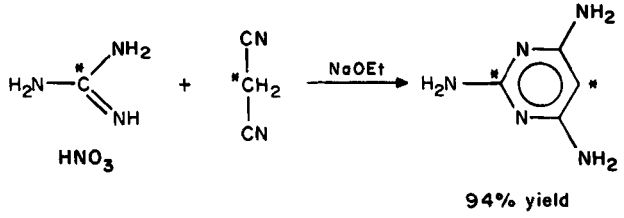
Although no results were obtained in early work on the condensation of guanidine with benzalacetone, acrolein or cinnamaldehyde[167], careful optimization of reaction conditions in the reaction of guanidine with acrolein has later given the product, 2-amino-6-hydroxy-1,4,5,6-tetrahydropyrimidine, in *ca* 75% yield[168].



β-Dicarbonyl compounds have also been widely used in the synthesis of pyrimidine and other six-membered heterocycles. For example, ethyl cyanoacetate gives good yields (80–82%) of 2,4-diamino-6-hydroxypyrimidine[169].

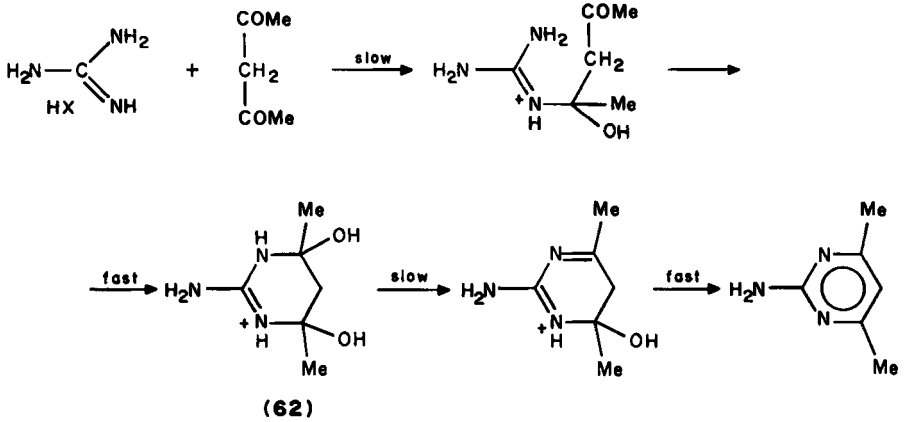


2,4,6-Triaminopyrimidine ^{13}C-labelled at 2,5-positions has been synthesized by the reaction of malononitrile-2-^{13}C with guanidine-^{13}C nitrate in the presence of sodium ethoxide[170]. Diethyl allylmalonate can also be used in these reactions[171].



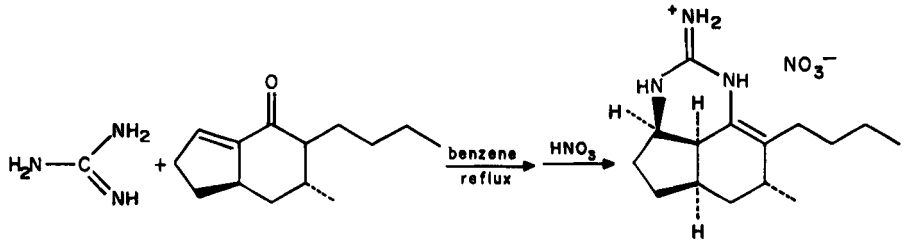
In order to obtain mechanistic insight into these reactions, the reactions of acetylacetone, methyl acetoacetate and dimethyl malonate with guanidinium salts, amidinium salts and ureas have been followed by ^{13}C NMR[172].

A diol **62** has been observed as the only intermediate in the reaction of acetylacetone with guanidine. The result suggests the mechanism shown below.



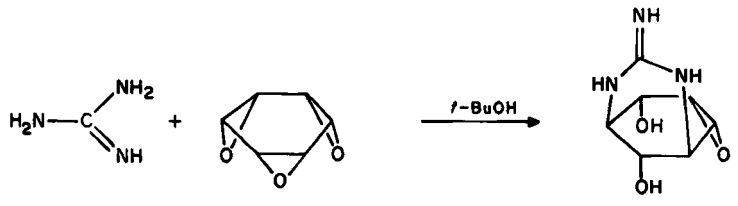
(62)

A cytotoxic six-membered ptilocaulin (**63**) has been synthesized recently by four groups. Three of them employed the reaction of guanidine with α,β-unsaturated ketone[173–175] in the final step. The fourth group used the reaction of 1-guanyl-3,5-dimethylpyrazole (see Section II.B.6) with a β-amino ketone derivative[37].



ptilocaulin (**63**)
35–50% yield

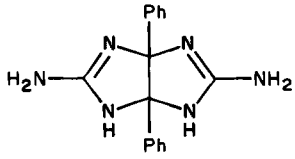
Reaction of *cis*-benzene trioxide with guanidine in buffered *tert*-butyl alcohol gives a 1,3-bridged six-membered ring adduct in 88–91% yield[176]. A five-membered adduct resulting from 1,2-bridging is also formed in 8–12% yield.



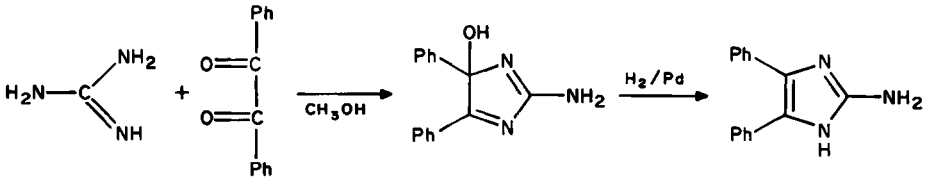
2. Synthesis of five-membered rings

The condensations of guanidine with α-dicarbonyl compounds have been studied most extensively in this area.

The reaction of benzil with guanidine has been reported to be solvent- and condition-sensitive. Thus, in dioxane, imidazoimidazole (**64**) is obtained but in methanol 2-amino-4-hydroxy-4,5-diphenyl-4*H*-imidazole (**65**) can be obtained instead[177]. Catalytic hydrogenation of compound **65** produces 2-amino-4,5-diphenylimidazole (**66**).



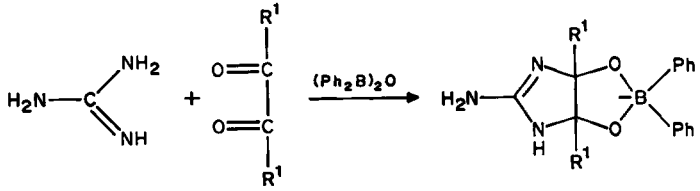
(64)



(65) (66)

85% yield

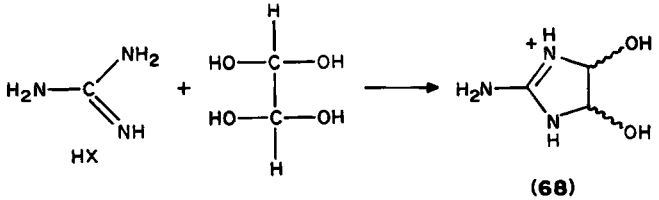
The adducts of α-dicarbonyl compounds with guanidine can be trapped by the formation of diphenylboron chelates (**67**). The chelates have been isolated from the reaction of an α-dicarbonyl compound, guanidine and oxybis(diphenylborane)[178].



(67)

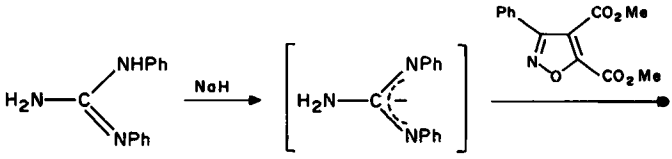
33—80% yield

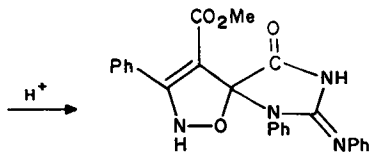
Reaction of guanidinium salts with glyoxal bis-hydrate gives *cis* and *trans* mixtures of the cyclic adducts (**68**) with the *trans* isomer being the major product (4:1)[179].



(68)

The spirocyclization of heterocyclic *o*-dicarboxylates with 1,3-diphenylguanidine in the presence of sodium hydride gives the heterospiro compounds (**69**)[180]. However, the reaction is confined to pyrimidine and isoxazole derivatives because it is influenced by the degree of heteroaromaticity of the starting material.

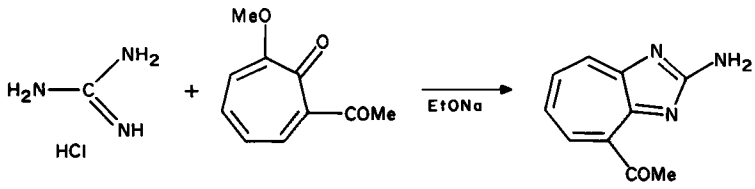




(**69**)

83% yield

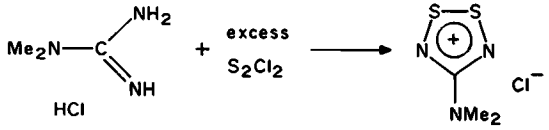
Reaction of 3-acetyltropolone methyl ether with guanidine has been reported to give the aminoimidazole derivative (**70**)[181].



(**70**)

43% yield

Excess sulfur monochloride reacts with *N,N*-dimethylguanidinium hydrochloride to give 4-(dimethylamino)-1,2,3,5-dithiadiazolium cation (**71**)[182].



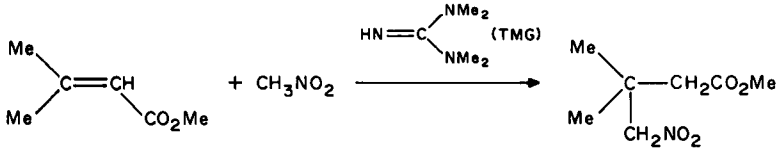
(**71**)

54% yield

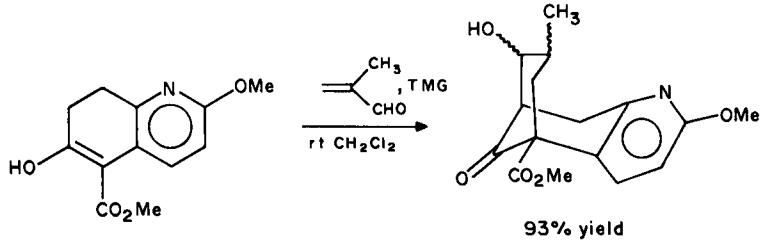
C. Miscellaneous Reactions

Recently, tetramethylguanidine (TMG) has been recognized as a useful, strong and hindered base for the Michael addition of nitroalkanes to α,β-unsaturated esters[183,184] and ketones[185].

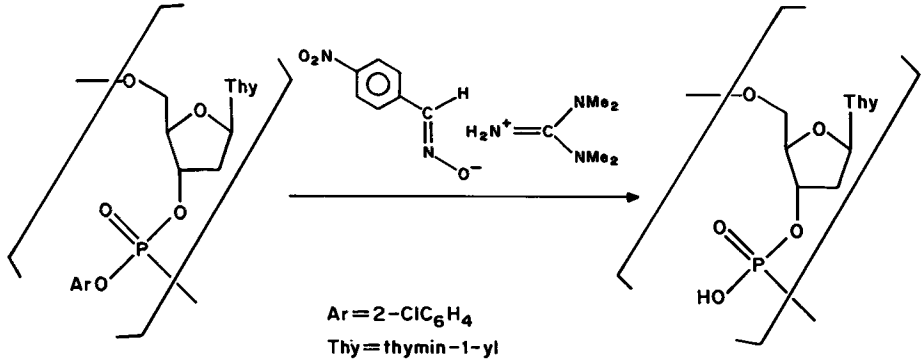
For example, the Michael addition of nitromethane to sterically hindered methyl 3-methylcrotonate does not proceed by use of usual Michael catalysts, but TMG catalyzes the reaction to form an adduct in 45% yield at room temperature in 2–4 days[184].



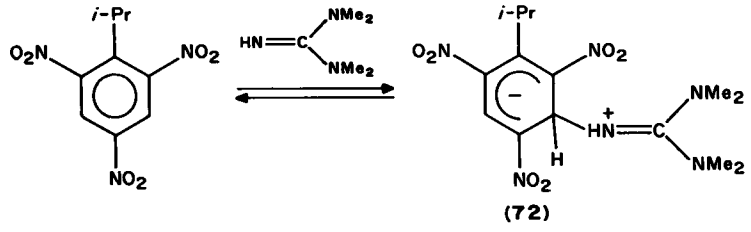
The use of TMG catalyst has given a good result (93% yield) in the reaction of the β-ketoester shown below with methacrolein[186].



In deprotection of oligonucleotide phosphotriesters, mixtures of TMG and/or 4- (or 2-) nitrobenzaldoxime (or pyridine-2-carboxaldoxime) have been reported to be clean reagents[187–189].



TMG is not quite sterically hindered toward 2,4,6-trinitrocumene, thus σ-complex formation with the benzene ring to form **72** has been observed[190,191].



VIII. ACKNOWLEDGMENT

We are heartily grateful to Professor Kin-ya Akiba of Hiroshima University, who gave us the chance to write this chapter and also supplied us with guidelines and encouragement.

IX. REFERENCES

1. S. Patai (Ed.), *The Chemistry of Amidines and Imidates*, Wiley–Interscience, Chichester, 1975.
2. S. Coffey (Ed.), *Rodd's Chemistry of Carbon Compounds*, Vol. Ic, Elsevier, Amsterdam, 1965, p. 341.
3. E. H. Sheers, *Kirk–Othmer Encycl. Chem. Technol.*, 2nd ed., **10**, 734 (1966).
4. E. Doehlemann, *Ullmann's Encykl. Tech. Chem.*, 4. Aufl., 12, 411 (1976).
5. G. W. Watt and R. C. Makosky, *Ind. Eng. Chem.*, **46**, 2599 (1954).
6. T. L. Davis, *Org. Synth., Coll. Vol.*, **1**, 302 (1941).
7. G. B. L. Smith, *Inorg. Synth.*, **1**, 96 (1939).
8. T. L. Davis, *Org. Synth., Coll. Vol.*, **5**, 589 (1973).
9. W. Marckwald and F. Struwe, *Chem. Ber.*, **65**, 457(1932).
10. W. J. Jones, *Trans. Faraday Soc.*, **55**, 524 (1959).
11. P. Oxley and W. F. Short, *J. Chem. Soc.*, 1252 (1951).
12. M. T. Smidt and L. F. Audrieth, *Inorg. Synth.*, **1**, 97 (1939).
13. G. W. Watt and R. C. Makosky, *Ind. Eng. Chem.*, **46**, 2599 (1954).
14. B. Rathke, *Chem. Ber.*, **17**, 297 (1884).
15. R. Phillips and H. T. Clarke, *J. Am. Chem. Soc.*, **45**, 1755 (1923).
16. G. B. L. Smith, *J. Am. Chem. Soc.*, **51**, 476 (1929).
17. S. J. Angyal and W. K. Warburton, *J. Am. Chem. Soc.*, **73**, 2492 (1951).
18. H. Lecher and F. Graf, *Chem. Ber.*, **56**, 1326 (1923).
19. J. Wityak, S. J. Gould, S. J. Hein and D. A. Keszler, *J. Org. Chem.*, **52**, 2179 (1987).
20. T. Teraji, Y. Nakai, G. J. Durant, PCT Int. Appl. 8100, 109 (1981); *Chem. Abstr.*, **94**, 192336z (1981).
21. A. E. Miller and J. J. Bischoff, *Synthesis*, 777 (1986).
22. R. A. B. Bannard, A. A. Casselman, W. F. Cockburn and G. M. Brown, *Can. J. Chem.*, **36**, 1541 (1958).
23. J. P. Greenstein, *J. Org. Chem.*, **2**, 480 (1937).
24. J.-A. Gautler, M. Miocque and C. C. Farnoux, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Chap. 7, Wiley–Interscience, Chichester, 1975, p. 292.
25. H. Bredereck and K. Bredereck, *Chem. Ber.*, **94**, 2278 (1961).
26. P. Pruszynski, *Can. J. Chem.*, **65**, 626 (1987).
27. D. F. Gavin, W. J. Schnabel, E. Kober and M. A. Robinson, *J. Org. Chem.*, **32**, 2511 (1967).
28. N. K. Hart, S. R. Johns, J. A. Lamberton and R. I. Willing, *Aust. J. Chem.*, **23**, 1679 (1970).
29. S. E. Forman, C. A. Erickson and H. Adelman, *J. Org. Chem.*, **28**, 2653 (1963).
30. S. J. C. Snedker, *J. Soc. Chem. Ind. (London)*, **45**, 353T (1927).
31. A. Kämpf, *Chem. Ber.*, **37**, 1681 (1904).
32. R. A. Corral, O. O. Orazi and M. F. de Petruccelli, *Chem. Commun.*, 556 (1970).
33. A. M. Monro, *Chem. Ind.*, 1806 (1964).
34. J. A. Carbon and S. H. Tabata, *J. Org. Chem.*, **27**, 2504 (1962).
35. F. L. Scott, D. G. O'Donovan and J. Reilly, *J. Am. Chem. Soc.*, **75**, 4053 (1953).
36. F. L. Scott and J. Reilly, *J. Am. Chem. Soc.*, **74**, 4562 (1952).
37. W. R. Roush and A. E. Walts, *J. Am. Chem. Soc.*, **106**, 721 (1984).
38. A. Heesing and R. Peppmoller, *Z. Naturforsch.*, **226**, 820 (1967).
39. E. Kühle, *Angew. Chem., Int. Ed. Engl.*, **8**, 20 (1969).
40. R. Gompper and W. Hägele, *Chem. Ber.*, **99**, 2885 (1966).
41. J. V. Rodricks and H. Rapoport, *J. Org. Chem.*, **36**, 46 (1971).
42. P. Rây, *Chem. Rev.*, **61**, 313 (1961).
43. A. F. Crowther, F. H. S. Curd, D. N. Richardson and F. L. Rose, *J. Chem. Soc.*, 1636 (1948).
44. K. Shirai and K. Sugino, *J. Org. Chem.*, **25**, 1045 (1960).
45. D. Karipides and W. C. Fernelius, *Inorg. Synth.*, **7**, 56 (1963).

46. L. A. Pinck, *Inorg. Synth.*, **3**, 43 (1950).
47. E. L. May, *J. Org. Chem.*, **12**, 437 (1947).
48. F. H. S. Curd, J. A. Hendry, T. S. Kenny, A. G. Murray and F. L. Rose, *J. Chem. Soc.*, 1630 (1948).
49. E. Brand and F. C. Brand, *Org. Synth., Coll. Vol.*, **3**, 440 (1955).
50. H. King, *J. Chem. Soc.*, 2374 (1930).
51. E. Brand and M. Sandberg, *Org. Synth., Coll. Vol.*, **2**, 49 (1943).
52. C. Lempert, *Chem. Rev.*, **59**, 667 (1959).
53. G. Edger and S. Hinegardner, *Org. Synth., Coll. Vol.*, **1**, 172 (1941).
54. I. S. Bengelsdorf, *J. Am. Chem. Soc.*, **75**, 3138 (1953).
55. J. Söll and A. Stutzer, *Chem. Ber.*, **42**, 4532 (1909).
56. F. H. S. Curd, D. G. Davey and D. N. Richardson, *J. Chem. Soc.*, 1732 (1949).
57. F. Kurzer, *Org. Synth., Coll. Vol.*, **4**, 502 (1963).
58. K. H. Slotta, R. Tschesche and H. Dressler, *Chem. Ber.*, **63**, 208 (1930).
59. R. Greenhalgh and R. A. B. Bannard, *Can. J. Chem.*, **37**, 1810 (1959).
60. A. F. McKay, W. G. Hatton and R. O. Braun, *J. Am. Chem. Soc.*, **78**, 6144 (1956).
61. E. Piers, J. M. Chong, K. Gustafson and R. J. Andersen, *Can. J. Chem.*, **62**, 1 (1984).
62. R. Greenhalgh and R. A. B. Bannard, *Can. J. Chem.*, **37**, 1810 (1959).
63. K. Matsumoto and H. Rapoport, *J. Org. Chem.*, **33**, 552 (1968).
64. L. A. Pinck and J. S. Blair, *J. Am. Chem. Soc.*, **49**, 509 (1927).
65. A. F. McKay, *Chem. Rev.*, **51**, 301 (1952).
66. T. L. Davis, *Org. Synth., Coll. Vol.*, **1**, 399 (1941).
67. R. J. J. Simkins and G. Williams, *J. Chem. Soc.*, 3086 (1952).
68. T. L. Davis and R. C. Elderfield, *J. Am. Chem. Soc.*, **55**, 731 (1933).
69. A. F. McKay and G. F. Wright, *J. Am. Chem. Soc.*, **69**, 3028 (1947).
70. A. F. McKay, *J. Am. Chem. Soc.*, **71**, 1968 (1949).
71. L. Fishbein and J. A. Gallaghan, *J. Am. Chem. Soc.*, **76**, 1877 (1954).
72. N. Heyboer, G. H. Visser and K. E. T. Kerling, *Recl. Trav. Chim. Pays-Bas*, **81**, 69 (1962).
73. T. L. Davis and E. N. Rosenquist, *J. Am. Chem. Soc.*, **59**, 2112 (1937).
74. K.-y. Akiba, S. Matsunami, C. Eguchi and N. Inamoto, *Bull. Chem. Soc. Jpn.*, **47**, 935 (1974).
75. A. F. McKay, *J. Am. Chem. Soc.*, **70**, 1974 (1948).
76. E. Lieber and G. B. L. Smith, *Chem. Rev.*, **25**, 213 (1939).
77. F. Kurzer and L. E. A. Godfrey, *Chem. Ind.*, 1584 (1962).
78. R. L. Shriner and F. W. Neumann, *Org. Syth., Coll. Vol.*, **3**, 73 (1955).
79. G. W. Kirsten and G. B. L. Smith, *J. Am. Chem. Soc.*, **58**, 800 (1936).
80. E. Roberts, British Patent 817, 749; *Chem. Abstr.*, **54**, 9775a (1960).
81. J. T. Thurston and L. P. Ferris, II, *Inorg. Synth.*, **3**, 45 (1950).
82. W. G. Finnegan, R. A. Henry and G. B. L. Smith, *J. Am. Chem. Soc.*, **74**, 2981 (1952).
83. J. B. Walker and M. S. Walker, *J. Biol. Chem.*, **234**, 1481 (1959).
84. G. D. Kalyankar, M. Ikawa and E. E. Snell, *J. Biol. Chem.*, **233**, 1175 (1958).
85. M. Frankel, Y. Knobler and G. Zvilichovsky, *J. Chem. Soc.*, 3127 (1963).
86. D. D. Nyberg and B. E. Christensen, *J. Am. Chem. Soc.*, **79**, 1222 (1957).
87. A. H. Ennor and L. A. Stocken, *Biochem. Prep.*, **5**, 9 (1957).
88. F. Cramer and A. Vollmar, *Chem. Ber.*, **91**, 911 (1958).
89. F. Cramer, E. Scheiffele and A. Vollmar, *Chem. Ber.*, **95**, 1670 (1962).
90. F. Cramer and A. Vollmar, *Chem. Ber.*, **91**, 919 (1958).
91. J. Strakosch, *Chem. Ber.*, **5**, 692 (1872).
92. A. Senning, *Acta Chem. Scand.*, **21**, 1293 (1967).
93. J. Goerdeler and M. Willig, *Chem. Ber.*, **88**, 1071 (1955).
94. J. Goerdeler and K. Doerk, *Chem. Ber.*, **95**, 154 (1962).
95. W. V. Farrar, *J. Chem. Soc.*, 856 (1965).
96. R. A. Davis, J. L. Kroon and D. A. Rausch, *J. Org. Chem.*, **32**, 1662 (1967).
97. D. J. Haas, D. R. Harris and H. H. Mills, *Acta Crystallogr.*, **19**, 676 (1965).
98. V. Shomaker and D. P. Stevenson, *J. Am. Chem. Soc.*, **63**, 37 (1941).
99. C. L. Angell, N. Sheppard, A. Yamaguchi, T. Shimanouchi, T. Miyazawa and S. Mizushima, *Trans. Faraday Soc.*, **53**, 589 (1957).
100. T. Maeda, T. Fujiwara and K. Tomita, *Bull. Chem. Soc. Jpn.*, **45**, 3628 (1972).
101. E. G. Steward, D. Warner and G. R. Clarke, *Acta Crystallogr., Sect. B*, **30**, 813 (1974).

102. K. Kanamori and J. D. Roberts, *J. Am. Chem. Soc.*, **105**, 4698 (1983).
103. R. E. Botto, J. H. Schwartz and J. D. Roberts, *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 23 (1980).
104. J. Thiele, *Ann. Chem.*, **270**, 16 (1892).
105. A. F. McKay, J. P. Picard and P. E. Brunet, *Can. J. Chem.*, **29**, 746 (1951).
106. R. E. Richards and R. W. Yorke, *Trans. Faraday Soc.*, **54**, 321 (1958).
107. S. S. Barton, R. H. Hall and G. F. Wright, *J. Am. Chem. Soc.*, **73**, 2201 (1951).
108. W. D. Kumler and P. P. T. Sah, *J. Org. Chem.*, **18**, 669 (1953).
109. J. H. Bryden, L. A. Burkardt, E. W. Hughes and J. Donohue, *Acta Crystallogr.*, **9**, 573 (1956).
110. W. J. Hale and F. C. Vibrans, *J. Am. Chem. Soc.*, **40**, 1046 (1918).
111. E. W. Hughes, *J. Am. Chem. Soc.*, **62**, 1258 (1940).
112. W. J. Jones and W. J. Orville-Thomas, *Trans. Faraday. Soc.*, **55**, 193 (1959).
113. J. B. Moffat, *J. Mol. Struct.*, **86**, 119 (1981).
114. M. Alléaume, A. Gulko, F. H. Herbstein, M. Kapon and R. E. Marsh, *Acta Crystallogr., Sect. B*, **32**, 669 (1976).
115. A. Boyar and R. E. Marsh, *J. Am. Chem. Soc.*, **104**, 1995 (1982).
116. S. Rice, M. Y. Cheng, R. E. Cramer, M. Mandel, H. F. Mower and K. Seff, *J. Am. Chem. Soc.*, **106**, 239 (1984).
117. G. R. Sullivan and J. D. Roberts, *J. Org. Chem.*, **42**, 1095 (1977).
118. F. L. Hirshfeld and H. Hope, *Acta Crystallogr., Sect. B*, **36**, 406 (1980).
119. J. Stals and M. G. Pitt, *Aust. J. Chem.*, **28**, 2629 (1975).
120. P. Gund, *J. Chem. Educ.*, **49**, 100 (1972).
121. J. Klein, *Tetrahedron*, **39**, 2733 (1983).
122. T. Ohwada, A. Itai, T. Ohta and K. Shudo, *J. Am. Chem. Soc.*, **109**, 7036 (1987); **110**, 2349 (1988).
123. N. S. Mills, J. Shapiro and M. Hollingsworth, *J. Am. Chem. Soc.*, **103**, 1263 (1981).
124. L. Pauling, in *The Nature of the Chemical Bond*, 3rd. ed., Cornell University Press, Ithaca, New York, 1960, p. 286.
125. P. J. Taylor and A. R. Wait, *J. Chem. Soc., Perkin Trans. 2*, 1765 (1986).
126. M. Charton, *J. Org. Chem.*, **30**, 969 (1965).
127. D. D. Perrin, B. Dempsey and E. P. Serjeant, *pK_a Predictions for Organic Acids and Bases*, Chapman and Hall, London, 1981, p. 133.
128. K. T. Leffek, P. Pruszynski and K. Thanapaalasingham, *Can. J. Chem.*, **67**, 590 (1989).
129. G. A. Olah and A. M. White, *J. Am. Chem. Soc.*, **90**, 6087 (1968).
130. I. Pattison, K. Wade and B. K. Wyatt, *J. Chem. Soc. (A)*, 837 (1968).
131. H.-O. Kalinowski and H. Kessler, *Topics in Stereochem.*, **7**, 295 (1973).
132. T. Bally, P. Diehl, E. Haselbach and A. S. Tracey, *Helv. Chim. Acta*, **58**, 2398 (1975).
133. H. Kessler and D. Leibfritz, *Tetrahedron*, **25**, 5127 (1969).
134. H. Kessler and D. Leibfritz, *Chem. Ber.*, **104**, 2158 (1971).
135. H. Kessler, *Chem. Ber.*, **103**, 973 (1970).
136. A. V. Santoro and G. Mickevicius, *J. Org. Chem.*, **44**, 117 (1979).
137. A. M. Sapse and L. J. Massa, *J. Org. Chem.*, **45**, 719 (1980).
138. L. Herzig, L. J. Massa, A. Santoro and A. M. Sapse, *J. Org. Chem.*, **46**, 2330 (1981).
139. M. Raban, *Chem. Commun.*, 1415 (1970).
140. M. Raban and E. Carlson, *J. Am. Chem. Soc.*, **93**, 685 (1971).
141. H. Kessler, *Tetrahedron Lett.*, 2041 (1968).
142. H. Kessler and D. Leibfritz, *Tetrahedron*, **26**, 1805 (1970).
143. J. F. Riordan, K. D. McElvany and C. L. Borders, Jr., *Science*, **195**, 884 (1977).
144. M. R. Schlabach and G. W. Bates, *J. Biol. Chem.*, **250**, 2182 (1975).
145. N. D. Chasteen, *Coord. Chem. Rev.*, **22**, 1 (1977).
146. R. Mehrota, *Compr. Coord. Chem.*, **2**, 281 (1987).
147. R. Snaith, K. Wade and B. K. Wyatt, *J. Chem. Soc. (A)*, 380 (1970).
148. R. Longhi and R. S. Drago, *Inorg. Chem.*, **4**, 11 (1965).
149. E. M. A. Ratilla and N. M. Kostić, *J. Am. Chem. Soc.*, **110**, 4427 (1988).
150. M. R. Snow, *Acta Crystallogr., Sect. B*, **30**, 1850 (1974).
151. L. Coghi, M. Nardelli, and G. Pelizzi, *Acta Crystallogr., Sect. B*, **32**, 842 (1976).
152. M. P. Fülscher nd E. L. Mehler, *J. Mol. Struct. (Theochem)*, **165**, 319 (1988).
153. D. A. Baldwin, L. Denner, T. J. Egan and A. J. Markwell, *Acta Crystallogr., Sect. C*, **42**, 1197 (1986).
154. C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).

155. J. A. Bandy, M. R. Truter, J. N. Wingfield and J. D. Lamb, *J. Chem. Soc., Perkin Trans. 2*, 1025 (1981).
156. K. Madan and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, 427 (1975).
157. E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 2564 (1977).
158. J. M. Lehn, P. Vierling and R. C. Hayward, *J. Chem. Soc., Chem. Commun.*, 296 (1979).
159. J. A. A. de Boer, J. W. H. M. Uiterwijk, J. Geevers, S. Harkema and D. N. Reinhoudt, *J. Org. Chem.*, **48**, 4821 (1983).
160. J. Bell, *J. Chem. Soc.*, 1216 (1926).
161. G. W. Watt and R. G. Post, *Ind. Eng. Chem.*, **45**, 846 (1953).
162. B. Lythgoe, *Quart. Rev.*, **3**, 181 (1949).
163. D. J. Brown, in *Chemistry of the Heterocyclic Compounds*, Vol. 16 (Ed. A. Weissberger), Wiley–Interscience, Amsterdam, 1962.
164. D. J. Brown, in *Comprehensive Heterocyclic Chemistry*, Vol. 3 (Eds. A. R. Katritzky and C. W. Rees), Pergamon Press, Oxford, 1984.
165. J.-A. Gautier, M. Miocque and C. C. Farnoux, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Chap. 7, Wiley–Interscience, Chichester, 1975, p. 327.
166. W. Traube and R. Schwarz, *Ber. Dtsch. Chem. Ges.*, **32**, 3163 (1899).
167. R. M. Dodson and J. K. Seyler, *J. Org. Chem.*, **16**, 461 (1951).
168. A. L. Weis and D. Zamir, *J. Org. Chem.*, **52**, 3421 (1987).
169. J. A. VanAllan, *Org. Synth., Coll. Vol.*, **4**, 245 (1963).
170. H. T. A. Cheung and P. G. Gray, *J. Labelled Compd. Radiopharm.*, **21**, 471 (1984).
171. M. Legraverend and E. Bisagni, *Tetrahedron Lett.*, **26**, 2001 (1985).
172. A. R. Katritzky and T. I. Yousaf, *Can. J. Chem.*, **64**, 2087 (1986).
173. B. B. Snider and W. C. Faith, *Tetrahedron Lett.*, **24**, 861 (1983); *J. Am. Chem. Soc.*, **106**, 1443 (1984).
174. A. Hassner and K. S. K. Murthy, *Tetrahedron Lett.*, **27**, 1407 (1986).
175. T. Uyehara, T. Furuta, Y. Kabasawa, J. Yamada, T. Kato and Y. Yamamoto, *J. Org. Chem.*, **53**, 3669 (1988).
176. W. Fritsche-Lang, P. Wilharm, E. Hädicke, H. Fritz and H. Prinzbach, *Chem. Ber.*, **118**, 2044 (1985).
177. T. Nishimura and K. Kitajima, *J. Org. Chem.*, **44**, 818 (1979).
178. W. Kliegel and H-W. Motzkus, *Chem. Ber.*, **121**, 1865 (1988).
179. R. A. McClelland, R. Panicucci and A. M. Rauth, *J. Am. Chem. Soc.*, **109**, 4308 (1984).
180. R. Nesi, S. Chimichi, M. Scotton, A. Degl'Innocenti and G. Adembri, *J. Chem. Soc., Perkin Trans. 1*, 1667 (1980).
181. Z-T. Jin, K. Imafuku, H. Matsumura, *J. Chem. Soc., Perkin Trans. 1*, 1037 (1982).
182. A. W. Codes, J. D. Goddard, R. T. Oakley and N. P. C. Westwood, *J. Am. Chem. Soc.*, **111**, 6147 (1989).
183. L. N. Nysted and R. R. Burtner, *J. Org. Chem.*, **27**, 3175 (1962).
184. G. P. Pollini, A. Barco and G. De Giuli, *Synthesis*, 44 (1972).
185. A. C. Forsyth, R. M. Paton and I. Watt, *Tetrahedron Lett.*, **30**, 993 (1989).
186. Y. Xia and A. P. Kozikowski, *J. Am. Chem. Soc.*, **111**, 4116 (1989).
187. C. B. Reese, R. C. Titmas and L. Yau, *Tetrahedron Lett.*, 2727 (1978).
188. C. B. Reese and P. A. Skone, *J. Chem. Soc., Perkin Trans. 1*, 1263 (1984).
189. M. D. Hagen and S. Chládek, *J. Org. Chem.*, **54**, 3189 (1989).
190. M. K. Biswas, A. Jarczewski and K. T. Leffek, *Can. J. Chem.*, **65**, 1007 (1987).
191. F. Terrier, *Chem. Rev.*, **82**, 77 (1982).

CHAPTER 11

Rearrangements in amidines and related compounds

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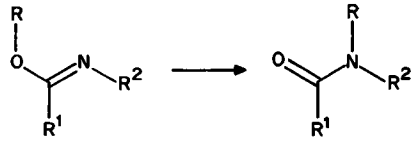
I. INTRODUCTION

In the preceding volumes of 'The Chemistry of Functional Groups' series, the reviews devoted to rearrangements of amidines and related compounds[1,2] dealt almost exclusively with thermal and catalyzed O → N transfers of alkyl, acyl, aryl and allyl groups in imidates of both acyclic and heterocyclic types, i.e. with various classes of the Chapman and Claisen rearrangements.

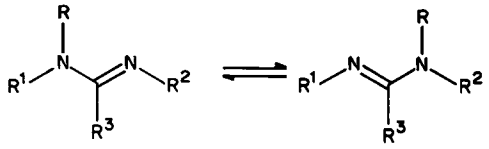
The Chemistry of Amidines and Imidates, Volume 2
Edited by S. Patai and Z. Rappoport



(1) (2) (1)

R=alkyl, aryl, allyl, acyl

Data on the analogous rearrangements of amidines themselves were scarce at that time (in the review, literature had been covered up to 1973), but since then rich material has been accumulated concerning the 1,3-transfers of various groups R in the amidine triad.



(3) (4) (2)

The migrants R include acyl, aryl, nitroso, trialkylsilyl, phospinyl, phosphoryl, phosphonio, sulfenyl, sulfinyl, chloro and various other groups. An important section of the rearrangements represented by equation 2 consists of the so-called degenerate rearrangements (when $R^1 = R^2$). Even though not of direct preparative interest, the investigation of degenerate rearrangements, mainly by studying their kinetics and sterochemistry with the aid of dynamic NMR spectroscopy, leads to a deeper insight into the intrinsic mechanism of the group transfer reactions and thus provides the synthetic chemist with a cue for the optimization of reaction procedures.

For the sake of comparison, the rearrangements of imidates **1** which have not been surveyed before are also included in the discussion. All the rearrangements of amidines and imidates are grouped according to the origin of the migrant R in the reactions (equations 1 and 2), which entails differentiation in reaction mechanisms. Some peculiar rearrangements of amidines associated with cyclizations and photoinitiated steps of group transfers within a molecule are considered separately.

No special section is devoted to conformational and configurational ($Z \rightleftarrows E$) isomerizations, but these reactions, which in some cases constitute the preliminary stages for the principal rearrangements given by equations 1 and 2, are considered where appropriate.

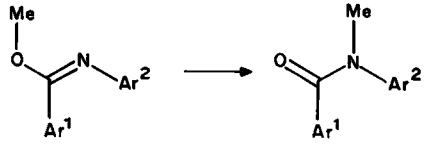
The subject of rearrangements involving group transfer reactions in amidines **3** and imidates **1** has grown immensely during the last 15 years after the appearance of the last review paper[2] covering this topic. Clearly, the present review does not aim at being exhaustive but, hopefully, it may serve as a helpful framework for systematizing the abundant and rapidly accumulating relevant information. The literature up to 1989 has been taken into account and emphasis placed on the more recent studies in order to make this review a useful complement to the previous ones[1-3].

II. REARRANGEMENTS INVOLVING MIGRATIONS OF CARBON-CENTERED GROUPS

A. 1,3-Shifts of Alkyl and Aralkyl Groups

The 1,3-*O*,*N*-migrations of alkyl groups in alkyl imidates **5** with the formation of amides **6** (equation 3) were described in considerable detail in the review articles[1-3]. Such

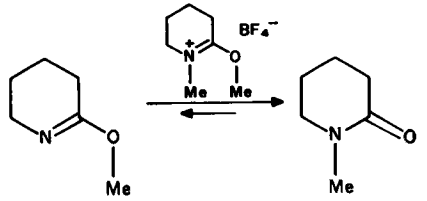
rearrangements occur, as a rule, under severe conditions (at 300 °C and higher) with low yields; they can, however, be fairly effectively catalyzed by electrophilic agents, such as quaternary salts of the rearranging alkyl imidates **7** or alkyl thioimidates **9**[4,5].



(3)

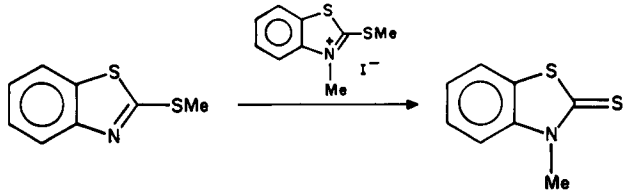
(5) **(6)**

The quaternary salts which are alkylated products common to both of the rearranged isomers serve in these reactions (equations 4 and 5) as the alkyl group carriers. The reactions cannot follow the intramolecular route, since the spatial structure of the triad systems **7**, **9** does not provide conditions for the realization of a trigonal–bipyramidal transition state structure, containing both the entering and the leaving nucleophilic centers in axial positions, which is inherent in the S_N2 reactions[6]. Therefore, all known reactions of *i,j*-shifts ($j = 3, 5, 7, 9$) of alkyl and aralkyl groups are realized in an intermolecular way[7–11] or include homolytic bond fission steps giving rise to the formation of radical pair intermediates[7,12].



(4)

(7) **(8)**

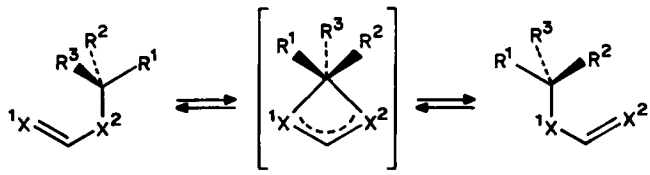


(5)

(9) **(10)**

A possibility of concerted intramolecular 1,3-shifts of C_{sp^3}-centered groups in model amidines **11**[13] and in the related *N*-methyl nitrosoamine[14] system with retention of configuration at the migrating center has been investigated computationally. MINDO/3 calculations[13] indicate the pentacoordinate carbon CH_5^+-like transition state structure **11c** (X = NH) of C_s symmetry for the intramolecular *N,N'*-transfer of methyl, fluoromethyl and trifluoromethyl groups (equation 6).

While very large values of energy barriers to concerted methyl and fluoromethyl 1,3-shifts were predicted, the case of the trifluoromethyl group migration in the amidine framework seems to be a challenge to experimentalists (Table 1). It was, indeed, shown recently that a purely intramolecular 1,3-migration of the benzyl group (equation 7) can be



(6)

(11a) (11b) (11c)

R^1	R^2	R^3	Migrant	
H	H	H	(Me)	
H	H	F	(CH_2F)	X = O, NH
F	F	F	(CF_3)	

traced in labeled benzyl benzoate (**12a**) in neat samples sealed under N_2, at 260 °C, with the energy barrier to *O,O'*-transfer amounting to 45 kcal mol^{-1} [15].

(7)

(12a) (12b)

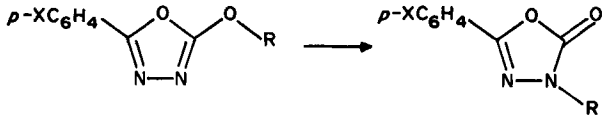
Noncatalyzed thermal rearrangements of alkyl imidates in compounds in which the isoimide moiety is incorporated in a heterocycle ring proceed, as a rule, under milder conditions than those needed for the open-chain derivatives (equation 1)[2,5]. Some rearrangements of cyclic imidates can proceed in the melt. Thus, 5-alkoxy-2-aryl-1,3,4-oxadiazoles **13** (R = alkyl) being melted at 180 °C undergo facile transformation to the corresponding oxadiazol-5-ones **14**[16]. No **13** → **14** rearrangement occurs in solution at this temperature.

When, however, methyl (R = Me) is the migrating group in compounds **13**, the rearrangement **13** → **14** (equation 8) proceeds in the melt at 120–140 °C; moreover, it occurs at an even faster rate in the crystalline state[17]. The degree of completeness of the reaction **13** → **14** amounts to 90–95% with no byproducts detected. The kinetics of this reaction both in the crystalline state and in the melt have been studied by means of ^{1}H NMR spectroscopy. The activation barriers in the **13** → **14** process are: 24 (**b**), 18 (**c**), 56 (**d**) kcal mol^{-1} in the solid state and 28 (**a**), 31 (**b**), 28 (**c**), 31 (**d**) kcal mol^{-1} in the melt. The

TABLE 1. MINDO/3 calculated[13] energy barriers (kcal mol^{-1}) of 1,3-migration of alkyl and fluoroalkyl groups in formamidine (X = NH) and formic acid (X = O) derivatives **11**

Migrant $CR^1R^2R^3$	X = O	X = NH
Me	80.6	60.0
CH_2F	80.0	61.3
CF_3	60.1	20.7

following conclusions were drawn by the authors[17] from these data: (1) In the melt, the energy barriers to the rearrangement for compounds **13** (**a**–**d**) are close in value; (2) the mechanism of the rearrangement in the solid state for compound **13d** ($X = NO_2$) is different from that for **13b** (X = Cl) and **13c** (X = OMe); (3) the activation energies for the rearrangements of compounds **13b** and **13c** are far smaller in the solid state than in the melt.



(8)

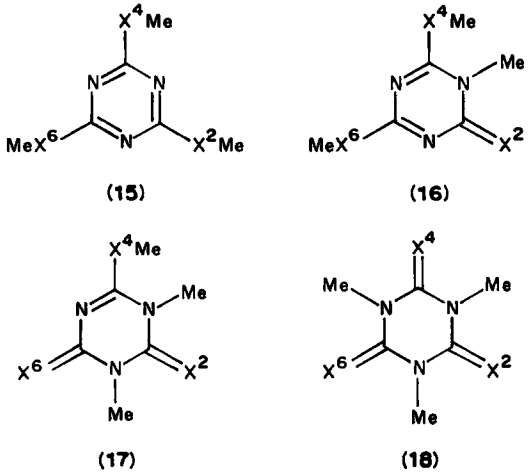
(13) **(14)**

Compound	(a)	(b)	(c)	(d)	(e)	(f)
R	Me	Me	Me	Me	CD_3	Me
X	H	Cl	OMe	NO_2	OCD_3	CN

The ratio of $t_{1/2}$(melt) to $t_{1/2}$(solid) for **13b** and **13c** is 384 and 281, respectively, showing that the rearrangement proceeds much faster in the crystalline state than in the melt.

The appearance of cross-products upon heating of a 50:50 mixture of **13c** and **13e**, both in the solid state and in the melt, points to an intermolecular mechanism of this rearrangement. The unexpectedly rapid **13** → **14** rearrangement in the solid state is explained by the favorable geometry of the crystal packing of compounds **13**. A similar enhancement of reaction rates of group-transfer reactions in the condensed phase brought about by proper orientation of the reacting groups in the crystal compared to either the melt or the solution has been documented[18,19]. It has been confirmed by means of differential scanning calorimetry experiments that the reaction in crystal (equation 8) occurs without preliminary melting of the reactants[20].

Some intermolecular migrations of methyl groups proceed in derivatives of sym-triazines **15**–**18** both in the solid state and in the melt. The conditions under which these



(15) **(16)**

(17) **(18)**

$X^2, X^4, X^6 = O, S$

occur depend strongly both on the migration type (O → S, O → N or N → S) and on the symmetry of the starting compounds[21–24]. For example, symmetrical methyl cyanurate (**15a**, $X^2 = X^4 = X^6 = O$) at 200 °C undergoes successive isomerizations by the scheme **15** → **16** → **17** → **18** given by equation 9[21] where O and N signify the atoms to which the methyl group is linked. Note that the intermediate compounds **16a** (O.O.N.) and **17a** (O.N.N.) in the rearrangement described by equation 9 are thermally unstable to such a degree as not to be capable of being isolated preparatively.

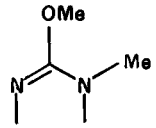
$$\text{O.O.O.} \longrightarrow \text{O.O.N.} \longrightarrow \text{O.N.N.} \longrightarrow \text{N.N.N.} \qquad (9)$$

In the case of symmetrical methyl thiocyanurate (**18b**, $X^2 = X^4 = X^6 = S$), a reverse high-temperature isomerization described by equation 10 takes place[22], and structures **16b** (S.S.N.) and **17b** (S.N.N.) are more stable than their oxygen analogs and can be isolated preparatively[23].

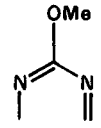
$$\text{N.N.N.} \longrightarrow \text{S.N.N.} \longrightarrow \text{S.S.N.} \longrightarrow \text{S.S.S.} \qquad (10)$$

Equally at a high temperature (200 °C), the less symmetrical compounds **15c** ($X^2 = X^6 = S$, $X^4 = O$) and **15d** ($X^2 = X^4 = O$, $X^6 = S$) isomerize to **16c** ($X^2 = O$, $X^4 = X^6 = S$) and **18d** ($X^2 = X^6 = O$, $X^4 = S$), respectively[24].

All other migrations of methyl groups in the asymmetrical compounds **16** and **17** proceed in the solid phase fairly readily: O → S at room temperature and O → N at about 100 °C[24]. In compounds **16** that contain two different methoxyl groups, a selectivity of isomerization is observed. In the first place, there occurs a fairly smooth migration of the methyl group located between the two nonequivalent nitrogen centres (**19**). When the methyl group is positioned more symmetrically (**20**), thermal isomerizations in both **15** and **16** occur at high temperatures (~ 200 °C). Such a behavior is thought to be accounted for by the difference in the polarization of reactive sites. In the compounds with the fragment **19**, the negative charge at the imine nitrogen is greater than in the case of **20**, while the methyl carbon is more deshielded as has been shown by the magnitudes of chemical shifts of the methyl protons in the ^1H NMR spectra.



(19)

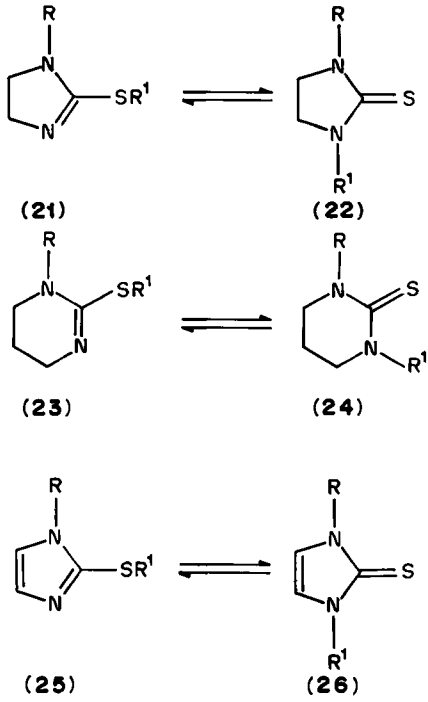


(20)

Intermolecular catalyzed rearrangements have been studied of heterocyclic alkyl thioimidates in the 1,3-diazole series: 1-*R*-2-alkylthio-Δ^2-imidazolines (**21**), 1-*R*-2-alkylthio-Δ^2-tetrahydropyrimidines (**23**)[25] and 1-*R*-2-alkylthioimidazoles (**25**)[26].

The rearrangements described by equation 11 can be catalyzed by I or alkylating agents (alkyl halides and alkyl *O*-tosylates), and in the case of derivatives of imidazoles **25** the corresponding *N*-alkyl imidazolium salts can equally serve as catalysts, as also in the rearrangements represented by equations 4 and 5. The rearrangements (equation 11) proceed by the autocatalytic S_N2 mechanism with subsequent regeneration of the catalyst. On allowing imidazole **25a** (R = Me) to stand at 120 °C for 2.5 h (with 3 mol% of the catalyst), an equilibrium is established with a 50:50 ratio between the rearrangement products **25a** and **26a**. The yield of rearrangement products in the imidazole (**25**) series grows on going from the R = Me to *i*-Pr migrants while on passing to *t*-Bu and Ph it falls due to a change in the electronic density at $N_{(3)}$ and to steric hindrances. An increase in the steric volume of the substituent at the sulfur impedes the rearrangement, particularly in the case of $R^1 = i$-Pr. From a comparison of data on the rearrangements of 1-*R*-2-

methylthio-Δ^2-imidazolines (**21**), 1-*R*-2-methylthio-Δ^2-tetrahydropyrimidines (**23**) and 1-*R*-2-methylthioimidazoles (**25**) it follows that, with the R's being identical, the facility of the rearrangement is diminished in the order **21** > **23** ≫ **25**. The pK_a of these compounds increases in the same order. The equilibrium ratio between rearrangement products grows with the rise in the temperature. Among the salts of 1,3-dimethyl-2-methylthioimidazolium (catalysts of the rearrangement of imidazoles **25**) the iodate is more active than the tosylate, and the latter is more active than the chloride: the degree of completeness of the rearrangement (140 °C, 1 h) amounts to 50, 37 and 10%, respectively, for I^-, TsO^- and Cl^-. When MeI and MeOTs are used for the quaternization of imidazoles **25**, the rearrangement is complete to 80 and 25%, respectively (140 °C, 2 h).

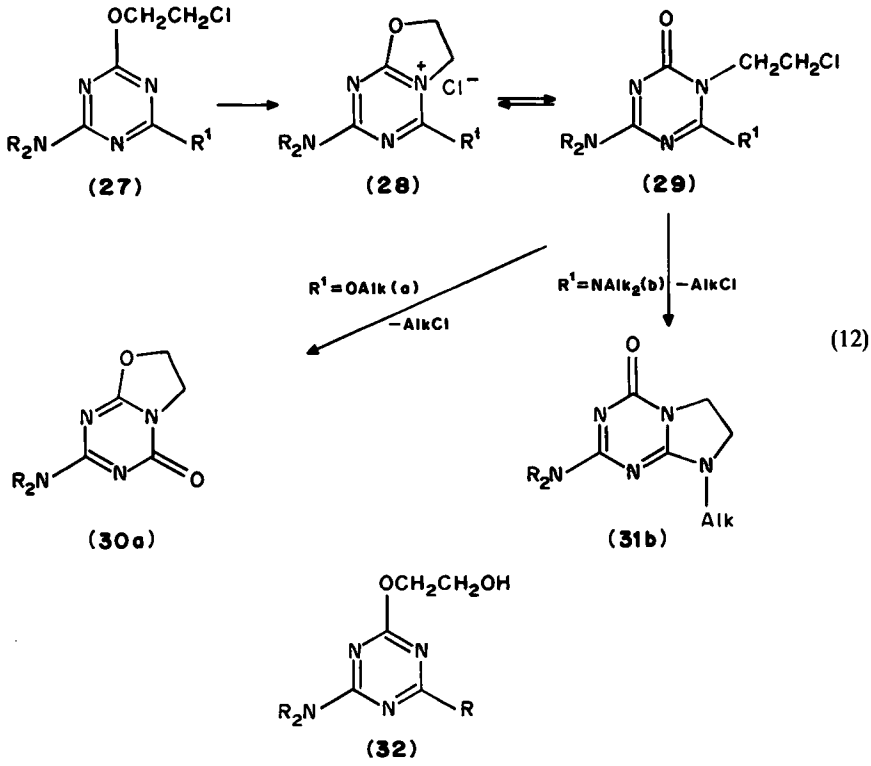


(11)

R = alkyl, Ph, R^1 = Me, Et, *i*-Pr, All, CH_2Ph, CH_2Ac

Opposed to the above-given examples of *inter*molecular migrations of alkyl groups, in derivatives of 1,3,5-triazines **27**, the noncatalyzed O → N shift of the chloroethyl group can proceed by an *intra*molecular two-step mechanism via intermediate formation of the cyclic quaternary ammonium salts **28**[27-30]. Upon brief boiling in toluene, derivatives of sym-triazines **27** undergo intramolecular quaternization to form the salts **28** which decompose under the action of the chloride anion giving rise to *N*-β-chloroethyl-sym-triazines **29** (equation 12). Further heating of the latters results in the elimination of alkyl chlorides and formation of the target products **30a** and **31b**.

The corresponding 2-hydroxyethoxy-sym-triazines **32** are not subject to thermal isomerization, even upon prolonged heating in inert solvents, since they do not form quaternary ammonium salts of type **28**.

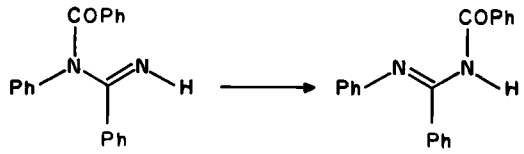


(12)

R = Me, Et
R^1 = SAlk, OAlk (a); $NAlk_2$ (b)

B. 1,3-Migrations of Acyl Groups in Amidines

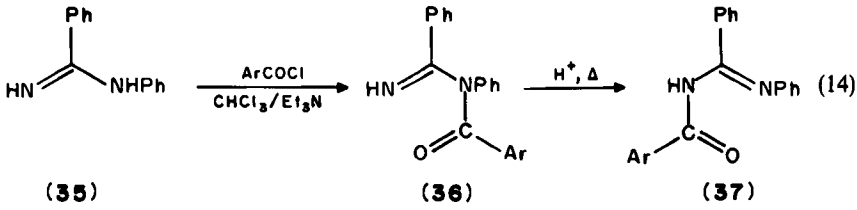
The 1,3-displacements of acyl groups in the series of the derivatives of amidines and *O*-acyl isoimides (acyl imidates) occur under much milder conditions than those needed for the transfer of alkyl groups. Possibly one of the first reactions of this type was detected and studied back in 1903 by Wheeler and coworkers[31]. It is the rearrangement of *N*-benzoyl-*N*-phenylbenzamidine (**33**) to its isomer, occurring in the course of the recrystallization of **33** from ethanol or when its solution is simply allowed to stand for some days at room temperature (equation 13).



(13)

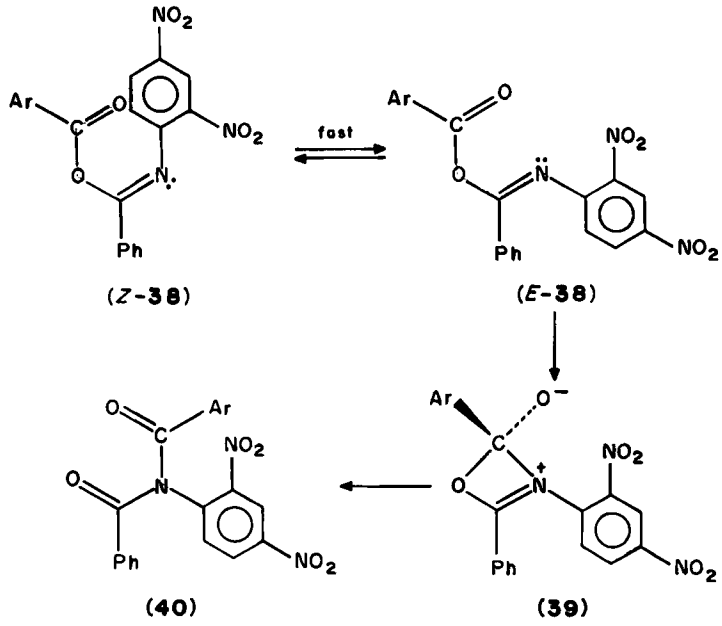
Later on, an analogous rearrangement proceeding under quite mild conditions was detected for *N*-acyl-*N*-phenylbenzamidines[32]. Thus, in the course of the aroylation of *N*-

phenylbenzamidine (**35**), *N*-aroyl-*N*-phenylbenzamidines **36** are formed in 62–75% yield. The latter, after brief heating in ethanol in the presence of strong acids (HCl, H_2SO_4), rearrange irreversibly, as a result of the 1,3-*N*,*N*′-acyl shift, into *N*-aroyl-*N*′-phenylbenzamidines **37** (equation 14).

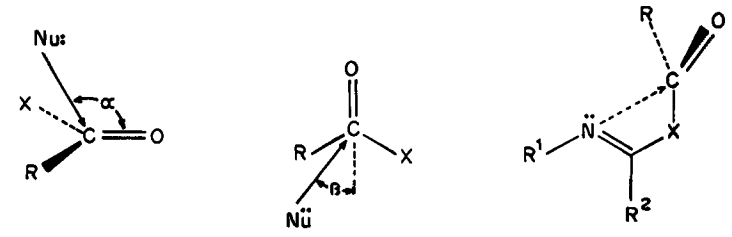


(14)

Under nearly as mild conditions as those above (in benzene or acetonitrile solution at 40–65 °C), the 1,3-transfers (O → N) of acyl groups are realized in acyl imidates **38** for which the mechanism (equation 15) involving the preliminary stage of the fast $Z \rightarrow E$ isomerization and the formation of a dipolar transition state structure **39** had been assumed[33]. The acyl group transfer reactions (equations 13–15) should be certainly viewed as examples of intramolecular addition–elimination substitutions at the sp^2-hybridized carbon center of the acyl group. From this standpoint it is easy to understand the necessity of the *Z* to *E* isomerization of acyl imidates which places the inner nucleophilic center (imine nitrogen) in a proper steric position for the approach of the carbonyl carbon being attacked. Although in the *E*-diastereomeric forms **33**, **36** and *E*-**38** a turn of acyl group to the plane perpendicular to the rest of the molecule does not render the reaction site to have optimal directionality for the nucleophilic attack on the carbonyl center **41a, b** (see References 6, 34, 35 for comprehensive reviews), while such directionality is by no means achieved in *Z*-diastereomers, the conformation **42** is sufficiently close to that required by the necessary steric demands[36–38].



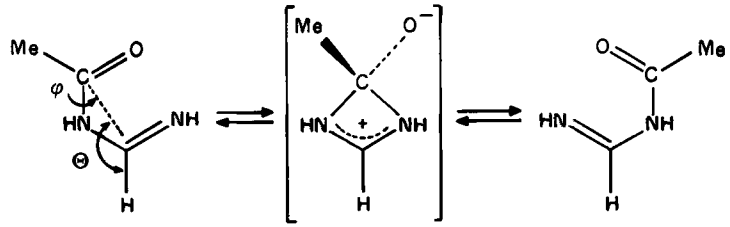
(15)



(41a) (41b) (42)

$\alpha_{opt} = 100-110°$ $\beta_{opt} = 0°$ (no $X^+ = C - O^-$ resonance) $\alpha = 126°$ $\beta = 50°$

MINDO/3 calculations[39] have been performed to study the topography of the potential energy surface (PES) of a model N $\rightleftharpoons$ N′ acyl group transfer reaction (equation 16).



(43a) (43c) (43b) (16)

As Figure 1 shows, the thermal rearrangement **43a** $\rightleftharpoons$ **43b** is initiated by a rotation of the acetyl group about the C—N bond that results in the emergence of the **42**-like reactive

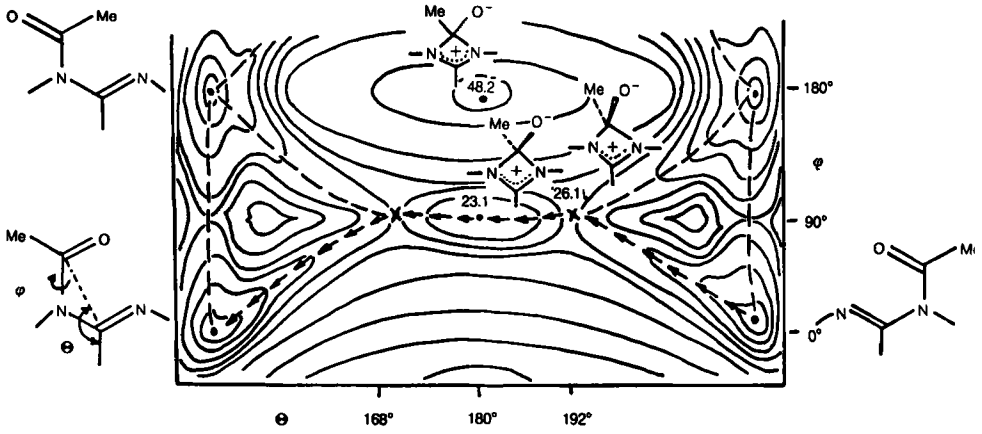
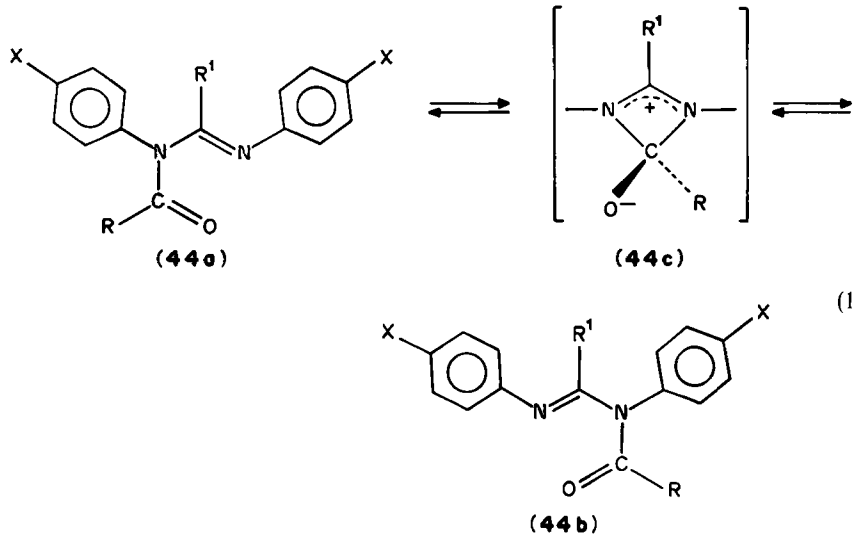


FIGURE 1. Potential energy surface of the thermal reaction **43a** ⇄ **43b** in the coordinates ϕ, θ from the data of MINDO/3 calculations[39]. The arrows indicate the minimal energy reaction path and the crosses denote the transition states

conformation preceding the formation of the late transition state structure ($\theta = 168°$) and the dipolar intermediate **43c** for which a very shallow minimum on the PES was predicted. The energy barrier to the degenerate rearrangement (equation 16), 25 kcal mol^{-1}, was calculated to lie in the upper limit of the range of the tautomeric energy scale[36,37]. This prediction agrees well with the results of extensive studies[40–42] of degenerate (equation 17) and nondegenerate (equation 18) acylotropic rearrangements of *N*-acyl-*N*,*N*'-diarylbenzamidines with the aid of dynamic ^{1}H NMR spectroscopy. In the ^{1}H NMR spectra of compounds **44**, the proton signals of different *p*-tolyl and *p*-methoxyphenyl groups are well separated at room temperature pointing to a low (on the ^{1}H NMR time scale) rate of the **44a** ⇄ **44b** exchange process. With the gradual increase in the temperature of the solution, the signals of the indicator methyl and methoxyl groups in the *N*-aryl fragments are broadened reversibly (usually above 100 °C) and coalesce (140–160 °C, 100 MHz). Such a spectral pattern can originate only from the **44a** ⇄ **44b** transformations (equation 17), since no process of rotation and inversion in the **44** molecules can lead to isochronicity of the *p*-tolyl and *p*-methoxyphenyl indicator groups. At lower temperature in ^{1}H NMR spectra of compounds **44**, processes were detected associated with their stereochemical nonrigidity.



(17)

X = Me, OMe
R^1 = H, 4-An, Ph, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 1-Naph
R = Me, 4-An, Ph, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$

Table 2 lists rate constants and activation parameters of acylotropic rearrangements of amidines, with the calculations based on the line shape analysis of the ^{1}H NMR spectra. The absence of a concentration dependence of the dynamics of the ^{1}H NMR spectra and of cross-exchange products after allowing the compounds (Nos. 9, 13 in Table 2) to stand in *o*-dichlorobenzene at 170 °C for 0.5 h bears witness to the intramolecular character of the process described by equation 17.

The rate of acyl migrations is influenced quite essentially by the substituent at the 2-carbon atom of the acyl amidines. As may be seen from Table 2 (compounds Nos. 1–4, 7–14), the acylotropic transformations proceed fairly rapidly, on the ^{1}H NMR time scale,

TABLE 2. Kinetic and activation parameters of degenerate acylotropic rearrangements **44a** ⇄ **44b** (equation 17) in *o*-dichlorobenzene according to the data in Reference 41

Compound	R	R^1	X	$k_{25°C} \times 10^5$ (s^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1})	$\Delta G^{\ddagger}_{25°C}$ (kcal mol^{-1})
1	4-$NO_2C_6H_4$	4-An	Me	17.4	23.2 ± 0.3	+ 2.3 ± 0.7	22.5
2	4-$NO_2C_6H_4$	Ph	Me	2.18	26.0 ± 0.3	+ 7.8 ± 0.8	23.7
3	4-$NO_2C_6H_4$	4-BrC_6H_4	Me	0.87	26.1 ± 0.4	+ 6.0 ± 1.0	24.3
4	4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	Me	0.44	25.6 ± 0.5	+ 3.0 ± 1.2	24.7
5	4-$NO_2C_6H_4$	1-Naph	Me	0	—	—	> 27.0
6	4-$NO_2C_6H_4$	H	Me	0.015	26.7 ± 1.0	0.0 ± 1.5	26.7
7	4-BrC_6H_4	Ph	Me	0.55	26.6 ± 0.2	+ 6.7 ± 0.5	24.6
8	4-ClC_6H_4	Ph	Me	0.87	26.3 ± 0.2	+ 6.7 ± 0.5	24.3
9	Ph	Ph	Me	1.17	26.0 ± 0.4	+ 2.9 ± 1.0	24.1
10	4-An	Ph	Me	0.14	27.2 ± 0.3	+ 6.0 ± 0.7	25.4
11	4-BrC_6H_4	4-An	Me	0.44	26.1 ± 0.2	+ 4.8 ± 0.6	24.7
12	4-BrC_6H_4	4-BrC_6H_4	Me	0.13	27.0 ± 0.3	+ 5.4 ± 0.7	25.4
13	4-$NO_2C_6H_4$	Ph	OMe	0.69	25.3 ± 0.2	+ 6.5 ± 0.5	23.4
14	Me	Ph	OMe	0.12	27.3 ± 0.4	+ 5.9 ± 0.7	25.5
15	Me	H	Me	0	—	—	> 27.0

only on condition that there is in position 2 an aryl group conjugated with the π-system of the amidine fragment. This is explained by the structure of the tetrahedral transition state (or intermediate) **44c** whose stabilization is promoted by the delocalization of the positive charge in the amidine triad onto the 2-aryl substituent. Accordingly, electron-donating substituents in the aryl group R^1 increase, while electron-withdrawing ones decrease the rate of acyl migrations (cf. compounds 1 and 4 in Table 2). Table 3 presents correlation equations that describe quantitatively the effect of the substituents R and R^1 on the rate of the acyl migrations **44a** ⇄ **44b**. Unlike the substituents in the 2-aryl group, the electron-withdrawing substituents in the migrating *N*-aryl group accelerate, while the electron-donating ones slow down the exchange (compounds 2 and 10 in Table 2). The best correlation is achieved by making use of the electrophilic σ^+ substituent constants of (Table 3). This result is identical to that found earlier in studying the acylotropic tautomerism of *cis*-(*Z*)-acylenols of acetylacetone[37,43], and it indicates that the concentration of the positive charge at the carbon of the migrating group leads to an increase in the rate of acyl migrations.

Nondegenerate acyl migrations have been studied in the series of *N*-*p*-nitrobenzoylamidines **45** with a variable *p*-substituent X in the *N*-aryl ring[42].

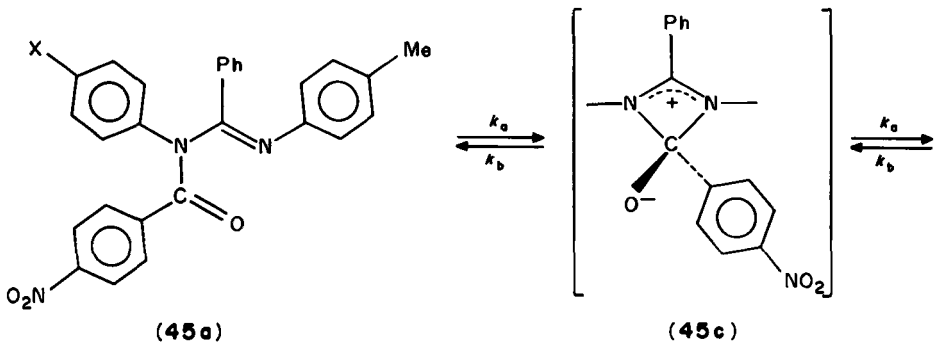
Data on the kinetics of the rearrangement **45a** ⇄ **45b** and the character of the equilibrium (equation 18) are given in Table 4. The equilibrium content of the tautomer **45a** decreases sharply when an electron-withdrawing substituent X is present in the *N*-aryl ring and, accordingly, the 1,3-acyl transfer rate (k_a) increases. The constants of the tautomeric equilibrium ($K = P_a/P_b$) are virtually insensitive to the temperature of the solution thus indicating that the value of $\Delta S°$ is close to zero.

The *E*-configuration of *N*-acyl-*N*,*N'*-diarylamidines **44a, b** and **45a, b** necessary for the intramolecular migration to occur does not always correspond to an energetically most favored structure. The spatial structure of compounds of the type-**46** series in CCl_4 solution (equation 19) has been studied by dipole moment and Kerr effect methods[44]. It has been found that the acyl group in the diastereomer **46a** is rotated by an angle $\varphi_3 \simeq 40$–$50°$, i.e. this conformation is sterically suited to its *N*,*N'* transfer within the molecule. The equilibrium content of **46a** for the amidines 1,3 and 4 amounts to 33, 28 and 71%, respectively, while for compound 2, in which 1,3-acyl migrations encounter the highest energy barrier[41], the conformer **46b** is predominant.

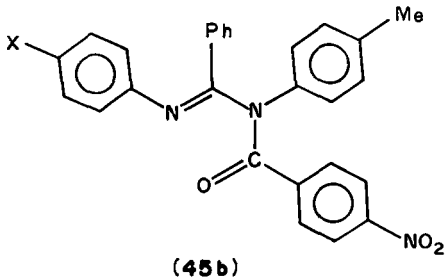
Using the dynamic ^1H NMR method, the kinetics has been studied of stereodynamic processes that determine the equilibrium (equation 20) in solution and are associated with amide (angle φ_3) and amidine (φ_5) rotations and the $Z \rightleftarrows E$ isomerization (planar inversion of the imine nitrogen)[41,42]. The order of magnitude of the energy barriers can be seen from the data of Table 5 obtained for *N*-(*p*-nitrobenzoyl)-*N*-(*p*-tolyl)-*N*-(*p*-methoxyphenyl)benzamidine (**47**). Since the $Z \rightleftarrows E$ isomerization and the amidine and

TABLE 3. Correlation equations describing the effect of R and R^1 on the rate of the acyl migrations **44a** ⇄ **44b**[40,41]

Reaction series				
Variable substituent	Permanent fragments	Nos. Table 2	Correlation equation	r(s)
R^1	R = 4-$NO_2C_6H_4$ X = Me	1–4	$\lg(k/k_0)_{150°C} = -1.15\sigma^0$	0.993 (0.103)
R	R^1 = Ph X = Me	2,7–10	$\lg(k/k_0)_{150°C} = 0.641\sigma^+$	0.996 (0.060)

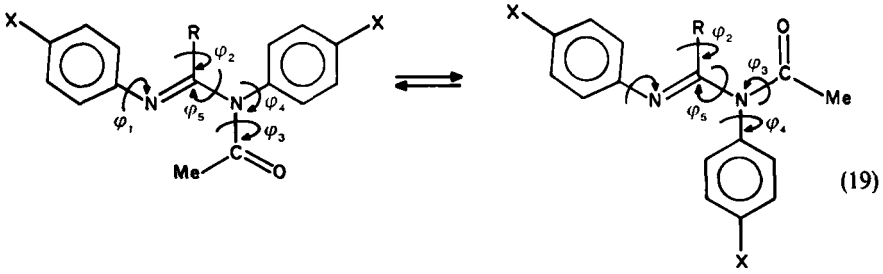


(45a) (45c)



(45b)

(18)



(46a) (46b)

(19)

	1	2	3	4
R	Ph	H	Ph	Ph
X	H	Me	Me	Br

amide rotations in acyl amidines proceed with activation barriers substantially lower than those for the 1,3-shift of the acyl group, they do not impede the latter process.

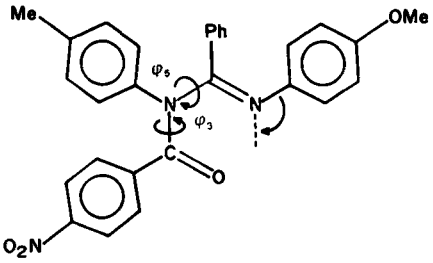
A study has been undertaken to assess the effect that the presence of a free-radical center in amidines exerts on the rate of *N,N'*-acyl rearrangements[45,46]. The oxidation of *N*-acyl-*N,N'*-diaryl-(3,5-di-*t*-butyl-4-hydroxyphenyl) amidines **48** leads to the corresponding phenoxyl radicals **49** which, according to ESR spectral data, exist predominantly as *E*-diastereomers (equation 21)[45].

TABLE 4. Kinetic, activation and thermodynamic parameters of nondegenerate acylotropic rearrangements **45a** ⇄ **45b** (equation 18) in *o*-dichlorobenzene, according to the data of Reference 42

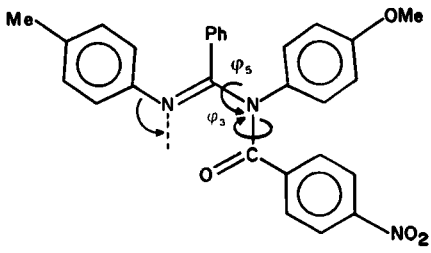
Compound	X	($k_{25°C}s^{-1}$)	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1})	$\Delta G^{\ddagger}_{25°C}$ (kcal mol^{-1})	P_a	P_b	$\Delta G^{\circ}_{25°C}$ (kcal mol^{-1})
1	OMe	1.75×10^{-5}	26.6 ± 0.3	$+0.9 \pm 0.6$	23.9	0.55	0.45	−0.12
2	Me	2.18×10^{-5}	26.0 ± 0.3	$+7.8 \pm 0.8$	23.7	0.50	0.50	0
3	H	3.27×10^{-5}	25.7 ± 0.1	$+7.5 \pm 0.3$	23.5	0.45	0.55	+0.12
4	Br	4.95×10^{-5}	25.6 ± 0.3	$+7.8 \pm 0.6$	23.3	0.33	0.67	+0.42
5	NO_2	18.6×10^{-5}	24.4 ± 0.3	$+6.2 \pm 0.7$	22.5	0.08	0.92	+1.45

TABLE 5. Kinetic and activation parameters of acylotropy and stereodynamics for amidine **47**, according to Reference 42

Dynamic process	Tautomer	$k_{150°C}(s^{-1})$	$\Delta G^{\ddagger}_{25°C}$ (kcal mol^{-1})
N,N'-migration	**a**→**b**	5.2	24.5
N,N'-migration	**b**→**a**	4.2	24.6
E→*Z*	**a**	1.68×10^3	18.9
E→*Z*	**b**	1.34×10^3	19.0
φ_5-rotation	**a** and **b**	$>3.5 \times 10^5$	<12.5
φ_3-rotation	**a**	3.68×10^4	14.5
φ_3-rotation	**b**	1.98×10^4	14.9



(47a)



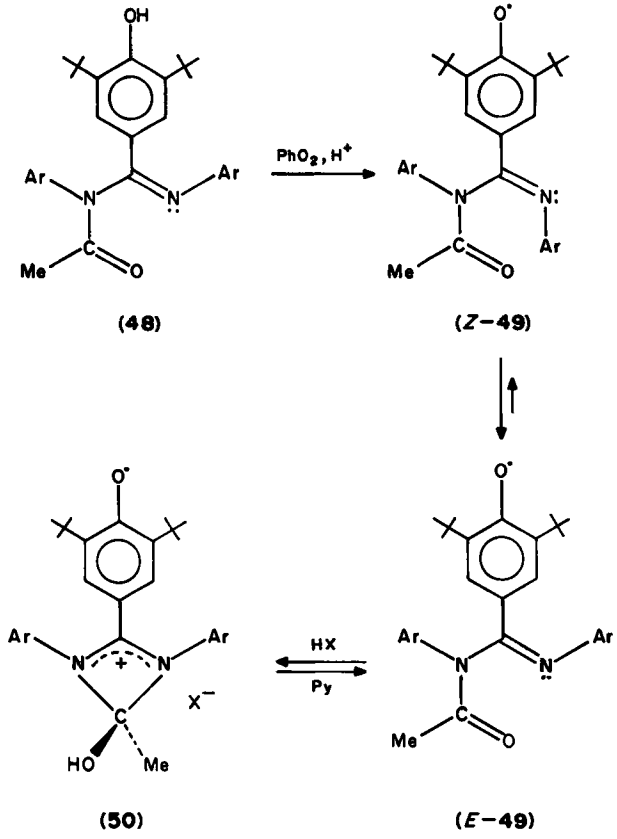
(47b)

(20)

Although the spin density in the radicals **49** is partly delocalized over the amidine fragment, the migration aptitude of the acetyl group in **49** does not grow stronger in comparison with **44** or **48**. In contrast to these two species, the protonation of **49** occurs at the acyl group oxygen thus leading to the formation of radical cations **50**[46]. The latter exhibit in the ESR spectra equivalent nitrogen atoms with a hyperfine splitting caused by the protonation of the carbonyl oxygen. Such a structure may serve as a proper model of the intermediate **44c** of the acid-catalyzed acylotropic rearrangement (equation 17).

C. 1,3-Migrations of Acyl Groups in Acyl Imidates

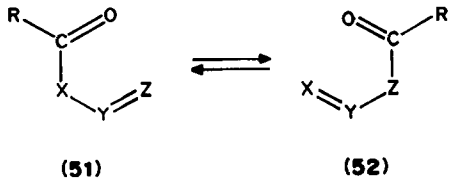
The acyl *N,N'*-rearrangements in amidines considered in the preceding section are a particular case of a more general type of rearrangement, namely that of 1,3-migrations of



(21)

Ar = 4-Tol, 4-$NO_2C_6H_4$
X = CF_3COO, Cl, ClO_4

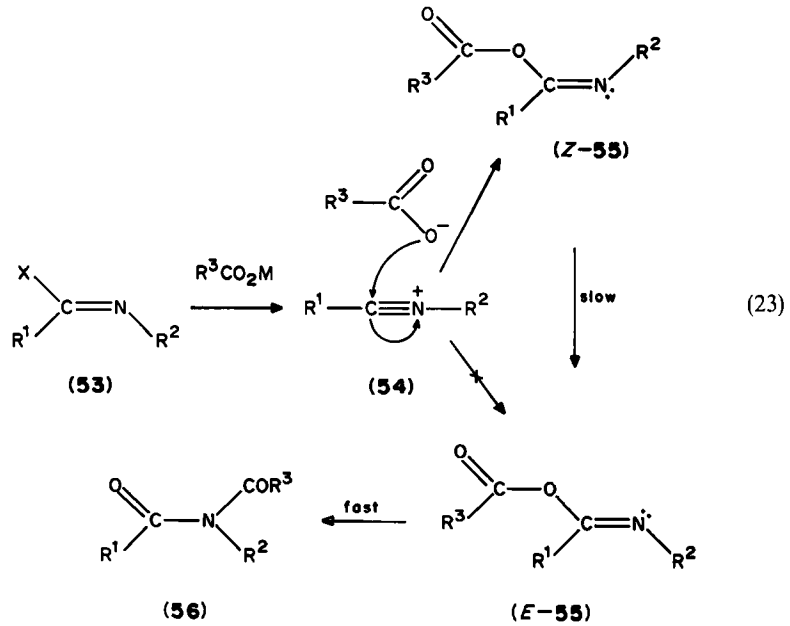
acyl groups in a triad system (equation 22). Such triad systems with a fixed imine center Z include triazines (X = Y = N), hydrazones (X = C, Y = N), thioimidates (X = S, Y = C) as well as imidates (X = O, Y = C). Data on the rearrangement described by equation 22 obtained prior to 1972, including those for compounds in which the triads **51, 52** form part of a cyclic system, were systematized[33,47] and reviewed[2,48]. Recently, considerable attention has been given to O → N acyl migrations in imidates whose investigation has further elucidated the role of the stereoelectronic factors that determine the kinetic stability and steric course of the acyl migrations in conjugated triad systems.



(22)

Unlike the thermally stable cyclic acyl imidates, their acyclic analogs are prone to fast O→N acyl transfer reactions whose driving force is the energy preference of the amide versus the isoimide conjugate system. This is the reason why the acyclic acyl imidates were preparatively isolated only not so long ago.

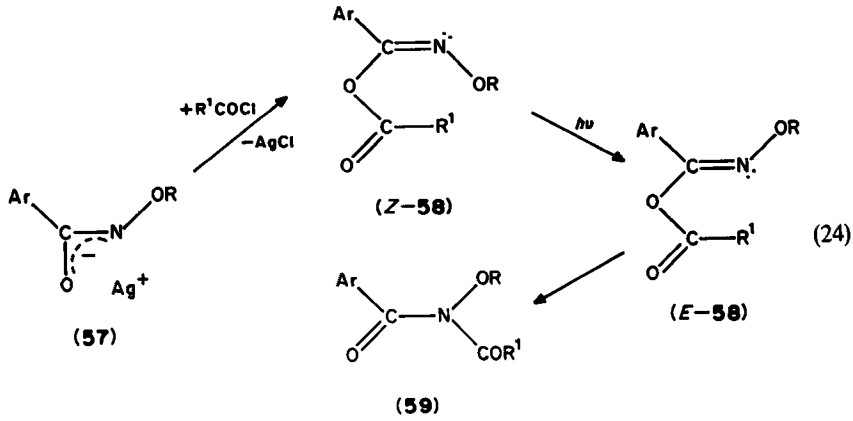
Hegarty and McCormack[49,50] have succeeded in obtaining acyl imidates **55**, stable below 60 °C, and studying their thermal rearrangement (in chlorobenzene and acetonitrile at 40–80 °C) into the corresponding *N*-acyl hydrazides **56** in accordance with equation 23. As a result of a stereospecific nucleophilic attack of carboxylic acid anions on the azocarbonium ions **54**, regenerated from the hydrazonyl halides **53**, there are formed, according to IR and ^{1}H NMR spectroscopic data, exclusively the (*Z*)-*O*-acyl isoimides *Z*-**55**, in which the *O*-acyl group and the electron lone pair of the imine nitrogen are located in a *trans* position. The stability of the compounds *Z*-**55** is explained by a high energy barrier of isomerization relative to the C=N bond. The heating of *O*-acyl isoimides *Z*-**55** above 60 °C or the use of acid catalysts under conditions that rule out hydrolysis results in their isomerization to *E*-**55**. A rapid intramolecular 1,3-*O*,*N*-acyl migration transforms the latter into corresponding *N*-acyl hydrazides **56**. This rearrangement is made possible by the sterically favorable position of the OC(O)R^3 group relative to the electron lone pair of the imine nitrogen. Depending on the substituents R^1, R^2 and R^3, the rate constants of the **55**→**56** process are varied from 0.13×10^{-4} to 10.5×10^{-4} s^{-1} with the *Z*→*E* isomerization (*Z*-**55**→*E*-**55**) being the limiting step of this process. The electron-withdrawing groups in the substituent R^2 lower the rate of the *Z*→*E* isomerization in **55**, thereby slowing down the 1,3-*O*,*N*-acyl migration in this system.



(23)

X = Cl, Br; M = Na, Ag; R^1 = Me, *t*-Bu, Ph; R^2 = N(Me)Ar; Ar = 2,4-$(NO_2)_2C_6H_3$, 4-$NO_2C_6H_4$; R^3 = Me, 4-An, Ph, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$

Another approach to obtaining stable derivatives of acyclic *O*-acyl isoimides **58**[51,52] is based on the stereospecific acylation of silver salts of *O*-alkylbenzohydroxamic acids **57** (equation 24).



(24)

R = Me, n-Pr, CH_2Ph
R′ = Me, Ph, 4-Tol, 4-ClC_6H_4, 3-ClC_6H_4, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$
Ar = Ph, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 3-ClC_6H_4

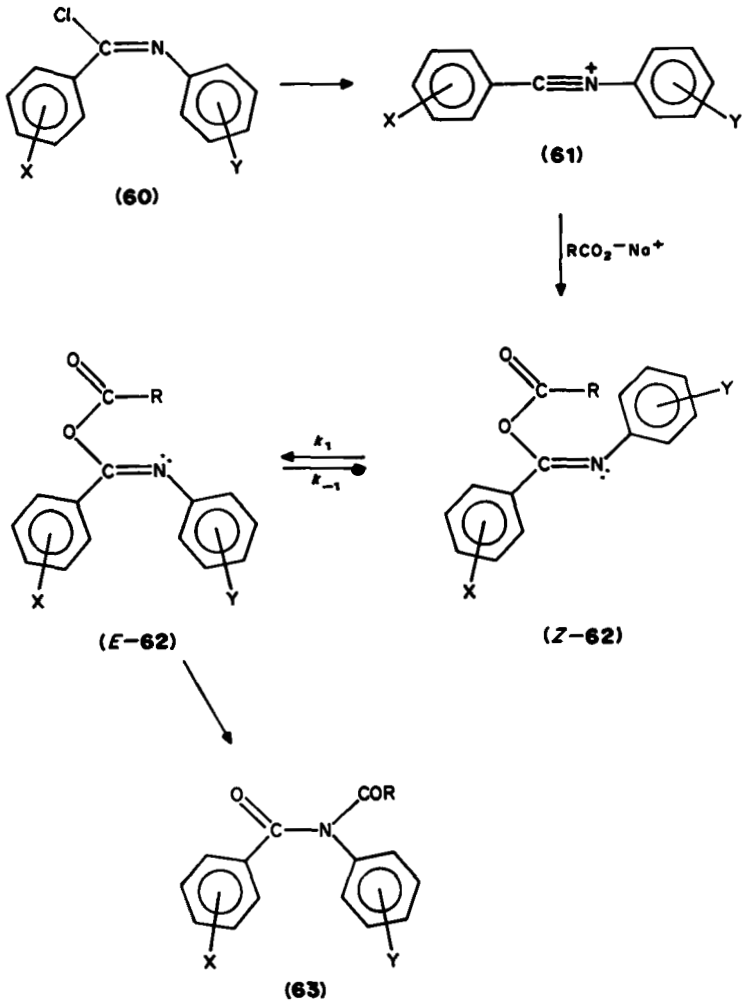
The products of the *O*-acylation **58** have all, without exception, *Z*-configuration, which can be accounted for by the chelate structure of the initial silver salt **57**. *Z*-acetic benzoalkoximic anhydrides (*Z*-**58**) have proved configurationally stable to such a degree as not to be isomerized even under reflux in toluene or chlorobenzene during 6–8 h. The *E*-isomers *E*-**58** were obtained in the end, in a preparative form, through UV irradiation of *Z*-**58** in benzene or hexane for six hours[52].

The heating of (*E*)-*O*-acyl isoimides *E*-**58** to 50–80 °C in solvents of different polarity led to *N*-acyl-*N*-benzoyl-*O*-alkylhydroxylamines (**59**) as a result of the isoimide–imide rearrangement *E*-**58** → **59** whose kinetics has been studied by IR, UV and ^1H NMR spectral methods. It has been shown[52] that the first-order rate constants for the *E*-**58** → **59** reaction depend on the origin of the substituents R, Ar, R^1 and vary in the 0.24×10^{-3} to 2.63×10^{-3} s^{-1} range (MeCN, 77 °C). The free energy of activation (E_{act}) of the 1,3-*O*,*N*-acyl shift associated with a rearrangement of the compounds *E*-**58a–c** [R = CH_2Ph; Ar = Ph; R^1 = Me (**a**), Ph (**b**), *p*-Tol (**c**)] amounts to 26.1, 26.3 and 25.8 kcal mol^{-1}, $\Delta S^{\ddagger} = 1.1$, 2.0 and 2.65 cal deg^{-1} mol^{-1}, respectively. All these values agree with an intramolecular reaction without any appreciable reorganization of the solvent shell in the transition state. It has been found[52], upon addition of catalytic amounts of acetic acid or CaH_2, as well as radical promoters and inhibitors, the rate of the *E*-**58** → **59** rearrangement does not change, which indicates very low probability of a free-radical mechanism. A dissociative ionic mechanism via the acylium cation and *O*-methylbenzohydroxamate followed by the *N*-acylation is ruled out since, after heating the mixture of the compounds *E*-**58b** and *E*-**58d** (R = Pr, Ar = Ph; R^1 = Me (**a**)), solely the *N*-acyl amides are formed without any trace of cross-products. Electron-donating substituents in Ar and R speed up the rate of the isoimide–imide rearrangement, while in R^1 they slow it down; note, however, that this effect is in either case insignificant ($|\rho| < 1$). Equally, the polarity of the solvent affects but slightly the rate of this process, which points to a low polarity of the transition state structure.

In the above-considered examples, the rate-determining step of the rearrangement of *O*-acyl imidates into *N*-acyl imides was the *Z* → *E* isomerization about the C=N double bond. This is understandable in light of the known data which show that the presence of

electronegative substituents at the imine nitrogen (OR, NR^1R^2 in compounds **55, 58**) leads to a considerable rise of the energy barrier of such an isomerization[53–55]. In contrast to this, the barriers to the $Z \rightarrow E$ isomerization in *N*-aryl-substituted imines lie within the characteristic time scale of the NMR spectroscopy, being lower than 25 kcal mol^{-1}[1,53,55,56]. For this reason, the $Z \rightarrow E$ isomerization in compounds **62** proceeds either very fast, or its rate is comparable with the $O \rightarrow N$ migration of the acyl group[57].

Upon dissolution of imidoyl chlorides **60** in aqueous dioxane (pH 3–13) in the presence of acetate or benzoate ions, the transient nitrilium cations **61** emerge yielding isoimides **62** *in situ*. At pH 6–11, the intramolecular rearrangement **62** → **63** (equation 25) proceeds at a rate which does not depend on pH of the solution in this interval nor on the composition of



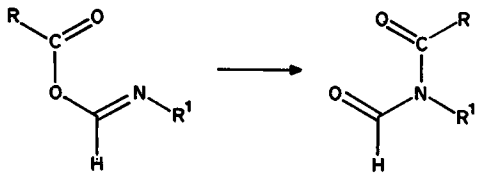
(25)

R = Me, C_6H_4R' (R' = *m*-NO_2, *m*-Cl, *p*-Cl, H, *m*-Me, *p*-MeO); X, Y = *p*-NO_2, *m*-NO_2, *m*-Cl, *p*-Cl, H, *p*-Me.

the binary solvent. The isoimide–imide rearrangement is as a rule, accelerated with the enhancement of the electron-acceptor properties of the substituent R in the order: Me, $ClCH_2CH_2$, Et, $MeOCH_2$, $H_3N^+CH_2$ and $ClCH_2$ (lg $k/k_o = 1.27\sigma^*$). In the case of compounds **62** [X = Y = H, R = $C_6H_4R^1$ (R^1 = *m*-NO_2, *m*-Cl, *p*-Cl, H, *m*-Me, *p*-Me, *p*-OMe)] the Hammett plot consists of two linear dependencies (with $\rho = 0.65$ for the acceptor and $\rho = 1.65$ for the donor R^1) crossing each other in the point R^1 = H. An analogous dependence has been found also for compounds **62** (X = H, Y = *p*-NO_2, R = $C_6H_4R^1$). The 1,3-*O*,*N*-migration of the acetyl group (R = Me) in compounds **62** is accelerated with the enhancement of the electron-releasing power of the substituents X(Y) in the order: *p*-NO_2, *m*-NO_2, *m*-Cl, *p*-Cl, H, *p*-Me ($\rho = -0.84$). According to the conclusions in Reference 57, the limiting stage of the rearrangement (equation 25) is the migration of the electrophilic RC(O) group in (*E*)-*O*-acyl isoimides *E*-**62**. This migration takes place after the fast *Z* ⇄ *E* isomerization of (*Z*)-*O*-acyl isoimides *Z*-**62** formed in the reaction. As for the donor substituents in the migrating ArC(O) group, the *Z* ⇄ *E* preequilibrium is shifted towards the *Z*-isomer *Z*-**62** thereby disturbing the linear Hammett plot.

A theoretical study of the mechanism of the formyl and acyl group 1,3-shifts from oxygen to nitrogen in compounds **64**, which may serve as models for **55**, **58** and **62**, has been carried out employing quantum chemical calculations by the semiempirical MNDO method[58,59].

According to calculations[58], amide **65a** is energetically more favored by 16.1 kcal mol^{-1} than *O*-acyl imidate **64a**, whereas structures **64b** and **65b** are in this respect roughly equivalent. The reaction path (equation 26) is fully analogous to that calculated for the *N*,*N'*-migration of the acetyl group in amidine **43** (Figure 1). Planar four-membered cyclic transition state structures containing tetracoordinate carbon centers have been located, and are shown in Figure 2.



(64) (65) (26)

R = H, R^1 = H (**a**), OH (**b**)[58]
R = n-Bu, R^1 = H (**c**)[59]

Taking into account the model character of structures **64**, **65** and the fact that the MNDO method in its standard parametrization[60] usually overestimates enthalpies of activation[61], the data obtained should be recognized as reproducing fairly well the experimental values for compounds **55**, **58** and **62**.

O(*S*)-acyliso(thio)ureas **66** containing an imidate moiety are also extremely unstable compounds rapidly rearranging into corresponding *N*-acylureas **67** (equation 27). However, they repeatedly occur as intermediates in a variety of important reactions. For example, the mechanism of the action of biotin in carboxylase reactions[62] includes an intramolecular 1,3 O → N acyl rearrangement of activated carbon dioxide linked via an oxygen atom to the imidazolidone fragment of biotin **68**. The carbodiimide reaction[63,64] (equation 28), important in peptide synthesis, proceeds fairly frequently via formation of the intermediate *O*-acylisourea **69**. The formation of the transient species **69** is confirmed

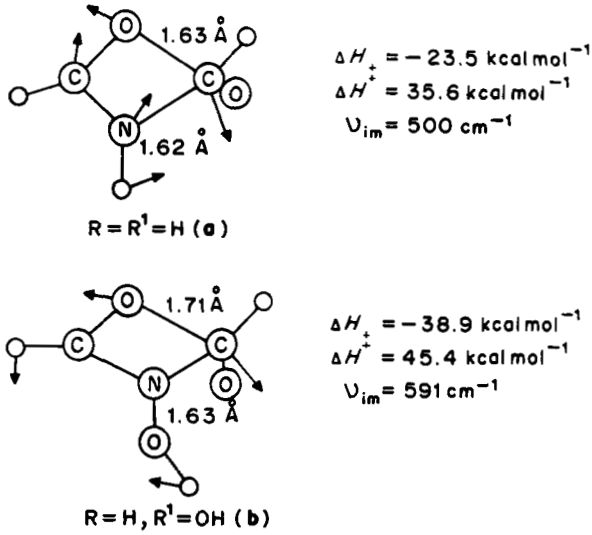
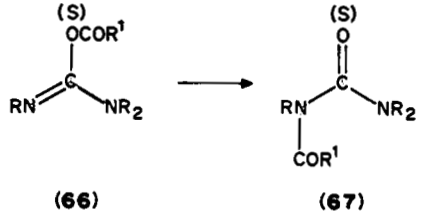
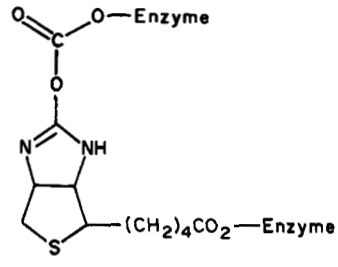


FIGURE 2. Structure of the transition states for the O → N acyl transfer reaction (**64** → **65**). Heats of formation, enthalpies of activation and imaginary vibration frequencies are given according to MNDO calculations[58]

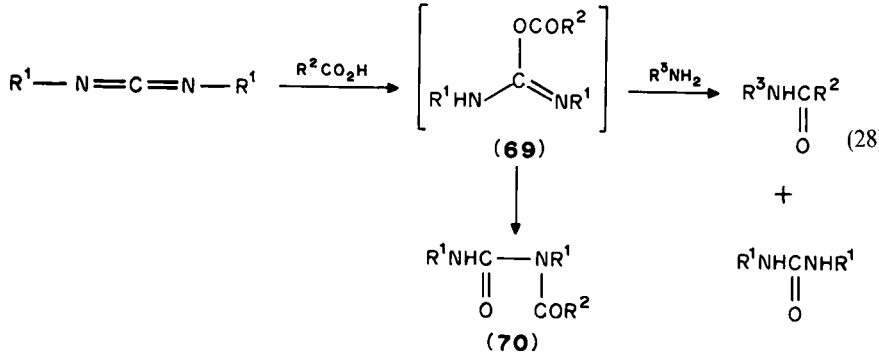
by the presence in products of the carbodiimide reaction (particularly in the absence or with insufficient amount of a nucleophile) of *N*-acylurea **70** resulting from *O*-acylisourea in consequence of a fast 1,3 O → N shift o the acyl group.



(66) (67) (27)

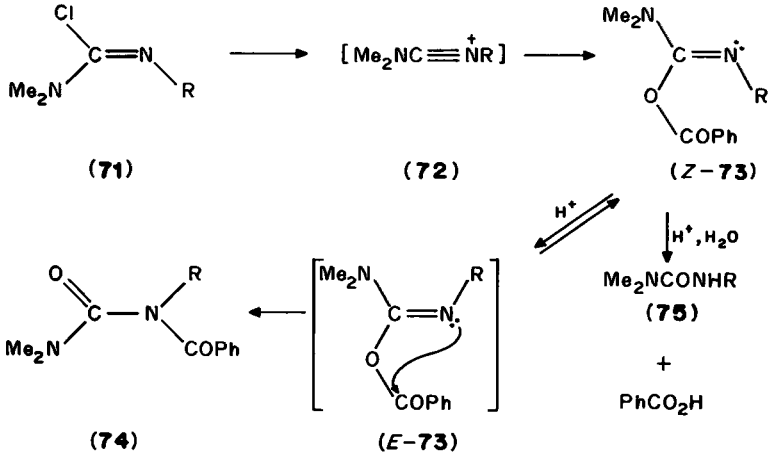


(68)



(28)

Stable acyclic derivatives of *O*-acylisoureas (**73**) that model the structure of the intermediate **69** in the carbodiimide reaction have been described by Hegarty and coworkers[65]. The reaction of the benzoate anion with the nitrilium cation **72**, obtained by treating imidoyl chloride **71** with silver benzoate in chloroform, proceeds stereospecifically to form as the only product (*Z*)-*O*-acylisourea *Z*-**73**, which at ambient temperature does not isomerize to *N*-acylurea **74** (equation 29). The *Z*-configuration of compound *Z*-**73** (*trans* position of the *O*-benzoyl group and the lone electron pair of the imine nitrogen) has been proven by X-ray diffraction study. The compound *Z*-**73** in aqueous dioxane solution undergoes at 25 °C in the presence of acids two competitive transformations associated with the acyl group transfer. One of these is an intermolecular reaction affording urea **75** and benzoic acid, the other is an intramolecular rearrangement, predominant for pH > 3, resulting in *N*-acylurea **74**.



(29)

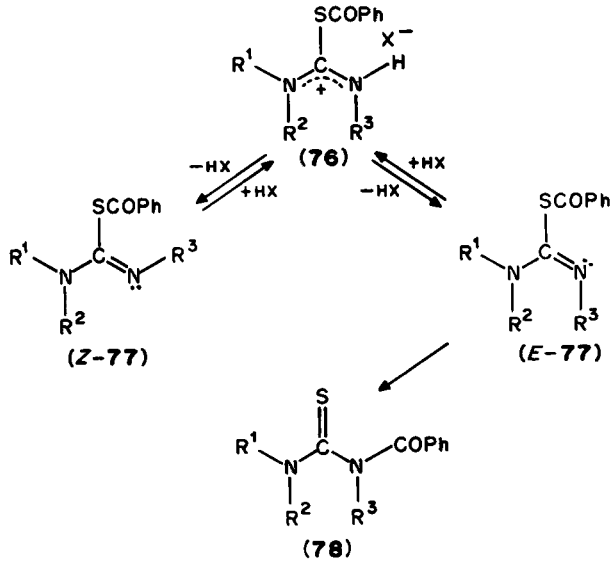
R = NMeC$_6$H$_3$(NO$_2$)$_2$- 2, 4

The intramolecular rearrangement of *O*-acylurea *Z*-**73** to *N*-acylurea **74** definitely includes the formation of the intermediate *E*-diastereomer *E*-**73** in which the favorable position of the lone electron pair of imine nitrogen and carbonyl carbon facilitates the intramolecular transfer of the acyl group from oxygen to nitrogen. The origin of the substituent R at the imine nitrogen determines the magnitude of the barrier to the $Z \rightarrow E$ isomerization and ultimately the stability of the *Z*-**73** structure. The acid catalysis (imine

nitrogen protonation) diminishes the double-bonding character of the C=N bond in *Z*-**73**, which facilitates its isomerization to the intermediate *E*-**73** and, in the end, to *N*-acylurea **74**. The protonation of *Z*-**73** also facilitates the competitive intermolecular acyl-group transfer (hydrolysis) under these conditions since it involves the formation of neutral urea **75** as a leaving group.

The interest in chemical properties of acylureas is all the stronger because some of their derivatives are efficient herbicides. A typical representative is given by 1-benzoyl-1-(4-chlorophenyl)-3,3-dimethylurea (Benzomark) used to protect corn[66]. Understandably, the reactions of *S*(*O*)-acyl iso(thio)ureas in various media and the S(O) → N acyl isomerizations occurring in the course of these have been studied in considerable detail[67–71].

It has been shown[67] that the *S*-benzoylisothiouronium salts **76** (protonated *S*-benzoylisothioureas) rearrange in water solution in the pH 3–5 range to the corresponding *N*-acylthioureas **78** in consequence of an intramolecular 1,3 S → N migration of the benzoyl group (equation 30). In the case of compounds **76a** ($R^1 = R^2 = R^3 = Me$, X = Br) and **76b** ($R^1 = R^2 = Me$, $R^3 = Et$, X = Br), the rate of the 1,3 S → N migrations increases with the lowering of the pH of solutions. This is explained by the fact that the rate-determining step is in this case the $Z \rightarrow E$ isomerization *Z*-**77** → *E*-**77** occurring via the protonated form **76** in which the rotation about the C=N bond proceeds readily enough.

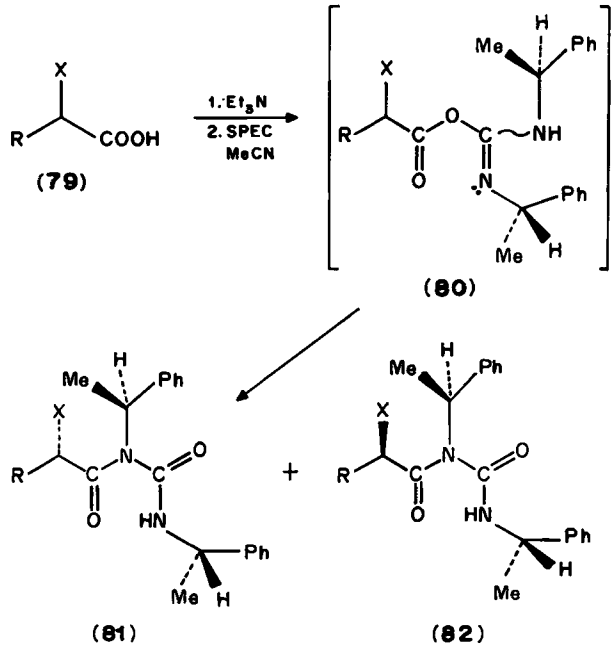


(30)

R^1, R^2, R^3 = H, Me, Et, *t*-Bu; X = Cl, Br

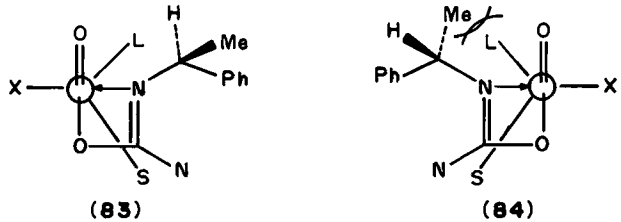
The structure of the intermediate that emerges during the rearrangement of *O*-acylisoureas to *N*-acylureas has been elucidated by studying the stereoselectivity of the rearrangement of chiral acylisoureas[72]. Chiral *O*-acylisoureas **80a–e** were regenerated *in situ* by means of a reaction of chiral *N*,*N*′-di-[(*S*)-L-phenylethyl] carbodiimide (SPEC) with α-substituted carboxylic acids **79a–e** (equation 31).

For two diastereoisomeric forms of the acylureas **80** (*S* and *R*) there are two transition states **83** and **84**, respectively (X is the polar group, L > S). In structure **83**, the nitrogen atom approaches the carbonyl carbon from the least sterically crowded side, whereas in **84** the same attack encounters steric hindrance. For that reason, the rearrangement of the stereoisomer **83** to *N*-acylurea **81** proceeds faster than that of **84** to **82**. When acids **79c–e**



(a) R = Me, X = Cl; (b) R = Ph, X = OH; (c) R = Me, X = OPh; (d) R = Me, X = Br; (e) R = i-Pr, X = Br

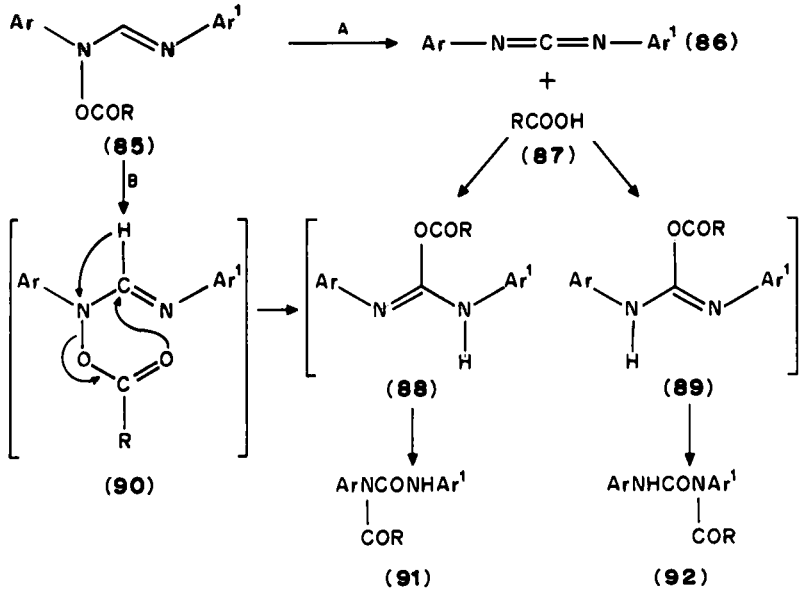
having bulky substituents participate in this reaction, it is characterized by a particularly high stereoselectivity (the yield of compounds **81c–e** attains 95%).



A thermal rearrangement of *N*-acyloxyformamidines **85** has been investigated[73] leading to a mixture of *N*-acylureas **91** and **92** (equation 32). An IR spectral study has shown that in the first step of the rearrangement carbodiimide **86** and carboxylic acid **87** are formed (path A). Their subsequent interaction leads to *O*-acylisoureas **88** and **89** that rearrange to the respective *N*-acylureas **91** and **92**. However, the occurrence of the rearrangement via a cyclic transition state **90** (path B) is not ruled out.

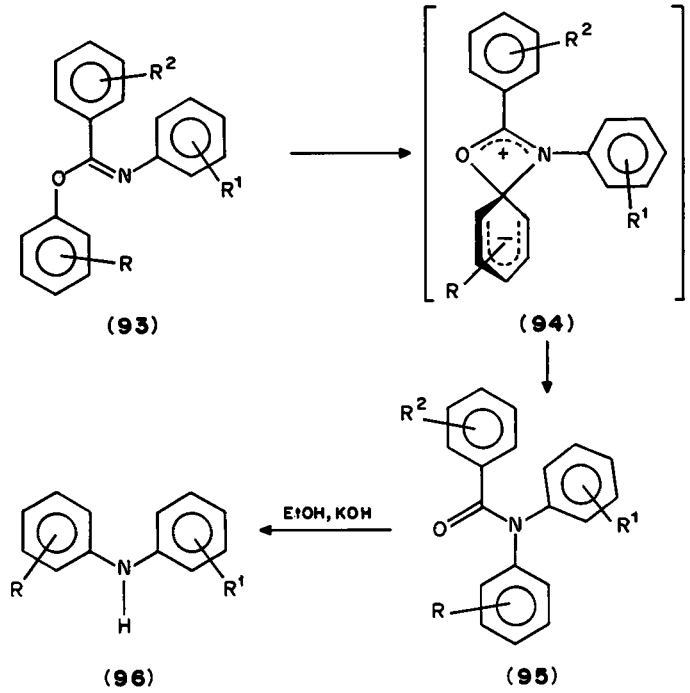
D. 1,3-Migrations of Aryl Groups in Amidines and Imidates

Thermal uncatalyzed rearrangements of *O*-aryl imidates **93** to *N*-aroyldiarylamides **95** (equation 33) proceeding at 150–300 °C via 1,3 O → N aryl shift were discovered by Mumm and coworkers in 1915[74]. However, this reaction became known as the Chapman



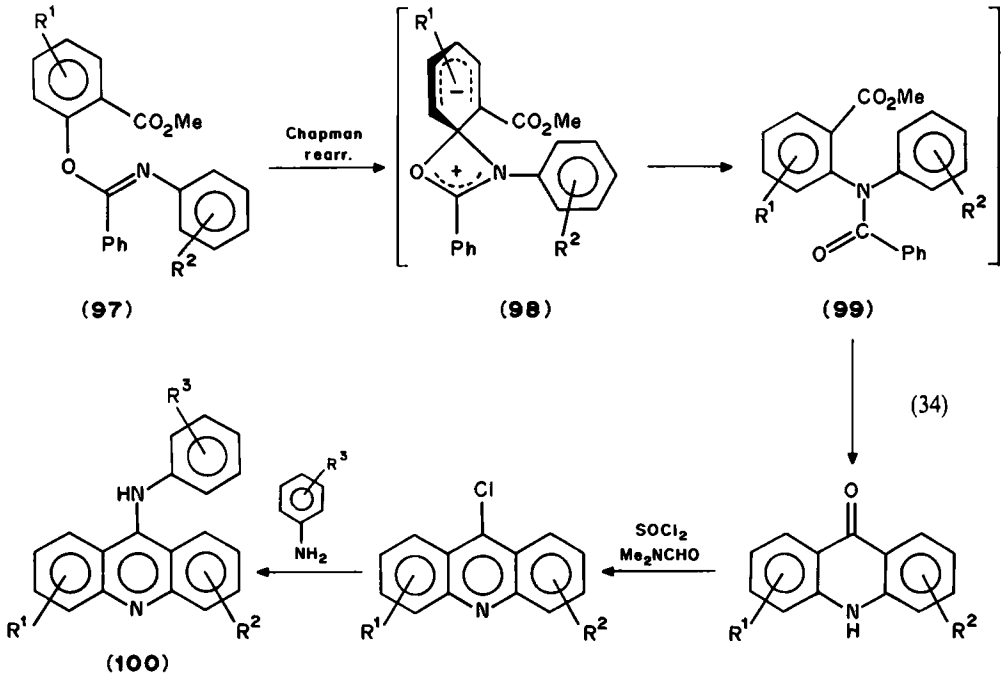
(32)

rearrangement as it happened to be Chapman who, over the period from 1925 to 1932, had been conducting intensive studies of its mechanism and expanding the area of its application[1–3].



(33)

The Chapman rearrangement provides a convenient way for transformation of phenols to anilines as well as for obtaining some not readily accessible diarylamines and nitrogen heterocycles. As an illustration, one may point to the general approach to the synthesis of 9-arylaminoacridines **100** (equation 34)[75] with the key step represented by the Chapman rearrangement **97** → **99**. The series of transformations features a method suggested by Cymerman-Craig and Loder[76]. The mechanism of the Chapman rearrangement has been studied in considerable detail. The reaction **33** is irreversible, intramolecular in nature, of first kinetic order, and occurs via the four-membered transition state structure **94** and may be regarded as an intramolecular aromatic nucleophilic substitution. The rate at which the rearrangement **93** → **95** takes place depends on the nature and position of substituents R, R^1 and R^2 in the aryl rings. In the aryloxy fragment R, the electron-withdrawing substituents accelerate the rearrangement, while in *N*-aryl R^1 and *C*-aryl R^2 rings they slow it down, with the substituents R having by far the greater effect. The presence of *ortho*-substituents in the aryloxy group provides for higher rates of the rearrangement, as opposed to imidates where the same substituents are located in the *p*-position.



A recent X-ray diffraction study[77] of 2-methoxycarbonyl-1-naphtyl-*N*-(1-naphthyl)benzimidate (**97**, $R^1 = R^2 = 2,3\text{-}C_4H_4$) has revealed that the conformation of the molecule in the ground state matches the requirements of the S_NAr substitution reaction route associated with the formation of a four-membered cyclic transition state (intermediate) structure of type **98**. As may be seen from Figure 3, the $N_{17} \cdots C_{(1)}$ distance is rather short, 2.648 Å, i.e. much less than the sum of the van der Waals radii (about 3.1 Å). The plane of the *O*-naphthalene ring is rotated by 73.5° relative to the plane formed by the $C_{(1)}$, $O_{(15)}$, $C_{(16)}$ and $N_{(17)}$ atoms thus facilitating the attractive two-electron n,π^*-orbital interaction when the nitrogen atom attacks the $C_{(1)}$ atom.

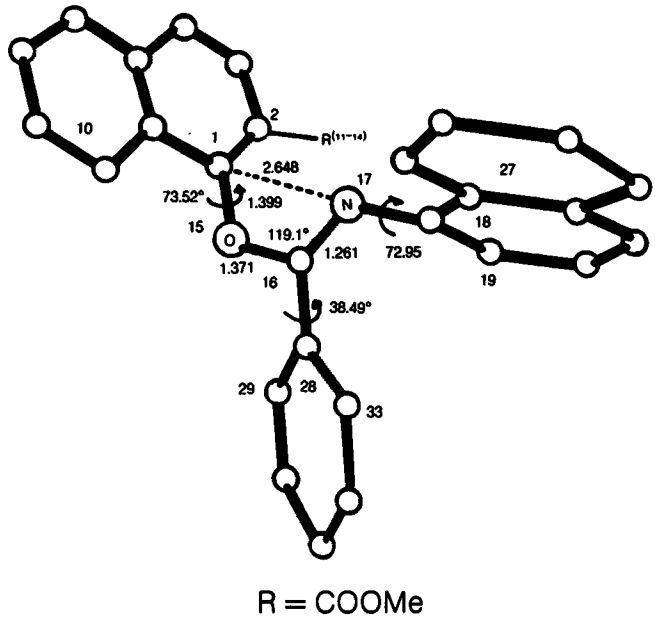
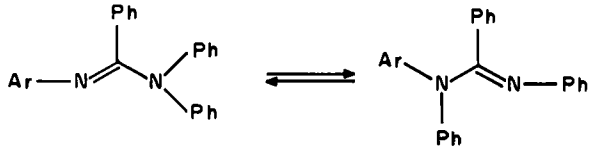


FIGURE 3. Stereoprojection, bond lengths and angles in molecule **97** ($R^1 = R^2 = 2,3\text{-}C_4H_4$) according to data of X-ray diffraction study[77]

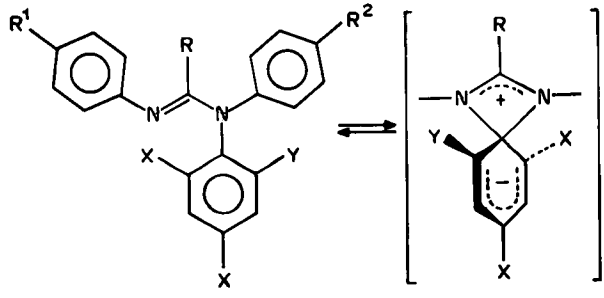
Chapman discovered also the reversible thermal rearrangements of *N*-aryl-*N*,*N*'-diphenylbenzamidines (**101**) occurring at 330–340 °C (equation 35); see the review in Reference 2.



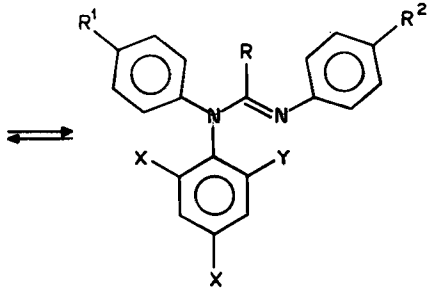
(101a) (101b) (35)

In the 1970s, a considerable lowering of the energy barrier to *N*,*N*'-migrations of aryl groups adjusting these to the tautomeric rearrangement scale was achieved[36,37,42,78–80]. This was made possible by activating the phenyl group through the introduction of electron-withdrawing substituents into the aryl moiety. Using dynamic ^{1}H NMR, degenerate and nondegenerate 1,3-migrations of 2,4,6-trinitrophenyl (picryl) and 2,4,6-tris(trifluoromethylsulfonyl)phenyl groups **102a** ⇄ **102b** have been studied; these may be viewed as processes of intramolecular nucleophilic substitution reactions (equation 36).

Compounds **102** are conformationally nonrigid; however, in their ^{1}H NMR spectra no additional dynamic processes are observed either when their solutions are cooled to − 50 °C or when protonic acids are added[79]. This is indicative of rather low activation barriers ($\Delta G^{\ddagger} < 13$ kcal mol^{-1}) to the amidine rotation and $Z \rightleftarrows E$ isomerization, which is in accord with the data[81–84] on barriers to rotation and on $Z \rightleftarrows E$ rearrangements in the series of derivatives of *N*-aryl-*N*,*N*'-dialkylbenzamidines[81–84]. Owing to low conformational barriers, the amidine molecules **102** can easily attain the reactive conformation



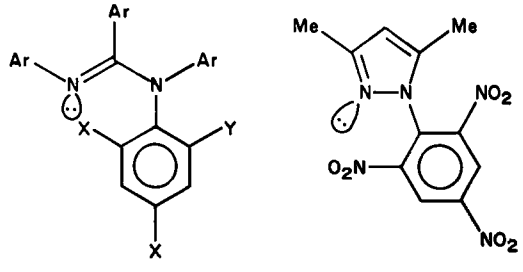
(102a) (102c)



(102b) (36)

R^1, R^2 = OMe, Me, H, Br, NO_2
R = H, 4-An, Ph, 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$, 1-$C_{10}H_7$
X = Y = NO_2; X = NO_2, Y = H; X = Y = SO_2CF_3

102d which provides necessary spatial condition for the intramolecular nucleophilic attack on the *ipso*-carbon center of the aryl ring activated with electron-withdrawing groups. The decisive role of the favorable orientation of interacting centers achieved in **102d** in the realization of rapid intramolecular migrations of nitroaryl groups is highlighted by the absence of the picryl exchange in 1-picryl-3,5-dimethylpyrazole (**103**) up to the temperatures (170–200 °C) at which **103** starts decomposing. Thus, there is inhibition of intramolecular N⇄N′ migrations even though the reactive centers lie closer to one another than in amidines. This can be explained only by the orientation of the electron lone-pair axis of the sp^2-hybridized pyrazole nitrogen which is unfavorable for the formation of a transition state (or intermediate) of type **102c**.



(*S-cis-E*-102d) (103)

The structure of the rapidly rearranging nitroarylamidine molecules **102** was ascertained in the crystalline state by X-ray diffraction[85,86]. Taking the case of *N*-(2,4,6-trinitrophenyl)-*N*,*N*'-di-(*p*-methoxyphenyl) benzamidine (**102**, R = Ph, $R^1 = R^2 = OMe$, $X = Y = NO_2$), it could be shown that it is the **102d** conformation, i.e. the one most favorable for the *N*,*N*'-aryl migrations **102a** ⇄ **102b**, that is stable among those of the arylamidines **102**. As may be seen from Figure 4, the distance $N_{(1)} \cdots\cdots C_{(4)}$ equals 2.66 Å, which is by 0.5 Å less than the sum of the van der Waals radii, thus pointing to strong attractive interaction between those centers in the ground state molecular conformation of **102**.

Tables 6 and 7 list kinetic and activation parameters of the degenerate and nondegenerate rearrangements of the activated aryl groups in amidines **102a** ⇄ **102b** obtained by dynamic ^1H NMR. Analysis of the data of Table 6 leads to the following conclusions. (1) The rate of the reversible 1,3-transfer of the picryl group increases 10^5–10^7 times and the free activation energy ($\Delta G^{\ddagger}_{25°C}$) is lowered by 7–10 kcal mol^{-1} when passing from formamidine (R = H, row 8 in Table 6) to benz- and naphthamidines (R = Ar, compounds 1–6, 9–14, Table 6). The aromatic substituent R in compounds **102** stabilizes the dipolar structure of the transition state (or intermediate) **102c** by delocalizing the positive charge in the amidine triad, thereby lowering activation energy of the exchange reaction (equation 36). (2) The greatest migration aptitude is possessed by the 2,4,6-tris (trifluoromethylsulfonyl) phenyl group (No. 9, Table 6). The free activation energy of its migration is lower by 2.1 kcal mol^{-1} than $\Delta G^{\ddagger}_{25°C}$ of the 2,4,6-trinitrophenyl group in the analogous amidine derivative (compound 2, Table 6), which agrees with the exceptionally high

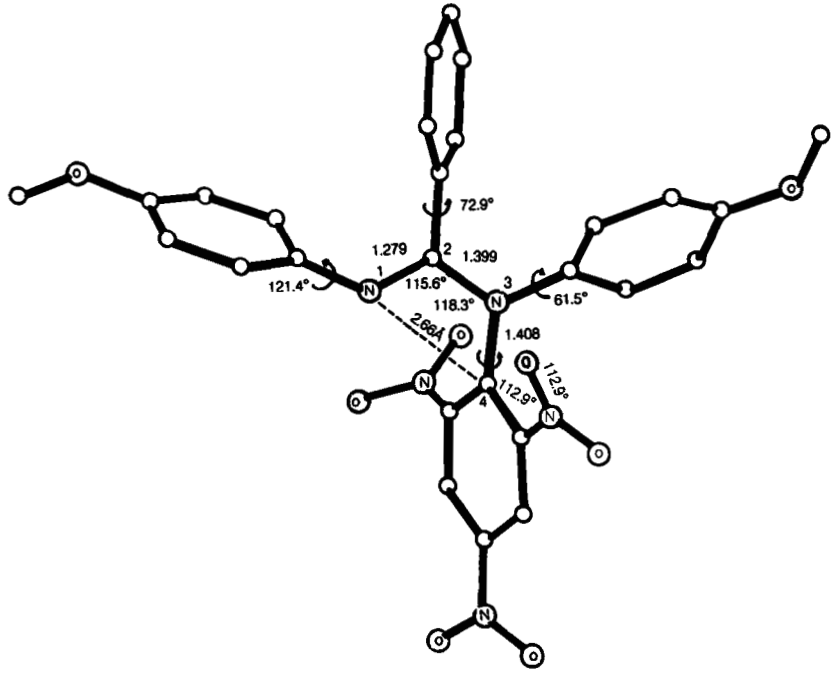


FIGURE 4. Stereoprojection, bond lengths and angles in molecule **102** (R = Ph, $R^1 = R^2 = OMe$, $X = Y = NO_2$) according to data of X-ray diffraction study[85,86]

TABLE 6. Kinetic and activation parameters of the arylotropic rearrangements **102a** ⇄ **102b** in chlorobenzene, according to reference 79

Compound											
No.	R	R^1	R^2	X	Y	$k_{25°C}$ (s^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1})	$\Delta G^{\ddagger}_{25°C}$ (kcal mol^{-1})	P_a	P_b
1	*p*-An	Me	Me	NO_2	NO_2	1.95	15.7 ± 0.1	−4.3103	17.0	0.5	0.5
2	Ph	Me	Me	NO_2	NO_2	0.69	16.3 ± 0.1	−4.4 ± 0.2	17.6	0.5	0.5
3	4-BrC_6H_4	Me	Me	NO_2	NO_2	0.31	16.2 ± 0.2	−6.4 ± 0.4	18.1	0.5	0.5
4	4-$NO_2C_6H_4$	Me	Me	NO_2	NO_2	0.078	17.3 ± 0.3	−5.5 ± 0.9	18.9	0.5	0.5
5	1-Naph	Me	Me	NO_2	NO_2	0.69	16.2 ± 0.1	−4.6 ± 0.4	17.6	0.5	0.5
6	Ph	OMe	OMe	NO_2	NO_2	1.25	15.5 ± 0.2	−6.0 ± 0.5	17.3	0.5	0.5
7	Ph	Me	Me	NO_2	H	$1.9 \cdot 10^{-6}$	25.2 ± 0.6	0.2 ± 1.2	25.2	0.5	0.5
8	H	OMe	OMe	NO_2	NO_2	10^{-7}	—	—	27.0	0.5	0.5
9	Ph	Me	Me	SO_2CF_3	SO_2CF_3	21.9	4.2 ± 0.5	−38.3 ± 0.7	15.6	0.5	0.5
10	4-An	Me	H	NO_2	NO_2	1.23	16.7 ± 0.1	−2.1 ± 0.4	17.4	0.60	0.40
11	Ph	Me	H	NO_2	NO_2	0.69	15.6 ± 0.2	−6.8 ± 0.6	17.6	0.60	0.40
12	4-ClC_6H_4	Me	H	NO_2	NO_2	0.27	16.8 ± 0.2	−4.7 ± 0.4	18.2	0.62	0.38
13	4-$NO_2C_6H_4$	Me	H	NO_2	NO_2	0.014	20.0 ± 0.3	−0.4 ± 0.7	19.9	0.63	0.37
14	1-Naph	Me	H	NO_2	NO_2	0.87	15.7 ± 0.1	−6.2 ± 0.4	17.5	0.68	0.32
15	Ph	Me	H	NO_2	H	$0.4 \cdot 10^{-6}$	25.0 ± 0.4	+0.3 ± 1.7	25.9	0.53	0.47

TABLE 7. Kinetic and activation parameters of nondegenerate migrations of the picryl group **102a** ⇄ **102b** (**102**, R = Ph, R^1 = Me, X = Y = NO_2) in chlorobenzene, according to Reference 42

Compound									
No.	R	$k_{25°C}$ (s^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1})	$\Delta G^{\ddagger}_{25°C}$ (kcal mol^{-1})	$k^{a\to b}_{100°C}$ (s^{-1})	$k^{b\to a}_{100°C}$ (s^{-1})	$\Delta G^{\circ}_{25°C}$ (kcal mol^{-1})	P_a	P_b
1	OMe	0.44	19.8 ± 0.3	+6.2 ± 0.6	17.9	200	300	−0.24	0.60	0.40
2	Me	0.69	16.3 ± 0.1	−4.4 ± 0.2	17.6	123	123	0	0.50	0.50
3	H	0.69	15.6 ± 0.2	−6.8 ± 0.5	17.6	112	75	+0.24	0.40	0.60
4	Br	0.25	16.9 ± 0.3	−4.0 ± 0.7	18.1	94.4	26.6	+0.75	0.22	0.78
5	NO_2	1.1×10^{-3}	18.0 ± 0.8	−7.0 ± 0.8	20.1	5.26	0.94	+1.02	0.15	0.85

TABLE 8. Correlation equations describing the effect of *p*-substituents in benzamidines **102** (R = *p*-$R^3C_6H_4$) on the rate of **102a** ⇄ **102b** rearrangements, according to data in Reference 79

Reaction series		Nos. in Table 6	Correlation equation	*r* (s)
Varied group	Constant groups			
R^3	$R^1 = R^2 = Me$ $X = Y = NO_2$	1–4	$\lg (k/k_0)_{80\,°C} = -1.30\sigma^0$	0.991 (0.135)
R^3	$R^1 = Me$, $R^2 = H$ $X = Y = NO_2$	10–13	$\lg (k/k_0)_{80\,°C} = -1.38\sigma^0$	0.997 (0.082)

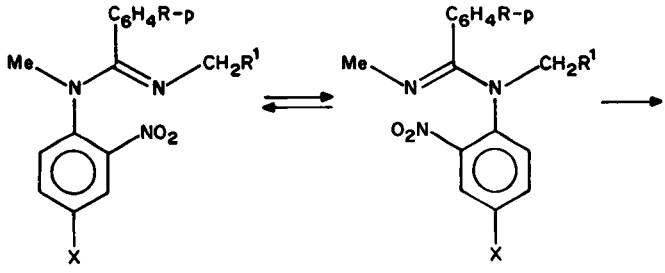
electrophilicity of the former group. Indeed, it is known[87,88] that the anionic σ-complexes of 1,3,5-tris(trifluoromethylsulfonyl)benzene are more stable to decomposition than the corresponding σ-complexes of 1,3,5-trinitrobenzene. Upon going from the migrating picryl group to the 2,4-dinitrophenyl group, the rate of the **102a** ⇄ **102b** rearrangement drops by about six orders of magnitude (compounds 2 and 7, 11 and 15, Table 6). No rearrangements of the *p*-nitrophenyl group into *N*-*p*-nitrophenyl-*N*,*N*'-diarylbenzamidines could be detected by dynamic ^1H NMR, even at temperatures close to + 200 °C. (3) In contrast to the strong acceleration of the 1,3-shifts of the 2,4,6-trinitrophenyl group brought about by an aryl substituent attached to the carbon atom of the amidine triad, the effect on the rate of reaction (equation 36) of the substituents in the *C*-aryl ring is relatively slight ($\Delta G^{\ddagger}_{25\,°C}$ varies within 2–2.5 kcal mol^{-1}). The correlation equations describing the dependence of the rate constants of the degenerate and nondegenerate exchanges **102a** ⇄ **102b** on the σ-constants of the substituents are given in Table 8. The electron-withdrawing substituents in the *C*-aryl ring slow down the process (equation 36), while the electron-donating ones speed it up. (4) Negative values of the activation entropy ($\Delta S^{\ddagger}$) that characterize the migration of the 2,4,6-tris-(trifluoromethylsulfonyl)phenyl and picryl groups, and the near-zero values for the 2,4-dinitrophenyl groups (Tables 6,7) suggest tight transition-state structures of **102a** ⇄ **102b**.

In the nondegenerate rearrangements, electron-withdrawing substituents R^2 reduce the equilibrium content of tautomers **102a**, in which the migrating group is linked to the nitrogen atom nearest to the substituent being varied (compounds 1–5, Table 7). No variation in the constants of tautomeric equilibrium ($K = P_a/P_b$) is observed when changing the temperature of the solution, which indicates a close-to-zero entropy term ($\Delta S° \approx 0$).

An enhancement of the nucleophilicity of nitrogens in the amidine moiety of **102**, between which there occurs the migration of the activated aryl group through replacement of *N*-aryl rings by alkyl groups, leads in *N*,*N*'-dialkylamidines **104** to a competition with the 1,3-migration by an irreversible ring closure reaction to form benzimidazolium nitrites **105** in 33–97% yields[89,90].

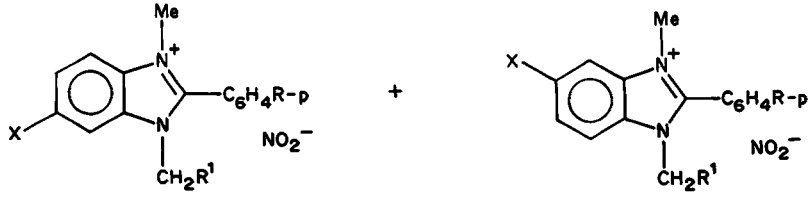
The cyclization **104** → **105** (equation 37) proceeds smoothly on heating to 100–150 °C bromobenzene or DMSO solutions of amidines **104** during the one hour. The successful cyclization of the benzamidines depends on the two *N*,*N*'-alkyl groups. In the case of *N*-ethyl-*N*'-methylbenzamidine (**104a**, $R^1 = CH_3$), the reversible 1,3-shift of the *N*-(2,4-dinitrophenyl) group is faster than the cyclization **104** → **105**, whereas with the *N*-(2-nitrophenyl) group the rates of the 1,3-displacement and of the ring closure are of comparable magnitude[90]. The intramolecular Chapman-like 1,3 O → N rearrangement (equation 38) has been studied with the tropolone derivative **106**[91] by ^1H NMR spectroscopy.

Thus at a temperature above 120 °C, as a result of the nucleophilic attack by the imine



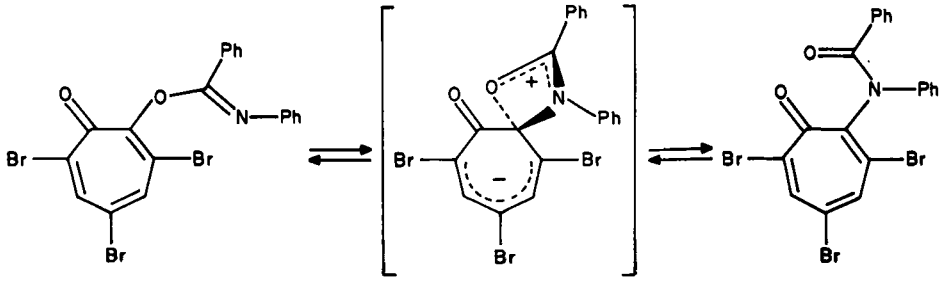
(104a) (104b)

(37)



(105a) (105b)

X = H, NO_2; R = H, OCH_3, NO_2; R^1 = H, CH_3



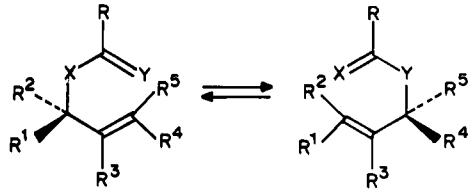
(106a) (106c) (107)

(38)

N atom upon the tropolone ring, *O*-imidoyl tropolone **106** rearranges irreversibly via a four-membered cyclic transition state (or intermediate) to 2-(*N*-phenyl-*N*-benzoyl) amino-3,5,7-tribromotropone **107** (equation 38)[91].

E. 3,3-Sigmatropic Rearrangements in *N*-Allyl Amidines and *O*-Allyl Imidates

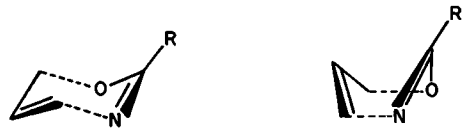
The title transformations represent a particular case of the polyhetero-Cope rearrangements which conform to the general equation 39.



(108) (109)

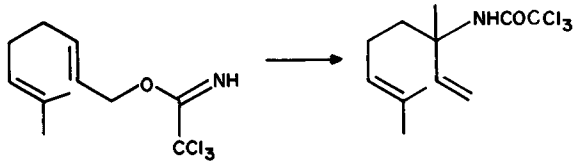
X,Y = O, NR, S (39)

The rearrangement of allyl imidates (X = O, Y = NR), discovered by Mumm and Möller in 1937[92] (see earlier reviews[1,2]), was one of the first among the general transformations (equation 39) to become known. The rearrangements of allyl imidates, which, according to the classification in Reference 93, belong to the 1-*O*,3-*N*-hetero-Cope class, proceed, as opposed to the migrations of alkyl groups in imidates (equation 3), in an intramolecular manner, at lower temperatures (heating at 200–215 °C for 3–4 h) often in high yields[94,95]. The reactions are of concerted character, and their transition states are highly ordered possessing either a chair-like or, if it is sterically inaccessible, a boat-like structure, **110** and **111**, respectively[96]. The high regio- and stereoselectivity as well as the possibility of chirality



(110) (111)

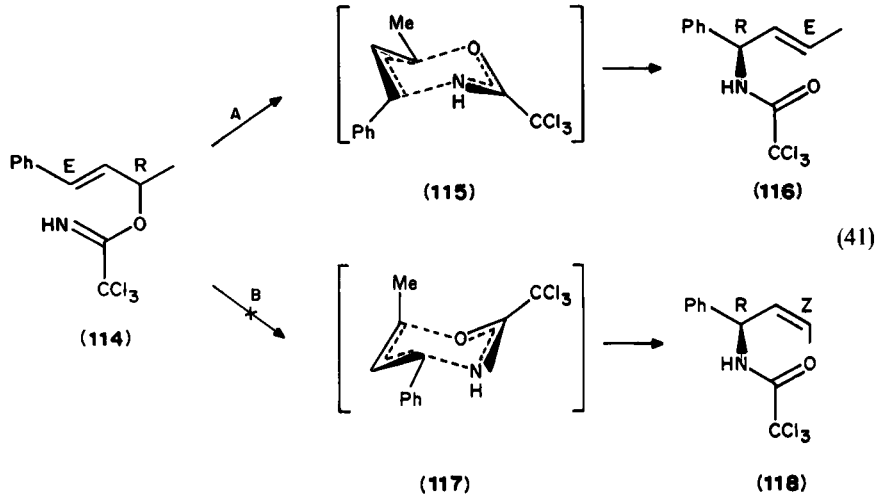
transfer (if present in the initial compound) have been conducive to the extensive use of these rearrangements in organic synthesis[95,97–99]. The ease with which the rearrangement (equation 39) occurs depends on the structure of the allyl imidates. It has been found that allyl trichloroacetimides **108** (X = O, Y = NH, R = CCl_3) undergo particularly readily the thermal 3,3-rearrangement[98]. The required temperature is for them 80–140 °C, and the time of the reaction ranges from several minutes to several hours. The activation parameters for the thermal rearrangement of trichloroacetimidate **112** to the corresponding amide **113** (equation 40) in xylene are as follows: $\Delta H^{\ddagger} = 23.8 \pm 0.5$ kcal mol^{-1}, $\Delta S^{\ddagger} = -18.6$ cal deg^{-1} mol^{-1} [100].



(112) (113) (40)

It has been shown[101] that the thermal rearrangements of allyl imidates proceed not only regio- and stereoselectively, but also with the retention of chirality if it was present in the

initial compound. Using the lanthanide shift reagent technique, it has been demonstrated by ^{1}H NMR spectra that the thermal rearrangement (equation 41) of optically active (*R,E*)-allyl trichloroacetimide (**114**) leads to optically active (*R,E*)-allyl trichloroamide (**116**) by route A. It follows from this that the rearrangement **114** → **116** occurs exclusively by the concerted suprafacial 3,3-sigmatropic shift pathway. Stereochemical regularities of this rearrangement can serve as evidence in favor of a transition state structure of type **115** where the Me and Ph groups take equatorial positions. An alternative transition state structure **117** that would lead to the *Z*-isomer **118** (route B) is less favored because of nonbonding interactions of the methyl group with the syn-axial hydrogen atom.



(41)

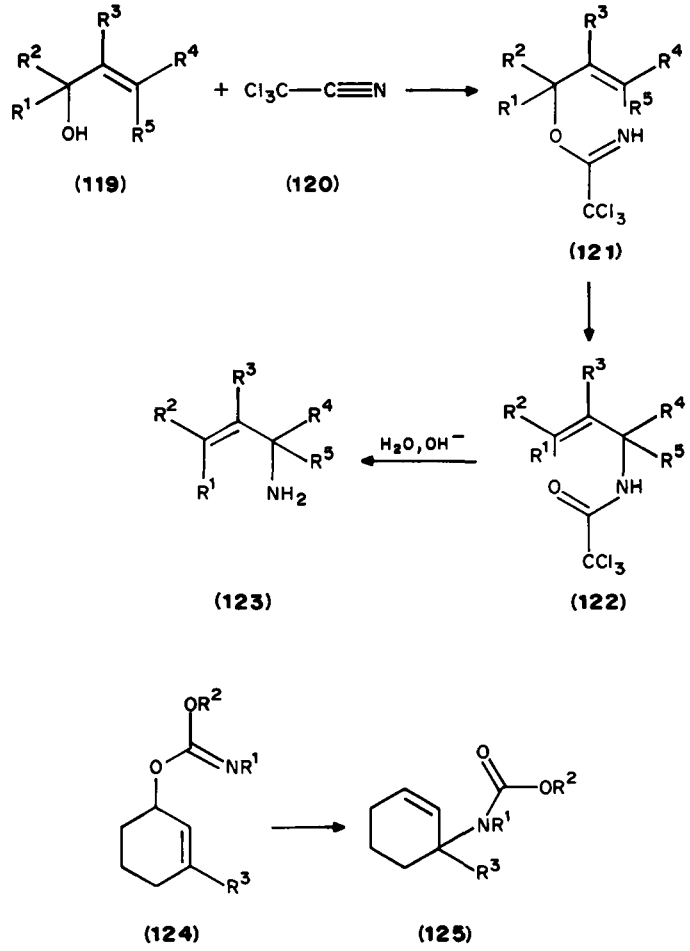
Considering the rearrangement of *O*-allyl trichloroacetimidates **121** produced by the condensation of allyl alcohols **119** with trichloroacetonitrile **120**, Overman[98,100] has developed a general method for transforming **119** into allyl amines **123** (equation 42). The trichloroacetyl group can be readily eliminated through hydrolysis of *N*-allyl imidates **122** at room temperature, which leads to allyl amines **123**. Acyl amides **122** and amines **123** obtained by reaction 42 are widely used as active dienes in the Diels–Alder synthesis of amino-functional carbocycles[98]. Thus, *trans*-1-(acylamino)-1,3-butadiene was used as a starting material in the total synthesis of the neurotropic alkaloids, *d,l*-pumiliotoxin-C[102,103] and *d,l*-perhydrogephyrodoxin[104].

The introduction of a nitrogen-centered group in the hindered 3-position of 3-substituted 2-cyclohexen-1-ols can be effected by means of the thermal rearrangement **124** → **125** (equation 43)[105].

By making use of the propensity of trichloroacetimides **127** to thermal rearrangement, a method could be developed for introducing functional groups in the allyl and homoallyl positions of allyl carbinols **126** (equation 44)[106,107].

2-Amino-1,3-diols **129** are obtained through hydrolysis of oxazoles **128** which form when imide **127** is treated with *N*-iodosuccinimide in $CHCl_3$ (route A). In a like manner, 3-amino-1,2-diols **132** were produced from amides **130**, formed by the thermal rearrangement of imides **127** (equation 44).

Thermal rearrangements of propargylic imidic esters **133** into amides **134** may be



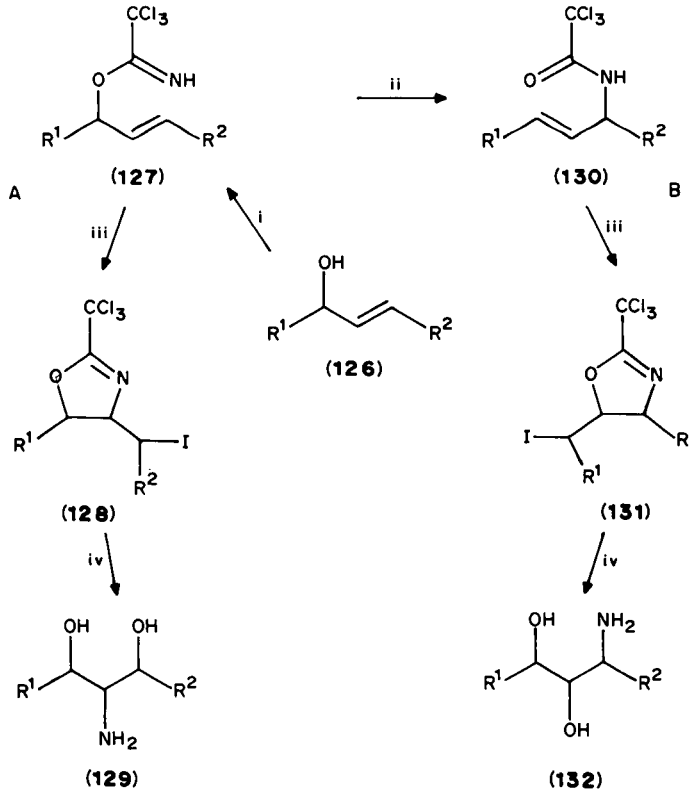
(42)

(43)

employed in the synthesis of substituted 2-pyridones **135**, provided that the substituent X is a potential leaving group[108,109] (equation 45).

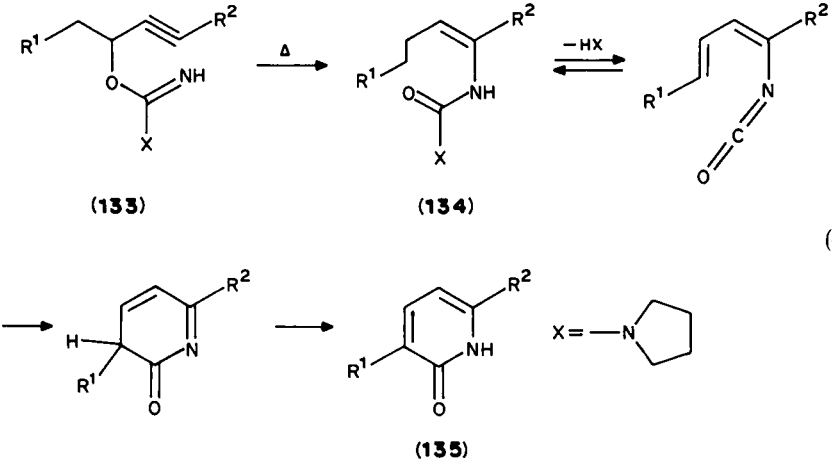
In some cases, the rather severe conditions under which the rearrangements occur (equation 39) are conducive to thermal decomposition of the starting substances and products, and to certain side-processes. On this account, beginning from the 1960s intensive work has been going on aimed at the catalysis of hetero-Cope rearrangements; see the reviews[2,93,97,98,110,111].

Salts of Hg^{2+} and Pd^{2+} employed as catalysts in allyl imidate rearrangements **108** → **109** have not only accelerated the reaction 39 by a factor of 10^{10}–10^{14} but also increased the yield of products and their regioselectivity as compared with the corresponding thermal rearrangements[93,100,110]. A cyclization-induced mechanism has been suggested to explain the catalysis by the Hg^{2+} salts of the allyl imidate transformations **136** → **138**[98,100]. It involves the emergence in the transition state of a six-membered 1,3-azaoxonium intermediate **137** and accounts for the exclusive formation of the products of the 3,3-shift and the stereoselectivity observed in this case (equation 46).

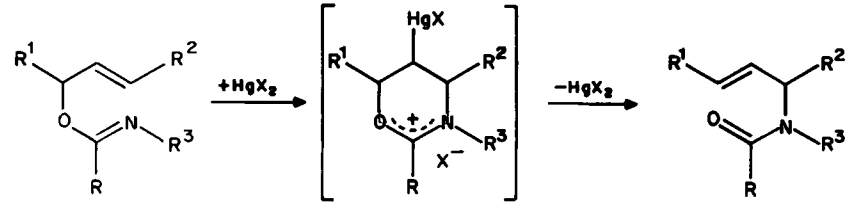


(44)

i—CCl_3CN
ii—110 °C
iii—*N*-iodosuccimimide in $CHCl_3$
iv—hydrolysis



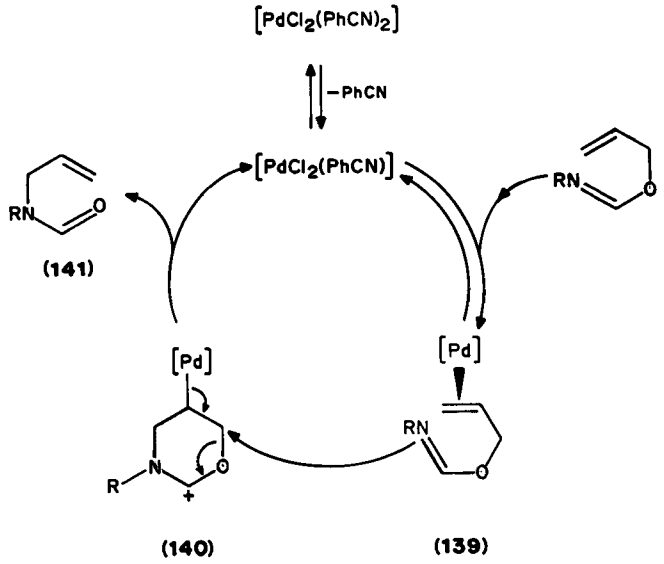
(45)



(136) (137) (138)

(46)

Detailed studies of Pd^{2+}- and Pd^0-catalyzed allyl imidate rearrangements with asymmetrically substituted or asymmetrically deuterium-labeled allyl groups have shown the following. The Pd^{2+}- catalyzed rearrangements proceed to give exclusively the product of the 3,3-transformations (equation 47), whereas with Pd^0 a mixture of products of the 3,3 and 1,3 shifts is formed (equation 48)[112].

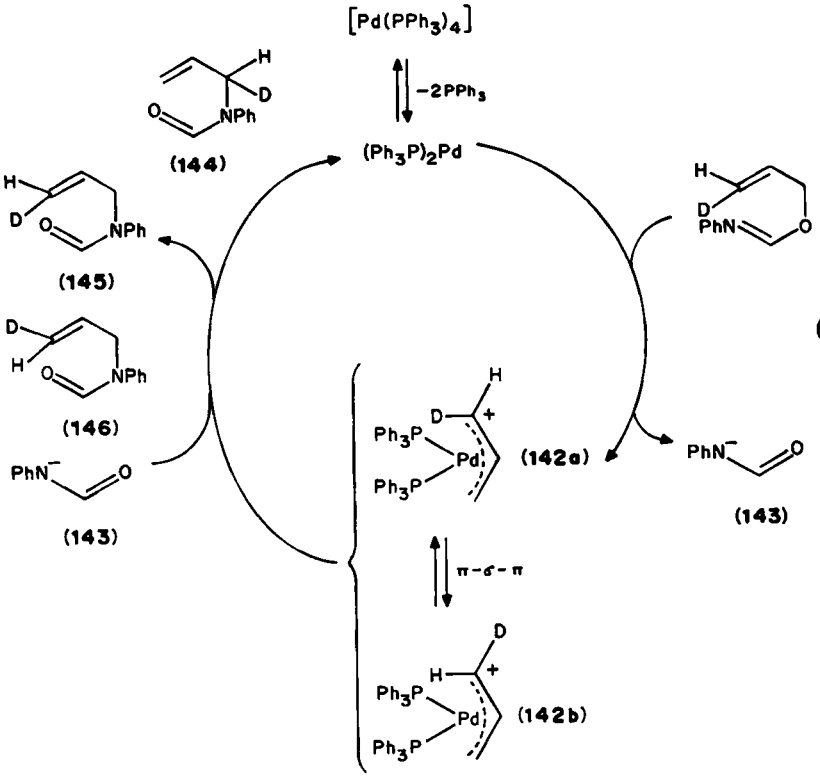


(47)

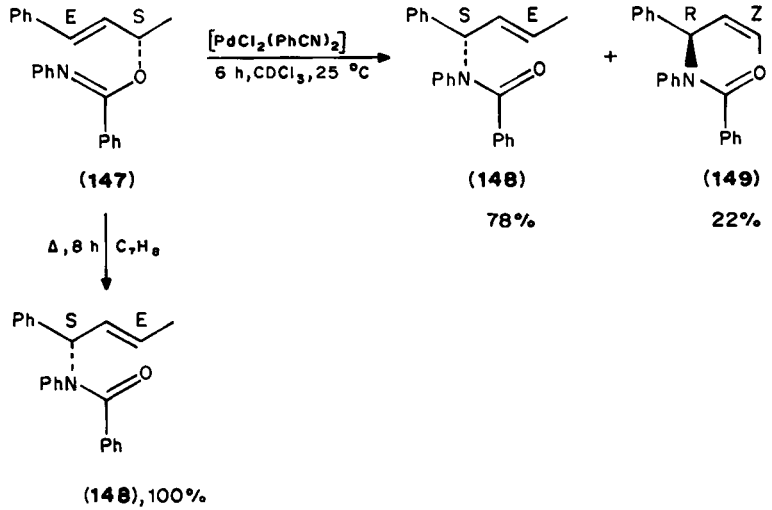
In the former case, the coordinated olefin **139** undergoes an intramolecular attack by the imidate nitrogen atom bearing an electron lone pair to form a metal-bound six-membered cyclic carbonium ion intermediate **140** which rapidly rearranges into **141** with the catalyst regenerating.

Under Pd^0 catalysis (equation 48), the process occurs by a nonconcerted mechanism with the formation of the π-allyl complexes **142a,b** as kinetically independent species. Their isomerization rate is determined by the *E*:*Z* ratio and the subsequent interaction between them and the imidate anion **143** leads to the products of 3,3-(**144**) as well as of the 1,3-rearrangements (**145**, **146**).

In order to study the stereoselectivity and the possibility of chirality transfer in the

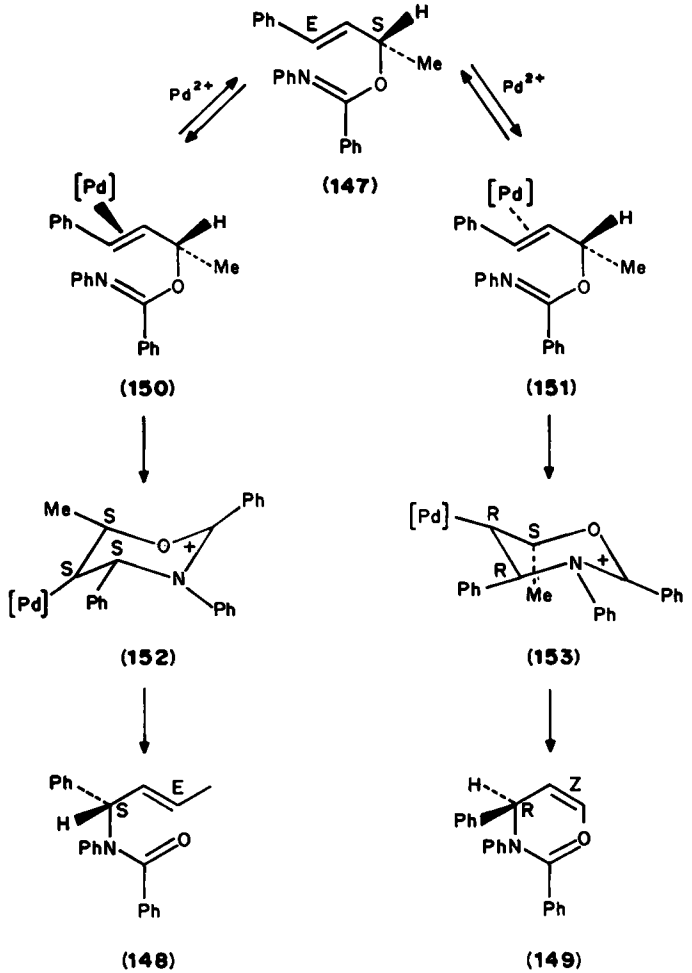

[Pd(PPh3)4]
-2PPh3
(Ph3P)2Pd
(144)
(145)
(146)
(143)
(142a)
(142b)
π-σ-π

(48)


[PdCl2(PhCN)2]
6 h, CDCl3, 25 °C
(147)
(148)
78%
(149)
22%
Δ, 8 h | C7H8
(148), 100%

(49)

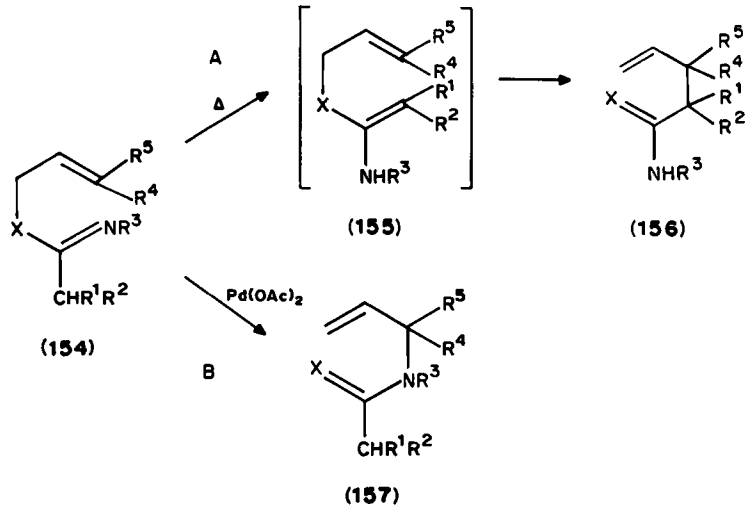
Pd^{2+}-catalyzed process, the optically active (*S*, *E*)-allyl imidate **147** was taken as the starting compound (equation 49). Whereas the thermal rearrangement yields pure (*E*)-allyl amide of *S*-configuration **148**, the catalytic reaction produces a *E* (**148**): *Z*(**149**) mixture in 78:22 ratio, with the *E* and *Z* olefin isomers possessing the *S* and *R* chirality, respectively. The authors explain this stereochemical outcome by the scheme presented in equation 50. Because of the presence of the chiral center, the olefin plane is diastereotopic so that, upon coordination of Pd^{2+} with olefin, two energetically different structures **150**, **151** are obtained, from which two different Pd six-membered intermediates **152**, **153** are then formed. The ring opening in these intermediates that proceeds by a concerted mechanism and is determined by the orbital symmetry conservation rules leads eventually to the products **148** and **149**. The predominance of allyl imidate **148** in the reaction products is predetermined by the fact that the structure of the intermediate **152** is energetically more favored than that of **153** since in the latter, as opposed to **152**, not all substituents are positioned equatorially.



(50)

Another subject treated in the same work is the catalysis of rearrangements of allyl imidates by Rh^{1+} and Ir^{1+} proceeding nonstereoselectively to give the products of the 3,3- and 1,3-shifts.

The thermal 1-*N*,3-*S*-hetero-Cope rearrangement of *S*-allyl imidates **154** (X = S) (160 °C, 1 h, 95% yield) is characterized by a concurrent side-process, the S → C migration of the allyl group, resulting in a mixture of diastereomers **156** (X = S)[113]. The formation of **156** is explained by the immediacy of ketene-*S*,*N*-acetal **155** (X = S) in the thermolysis (equation 51). The $Pd(OAc)_2$ catalysis of this rearrangement leads exclusively to the thioamide **157** (X = S). The imidates **154** (X = O) are also subject to such a rearrangement[114]. Both directions of the process (A and B, equation 51) develop thermally. When



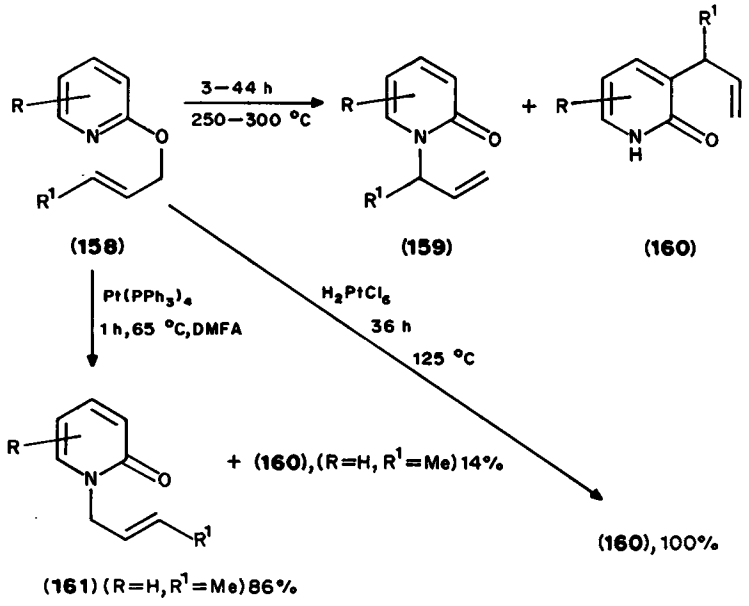
(51)

methyl is the substituent at the $C_{(2)}$ carbon atom of the imide fragment ($R^1 = R^2 = H$), a 3,3 O → N allyl shift (route B) occurs in the thermolysis. If, on the other hand, there are at $C_{(2)}$ substituents capable of stabilizing the double bond of the isomeric ketene-*O*,*N*-acetals **155** (X = O) (such as Et, *i*-Pr or CH_2Ph groups), then the reaction proceeds preferably along route A (O → C shift).

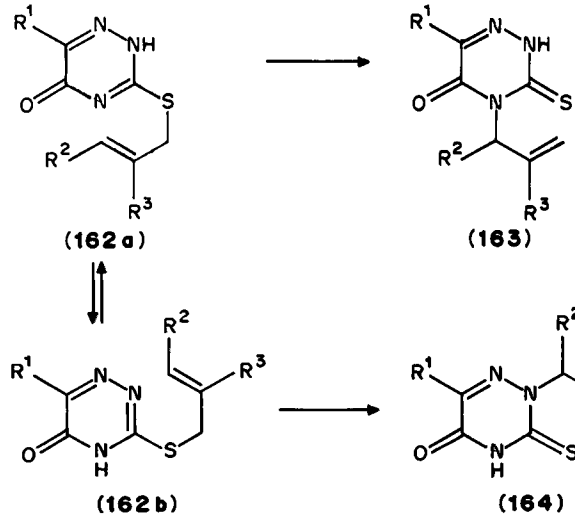
High-temperature thermal and moderate-temperature catalyzed 3,3 and 1,3 O(S) → N shifts of allyl groups are observed also for compounds in which the imidate or thioimidate fragment is included in a heterocycle[1,2,93–98,110].

The allyl and crotyl derivatives of 2-oxypyridine **158** (R = H) and quinoline **158** (R = 5,6-C_4H_4) undergo thermal 3,3-rearrangement to give a mixture of the products of *N*- and *C*-allylation (**159** and **160**, respectively) in nearly one-to-one ratio[94]. The total yield of the products ranges from 14 to 67%. The H_2PtCl_6 catalysis of the rearrangements (equation 52) of allyl oxypyridines **158** leads exclusively to N-products of the 3,3-allyl shift **159**, while the use of $Pt(PPh_3)_4$ gives, as a result of 1,3- and 3,3-shifts, a mixture of compounds **160** and **161**[115].

It has been shown[116,117] that the regioselectivity of allyl rearrangements of 3-(allylthio)-1,2,4-triazin-5(2*H*)-ones **162** (formation of N-2 or N-4 products), with Pd^{2+} salts acting as catalysts, is strongly dependent on the character of substitution in the allyl fragment (equation 53). So through catalysis of the rearrangement of **162** (R^1 = Ph, R^2 = Me,



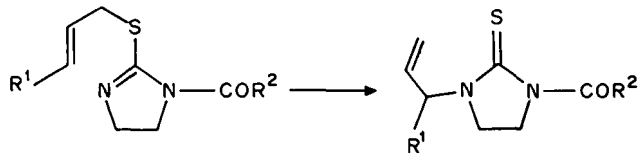
(52)



(53)

$R^3 = H$), a mixture of isomers **163** and **164** is formed in 30:70 ratio, while the rearrangement of **162** with $R^1 = Ph$, $R^2 = H$, $R^3 = Me$ gives isomers **163** and **164** in 74:26 ratio.

Using ^1H NMR, it has been found that *N*-acetyl-2-allyl (**165a**) and *N*-acetyl-2-crotylthioimidazoline (**165c**) rearrange at 145 °C during 72 and 30 h, respectively, to give the products of a 3,3-sigmatropic shift, i.e. imidazolidinethiones **166a** and **166c** in 75% and



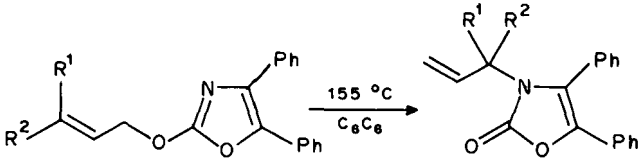
(54)

(165) (166)

	R^1	R^2
a	H	Me
b	H	OMe
c	Me	Me

30% yields, respectively[118]. The reaction (equation 54) is of first order and, in the case of thioimidazoline **165c**, $k_1 = 8.3 \times 10^{-6}\ s^{-1}$ in benzene solution in sealed tubes at 141 °C. In the thermolysis of *N*-methoxycarbonyl-2-allylthioimidazoline (**165b**), instead of the expected imidazolidinethione **166b**, *N*-methyl-*N'*-allyl- (65%) and *N*-methyl-imidazolidinethione (25%) are formed as a result of decarboxylation.

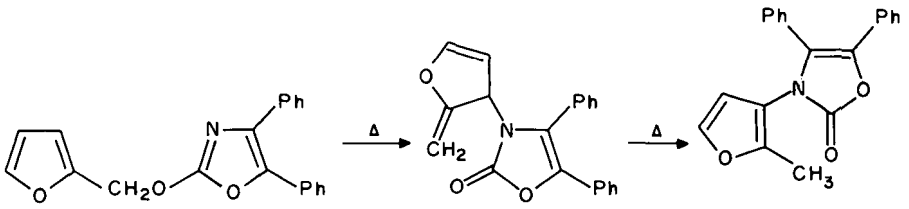
Also studied was the thermal rearrangement of 2-allyloxy substituted 4,5-diphenyl-oxazoles (**167a–c**) into 3-allyl-4,5-diphenyl-4-oxazoline-2-ones (**168a–c**) proceeding by a 3,3-sigmatropic shift[119,120] (equation 55). A similar mechanism (equation 56) is operative



(55)

(167) (168)

	R^1	R^2
a	H	H
b	H	Me
c	Me	OMe



(56)

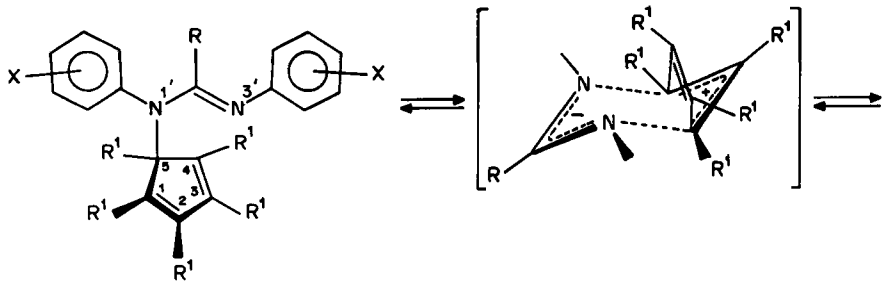
(169) (170) (171)

in the thermal isomerization of 2[(furyl)oxy]-4,5-diphenyloxazole (**169**) to 2-methyl-3-(4,5-diphenyl-4-oxazolin-2-on)furan (**171**) (6 h at 80 °C). This has been confirmed by the preparative isolation of the intermediate **170** and its subsequent transformation into the furan **171** by heating or treatment with acids.

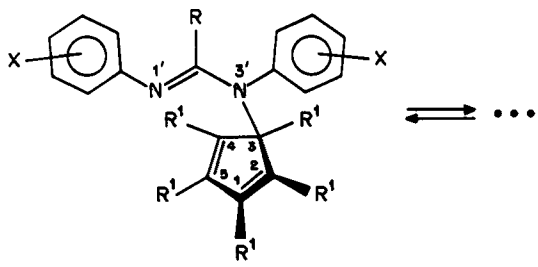
Unlike allyl imidates, thioimidates and allylcarboxylates **108** (X = Y = O)[93], the 3,3-sigmatropic shifts of allyl groups in amidine 1-*N*,3-*N* systems have not yet been studied adequately. No such rearrangement was observed in *N*,*N*'-dimethyl-*N*-allyl benzamidine when heating its solutions to 175 °C[121]. When, however, an allyl fragment is attached to a cyclopentadiene ring activated with electron-withdrawing substituents, the above rearrangements do proceed and the conditions for their occurrence are fairly mild[122].

In dynamic ^{1}H NMR spectra of compounds **172**, one may observe at elevated temperatures synchronized broadening and coalescence of the signals of the methyl groups X = Me and R^1 = COOMe, which bears witness to the occurrence of the intramolecular hetero-Cope rearrangement with a low-energy barrier.

Table 9 lists kinetic and activation parameters of the rearrangement **172a** ⇄ **172b** (equation 57) found by means of line-shape analysis of the ^{1}H NMR spectrum. The 1-*N*, 3-



(57)



R^1 = COOMe; X = *p*-Me, *m*-Me; R = 1-Naph, 4-$NO_2C_6H_4$, 4-BrC_6H_4, Ph, *p*-Tol, *p*-An

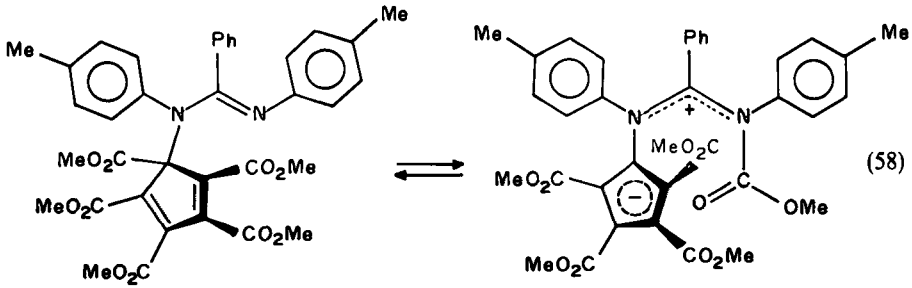
N-hetero-Cope rearrangements proceed most rapidly in naphthamidines **172** (compounds 1,2 in Table 9). In the benzamidine series **172** (compounds 3–7), electron-withdrawing substituents in the aryl at the $C_{(2)}$ atom of the amidine triad increase the rate of the process (equation 57), while electron-releasing ones slow it down.

Upon heating *o*-dichlorobenzene solutions of benzamidine **172** (compound 5, Table 9)

TABLE 9. Kinetic and activation parameters of degenerate rearrangements **172a** ⇄ **172b** in *o*-dichlorobenzene, according to data in References 122 and 123

Compound			$k_{90\,°C}$	$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$	$\Delta G^{\ddagger}_{90\,°C}$
No.	R	X	(s^{-1})	(kcal mol^{-1})	(cal deg^{-1} mol^{-1})	(kcal mol^{-1})
1	1-Naph	*p*-Me	3.9	15.1 ± 0.3	−14.7 ± 0.7	20.4
2	1-Naph	*p*-Me	2.0	15.7 ± 0.4	−14.3 + 0.9	20.9
3	4-$NO_2C_6H_4$	*p*-Me	0.84	19.9 ± 0.3	−4.3 ± 0.8	21.5
4	4-BrC_6H_4	*p*-Me	0.21	20.6 ± 0.5	−5.2 ± 1.1	22.5
5	Ph	*p*-Me	0.11	22.5 ± 0.4	−1.5 ± 0.5	23.0
6	4-Tol	*p*-Me	0.069	22.7 ± 0.2	−1.6 ± 0.4	23.3
7	4-An	*p*-Me	0.034	23.4 ± 0.3	−1.1 ± 0.6	23.8

at 130 °C for 0.5 h, equilibrium is established with the dipolar isomer **173a** (**172**:**173a** = 0.70:0.30) formed in consequence of the 1,4-shift of the methoxycarbonyl group to the imine nitrogen (equation 58). The conformation **173b** in the solid state has been proved by an X-ray diffraction study (Figure 5)[123].

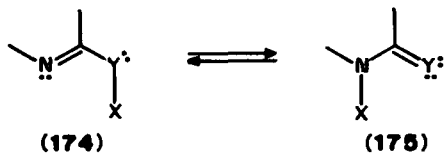


(58)

III. 1,3-SHIFTS OF MAIN-GROUP 5–7 ELEMENT-CENTERED MIGRANTS

The study of rearrangements of this type in the series of amidines and imidates began in the past decade.

The majority of the rearrangements (equation 59) known to date have intramolecular character, and in their mechanism they correspond to reactions of nucleophilic substitution at the central atom of a migrating group. These reactions may be regarded as



(59)

Y = NR, O, S

X = NO, NO_2, PR^1R^2, $\overset{+}{P}R^1R^2R^3$, $P(Y)R^1R^2$, $PR^1R^2R^3R^4$, SR, S(O)R, Hal

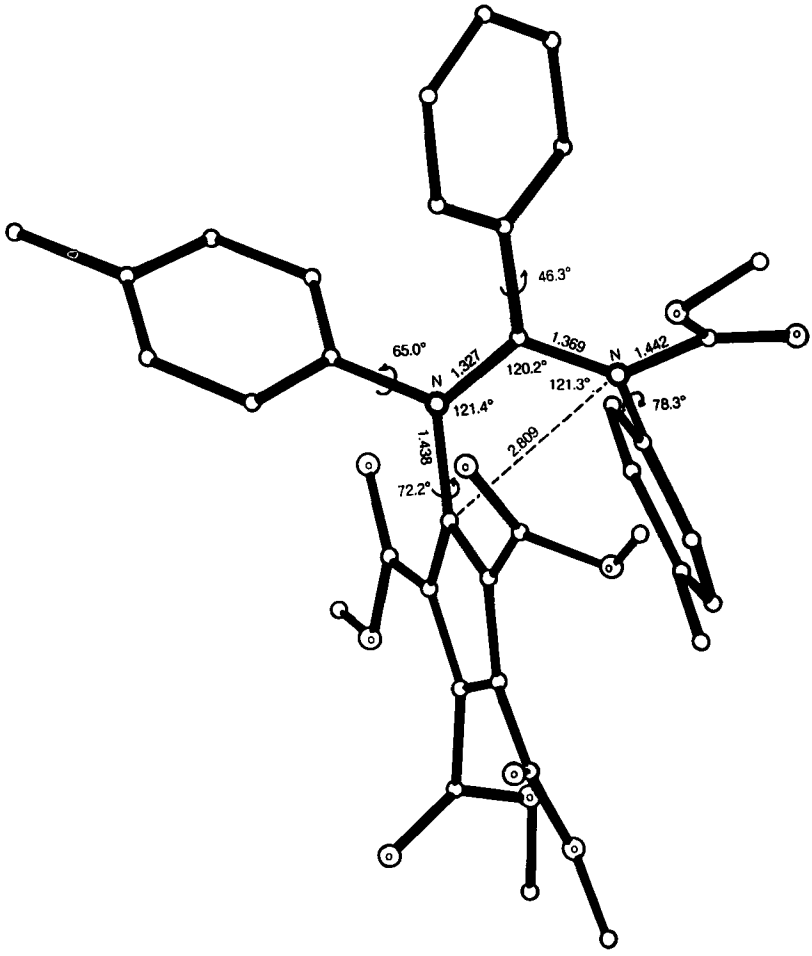


FIGURE 5. Stereoprojection, bond lengths and angles in molecule **173b** according to data of X-ray diffraction study[123]

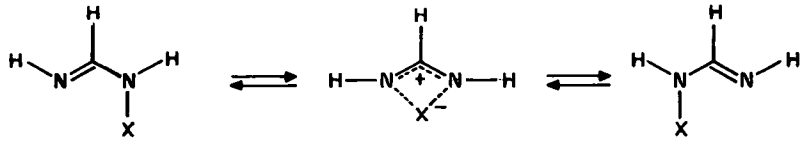
belonging to a variety of the so-called 'X-philic' reactions[124]. Unlike reactions of nucleophilic substitution at sp^3- and sp^2-hybridized carbon atoms, the pathways of substitution reactions at the main-group 5–7 element centers have not been studied in great detail. Therefore, in this section we shall present experimental data on the rearrangements represented by equation 59 along with some results of their theoretical analysis.

A. 1,3-Shifts of Nitroso and Nitro Groups

MINDO/3 calculations of reactions of nucleophilic substitution at sp^2-hybridized nitrogen atoms of the nitroso and nitro groups have shown[125] that the steric course of the reaction is very similar to that of nucleophilic substitution at a C_{sp^2}-center (**41a, 41b**).

Hence, similarly to the case of *N*-acyl amidines, it may be expected that *N*-nitroso and *N*-nitro amidines will undergo intramolecular *N,N'*-shifts.

MINDO/3-calculated energy profiles of the model reactions (equation 60) are quite

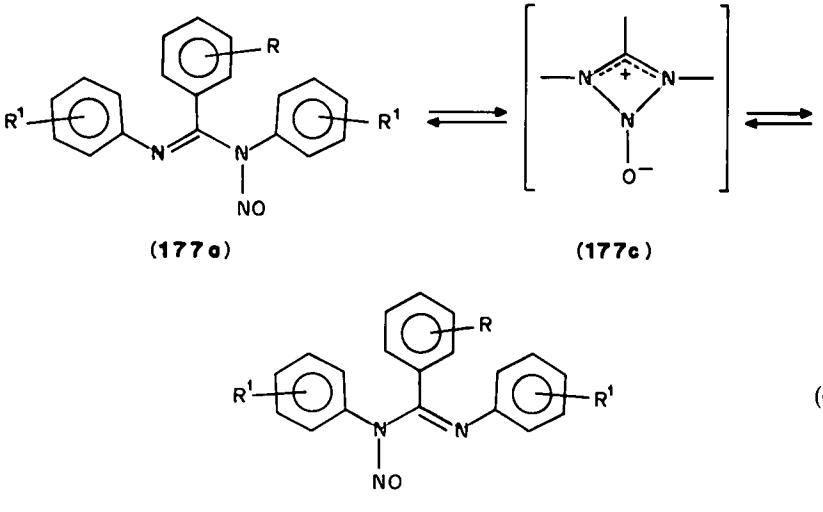


(176a) (176c) (176b) (60)

$X = NO$, $\Delta E^{\ddagger} = 22.1$ kcal mol^{-1}; $X = NO_2$, $\Delta E^{\ddagger} = 32.7$ kcal mol^{-1} (MINDO/3 calculations[125])

close to the one given in Figure 1 for the analogous *N,N'*-transfer of the acetyl group. In both reactions, the symmetrical structure **176c** is expected to be a short-lived intermediate located along the reaction path in close vicinity to the transition state structure. Calculated activation enthalpies warranted the conclusion that in amidines **176**, provided there is suitable substitution, the migration of nitroso and nitro groups can be realized on the tautomeric energy scale.

It has indeed been recently found[122] that in *N*-nitroso-*N,N'*-diarylbenzamidines **177**, readily obtained by treatment of *N,N'*-diarylamidines with 5-nitro-1,2,3,4,5-pentakismethoxycarbonylcyclopentadiene, rapid degenerate *N,N'*-migrations of the nitroso group occur, manifested in temperature-variable ^{1}H NMR spectra of **177** by the averaging of signals of the groups R^1 and of the protons in the aryl rings. There is no dependence of the temperature-variable ^{1}H NMR spectra of amidines **177** (compounds 1–7 in Table 10) on the concentration and no free-radical species are detected upon heating the solutions. Kinetic and activation parameters of the degenerate rearrangements (equation 61) calculated from line-shape measurements of the indicator signals R^1 are presented in Table 10, from which it follows that electron-withdrawing substituents R in



(177a) (177c)

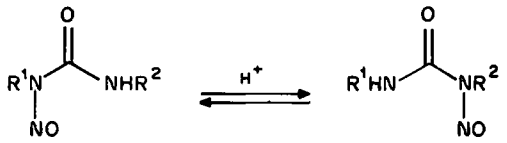
(177b) (61)

TABLE 10. Kinetic and activation parameters of rearrangements **177a** ⇄ **177b**, according to References 122 and 126

No.	R	R^1	$k_{90\,°C}$ (s^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1})	$\Delta G^{\ddagger}_{90\,°C}$ (kcal mol^{-1})	Reference
1	2,3-C_4H_4	*p*-Me	57	14.4 ± 0.4	-11.5 ± 0.9	18.5	122
2	2,3-C_4H_4	*m*-Me	103	17.3 ± 0.5	-2.0 ± 1.0	18.0	122
3	4-An	*p*-Me	2.8	—	—	20.6	126
4	4-Tol	*p*-Me	4.0	—	—	20.4	126
5	Ph	*p*-Me	5.1	—	—	20.2	122
6	4-BrC_6H_4	*p*-Me	7.9	—	—	19.9	126
7	4-$NO_2C_6H_4$	*p*-Me	8.5	—	—	19.8	126

the aryl group at the carbon atom of the amidine triad increase the velocity of the degenerate rearrangement **177a** ⇄ **177b** while electron-donating ones slow it down.

The system **177** is a convenient model for studying various structural effects as well as those of solvents on the nitroso group transfer reactions. The reactions of these compounds containing an *N*-nitrosoamine function have been attracting considerable attention lately in view of the fact that *N*-nitrosoamines are widely occurring carcinogens[127]. Theoretical[128,129] and experimental[130] data indicate catalysis of different nitroso group transfer reactions due to the protonation of *N*-nitroso compounds. There are also quite a few examples of intermolecular 1,3-nitroso group transfers promoted by acidic catalysts in the series of urea derivatives (equation 62).



(178) **(179)** (62)

$R^1 = Me$; $R^2 = H$[131]
$R^1 = 3\text{-}CH_2C_5H_4N$, $4\text{-}CH_2C_5H_4N$; $R^2 = CH_2CH_2Cl$, $CHMe_2$, CH_2CHMe_2, *c*-Hex[132]

There are reasons to assume[130] that the reaction of **178** may include an intermediate step of the 1,3-shift of the nitroso group towards the oxygen atom, involving successive *N,O*- and *O,N'*-shifts.

The relative content of the nitroso derivatives of the ureas **180** and **181** that form in the course of nitrosation of the initial *N,N'*-substituted ureas **182** depends on the nature of the substituents R^1 and R^2. After the separation of the isomers and treatment of each of them with formic acid (in the presence of HCl, H_2SO_4), a mixture is obtained of 1- and 3-nitroso ureas togethers with the product of denitrosation (equation 63).

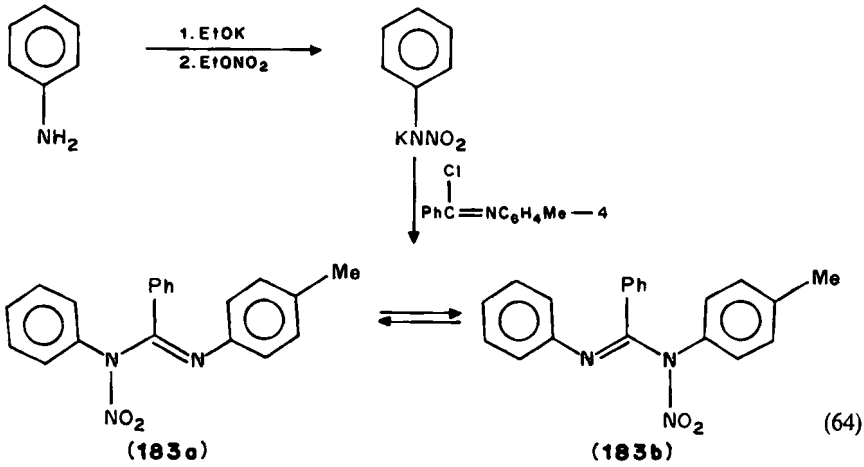
$$\underset{\text{NO}}{\underset{|}{R^1NCONHR^2}} + HCOOH \rightleftarrows R^1NHCONHR^2 + HCOONO \rightleftarrows R^1NHCONR^2 + HCOOH \qquad (63)$$
$$\underset{\text{NO}}{\underset{|}{}}$$

(180) **(182)** **(181)**

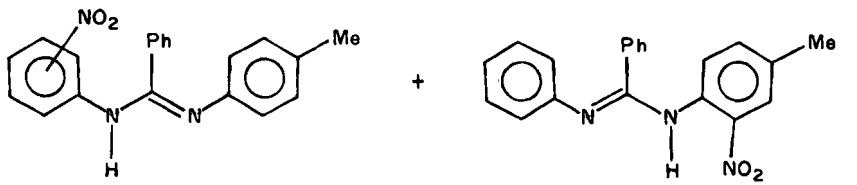
It is believed that the mechanism of the intermolecular rearrangement (equation 63) of *N*-nitroso ureas[132] is similar to that of the Fischer–Hepp reaction[130]. *N*-nitroso ureas **180**, **181** interact with formic acid to give nitrosonium formate which then acts as the nitrosating agent.

1,3-Migrations of nitro groups in amidine systems similar to the nitroso group rearrangements (equation 61) have not been observed so far. However, the transformations described by equation 64[133] may be regarded as indirect evidence that a nitro group is capable of the *N,N'*-migration in the amidine system, even though the *N*-nitro amidines **183a** and **183b**, which serve as precursors for **184**, **185** and **186** respectively, could not be isolated.

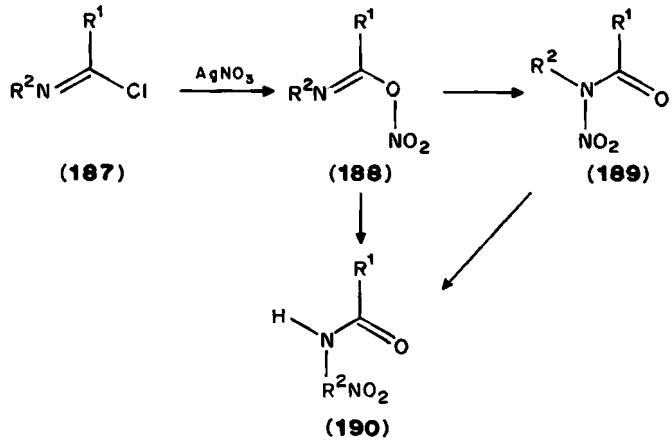
A similar problem, namely the migration of the nitro group from an N atom to an *N*-aryl ring, has been encountered by Carvalho and coworkers[134] in studying the rearrangement of imidoyl nitrates **188** into *N*-nitro amides **189** (equation 65). They have shown that the addition of $AgNO_3$ to imidoyl chloride **187** (R^1 = Ph, R^2 = Me) in acetonitrile leads to *N*-nitro amide **189** (R^1 = Ph, R^2 = Me). At the same time, when compound **187** (R^1 = R^2 = Ph) is used in this reaction, a mixture of 2- and 4-nitro substituted benzanilides **190** (R^1 = Ph; $R^2 = 2\text{-}NO_2C_6H_4$, $4\text{-}NO_2C_6H_4$) is formed as a result of the migration of the nitro



(64)



(184) *o*-NO_2, 21%
(185) *p*-NO_2, 28%
(186) 51%

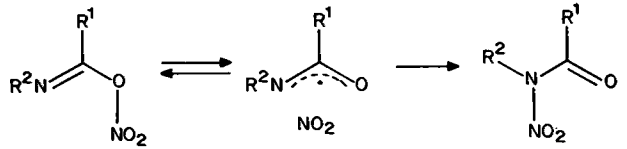


(65)

R^1 = Ar; R^2 = Me, Ar

group into the *N*-phenyl ring. Even the presence of two nitro groups in the *N*-aryl ring [compound **187**; $R^1 = Ph$, $R^2 = 2,4\text{-}(NO_2)_2C_6H_3$] does not impede this migration which leads to 2,4,6-trinitro-substituted benzamide **190**, $R^1 = Ph$, $R^2 = 2,4,6\text{-}(NO_2)_3C_6H_2$. However, when the 2,4 and 6 positions in the *N*-aryl nucleus are blocked by substituents [compounds **187**; $R^1 = Ar$, $R^2 = 2,4,6\text{-}(Me, Cl)_3C_6H_2$], imidoyl nitrites **188** are detected by ^1H NMR and their rearrangement into corresponding *N*-nitro amines **189** is observed. The reaction **188** → **189** is first order, and at 22 °C its rate constants vary from $1.09 \times 10^{-3}\,s^{-1}$ (**188**; $R^1 = 4\text{-}NO_2C_6H_4$, $R^2 = 2,4,6\text{-}Me_3C_6H_2$) to $18 \times 10^{-3}\,s^{-1}$ (**188**; $R^1 = 4\text{-}NO_2C_6H_4$, $R^2 = 4\text{-Br-}2,6\text{-}Me_2C_6H_2$). The rate of the reaction is not affected by the reactant concentration, which indicates its intramolecular character, and the merely weak influence of the solvent on the rearrangement kinetics points to the absence of an ionization process, such as the dissociation of **188** to the cation NO_2^+ and benzanilide anion. The last point accords well with the insignificance of the effect the substituent R^1 has on the reaction rate. The value of the enthalpy of activation ($\Delta S^{\ddagger}$) for the rearrangement **188** → **189** calculated for compound **188** ($R^1 = 4\text{-}NO_2C_6H_4$, $R^2 = 2,4,6\text{-}Me_3C_6H_2$) amounts to 0 ± 1.2 cal deg^{-1} mol^{-1}.

From the foregoing the conclusion has been drawn[134] that the rate-determining step of the rearrangement **188** → **189** is the homolytic fission of the imidate O—N bond, followed by recombination of the thus formed radical pair **191** at the nitrogen atom (equation 66).



(66)

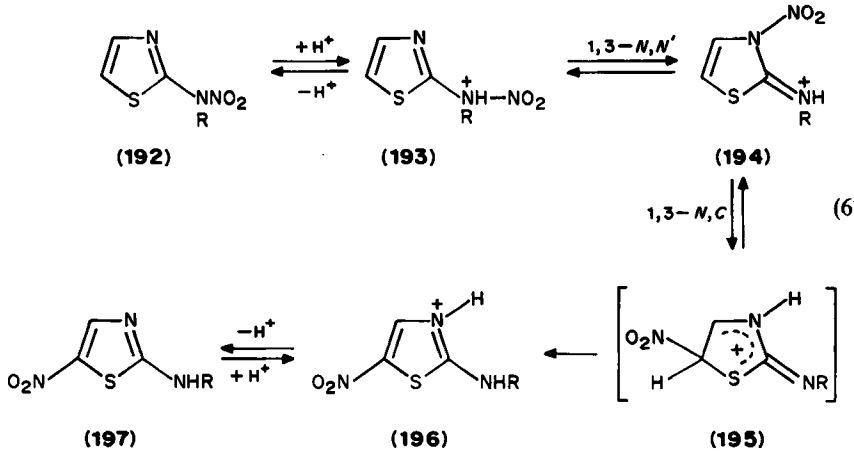
(188) **(191)** **(189)**

The absence of a specific *ortho*-directing effect when the nitro group migrates into the *ortho*- and *para*-positions of the *N*-aryl ring[134] also fits a radical mechanism for the nitration of the *N*-aryl fragment (equation 65).

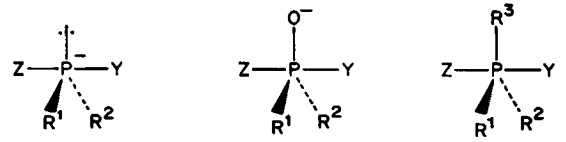
Another example of a 1,3-*N*,*N'*-transfer of the nitro group which, unlike the preceding case, occur by a heterolytic mechanism, has been discovered in studying the $N—NO_2 \rightarrow C—NO_2$ rearrangement in 2-aminothiazoles **192**[135–137]. The ^1H, ^{13}C and ^{15}N NMR spectral study of the rearrangement (equation 67) in D_2SO_4 at −10 °C has shown the formation of all the transition forms **193**, **194** and **196**. This study resulted in the following conclusions: The protonation of the 2-nitroamine derivatives of thiazole **192** gives rise to **193**, which undergoes a heterolytic 1,3-shift of the nitro group to produce the nonaromatic intermediate **194**. Due to a heterolytic 1,3-*N*,*C*-shift, the σ-complex **195** emerges from compound **194**. Its descomposition into compound **196** is a relatively slow process as was inferred from the study of the rearrangement (equation 67) of compounds labeled with deuterium in the 5-position. The deprotonation of compound **196** leads to the final product of the rearrangement, 5-nitro-2-aminothiazole **197**.

B. 1,3-Shifts of Phosphorus-containing Groups

In nucleophilic substitution reactions at a tri- and tetracoordinate phosphorus atom in sterically nonconstrained molecular systems, both entering Z^- and leaving Y groups take up axial positions in trigonal bipyramidal transition state structures[138].



(67)



(198) X = PR^1R^2 (199) X = $P(O)R^1R^2$ (200) X = $P^+R^1R^2R^3$

Such a position of the Z and Y groups cannot be realized in a four-membered cycle of **176c** type. On this account, the one-step concerted 1,3-transfer of phosphorus-containing groups X (equation 59, Z = N) cannot occur intramolecularly. There exists, however, an important complementary possibility of the occurrence of intramolecular migration inherent in the second and lower row element-centered groups in structural environments not suitable for a linear alignment of the forming and breaking bonds as featured by the structures **198–200**. Such a possibility is provided by the stepwise mechanism predicted by Westheimer[139]. The structural and electronic requirements imposed upon the migrants, which may be involved in the stepwise intramolecular displacements, and the stereochemical consequences were considered in detail elsewhere[37,140,141].

The necessary condition for the axial approach of the attacking nucleophile and the departure of the leaving group from another axial position can be met if the initially formed intermediates (Figure 6) containing the former group in the axial and the latter one in the equatorial positions are capable of a low-energy barrier polytopal rearrangement, resulting in the interchange of their positions. The departure of the leaving group proceeds then from the axial position in accordance with the demand of the principle of microscopic reversibility. Figure 6 portrays the energy profile of such an addition–rearrangement–elimination (AdRE) mechanism of the intramolecular 1,3-displacements of phosphorus-containing groups in sterically constrained amidines and similar molecular systems. The crucial step of the total reaction is the polytopal rearrangement of the intermediates to

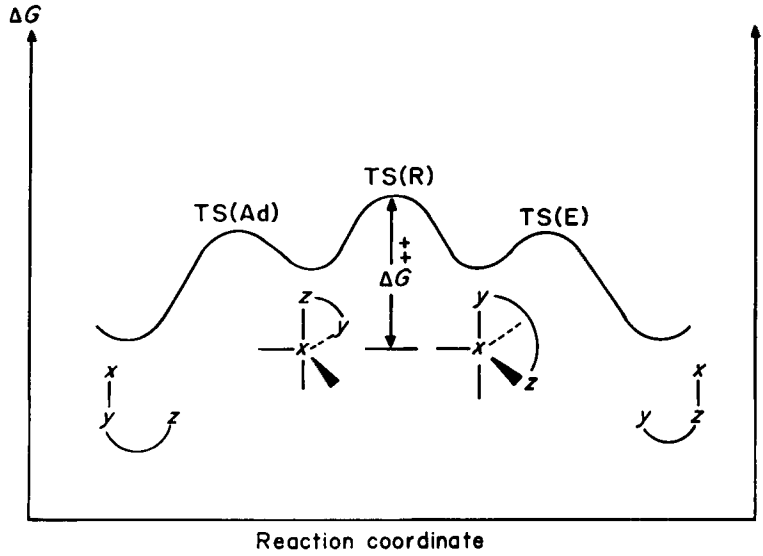
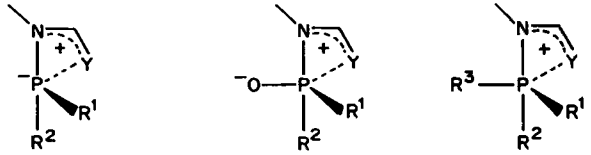


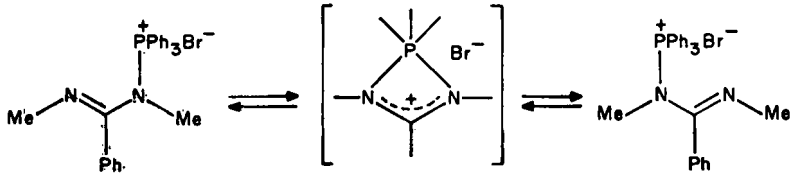
FIGURE 6. Energy profile of the degenerate (Y = Z) rearrangement governed by the AdRE mechanism. TS(Ad), TS(R) and TS(E) are the transition states of, respectively, addition, rearrangement and elimination steps of the intramolecular group X transfer reactions[140]

which the local minima on the potential energy curve (Figure 6) correspond. The most feasible ligand permutation made in trigonal bipyramid-based structures is the Berry-pseudorotation (ψ-Berry). Its energy barrier is known to be strongly affected by apicophilicities of the substituents at the central atom[142,143]. It is therefore important to choose properly the substituents R^1, R^2, R^3 in the phosphorus-centered migrants to warrant the sufficiently low energy barrier to interconversion of the intermediates of **201**–**203**. Since the Berry-pseudorotation leads to pairwise interchanges of ligands, the lowest



(**201**) X = PR^1R^2 (**202**) X = $P(O)R^1R^2$ (**203**) X = $P^+R^1R^2R^3$

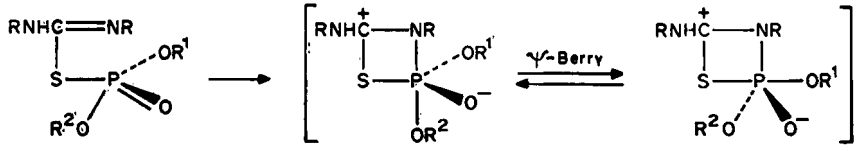
energy barriers of reversible rearrangements are to be expected in those relating to the degenerate type (Y = N and $R^1 = R^2$). It is precisely this type to which the first known rearrangement belonged, involving fast 1,3-migrations of the triphenylphosphonio group between nitrogen atoms in the *N,N'*-dimethylbenzamidine derivative[144]. The activation parameters of the process **204a** ⇄ **204b** are as follows: $\Delta G^{\ddagger}_{43\,^{\circ}C} = 17.2 \pm 0.9$ kcal mol^{-1}, $\Delta H^{\ddagger} = 14.2 \pm 0.7$ kcal mol^{-1}. When the anion in the salt **204** is replaced by Cl^- for Br^-, the energy barrier of the rearrangement (equation 68) is markedly lowered with $\Delta G^{\ddagger}_{7} = 13.9$



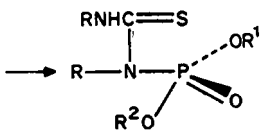
(204a) (204c) (204b) (68)

kcal mol^{-1}, $T_c = 0 \pm 2$ °C, using CH_2Cl_2 as the solvent[145]. Energy barriers close to the above value have been found for the salts **204** with the anions ClO_4^- and BPh_4^- (Table 11 below).

As expected the stereochemical outcome of the AdRE rearrangements is the retention of configuration at the central atom of the migrating group[38,140,146]. This prediction was elegantly verified by Mikolajczyk and coworkers[147], who studied the mechanism and stereochemistry of the rearrangement of *S*-phosphorylisothioureas **205** into *N*-phosphorylthioureas **207**. The rearrangement (equation 69) is of the first order, and



(205) (206c$_1$) (206c$_2$)

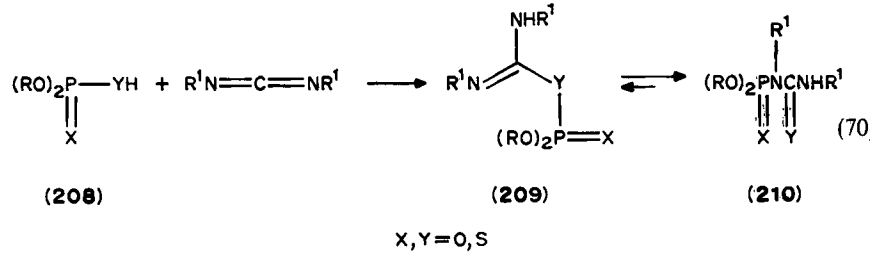


(207) (69)

proceeds stereoselectively with retention of configuration at the phosphorus atom. In the first step, the nitrogen atom in *S*-phosphorylisothiourea **205** attacks the phosphorus to give a betaine-like phosphorane intermediate **206c$_1$**, which undergoes pseudorotation that transfer the sulfur atom into the axial position resulting in the intermediate **206c$_2$**. The rupture of the P—S bond in the latter affords *N*-phosphorylthiourea **207** with retained configuration at phosphorus.

There is a fairly detailed review[148] of the triad 1,3-O(S),N-rearrangements (equation 59, Y = O, S) of phosphorus-containing groups where primarily the synthetic aspect of these reactions has been considered. This section will therefore concentrate on 1,3-*N*,*N'*-migrations of phosphorus-centered groups in amidines and their structural analogs.

In the carbodiimide synthesis widely used for obtaining biologically important esters of phosphoric acid[149,150], *N*-phosphorylated ureas **210** have been isolated (equation 70) among other products. As opposed to the oxygen analogs of **208** (X = Y = O), in the case of

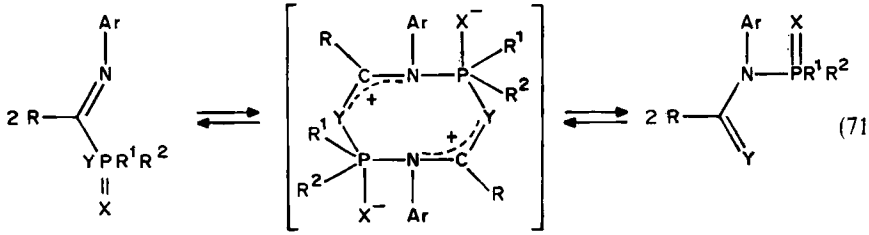


(70)

(208) (209) (210)

the thio derivatives of **208** (X = Y = S or X = O, Y = S) *S*-phosphorylisothioureas **209** could be isolated which are in equilibrium with *N*-phosphorylthioureas **210**. The position of the equilibrium is determined by the substituents both at the phosphorus and at the nitrogen atoms[150,151].

In imidoyl phosphates **211** (X = O, S; Y = O), the 1,3-O,N-rearrangement is irreversible, while for the thio analogs of **211** (X = O, S; Y = S) a tautomeric equilibrium (equation 71) is established ($\Delta G^{\ddagger}$ = 20–21 kcal mol^{-1})[148,152–154]. The dependence of the rate of



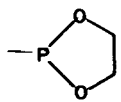
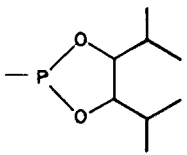
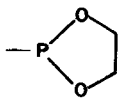
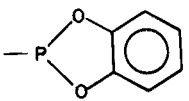
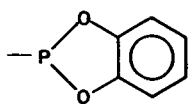
(71)

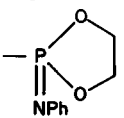
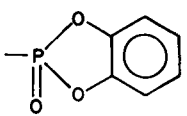
(211a) (211c) (211b)

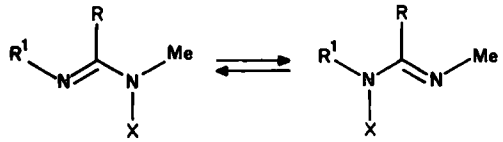
equilibration **211a** ⇄ **211b** for *N*-thiophosphorylthioimides on the concentration of the solution, as well as cross-over results, point to an intermolecular character of the phosphoryl migrations (equation 71) that proceed via the cyclic dimeric bipolar intermediate **211c**. The position of the equilibrium **211a** ⇄ **211b** depends in an essential manner on the nature of the solvent, and with rising temperature it is shifted towards the imidothiol form **211a**.

A systematic and thorough study of the phosphorotropic tautomerism and stereodynamics in the series of amidines, their heterocyclic analogs and isothioureas by means of dynamic ^{1}H, ^{13}C and ^{31}P NMR methods was carried out by Negrebetski and coworkers[155–172]. Both degenerate and nondegenerate intramolecular 1,3-migrations of tricoordinate phosphorus (**212**)[155–157], tetracoordinate phosphorus (**213**)[158–161] as well as of triphenylphosphonium groups (**214**)[162] have been studied (equation 72). The NMR results showed that phosphorylated amidines **212–214** exist in solution predominantly in the form of the *E*-isomer, sterically preferable for the migration of the phosphorus group, in which the electron lone pair of imine nitrogen and phosphorus are located in *cis*-position with respect to each other. The largely intramolecular character of the phosphorotropic tautomerism of compounds **212–214** has been demonstrated by special experiments. The amidine hydrochloride catalysis of the phosphorotropic **212a** ⇄ **212b** rearrangement has been detected[173].

TABLE 11. Kinetic and activation parameters of degenerate 1,3-migrations of phosphorus-centered groups (equation 72) in amidines and isothioureas 212–214

No.	Structural type	R	X	Solvent	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1})	$\Delta G^{\ddagger}_{25\,°C}$ (kcal mol^{-1})	$k_{25\,°C}$ (s^{-1})	Reference
1	212	Ph		C_6D_6	12.4 ± 0.4	−15.3 ± 1.3	17.0	2.05	155
2		Ph		C_6D_{12}	13.5 ± 0.3	−5.9 ± 1.0	15.3	36.3	155
3		CF_3		C_6D_6	17.7 ± 0.5	−7.5 ± 1.3	19.9	1.4×10^{-2}	155
4		Ph		$CDCl_3$	10.1 ± 0.3	−10.8 ± 1.0	13.3	980	155
5		CF_3		C_6D_{12}	14.7 ± 0.3	−14.4 ± 0.6	19.0	7.0×10^{-2}	155
6		Ph	$-P(OEt)_2$	C_6D_6	18.0 ± 1.0	−15.3 ± 2.2	22.6	1.7×10^{-4}	155
7		Ph	$-PPh_2$	C_6D_{12}	—	—	24.9 (178 °C)	—	155

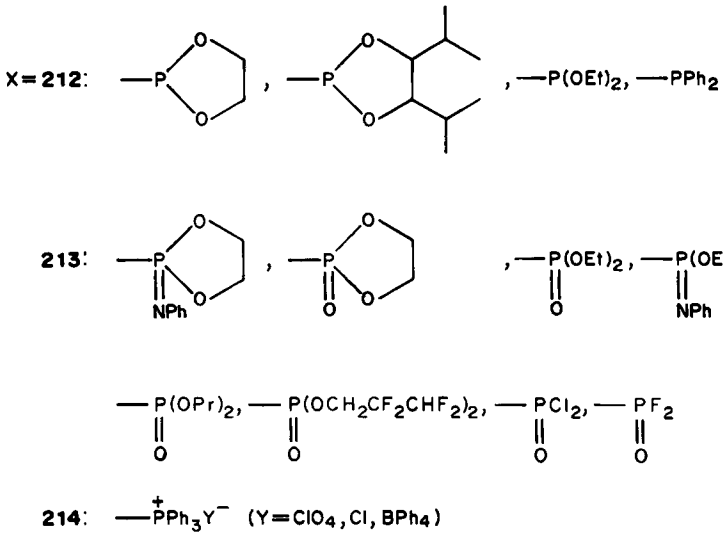
1	**213**	SMe	$-P(OEt)_2$ $\parallel$ O	C_6D_6	—	—	26.0 (200 °C)	—	160
2		CCl_3	$-PF_2$ $\parallel$ O	C_6D_6	19.8 ± 0.2	0.3 ± 0.6	19.7	2.1×10^{-2}	159
3		CCl_3	$-PCl_2$ $\parallel$ O	C_6D_6	—	—	20.0 (125 °C)	—	159
4		CF_3	$-PCl_2$ $\parallel$ O	C_6D_6	21.9 ± 0.5	2.0 ± 1.3	21.3	1.4×10^{-3}	159
5		CF_3		C_6D_6	—	—	21.7 (174 °C)	—	159
6		Ph	$-P(OEt)_2$ $\parallel$ O	C_6D_{12}	—	—	24.9 (174 °C)	—	158
7		Ph	$-P(OEt)_2$ $\parallel$ NPh	C_6D_6	18.1 ± 0.6	-12.4 ± 1.4	21.8	6.1×10^{-4}	158
8		Ph	$-P(OCH_2CF_2CHF_2)_2$ $\parallel$ O	C_6D_6	9.5 ± 0.3	-26.1 ± 1.0	17.3	1.28	159
9		Ph		$(CD_3)_2CO$	—	—	$\leqslant 8$ (-90 °C)	—	159
10		Ph	$-PF_2$ $\parallel$ O	$(CD_3)_2CO$	—	—	$\leqslant 8$ (-90 °C)	—	159
1	**214**	$CHCl_2$	$-\overset{+}{P}Ph_3ClO_4^-$	$CDCl_3$	14.8 ± 0.3	-3.6 ± 0.8	15.9	14.1	162
2		Ph	$-\overset{+}{P}Ph_3Cl^-$	$CDCl_3$	9.4 ± 0.2	-15.2 ± 0.6	13.9	368	162
3		Ph	$-\overset{+}{P}Ph_3ClO_4^-$	$CDCl_3$	9.9 ± 0.2	-13.3 ± 0.7	13.9	368	162
4		Ph	$-\overset{+}{P}Ph_3BPh_4^-$	$(CD_3)_2CO$ + $(CD_3)_2SO$, 1:1	10.3 ± 0.6	-12.0 ± 1.6	13.9	368	162



(72)

(212a–214a) (212b–214b)

R = Ph, $CHCl_2$, CCl_3, CF_3, SMe
R^1 = Me, Et, *i*-Pr, *t*-Bu, Ph



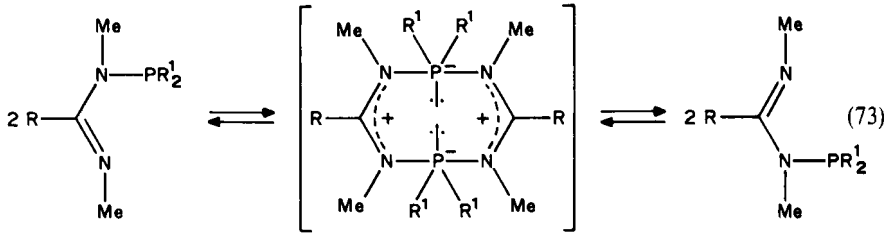
When the degeneracy of the rearrangement was cancelled in nonsymmetrical amidines **212** (R^1 = Et, *i*-Pr, *t*-Bu, Ph)[157], it was only in the case of N^1-methyl-N^2-ethyldiethoxyphosphinylbenzamidine **212**, R^1 = Et, X = – $P(OEt)_2$ that rapid 1,3-migrations of the phosphorus-containing group could be observed (equation 72). In benzene solution, this amidine contains in an equilibrium mixture 80% of isomer **212a** and 20% of **212b**, while in all other cases the equilibrium is completely shifted toward the less sterically hindered form **212a**. Unlike compounds **212**, **214**, phosphorylated amidines **213** are present in solution as a mixture of *Z* and *E* isomers relative to the C=N bond so that the dynamics of their molecules is governed by the relative velocity of two processes, i.e. the phosphorotropic tautomerism **213a** ⇄ **213b** and the *Z* ⇄ *E* isomerization.

The kinetic and activation parameters of the phosphorotropic tautomerism (equation 72), calculated on the basis of the line shape analysis of indicator N—Me signals in the ^1H and ^{13}C NMR spectra, are given in Table 11. The energy barriers ($\Delta G^{\ddagger}$) of the phosphorotropic migrations (equation 72) are determined by the coordination state of phosphorus, the nature of the substituents at the P and C atoms of the amidine and by the conformation of the triad system. The values of $\Delta G^{\ddagger}$ vary in a broad range from $\leqslant 8$ to > 25 kcal mol^{-1}. The nature of the solvent does not affect in any significant way the rate of the intramolecular migrations. The most pronounced impact upon the magnitude of $\Delta G^{\ddagger}$

comes from the substituents at the migrating phosphorus. The migrations are accelerated by electron-withdrawing substituents which greatly enhance the electrophilicity of phosphorus and especially by the inclusion of phosphorus into the dioxaphospholane cycle—an effect well-known in the chemistry of organophosphorus compounds[138]. The replacement of electron-withdrawing substituents at the carbon atom of the amidine triad (R = $CHCl_2$, CCl_3, CF_3, SMe) with a phenyl group that enhances the nucleophilicity of the imine nitrogen and promotes delocalization of the positive charge in the intermediates **201–203**, markedly increases the rate of the phosphorotropy. Highly negative values of the entropy of activation (from -10 to -20 cal deg^{-1} mol^{-1}) are evidence in favor of a stepwise mechanism of phosphorus migration in the amidine triad (equation 72) which requires considerable reorganization of the initial molecular structure.

A direct confirmation of the intramolecular character of tautomeric migrations (equation 72) as well as of the retention of configuration at the migrating center implied by the AdRE mechanism was obtained in an NMR study of *N*-dioxaphospholanyl-*N*,*N*'-dimethyl benz- and trifluoroacetyl amidines **212** (Nos 1, 3 in Table 11)[155]. It has been shown that the spin–spin coupling of N-Me protons with the ^{31}P nucleus is not disturbed even at fairly high rates of the P^{III}-centered group migration ($k_{40°C} = 12\,s^{-1}$). Under these conditions, even with the temperature raised to 170 °C (compound No 3), the diastereotopy of methylene protons in the dioxaphospholane ring is retained, manifesting retention of the chirality at the phosphorus center in the course of the migration.

At elevated temperatures, in polar solvents and at increased solution concentrations, these and other amidines containing P^{III}-centered migrants manifest, in addition to intramolecular migrations, also the slower intermolecular ones that proceed with inversion of configuration at phosphorus[163]. The proposed mechanism of the intermolecular migrations includes the formation, as a transition state or an intermediate, of the dimeric form **212c** with diaxial position of the entering and leaving groups (equation 73).

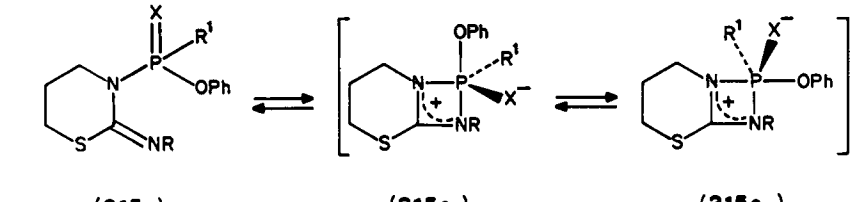


(73)

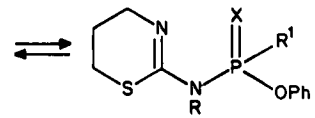
(212a) **(212c)** **(212b)**

In heterocyclic analogs of amidines, the processes of phosphorotropic tautomerism represented by fast reversible intramolecular migrations of phosphoryl and thiophosphoryl groups between the exo- and endocyclic nitrogen atoms have been studied in phosphorylated 2-*R*-aminodihydro(iminotetrahydro)-1,3-thiazines (**215**, equation 74)[164] and 2-*R*-amino(imino)thiazoli(di)nes (**216**, equation 75)[165]. In phosphorylated 2-*R*-amino(imino)pyrroli(di)nes (**217**), the intermolecular phosphorotropic tautomerization (equation 76) proceeds via the dimeric intermediate **217c**[166]. The intermolecular phosphorotropy of this type has been thoroughly studied in thiophosphorylated derivatives of 1,3,5-triazine **218**[174–176].

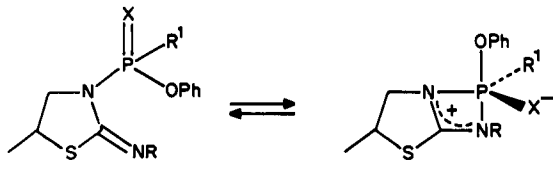
Whereas 2,4,6-tris(dialkoxydithiophosphoryl)-1,3,5-triazines (**218a**, X = S) do not manifest propensity towards tautomeric processes, 2,4,6- tris(dialkoxyphosphorylthio)-



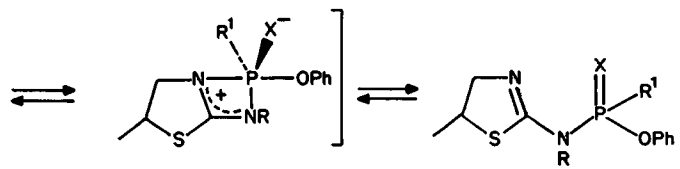
(215a) (215c$_1$) (215c$_2$) (74)



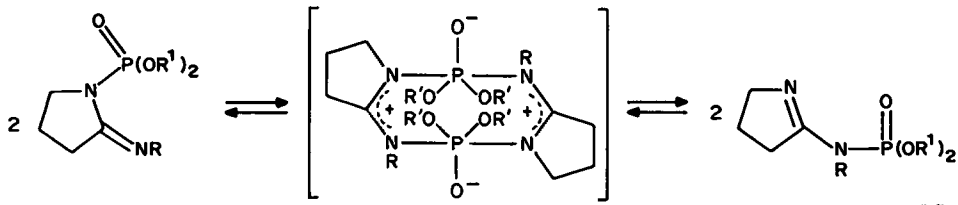
(215b)



(216a) (216c$_1$)



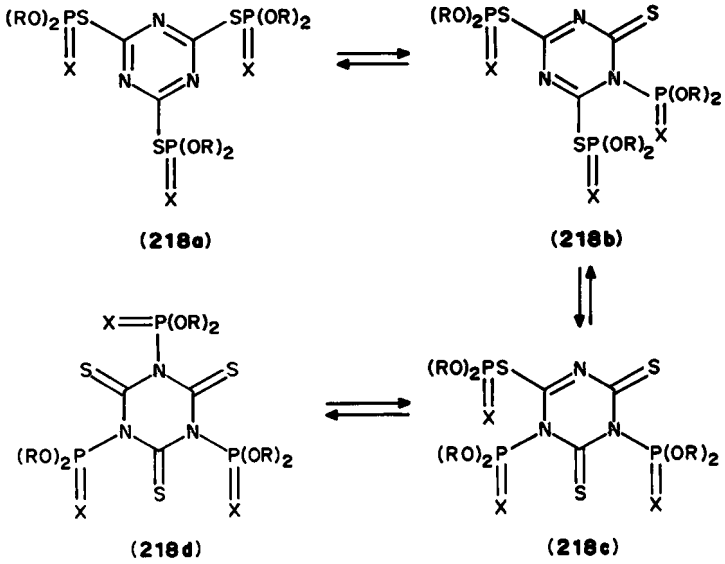
(216c$_2$) (216b) (75)



(217a) (217c) (217b) (76)

1,3,5-triazines (**218a**, X = O) are capable of tautomerization occurring through S⇄N migrations of the phosphoryl groups (equation 77). This process is stepwise and intermolecular[174]. The absence of phosphorotropy in dithio analogs of **218a** (X = S) is explained by a decrease in the electrophilicity of phosphorus included in the P=S bond as compared to the P=O bond[175]. As one goes from dihydro(tetrahydro)-1,3-thiazines **218** that provide optimum geometry conditions for the formation of transition states

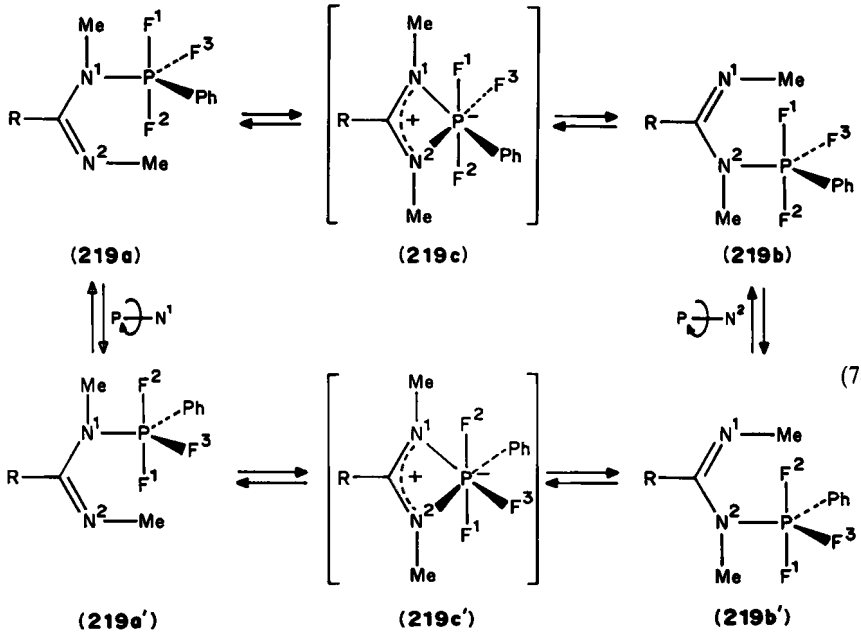
(intermediates) to acyclic amidines **213** and then to thiazoli(di)nes **216**, the free energy of activation for migrations of the phosphoryl groups of the same type increases[165]. The geometry of pyrroli(di)nes **217** provides only for slow intermolecular migrations of phosphoranyl groups via dimeric transition states **217c**[165].



(77)

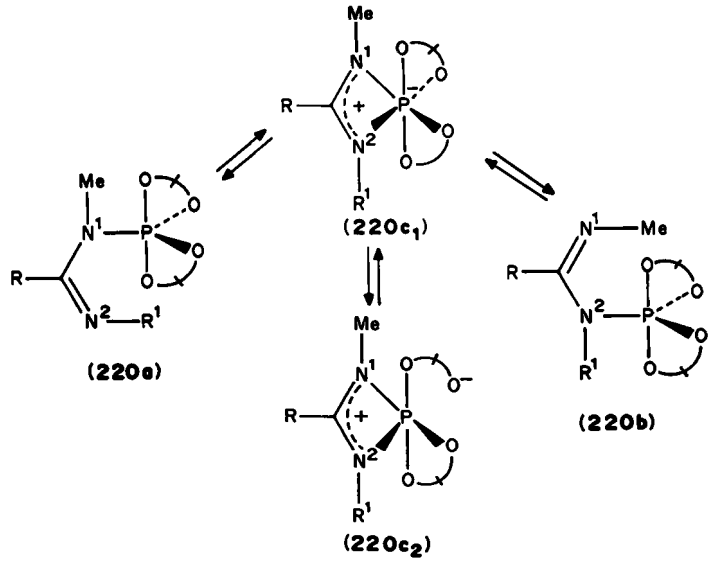
MINDO/3 calculations[177,178] have shown that a possibility exists for tautomeric migrations of the groups with pentacoordinate phosphorus in amidine systems. The reaction of nucleophilic substitution at the pentacoordinate phosphorus atom is associated with an equatorial *cis*-approach of the nucleophile to the leaving group and a *cis*-departure of this group in the stable octahedral intermediate formed. Experimental realization of the phosphorotropic tautomerism with a migrating pentacoordinate phosphorus atom was effected in the case of phenyltrifluorophosphoranyl trihalogenacetamidines (**219**, R = CF_3, CCl_3)[167,168] and bis(*ortho*-phenylenedioxa)phosphoranyl trihalogenacetamidines (**220**, R = CF_3, CCl_3)[163,169]. When a phenyl group in benzamidinium tetra- or phenyltrifluorophosphates that exist in crystal and in solution as a cyclic hexacoordinate species **219c,c'** (R = Ph) is replaced by an electron-withdrawing trifluoro- or trichloromethyl group, opening of the four-membered ring of **219c,c'** takes place with the formation of N^1,N^2-dimethyl-N^1-phenyltrifluorophosphoranyl trihalogenacetamidines (**219a,b**). The temperature-dependent ^1H and ^{31}P NMR spectra display three dynamic processes occurring in compounds **219** (R = CF_3, CCl_3) (equation 78). At temperatures from 0 to 20 °C, a hindered rotation about the N—P bond is observed ($\Delta G^{\ddagger}$ = 15.2–16.4 kcal mol^{-1}); in the 90 to 145 °C range, permutational isomerization in the trigonal bipyramid of phosphorus takes place ($\Delta G^{\ddagger}$ = 18.6–18.9 kcal mol^{-1}); in the range of 160 to 200 °C, the phosphorotropic tautomerization **219a,a'** ⇄ **219b,b'** has been detected and is characterized by the following activation parameters: $\Delta G^{\ddagger}_{175°C}$ = 23.7 (**219**, R = CF_3), $\Delta G^{\ddagger}_{131°C}$ = 21.5 kcal mol^{-1} (**219**, R = Cl_3).

As in the case of benzamidinium fluorophosphorates **219** (R = Ph), benzamidinium bis(*ortho*-phenylenedioxa)phosphorates **220** (R = Ph) exist in crystal and solution in the mesoionic hexacoordinate form **220c$_1$**. In compounds **220c$_1$** (R = Ph), similarly to phosphorates **219c** (R = Ph), using dynamic ^1H and ^{31}P NMR, permutational isomerizations have been detected and studied (equation 79). They proceed with the dissociation



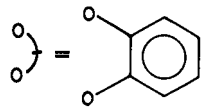
(78)

R = Ph, CF_3, CCl_3



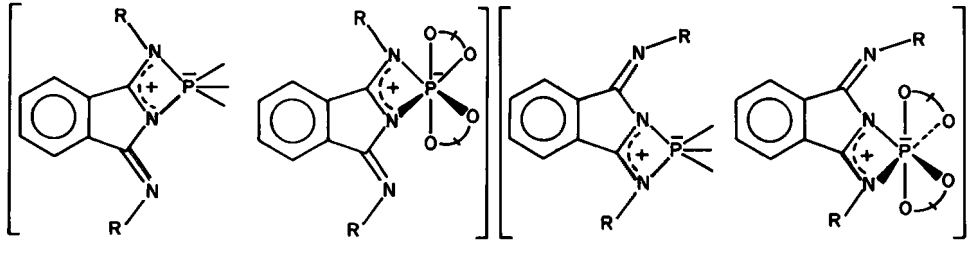
(79)

R = Ph, CF_3, CCl_3; R^1 = Me, *i*-Pr

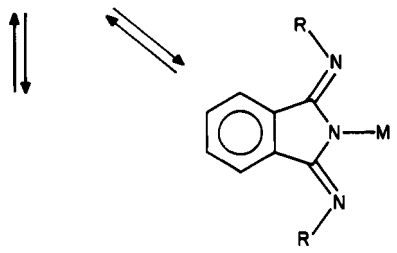


of the P—N and P—O bonds of bidentate ligands via pentacoordinate intermediates **220a,b,c**$_2$ ($\Delta G^{\ddagger}_{25\,°C} = 16$–$24$ kcal mol^{-1})[163,168].

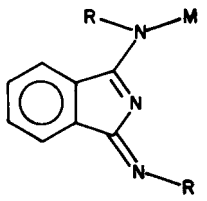
The phosphorotropic tautomerism has been studied in the case of dimethyl and diaryl derivatives of 1,3-isoindolenines **221**, **222**[170–172]. The phosphorotropic migrations in compounds **221**, **222** occur as successive 1,3-shifts by a multistep mechanism (equation 80).



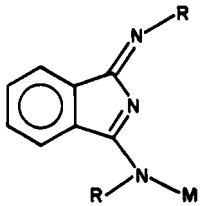
(221d) (222d) (221e) (222e)



(221b, 222b) (80)

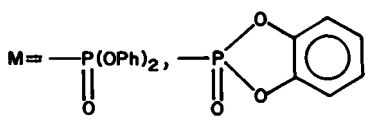


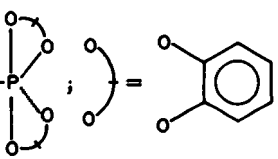
(221a, 222a)



(221c, 222c)

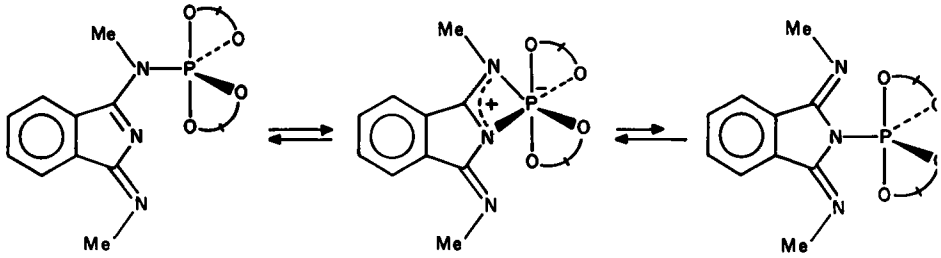
221: R=Me, 4-Tol, 4-An



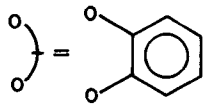
222: R=4-Tol, 4-An; M= 

The transient forms in these migrations are represented by the structures with a penta- (**221d,e**) and a hexacoordinate (**222d,e**) phosphorus for, respectively, tetra- (**221**) and pentacoordinate (**222**) migrants. The free energy of activation ($\Delta G^{\ddagger}_{130\,°C}$) for the phosphorotropic rearrangements (equation 80) of compounds **221**, **222** ranges from 16.0 to 27.3 kcal mol^{-1} with the lower value corresponding to the migration of the phosphoranyl group in **222** (R = 4-Tol).

In 1-methyl-bis(*ortho*-phenyleneoxa)phosphoranylamino-3-methyliminoindolenine (**223**), using dynamic ^{1}H and ^{31}P NMR a fast ($\Delta G^{\ddagger} \leqslant 6$ kcal mol^{-1}), reversible intramolecular valence isomerization (coordinational isomerism $P^{V} \rightleftarrows P^{VI}$) has been detected. It consists of a rapid (on the NMR time scale) process of bond-making, bond-breaking between the endocyclic nitrogen atom and the phosphorus atom in **223a** and **223b**[163] (equation 81).



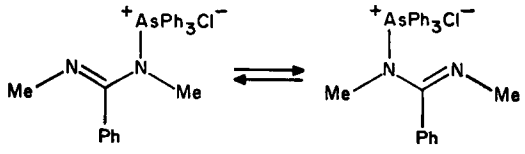
(**223a**) (**223b**) (**223c**)



(81)

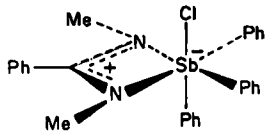
Only one well-documented example of the tautomeric migration of an arsenic-containing group in the amidine system is known to date. An exchange of the triphenylphosphonio group in amidine **212** for the triphenylarsenio migrant substantially accelerates 1,3-*N*,*N*′-shifts.

The energy barrier to such a migration (equation 82) was found to be lower than 10 kcal mol^{-1} at $-90\,°C$[145]. The antimonio analogs of compound **224** are stable as Sb(VI) amidinium chlorotriphenylantimonates (**225**), which in solutions are susceptible to permutational isomerization like that shown by their P(VI) congeners **219**, **220**.



(**224a**) (**224b**)

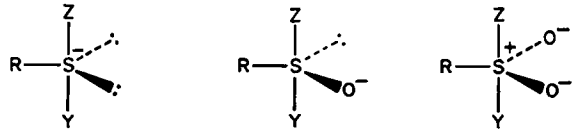
(82)



(**225**)

C. 1,3-Shifts of Sulfur-containing Groups

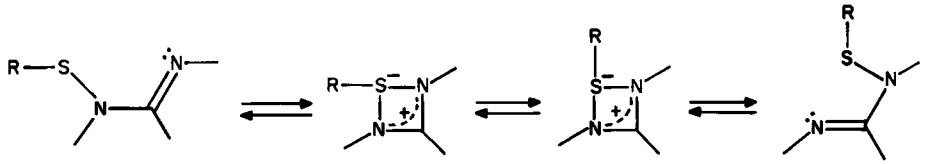
The stepwise addition–rearrangement–elimination mechanism was also found to operate in intramolecular rearrangements of amidines involving 1,3-displacements of sulfur-containing groups. The intermediates which should exhibit the low-energy barrier polytopal rearrangement in the cases of sulfenyl, sulfinyl and sulfonyl migrations are represented by, respectively, the structures **226**–**228**, in which X represents the migrating groups specified in equation (59).



(226) X=SR **(227)** X=S(O)R **(228)** X=SO_2R

In the pentacoordinate structure **228**, a pairwise ligand permutation (Berry-pseudorotation, i.e. the most feasible rearrangement process) results in the transference of at least one O^--group to the axial position. Since the apicophilicity of this group is extremely low (according to 3–21 G* calculations[143] it takes 9.3 kcal mol^{-1} to displace one O^--group from its energy preferable axial position in trigonal bipyramidal phosphorane to the equatorial one), it may be expected that the total energy barrier of a 1,3-transfer of a sulfonyl group in amidines will be sufficiently high. In actual fact, no such migration has yet been reported[140], and the ^1H NMR spectrum of *N*-phenylsulfonyl-*N*,*N*′-di(*p*-tolyl)amidine showed no averaging on heating its diphenyl ether solution up to 180–200 °C[179].

If the T-shaped structures **226**, which should be viewed as trigonal bipyramids with two lone pairs as the phantom-ligands, were prone to a Berry-pseudorotation type of polytopal rearrangement, this would also lead to the energy-rich structure holding the less apicophilic phantom-ligands in axial positions. However, the principal mode of the polytopal rearrangement of the T-shaped structures was predicted by quantum mechanical calculations[140,180] on a series of model compounds to be rather peculiar, being represented by a simple in-plane shift of one of the ligands. Therefore, in *N*-sulfenyl amidines the AdRE mechanism of 1,3-*N*,*N*′-transfer of the sulfenyl group is expected to be shown by equation 83. By inclusion of a step of the formation of intermediate **229c**, this scheme provides the necessary condition for the axial attack by the nucleophile and the axial departure of the nucleofugal group. This intermediate must have sufficient lifetime for the polytopal rearrangement into **229**c_2.

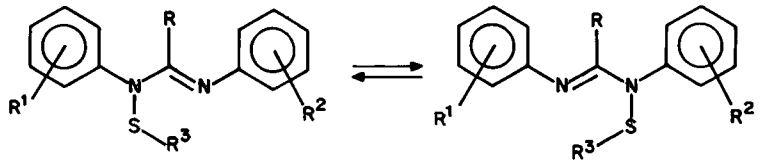


(83)

(229a) **(229**c_1**)** **(229**c_2**)** **(229b)**

Indeed, in the series of *N*-sulfenyl-*N*,*N*′-diaryl benzamidines **230**, using dynamic ^1H NMR, the kinetics of the 1,3-*N*,*N*′-transfer of arensulfenyl groups could be detected and studied[181,182]. The intramolecular character of this reaction (equation 84) has been proven by cross-experiments and by the absence of any concentration dependence of the

rearrangement rate in various solvents. The effect of electronic and structural factors on the rate of sulfenyl migrations in amidines **230** has been studied in detail[182]. Kinetic and activation parameters of these migrations, given in Table 12, calculated by the line-shape analysis technique suggest the following conclusions.



(84)

(230a) **(230b)**

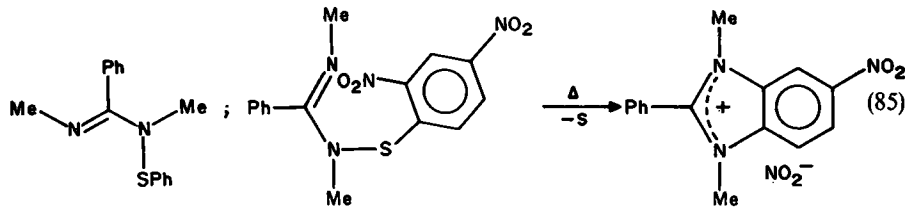
(1) The migration of the sulfenyl group is observed on the ^{1}H NMR time scale only in the presence of an aromatic substituent (R = Ar) at the carbon atom of the amidine triad. Formamidines (R = H, Nos. 8, 14 in Table 12) do not exhibit a sufficiently fast exchange reaction up to 160–180 °C. The aromatic substituent R promotes the stabilization of the dipolar intermediates **229c$_1$,c$_2$** so that the activation parameters of the rearrangement (equation 84) fall into the tautomeric scale.

(2) The electron-withdrawing groups in the substituent R accelerate (No. 5 in Table 12, R = *p*-$NO_2C_6H_4$) the migration rate of arenesulfenyl groups, while the electron-donating ones slow it down (No. 1, R = *p*-An). The correlation equation has the form: $\lg(k/k_0)_{25\,°C} = 1.26\sigma^+ + (r = 0.985, s = 0.178)$.

(3) The high negative values of the entropy of activation (from -14 to -24 cal deg^{-1} mol^{-1}) are in agreement with the two-step mechanism of 1,3-migrations of the sulfenyl group (equation 83) in compounds **230**, which requires a substantial reorganization and ordering of the molecular structure as compared to the initial form **230a**.

(4) The introduction of substituents in the *ortho* position in the *N,N'*-aryl rings of benzamidines (Nos. 11, 12) sterically inhibits the *N,N'*-transfer of the arenesulfenyl group.

In contrast to *N*-arenesulfenyl-*N,N'*-diarylbenzamidines, there are no tautomeric migrations of arenesulfenyl groups in the corresponding derivatives of *N,N'*-dimethylbenzamidines **231**, **232**[89,145]. ^{1}H NMR spectra of compound **231** in diphenyl oxide are temperature-independent up to 190 °C[145], while compound **232** undergoes, already at 100 °C, elimination of sulfur and nucleophilic substitution of the nitro group to give benzimidazolium nitrite **233** (20% yield)[89] (equation 85).



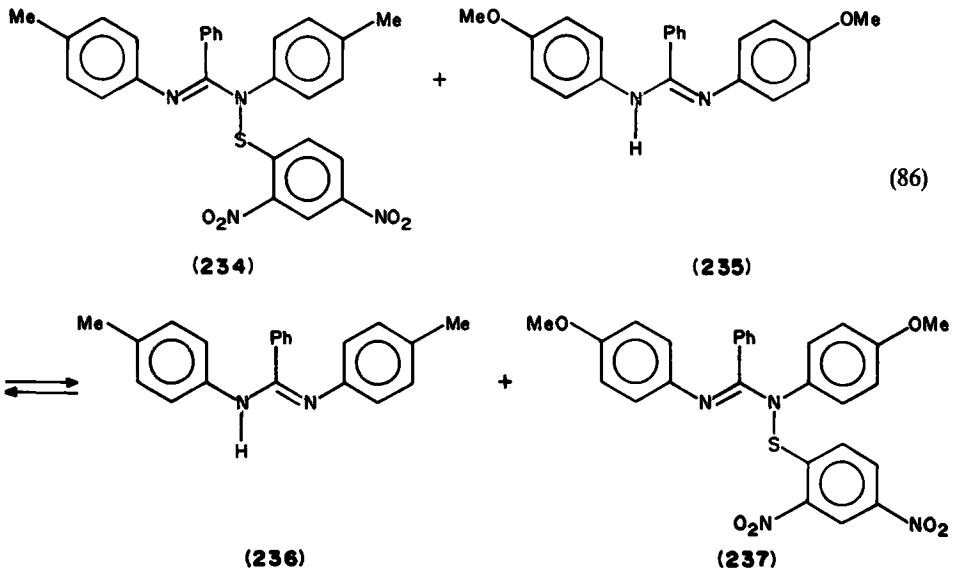
(85)

(231) **(232)** **(233)**

When the arenesulfenylbenzamidine **234** and the N-unsubstituted benzamidine **235** are mixed, an interchange of positions is observed between the two migrating groups, namely the arenesulfenyl fragment and the proton[181] (equation 86).

TABLE 12. Kinetic and activation parameters of sulfenyl rearrangements in chlorobenzene (equation 84), according to References 181 and 182

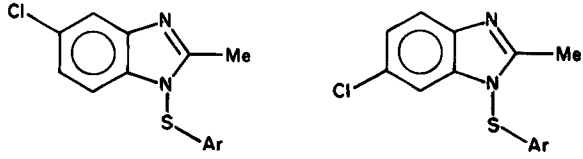
No.	Compound R	R^3	R^1	R^2	$k_{25°C}^{a\to b} \times 10^2$ (s^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1})	$\Delta G_{25°C}^{\ddagger}$ (kcal mol^{-1})
1	*p*-An	2,4-$C_6H_3(NO_2)_2$	*p*-Me	*p*-Me	1.7	15.4 ± 0.5	-14.8 ± 1.4	19.8
2	Ph	2,4-$C_6H_3(NO_2)_2$	*p*-Me	*p*-Me	6.3	15.0 ± 0.6	-13.6 ± 1.2	19.0
3	*p*-C_6H_4Br	2,4-$C_6H_3(NO_2)_2$	*p*-Me	*p*-Me	12.2	13.3 ± 0.5	-18.5 ± 1.4	18.8
4	*p*-C_6H_4Cl	2,4-$C_6H_3(NO_2)_2$	*p*-Me	*p*-Me	15.5	11.9 ± 0.3	-22.2 ± 0.8	18.5
5	*p*-$C_6H_4NO_2$	2,4-$C_6H_3(NO_2)_2$	*p*-Me	*p*-Me	309	9.8 ± 0.3	-23.2 ± 0.9	16.7
6	Ph	2,4-$C_6H_3(NO_2)_2$	*p*-OMe	*p*-OMe	12.2	13.4 ± 0.7	-18.1 ± 1.1	18.8
7	Ph	2-$C_6H_4NO_2$	*p*-OMe	*p*-OMe	10.0	13.4 ± 0.4	-17.7 ± 1.3	18.7
8	H	2,4-$C_6H_3(NO_2)_2$	*p*-Me	*p*-Me	0	—	—	> 27
9	Ph	2,4-$C_6H_3(NO_2)_2$	*p*-Me	H	22.0	11.9 ± 0.4	-21.6 ± 1.0	18.3
10	Ph	2,4-$C_6H_3(NO_2)_2$	*p*-Me	*p*-OMe	62.0	10.7 ± 0.2	-23.6 ± 0.9	17.7
11	Ph	2,4-$C_6H_3(NO_2)_2$	*o*-OMe	*o*-OMe	0	—	—	> 27
12	Ph	2-$C_6H_4NO_2$	*o*-OMe	*o*-OMe	0	—	—	> 27
13	Ph	CCl_3	*p*-Me	*p*-Me	2.2	13.6 ± 0.6	-20.1 ± 1.1	19.6
14	H	2-$C_6H_4NO_2$	*o*-OMe	*o*-OMe	0	—	—	> 27



(234) (235) (86)

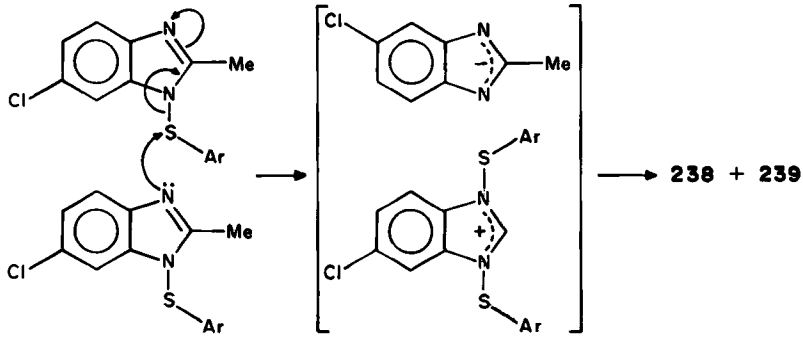
(236) (237)

Intermolecular 1,3-*N*,*N'*-rearrangements of arenesulfenyl groups from one nitrogen atom to another have been detected in heterocyclic analogs of amidines, namely 5(6)-chloro-*N*-[(2,4-dinitrophenyl)thio]-2-methylbenzimidazoles **238**, **239**[183]. The mixture of the isomers **238** and **239** obtained upon sulfenylation of 5-chloro-2-methylbenzimidazole with 2,4-dinitrophenylsulfenyl chloride in THF in the presence of triethylamine was separated by means of fractional crystallization. Upon heating, these isomers transform into each other, with the rate of their interconversion depending on the concentration (in toluene at 65 °C, $k_2 = 1.65 \times 10^{-3}\,M^{-1}\,s^{-1}$). The addition of unsubstituted methylchlorobenzimidazole substantially increases the rate of migration of the arenesulfenyl groups in compounds **238**, **239** ($k_c = 14.3 \times 10^{-3}\,M^{-1}\,s^{-1}$, toluene, 65 °C). According to Reference 183, the bimolecular mechanism of migrations of the arenesulfenyl groups in **238** and **239** consists of a nucleophilic attack by the pyridine-type nitrogen of one sulfenamidine molecule on the sulfenyl sulfur of another (equation 87).



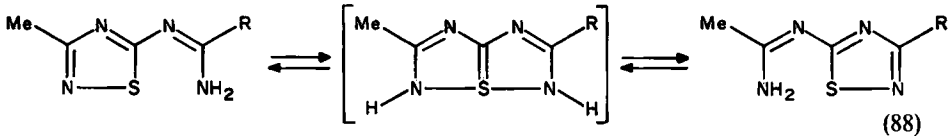
(238) (239)

Intramolecular rearrangements (equation 88) associated with the transfer of an anchored S^{II}-centered migrant between nitrogen atoms in derivatives containing amidine fragments have been studied by Akiba and coworkers[184,185]. In the course of this reaction, the tetraazathiopentalene **242** emerges in the role of an intermediate with a linear N—S—N group. The position of the equilibrium **242** ⇄ **243** is dependent on the solvent, temperature and the substituent R. Bulky groups and electron-withdrawing substituents facilitate the formation of the isomer **243**.



(239) (240)

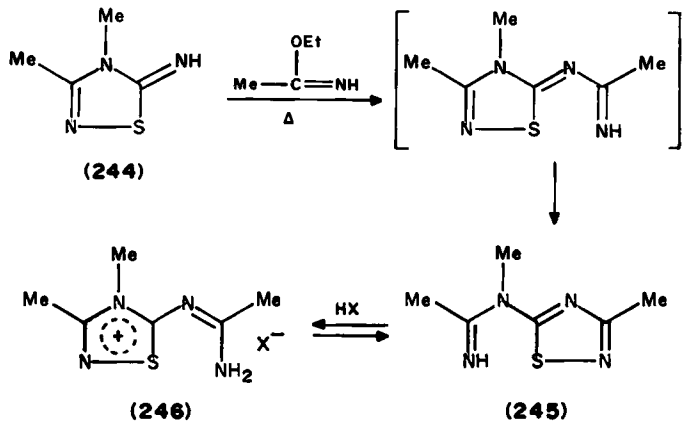
(87)



(241) (242) (243)

(88)

Two successive rearrangements of this type (equation 89), the first of which leads to the formation of compound **245** from **244** while the second results in the salt **246**, have been described[186].

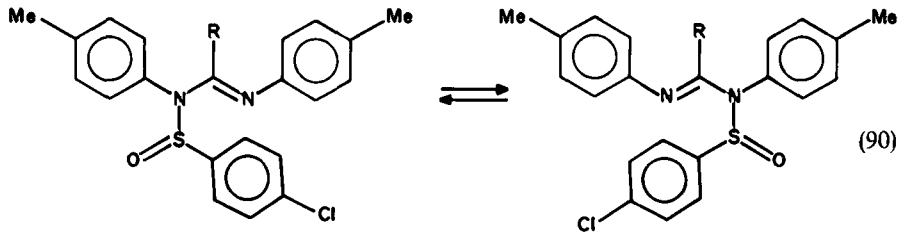


(244) (246) (245)

(89)

$HX = HBF_4$, CF_3COOH

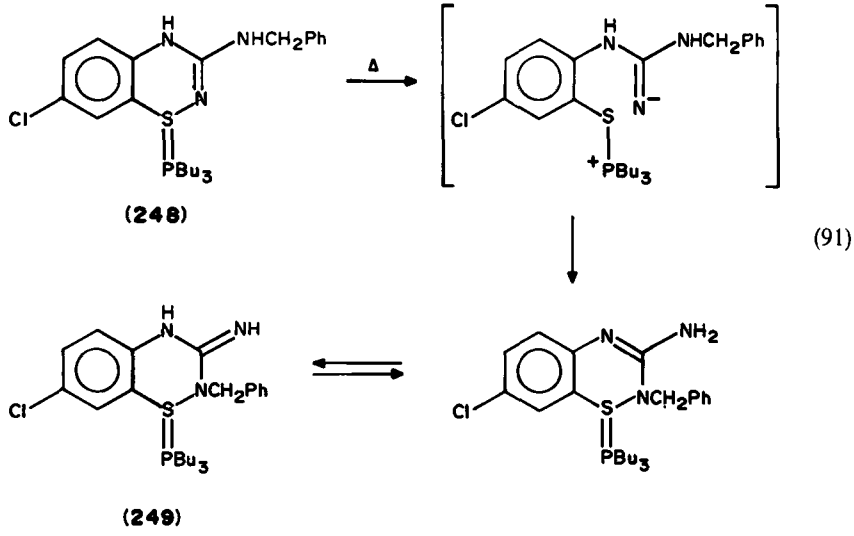
1,3,-Migrations of sulfinyl groups in amidine systems have been studied to a lesser extent. The possibility has been shown of an intramolecular tautomerization realized through rapid *N,N'*-migrations of an arenesulfinyl group in the corresponding derivatives of *N,N'*-(di-*p*-tolyl)form- and benzamidines **247a** ⇄ **247b** (in chlorobenzene)[187] (equation 90).



(247a) (247b) (90)

R	$\Delta G^{\neq}_{25}$ °C, kcal mol^{-1}
H	21.5
Ph	20.9

The rearrangement[188] of thiophosphorane **248** into **249** (equation 91) may be considered as an intramolecular migration of the anchored tricoordinate sulfur group.



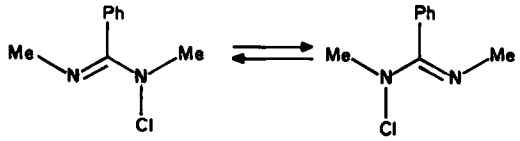
(248) (91)

(249)

D. 1,3-Shifts of Chlorine in Amidine Systems

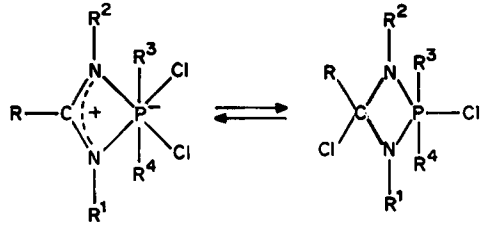
There are but a few examples known of the reversible 1,3-shifts of halogens in triad systems[189]. The only one pertaining to amidine derivatives was described by Wolf and Hartke[145], who found that in diphenyl ether or hexachlorobutadiene solutions of *N*-chloro-*N*,*N'*-dimethyl benzamidine (**250**) migration of chlorine occurs at elevated temperatures, accompanied by partial decomposition of **250** (equation 92). Not details on the mechanism of the rearrangement were given, but the ionic or ion-pair pathways of the rearrangement seem to be the most plausible ones.

Intramolecular 1,3-*P*,*C*-migrations of chlorine in amidinium chlorophosphates have been studied by Markovski and coworkers[190–192]. Using ^{1}H and ^{31}P NMR, they detected



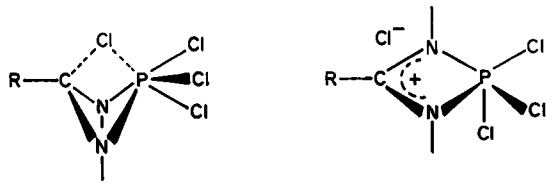
(250a) (250b) (92)

both reversible and irreversible migrations of chlorine in the C—N—P triad (**251a** ⇄ **251b**) accompanied by a change in the coordination of phosphorus (equation 93). Benzamidinium chlorophosphates (R = Ph; R^1, R^2 = Alk, Ar; $R^3 = R^4$ = Cl) exist in solution exclusively in the form with a hexacoordinate phosphorus atom. The presence of two phenyl groups at the phosphorus ($R^3 = R^4$ = Ar) stabilizes the phosphorane P^V-form and facilitates the irreversible migration of the chlorine atom from phosphorus to the carbon of the amidine triad. The same result is achieved when the phenyl group at the carbon atom of the amidine triad (R = Ph) is replaced with the electron-withdrawing trichloro- and trifluoromethyl groups (R = CCl_3, CF_3) incapable of the delocalization of the positive charge. In the case of chlorine-substituted compounds (R = CCl_3, CF_3; R^1, R^2 = Alk; $R^3 = R^4$ = Cl) with equalized nucleophilicities of the carbon and phosphorus atoms, it proved possible to realize reversible migrations of the chlorine atom in the C—N—P triad **251a** ⇄ **251b**, that proceed with the free energies of activation $\Delta G^{\ddagger}_{25°C}$ = 15.6–16.9 kcal mol^{-1} (equation 93).



(251a) (251b) (93)

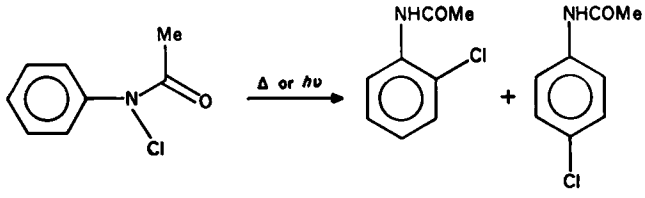
Of the two transition states of the process in equation 93, preference was given to structure **253** since the great negative values of the entropy of activation of the rearrangement ($\Delta S^{\ddagger}$ ranges from − 16 to − 34 cal deg^{-1} mol^{-1}) and the dependence of the free activation energy on the solvent polarity are, apparently, due to the formation of a tight ion pair in the transition state.



(252) (253)

1,3-*O*,*N*- or *N*,*O*-migrations of chlorine in the corresponding derivatives of imides and amides are unknown. There is, however, a method for obtaining *o*- and *p*-halogeno

anilines, based on the halogenation of *N*-acylamines, that includes a rearrangement (equation 94) associated with the migration of the chlorine atom into the *ortho* and *para* positions of the *N*-aryl ring[193]. Based on kinetic studies of this rearrangement in water solution at various temperatures and pressures, the scheme in equation 95 was suggested and it was shown that the limiting step of this reaction is the ionization **257** → **258**[194]. The ratio between the *ortho* and *para* products (**255**:**256**) increases with rising temperature and with falling pressure, which is thought to be associated with a lesser degree of hydration of the intermediate complex for the *ortho* isomer **255**.



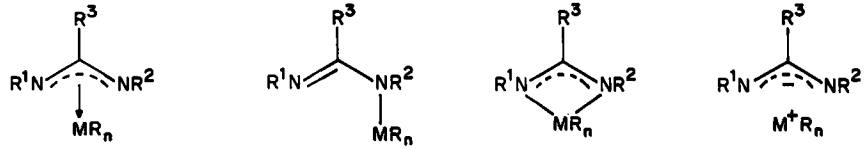
(94)

(254) **(255)** **(256)**

$$\mathbf{254} \overset{H^+}{\rightleftharpoons} \underset{\textbf{(257)}}{ClNH(Ph)Ac} \overset{-Cl^+}{\rightleftharpoons} \underset{\textbf{(258)}}{NH(Ph)Ac} \overset{+Cl_2}{\rightleftharpoons} \mathbf{255} + \mathbf{256} \qquad (95)$$

IV. REARRANGEMENTS INVOLVING ORGANOMETALLIC DERIVATIVES OF AMIDINES

Amidines are aza analogs of the allyl system and, similarly to metal–allyl compounds, they may, in principle, form with organometallic groups structures of various bonding types, such as **259**–**262**. The π-complexes **259** in which the pseudo-allyl η^3 bonding mode would be realized are not known. Also the ionic bonding in **262** is quite a rare case, whereas monodentate σ-*N* **260**[145,195–198] and bidentate (chelate) σ-*N*,*N*′ **261**[145,199–203] forms represent the most commonly encountered bonding type in organometallic derivatives of amidines. Two types of rearrangement are possible for these compounds: (1) The 1,3-shift of the organometallic group in η^1-structural type compounds and (2) the η^1-η^3 haptotropic rearrangement where the η^3-form may serve as the energy-rich intermediate or transition state. Although the latter rearrangement mode is rather typical in the case of metal–σ-allyl compounds[204], in amidine rearrangements the η^1–η^3 transformations were invoked to describe the reaction mechanism in few cases only [198].

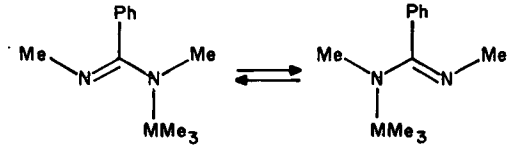


(259) **(260)** **(261)** **(262)**

The present section concentrates on 1,3-shifts of organometallic moieties in the amidine triad. Among the migrants, Si-centered groups will also be considered. Even though the silicon groups cannot, strictly speaking, be classified as organometallic, there is, in view of common mechanisms operative in reactions of organosilicon and main-group-metal

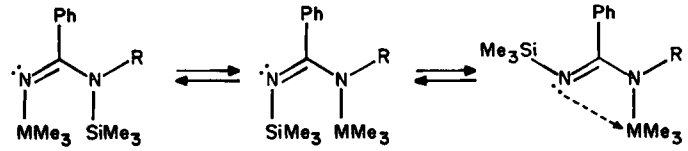
organic compounds, a customary practice[205] to examine jointly reactions of both classes of compounds.

It has been found[145,196] that *N*-trimethylsilyl and *N*-trimethylstannyl *N,N'*-dimethylbenzamidines **263** are rapidly isomerized as a result of the intramolecular 1,3-*N,N'*-shift of the corresponding organometallic group (equation 96). The degenerate exchange reaction **263a** ⇄ **263b** can be frozen only at −60 °C.



(263a) M = Si, Sn (263b) (96)

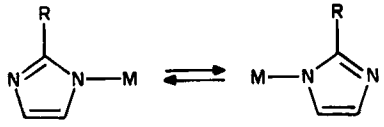
Bis-trimethylsilyl derivatives of benzamidines **264** were shown by ^{1}H NMR[196] to undergo a reversible intramolecular 1,3-exchange of positions of both trimethylsilyl groups ($\Delta G^{\ddagger}_{-43\,°C} = 11.7$ kcal mol^{-1}). The substitution of silicon in compounds **264** by germanium, tin or lead makes the **264a** → **264b** reaction irreversible. This is explained[196] by the propensity of Ge, Sn and Pb for additional coordination, which indeed is achieved in the structure **264c**. It is assumed[196] that the intramolecular process represented by equation 97 proceeds synchronously.



(264a) (264b) (264c) (97)

R = Me, M = Si, Ge, Sn, Pb
R = Et, M = Si

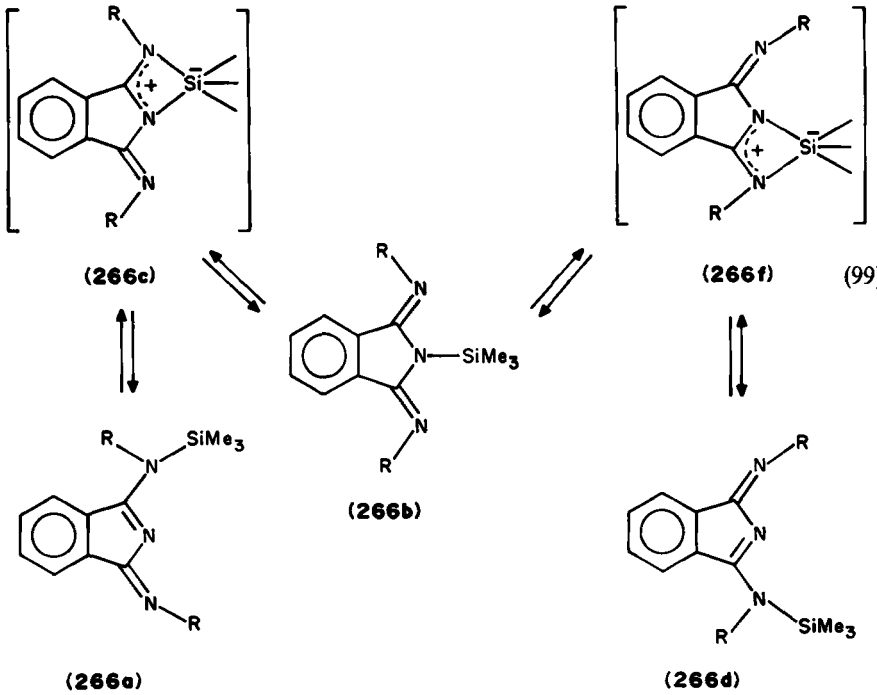
Whereas in the cyclic analogs of amidines, namely in imidazoles **265**, migrations of the trimethylsilyl and trimethylgermyl groups occur intermolecularly[206,207] (equation 98), in the corresponding derivatives of 1,3-indolenines **266** containing two amidine fragments with a common exocyclic nitrogen atom, the silylotropy is predominantly realized in an intramolecular way[170–172]. The dimethyl derivatives **266** exist in solution mainly in the form of 1-methylamino-3-methyl-iminoisoindolenines (**266a,d**), while the diaryl ones are in the tautomeric equilibrium of 1-arylamino-3-aryliminoisoindelenine (**266a,d**) and 1,3-diaryliminoisoindoline (**266b**). Intramolecular silylotropic migrations in compounds **266** proceed as successive 1,3-shifts by a three-positional exchange scheme (equation 99). The structures **266c,b,f** with the N_{endo}-migrant



(265a) (265b) (98)

R = H, Cl; M = $SiMe_3$, $GeMe_3$

bond serve as intermediates in the process. The geometry of the triad N=C=N in **266c,f** must meet the following necessary conditions: an axial-equatorial position of nitrogen atoms and permutational isomerization in the trigonal bipyramid of silicon atoms[208]. The free activation energy of silylotropic migrations in compounds **266** ranges from 20.8 to 23.2 kcal mol^{-1}, which exceeds a good deal the $\Delta G^{\ddagger}$ values of 1,3-migrations in silylated dimethylbenzamides[145,196].



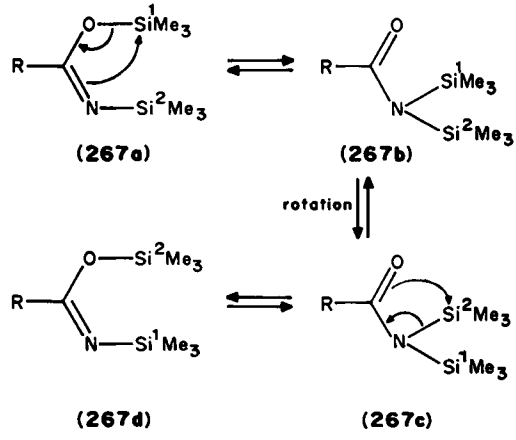
(99)

R = Me, 4-Tol, 4-An

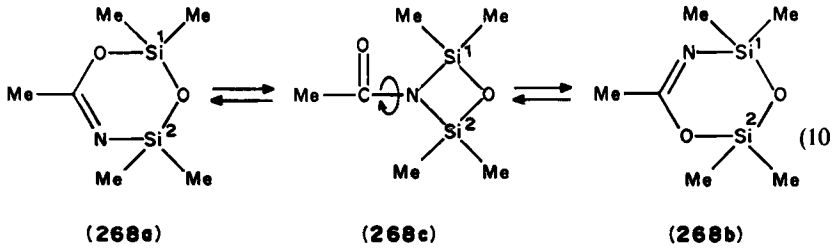
First the intramolecular 1,3-*N*,*O*-migrations of the trimethylsilyl group were detected in bis(trimethylsilyl)acetamide (**267**, R = Me)[209]. Later on[210–212], after studying the NMR and IR spectra of the ^{15}N-labeled compound **267** and measuring activation parameters of the silyl exchange, a scheme was suggested (equation 100) for migrations of the trimethylsilyl groups in bis(trimethylsilyl)amide **267**. This scheme[210–212] as well as all others[213–216] that describe silylotropic rearrangemnets involves unhindered rotation about the carbon–nitrogen bond of **267b** ⇄ **267c** type in the *N*,*N*′-disilylamides.

Migrations of silyl groups have been studied[215] in six-membered disilylacetimidate **268** that occur through the four-membered intermediate **268c** (equation 101). The intermediate **268c** is so stable that it can be isolated preparatively. The equilibrium content of *N*-acetyltetramethylcyclosilazoxane (**268c**) and disilylacetamide **268a,b** grows with falling temperature and with increasing polarity of the solvent.

As opposed to the six-membered cyclic disilylbenzimidates of type **268** which are not susceptible to tautomerization[215], the eight-membered ring benzimidates **269**[216] undergo rapid intramolecular 1,3-*N*,*O*-silyl migrations via a six-membered ring intermediate **269c** amido form (equation 102). The free activation energy ($\Delta G^{\ddagger}$) of 1,3-migrations of the silyl groups in compounds **269** amounts, depending on the substituent R, to 13.7–



(100)



(101)

15.5 kcal mol^{-1}. Electron-donating substituents R accelerate the rearrangement (equation 102) because they promote the transannular nucleophilic attack by nitrogen on silicon-1 or 2 by increasing the electron density on nitrogen.

A comparison was made[217] between activation parameters for the exchange of silyl groups in the acyclic **270** and cyclic **271** (R = Ph) disilylbenzamides (equations 103 and 104, respectively).

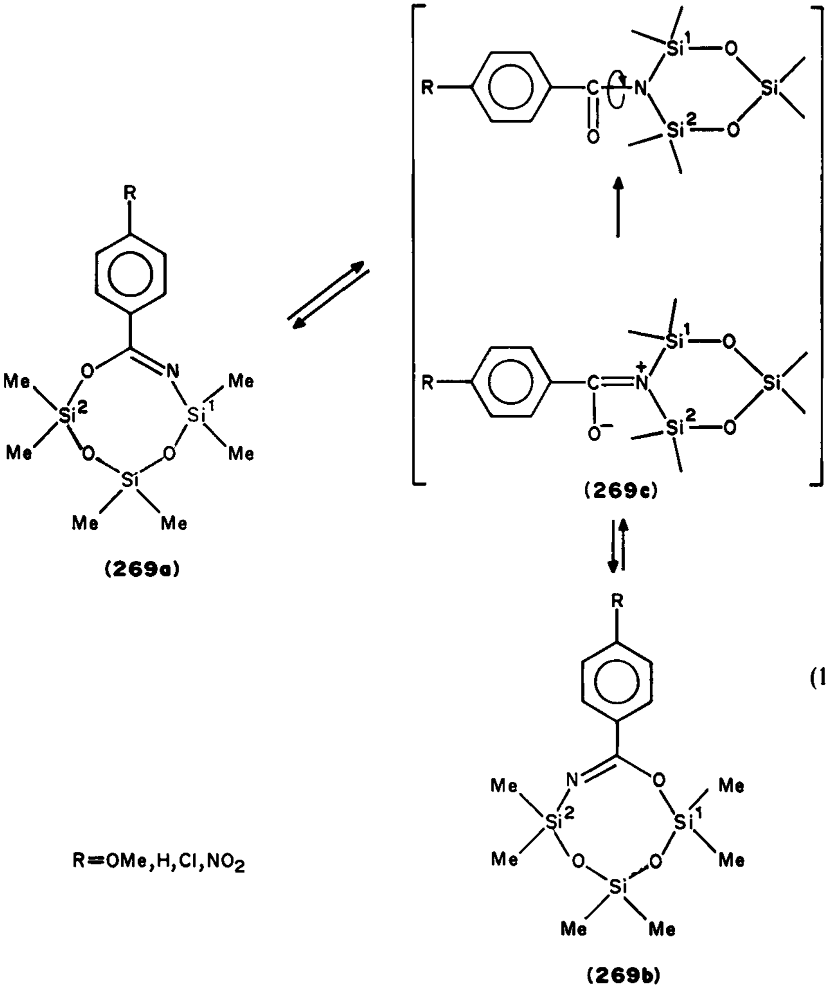
While for the exchange of silyl groups in acyclic disilylbenzamide the free activation energy ($\Delta G^{\ddagger}_{70°C}$) amounts to 18.3 kcal mol^{-1}, upon coordination of the phosphine donors to the $Ni(CO)_2$ fragment a sharp increase occurs in the rate of the silyl group migration **271a** ⇄ **271b** ($\Delta G^{\ddagger}$ = 14.6 kcal mol^{-1}, R = Ph). This effect is explained by the fact that in the 10-membered chelate ring **271b** there occurs a drawing together of the lone pair of the imidate nitrogen atom and the $OSiMe_2$ group, which facilitates transannular attack[217] on silicon by the imidate nitrogen to form the *N,N*-disilylamide **271a**.

Nondegenerate intramolecular 1,3-*N,O*-migrations of the trimethylsilyl group (equation 105) occur also in monosilyl amides **272**[218–222]. It has been found[220,221] that the activation parameters of the process (equation 105) and the position of the equilibrium **272a** ⇄ **272b** depend to a great extent on the substituents both in the amide fragment (R, R^1) and at the silicon atom (R^2).

The 1,3-*N,O*-shift of the trimethylsilyl group in amides **273** has been studied[222,223] by dynamic ^1H NMR (equation 106).

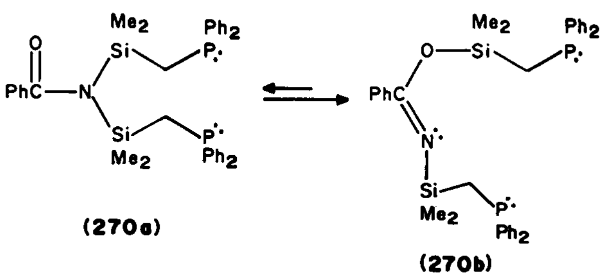
A number of other examples of migrations of the trimethylsilyl group in the amide system have been described in review articles[198,224].

N,N'-Dimethylborylbenzamidines **274**[199] exist in solution in an equilibrium mixture of



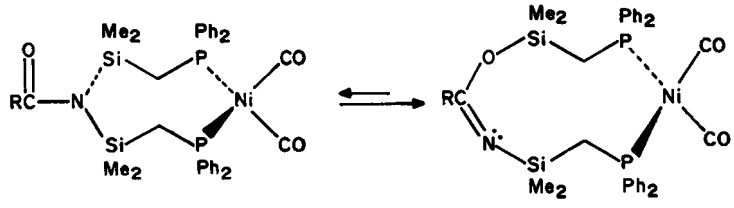
(269a) (269c) (269b)

(102)



(270a) (270b)

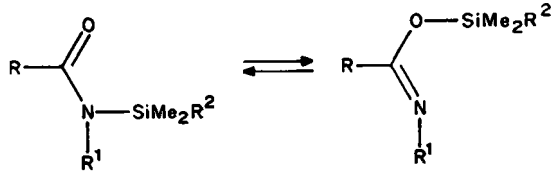
(103)



(104)

(271a) (271b)

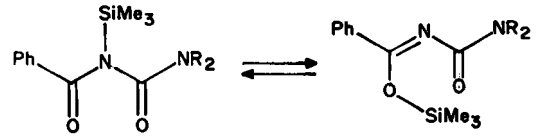
R = Me, All, $CH{=}CH_2$, Ph



(105)

(272a) (272b)

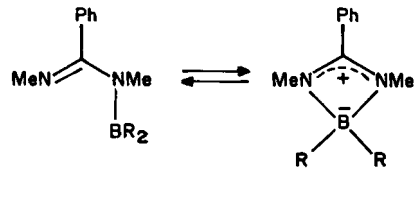
R^2 = Me, *t*-Bu



(106)

(273a) (273b)

the open **274a** and the cyclic **274b** forms (equation 107). 1,3-*N*,*O*-tautomeric migrations of the BR_2[225] and $AlMe_3$[226] groups have been detected in the corresponding derivatives of amides.



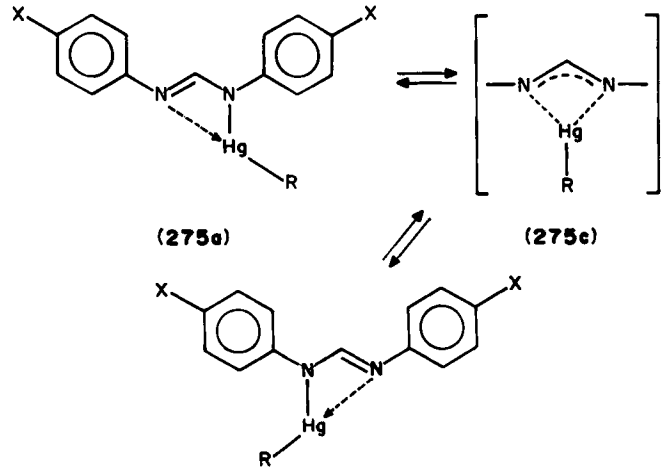
(107)

(274a) (274b)

R = n-Pr, *i*-Bu

In the ^1H, ^{13}C and ^{19}F NMR spectra of methyl- and phenylmercury derivatives of *N*,*N'*-diarylformamidines **275**, the indicator groups X are isochronic down to the temperature of $-100\,°C$[197]. This spectral behavior may be accounted for by either a fast, on the NMR time scale, exchange **275a** ⇄ **275b** or by the existence of the compounds in the stable symmetrical form **275c** (equation 108), resembling **261**. The latter explanation contradicts the X-ray diffraction study[197] according to which the phenylmercury derivative of *N*,*N'*-di-*p*-tolylformamidine (**275**; X = Me, R = Ph) exists in the crystalline

state as the structure **275a** where the Hg atom has the T-shaped configuration with one covalent ($r = 2.13$ Å) and one dative ($r = 2.68$ Å) Hg—N bond.



(275a) **(275c)**

(275b)

(108)

X = Me, OMe, F; R = Ph, Me

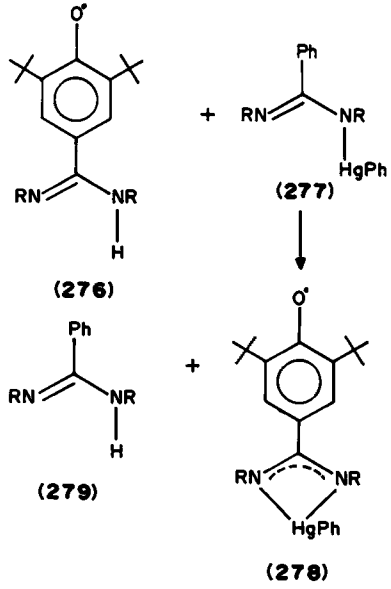
The same conclusion has been arrived at by studying the ^{19}F and ^{15}N NMR spectra of the phenylmercury derivatives of *N,N'*-bis(4-fluorophenyl)formamidine (**275**, X = F; R = Ph) and $^{15}N,^{15}N'$-diphenylformamidine (**275**, X = H; R = Ph)[227]. In the former case (in solution in a 2:3 THF–pyridine mixture), a singlet signal with $\delta = 14.14$ ppm is observed in the ^{19}F NMR spectra down to $-110\,°C$. In the latter (solution in pyridine, 20 °C) the ^{15}N NMR spectrum contains one signal of ^{15}N with $\delta = 193$ ppm. No satellites caused by the ^{199}Hg and ^{15}N spin–spin coupling have been observed, which indicates very fast, on the NMR time scale, migration of the phenylmercury group in this system.

At the same time, when an amidine fragment is included in the structure of the stable phenoxyl radical **278**, the **261** bonding type can be realized. The compound **278** is obtained[228] in the interaction of *N,N'*-di-*p*-tolyl-*tert*-butylbenzamidine phenoxyl (**276**) with *N*-phenylmercury-*N,N'*-di-*p*-tolylbenzamidine (**277**) in THF at room temperature when, by an intermolecular exchange, the proton is replaced by the phenylmercury fragment (equation 109). On the ESR time scale (the characteristic time is within the 10^{-4}–10^{-8} s range), compound **278** behaves as possessing C_{2v} symmetry[228].

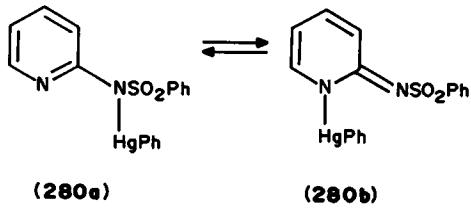
1,3-Rearrangements of transition and main-group metal-centered groups have been described[198,229–233] that proceed in compounds in which the amidine triad is incorporated in a heterocycle.

Making use of the UV (visible) adsorption spectroscopy, nondegenerate 1,3-*N,N'*-displacement of the phenylmercury group has been studied[229] in phenylmercury derivatives of 2-phenylsulfonylaminopyridine (**280**). The coexistence in acetonitrile solution of aminopyridine (**280a**) and pyridone imine (**280b**) tautomeric forms of compound **280** has been shown as well as their interconversion by way of *N,N'*-migration of the phenylmercury moiety (equation 110). The dependence of the ratio between the tautomers on the character of the solvent has been established.

Whereas the trimethylsilyl derivative of 2-pyridone (**281**, $MR_n = SiMe_3$) exists exclusively in the form of the O—Si derivative **281a**[230], in the case of the phenylmercury,

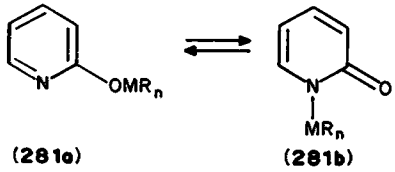


(109)

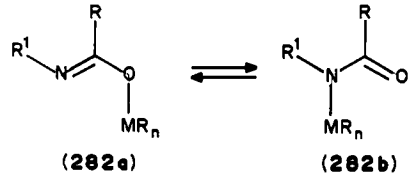


(110)

triaryltin, triaryllead and diarylantimony derivatives of 2-pyridone **281**[231,232] and of amides **282**[231,233], dynamic tautomeric equilibria take place (equations 111 and 112). The phenylmercury derivatives **281**, **282** (MR_n = HgPh) exist in solution predominantly as the O-derivatives **281a**, **282a**, while the triaryllead and tin derivatives **281**, **282** (MR_n = $PbAr_3$,



(111)

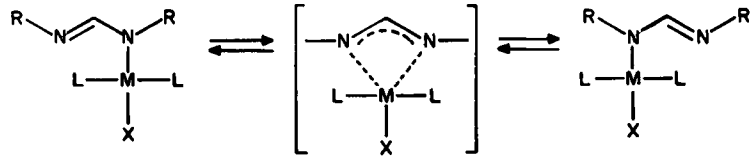


(112)

MR_n = HgPh, $SnAr_3$, $PbAr_3$, $SbAr_2$

$SnAr_3$) are more stable in the tautomeric forms **281b**, **282b** in which the organometallic group is bonded to nitrogen. Thio analogs of the compounds **281**, **282** exist, in the solid state and solution alike, exclusively as S-derivatives **281a**, **282a**[231,233].

It has been revealed by dynamic ^{1}H NMR that the di-(*p*-tolyl)formamidine Pt and Pd complexes of the monodentate σ-N bonding **283** type[195, 234] exhibit in solution fluxional behavior associated with intramolecular low-energy metal 1,3-shifts in the amidine triad. The process (equation 113) proceeds via the pentacoordinate intermediate **283c** in which both nitrogen atoms form σ-bonds with the metal using their electron lone pairs.

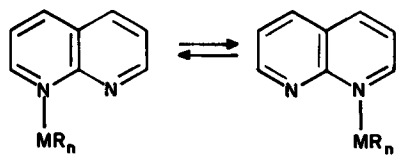


(113)

(283a) **(283c)** **(283b)**

R = 4-Tol; M = Pt, Pd
L, L, X = $C_6H_3(CH_2NMe_2)_2$-2,6[195]
L = PPh_3; X = H, Cl[234]

An analog of the metallotropic transformations of amidines (equation 113) is represented by fast reversible intramolecular 1,3-*N*,*N*′-shifts of organometallic groups in the 1,8-naphthyridine system studied[235–237] by dynamic ^{1}H NMR. In compounds **284** the fastest migrations (equation 114) between the nitrogens of the naphthyridine cycle occur in the case of the Au-centered group[236] whose intramolecular migrations **284a** ⇄ **284b** could be 'frozen' only at −90 °C.

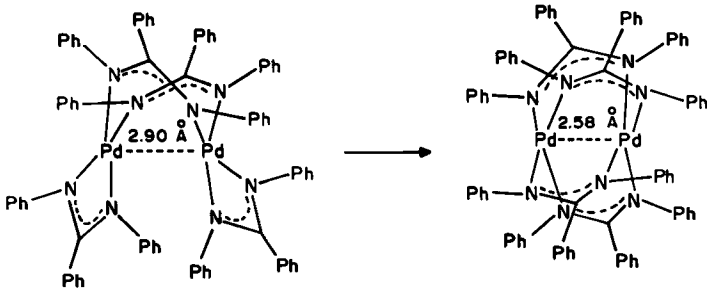


(114)

(284a) **(284b)**

MR_n = $Cr(CO)_5$, $W(CO)_5$[235]
Me_2AuX (X = Hal, OCN, SeCN)[236]
$Pt(PEt_3)Cl$[237]

An intermolecular shift of Pd in the amidine system takes place in the course of the irreversible rearrangement **285** → **286** (equation 115). An X-ray diffraction study has shown[203] that the complex **285** {[(dpb)Pd]$_2$(μ-dpd)$_2$} contains two Pd^{II} ions bridged by two *N*,*N*′-diphenylbenzamidine (dpd) ligands with an additional dpb moiety chelated to each of the metals forming four-membered rings. Due to steric hindrance caused by the chelating ligands, the Pd atoms in the complex **285** are spaced 2.90 Å apart so that no covalent Pd···Pd bond exists. When the complex **285** is refluxed in methanol (2 h), the two chelating ligands rearrange to form the tetra-bridged complex **286** [Pd_2(μ-dpb)$_4$] in 40% yield in which the Pd···Pd distance is reduced to 2.58 Å permitting the binding of these atoms.



(285) (286) (115)

V. OTHER REARRANGEMENTS

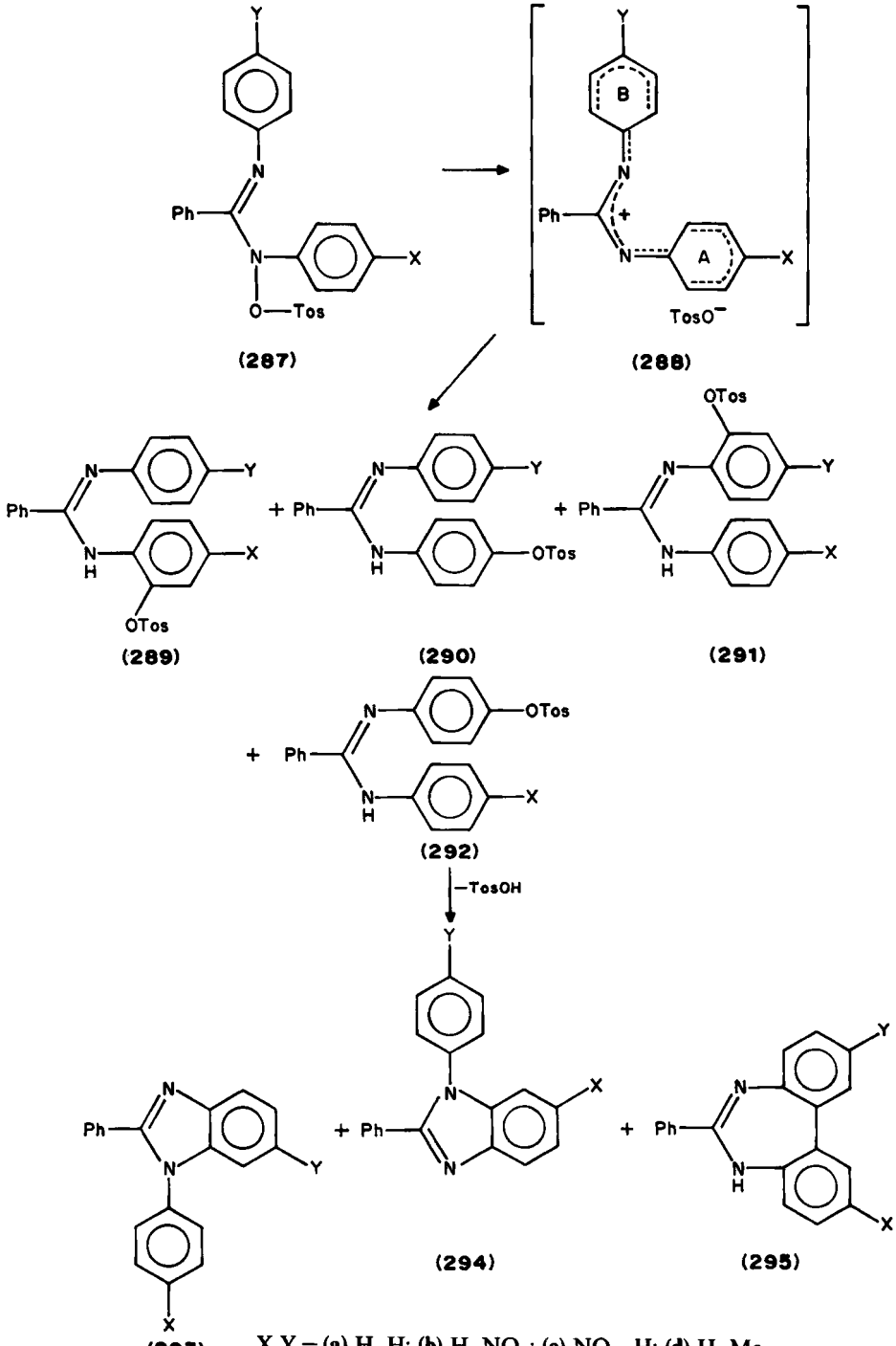
Of course, the 1,3- and 3,3-migrations do not represent all the types of molecular rearrangements inherent in amidines, imidates and related compounds. Next we examine, by no means claiming to exhaust the subject, some other cases not reducible to the above migrations as well as rearrangements that lead to cyclization.

A. Migration of Groups N-Anchored to Aromatic Rings

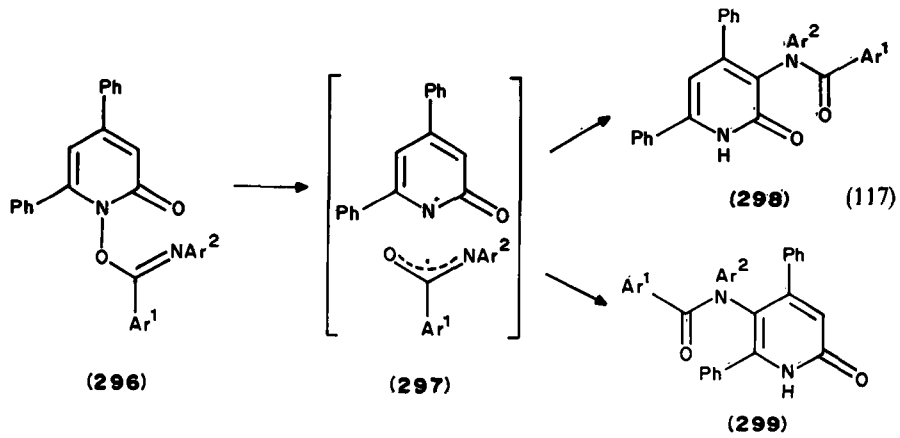
Such migration is characteristic of O-centered groups attached to amidine or imidate nitrogen. So *N*-tosyloxy-*N,N'*-diarylbenzamidines **287**, under mild conditions ($CHCl_3$, 10 °C), readily undergo N → C displacements of the tosyloxy group to the *ortho*-carbons in both *N*-aryl rings[238]. In addition to the rearrangement products **289**, **291**, the products of substitution **290**, **292** are also formed when in **287** X or Y = NO_2 (equation 116). The ratio between the products **289** and **292** is dependent upon the substituents X and Y.

The mechanism of the reaction (equation 116) studied by ^{15}N and ^{18}O labeling experiments implies heterolytic ionization of the N—O bond with the formation of the intermediate tight ion-pair structure **288**, which then undergoes intramolecular rearrangement. In the case of amidines **287a,d**, a particular memory effect is evidenced in that the rearrangement (equation 116) proceeds regioselectively, i.e. the tosyloxy group attacks the *ortho* position of the neighboring aromatic ring (A) to produce compounds **289a,d**, respectively. This behavior is explained by the structure of the tight ion pair **288** in which the recombination of counter-ions takes place faster than the migration to the remote aromatic nucleus (B). In the case of compounds **287b,c** containing an NO_2 group in one of the *N*-aryl rings, the memory effect is outbalanced by the electronic effect of the substituent so that both *ortho* and *para* isomers are formed. Like benzamidines **104** and **232**, the compounds **289–292** are readily cyclized with the elimination of TosOH to give a mixture of benzimidazoles **293**, **294** and 1,3-diazepine **295** whose relative yields strongly depend on the substituents X, Y.

In contrast to the rearrangement (equation 116), the photoinitiated rearrangement of 1-imidoyloxy-4,6-diphenyl-2-pyridones **296**[239,240] (MeCN, irradiation at $\lambda_{max} = 254$ and 350 nm) follows, according to References 241 and 242, a homolytic N—O bond fission pathway (equation 117) resulting in the formation of the radical pair **297** and subsequent displacement of the imidoyl radical to the 3 and 5 positions of the pyridine ring. This mechanism (which may also be explained in terms of the Doering biradicaloid mechanism of 3,3-sigmatropic shifts; see References 241 and 242) was suggested by the effect the substituents in the imidoyl fragment have on the ratio between the products **298**, **299** as well as by the formation of a number of by-products of the rearrangement.

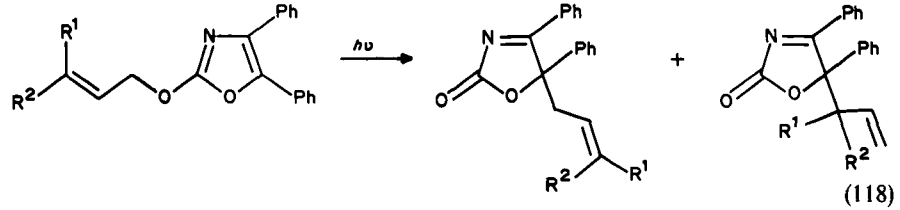


X,Y = (a) H, H; (b) H, NO_2; (c) NO_2, H; (d) H, Me



(296) (297) (298) (299) (117)

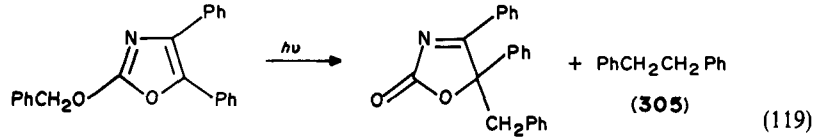
It is argued that the free-radical mechanism of the photoinduced O,C-shift of allyl groups with a transient loose radical pair is also responsible for the rearrangement of 2[(2-butenyl)-oxy]-4,5-diphenyloxazolone (**300a**) leading to the formation of 5-allyl-4,5-diphenyl-3-oxazolinones (**301a**, 83% and **302a**, 17%)[119,120]. The rearrangement (equation 118) is regiospecific. The isomers **301** are formed in higher yields than **302**, which is due to steric hindrance when the transient allyl radical approaches the heterocyclic radical formed upon homolytic photodissociation of **300** from the side shielded by substituents.



(300) (301) (302) (118)

(a) $R^1=H, R^2=Me$ (b) $R^1=R^2=Me$

The radical mechanism of the transformations (equation 119) is corroborated by results of the photochemical rearrangement of 2-(benzyloxy)-4,5-diphenyloxazole (**303**)[120] which produces oxazolinone **304** and bibenzyl **305**.



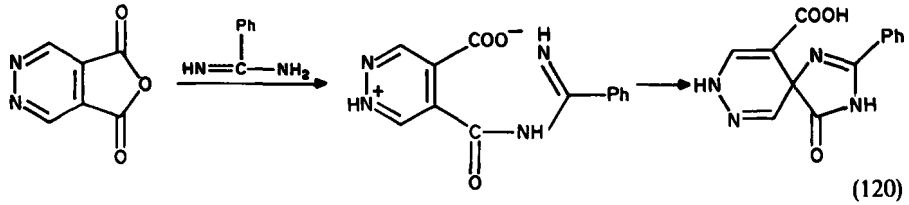
(303) (304) (305) (119)

B. Rearrangements Resulting in Cyclization

This class of rearrangements can be divided into two groups. One of these comprises processes in which the ring closure is a direct act of the amidine or imidate rearrangement,

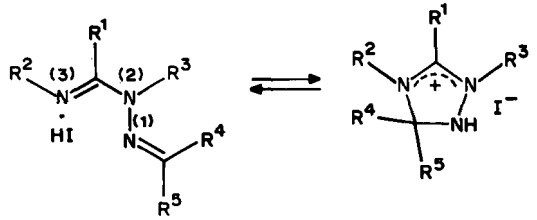
the other consists of the rearrangements of amidines or imidates that lead to compounds with such a position of functional groups as to provide conditions for further development of the ring closure reaction.

Rearrangements of the former type may be exemplified by the formation, in good yields, of derivatives of 1,3,7,8-tetraazaspiro[4,5]decane **308** from the interaction of pyridazine-4,5-dicarboxy anhydride (**306**) with 1,3 binucleophiles (substituted guanidines, thioureas and benzamidines) under mild conditions[243] (equation 120).



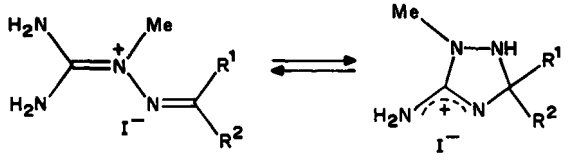
(306) (307) (308) (120)

For salts of arylideneamidrazones **309** (R^1 = Ph), using ^1H and ^{13}C NMR, the ring-chain tautomeric equilibrium 1-arylidenamidrazone (**309a**) ⇄ 1,2,4-triazoline (**309b**) has been observed[244] (equation 121). The presence of a substituent at the $N_{(2)}$ atom facilitates the formation of the cyclic form **309b** (R^1 = Ph, R^2 = H, $R^3 = R^4 = R^5$ = Me), while in its absence the form **309a** prevails (R^1 = Ph, $R^2 = R^3 = R^4 = R^5$ = H). The substituents R^2, R^4, R^5 exert little influence on the position of the ring-chain equilibrium.



(309a) (309b) (121)

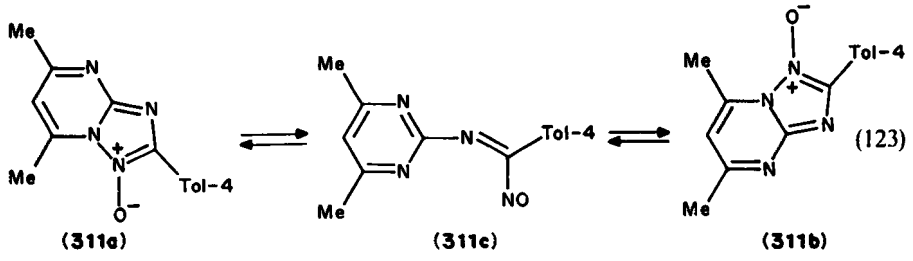
Methyguanylhydrazonium iodides **310** also undergo a ring-chain rearrangement of this type[245]. They can exist in solution in a chain form **310a**, a cyclic form **310b** or as a mixture of both of them (equation 122). The arylidene derivatives **310** (R^2 = Ar) exist in solution exclusively as the chain tautomers **310a** on account of the stabilization brought about by conjugation. On the other hand, the alkylidene derivative **310** ($R^1 = R^2$ = Me) contains in DMSO at ambient temperature 47% of the chain isomer **310a** and 53% of the cyclic isomer **310b**.



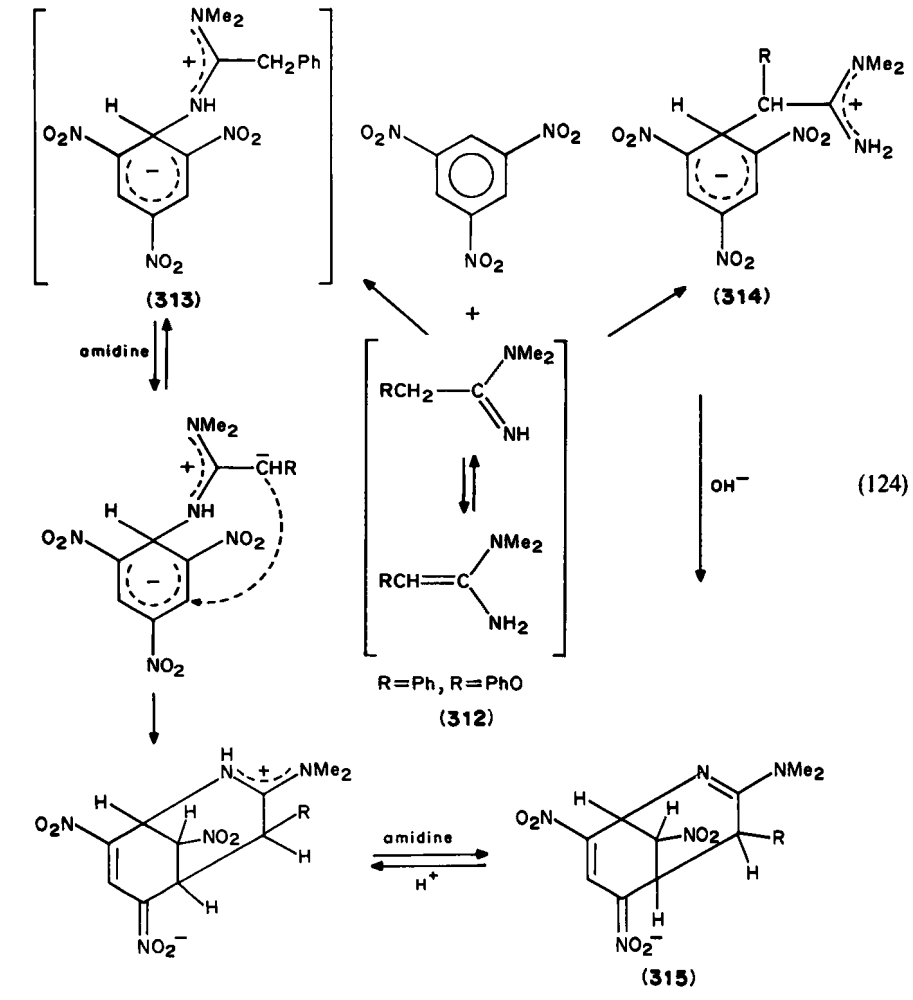
(310a) (310b) (122)

R^1, R^2 = Ar, H, Alk

A more complex ring-chain equilibrium was found to occur in *o*-dichlorobenzene solution of 5,7-dimethyl-2-(*p*-tolyl)-*S*-triazino[1,5-*f*]pyrimidine-1-oxide (**311a**), a molecule which contains a guanidine fragment[246]. The free energy barrier to degenerate isomerization was evaluated ($\Delta G^{\ddagger}_{120\,°C} = 20.2$ kcal mol^{-1}) and the formation of a nitroso imine intermediate **311c** detected (equation 123).



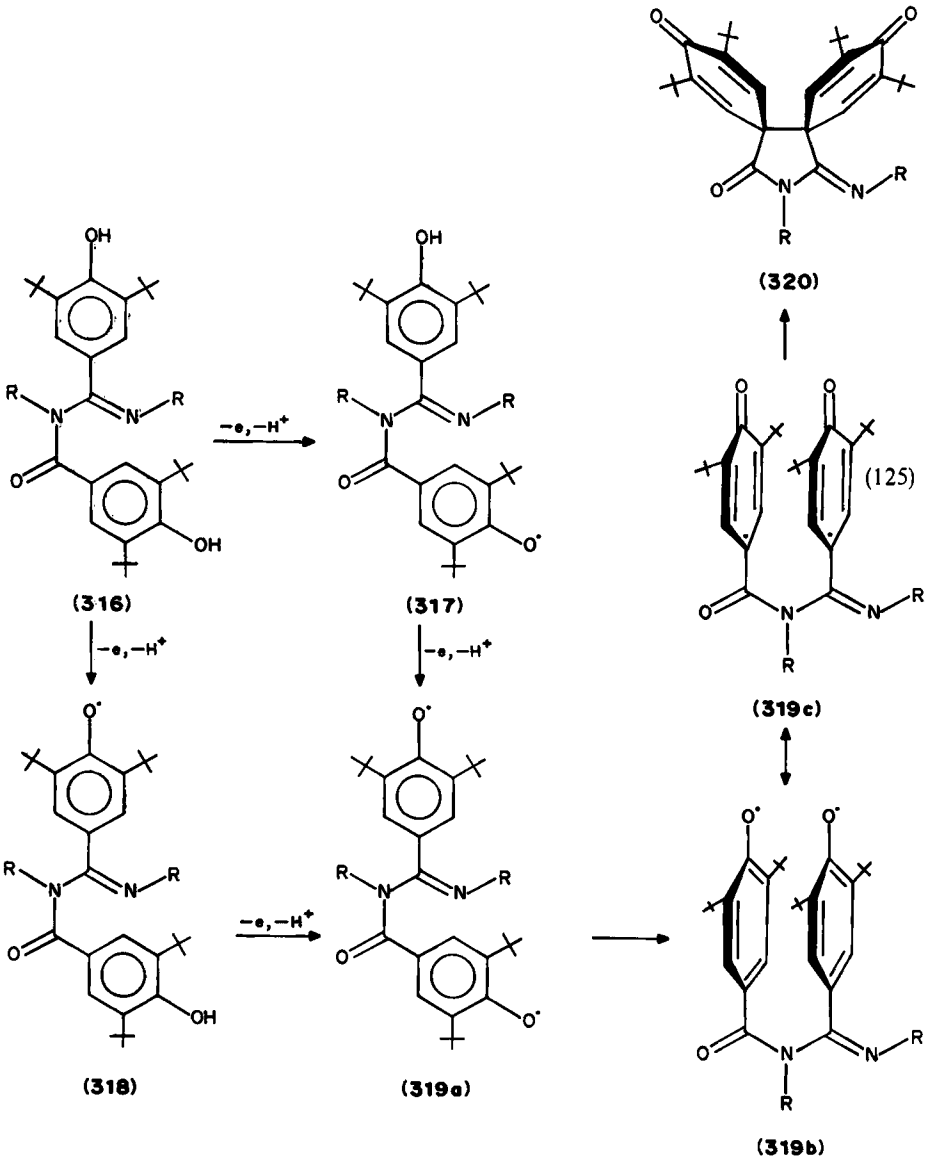
(123)



(124)

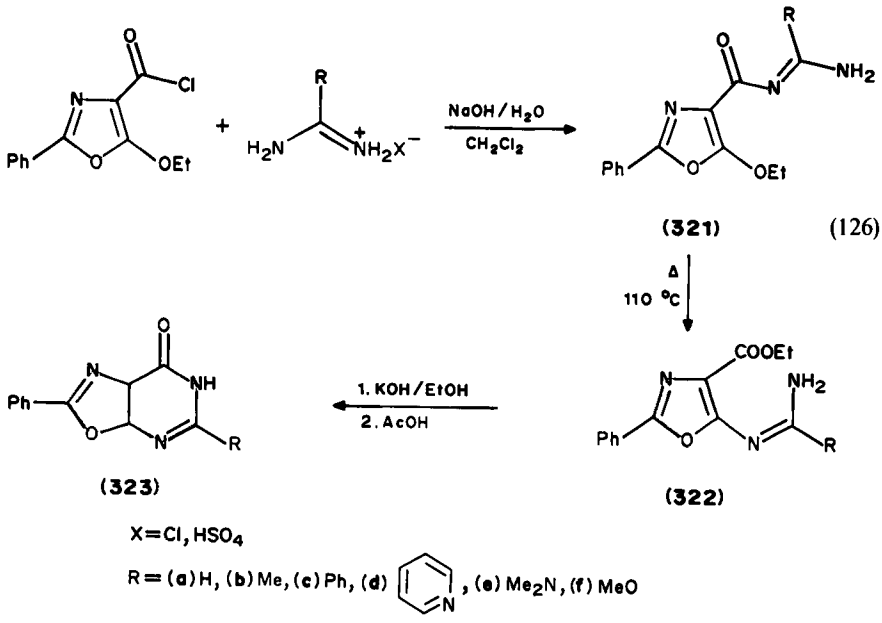
Upon interaction of trinitrobenzene and various di-, tri- and tetranitronaphthalenes with amidines **312**, the products of both N- and C-arylation are formed (**313** and **314**, respectively) which, under the action of bases (amidine or alkali), ultimately rearrange into the bicyclic adduct **315** (equation 124)[247–250]. This process is known under the general term of *meta*-bridging[251,252].

An unusual cyclization of derivatives of amidines **316** containing two phenoxyl moieties was recently reported[253]. Single-electron oxidation of **316** with ferricyanide or PbO_2 leads to the formation of stable radicals **317**, **318** giving well-resolved ESR spectra. Further oxidation results in the biradical **319** which readily undergoes ring-closure to afford a bis-



spirocyclic derivative of 2,5-pyrrolidine-2,5-dione **320** in 95% yield (equation 125). The **320** to **316** conversion can be realized by smooth reduction of **320** with $LiAlH_4$ in ether solution. The molecular structure of compound **320** was confirmed by an X-ray diffraction study[253].

Ring-closure reactions preceded by rearrangement of amidines or imidates are often very useful in synthetic practice. An illustrative example is a convenient synthesis of *N*-(5-oxazolyl) derivatives of amidines (**322a–d**), guanidine (**322e**), isourea (**322f**) and of oxazolo[5,4-*d*]pyrimid-7-ones (**323a–f**)[254]. The key step in this sequence of transformations in the intramolecular rearrangement of oxazoles **321a–f** to **322a–f** upon boiling their toluene solution (equation 126). The proposed procedure may be utilized in the preparation of some of the biologically important purine and hypoxanthine systems.



(126)

C. Rearrangements of Imidates due to Heterolytic O—C Bond Fission

These rearrangements can occur within a molecule possessing a nucleophilic center in a spatial position favorable for attack upon the imidate C_{sp^2}-center.

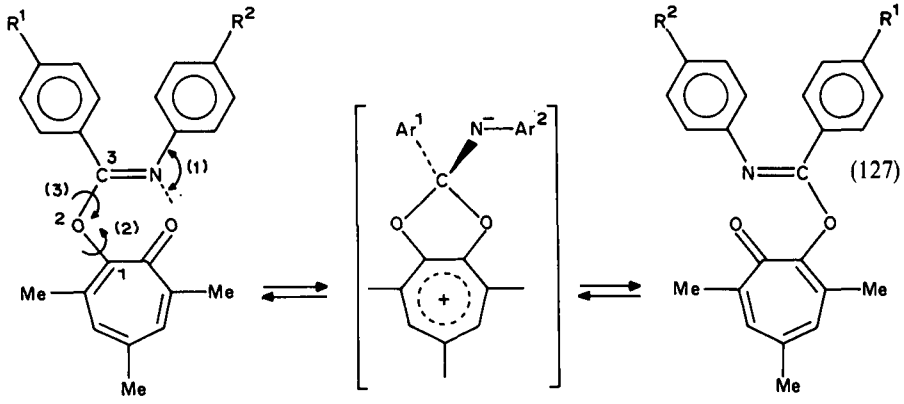
It has been shown[91] by dynamic ^1H NMR that the *O*-(*N*-phenyl)benzimidoyl derivatives of tropolone **324** exhibit fluxional behavior associated with degenerate rapid reversible intramolecular *O,O'*-migrations of imidoyl moiety that proceed by an associative mechanism via a five-membered cyclic transition state (or intermediate) **324c**.

Table 13 lists kinetic and activation parameters of the process (equation 127). Migrations of imidoyl groups in compounds **324** are accompanied by two stereodynamic processes, viz. (1) the $Z \rightleftarrows E$ inversion of the imine nitrogen and (2) hindered rotation about the bonds $C_{(1)}—O_{(2)}$ and $C_{(3)}—O_{(2)}$.

An X-ray diffraction study has shown[255,256] that the structure of compounds **324** (Nos. 3,5 in Table 13) in the solid state favors the intramolecular *O,O'*-migrations of the imidoyl groups. Indeed, the imidoyl moieties are deviated from the plane of the tropolone cycle and rotated about the $C_{(1)}—O_{(2)}$ bond by 69.8° and 48.9°, respectively. The distances between

TABLE 13. Kinetic and activation parameters of degenerate rearrangements **324a** ⇄ **324b**, according to Reference 91

No.	R^1	R^2	$k_{25°C}$ (s^{-1})	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal deg^{-1} mol^{-1})	$\Delta G^{\ddagger}_{25°C}$ (kcal mol^{-1})
1	H	H	6.4×10^2	7.4 ± 0.3	-21.1 ± 1.0	13.6
2	OMe	H	1.3×10^{-1}	15.0 ± 0.3	-12.2 ± 0.7	18.6
3	H	NO_2	1.5×10^3	8.6 ± 0.3	-15.6 ± 0.5	13.2
4	H	OMe	2.7×10^{-1}	18.2 ± 0.3	0.0 ± 0.7	18.2
5	NO_2	H	1.3×10^2	9.1 ± 0.3	-17.9 ± 1.0	14.6
6	NO_2	OMe	8.5×10	9.3 ± 0.3	-17.9 ± 1.0	14.8
7	NO_2	NO_2	4.3×10^3	8.6 ± 0.3	-12.9 ± 1.0	12.4

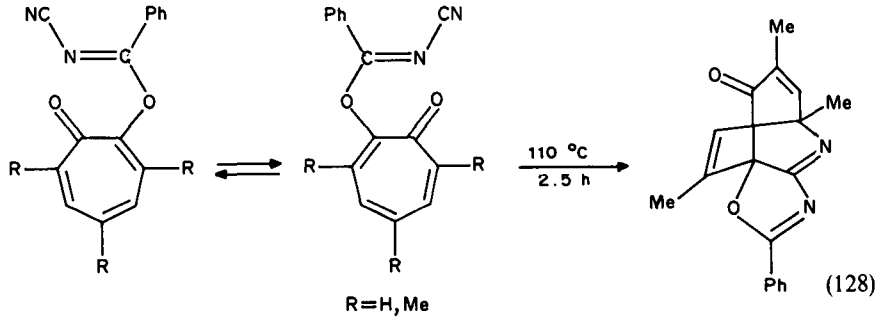


(324a) **(324c)** **(324b)**

R^1, R^2 = H, OMe, NO_2

the carbon atoms of the isoamide triad and the tropolone carbonyl oxygen atom, 2.74 Å and 2.58 Å, are shorter than the respective Van der Waals contacts.

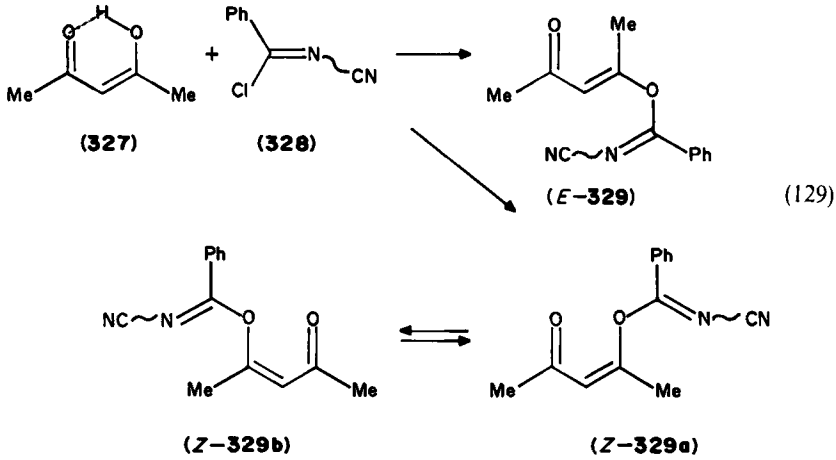
A rapid degenerate *O,O'*-migration of the (cyanoimino)alkyl group in tropolones **325** has been studied[257,258]. By heating **325** (R = Me) in boiling toluene (2.5 h) the Diels–Alder adduct **326** was formed (equation 128).



R = H, Me

(325a) **(325b)** **(326)** (128)

Similar migrations of the (cyanoimino)alkyl group have also been detected in 1,3-diketone systems[259]. So the reaction of acetylacetone **327** with *N*-cyanobenzimidoyl chloride **328** in the presence of triethylamine/dimethylaminopyridine produces a mixture of the *E*- and *Z*-isomers of the O-substitution product **329** (equation 129). A rapid degenerate intramolecular *O,O'*-migration (*Z*-**329a** ⇄ *Z*-**329b**) of the (cyanoimino)alkyl group has been shown[259] by dynamic ^{1}H NMR to occur in *Z*-**329** (equation 129).



(129)

VI. REFERENCES

1. C. G. McCarty, in *The Chemistry of the Carbon–Nitrogen Double Bond* (Ed. S. Patai), Chap. 9, Wiley, London, 1970, pp. 439–447.
2. C. G. McCarty and L. A. Garner, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Chap. 4, Wiley, London, 1975, pp. 189–241.
3. J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 1 (1965).
4. P. Beak, J. Bonham and J. T. Lee, *J. Am. Chem. Soc.*, **90**, 1569 (1968).
5. P. Beak, T. S. Woods and D. S. Mueller, *Tetrahedron*, **28**, 5507 (1972).
6. V. I. Minkin, B. Ya. Simkin and R. M. Minyaev, in *Quantum Chemistry of Organic Compounds. Mechanisms of Reactions*, Chap. 5, Springer, Berlin–Heidelberg–New York, 1990.
7. V. I. Minkin, L. P. Olekhnovich and Yu. A. Zhdanov, in *Molecular Design of Tautomeric Compounds*, Chap. 4, D. Reidel, Dordrecht–Boston–Tokyo 1988, pp. 170–220.
8. J. F. King and M. J. McGarrity, *J. Chem. Soc., Chem. Commun.*, 1140 (1979).
9. K. B. Wilberg and B. I. Rowland, *J. Am. Chem. Soc.*, **77**, 2205 (1955).
10. J. E. Baldwin, S. E. Brauz and J. A. Walker, *J. Org. Chem.*, **42**, 4142 (1977).
11. A. R. Katritzky, K. Y. Yanakopoulou, W. Kuzmierkiewicz, J. M. Auerrecoeches, G. J. Palenik, A. Koziol, M. Szczesniak and R. Skarjune, *J. Chem. Soc., Perkin Trans 1*, 2673 (1987).
12. H. Langhals, G. Range, E. Wistuba and C. Rüchardt, *Chem. Ber.*, **114**, 3843 (1981).
13. V. I. Minkin, M. E. Kletski, R. M. Minyaev, B. Ya. Simkin and V. A. Pichko, *Zh. Org. Khim.*, **19**, 9 (1983).
14. C. A. Reynolds and C. Thomson, *J. Chem. Soc., Faraday Trans. 2*, **83**, 961 (1987).
15. D. J. Young and M. J. T. Robinson, *Tetrahedron Lett.*, **28**, 3631 (1987).
16. M. Golfier and R. Milcent, *Tetrahedron Lett.*, 4465 (1973).
17. M. Dessolin and M. Golfier, *J. Chem. Soc., Chem. Commun.*, 38 (1986).
18. C. N. Sukenik, J. A. P. Bonapace, N. S. Mandel, P-Y. Lau, G. Wood and R. G. Bergman, *J. Am. Chem. Soc.*, **99**, 851 (1977).
19. A. Gavezzotti and M. Simonetta, *Chem. Rev.*, **82**, 1 (1982).
20. M. Dessolin, M. Golfier, A. Vassal and H. Szwarc, *Nouv. J. Chem.*, **10**, 753 (1986).

21. I. Paolini, M. L. Tosato and M. Cigitti, *J. Heterocycl. Chem.*, **5**, 553 (1968).
22. I. Paolini, M. Cigitti and M. L. Tosato, *Jerusalem Symp. Quantum Chem. Biochem. II*, 324 (1970).
23. M. L. Tosato, *J. Chem. Soc., Perkin Trans. 2*, 1371 (1979).
24. M. L. Tosato and L. Soccorsi, *J. Chem. Soc., Perkin Trans. 2*, 1321 (1982).
25. J. Kister, G. Assef, G. Mille and J. Metzger, *Can. J. Chem.*, **57** 813 (1979).
26. J. Kister, G. Assef, G. Mille and J. Metzger, *Can. J. Chem.*, **57**, 822 (1979).
27. V. V. Dovlatyan, K. A. Eliazyan and L. G. Agadzhanyan, *Khim. Geterocycl. Soedin.*, 262 (1977).
28. V. V. Dovlatyan, K. A. Eliazyan and A. V. Dovlatyan, *Khim. Geterocycl. Soedin.*, 989 (1977).
29. V. V. Dovlatyan, A. V. Dovlatyan, K. A. Eliazyan and R. G. Mirzoyan, *Khim. Geterocycl. Soedin.*, 1420 (1970).
30. V. V. Dovlatyan and A. V. Dovlatyan, *Khim. Geterocycl. Soedin.*, 124 (1979).
31. H. L. Wheeler, T. B. Johnson and D. F. McFarland, *J. Am. Chem. Soc.*, **25**, 790 (1903).
32. N. E. Patricio, R. C. Hernau, P. A. Hernau and M. V. Amelia, *Bol. Soc. Chil. Quim.*, **27**, 227 (1982).
33. D. Y. Curtin and L. L. Miller, *J. Am. Chem. Soc.*, **89**, 637 (1967).
34. H. B. Bürgi, *Angew. Chem., Int. Ed. Engl.*, **14**, 460 (1975); *Tetrahedron*, **30**, 1563 (1974).
35. H. B. Bürgi and J. D. Dunitz, *Acc. Chem. Res.*, **16**, 153 (1983).
36. Reference 7, Chap. 2. pp. 50–134.
37. V. I. Minkin, L. P. Olekhnovich and Yu. A. Zhdanov, *Acc. Chem. Res.*, **14**, 210 (1981).
38. V. I. Minkin, *Pure Appl. Chem.*, **61**, 661 (1989).
39. B. Ya. Simkin, M. E. Kletski, R. M. Minyaev and V. I. Minkin, *Zh. Org. Khim.*, **19**, 3 (1983).
40. V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, I. E. Mikhailov and V. P. Metlushenko, *Zh. Org. Khim.*, **11**, 448 (1975).
41. V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, I. E. Mikhailov, V. P. Metlushenko, N. M. Ivanchenko and N. I. Borisenko, *Zh. Org. Khim.*, **12**, 1261 (1976).
42. L. P. Olekhnovich, I. E. Mikhailov, N. M. Ivanchenko, V. P. Metlushenko, Yu. A. Zhdanov and V. I. Minkin, *Zh. Org. Khim.*, **14**, 340 (1978).
43. V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, V. V. Kiselev, M. A. Voronov and Z. N. Budarina, *Zh. Org. Khim.*, **9**, 1319 (1973).
44. S. B. Bulgarevich, T. A. Yusman, O. A. Lukova, L. P. Olekhnovich, I. E. Mikhailov, D. Ya. Movshovich and V. I. Minkin, *Zh. Obsch. Khim.*, **57**, 1357 (1987).
45. E. P. Ivachenko, A. I. Shif, A. I. Prokofyev, L. P. Olekhnovich and V. I. Minkin, *Zh. Org. Khim.*, **25**, 357 (1989).
46. E. P. Ivachnenko, A. I. Prokofyev, A. I. Shif, L. P. Olekhnovich, V. I. Minkin and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2113 (1988).
47. D. Y. Curtin and J. H. Engelman, *J. Org. Chem.*, **37**, 3439 (1972).
48. I. C. Paul and D. Y. Curtin, *Acc. Chem. Res.*, **6**, 217 (1973); *Science*, **187**, 19 (1975).
49. A. F. Hegarty and M. T. McCormark, *J. Chem. Soc., Chem. Commun.*, 168 (1975).
50. M. T. McCormark and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1701 (1976).
51. D. G. McCarthy and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1080 (1977).
52. D. G. McCarthy and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1085 (1977).
53. L. M. Jackman and F. A. Cotton (Eds.), *Dynamic Nuclear Magnetic Resonance Spectroscopy*, Academic Press, New York, 1975.
54. H. Kessler, *Tetrahedron*, **30**, 1861 (1974).
55. A. V. Prosyanik, N. Yu. Koltsov and V. A. Romanenko, *Zh. Org. Khim.*, **22**, 1474 (1986).
56. F. Asano, T. Okada and W. G. Herkstroeter, *J. Org. Chem.*, **54**, 379 (1989).
57. K. Brady and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 121 (1980).
58. H. S. Rzepa, *Tetrahedron*, **37**, 3107 (1981).
59. V. A. Vinokurov, E. G. Gayevoi and R. A. Karakhanov, *Dokl. Acad. Nauk SSSR*, **304**, 358 (1989).
60. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899 (1977).
61. Reference 6, Chap. 2.
62. R. F. Pratt and T. G. Bruice, *Biochemistry*, **10**, 3178 (1971).
63. H. G. Khorana, *Chem. Ind. (London)*, 1087 (1955).
64. F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev.*, **67**, 107 (1967).
65. A. F. Hegarty, M. T. McCormark, G. Ferguson and P. J. Roberts, *J. Am. Chem. Soc.*, **99**, 2015 (1977).
66. N. N. Melnikov, *Khimiya i Teknologiya Pesticidov*, Izdatelstvo Khimiya, Moscow, 1974, p. 377.

67. R. F. Pratt and T. C. Bruice, *J. Am. Chem. Soc.*, **94**, 2823 (1972).
68. J. Kovalek, J. Novak and V. Sterba, *Coll. Czech. Chem. Commun.*, **47**, 2702 (1982).
69. J. Kovalek, S. F. Banaie and V. Sterba, *Coll. Czech. Chem. Commun.*, **49**, 2103 (1984).
70. J. Kovalek, J. Jirman and V. Sterba, *Coll. Czech. Chem. Commun.*, **50**, 766 (1985).
71. J. Kovalek, J. Jirman, V. Machacek and V. Sterba, *Coll. Czech. Chem. Commun.*, **53**, 593 (1988).
72. K. Yamoda, K. Kishikawa, S. Kohmoto and M. Yamamoto, *Chem. Lett.*, 351 (1988).
73. G. Zinner, H. G. Scheeker and W. Hever, *Chem-Ztg.*, **103**, 175 (1979).
74. O. Mumm, H. Hesse and H. Volquartz, *Chem. Ber.*, **48**, 379 (1915).
75. B. F. Cain, R. N. Seelye and G. J. Atwell, *J. Med. Chem.*, **17**, 922 (1974).
76. J. Cymerman-Craig and J. W. Loder, *J. Chem. Soc.*, 4309 (1955).
77. M. Kimura, *J. Chem. Soc., Perkin Trans. 2*, 205 (1987).
78. V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, I. E. Mikhailov, N. M. Ivanchenko and Z. N. Budarina, *Dokl. Akad. Nauk SSSR*, **219**, 357 (1974).
79. V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, I. E. Mikhailov, V. P. Metlushenko and N. M. Ivanchenko, *Zh. Org. Khim.*, **12**, 1271 (1976).
80. I. E. Mikhailov, V. I. Minkin, L. P. Olekhnovich, V. N. Boiko, N. V. Ignatyev and L. M. Yagupolski, *Zh. Org. Khim.*, **20**, 454 (1984).
81. Z. Rappoport and R. Ta-Shma, *Tetrahedron Lett.*, 5281 (1972).
82. J. S. McKennis and P. A. S. Smith, *J. Org. Chem.*, **37**, 4173 (1972).
83. P. Jalobsen and S. Tuppendaul, *Tetrahedron*, **33**, 3137 (1977).
84. I. D. Cunningham and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 537 (1986).
85. N. G. Furmanova, *Zh. Struct. Khim.*, **28**, 122 (1987).
86. N. G. Furmanova, I. A. Verin, I. E. Mikhailov, V. I. Minkin and L. P. Olekhnovich, *Zh. Org. Khim.*, **25** (1990).
87. G. A. Artamkina, M. P. Egorov and I. P. Beletskaya, *Chem. Rev.*, **82**, 427 (1982).
88. F. Terrier, *Chem. Rev.*, **82**, 77 (1982).
89. H.-M. Wolff and K. Hartke, *Tetrahedron Lett.*, 3453 (1977).
90. H.-M. Wolff and K. Hartke, *Arch. Pharm.*, **313**, 266 (1980).
91. L. P. Olekhnovich, S. V. Kurbatov, N. I. Borisenko, Z. N. Budarina, V. I. Minkin and Yu. A. Zhdanov, *Zh. Org. Khim.*, **23**, 1813 (1987).
92. O. Mumm and F. Möller, *Chem. Ber.*, **70**, 2214 (1937).
93. R. P. Lutz, *Chem. Rev.*, **84**, 205 (1984).
94. S. J. Rhoads and N. R. Raulings, in *Organic Reactions*, Vol. 22, Chap. 1, Wiley, New York, 1975, pp. 1–252.
95. H. Heimgartner, H.-J. Hansen and H. Schmid, in *Iminium Salts in Organic Chemistry* (Eds. H. Böhme and H. G. Viehe), Part 2, Wiley, New York, 1979, 658 pp.
96. H.-J. Hansen and H. Schmid, *Tetrahedron*, **30**, 1959 (1974).
97. N. M. Prezhevalski and I. I. Grandberg, *Usp. Khim.*, **56**, 814 (1987).
98. L. E. Overman, *Acc. Chem. Res.*, **13**, 218 (1980).
99. S. Blechert, *Synthesis (BDR)*, 71 (1989).
100. L. E. Overman, *J. Am. Chem. Soc.*, **98**, 2901 (1976).
101. Yu. Yamamoto, H. Shimoda, J. Oda and Yu. Inouye, *Bull. Cem. Soc. Jpn.*, **49**, 3247 (1976).
102. L. E. Overman and P. J. Jessup, *J. Am. Chem. Soc.*, **100**, 5179 (1978).
103. L. E. Overman and P. J. Jessup, *Tetrahedron Lett.*, 1253 (1977).
104. L. E. Overmann and C. Fukaya, *J. Am. Chem. Soc.*, **102**, 1454 (1980).
105. S. Knapp and P. V. Pafel, *Tetrahedron Lett.*, **23**, 3539 (1982).
106. G. Cardillo, M. Orena, G. Parzi and S. Sandri, *J. Chem. Soc., Chem. Commun.*, 1308 (1982).
107. G. Cardillo, M. Orena and S. Sandri, *J. Chem. Soc., Chem. Commun.*, 1489 (1983).
108. L. E. Overman, S. Tsubai, J. P. Roos and G. F. Taylor, *J. Am. Chem. Soc.*, **102**, 747 (1980).
109. L. E. Overman and S. Tsuboi, *J. Am. Chem. Soc.*, **99**, 2813 (1977).
110. L. E. Overman, *Angew. Chem.*, **96**, 567 (1984).
111. F. E. Zigler, *Chem. Rev.*, **88**, 1423 (1988).
112. T. S. Schenek and B. Bosnich, *J. Am. Chem. Soc.*, **107**, 2058 (1985).
113. Y. Tamaru, M. Kagotani and L. Yoshida, *Tetrahedron Lett.*, **22**, 4245 (1981).
114. P. Metz and C. Muec, *Tetrahedron*, **44**, 6841 (1988).
115. G. Balvonine and F. Guibe, *Tetrahedron Lett.*, 3949 (1979).
116. M. Mizutani, Y. Sanemitsu, Y. Tamary and L. Yoshida, *J. Org. Chem.*, **48**, 4585 (1983).
117. M. Mizutani, Y. Sanemitsu, Y. Tamary and L. Yoshida, *Heterocycles*, **21**, 515 (1984).

118. H. Kohn and J. H. Arconeaux, *J. Org. Chem.*, **42**, 2339 (1977).
119. A. Padwa and L. A. Cohen, *Tetrahedron Lett.*, **23**, 915 (1985).
120. A. Padwa and L. A. Cohen, *J. Org. Chem.*, **49**, 399 (1984).
121. H.-M. Wolff and K. Hartke, *Arch. Pharm.* **313**, 215 (1980).
122. V. I. Minkin, I. E. Mikhailov and G. A. Dushenko, *J. Chem. Soc., Chem. Commun.*, 1182 (1988).
123. I. E. Mikhailov, G. A. Dushenko, O. E. Kompan and V. I. Minkin, *Zh. Org. Khim.*, in press.
124. N. S. Zefirov and D. I. Makhon'kov, *Chem. Rev.*, **82**, 615 (1982).
125. M. E. Kletski, R. M. Minyaev and V. I. Minkin, *Zh. Org. Khim.*, **16**, 686 (1980).
126. I. E. Mikhailov, G. A. Dushenko and V. I. Minkin, unpublished work.
127. C. Eisenbrand in *N-Nitrosoverbindungen, in Nahrung und Umwelt*, Wissenschaft, Verlag, Stuttgart, 1981.
128. M. T. Nguyen and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 345 (1987).
129. K. A. Jorgensen, *J. Org. Chem.*, **50**, 4758 (1985).
130. D. L. H. Williams, in *The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives* (Ed. S. Patai), Chap. 4, Wiley, Chichester, 1982, pp. 127–153.
131. B. Eistert, *Angew. Chem.*, **54**, 99 (1941).
132. S. Secyoshi and S. Kamiya, *Chem. Pharm. Bull.*, **29**, 1267 (1981).
133. I. E. Mikhailov, G. A. Dushenko, I. A. Kamenetskaya and V. I. Minkin, unpublished work.
134. E. Carvalho, J. Iley and E. Rosa, *J. Chem. Soc., Chem. Commun.*, 1249 (1988).
135. G. Toth and B. Podanyi, *J. Chem. Soc., Perkin Trans. 2*, 91 (1984).
136. A. Nemes and G. Toth, *Acta. Chim. Acad. Sci. Hung.*, **87**, 257 (1975).
137. G. Toth, A. Nemes, J. Tamas and J. Volford, *Acta Chim. Acad. Sci. Hung.*, **88**, 319 (1976).
138. R. Luckenbach, *Dynamic Stereochemistry of Pentacoordinated Phosphorus and Related Elements*, G. Thieme, Stuttgart, 1973.
139. F. H. Westheimer, *Acc. Chem. Res.*, **1**, 70 (1968).
140. Reference 7, Chap. 3, pp. 135–169.
141. V. I. Minkin, *Sov. Sci. Rev. B, Chem.* **7**, 51 (1985).
142. S. Trippett, *Pure Appl. Chem.*, **40**, 595 (1974); *Phosphorus and Sulfur*, **1**, 89 (1976).
143. R. S. McDowell and A. Streitwieser, *J. Am. Chem. Soc.*, **107**, 5849 (1985).
144. T. Winkler, W. Philipsborn, J. Stroh, W. Silhan and E. Zbiral, *J. Chem. Soc. (D)*, 1645 (1970).
145. K. Hartke and H.-M. Wolf, *Chem. Ber.*, **113**, 1394 (1980).
146. K. Mislow, *Acc. Chem. Res.*, **3**, 321 (1970).
147. M. Mikolajczyk, P. Kielbasinski and A. Sut, *Tetrahedron*, **42**, 4591 (1986).
148. A. N. Pudovik and M. G. Zimin, *Usp. Khim.*, **52**, 1803 (1983).
149. H. G. Khorana, *Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest*, Wiley, New York, 1961.
150. D. M. Braun, in *Advances of Organic Chemistry*, Vol. 3 (Ed. I. L. Knunyants), Mir, Moscow, 1966, p. 79.
151. C. Blonski, M. B. Gasc, A. Klaebe, J. J. Perie, R. Rogues, J. P. Declercq and G. Germain, *J. Chem. Soc., Perkin Trans. 2*, 7 (1982).
152. M. G. Zimin, M. M. Afanasyev and A. N. Pudovik, *Zh. Obshch. Khim.*, **49**, 2621 (1979).
153. M. G. Zimin, A. R. Burilov and A. N. Pudovik, *Zh. Obshch. Khim.*, **51**, 469 (1981).
154. M. G. Zimin, R. M. Kamalov, M. M. Afanasyev and A. N. Pudovik, *Zh. Obshch. Khim.*, **56**, 2666 (1986).
155. V. V. Negrebtski, L. Ya. Bogelfer, A. D. Sinitsa, V. I. Kalchenko, V. S. Krishtal and L. N. Markovski, *Zh. Obshch. Khim.*, **52**, 40 (1982).
156. V. V. Negrebetski, L. Ya, Bogelfer, V. I. Kalchenko, V. S. Krishtal, A. D. Sinitsa and L. M. Markovski, *Zh. Obshch. Khim.*, **50**, 2133 (1980).
157. V. V. Negrebetski, A. D. Sinitsa, V. I. Kalchenko, L. I. Atamas and L. N. Markovski, *Zh. Obshch. Khim.*, **53**, 343 (1983).
158. V. V. Negrebetski, L. Ya. Bogelfer, A. D. Sinitsa, V. S. Krishtal, V. I. Kalchenko and L. N. Markovski, *Zh. Obshch. Khim.*, **50**, 2806 (1980).
159. V. V. Negrebetski, L. Ya. Bogelfer, A. D. Sinitsa, V. I. Kalchenko, V. S. Krishtal and L. N. Markovski, *Zh. Oshch. Khim.*, **52**, 1496 (1982).
160. V. V. Negrebetski, A. F. Grapov, V. N. Zontova, V. I. Ivanchenko and N. N. Melnikov, *Dokl. Akad. Nauk SSSR*, **265**, 106 (1982).
161. V. V. Negrebetski, A. F. Grapov, V. N. Zontova, V. I. Ivanchenko and N. N. Melnikov, *Zh. Obshch. Khim.*, **53**, 312 (1983).

162. V. V. Negrebetski, L. Ya. Bogelfer, V. I. Kalchenko, V. S. Krishtal, A. D. Sinitsa and L. N. Markovski, *Zh. Obshch. Khim.*, **50**, 2420 (1980).
163. V. V. Negrebetski, Doctorate Thesis, Vses. Nauchn-Issled. Inst. Khim. Sredstv Zashch. Rast., Moscow, USSR, 1985.
164. L. Ya. Bogelfer, E. P. Goncharova, A. F. Grapov, V. V. Negrebetski, L. V. Rasvodovskaya, V. M. Englin and N. N. Melnikov, *Dokl. Acad. Nauk SSSR*, **271**, 633 (1983).
165. V. V. Negrebetski, N. N. Vorobyova, L. V. Razvodovskaya, L. Ya. Bogelfer, V. I. Ivanchenko, A. F. Grapov and N. N. Melnikov, *Zh. Obshch. Khim.*, **56**, 1764 (1986).
166. A. F. Grapov, V. V. Negrebetski, E. A. Chertopolokhova and N. N. Melnikov, *Dokl. Akad. Nauk SSSR*, **265**, 92 (1982).
167. V. V. Negrebetski, V. I. Kalchenko, R. B. Rudy and L. N. Markovski, *Zh. Obshch. Khim.*, **54**, 71 (1984).
168. V. V. Negrebetski, V. I. Kalchenko, R. B. Rudy and L. N. Markovski, *Zh. Obshch. Khim.*, **55**, 271 (1985).
169. V. V. Negrebetski, L. Ya. Bogelfer, A. D. Sinitsa, V. S. Krishtal, V. I. Kalchenko and L. N. Markovski, *Zh. Obshch. Khim.*, **51**, 956 (1981).
170. V. V. Negrebetski, O. V. Balitskaya, V. I. Kalchenko and M. Yu. Kornilov, *Zh. Obshch. Khim.*, **54**, 76 (1984).
171. V. V. Negrebetski, V. I. Kalchenko, O. V. Balitskaya, M. Yu. Kornilov and L. N. Markovski, *Zh. Obshch. Khim.*, **54**, 1764 (1984).
172. V. V. Negrebetski, V. I. Kalchenko, O. V. Balitskaya, L. N. Marvski and M. Yu. Kornilov, *Zh. Obshch. Khim.*, **56**, 114 (1986).
173. E. E. Nifantyev, M. K. Grachov and A. R. Bekker, *Zh. Obshch. Khim.*, **59**, 2127 (1989).
174. M. G. Zimin, E. V. Fomakhin, R. G. Islamov and A. N. Pudovik, *Zh. Obshch. Khim.*, **55**, 2681 (1985).
175. M. G. Zimin, E. V. Fomakhin, E. I. Goldfarb and A. N. Pudovik, *Zh. Obshch. Khim.*, **56**, 553 (1985).
176. M. G. Zimin, E. V. Fomakhin, A. N. Pudovik, L. V. Zheleznova and E. I. Goldfarb, *Zh. Obshch. Khim.*, **56**, 756 (1986).
177. V. I. Minkin, L. P. Olekhnovich and Yu. A. Zhdanov, *Zh. Vses. Khim. Obsch.*, **22**, 274 (1977).
178. P. M. Minyaev and V. I. Minkin, *Zh. Struct. Khim.*, **20**, 842 (1979).
179. N. M. Ivanchenko, Candidate Thesis, Rostov State University, Rostov on Don, USSR, 1982.
180. R. Hoffman, in *IUPAC Frontiers of Chemistry* (Ed. H. J. Laidler), Pergamon, Oxford, New York, 1982, p. 247.
181. L. P. Olekhnovich, V. I. Minkin, I. E. Mikhailov, N. M. Ivanchenko and Yu. A. Zhdanov, *Dokl. Akad. Nauk SSSR*, **233**, 874 (1977).
182. L. P. Olekhnovich, I. E. Mikhailov, N. M. Ivanchenko, Yu. A. Zhdanov and V. I. Minkin, *Zh. Org. Khim.*, **15**, 1355 (1979).
183. M. Raban, H. Chang, L. Graine and E. Hortelano, *J. Org. Chem.*, **50**, 2205 (1985).
184. K. Akiba, T. Kobayashi and S. Arai, *J. Am. Chem. Soc.*, **101**, 5857 (1979).
185. K. Akiba, A. Noda, K. Ohkata, T. A. Kiyama, Y. Murata and Y. Yamamoto, *Heterocycles*, **15**, 1155 (1981).
186. K. Akiba, S. Arai, T. Tsuchiya, Y. Yamamoto and F. Iwasaki, *Angew. Chem., Int. Ed. Engl.*, **18**, 166 (1979).
187. I. E. Mikhailov, N. M. Ivanchenko, L. P. Olekhnovich, V. I. Minkin and Yu. A. Zhdanov, *Dokl. Akad. Nauk SSSR*, **263**, 366 (1982).
188. N. Finch, S. J. Ricca, L. H. Werner and R. Rodebaugh, *J. Org. Chem.*, **45**, 3416 (1980).
189. Reference 7, Chap. 1, pp. 1–49.
190. V. I. Kalchenko, V. V. Negrebetski, R. B. Rudy, L. I. Atomas, M. I. Povolotski and L. N. Markovski, *Zh. Obshch. Khim.*, **53**, 932 (1983).
191. V. I. Kalchenko, R. B. Rudy, V. V. Negrebetski, M. I. Povolotski and L. N. Markovski, *Zh. Obshch. Khim.*, **54**, 2207 (1984).
192. V. I. Kalchenko, V. V. Negrebetski, R. B. Rudy and L. N. Markovski, *Zh. Obshch. Khim.*, **58**, 1216 (1988).
193. W. J. Hickinbottom, *Egypt. J. Chem., Spec. Issue*, 189 (1973).
194. T. Fijtt, *Rev. Phys. Chem. Jpn.*, **44**, 38 (1974).
195. D. M. Grove, G. van Koten, H. J. C. Ubbels and K. Vrieze, *J. Chem. Soc., Dalton Trans.*, 717 (1986).

196. O. J. Scherer and P. Hornig, *Chem. Ber.*, **101**, 2533 (1968).
197. M. G. Kuzmina, N. G. Boki, Yu. T. Struchkov, V. I. Minkin, L. P. Olekhnovich and I. E. Mikhailov, *Zh. Struct. Khim.*, **18**, 122 (1977).
198. L. A. Fyodorov, D. N. Kravtsov and A. S. Peregudov, *Usp. Khim.*, **50**, 1304 (1981).
199. B. M. Mikhailov, *Pure Appl. Chem.*, **49**, 749 (1977).
200. E. W. Abel and J. Skittral, *J. Organomet. Chem.*, **185**, 391 (1980).
201. A. D. Robinson, S. D. Robinson, A. Sahajral and M. B. Hursthouse, *J. Chem. Soc., Dalton Trans.*, 1327 (1981).
202. E. Forsellini, U. Cassellato, R. Graziani, L. Toniolo, R. Ressi and L. Magon, *Inorg. Chim. Acta*, **61**, 255 (1982).
203. C.-L. Yao, L.-P. He, J. D. Korp and J.-L. Bear, *Inorg. Chem.*, **27**, 4389 (1988).
204. Reference 53, Chap. 11, pp. 441–487.
205. F. G. Stone and R. West (Eds.), *Adv. Organomet. Chem.*, Vol. 16, Molecular Rearrangements, 1977.
206. R. E. Wasylishen, G. S. Birdi and A. F. Janzen, *Inorg. Chem.*, 3054 (1976).
207. V. N. Torocheshnikov, N. M. Sergeeyev, N. A. Viktorov, G. S. Goldin V. G. Poddubny and A. N. Koltsova, *J. Organomet. Chem.*, **70**, 347 (1974).
208. H. J. Reich and D. A. Murcia, *J. Am. Chem. Soc.*, **95**, 3418 (1973).
209. C. Kruger, E. G. Rochow and U. Wannagat, *Chem. Ber.*, **96**, 2138 (1963).
210. C. H. Yoder and D. Bonelli, *Inorg. Nucl. Chem. Lett.*, **8**, 1027 (1972).
211. C. Yoder, W. C. Copenhafer and B. DuBeshter, *J. Am. Chem. Soc.*, **96**, 4283 (1974).
212. A. Komoriya and C. H. Yoder, *J. Am. Chem. Soc.*, **94**, 5285 (1972).
213. W. C. Copenhafer, B. DuBeshter and C. H. Yoder, *J. Am. Chem. Soc.*, **96**, 4286 (1974).
214. K. Itoh, M. Katsuda and Y. Ishii, *J. Chem. Soc. (B)*, 302 (1970).
215. B. Dejak and Z. Lasocki, *J. Organomet. Chem.*, **246**, 151 (1983).
216. B. Dejak, Z. Lasocki and H. Jancke, *Bull. Pol. Acad. Sci., Chem.*, **33**, 275 (1985).
217. M. D. Fryzuk and P. A. MacNeil, *J. Am. Chem. Soc.*, **106**, 6993 (1984).
218. J. F. Klebe, *J. Am. Chem. Soc.*, **90**, 5246 (1968).
219. J. F. Klebe, *Acc. Chem. Res.*, **3**, 299 (1970).
220. M. Fukui, K. Itoh and Y. Ishii, *J. Chem. Soc., Perkin Trans. 2*, 1043 (1972).
221. C. L. Hausman and C. H. Yoder, *J. Organomet. Chem.*, **161**, 313 (1978).
222. J. Matsuda, K. Itoh and Y. Ishii, *J. Chem. Soc., Perkin Trans. 2*, 1678 (1972).
223. K. Itoh, N. Kato and Y. Ishii, *J. Organomet. Chem.*, **22**, 49 (1970).
224. A. G. Brook and A. R. Bassindale, in *Rearrangements in Ground and Excited States*, Vol. 2 (Ed. P. de Mayo), Chap. 9, Academic Press, New York, 1980, pp. 149–221.
225. W. Maringgele and A. Meller, *J. Organometal. Chem.* **141**, 241 (1977).
226. T. Hirabayshi, T. Sakakibara and Y. Ishii, *J. Organomet. Chem.*, **32**, C5 (1971).
227. E. B. Borisov, Candidate Thesis, Inst. Elem. Org. Soed. Akad. Nauk SSSR, Moscov, USSR, 1983.
228. E. P. Ivachnenko, I. E. Mikhailov, V. I. Minkin, A. I. Prokofyev and M. I. Kabachnik, *Dokl. Akad. Nauk SSSR*, **288**, 1117 (1986).
229. D. N. Kravtsov, *Dokl. Akad. Nauk SSSR*, **162**, 581 (1965).
230. L. Birkofer, A. Ritter and H. P. Kühlthau, *Chem. Ber.*, **97**, 934 (1964).
231. D. N. Kravtsov and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1747 (1967).
232. A. N. Nesmeyanov, L. Alfonso, D. N. Kravtsov and B. V. Lokshin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 296 (1968).
233. A. N. Nesmeyanov, D. N. Kravtsov and E. M. Rokhlina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1038 (1968).
234. L. Toniolo, U. Croatto, A. Immirzi and G. Bombieri, *Inorg. Chim. Acta*, **19**, 209 (1976).
235. K. R. Dixon, D. T. Eadie and S. R. Stobart, *Inorg. Chem.*, **21**, 4319 (1982).
236. H. Schmidbaur and K. C. Dash, *J. Am. Chem. Soc.*, **95**, 4855 (1973).
237. K. R. Dixon, *Inorg. Chem.*, **16**, 2618 (1977).
238. N. Binding and A. Husing, *Chem. Ber.*, **116**, 1822 (1983).
239. A. R. Katritzky, A. V. Chapman, M. J. Cook and G. H. Millet, *J. Chem. Soc., Chem. Commun.*, 395 (1979).
240. A. R. Katritzky, A. V. Chapman, M. J. Cook and G. H. Millet, *J. Chem. Soc., Perkin Trans. 1*, 2743 (1980).
241. W. v. E. Doering, V. G. Toscano and G. H. Beasley, *Tetrahedron*, **27**, 299 (1971).

242. M. J. S. Dewar and C. Jie, *J. Am. Chem. Soc.*, **109**, 5893 (1987).
243. S. Chimichi, R. Nesi and M. Nesi, *J. Chem. Soc., Perkin Trans. 1*, 2491 (1984).
244. V. A. Khrustalyov, V. P. Sergutina, K. N. Zelenin and V. V. Pinson, *Khim. Geterocycl. Soedin.*, 1264 (1982).
245. K. N. Zelenin, V. P. Sergutina, O. V. Solod and V. V. Pinson, *Khim. Geterocycl. Soedin.*, 1071 (1987).
246. T. L. Gilchrist, C. J. Hannis, C. J. Moady and C. W. Rees, *J. Chem. Soc., Chem. Commun.*, 486 (1974).
247. M. J. Strauss and F. Terrier, *Tetrahedron Lett.* 313 (1979).
248. R. R. Bard and M. J. Strauss, *J. Org. Chem.*, **41**, 2421 (1976).
249. M. J. Strauss and R. R. Bard, *J. Org. Chem.*, **43**, 3600 (1978).
250. F. Terrier, A.-P. Chatrousse and M. J. Strauss, *J. Org. Chem.*, **49**, 4172 (1984).
251. M. J. Strauss, *Acc. Chem. Res.*, 7, 381 (1974).
252. S. S. Gitis and A. Ya. Kaminskii, *Usp. Khim.*, **47**, 1970 (1978).
253. V. I. Minkin, E. P. Ivachnenko, A. I. Shif, L. P. Olekhnovich, O. E. Kompan, A. I. Yanovskii and Yu. T. Struchkov, *J. Chem. Soc., Chem. Commun.*, 990 (1988).
254. K. Smith and L. French, *Synthesis*, **10**, 837 (1983).
255. N. G. Furmanova, V. I. Andrianov and T. N. Safonova, *Kristallografia*, **32**, 1530 (1987).
256. N. G. Furmanova, L. P. Olekhnovich, V. I. Andrianov, A. V. Lesin, Z. N. Budarina, S. V. Kurbatov, V. I. Minkin and Yu. A. Zhdanov, *Zh. Org. Khim.*, **24**, 903 (1988).
257. K. Hartke, W. F. Richter, W. Massa and G. Baum, *Tetrahedron Lett.*, **27**, 2743 (1986).
258. K. Hartke, W. F. Richter, W. Massa and G. Baum, *Chem. Ber.*, **122**, 657 (1989).
259. K. Hartke, W. F. Richter and T. Kämpchen, *Chem. Ber.*, **122**, 669 (1989).

CHAPTER 12

Basicity, H-bonding, tautomerism and complex formation of imidic acid derivatives

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I. INTRODUCTION

Tautomerism, H-bonding and complex formation of amidines all depend on their acid–base properties. Hydrogen bonding between amidine molecules and tautomerism are strictly related, but hydrogen bonding with another proton-donating compound is discussed separately in the section on complexes.

In the section on basicity, the influence of substitution at various sites of the functional group on pK_a values is discussed in terms of correlations with Hammett-type substituent constants or with pK_a values of corresponding amines. In such cases regression coefficients are given with confidence intervals calculated at a significance level of 0.95, except when a literature source did not state which values of the independent variables (σ) were used.

Comparability of the pK_a values is very important for the investigations on structure–basicity relations. The pK_a values of many amidines reported in the literature were measured in various solvents, such as methanol, ethanol, water, acetonitrile and water–ethanol or water–cellosolve mixtures because their solubility in water is insufficient for the purpose. However, the pK_a value of any compound depends on the solvent, or on the composition of binary solvents. As the most convenient solvent for pK_a determinations 95.6% ethanol was recommended[1,2] because, as an azeotrope, it always possesses the same composition. Investigations on relations between pK_a values of amidines or the ρ values and the solvent parameters are quite recent[3–5] and no general conclusions may as yet be drawn.

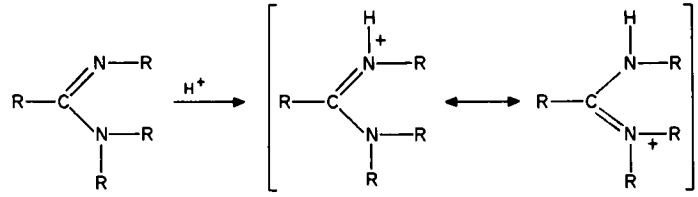
It is well known that the reliability of conclusions based on comparison of ρ values depends on the number of compounds in the series, as well as on the range of the substituent effects. Another substantial factor to which not enough attention is paid, is the comparability of the series. Since the regression line very seldom passes through all the experimental points, and usually it is only the 'line of the best fit', it is obvious that addition or subtraction of some experimental points may alter the slope of a regression line. Therefore, for some series several ρ values are given, one for the whole series studied and the others for shorter sets.

In addition to the commonly used correlation coefficient r, an additional estimator—Exner's ψ function[6]—is often given, since the latter takes into account also the number of experimental points and hence provides more reliable information about the goodness of fit. For example, considering just two experimental points, the correlation coefficient r is equal to unity, suggesting ideal correlation, but according to Exner's ψ function it is immediately seen that the quality of the correlation is very poor.

In each section, wherever possible, ambiguities of the literature data or their interpretation are discussed and some suggestions or assumptions are presented. It is the author's hope that these assumptions will serve as starting points for new investigations in the field.

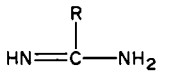
II. BASICITY

The amidino group contains an amino nitrogen atom with a free electron pair conjugated with the π-electrons of the C=N double bond. On protonation of the imino nitrogen atom, a resonance-stabilized symmetrical amidinium ion **1** is obtained, and therefore amidines are strong bases.



(1)

Depending on the substitution at both nitrogen atoms, amidines are classified into various general types: unsubstituted (**2**), monosubstituted (**3**), symmetrically *N*,*N*′-disubstituted (**4a**), unsymmetrically *N*,*N*′-disubstituted (**4b**), N^1,N^1-disubstituted (**5**) and trisubstituted (**6**) amidines.



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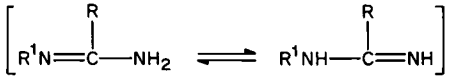
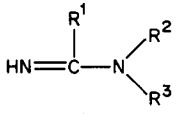


(3)

(4a)

(4b)



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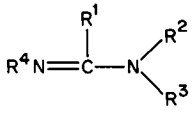


(6)

N,*N*′-Disubstituted amidines in general are often erroneously called symmetrical, however this name should be used only for amidines where substituents at both nitrogen atoms are identical. On the other hand N^1,N^1-disubstituted amidines (**5**) are sometimes called unsymmetrical amidines, but this should be avoided as it may lead to confusion with **4b**.

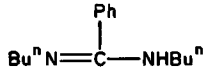
Only trisubstituted and N^1,N^1-disubstituted amidines (**5** and **6**) do not undergo prototropic tautomerization. All other amidines may exist in two tautomeric forms. For unsubstituted (**2**) and symmetrically disubstituted (**4a**) amidines tautomerization is usually neglected, since in these cases both tautomeric forms are identical. However, when considering their pK_a values, this tautomerization should be taken into account (cf. Section II.B.1).

For years it was not entirely clear which of the two nitrogen atoms is being protonated as a result of salt formation. Even in the review on basicity of amidines published in 1975 in

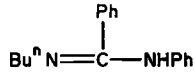
this series[7] it was stated: 'it is impossible to decide which of the two nitrogen atoms is being protonated, even though some sources state that the protonation occurs at the sp^2 nitrogen'. After that review was written, all reliable experimental results, such as the pK_a values of amidines compared with those of amines[8], the ρ values obtained for correlations of pK_a values with substituent constants at both nitrogen atoms[9-12], as well as analysis of the IR spectra of amidines and their salts[13] indicated unambiguously that protonation occurs at the imino nitrogen atom. Even so, in a recent paper[14] as a result of intricate discussion of the UV and IR spectra of N^1,N^1-dimethyl-N^2-(1-anthraquinono) amidines, the rather surprising conclusion was drawn that protonation occurs at the dimethylamino group, i.e. at the amino nitrogen atom.

Investigations on quantitative relations between basicity and the structure of amidines are comparatively recent. In the above-mentioned review[7] it was concluded that the basicity of amidines increases in the order: trisubstituted amidines; N,N'-disubstituted amidines; N-monosubstituted; N^1,N^1-disubstituted and unsubstituted amidines. But it was pointed out that 'this classification is not valid if strongly polar substituents are present at the nitrogen atoms'[7a].

In another review on amidines[15] the pK_a values (in 50% EtOH) of **7**, **8** and **9** were compared, and the conclusion was drawn that 'introduction of a phenyl group on the amino nitrogen in benzamidine causes a reduction in basicity by a factor of about 10, but the introduction of the same group on the imino nitrogen reduces the basicity by a factor of about 1000'[15].



(7)



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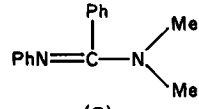


(9)

Although it seemed obvious that basicity of amidines depends on substitution at all three sites (at both nitrogen atoms and at the functional carbon atom), until the second half of the 1970s investigations on the quantitative relations between substitution and basicity were few. Only at the beginning of the eighties was a systematic study on relations between substitution at both nitrogen atoms and the functional carbon atom and the basicity of amidines undertaken by Oszczapowicz and coworkers[1-4,9-12,16-27].

A. Basicity of Trisubstituted Amidines

1. Correlations with substituent constants

Values of the pK_a of acids and bases containing a substituted phenyl ring obey the Hammett equation 1, which for pK_a values is now written[28] in the rearranged form given in equation 2.

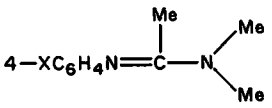
$$\lg(K/K^\circ) = \rho\sigma \tag{1}$$

$$pK_a = pK_a^\circ - \rho\sigma \tag{2}$$

In any kind of investigation on the relation between properties of organic compounds and substituent constants, the proper choice of σ values is a crucial point. In early works on the basicity of amidines their pK_a values were correlated with ordinary σ values. Only Passet[29] for monosubstituted phenylacetamidines (**10**), and later Katritzky[30] for *p*-substituted N^1,N^1-dimethyl-N^2-phenylacetamidines (**11**) have applied σ° values.

Recently Oszczapowicz and coworkers[2,24] have shown that the proper choice of parameters can be achieved by considering the possible interactions of the substituents

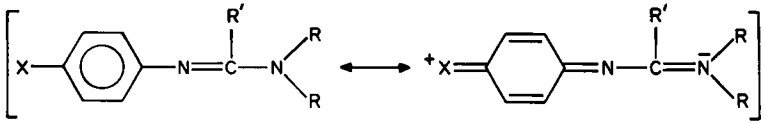
(10)



(11)

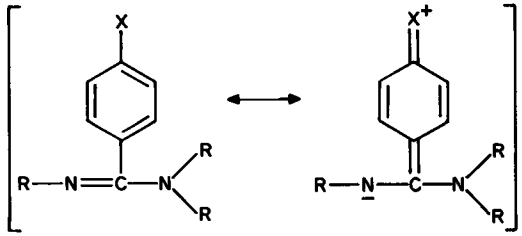
with the reaction centre. In the case of amidines there are three possible sites to which substituents may be bonded—both nitrogen atoms and the functional carbon atom.

Substituents on the phenyl ring at the amino nitrogen atom cannot conjugate with the reaction centre. Electron-withdrawing substituents at the imino nitrogen atom conjugate with the amidine system but, as shown by structure **12**, the effect of the substituent produces neither charge formation nor electron configuration on the imino nitrogen atom, which is a protonation centre.



(12)

Therefore it was concluded[2] that for amidines containing variable substituents at a phenyl ring bound to either of the nitrogen atoms, most suitable should be σ° values. Correlations for several series of amidines[2,4,5,25–27] provided good support for this conclusion. On the other hand, for substituents on the phenyl ring at the functional carbon atom, ordinary σ values are suitable, because in this case conjugation may considerably alter the electron configuration on the imino nitrogen atom (**13**). This was confirmed[24] for a series of substituted benzamidines: the best results are obtained with ordinary σ values, but for the *p*-nitro group the σ^{-} value should be used instead of σ.

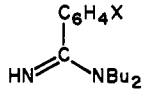


(13)

The imino nitrogen atom is the protonation site of the amidino group. Therefore it is obvious that the strongest influence on basicity will be exerted by a substituent at this atom, a smaller effect by substitution at the functional carbon and the smallest one by substitution at the amino nitrogen.

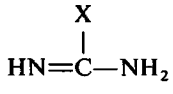
a. Substitution at the functional carbon atom. The first attempt at relating the pK_a values of amidines to substituent constants was made in 1953 by Jaffé[31] and concerned only substitution at the amidino carbon atom. Jaffé correlated σ constants with the pK_a values of N^1,N^1-dibutylbenzamidines (**14**) measured in 50% methanol by Lorz and Baltzly[32], and found that the pK_a values of the amidines obey the Hammet equation 1. The ρ values of 1.41 was obtained.

Hammett-type constants σ were introduced for compounds containing phenyl rings



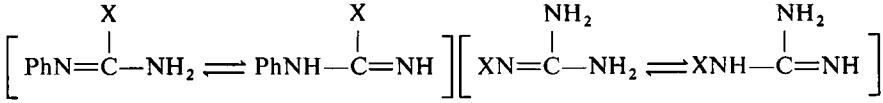
(14)

substituted in the *para* or *meta* position (or in both positions). Attempts have been made also to apply these constants to amidines which did not contain a phenyl ring. In 1965 Charton[33] collected the literature pK_a values measured in water for unsubstituted amidines (**15**), containing various substituents bonded directly to the amidine carbon atom, and attempted to establish correlations with three different sets of substituent constants: σ_m and σ_p constants taken from the compilation of McDaniel and Brown[34] and the σ_I constants (wherever possible) given by Lewis and Taft[35].

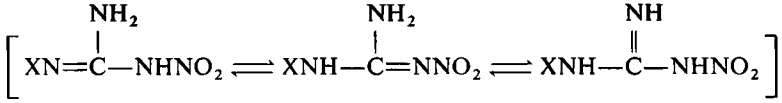


(15)

Charton has applied the same approach to monosubstituted *N*-phenylamidines (**16**), *N*-substituted guanidines (**17**) and *N*-substituted *N'*-nitroguanidines (**18**) containing various substituents bonded directly to a nitrogen atom. He found that the best correlations are obtained with σ_I values, however in the case of *N*-phenylamidines (**16**) the best results (Table 1) seemed to be obtained with σ_m values.

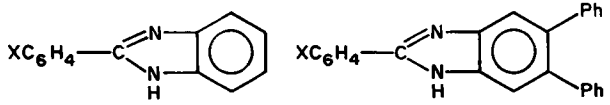


(16) (17)

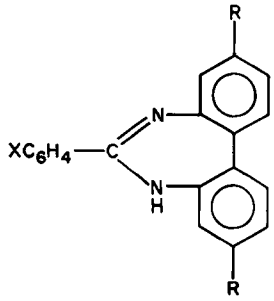


(18)

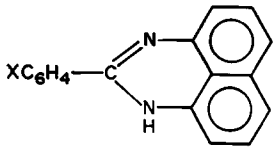
In 1968–69 Minkin and coworkers[36–38] correlated the pK_a values (Table 2) measured in anhydrous acetonitrile for various series of benzamidines, namely 2-arylbenzimidazoles[37] (**19**), 2-aryl-5,6-diphenylbenzimidazoles[37] (**20**), *N,N'*-(2,2'-biphenylene)benzamidines[36] [(**21**) referred to as 5-*H*-dibenzo-(*d,f*) (1,3)diazepines], *N,N'*-[2,2'(4,4'-dichloro-)-biphenyl]-benzamidines[36] (**22**), *N,N'*-(1,8-naphthylene)-benzamidines[38] (**23**, referred to as *meso*-arylperimidines) and *N,N'*-diphenylbenzamidines[38] (**24**).



(19) (20)



(21) R=H
(22) R=Cl



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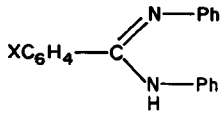


(24)

The ρ values were reported to the third decimal point, but the authors did not state confidence intervals nor the source of the σ values used. The regression parameters of these pK_a values with reliable and the most commonly used σ values[34] calculated later[19] with confidence intervals at a significance level of 0.95 (Table 3) indicated that substitution at the nitrogen atoms may influence the obtained ρ values for substitution at a phenyl ring bound to the amidino carbon atom. However, on account of considerable confidence intervals, these differences were not regarded as significant.

The ρ values reported by Charton[33] are much higher than those obtained by other authors, but it must be remembered that in the case of structures **15–16** the substituent X was directly bonded to the functional carbon atom, whereas in benzamidines the polar effects of the substituents X are transmitted through a phenyl ring.

b. Substitution at the imino nitrogen atom. In the first paper concerning the influence of substitution at the imino nitrogen atom on the basicity of amidines, Katritzky and coworkers[39] measured the pK_a values (Table 4) in water for N^1,N^1-dimethyl-N^2-arylacetamidines (**11**) anc correlated them (equation 1) with σ^-, σ and σ° constants,

TABLE 1. Parameters of regression (equation 1) of pK_a values of C-substituted amidines (**15**, **16**) and N-substituted guanidines (**17** and **18**) with various sets of substituent constants[33]

Series	σ	ρ	r	n
15	σ_I	−11.01	0.815	10
	σ_m	−11.98	0.965	10
	σ_p	−4.64	0.619	10
16	σ_I	−14.63	0.931	5
	σ_m	−12.08	0.999	5
	σ_p	−6.37	0.877	5
17	σ_I	−24.09	0.990	8
	σ_m	−17.70	0.908	8
	σ_p	−7.80	0.648	8
18	σ_I	−16.44	0.980	7
	σ_m	−8.28	0.779	7
	σ_p	−2.83	0.559	7

TABLE 2. pK_a values of benzamidines **19–24** in anhydrous acetonitrile at 25 ± 0.1 °C

X	**19**[a]	**20**[a]	**21**[b]	**22**[b]	**23**[c]	**24**[c]
p-NO_2	10.93	11.27	12.33	—	11.92	13.19
m-NO_2	11.11	—	12.47	10.69	—	13.38
m-Br	—	—	—	—	12.69	13.81
m-Cl	11.76	—	—	—	—	—
m-F	—	—	13.13	11.58	—	—
p-Br	11.98	12.31	13.35	11.80	12.84	14.05
p-Cl	12.00	—	—	—	—	—
m-OMe	—	—	13.85	12.39	—	—
p-F	—	—	13.66	—	—	—
H	12.65	12.76	13.93	12.42	13.44	14.65
p-Me	12.99	13.05	14.26	13.02	13.74	14.92
p-OMe	13.18	13.32	14.60	—	13.92	15.27
p-NMe_2	14.30	14.28	—	—	—	—

[a]Reference 36.
[b]Reference 37.
[c]Reference 38.

TABLE 3. Parameters of regression of pK_a values measured in anhydrous acetonitrile with substituent constants (equation 2) for various benzamidines[19]

Series	pK_a°	ρ (lit)	Ref.	ρ	r
19	12.57	2.124	36	2.12 ± 0.11	0.998
20	12.76	1.880	36	1.88 ± 0.09	0.999
21	13.93	2.118	37	2.12 ± 0.22	0.992
22	12.53	2.591	38	2.59 ± 0.46	0.998
23	13.40	1.920	37	1.88 ± 0.23	0.996
24	14.62	1.873	38	1.87 ± 0.24	0.994

TABLE 4. pK_a values of *N*-aryl-amidines (**11**) in water at 25 ± 0.1 °C[39]

X =	H	OMe	NO_2	Me	CN	Cl	COOEt
pK_a =	9.85	11.15	7.42	10.81	7.70	9.28	8.69

obtaining the following results:

with σ^- values: $\rho = -0.948$, $r = 0.979$;
with σ values: $\rho = -3.60$, $r = 0.999$;
with σ° values: $\rho = -3.36$, $r = 0.992$.

Thus it was found that σ or σ° rather than σ^- values should be used for correlations 'however, discussion on the relative merits of using σ or σ° values for the range of substituents in the series **11** hardly seems meaningful'[39].

Later it was found that the ρ value for substitution at the imino nitrogen atom is not identical for various series of amidines. Ševčik7[b,40] found a ρ value of 2.48 for pK_a values of N^1,N^1-(pentamethylene-1,5)-N^2-phenylbenzamidines (**25**) measured in 50% ethanol.

TABLE 5. pK_a values of N^1,N^1-pentamethylenebenzamidines **25** in binary ethanol–water solutions at 25 ± 0.1 °C[3]

R[x]	99.98%EtOH	95.6%EtOH	50%EtOH
m-C_6H_4Br	6.38 ± 0.04	5.93 ± 0.08	5.61 ± 0.10
m-C_6H_4Cl	6.45 ± 0.06	6.00 ± 0.08	5.65 ± 0.05
p-C_6H_4Br	6.65 ± 0.05	6.23 ± 0.08	5.93 ± 0.09[a]
p-C_6H_4Cl	6.77 ± 0.07	6.37 ± 0.05	6.05 ± 0.06[b]
m-$C_6H_4OCH_3$	7.35 ± 0.06	6.92 ± 0.08	6.57 ± 0.09
m-$C_6H_4OC_2H_5$	7.58 ± 0.05	6.91 ± 0.05	6.47 ± 0.09
C_6H_5	7.45 ± 0.05	6.89 ± 0.14	6.67 ± 0.03[c]
m-$C_6H_4CH_3$	7.72 ± 0.08	7.14 ± 0.07	6.84 ± 0.03
p-$C_6H_4CH_3$	7.90 ± 0.03	7.49 ± 0.04	7.04 ± 0.03[d]
p-$C_6H_4OC_2H_5$	8.17 ± 0.03	7.57 ± 0.04	7.20 ± 0.04
p-$C_6H_4OCH_3$	8.19 ± 0.04	7.71 ± 0.05	7.19 ± 0.04
$CH_2C_6H_5$		9.75 ± 0.05	
Cyclohexyl		10.60 ± 0.05	
Isopropyl		10.72 ± 0.09	

[a] 7.10 ± 0.05 (Reference 7b).
[b] 6.44 ± 0.09 (Reference 7b).
[c] 7.56 ± 0.05 (Reference 7b).
[d] 7.86 ± 0.04 (Reference 7b).

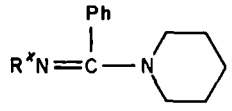
TABLE 6. Parameters of regression of pK_a values of N^1,N^1-pentamethylenebenzamidines **25** in binary ethanol–water solutions with substituent constants[3]

Solvent	pK_a°	ρ	r
99.98% EtOH	7.50	2.80 ± 0.48	0.995
99.98% EtOH	7.45	2.85 ± 0.23	0.996[a]
95.6% EtOH	6.99	2.69 ± 0.42	0.979
95.6% EtOH	6.95	2.72 ± 0.29	0.993[a]
50% EtOH	6.63	2.49 ± 0.32	0.986
50% EtOH	6.60	2.52 ± 0.19	0.996[a]

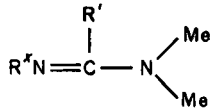
[a] Without the *m*-alkoxy derivatives.

Since the difference of ρ values can be attributed to solvent effects, Oszczapowicz and coworkers[3] compared the basicities of amidines of these series in three different binary solvents (Table 5).

It was found that the relation between pK_a of the amidine and percent composition of water–ethanol mixtures, contrary to that for carboxylic acids, is not linear. The pK_a values were correlated with Hammett σ constants (Table 6). The pK_a values of *m*-alkoxyphenyl benzamidines evidently deviate from the obtained relation, and correlations without this derivative are of considerably higher quality. Similar deviations for *m*-alkoxy derivatives are observed also with other N^2-arylamidines[1,9,10,12,16,17,23] and N^2-aryltetramethylguanidines[11]. It was assumed[1] that the σ value given in literature for the *m*-alkoxy substituent does not fit this group of compounds. The differences between pK_a values as well as the ρ values (Table 6) show that, for investigations on structure–basicity relations, the same solvent should be used to ensure comparability of the results.



(25)



(26) R′ = H
(27) R′ = Me

It was found that for N^1,N^1-dimethylformamidines[1] (**26**, Table 7) and N^1,N^1-dimethylacetamidines[2] (**27**, Table 8) different ρ values are obtained. The pK_a values of three types of amidines (**26**, **27** and **25**) obtained in various solvents (Table 9) were correlated both with σ and with σ° values. The test of parallelism for regression lines, calculated for amidines containing identical substituents in both compared series, disclosed that the slopes of the regression lines are undoubtedly different. Thus it was concluded[2] that the sensitivity of the amidine group to substitution on the phenyl ring at the imino nitrogen atom depends on the substitution on the functional carbon atom. The pK_a values of amidines containing two variable substituents do not obey the linear equation 3, where σ_{Im} and σ_{Am} relate to substituents at imino and amino nitrogen atoms, respectively. In such cases some additional term, accounting for the changes of the observed ρ value, should be introduced.

$$pK_a = pK_a^\circ - \rho_{Im}\sigma_{Im} - \rho_{Am}\sigma_{Am} \tag{3}$$

TABLE 7. pK_a values of N^1,N^1-dimethylformamidines **26** in 95.6% ethanol at 25 ± 0.1 °C[1]

R^x	pK_a
p-$C_6H_4NO_2$	5.25 ± 0.05
m-C_6H_4Br	6.45 ± 0.05
m-C_6H_4Cl	6.50 ± 0.03
p-C_6H_4Br	6.69 ± 0.05
p-C_6H_4I	6.75 ± 0.04
p-C_6H_4Cl	6.84 ± 0.07
m-$C_6H_4OCH_3$	7.45 ± 0.07
m-$C_6H_4OC_2H_5$	7.45 ± 0.04
C_6H_5	7.45 ± 0.05
m-$C_6H_4CH_3$	7.63 ± 0.04
p-$C_6H_4CH_3$	7.75 ± 0.05
p-$C_6H_4OC_2H_5$	7.83 ± 0.05
p-$C_6H_4OCH_3$	7.91 ± 0.08
p-$CH_2C_6H_4NO_2$	9.25 ± 0.09
p-$CH_2C_6H_4Cl$	9.71 ± 0.06
$CH_2C_6H_5$	10.04 ± 0.05
m-$CH_2C_6H_4OCH_3$	10.14 ± 0.02
p-$CH_2C_6H_4CH_3$	10.28 ± 0.03
i-Butyl	10.70 ± 0.08
n-Hexyl	10.75 ± 0.05
n-Butyl	10.80 ± 0.05
n-Propyl	10.84 ± 0.05
Cyclohexyl	10.90 ± 0.05
Isopropyl	10.95 ± 0.05

TABLE 8. pK_a values of N^2-substituted N^1,N^1-dimethylacetamidines (**27**) in 95.6% ethanol at 25 ± 0.1 °C[2]

R^x	pK_a
p-$C_6H_4NO_2$	5.69 ± 0.02
m-C_6H_4Br	7.19 ± 0.02
m-C_6H_4Cl	7.25 ± 0.04
p-C_6H_4Br	7.55 ± 0.04
p-C_6H_4Cl	7.65 ± 0.04
m-$C_6H_4OCH_3$	8.22 ± 0.06
m-$C_6H_4OC_2H_5$	8.26 ± 0.06
C_6H_5	8.32 ± 0.07
m-$C_6H_4CH_3$	8.41 ± 0.06
p-$C_6H_4CH_3$	8.65 ± 0.06
p-$C_6H_4OC_2H_5$	8.90 ± 0.05
p-$C_6H_4OCH_3$	8.96 ± 0.08
p-$CH_2C_6H_4Cl$	11.24 ± 0.05
$CH_2C_6H_5$	11.70 ± 0.05
i-Butyl	12.30 ± 0.05
n-Hexyl	12.37 ± 0.07
n-Butyl	12.34 ± 0.05
n-Propyl	12.46 ± 0.07
Cyclohexyl	12.55 ± 0.07
Isopropyl	12.56 ± 0.05

TABLE 9. Parameters of regression of pK_a values of N^2-substituted N^1,N^1-dialkylamidines **25**, **26** and **27** with various substituent constants[2]

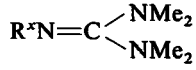
Series	σ	pK_a°	ρ	r	n	Solvent	Based on data from Ref.
26	σ°	7.46	2.60 ± 0.28	0.990	11	95.6% EtOH	1
	σ	7.39	2.52 ± 0.40	0.973	13	95.6% EtOH	1
	σ°	8.13	2.65 ± 0.25	0.998	6	water	40
	σ	8.08	2.55 ± 0.22	0.998	6	water	40
27	σ°	8.32	3.08 ± 0.27	0.994	10	95.6% EtOH	2
	σ	8.29	3.00 ± 0.38	0.984	12	95.6% EtOH	2
	σ°	10.20	3.51 ± 0.49	0.993	7	water	39
	σ	10.10	3.57 ± 0.36	0.996	7	water	39
25	σ°	7.04	2.90 ± 0.38	0.990	9	95.6% EtOH	2
	σ	7.00	2.66 ± 0.37	0.984	11	95.6% EtOH	3
	σ°	6.67	2.70 ± 0.30	0.992	9	50% EtOH	3
	σ	6.63	2.49 ± 0.32	0.986	11	50% EtOH	3
	σ°	7.52	2.38 ± 0.73	0.946	9	50% EtOH	40
	σ	7.45	2.34 ± 0.70	0.948	9	50% EtOH	40

Additional evidence for this conclusion was provided by the pK_a values of N^2-substituted tetramethylguanidines[11] (**28**, Table 10), where a ρ value of 2.28 ± 0.4 was found. Guanidines can be regarded as amidines containing an amino group at the amidino carbon atom, and thus the differences between the ρ values also indicated that sensitivity

TABLE 10. pK_a values of N^2-alkyl-tetramethyl-guanidines (**28**) in 95% ethanol at 25 ± 0.1 °C[11]

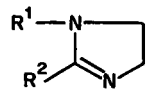
R^x	pK_a
m-ClC_6H_4	10.55 ± 0.02
p-ClC_6H_4	10.98 ± 0.02
m-$MeOC_6H_4$	11.44 ± 0.03
m-$EtOC_6H_4$	11.38 ± 0.02
C_6H_5	11.52 ± 0.07
m-MeC_6H_4	11.74 ± 0.01
p-MeC_6H_4	11.94 ± 0.04
p-$EtOC_6H_4$	12.08 ± 0.03
p-$MeOC_6H_4$	12.16 ± 0.02
Benzyl	14.19 ± 0.04
n-Hexyl	14.95 ± 0.07
n-Butyl	14.83 ± 0.10
Cyclohexyl	15.18 ± 0.06

to substitution at one site of the amidine group may depend on substitution at another site.

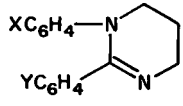


(**28**)

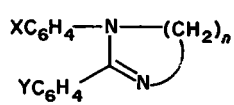
c. Substitution at the amino nitrogen atom. Perillo, Fernández and Lamdan[8,41,42] measured pK_a values (Tables 11–13) for three series of cyclic *N*-arylamidines, namely 1,2-diaryl-2-imidazolines[8] (**29**), 1,2-diaryl-1,4,5,6-tetrahydropyrimidines[41] (**30**), 1,2-diaryl-4,5,6,7-tetrahydro-1*H*-1,3-diazepines[42] (**31**, $n = 4$) and 1,4,5,6,7,8-hexahydro-1,3-diazocines[42] (**31**, $n = 5$).



(**29**)



(**30**)



(**31**)

The pK_a values of imidazolines **29** were compared[8] to those of the corresponding arylamines and it was shown that the pK_a values of the imidazolines are a few p*K* units higher, indicating that protonation occurs at the imino nitrogen atom. The ρ value obtained for the correlation of the pK_a values with Hammett σ constants ($\rho = 1.28$) was compared with that for anilines ($\rho = 2.73$) and for amidines **14** ($\rho = 1.41$). This comparison provided further support for the conclusion that protonation occurs at the imino nitrogen atom. The authors also noticed that the further the substituent is from the imino nitrogen atom, the lower is the ρ value obtained.

For tetrahydropyrimidines **30** a ρ value of 0.948 was obtained[41]. Even though the substituted phenyl ring in **30** was at the same distance from the protonation site as in the imidazolines, i.e. at the amino nitrogen atom, this ρ value was considerably lower, but this fact was not discussed.

Comparison[42] of the pK_a values of the **31** homologs have shown that the basicity of cyclic amidines depends to a considerable degree on the ring size, decreasing in the order:

TABLE 11. pK_a values for cyclic benzamidines **29**[41]

R^1	R^2	pK_a
Ph	Ph	9.26
4-An	Ph	9.64
3,4-$(MeO)_2C_6H_4$	Ph	9.55
4-$EtOC_6H_4$	Ph	9.60
4-HOC_6H_4	Ph	9.62
4-Tol	Ph	9.48
3-Tol	Ph	9.36
4-ClC_6H_4	Ph	8.98
4-$NO_2C_6H_4$	Ph	7.65
2-$NO_2C_6H_4$	Ph	7.51
2,4-$(NO_2)_2C_6H_4$	Ph	6.65
1-Naph	Ph	8.67
2-Naph	Ph	8.63
Ph	4-$NO_2C_6H_4$	7.66
Ph	3-$NO_2C_6H_4$	7.75
4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	6.74

TABLE 12. pK_a values of cyclic benzamidines **30**[8]

X	Y	pK_a
H	H	11.67
4-Me	H	11.99
4-OMe	H	11.87
4-Cl	H	11.36
4-NO_2	H	10.51
2-NO_2	H	10.55
2-NO_2	4-NO_2	9.23
4-NO_2	4-NO_2	9.16

TABLE 13. pK_a values of cyclic benzamidines **31**[42]

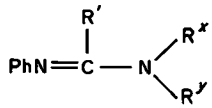
X	Y	*n*	pK_a
4-NO_2	H	4	8.43
4-NO_2	NO_2	4	7.38
2-NO_2	H	4	10.39
2-NO_2	NO_2	4	9.15
4-NO_2	H	5	7.78
4-NO_2	NO_2	5	6.75

tetrahydropyrimidines > tetrahydrodiazepines > hexahydrodiazocines > imidazolines. This decrease of basicity with decrease of the ring size was discussed in terms of possible conformations of the ring.

The pK values (Table 14) of N^2-phenylformamidines (**32**) and N^2-phenylacetamidines (**33**) containing a variable substituent in the phenyl ring at the amino nitrogen atom

TABLE 14. pK_a values of N^1,N^2-phenylformamidines (32) and N^2-phenylacetamidines (33) in 95.6% ethanol at 25 ± 0.1 °C[26]

R^x	R^y	32	33
CH_3	p-$C_6H_4NO_2$	—	5.83 ± 0.09
CH_3	m-$C_6H_4NO_2$	—	6.00 ± 0.09
CH_3	m-C_6H_4Cl	5.00 ± 0.04	6.52 ± 0.04
CH_3	p-C_6H_4Cl	5.15 ± 0.03	6.68 ± 0.02
CH_3	Ph	5.29 ± 0.05	7.00 ± 0.02
CH_3	p-Tol	5.46 ± 0.03	7.22 ± 0.02
CH_3	p-An	5.50 ± 0.06	7.37 ± 0.03
CH_3	p-C_6H_4OEt	5.72 ± 0.06	7.34 ± 0.03
CH_3	CH_2Ph	7.07 ± 0.01	9.83 ± 0.02
—$(CH_2)_2O(CH_2)_2$—		6.57 ± 0.05	9.25 ± 0.03
—$(CH_2)_5$—		7.42 ± 0.03	10.50 ± 0.04
—$(CH_2)_4$—		8.12 ± 0.04	10.60 ± 0.03



(32) R′ = H
(33) R′ = Me

were correlated[26] with σ and σ° values. The following parameters of regression were obtained:

Series	σ	pK_a°	ρ	r	ψ	n
32	σ	5.31	0.78 ± 0.14	0.9954	0.1233	5
32	σ°	5.32	0.84 ± 0.20	0.9917	0.1665	5
33	σ	7.00	1.43 ± 0.08	0.9986	0.0616	8
33	σ°	7.02	1.44 ± 0.05	0.9994	0.0401	8

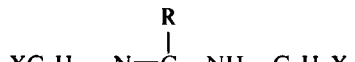
It was shown that correlations with σ° values, as expected (cf. Section II.A.1), are of higher quality. The ρ values for substitution at the amino nitrogen in formamidines and in acetamidines are lower than those for substitution at the imino nitrogen because in the former case the substituents are at a greater distance from the imino nitrogen atom, which is the protonation centre. Differences between the ρ values also show that the sensitivity of the amidino group to substituent effects at the two nitrogen atoms also depends on substitution at the amidino carbon atom. Thus, replacement of a hydrogen atom at the functional carbon atom by a methyl group (acetamidines vs formamidines) causes a 1.7-fold increase in the ρ value for substitution at the amino nitrogen atom, but only a 1.2-fold increase in the ρ value for substitution at the imino nitrogen atom.

d. Substitution at two and more sites of the amidino group. Preliminary investigations[16] of the influence of substitution at the two different sites on the basicity of amidines were carried out with the example of symmetrically disubstituted N,N'-diphenyformamidines (34) N,N'-diphenylacetamidines (35) and N,N'-diphenylbenzamidines (36) (Table 15). The

TABLE 15. pK_a values of symmetrically disubstituted *N,N'*-diphenylformamidines (34), acetamidines (35) and benzamidines (36) in 98.5% ethanol at 25 ± 0.1 °C[16]

X	34	35	36
m-Cl	5.25	6.86	5.80
p-Br	6.22	7.25	6.42
p-Cl	6.40	7.40	6.51
m-OCH_3	6.65	8.05	6.83
m-OC_2H_5	7.12	—	—
H	7.17	8.35	7.43
m-CH_3	7.43	8.28	7.78
p-CH_3	7.63	8.54	8.24
p-OC_2H_5	7.85	9.40	—
p-OCH_3	8.04	9.57	8.60

identity of both tautomeric forms in these amidines made it possible to disregard the usual problem of the contribution of the two tautomers to the measured pK_a value. The pK_a values obey the Hammett equation 2, and for the correlations with σ constants the following parameters have been obtained:



(34) R = H
(35) R = Me
(36) R = Ph

34 $pK_a^\circ = 7.12$ $\rho = 3.26 \pm 0.03$ $r = 0.996$

35 $pK_a^* = 8.29$ $\rho = 4.03 \pm 0.04$ $r = 0.991$

36 $pK_a^\circ = 7.43$ $\rho = 4.12 \pm 0.03$ $r = 0.995$

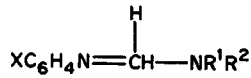
In these series it was observed for the first time that the sensitivity of the amidine group to substitution at nitrogen atoms depends also on substituents at the amidino carbon atom. Here it was also shown that explanations based on only a few compounds may lead to confusing results. Acetamidines were more basic than formamidines, in agreement with the inductive effect of the methyl group at the amidino carbon atom. However, the regression lines for benzamidines and formamidines cross each other near the σ value of 0.36. This means that benzamidines and formamidines containing strong electron-withdrawing substituents at the nitrogen atoms offer a satisfactory explanation for the influence of the negative inductive effect of the C-phenyl group causing a decrease in the basicity of the amidine group. On the other hand, benzamidines and formamidines containing less electronegative substituents at the nitrogen atoms can serve as an example that the conjugation of the C-phenyl ring with the amidine group leads to an increase in basicity.

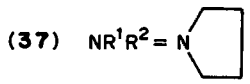
In all these series substituents at both nitrogen atoms were varied, and thus it was impossible to conclude whether, and to what extent, the changes in the observed ρ values are due to changes in the influence of substitution at imino or amino nitrogen atom or at both sites.

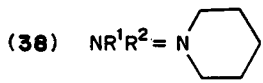
Taking into account that the pK_a values of symmetrically disubstituted *N,N'*-diphenylamidines, as well as formamidines containing only one substituted phenyl ring at

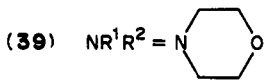
the imino nitrogen atom, obey the Hammett equation, it was concluded that the basicity of amidines containing a substituted phenyl ring at each nitrogen atom should obey the two-parameter equation 3.

Later, the influence of substitution on a phenyl ring bound to the imino nitrogen atom on the basicity of the three series of N^1,N^1-(alkylene-α,ω)-N^2-phenylformamidines **37**, **38** and **39**, containing also a cyclic secondary amine moiety, has been studied[17].









The pK_a values shown in Table 16 were correlated with σ values and the following results were obtained:

Series	pK_a°	ρ	r	n
37	9.33	2.07 ± 0.27	0.988	10
38	8.64	2.29 ± 0.24	0.992	10
39	7.71	2.05 ± 0.43	0.963	11

TABLE 16. pK_a values of N^1,N^1-(alkylene-α,ω)-N^2-arylformamidines in 98.5% ethanol at 25 ± 0.1 °C[17]

X	**37**	**38**	**39**
m-Br	8.46	7.70	6.80
m-Cl	8.52	7.83	6.96
p-Br	8.75	7.95	7.02
p-Cl	8.85	8.09	7.10
m-OCH_3	9.22	8.47	7.68
m-OC_2H_5	—	—	7.77
H	9.31	8.69	7.81
m-CH_3	9.53	8.74	7.92
p-CH_3	9.75	9.10	8.02
p-OC_2H_5	9.70	9.10	8.16
p-OCH_3	9.97	9.38	8.82

The ρ values for all three series are approximate and lower than the ρ value (2.48) obtained by Ševčik[7,40] for series of N^1,N^1-(pentylene-1,5)-benzamidines (**25**) containing the piperidine moiety, and are much lower than the ρ value found for N,N'-diphenylformamidines (**34**). Thus it was concluded[17] that the basicity of the amidino group depends to a higher degree on substitution at the imino than at the amino nitrogen atom. It was also assumed that for symmetrically N,N'-disubstituted amidines, the observed ρ value is the sum of the two ρ values for substitution at each of the nitrogen atoms.

In all three series, the pK_a values increase in the same order as the basicities of the corresponding cyclic amines built into their molecules (pyrrolidine, piperidine and morpholine).

For N^2-aryl-N^1,N^1-dialkylformamidines[4] **26**, **38** and **39** the influence of ethanol concentration on the basicity of amidines was studied (Tables 17–19). It was found that, like in the case of **25**, pK_a values are not changed linearly with solvent composition. For all amidines studied the pK_a values pass through a minimum at about 80% (w/w) of ethanol. The ρ values (Table 20) change with the solvent composition differently for each series studied. For the **26** series the ρ value passes through a minimum at about 50% (w/w) of ethanol, and for water solutions it is lower than for 95.6% ethanol. For the **38** series, on the contrary, the ρ value seems to pass through a maximum at about 80% ethanol. The strongest influence on the ρ values is observed for the **39** series, where the ρ value for 50% ethanol is much higher than for 95.6% ethanol. Determination of the quantitative relation between the pK_a values or ρ values and the solvent parameters requires a large number of experimental data and its most crucial point is the proper choice of solvent parameters.

For compounds containing two substituted phenyl rings at the two sites, the linear equation 4 is usually applied:

$$pK_a = pK_a^\circ - \rho_1\sigma_1 - \rho_2\sigma_2 \qquad (4)$$

This equation implies that for substitution at a certain site the same ρ value should be obtained in all series of compounds, no matter what kind of substituents are at other sites. However, study of various series of amidines indicated that the pK_a values of amidines

TABLE 17. pK_a values of N^1,N^1-dimethyl-N^2-arylformamidines (**26**, $R^x = XC_6H_4$) in ethanol–water solutions at 25 ± 0.1 °C[4]

X	Ethanol (w/w%)				
	95.6	80	50	30	0
p-NO_2	5.57 ± 0.05	4.88 ± 0.01	5.81 ± 0.05	6.32 ± 0.06	6.71 ± 0.03
m-NO_2	5.92 ± 0.01	5.12 ± 0.01	6.04 ± 0.01	6.94 ± 0.06	7.29 ± 0.03
m-Br	6.77 ± 0.05	6.05 ± 0.01	7.04 ± 0.04	7.60 ± 0.05	8.08 ± 0.04
m-Cl	6.82 ± 0.03	6.07 ± 0.02	6.95 ± 0.06	7.58 ± 0.05	7.97 ± 0.02
p-I	7.07 ± 0.04	6.36 ± 0.02	7.18 ± 0.02	7.84 ± 0.04	—
p-Br	7.01 ± 0.05	6.38 ± 0.01	7.27 ± 0.03	7.91 ± 0.06	8.10 ± 0.02
p-Cl	7.16 ± 0.07	6.37 ± 0.02	7.37 ± 0.02	7.89 ± 0.02	8.46 ± 0.03
m-OMe	7.77 ± 0.07	7.01 ± 0.02	7.56 ± 0.04	8.31 ± 0.05	8.60 ± 0.03
m-OEt	7.77 ± 0.04	7.06 ± 0.01	7.75 ± 0.04	8.46 ± 0.03	8.87 ± 0.04
H	7.77 ± 0.05	7.19 ± 0.08	7.59 ± 0.02	8.66 ± 0.08	9.00 ± 0.07
m-Me	7.95 ± 0.04	7.22 ± 0.02	8.07 ± 0.02	8.65 ± 0.02	9.11 ± 0.03
p-Me	8.07 ± 0.05	7.40 ± 0.02	8.15 ± 0.04	8.78 ± 0.01	9.21 ± 0.02
p-OEt	8.15 ± 0.05	7.43 ± 0.01	8.22 ± 0.02	8.74 ± 0.02	9.24 ± 0.04
p-OMe	8.23 ± 0.08	7.47 ± 0.01	8.25 ± 0.02	8.83 ± 0.06	9.35 ± 0.05

TABLE 18. pK_a values of N^1,N^1-pentamethylene-N^2-phenylformamidines (**38**) in ethanol–water solutions at 25 ± 0.1 °C[4]

	Ethanol (w/w %)			
X	95.6	80	50	30
p-NO_2	5.83 ± 0.03	4.85 ± 0.05	5.78 ± 0.03	—
m-Cl	6.83 ± 0.02	5.93 ± 0.02	6.85 ± 0.01	7.47 ± 0.04
p-Cl	7.14 ± 0.03	6.37 ± 0.03	7.16 ± 0.01	7.76 ± 0.05
m-OMe	7.75 ± 0.02	6.95 ± 0.01	7.66 ± 0.02	8.07 ± 0.07
H	7.83 ± 0.02	7.06 ± 0.02	7.86 ± 0.07	—
m-Me	7.91 ± 0.02	7.15 ± 0.03	7.91 ± 0.02	8.40 ± 0.08
p-Me	8.08 ± 0.03	7.38 ± 0.04	8.13 ± 0.07	—
p-OMe	8.25 ± 0.03	7.56 ± 0.05	8.17 ± 0.03	—

TABLE 19. pK_a values of N^1,N^1-(3-oxapentamethylene)-N^2-phenylformamidines (**39**) in ethanol–water solutions at 25 ± 0.1 °C[4]

	Ethanol (w/w %)			
X	95.6	80	50	30
p-NO_2	5.67 ± 0.05	4.45 ± 0.01	4.97 ± 0.05	—
m-Cl	5.99 ± 0.04	5.14 ± 0.02	5.92 ± 0.03	6.51 ± 0.02
p-Cl	6.27 ± 0.03	5.55 ± 0.04	6.39 ± 0.08	6.92 ± 0.04
m-OMe	6.77 ± 0.02	5.95 ± 0.01	6.86 ± 0.02	7.16 ± 0.02
H	6.76 ± 0.01	6.09 ± 0.02	6.96 ± 0.04	—
m-Me	6.99 ± 0.03	6.17 ± 0.03	7.02 ± 0.02	7.48 ± 0.03
p-Me	7.02 ± 0.01	6.31 ± 0.01	7.10 ± 0.01	—
p-OMe	7.07 ± 0.03	6.34 ± 0.03	7.12 ± 0.03	—

containing one substituent at a nitrogen atom and a second at the functional carbon atom do not obey this equation. Hence, it has been proposed[2] that the pK_a values for such amidines obey the following relationship:

$$pK_a = pK_a^\circ - \rho_1\sigma_1 - \rho_2\sigma_2 - \mu\sigma_1\sigma_2 \tag{5}$$

where σ_1 and σ_2 are the σ values of substituents on phenyl rings at the two sites and the coefficient μ represents the mutual interaction of substituents, and is responsible for the 'twist' of the regression line. This type of equation has been discussed earlier among other equations by Exner[43]. Using this equation, if the substituent at one of the sites is not varied (e.g. $\sigma_2 =$ constant) the constant $\rho_2\sigma_2$ is included in a new pK_4° value and the term $\mu\sigma_2$ in a new ρ value. As a result a linear correlation (equation 6) will be obtained, but the slope of the correlation line for each series depends on the σ value of the invariant substituent and on the term μ.

$$pK_a = pK_a^\circ - \rho_2\sigma_2 - (\rho_1 + \mu\sigma_2)\sigma_1 \tag{6}$$

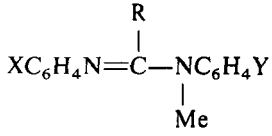
To verify this hypothesis and to determine to what extent replacement of the hydrogen at the amidino carbon increases the sensitivity of the amidino group to the effects of substitution at the nitrogen atoms, three series of trisubstituted amidines, namely N^1-methyl-N^1,N^2-diarylformamidines[9] (**40**), N^1-methyl-N^1,N^2-diarylacetamidines[19] (**41**)

TABLE 20. Parameters of regressions of pK_a values with substituent constants[4]

Series	% EtOH (w/w)	Type of σ	pK_a°	ρ	r	ψ	n
26	95.6	σ°	7.77	2.62 ± 0.21	0.993	0.126	12[a]
		σ	7.71	2.52 ± 0.33	0.979	0.221	14
		σ	7.71	2.56 ± 0.33	0.984	0.194	12[a]
	80	σ°	7.06	2.66 ± 0.22	0.993	0.127	12[a]
		σ	7.00	2.56 ± 0.33	0.979	0.218	14
		σ	7.00	2.60 ± 0.32	0.985	0.188	12[a]
	50	σ°	7.81	2.38 ± 0.23	0.991	0.149	12[a]
		σ	7.77	2.32 ± 0.27	0.983	0.196	14
		σ	7.76	2.33 ± 0.28	0.985	0.186	12[a]
	30	σ°	8.49	2.40 ± 0.26	0.989	0.158	12[a]
		σ	8.42	2.28 ± 0.35	0.972	0.256	14
		σ	8.43	2.35 ± 0.35	0.978	0.228	12[a]
	0	σ°	8.90	2.48 ± 0.26	0.990	0.155	11[a]
		σ	8.86	2.37 ± 0.33	0.978	0.226	13
		σ	8.86	2.42 ± 0.34	0.983	0.206	11[a]
38	98.5	σ°	8.71	2.65 ± 0.28	0.993	0.135	9[a]
		σ	8.65	2.39 ± 0.29	0.989	0.165	10
	95.6	σ°	7.78	2.40 ± 0.28	0.993	0.135	8
		σ	7.75	2.37 ± 0.38	0.987	0.184	8
	80	σ°	7.03	2.68 ± 0.28	0.995	0.118	8
		σ	6.98	2.66 ± 0.37	0.990	0.160	8
	50	σ°	7.77	2.42 ± 0.25	0.995	0.120	8
		σ	7.73	2.30 ± 0.37	0.988	0.176	8
39	98.5	σ°	7.75	2.38 ± 0.37	0.985	0.195	9[a]
		σ	7.72	2.14 ± 0.46	0.961	0.306	11
	95.6	σ°	6.78	1.52 ± 0.41	0.966	0.299	8
		σ	6.75	1.51 ± 0.40	0.966	0.299	8
	80	σ°	6.02	1.97 ± 0.29	0.990	0.167	8
		σ	5.99	1.95 ± 0.34	0.985	0.199	8
	50	σ°	6.85	2.23 ± 0.43	0.982	0.221	8
		σ	6.81	2.19 ± 0.54	0.971	0.276	8

[a] Without the OEt derivatives.

and N^1-methyl-N^1,N^2-diarylbenzamidines[10] (**42**), have been synthesized and their pK_a values (Tables 21–23) determined.



R	H	Me	Ph
Series	**40**	**41**	**42**

The pairs of substituents for this study were selected in such a manner that their Hammett constants were not collinear. Therefore the obtained correlations represent the

TABLE 21. pK_a values of N^1-methyl-N^1,N^2-diarylformamidines (**40**) in 99.8% ethanol at 25 ± 0.1 °C[9]

X	Y	pK_a
m-Br	H	5.62
m-Br	*p*-OMe	5.46
p-Br	H	5.69
p-Br	*p*-OMe	6.42
p-Me	H	7.02
p-Me	*p*-Me	7.15
p-Me	*p*-OMe	7.21
p-OMe	*p*-Cl	6.61
p-OMe	*p*-OMe	7.70

TABLE 22. pK_a values of N^1-methyl-N^1,N^2-diarylacetamidines (**41**) in 95.6% ethanol at 25 ± 0.1 °C[12]

X	Y	pK_a
m-Cl	*m*-Cl	5.40 ± 0.03
m-Cl	H	5.90 ± 0.02
m-Cl	*p*-OCH_3	6.05 ± 0.02
p-Br	*p*-Br	5.77 ± 0.02
p-Br	H	6.10 ± 0.03
p-Br	*p*-CH_3	6.29 ± 0.03
H	*m*-Cl	6.45 ± 0.03
H	*p*-Br	6.48 ± 0.02
H	H	6.96 ± 0.01
H	*p*-CH_3	7.19 ± 0.04
H	*p*-OCH_3	7.24 ± 0.04
m-CH_3	H	7.07 ± 0.03
m-CH_3	*p*-OCH_3	7.44 ± 0.03
p-CH_3	*m*-Cl	6.78 ± 0.03
p-CH_3	H	7.34 ± 0.03
p-CH_3	*p*-CH_3	7.41 ± 0.03
p-OCH_3	*m*-Cl	6.89 ± 0.03
p-OCH_3	H	7.58 ± 0.02
p-OCH_3	*p*-OCH_3	7.17 ± 0.02

influence of substitution at the two nitrogen atoms of the amidine group. The number of experimental points was insufficient for finding the parameters of equation 5; for equation 3 the following parameters have been found:

	pK_a°	ρ_{Im}	ρ_{Am}	R	Ref.
40	6.38	2.59 ± 0.28	1.36 ± 0.43	0.995	9
41	6.90	2.88 ± 0.18	1.42 ± 0.16	0.995	12
42	7.10	2.69 ± 0.22	1.54 ± 0.22	0.994	10

TABLE 23. pK_a values of N^1-methyl-N^1-N^2-diaryl-benzamidines (**42**) in 99.8% ethanol at 25 ± 0.1 °C[10]

X	Y	pK_a
m-Cl	H	6.11 ± 0.14
p-Br	*p*-Br	5.94 ± 0.12
p-Br	H	6.47 ± 0.15
p-Br	*p*-OCH_3	6.72 ± 0.08
m-OCH_3	*p*-Br	6.28 ± 0.23
m-OCH_3	H	6.86 ± 0.20
m-OCH_3	*p*-OCH_3	7.23 ± 0.12
H	*p*-Br	6.59 ± 0.21
H	H	7.10 ± 0.06
p-CH_3	*p*-Br	7.03 ± 0.06
p-CH_3	H	7.67 ± 0.06
p-CH_3	*p*-OCH_3	8.09 ± 0.22
p-OCH_3	*m*-Cl	7.41 ± 0.04
p-OCH_3	H	8.01 ± 0.06
p-OCH_3	*p*-OCH_3	8.36 ± 0.10

The considerably higher values of ρ_{Im} than those of ρ_{Am} for all three series leave no doubt that the protonation site in amidines is the imino nitrogen atom.

The influence of substitution at the amidino carbon atom on the sensitivity to substitution at either of the two nitrogen atoms was less evident from the ρ values only, because the differences between the two series were within the confidence intervals. But the ρ_{Im}:ρ_{Am} ratios (1.90, 2.03 and 1.75 for the three series) provide satisfactory evidence that substitution at the carbon atom changes the sensitivity of the amidine group to the effects of substituents at the nitrogen atoms.

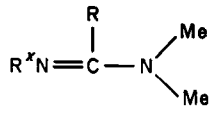
The ρ_{Im} value for N^1-methyl-N^1-arylformamidines (**40**) was close to that obtained for N^1,N^1-dialkylformamidines (**37**–**39**), ranging from 2.05 ± 0.43 to 2.29 ± 0.24. Thus it was concluded that substitution at the amino nitrogen has a rather small influence on the sensitivity of the amidino group to substitution at the imino nitrogen.

For N^1-methyl-N^1,N^2-diarylacetamidines[12] (**41**), pK_a values were also correlated with σ° values using equation 5, but the ρ values obtained for substitution at the imino and amino nitrogen atoms (2.94 ± 0.15 and 1.46 ± 0.13) were identical within the confidence intervals to those obtained using the linear disubstituent regression (equation 4), and the 'cross term' μ of equation 5 was highly uncertain, as the confidence intervals amounted to $> 75\%$ of the μ value. The correlation for N^1-methyl-N^1,N^2-diarylacetamidines was compared[2] with that for N^1,N^1-dimethylacetamidines **27** and it was found that the slopes of regression lines cannot be treated as different. Thus it was concluded that the pK_a values of N^1-methyl-N^1,N^2-diarylamidines are best explained by the equation of a plane 4.

It was then assumed that it is possible to find an equation which makes it possible to predict pK_a values of amidines containing substituted phenyl rings at all three sites of the amidine group.

Evidence for this hypothesis was found in an investigation[23] of several series of amidines containing alkyl substituents of increasing inductive effect, such as hydrogen methyl, ethyl, isopropyl and *t*-butyl (Table 24).

Comparing the series of N^1,N^1-dimethylacetamidines (**27**), propionamidines (**43**), isobutyramidines (**44**) and pivalamidines (**45**) one can readily see that the ρ value (Table 25) increases with the number of methyl groups at the α-carbon atom. In fact there



(43) R = Et
(44) R = Pr^i
(45) R = Bu^t
(46) R = Ph

is a good linear correlation between the ρ values and the number of methyl groups. This indicated that the ρ value may depend on the inductive effect of an alkyl substituent at the amidino carbon atom. It was shown[23] that the ρ_{Im} values of these series together with the dimethylformamidine (26) series can be correlated with the σ^* values[44] of the alkyl substituents at the amidino carbon atom:

$$\rho_{Im} = \rho^{\circ}_{Im} + \mu\sigma^*_F \tag{7}$$

In this equation ρ_{Im} is the observed ρ value for a series of amidines containing various substituents at the phenyl ring on the imino nitrogen atom and a fixed substituent at the amidino carbon atom; ρ°_{Im} is the ρ_{Im} value for acetamidines (for the Me group $\sigma^* = 0$).

TABLE 24. pK_a values of N^1,N^1-dimethylamidines in 95.6% ethanol at 25 ± 0.1 °C[23]

R^x	43	44	45	27
p-$C_6H_4NO_2$	5.65 ± 0.03	5.52 ± 0.03	5.18 ± 0.04	—[a]
m-$C_6H_4NO_2$	6.06 ± 0.06	6.14 ± 0.03	5.86 ± 0.03	6.38 ± 0.03
m-C_6H_4Br	7.13 ± 0.03	7.03 ± 0.01	6.81 ± 0.03	—[a]
m-C_6H_4Cl	7.15 ± 0.07	7.10 ± 0.01	7.01 ± 0.06	—[a]
p-C_6H_4I	7.36 ± 0.01	7.54 ± 0.07	7.17 ± 0.01	7.53 ± 0.02
p-C_6H_4Br	7.43 ± 0.07	7.41 ± 0.02	7.20 ± 0.01	—[a]
p-C_6H_4Cl	7.55 ± 0.02	7.51 ± 0.02	7.19 ± 0.09	—[a]
m-$C_6H_4OCH_3$	8.13 ± 0.03	8.12 ± 0.01	7.91 ± 0.02	—[a]
m-$C_6H_4OC_2H_5$	8.16 ± 0.01	8.15 ± 0.01	7.93 ± 0.03	—[a]
Ph	8.30 ± 0.03	8.22 ± 0.02	8.03 ± 0.04	—[a]
m-$C_6H_4CH_3$	8.38 ± 0.07	8.41 ± 0.03	8.24 ± 0.03	—[a]
p-$C_6H_4CH_3$	8.44 ± 0.08	8.63 ± 0.02	8.43 ± 0.01	—[a]
p-$C_6H_4OC_2H_5$	8.89 ± 0.03	8.93 ± 0.01	8.63 ± 0.05	—[a]
p-$C_6H_4OCH_3$	8.94 ± 0.03	8.89 ± 0.03	8.62 ± 0.02	—[a]
p-$CH_2C_6H_4Cl$	11.11 ± 0.09	11.13 ± 0.07	9.96 ± 0.02	—[a]
CH_2Ph	11.41 ± 0.04	11.36 ± 0.04	10.30 ± 0.05	—[a]
m-$CH_2C_6H_4OCH_3$	11.48 ± 0.09	11.31 ± 0.05	10.28 ± 0.02	11.60 ± 0.03
p-$CH_2C_6H_4CH_3$	11.66 ± 0.05	11.72 ± 0.06	10.54 ± 0.04	11.64 ± 0.03
Allyl	11.59 ± 0.04	11.88 ± 0.05	10.65 ± 0.04	11.75 ± 0.03
Isobutyl	11.96 ± 0.06	11.93 ± 0.09	10.76 ± 0.03	—[a]
n-Hexyl	12.11 ± 0.09	11.95 ± 0.09	10.98 ± 0.09	—[a]
n-Butyl	12.13 ± 0.03	12.22 ± 0.09	10.91 ± 0.03	—[a]
n-Propyl	12.20 ± 0.09	12.33 ± 0.07	10.94 ± 0.03	—[a]
Cyclohexyl	12.28 ± 0.05	12.16 ± 0.09	10.91 ± 0.03	—[a]
Isopropyl	12.20 ± 0.09	12.26 ± 0.06	10.88 ± 0.05	—[a]

[a]cf. Table 8.

TABLE 25. Parameters of regressions of pK_a values of N^1,N^1-dimethylamidines with substituent constants[23]

Series	σ	pK_a°	ρ	r	ψ	n
26	σ	7.39	2.53 ± 0.33	0.979	0.220	14
	σ°	7.45	2.63 ± 0.21	0.994	0.096	12
27	σ	8.27	2.91 ± 0.34	0.984	0.196	14
	σ°	8.33	2.97 ± 0.25	0.993	0.129	12
43	σ	8.19	3.01 ± 0.34	0.984	0.191	14
	σ°	8.24	3.07 ± 0.22	0.995	0.111	12
44	σ	8.21	3.11 ± 0.29	0.989	0.160	14
	σ°	8.26	3.14 ± 0.23	0.995	0.114	12
45	σ	7.97	3.15 ± 0.37	0.983	0.200	14
	σ°	8.04	3.23 ± 0.27	0.993	0.128	12

The term μ has a negative value, which indicates that the increase in the electron density at the C=N double bond, caused by the inductive effect of a substituent at the amidino carbon atom, increases the sensitivity of the amidino group to the effect of substituents at the imino nitrogen atom.

The parameters for equation 5 have been calculated using the pK_a values of all five series (a total of 60 compounds).

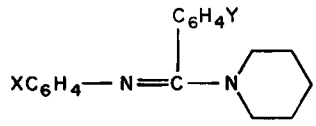
pK_a°	ρ_{Im}	ρ_F[a]	μ	r	ψ
8.04	2.99 ± 0.20	0.93 ± 0.27	0.76 ± 0.72	0.973	0.239

[a] ρ_F if the rho value for substitution at the functional carbon of the amidine group.

The correlation has a predictive value. The difference between the pK_a values obtained experimentally, and those calculated from equation 5 using the above parameters, in 80% of the cases does not exceed 0.3 pK_a units, and in 92% of the cases does not exceed 0.35 pK_a units. The largest deviations (0.44–0.48 pK_a units) are observed in the case of the *meta*- and *para*-methoxy derivatives.

Amidines containing a phenyl ring at the amidino carbon atom, i.e. N^1,N^1-dimethylbenzamidines (**46**), do not fit this correlation, as shown by point 6 in Figure 1. The most probable reason for this is that the σ^* values represent only inductive effects, while with benzamidines the resonance effects may also be involved. Thus it can be concluded that a general equation should contain additional terms.

For substituents at the functional carbon and at the imino nitrogen atom, the influence of substitution at one site on the sensitivity to substitution at the second site was, in the case of benzamidines, not so evident.



(47) X = *p*-Cl
(48) X = *p*-Me

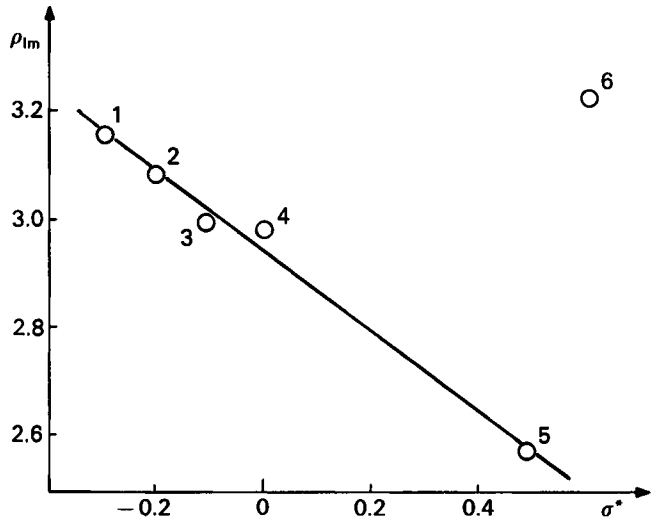


FIGURE 1. Correlation of the ρ_{lm} values with the σ^* values of the substituent at the amidino carbon atom. 1, **45**; 2, **44**; 3, **43**; 4, **27**; 5, **26**; 6, **46** series

The pK_a values for the series of N^1,N^1-pentamethylene-N^2-*p*-chlorophenylbenzamidines (**47**) and N^1,N^1-pentamethylene-N^2-*p*-tolylbenzamidines (**48**), containing an invariant substituent at the imino nitrogen atom and variable substituent at the functional carbon atom (Table 26), were correlated[19] with the σ values using both equations 4 and 5. For the linear regression (equation 4) the following parameters were obtained:

for **47**: $\rho = 1.85 \pm 0.13$, $r = 0.998$, $\psi = 0.07$;
for **48**: $\rho = 1.95 \pm 0.23$, $r = 0.995$, $\psi = 0.12$.

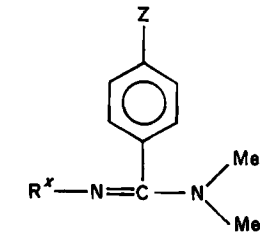
The polar effects of Cl and Me are opposite and the difference in σ values for the two substituents amounts to 0.39 units. Thus it is expected that a considerable difference between the ρ values for the two series will be observed. However, the obtained correlations indicated that exchange of a methyl group for the chlorine atom in the *para* position of the phenyl ring at the imino nitrogen has no observable influence on the sensitivity of the amidine group to substitution at the amidino carbon atom, and the only difference is in the pK_a° values.

Similar results[22] were obtained for N^1,N^1-dimethylbenzamidines (**49**), N^1,N^1-dimethyl-*p*-chlorobenzamidines (**50**) and N^1,N^1-dimethyl-*p*-methylbenzamidines (**51**), containing a variable substituent at the imino nitrogen and an invariant one at the phenyl ring at the amidino carbon atom (Table 27). Parameters of regression (Table 28) indicated that in this case again correlations with σ° values are of higher quality, however correlations with ordinary σ values are also satisfactory.

Comparison of the obtained correlations with those for N^1,N^1-dimethylformamidines (**26**) and acetamidines (**27**) provided further support for the conclusion that the sensitivity of the amidino group to substitution at the imino nitrogen depends on the substituent at the amidino carbon atom. The regression coefficients for benzamidines are very close to those for acetamidines but definitely different from those for formamidines. The difference between individual series of benzamidines was not evident, particularly if compared with

TABLE 26. pK_a values of N^1,N^2-(pentamethylene)-N^2-aryl-benzamidines (**47** and **48**) in 95.6% ethanol at 25 ± 0.1 °C[19]

X	Y	pK_a
p-Cl	*m*-Br	5.65 ± 0.07
p-Cl	*m*-Cl	5.61 ± 0.02
p-Cl	*p*-Cl	5.89 ± 0.04
p-Cl	H	6.37 ± 0.05
p-Cl	*m*-CH_3	6.47 ± 0.04
p-Cl	*p*-CH_3	6.63 ± 0.03
p-Cl	*p*-OCH_3	6.86 ± 0.06
p-CH_3	*m*-Br	6.65 ± 0.12
p-CH_3	*m*-Cl	6.74 ± 0.04
p-CH_3	*p*-Cl	7.03 ± 0.04
p-CH_3	H	7.49 ± 0.04
p-CH_3	*m*-CH_3	7.62 ± 0.07
p-CH_3	*p*-CH_3	7.68 ± 0.02
p-CH_3	*p*-OCH_3	8.01 ± 0.05



(**49**) Z = H (**52**) Z = OMe
(**50**) Z = Cl (**53**) Z = NO_2
(**51**) Z = Me

the results obtained for benzamidines containing variable substituents at the amidino carbon atom. Only further study on two additional series[24], *p*-methoxybenzamidines (**52**) and *p*-nitrobenzamidines (**53**), and extension of the series of *p*-chlorobenzamidines (**50**, Table 29) makes it possible to draw reliable conclusions. Correlations of the pK_a values for these series with σ values (Table 30 and 31), using both equations 4 and 5, left no doubt that the effect of substitution at one site on the ρ value for substitution at another site is observed also in the case of benzamidines, and that equation 5 should be used to predict the pK_a values for benzamidines.

The term μ obtained in this equation has a negative value. This indicates that the increase in the electron density at C=N, caused by the polar effect of a substituent on the phenyl ring at the amidino carbon, increases the sensitivity of the amidino group to the effect of substituents on the imino nitrogen. On the other hand, electron-donating substituents at the imino nitrogen increase the sensitivity of the amidino group to substitution at the amidino carbon atom.

Some support for the postulate concerning the influence of substitution at one site on the sensitivity to substitution at other sites was provided by the *ab initio* optimizations of molecular structures. Häfelinger, Oszczapowicz and coworkers[45,46] studied sixteen

TABLE 27. pK_a values of N^1,N^1-dimethyl-N^2-substituted benzamidines in 95.6% ethanol at 25 ± 0.1 °C[22]

R^x	49	50	51
p-$C_6H_4NO_2$	4.58 ± 0.02	4.27 ± 0.03	4.96 ± 0.02
m-C_6H_4Br	6.27 ± 0.03	5.85 ± 0.05	6.53 ± 0.04
p-C_6H_4Cl	6.52 ± 0.02	6.02 ± 0.01	6.81 ± 0.03
m-An	7.16 ± 0.03	6.62 ± 0.03	7.36 ± 0.01
Ph	7.26 ± 0.01	6.75 ± 0.01	7.59 ± 0.04
p-Tol	7.57 ± 0.02	7.19 ± 0.04	7.83 ± 0.01
p-An	8.05 ± 0.02	7.45 ± 0.02	8.08 ± 0.02
p-$CH_2C_6H_4Cl$	9.76 ± 0.03	8.92 ± 0.04	9.90 ± 0.08
CH_2Ph	10.12 ± 0.02	9.46 ± 0.03	10.17 ± 0.03
p-$CH_2C_6H_4CH_3$	10.32 ± 0.05	9.58 ± 0.02	10.31 ± 0.02
n-Hexyl	10.44 ± 0.10	9.80 ± 0.07	11.02 ± 0.04
Cyclohexyl	10.60 ± 0.11	9.69 ± 0.10	11.08 ± 0.02

TABLE 28. Parameters of regressions of pK_a values of N^2-substituted N^1,N^1-dimethylbenzamidines with substituent constants[22]

Series	σ	pK_a^o	ρ	r	ψ	n
49	σ^o	7.32	3.22 ± 0.42	0.994	0.134	7
	σ	7.27	3.15 ± 0.64	0.985	0.205	7
50	σ^o	6.82	3.02 ± 0.31	0.996	0.105	7
	σ	6.77	2.96 ± 0.52	0.998	0.180	7
51	σ^o	7.53	3.00 ± 0.36	0.994	0.125	7
	σ	7.48	2.93 ± 0.61	0.984	0.209	7

amidines, namely *trans* and *cis* formamidines with up to three fluorine atoms, and the corresponding amidinium cations. Again it was found that the ρ value for substitution at one site depends on substituents at another site. In equation 6 this is represented by the term $\mu\sigma_2$. The strongest influence is exerted if one of the substituents is at the carbon and the second at imino nitrogen. Electron-withdrawing substituents at either of these sites cause a decrease in the ρ value. The effect is much lower if the substituents are at the two nitrogens. However, if one of the substituents is at the carbon and the second at the amino nitrogen, the ρ value is changed to a small extent, but in the opposite direction, so that for an electron-withdrawing substituent an increase in the ρ value occurs. This provides good support for an assumption[25] made regarding the changes in ρ values observed for some series of symmetrically disubstituted *N,N'*-diphenylformamidines, acetamidines and propionamidines.

It was also found that the ρ values as well as changes caused by substitution at another site depend on the configuration at the C=N double bond and those for *cis* amidines[46] differ considerably from those for *trans* isomers[45].

2. *Correlations with pK_a values of amines*

a. Substitution at the imino nitrogen atom. Hammett-type equations are unfortunately limited to compounds containing either *m*- or *p*-substituted phenyl rings or alkyl

TABLE 29. pK_a values of N^2-substituted N^1,N^1-dimethylbenzamidines (**50**, **52** and **53**) in 95.6% ethanol at 25 ± 0.1 °C[24]

R^x	**50**	**52**	**53**
p-$C_6H_4NO_2$	—[a]	5.28 ± 0.01	2.55 ± 0.11
m-$C_6H_4NO_2$	4.97 ± 0.03	5.71 ± 0.03	3.03 ± 0.11
m-C_6H_4Br	—[a]	6.96 ± 0.06	3.19 ± 0.11
m-C_6H_4Cl	5.77 ± 0.03	6.79 ± 0.03	3.28 ± 0.16
p-C_6H_4I	6.13 ± 0.06	6.95 ± 0.02	3.34 ± 0.07
p-C_6H_4Br	6.08 ± 0.05	7.18 ± 0.01	3.41 ± 0.06
p-C_6H_4Cl	—[a]	7.15 ± 0.03	3.69 ± 0.04
m-An	—[a]	7.91 ± 0.06	4.15 ± 0.09
m-$C_6H_4OC_2H_5$	6.81 ± 0.09	8.16 ± 0.03	4.10 ± 0.15
Ph	—[a]	8.39 ± 0.16	4.14 ± 0.17
m-Tol	7.02 ± 0.04	8.21 ± 0.03	4.12 ± 0.12
p-Tol	—[a]	8.79 ± 0.08	4.35 ± 0.05
p-$C_6H_4OC_2H_5$	—[a]	8.68 ± 0.06	4.55 ± 0.12
p-An	7.53 ± 0.01	8.83 ± 0.06	4.66 ± 0.04
p-$CH_2C_6H_4Cl$	—[a]	9.99 ± 0.03	5.78 ± 0.05
CH_2Ph	—[a]	10.37 ± 0.03	5.86 ± 0.05
m-$CH_2C_6H_4OCH_3$	9.37 ± 0.03	10.42 ± 0.05	5.87 ± 0.02
p-$CH_2C_6H_4CH_3$	—[a]	10.52 ± 0.04	5.99 ± 0.05
Allyl	9.78 ± 0.03	10.59 ± 0.04	6.02 ± 0.02
Isobutyl	10.19 ± 0.04	11.06 ± 0.02	6.15 ± 0.07
n-Hexyl	—[a]	11.25 ± 0.02	6.09 ± 0.05
n-Butyl	10.32 ± 0.02	11.06 ± 0.04	6.24 ± 0.04
n-Propyl	10.32 ± 0.02	11.35 ± 0.04	6.20 ± 0.06
Cyclohexyl	—[a]	11.39 ± 0.03	6.00 ± 0.05
Isopropyl	10.42 ± 0.03	11.23 ± 0.11	6.11 ± 0.04

[a]cf. Table 27.

TABLE 30. Parameters of regressions of pK_a values of N^2-substituted N^1,N^1-dimethylbenzamidines with substituent constants[24]

Series	σ	pK_a°	ρ_{Im}	r	ψ	n
50	σ	4.07	1.88 ± 0.38	0.952	0.329	14
	σ°	4.09	1.89 ± 0.38	0.962	0.299	12[a]
52	σ	8.07	3.40 ± 0.49	0.975	0.240	14
	σ°	8.15	3.53 ± 0.32	0.992	0.141	12[a]
53	σ	6.80	2.86 ± 0.32	0.984	0.190	14
	σ°	6.83	2.87 ± 0.24	0.993	0.130	12[a]

[a]Without the *p*-OEt and *m*-OEt derivatives.

substituents, and treat both types of compounds separately. This is not sufficient to predict the properties of most of the amidines. Therefore it was necessary to search for a relation enabling calculation of pK_a values of all amidines using just one general equation.

Since pK_a values of substituted *N*-phenylamidines obey the Hammett equation, and pK_a values of substituted anilines also obey this equation, Oszczapowicz and Orliński proposed[18] that the pK_a values of amidines should correlate with the pK_a values of the

TABLE 31. Dual parameter regressions of pK_a values of N^1,N^1-dimethylbenzamidines with σ° and σ value of substituents at phenyl rings at the imino nitrogen atom and at the amidino carbon atom (equations 4 and 5)[24]

pK_a°	ρ_{Im}	ρ_F	μ	R	ψ	n
7.22	3.06 ± 0.30	3.75 ± 0.28	-1.40 ± 0.73	0.984	0.184	50[a]
7.18	2.86 ± 0.32	3.44 ± 0.25	—	0.979	0.209	50[b]
7.33	3.09 ± 0.18	2.60 ± 0.11	-0.97 ± 0.28	0.995	0.105	50[a,c]
7.29	2.85 ± 0.23	2.39 ± 0.12	—	0.990	0.148	50[b,c]

[a]According to equation 5.
[b]According to equation 4.
[c]For the NO_2 group at the phenyl ring at the amidino carbon atom the σ^- value was used.

corresponding anilines, as expressed by equation 8.

$$pK_a(\text{amidine}) = \alpha \cdot pK_a(\text{amine}) + \beta \tag{8}$$

It was assumed that this correlation could be applied to amidines containing alkyl, aryl or aralkyl substituents bonded directly to the nitrogen atoms of the amidine system. However, the interactions between substituent and protonation centre in anilines and *N*-phenylamidines are different, and this may affect the quality of the correlation and the accuracy of pK_a predictions based on it.

The first attempt at such a correlation was made for symmetrically *N,N'*-disubstituted diphenylformamidines (**34**, Table 15) and symmetrically *N,N'*-disubstituted dialkylformamidines (**54**, Table 32), and yielded unexpectedly good results. The experimental points for alkyl and aralkyl substituents fall exactly on the extension of the correlation line for the aromatic ones (Figure 2). The values $\alpha = 0.96 \pm 0.04$, $\beta = 1.62$ and $r = 0.996$ were found, and the correlation was of a very good quality.

$$[R^xN{=}CH{-}NHR^x \rightleftharpoons R^xNH{-}CH{=}NR^x]$$

(54)

Oszczapowicz and coworkers studied the applicability of this relation to trisubstituted amidines containing a variable substituent at the imino nitrogen atom[1-3,5,11,22-25]. The results indicated that the existence of such correlations can be taken as a rule.

For amidines containing variable substituents at the imino nitrogen primary amines R^xNH_2 (PA) were taken as the most appropriate independent variables and equation 9

TABLE 32. pK_a values of *N,N'*-dialkylformamidines (**54**) in 98.5% ethanol at 25 ± 0.1 °C[18]

R^x	pK_a
Benzyl	10.94
Isobutyl	12.12
n-Hexyl	12.35
n-Butyl	12.26
n-Propyl	12.22
Cyclohexyl	12.49
Isopropyl	12.85

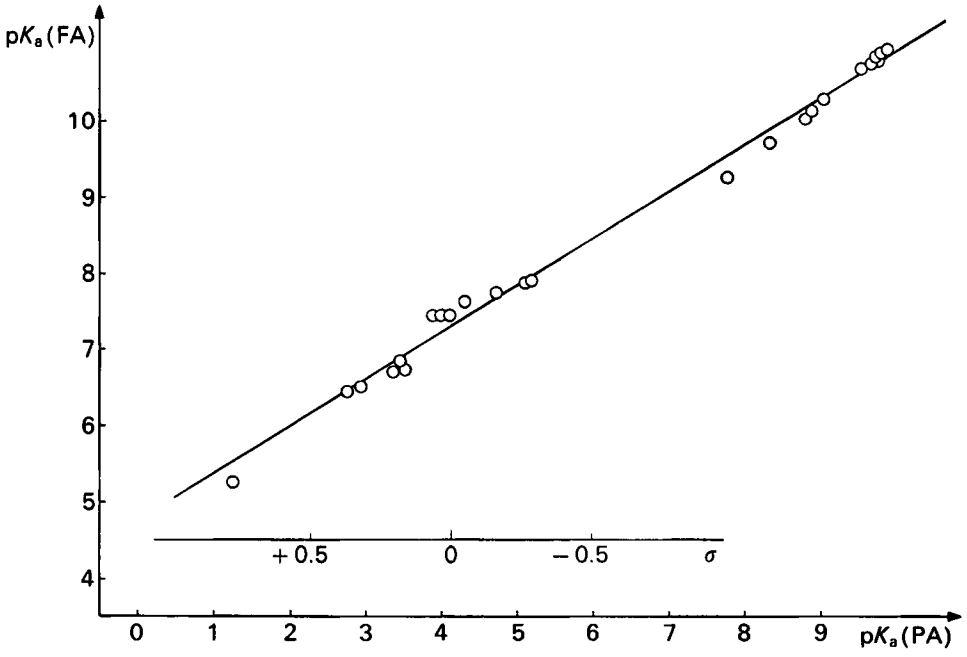


FIGURE 2. Correlation of pK_a values of symmetrically *N,N'*-disubstituted formamidines (FA) with pK_a values of the corresponding primary amines (PA). Inset σ scale. From data in reference 18

was proposed[18].

$$pK_a(\text{amidine}) = \alpha_{lm} pK_a(\text{PA}) + \beta \tag{9}$$

For N^2-substituted N^1,N^1-dimethylformamidines (**26**), a very good correlation with the pK_a values of primary amines ($\alpha = 0.62 \pm 0.02$; $r = 0.996$) was obtained[1]. For N^2-substituted N^1,N^1-pentamethylenebenzamidines (**25**) the correlation ($\alpha = 0.65 \pm 0.04$; $r = 0.995$) was also very good[3].

Correlations of the pK_a values of amidines and amines appeared to be very useful tools with which to study the influence of a substituent at one site on the sensitivity of the amidine to polar effects of substituents at other sites. Such correlations obtained for series containing alkyl, aryl and aralkyl substituents are of higher diagnostic value, because the range of the considered pK_a values is twice as large as that with substituted anilines covering the range of σ values only.

For N^1,N^1-dimethylacetamidines (**27**) the α values of 0.75 ± 0.02 ($r = 0.998$) was found to be higher than that for N^1,N^1-dimethylformamidines (**26**). The ratio of these two α values (1.23) is almost the same as the ratio (1.1) of the ρ values[2] (Table 33).

In equations 8 and 9 the term β corresponds to the pK_a value of a hypothetical amidine, whose pK_a value is equal to zero. Therefore it was found convenient to normalize this equation by subtraction of the pK_a value of unsubstituted aniline from the pK_a value of primary amine (equation 10).

$$pK_a(\text{amidine}) = pK_a^{\circ}(\text{amidine}) + \alpha_{lm}[pK_a(\text{PA}) - pK_a(\text{PhNH}_2)] \tag{10}$$

In the normalized equation 10 the term pK_a° has the same meaning as in the Hammett

TABLE 33. Parameters of regressions of pK_a values of N^1,N^1-dimethylamidines with pK_a values of corresponding primary amines (equation 10)[23]

Series	pK_a°	α_{lm}	r	ψ	n
26	7.29	0.62 ± 0.02	0.997	0.010	24[a]
	7.34	0.69 ± 0.10	0.979	0.223	13[b]
	6.24	0.82 ± 0.05	0.997	0.020	11[c]
27	8.16	0.75 ± 0.02	0.998	0.061	24[a]
	8.21	0.82 ± 0.08	0.990	0.157	13[b]
	7.44	0.89 ± 0.12	0.983	0.201	11[c]
43	8.07	0.73 ± 0.02	0.998	0.065	24[a]
	8.12	0.82 ± 0.09	0.986	0.180	13[b]
	7.78	0.78 ± 0.07	0.993	0.127	11[c]
44	8.06	0.74 ± 0.03	0.997	0.080	24[a]
	8.14	0.87 ± 0.07	0.993	0.129	13[b]
	7.96	0.75 ± 0.22	0.931	0.403	11[c]
45	7.73	0.58 ± 0.04	0.987	0.168	24[a]
	7.90	0.88 ± 0.10	0.985	0.187	13[b]
	7.40	0.63 ± 0.15	0.955	0.330	11[c]

[a]Without *m*-NO_2 derivatives.
[b]Only N^2-phenyl derivatives.
[c]Only N^2-alkyl and N^2-benzyl derivatives.

equation and represents the pK_a value of the amidine containing (as a variable substituent R^x) an unsubstituted phenyl ring. In both equations 10 and 9, the numerical value of α is the same.

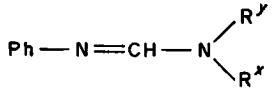
It was found[25] that the changes of α values for N^1,N^1-dimethylpropionamidines (**43**), N^1,N^1-dimethylisobutyramidines (**44**) and N^1,N^1-dimethylpivalamidines (**45**), following the changes of the σ^* values of the substituent at the functional carbon atom (Table 33), were not so evident as in the case of the ρ_{lm} values (cf. Section II.A.1.d). Thus it was not possible to derive a general equation for predicting the pK_a values of amidines containing varied substituents at the imino nitrogen and at the functional carbon atom. It was noted[25] that the quality of correlations common for both alkyl and aryl substituents is decreasing with an increase in substitution at the α carbon atom, and thus with an increase in the σ^* value. Therefore separate correlations for *N*-aryl and *N*-alkyl derivatives were also calculated. For pivalamidines the α values were found to be 0.88 ± 0.10 for aryl and 0.63 ± 0.5 for alkyl derivatives. The authors assumed that this may be due to different influences of the substituent at the amidino carbon atom on *N*-alkyl- and on *N*-arylamidines. The α_{lm} values for N^2-alkylamidines seem to decrease with an increase in the σ^* value of the substituent at the amidino carbon atom, whereas for N^2-phenylamidines they increase, as exepected on the basis of equation 7.

A good explanation for these discrepancies was found recently. It was shown[47] that in the case of bulky substituents at the functional carbon atom in amidines with alkyl groups at the amino nitrogen atom, the geometrical isomer where the substituent at the imino nitrogen atom is in a *cis* position with respect to the amino nitrogen atom is more stable. The steric hindrance increases in the order: H < Ph < Me < Pr^i < Bu^t. On the other hand, it was shown[46] that the change of configuration at the C=N double bond in amidines involves not only changes in pK_a values but also a considerable change in the ρ values. Thus the conclusion can now be drawn that the differences between the α values can be taken as an indication of the presence of a *cis* isomer in N^2-alkylamidines. The question of the ratio of *cis* to *trans* isomers in such amidines and the influence of the substituent at the amidino carbon atom on the regression parameters is at present under investigation[48].

All N^2-phenylbenzamidines studied so far were *trans* isomers (N-phenyl is *trans* with respect to the amino nitrogen)[47]. Steric hindrance between two phenyl rings, or a phenyl ring and an n-alkyl group, is much lower than between any two alkyl groups, because they can be twisted out-of-plane of the amidine group. Therefore, for N^1,N^1-dimethyl-N^2-phenylbenzamidines **49–53**, the correlations with the pK_a values of corresponding primary amines[22,24] are of high quality ($r > 0.991$ for the full series, and higher if *p*-nitrophenyl derivatives are excluded). The influence of substitution at one site on the sensitivity to polar effects at the second site is less evident because the α values are in the range 0.60–0.65 with a confidence interval of 0.05. The only exception providing good support for the statement that in benzamidines the regression coefficient α for substitution at the imino nitrogen also depends on substitution at the functional carbon, is the series of *p*-nitrophenylbenzamidines (**53**), where the α value of 0.41 ± 0.03 ($r = 0.989$) was found.

For substitution at the imino nitrogen atom in tetramethylguanidines[11] (**28**), a good correlation was also found ($\alpha = 0.61 \pm 0.03$, $r = 0.997$).

b. Substitution at the amino nitrogen atom. It seemed reasonable that a relation with amines should be found also for amidines with variable substituents at the amino nitrogen atom. Therefore Oszczapowicz and coworkers[21] correlated the pK_a values (Table 34) of N^2-phenylformamidines containing variable substituents at the amino nitrogen atom (**55**) with those of the corresponding secondary amines (SA).



(55)

The relation obeyed equation 11:

$$pK_a(\text{amidine}) = \alpha_{Am} pK_a(\text{SA}) + \beta \tag{11}$$

TABLE 34. pK values of N^2-phenylformamidines (**55**) in 95.6% ethanol at 25 ± 0.1 °C[21]

NR^xR^y	pK_a
$N(Me)C_6H_5$	5.29 ± 0.05
$N(Et)C_6H_5$	5.41 ± 0.03
$N(Me)C_6H_4OEt$-*p*	5.72 ± 0.06
$N(Me)C_6H_4OMe$-*p*	5.50 ± 0.06
	6.57 ± 0.05
$N(Bu^i)_2$	6.92 ± 0.03
$N(Pr^n)_2$	7.42 ± 0.03
NMe_2	7.45 ± 0.02
	7.42 ± 0.03
	8.12 ± 0.04

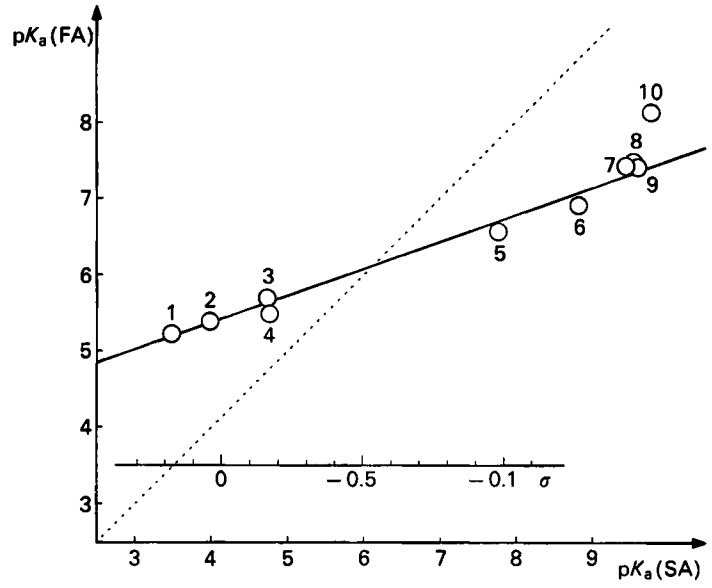


FIGURE 3. Correlation of pK_a values of N^2-phenylformamidines (FA) with pK_a values of corresponding secondary amines (SA). Inset σ scale. From data in reference 21

The following parameters were obtained:

$$pK_a(\text{amidine}) = 3.97 + (0.35 \pm 0.04)pK_a(\text{SA})$$
$$r = 0.991,\ \psi = 0.150$$

Figure 3 illustrates a particular feature of the basicity of amidines. The bisection of the axes (dotted line) crosses the regression line, which means that amidines containing the moiety of the secondary amine, whose pK_a values are below this point, are stronger bases than the corresponding amines; the other amidines are weaker bases than the corresponding amines. This should be considered in discussions whether amidines are stronger or weaker bases than the corresponding amines.

Equation 11 was normalized in a similar way to equation 9 by subtracting the pK_a value of unsubstituted *N*-methylaniline (NMA) from the pK_a value of the secondary amines (SA, equation 12).

$$pK_a(\text{amidine}) = pK_a^\circ + \alpha \cdot [pK_a(\text{SA}) - pK_a(\text{NMA})] \qquad (12)$$

In this equation the term pK_a° has the same meaning as in the Hammett equation for *N*-methylanilines.

The validity of this relation was later confirmed[26] by the series of N^2-phenylformamidines (**32**) and N^2-phenylacetamidines (**33**). The following parameters of this equation (for 9 compounds in each series) were found:

Series	pK_a°	α	r	ψ
32	5.31	0.60 ± 0.06	0.994	0.121
33	7.00	0.40 ± 0.08	0.975	0.255

The parameters of these equations indicate that the α values for substitution at the amino nitrogen also depend on substitution at the functional carbon.

These results supported the assumption[21] that, in order to predict the pK_a values of trisubstituted amidines (TSA) containing substituents of any kind, a two-parameter equation 13 can be applied where pK_a(PA) and pK_a(SA) are the pK_a values of the corresponding amines built into a molecule of amidine.

$$pK_a(TSA) = \alpha_{Im} pK_a(PA) + \alpha_{Am} pK_a(SA) + \beta \tag{13}$$

This equation can be also normalized, giving equation 14:

$$pK_a(TSA) = pK_a^\circ + \alpha_{Im}[pK_a(PA) - pK_a(PhNH_2)] + \alpha_{Am}[pK_a(SA) - pK_a(PhNhMe)] \tag{14}$$

An important advantage of this approach is that the amines are substrates for the synthesis of amidines and the pK_a values of the latter can be predicted prior to the synthesis.

B. Basicity of Tautomerizing Amidines

1. General relations

In the literature the pK_a values of compounds containing a mono- or disubstituted amidino group are usually given without comment as to the meaning of the reported values. Therefore we have to consider what really is measured in pK_a determinations of tautomerizing compounds.

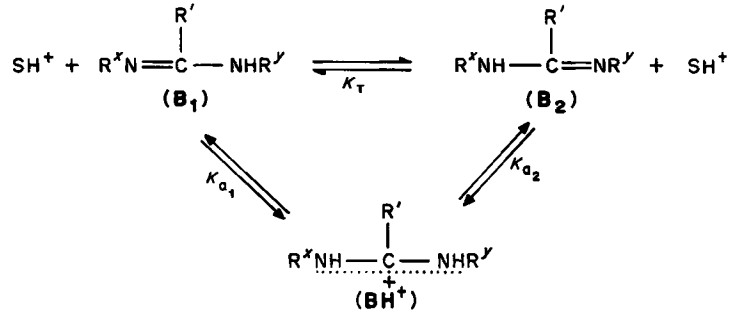
Equations enabling prediction of microscopic pK_a values of individual tautomers and the measured macroscopic pK_{a_m} value of the tautomeric mixture have been derived on the basis of correlation analysis[20].

For the sake of clarity the tautomer in which the substituent R^x is at the imino nitrogen atom will be called B_1 and the other one, in which R^x is at the amino nitrogen, will be called B_2 (Scheme 1).

Protonation of either tautomer yields the same salt, which is the conjugate acid BH^+ of both B_1 and B_2. In a solvent S this salt undergoes dissociation as shown in Scheme 1. The values K_{a_1} and K_{a_2} are called the microscopic dissociation constants[49] of the conjugate acid BH^+ to B_1 and B_2. The Brönsted theory defines K_{a_1} and K_{a_2} as follows:

$$K_{a_1} = \frac{(B_1)(SH^+)}{(BH^+)} \tag{15}$$

$$K_{a_2} = \frac{(B_2)(SH^+)}{(BH^+)} \tag{16}$$



SCHEME 1

It is obvious that if substituents R^x and R^y are not identical, the microscopic constants pK_{a_1} and pK_{a_2} of the tautomers B_1 and B_2 are different.

Tautomerization of amidines is a very fast reaction. In the case of *N,N'*-dimethylformamidines the lifetime of a tautomer in $CDCl_3$ solution at 25 °C[50] is about 10^{-2} s, and in the case of *N,N'*-di-(*p*-fluorophenyl)formamidines it is between 10^{-2} and 10^{-3} s, depending on the temperature (−70 to +62 °C). This rate of proton transfer is about 30 times higher than that between water molecules under identical conditions[51]. In the case of other *N,N'*-diphenylamidines the rate of proton transfer, as estimated on the basis of ^1H and ^{13}C NMR spectra, is between 10^2 and 10^3 per second depending on the substitutions at the amidine carbon and at both nitrogen atoms[48]. Hence, the pK_a values of individual tautomers are not experimentally accessible.

All direct empirical methods measure only the macroscopic dissociation constant, which is defined[50] as

$$K_{a_m} = \frac{[(B_1) + (B_2)](SH^+)}{(BH^+)} \tag{17}$$

This measured constant is the sum of the two microscopic constants:

$$K_{a_m} = K_{a_1} + K_{a_2} \tag{18}$$

In the case $R^x = R^y$ both microscopic constants are identical and can be written as K_a, i.e. $K_a = K_{a_1} = K_{a_2}$. The experimentally accessible pK_{a_m} value is not equal to the pK_a value of any of the two tautomers, and is given by equation 19.

$$pK_{a_m} = pK_a - \log 2 \tag{19}$$

It was already shown that the pK_a values of trisubstituted amidines containing a variable substituent either at the imino[1-3,9,10,12,17,22,25,39,40,52] or at the amino nitrogen atom[8-10,12,26,41,42] obey the Hammett equation 2. Since symmetrically disubstituted *N,N'*-diphenylamidines also obey this relation[16] it can be assumed that in the case of unsymmetrically disubstituted *N,N'*-diphenylamidines (**56**) the pK_a value of tautomer B_1 can be determined as follows:

$$\underset{(B_1)}{XC_6H_4N{=}C(R)-NHC_6H_4Y} \overset{K_T}{\rightleftharpoons} \underset{(56)}{XC_6H_4NH-C(R){=}NC_6H_4Y} \qquad \underset{(B_2)}{}$$

$$pK_{a_1} = pK_a^\circ - \rho_{Im}\sigma_X^\circ - \rho_{Am}\sigma_Y^\circ \tag{20}$$

Here σ_X° and σ_Y° are the σ° values of substituents X and Y respectively, ρ_{Im} and ρ_{Am} relate to substitution at the imino and amino nitrogens and pK_a° is the microscopic pK_a value of the amidine containing unsubstituted phenyl rings at both nitrogen atoms.

Consequently for the tautomer B_2

$$pK_{a_2} = pK_a^\circ - \rho_{Am}\sigma_X^\circ - \rho_{Im}\sigma_Y^\circ \tag{21}$$

By replacing K_{a_1} and K_{a_2} in equation 18 by these terms obtained from equations 20 and 21 respectively, after rearrangement, equation 22 is obtained:

$$pK_{a_m} = pK_a^\circ - \log[10^{(\rho_{Im}\sigma_X^\circ + \rho_{Am}\sigma_Y^\circ)} + 10^{(\rho_{Am}\sigma_X^\circ + \rho_{Im}\sigma_Y^\circ)}] \tag{22}$$

On the plot in Figure 4 the pK_a values (equation 22) are represented by a curved surface lying below the pK_{a_1} and pK_{a_2} planes and approaching them asymptotically.

There are several implications of equation 22 relating to the basicity of tautomerizing amidines. The most important conclusion is that, even for *N*-phenylamidines with only one variable substituent X, the relation between pK_a values obtained experimentally (i.e.

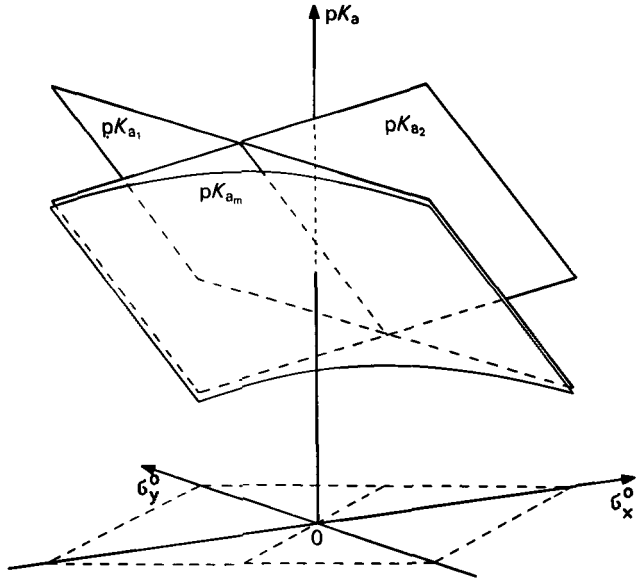


FIGURE 4. Plots of macroscopic pK_{a_m} and microscopic pK_{a_1} and pK_{a_2} values vs σ values of substituents at both nitrogen atoms in tautomerizing amidines (**56**). From J. Oszczapowicz, unpublished results

pK_{a_m} values) and substituent constants is not a straight line. Relation between substituent constants and pK_a values for *N,N'*-diphenylamidines with only one variable substituent X is presented in Figure 5.

In this case again the dependence of pK_a values on σ constants is not a Hammett-type linear relation, but yields a curve the shape of which depends on both ρ values. For this reason we believe that linear regressions between observed pK_a values of tautomerizing amidines and σ values, reported in the literature[7b,29,40,52], are based on an erroneous assumption.

The lines representing pK_{a_1} and pK_{a_2} values cross each other at the point corresponding to the σ value of the constant substituent Y in the series. This point represents the pK_a value of a symmetrically disubstituted (X = Y) *N,N'*-diphenylamidine.

Equation 22 shows that the pK_{a_m} value is always lower than any of the two microscopic pK_a values, and that it is closer to the pK_a value of a less basic tautomer. It shows also that if the experimentally obtained pK_a values of tautomerizing amidines (which in fact are pK_{a_m} values) are correlated with substituent constants, satisfactory linear regression can sometimes be obtained, but the apparent ρ value will depend mainly on the range (A, B or C on Figure 5) in which the majority of experimental points is found. This means that for amidines of the same type, e.g. formamidines, acetamidines etc., with the same set of variable substituents X, various apparent ρ values can be obtained depending on the substituent constant of the invariant substituent Y in the series.

The only exceptions are symmetrically disubstituted *N,N'*-diphenylamidines (X = Y). Equation 22 implies that in this case pK_{a_m} values should obey the linear Hammett equation 23, where the observed ρ value is the sum of the ρ_{Im} and ρ_{Am} values as has already been discussed[16].

$$pK_{a_m} = pK_a^\circ - \log 2 - (\rho_{Im} + \rho_{Am})\sigma_X \qquad (23)$$

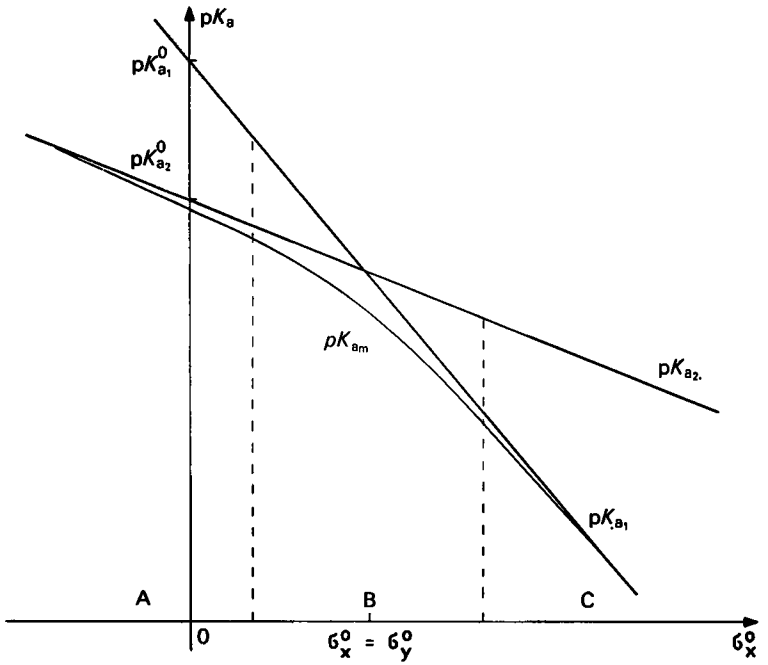
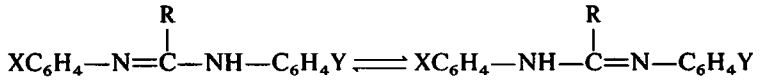


FIGURE 5. Plot of macroscopic pK_{a_m} and microscopic pK_{a_1} and pK_{a_2} values vs σ values for *N,N'*-disubstituted amidines containing only one variable substituent. From reference 20

On the plot in Figure 4 these pK_{a_1} and pK_{a_2} values (equations 20 and 21) are represented by two planes crossing each other along the straight line representing the microscopic pK_a values of symmetrically *N,N'*-disubstituted ($\sigma_X = \sigma_Y$) amidines.

2. *Basicity of monosubstituted and N,N'-disubstituted amidines*

The derived equations were applied to unsymmetrically *N,N'*-disubstituted acetamidines (**57**) and benzamidines (**58**). The experimentally obtained pK_a values are nearly identical with the calculated pK_a values (Table 35).



(**57**) R = Me
(**58**) R = Ph

This provided support for the assumption that, in order to estimate microscopic pK_a values of tautomers and thus to estimate equilibrium constants, the ρ values obtained for analogous series of trisubstituted *N*-methyl derivatives can be applied satisfactorily. However, it should be remembered that, no matter how accurate, this is an estimation only, since it was found[5,45,46] that substitution at one of the nitrogen atoms has a small, but discernible, influence on the ρ value for substitution at another site. Therefore the real

TABLE 35. pK_a values of *N,N'*-disubstituted acetamidines (**57**) and benzamidines (**58**) in 95.6% ethanol at 25 ± 0.1 °C[20]

	X	Y	%B_1 (mol)	pK_{a_m} exp.	pK_{a_m} calc.
57	*p*-Me	*p*-Me	50	7.66 ± 0.03	7.55 ± 0.07
57	H	H	50	6.97 ± 0.03	
57	*p*-Br	*p*-Br	79 ± 6	6.51 ± 0.03	6.60 ± 0.05
57	*p*-Br	H	71 ± 4	6.19 ± 0.05	6.36 ± 0.08
57	*p*-Br	*p*-Br	50	5.52 ± 0.10	5.52 ± 0.11
57	*p*-Cl	*p*-Cl	50	5.63 ± 0.12	5.63 ± 0.11
58	*p*-OMe	H	37 ± 7	6.78 ± 0.04	6.64 ± 0.10
58	*p*-Me	H	40 ± 8	6.52 ± 0.04	6.45 ± 0.06
58	*m*-Me	H	45 ± 2	6.36 ± 0.03	6.29 ± 0.06
58	H	H	50	6.15 ± 0.04	
58	*m*-OMe	H	57 ± 4	6.04 ± 0.02	5.91 ± 0.07
58	*p*-F	H	61 ± 5	5.90 ± 0.03	5.76 ± 0.10
58	*p*-Cl	H	68 ± 8	5.46 ± 0.03	5.56 ± 0.12
58	*p*-Br	H	69 ± 9	5.42 ± 0.03	5.50 ± 0.12
58	*p*-I	H	70 ± 9	5.43 ± 0.08	5.47 ± 0.13
58	*m*-Cl	H	75 ± 11	5.23 ± 0.05	5.24 ± 0.16
58	*m*-Br	H	76 ± 12	5.25 ± 0.03	5.23 ± 0.16
58	*m*-NO_2	H	87 ± 16	4.24 ± 0.04	4.27 ± 0.27

ρ values for the two tautomeric forms may be different from those obtained for model *N*-alkylated compounds.

Correlations of pK_a values with substituent constants for other tautomerizing amidines were reported. Charton[33] found for unsubstituted amidines with a variable substituent bonded directly to the amidine carbon (**59**) that the pK_a values were correlated with the σ_m, σ_p and σ_I constants. Since unsubstituted amidines can be treated as symmetrically *N,N'*-disubstituted ones, linear regression can be applied. The best results were obtained for correlations with σ_m constants ($\rho = 11.98$, $r = 0.965$).

$$HN{=}CX{-}NH_2$$

(59)

TABLE 36. pK_a values of N-substituted phenylacetamidines (**10**) in ethanol at 25 ± 0.5 °C[29]

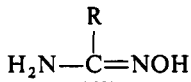
X	pK_a	X	pK_a
H	8.93	*m*-Me	8.85
m-NMe_2	9.09[a]	*p*-Me	9.17
p-NMe_2	9.68[b]	*o*-Cl	7.76
o-OMe	9.14	*m*-Cl	7.92
p-OEt	8.85	*p*-Cl	8.29
o-Me	9.09		

[a]For the NMe_2 group $pK_a = 2.98$.
[b]For the NMe_2 group $pK_a = 3.34$.

Passet and coworkers[29] correlated the pK_a values of *N*-arylphenylacetamidines (**10**, Table 36) with σ° constants and reported a ρ value of 2.089 ± 0.127.

C. Basicity of Amidoximes

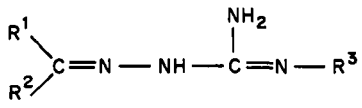
Amidoximes are useful analytical reagents with interesting applications[53] and their properties were studied extensively. By analogy to amidines it can be assumed that protonation occurs at the oxime nitrogen atom, as only in this case can a resonance-stabilized cation be formed. This, nevertheless, was for long a matter of controversy[7]. Papers dealing with this problem are still scarce. Gonçalves and Secches[54] compared the pK_a values of aminoamidoximes (**60**, R contains an amino group) with the pK_a of the corresponding aminonitriles (Table 37) and on this basis suggested that protonation occurs on the oxime nitrogen atom. In another paper[55] the pK_a values of three 4-isoxazolylamidoximes were determined with high accuracy but the question of protonation site was not mentioned.

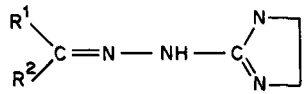


(60)

D. Basicity of Amidrazones

The pK_a values of several amidrazones **61**, **62** and **63**, referred to as guanylhydrazones, were correlated[56] with Taft σ^* constants and with inductive field constants[57,58] *F*. The pK_a values calculated on the basis of parameters of both correlations do not differ more than 0.3 pK_a units from those obtained experimentally (Table 38).





(61) $R^3 = H$
(62) $R^3 = Ph$

(63)

TABLE 37. pK_a values of amidoximes (**60**)[54]

R	Amino group	OH
$NH_2CH_2CH_2$	9.15	3.75
$NH_2(Me)CHCH_2$	9.15	3.65
$NH_2CH(Me)CH_2$	9.15	3.75
$NH_2CH(Ph)CH_2$	8.00	3.75
NH_2CHPh	7.15	2.30
$2\text{-}NH_2C_6H_4$	2.20[a]	4.50[a]
$PhNHCH_2CH_2$	2.45[a]	5.35[a]
$MeNHCH_2CH_2$	9.60	3.60
$Bu^nNHCH_2CH_2$	9.60	3.75

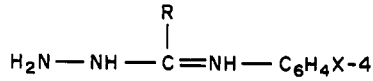
[a]According to the authors, the NH_2 and OH values in these two entries may possibly be interchanged.

TABLE 38. pK_a values of amidrazones **61**, **62** and **63**[56]

			pK_a		
				calculated	
	R^1	R^2	exp	from σ	from F
61	n-Pr	n-Pr	10.10	9.85	9.80
61	n-Hex	Me	10.00	9.79	9.71
61	n-Pentyl	n-Pr	9.85	9.87	9.80
61	2-Thienyl	H	8.48	8.63	8.80
61	Ph	H	8.75	8.88	8.89
61	2-Thienyl	Me	8.90	9.00	8.98
61	2-Thienyl	Ph	8.50	8.55	8.43
61	2-Quinolyl	H	8.05	—	8.21
62	n-Bu	Me	8.90	8.87	8.93
62	n-Pr	n-Pr	8.98	8.94	9.02
62	n-Hex	Me	8.90	8.88	8.93
62	n-Pentyl	n-Pr	8.80	9.04	9.02
62	2-Quinolyl	H	7.52	—	7.42
62	Ph	Me	8.10	8.32	8.29
62	Ph	Et	8.42	8.41	8.38
62	Ph	Ph	8.10	7.89	7.74
63	2-Thienyl	Ph	7.80	7.64	7.65
63	n-Pentyl	n-Hex	9.35	9.31	9.29
63	n-Octyl	Me	9.20	9.22	9.20
63	n-Pr	n-Hex	9.20	9.30	9.29
63	Ph	H	8.25	8.30	8.38
63	2-Thienyl	Ph	8.10	7.97	7.93

TABLE 39. pK_B values of amidrazones (**64**) in 80% ethanol at 25 °C[59]

R′	X	pK_B
p-$Me_2NC_6H_4$	H	7.10
Ph	OMe	7.88
Ph	Me	8.18
Ph	H	8.48
Ph	NO_2	10.47
2-Pyridyl	Me	9.39
2-Pyridyl	H	9.77
2-Pyridyl	NO_2	10.83

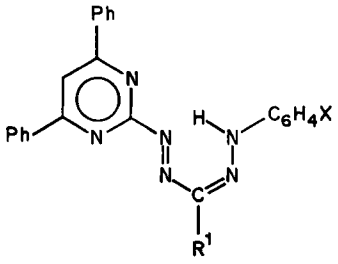


(**64**)

Basicities of several N^3-substituted amidrazones (**64**) were given[59] as the pK_B values (Table 39).

E. Basicity of Formazans

Papers on the basicity of formazans are not numerous. Acid–base properties of 1-aryl-2-[(4,6-diphenyl)-2-pyrimidynyl]-formazans (**65**) and 1-(2-hydroxyphenyl)-3-alkyl-5-(2-benzazolyl)-formazans (**66**) and their pK_a values (Tables 40 and 41) were reported[60–62], but neither the solvent nor the temperature of the measurements were specified.



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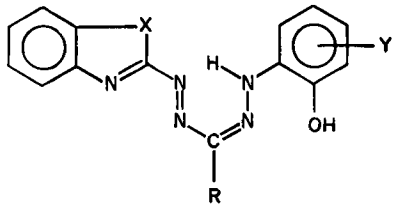
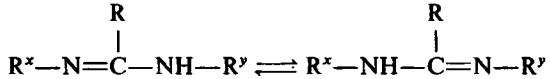


(66)

III. TAUTOMERISM AND H-BONDING

N,N'-disubstituted and monosubstituted amidines undergo prototropic tautomerism.



The tautomerization in amidines is very fast, and according to NMR studies[48,50,51] proton exchange occurs several times per second. When both substituents are identical both tautomeric forms are also identical, and the tautomeric equilibrium constant is equal to unity, while in all other cases it depends on the substituents.

TABLE 40. pK_a values[a] 1-aryl-3-phenyl-5-[(4,6-diphenyl)-2-pyrimidynyl]-formazans (**65**)[60]

R^1	X	pK_a
Ph	H	13.57 ± 0.08
Ph	*p*-Me	13.62 ± 0.02
Ph	*p*-OMe	13.94 ± 0.14
Ph	*p*-Cl	13.17 ± 0.08
Ph	*p*-Br	13.03 ± 0.05
Ph	*p*-COOH	13.06 ± 0.02
Ph	*p*-COOMe	12.85 ± 0.09
Ph	*o*-OMe	14.05 ± 0.09
Me	H	12.51 ± 0.11

[a]Probably in water solution; solvent and temperature not given.

TABLE 41. pK_a values[a] of 1-(2-hydroxyphenyl)-5-(2-benzazolyl)formazans (66)

R	X	Y	pK_a NH	pK_a OH	Ref.
Et	O	4-NO_2	5.78 ± 0.03	8.25 ± 0.04	61
Me	S	5-NO_2	8.60 ± 0.02	6.30 ± 0.01	61
Et	S	5-NO_2	8.52 ± 0.03	6.70 ± 0.02	61
Me	NH	4-NO_2	10.79 ± 0.28	7.45 ± 0.03	61
Me	NH	5-NO_2	10.67 ± 0.27	7.00 ± 0.02	61
Me	NCH_2Ph	5-NO_2	—[b]	6.84 ± 0.04	61
Et	NCH_2Ph	5-NO_2	—[b]	7.04 ± 0.01	61
Et	S	H	—[b]	9.51 ± 0.02	61
Et	O	H	—[b]	9.36 ± 0.02	61
Me	S	4-NO_2	6.68 ± 0.05	9.62 ± 0.03	62
Et	S	4-NO_2	6.75 ± 0.04	9.75 ± 0.01	62
Me	NCH_2Ph	4-NO_2	8.62 ± 0.06	10.20 ± 0.05	62
Et	NCH_2Ph	4-NO_2	8.86 ± 0.06	10.50 ± 0.05	62

[a]References 61 and 62 give neither solvent nor temperature.
[b]Given as 'determination unsuccessful'.

A. Tautomeric Equilibria, General Relations

Tautomerism of amidines was for years a matter of controversy. Prevoršek[63,64] investigating the IR spectra of monosubstituted and *N,N'*-disubstituted amidines stated: 'alkyl substituents tend to prefer attachment to the amino nitrogen atom of the amidine group, but the reverse is true for aryl groups'. His conclusions were in agreement with earlier work on *N*-arylamidines by Pyman[65,66] and were supported later by Moritz[67], who criticized the work of Grivas and Taurins[68,69].

The question, in which form an amidine exists, was often discussed in early studies. However, in the 1970s it became understood that there is always an equilibrium state, and that even if the amount of one of the forms may be over 99%, an equilibrium still exists. Thus the question became: which of the tautomers predominates in different cases? The groups of Gautier[70] and Reynaud[71] have determined the structure of the predominant tautomer by acylation or alkylation of the tautomeric mixture and study of the products. The tautomerism of *N*-phenylbenzamidines[29], sulphonylbenzamidines[72] and some cyclic amidines[73] was also studied by IR or NMR spectroscopy. However, no quantitative information on the position of the tautomeric equilibrium was obtained in these papers.

In 1964 Katritzky and coworkers[30,39] proposed a method based on measurements of pK_a values of two methyl derivatives, assuming that the difference between them is equal to the difference between the pK_a values of the two tautomers (equation 26), and applied this method to estimate equilibrium constants of monosubstituted acetamidines.

Development of NMR spectroscopy also enabled determination of tautomeric equilibria[74]. No relations between structural parameters and tautomeric equilibria were reported until 1985, when it was shown[20] that tautomeric equilibria for amidines can be predicted on the basis of polar effects of substituents at both nitrogen atoms.

1. Compounds with two tautomeric forms

In the case of *N,N'*-disubstituted amidines the equilibrium constant between tautomers B_1 and B_2 is defined as

$$K_T = \frac{(B_1)}{(B_2)} = \frac{x}{1-x} \tag{24}$$

where x is the molar fraction of tautomer B_1. Equations 15 and 16 indicate that the lower the basicity of a tautomer (i.e. the higher the acidity of its conjugated acid), the higher is its relative content in the equilibrium mixture. Dividing equation 15 by 16 we obtain

$$K_T = K_{a_1}/K_{a_2} \tag{25}$$

or, in logarithmic form,

$$pK_T = pK_{a_1} - pK_{a_2} = \Delta pK_a \tag{26}$$

Equation 26 implies that the molar fraction (x) of the base B_1 in the equilibrium mixture is determined by the difference between the pK_a values of both tautomers:

$$\log\left(\frac{1-x}{x}\right) = \Delta pK_a \tag{27}$$

The plot of this relation (Figure 6) shows that, if the pK_a values of both tautomers differ by one pK_a unit, the tautomeric mixture contains 90% of the less basic tautomer, i.e. the tautomer in which the stronger electron-withdrawing substituent is bound to the imino nitrogen atom. When the difference between pK_a values is about two pK_a units, practically only one of the two tautomers is present in the mixture.

Figure 6 presents a general relation for prototropic tautomerization of any compound with two tautomeric forms. In the case of amidines, the equilibria can be related to the polar effects at all the three sites[48], i.e. at both nitrogen atoms and the amidino carbon atom.

The relation between substituent constants and K_T values can be derived by substitution of pK_{a_1} and pK_{a_2} in equation 26 by values from equations 20 and 21, respectively. After rearrangement, a Hammett-type disubstituent equation 28 is obtained, where $\rho_T = \rho_{Im} - \rho_{Am}$. Equation 28 does not contain the term pK_T° because it is the pK_T of unsubstituted *N,N'*-diphenylamidine (X = Y = H), and thus is equal to 0. After replacement of $\sigma_X - \sigma_Y$ by $\Delta\sigma$ and $\rho_{Im} - \rho_{Am}$ by $\Delta\rho$ and further rearrangement, we obtain

$$pK_T = -\rho_T(\sigma_X^\circ - \sigma_Y^\circ) \tag{28}$$

$$K_T = 10^{\Delta\rho\Delta\sigma} \tag{29}$$

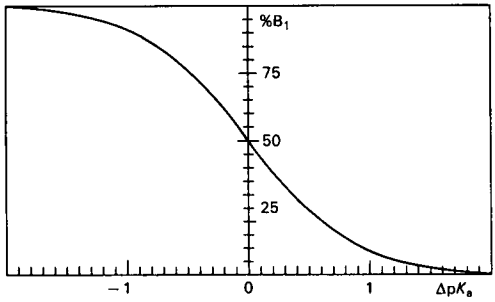


FIGURE 6. Plot of amounts (molar %) of individual tautomers in the equilibrium mixture vs the differences between pK_a values of individual tautomers (ΔpK_a). From J. Oszczapowicz, in preparation

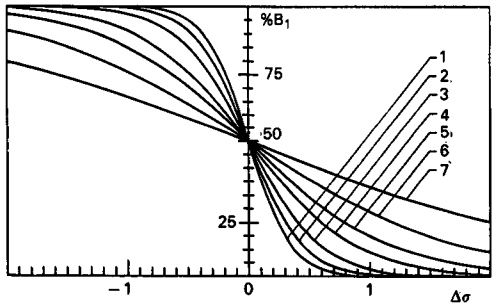


FIGURE 7. Plots of amounts (molar %) of individual tautomers in the equilibrium mixture vs the differences between σ values ($\Delta\sigma$) of substituents at both nitrogen atoms of the amidine group for various differences between the ρ values ($\Delta\rho$): 1, 2.5; 2, 2.0; 3, 1.5; 4, 1.0; 5, 0.75; 6, 0.50; 7, 0.30. From J. Oszczapowicz, in preparation

The plot of this relation for various $\Delta\rho$ values is presented in Figure 7. This shows that for the same pair of substituents X and Y on phenyl rings at the nitrogen atoms, and consequently for any pair of substituents R^x and R^y of any kind (aryl, alkyl or aralkyl), the equilibrium depends on the difference between the ρ values for substitution at the imino (ρ_{Im}) and amino (ρ_{Am}) nitrogen atoms, but not on the ρ values. As has already been shown, the two ρ values depend to a different degree on the substitution at the functional carbon atom[9,10,12,23,26], which therefore also influences the equilibrium state.

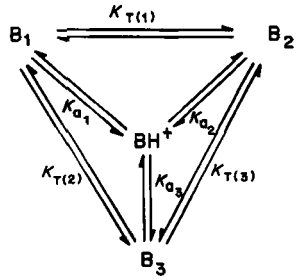
Support for the above conclusions was recently provided by *ab initio* calculations for several fluoroformamidines[45,46]. It was shown that the equilibrium is shifted towards the tautomer containing the electron-withdrawing substituent at the imino nitrogen atom, i.e. the less basic tautomer predominates in the equilibrium mixture. The substituent at the amidino carbon atom also causes considerable differences in the equilibrium constants of amidines identically substituted at both nitrogen atoms.

From a comparison of the total energies of pairs of tautomers, the general conclusion was drawn that the more basic is an amidine, the larger is the difference between the energy of the two tautomeric forms and, in consequence, the higher is the difference between the concentrations of tautomers. This was the reason why some authors[68,69] have claimed that some amidines exist in one tautomeric form only, since their conclusions concerned strongly basic amidines, with substituents of considerably differing polar effects at the two nitrogen atoms.

Obviously the equilibrium state depends also on the solvent, because it exerts an influence on both ρ values to a different degree[4,5,27,48].

2. *Compounds with three tautomeric forms*

General relations for compounds such as guanidines, 2-azolylamidines or 2-azolylformazans with three possible tautomeric forms can be derived[48]. Compounds which may exist in three tautomeric forms B_1, B_2 and B_3, but yield a common conjugated acid BH^+, have three microscopic dissociation constants: K_{a_1}, K_{a_2} and K_{a_3} (Scheme 2). The equilibrium in such systems is represented by three tautomeric equilibrium constants,



SCHEME 2

$K_{T(1)}$, $K_{T(2)}$ and $K_{T(3)}$, which can be defined as follows:

$$K_{T(1)} = \frac{(B_1)}{(B_2)} = \frac{K_{a_1}}{K_{a_2}} \tag{30a}$$

$$K_{T(1)} = \frac{(B_1)}{(B_3)} = \frac{K_{a_1}}{K_{a_3}} \tag{30b}$$

$$K_{T(1)} = \frac{(B_2)}{(B_3)} = \frac{K_{a_2}}{K_{a_3}} \tag{30c}$$

Equilibrium constants so defined obey equation 31:

$$K_{T(1)} = K_{T(2)}/K_{T(3)} \tag{31}$$

In such systems, again the least basic tautomer predominates. In the case of N^1,N^2,N^3-trisubstituted guanidines this will be the tautomer with the strongest electron-withdrawing substituent at the imino nitrogen atom. The ratio of tautomeric forms in an equilibrium mixture is given by the relation

$$B_1:B_2:B_3 = K_{a_1}:K_{a_2}:K_{a_3} \tag{32}$$

The macroscopic dissociation constant K_{a_m} in this case is defined as

$$K_{a_m} = \frac{[(B_1)+(B_2)+(B_3)](SH^+)}{(BH^+)} \tag{33}$$

Thus, as in equation 18, K_{a_m} is again the sum of the microscopic constants:

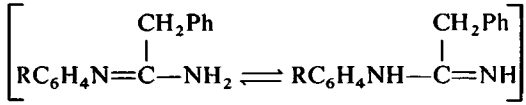
$$K_{a_m} = K_{a_1} + K_{a_2} + K_{a_3} \tag{34}$$

B. Tautomerism of Amidines

1. *Prototropic tautomerism*

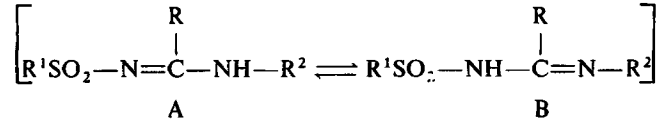
Granik[75] pointed out that in many cases only one of the two tautomeric forms was detected by physicochemical methods, and in the presence of an electron-withdrawing substituent the tautomer with this substituent at the imino nitrogen atom predominates. Passet[29] and coworkers stated: 'it is known that *N*-alkylated amidines exist in solutions as a mixture of two tautomeric forms with predomination of N^1-alkylated form; in contrast to that *N*-arylamidines exist as N^2-arylamidines'. But whether it is a mixture of two tautomers or a single tautomer was not discussed.

IR spectra have shown[29] that monosubstituted phenylacetamidines (**67**) in carbon tetrachloride solutions exist only in the form in which the aryl group is at the imino nitrogen atom.



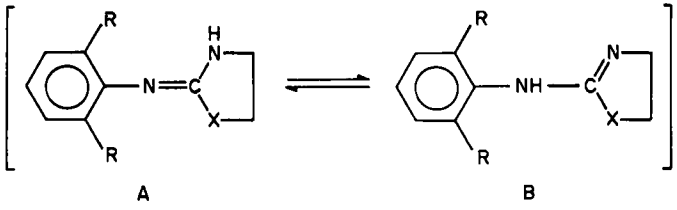
(67)

Tinkler[72] compared the pK_a values of sulphonylamidines (**68**) with those of sulphonylamides and sulphonylureas, assuming that the pK_a value of a sulphonylamidine should distinguish between the two tautomeric forms A and B if they exist separately. On the basis of the IR spectra he has found that in solutions of *N*-alkylsuphonylamidines the form with the sulphonyl group at the imino nitrogen atom predominates. Changes in the IR spectra on dilution indicated that monosubstituted *N*-sulphonylbenzamidines (**68**, $R^2 = H$), in contrast to the substituted compounds, displayed intermolecular hydrogen bonding.



(68)

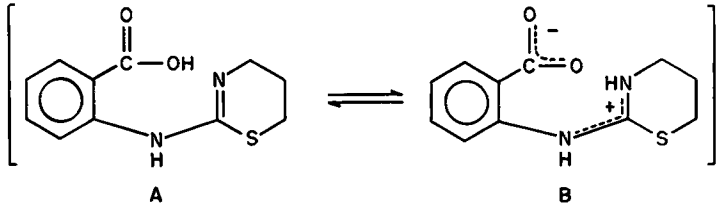
Jackman and Jen[73] investigated the structure of the predominant tautomer in cyclic amidines (**69**) using ^1H NMR and ^{13}C NMR spectra and found that in all cases the imino tautomer A predominates. They have also shown that this is true also for oxa analogs (X = O) as well as for cyclic guanidines (X = NH). In open-chain guanidines also the form with the phenyl ring at the imino nitrogen atom predominates. However, the paper does not state whether the presence of the second tautomer is detectable or not.



(69)

The tautomeric structure of 2-amino(imino)thiazines (**69**, X = SCH_2) was a matter of interest and confusion for many years, and may serve as a good example of how the reliablity of conclusions on tautomerization depends on the techniques of structure determination available at the time, as well as on the proper application of these techniques. The 2-phenylimino thiazine (**69**, R = H), was synthesized by Tisler[76,77] and on the basis of IR and UV spectra of the compound and its methylated derivatives, was assigned the imino form. A few years later it was shown[78] that the structures of the methylated compounds were improperly assigned, and it was concluded[78,79] that the amino structure must be assigned to it. However, just two years later Rabinovitz[80,81], considering the coupling between methylene protons and an NH proton in the spectrum of the protonated compound, supported Tisler's assignment. Jackman and Jen[73] have shown that in fact the compound exists in the imino form, although they found Rabinovitz's

interpretation unconvincing, because the *ortho*-carboxyl derivative (**70**) most likely exists as a zwitterion and the question of tautomerism does not arise.

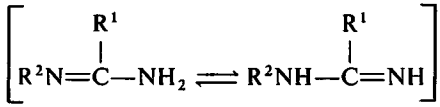


A B

(**70**)

Jakobsen and Treppendahl[82,83], while investigating *N*-sulphonylformamidines, have also found that the sulphonyl group is at the imino nitrogen atom. The tautomer containing the electron-withdrawing group at the imino nitrogen atom predominates also in *N*-thiophosphorylbenzamidines[84].

Quantitative estimations of tautomeric equilibria in *N*-acylamidines (**71**, $R^2 = RCO$) and sulphonylamidines (**71**, $R^2 = RSO_2$) were conducted on the basis of the difference between pK_a values of the two corresponding *N*-methyl derivatives by Katritzky and coworkers[30]. They found that in all cases the form with the acyl or sulphonyl group at the imino nitrogen atom predominates, and the K_T value is *ca* 30 for acylamidines and *ca* 10^7 for the sulphonyl compounds.



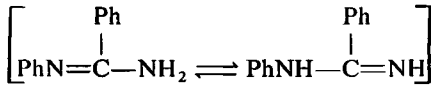
(**71**)

For *N*-phenylacetamidines[39], on the basis of UV spectra it was found that the imino *N*-aryl tautomer predominates and the pK_T value of 2.4 was obtained from basicity measurements.

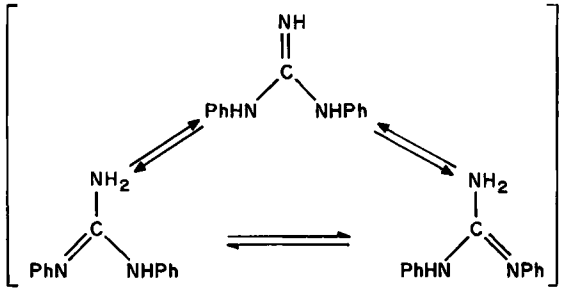
An attempt was made at combining the correlation method[20] with the approach based on the differences between pK_a values of the corresponding methylated derivatives[85,86], and the equilibrium constants estimated by Katritzky and coworkers[30] for mono-substituted acetamidines (**71**, $R^1 = Me$, $R^2 = XC_6H_4$) were called into question[85]. However, the reasoning was based on the erroneous assumption that substitution at one of the nitrogen atoms bears no influence on the ρ value for substitution at the second nitrogen atom. Therefore the microscopic pK_a values of tautomers obtained are only estimates. Proper evidence for accuracy of such estimations could only be provided by agreement of predicted and experimentally obtained macroscopic pK_{a_m} values for series of amidines in which the amount of a certain tautomer would be varied over the wide range of 0 to 100%. Evidence could be provided also by good agreement with the determinations of equilibrium constants obtained by NMR spectroscopy for solutions in the same solvent in which the pK_a values were determined, but in neither of the two papers[85,86] was any experimental evidence given for the presented assumptions.

Tautomeric equilibria in N-monosubstituted benzamidine (**72**) and *N,N'*-diphenylguanidine (**73**) were studied by Clement and Kämpchen[74]. On the basis of ^{15}N NMR spectra they found that the tautomer containing the phenyl ring at the imino nitrogen atom predominates in the mixture. The amount of the second tautomer, in *N*-phenylbenzamidine (**72**) in water solution, was found to be 2% or 11%, depending on which of the two nitrogen atoms in the corresponding methylated derivatives was taken as

the basis for calculation (cf. Sections III.A and III.C, chapter on detection and determination, this volume).



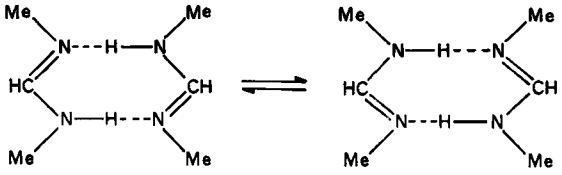
(72)



(73)

Tautomerization of amidines was also a subject of *ab initio* calculations[45,46,87-89]. The results have shown that tautomerization is facilitated by hydrogen bonding between amidine molecules, or by hydrogen bonding with other molecules[88,89]. It was also shown that the more stable tautomer is that containing the electron-withdrawing substituent at the imino nitrogen atom[45,46], and that the difference of energies between the two tautomers depends on the substitution at the amidino carbon atom and on the configuration (*cis–trans*) on the C=N double bond[46].

Prototropic tautomerism in amidines is facilitated by intermolecular hydrogen bonding, for which experimental evidence was provided by several studies. Halliday, Symons and Binder[50], on the basis of ^{1}H NMR and IR spectra of *N,N'*-dimethylformamidine, assumed that tautomerization occurs through a hydrogen-bonded cyclic dimer (**74**). Effectively 100% association was shown for the neat compound. From



(74)

^{1}H NMR data the following rate constants of tautomerization were found for **74** in various concentrations and solvents (in s^{-1}):

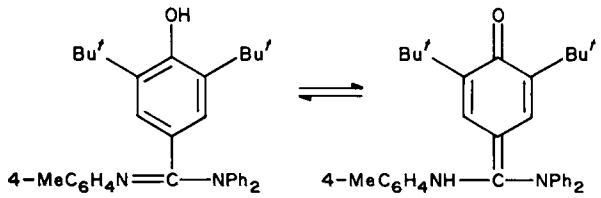
neat liquid	CD_3NH_2 (1.4 m)	$CDCl_3$ (0.5 m)	$CDCl_3$ (2.9 m)
8.2×10^2	7.4×10^2	6.3×10^3	4.2×10^3

Differences in the lifetime of tautomers may be caused by changes in the monomer–

hydrogen-bonded dimer equilibrium with dilution. The authors[50] assumed that the effects are also caused by changes in the dimer structure in different solvents.

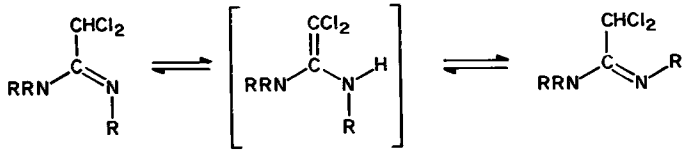
Amidines may also form a hydrogen bond with other groups or molecules containing nitrogen atoms. Baudet and Rao[90] postulated H-bonding between the hydrogen atom of the amidino group and the nitrogen atom of benzothiazolyl moiety in 2-benzothiazolylamidines to explain a considerable decrease of γ_s(NH) and γ_{as}(NH) frequencies in the IR spectra. Intramolecular H-bonding between an amidino NH group and the nitrogen atom of a thiazole ring in some histamine receptor antagonists was studied by ^{1}H NMR spectroscopy[91].

Another type of prototropic tautomerization was observed[92] in the case of N^1,N^1-diphenyl-N^2-*p*-tolyl(4-hydroxy-3,5-di-*t*-butyl)benzamidine (**75**) where the proton of the phenol group migrates to the imino nitro nitrogen atom, and a quinoid tautomer is formed. In this particular case both tautomers were isolated and their structures confirmed by IR and ^{1}H NMR spectra.



(**75**)

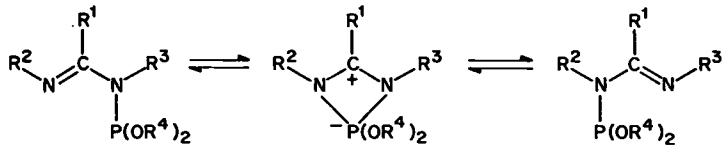
A similar type of tautomer, with two amino groups and a C=C double bond, was postulated[93] as an intermediate to explain the *Z*–*E* isomerization in chloroacetamidines (**76**).



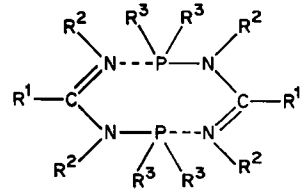
Z (**76**) *E*

2. Other tautomerisms

In addition to proton migration, other tautomerisms were also observed. In the case of amidines containing a strongly electron-withdrawing group at the amino nitrogen atom, other types of tautomerism referred to as tautomeric migration[94–97], permutative isomerization[98,99] or 1,3-migration[97,100] were reported. For amidines containing a N—P bond (**77**), migration of the phosphorus-containing group was observed in the NMR



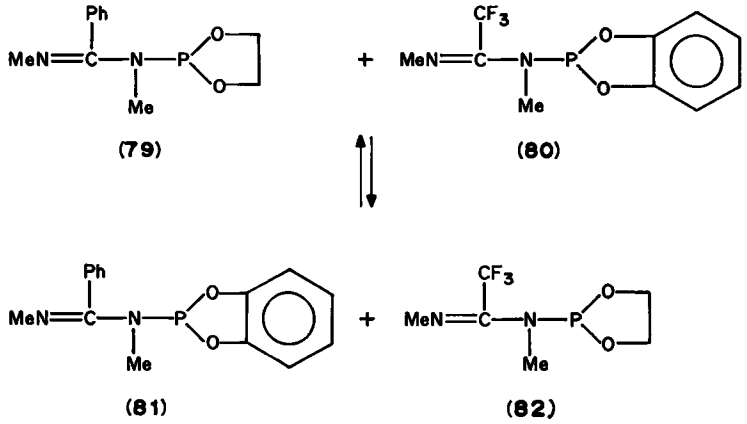
(**77a**) (**77b**) (**77c**)



(78)

spectra[94-96,98,99]. It was assumed that tautomerization occurs either via a cyclic form[94-96,98,99] **77b** or by a cyclic dimer **78**.

Chemical evidence for such processes was provided by heating equimolar mixtures of either **79** with **80**, or of **81** with **82**, when all four exchange products are formed[95] (Scheme 3).



SCHEME 3

Migration of an electron-withdrawing group was reported[98] for N^1-*p*-chlorosulphinyl-N^1,N^2-di(*p*-tolyl)-amidine (**83**), as well as for *N*,*N*′-di-(*p*-tolyl)-*N*-2,4,6-tris(trifluoromethylsulphonyl)phenylbenzamidine (**84**)[100] (Scheme 4).

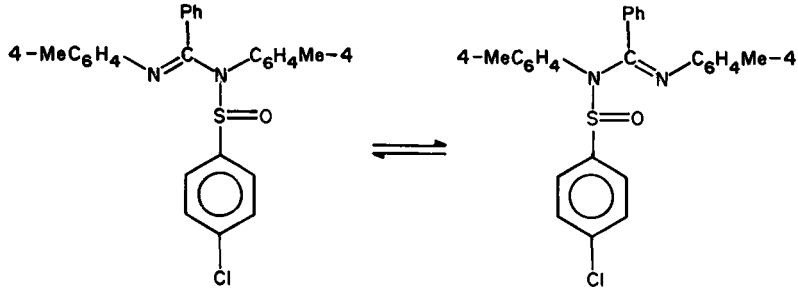
The last process is very fast, and in the ^{1}H NMR spectra separate signals of the methyl groups in the two tautomers are observed only below $-10\,^{\circ}C$.

C. Tautomerism of Amidrazones

Amidrazones undergo prototropic tautomerism and may exist in the amide hydrazone form (**85a**), usually referred to as amidrazone, and in the hydrazide imide form (**85b**), the former being the preferred one[101-104].

In previous review[105,106], amidrazones were classified as those capable of existing in tautomeric forms and those which cannot tautomerize. It was stated[106] that even where tautomerism is possible 'only one tautomer is normally obtained, there being no evidence for the presence of tautomeric mixtures', and further: 'The structure of some substituted amidrazones is less clear cut'.

To understand tautomerism in amidrazones they have to be considered as amidines containing a substituted or unsubstituted amino group NR^2R^3 at one of the amidino



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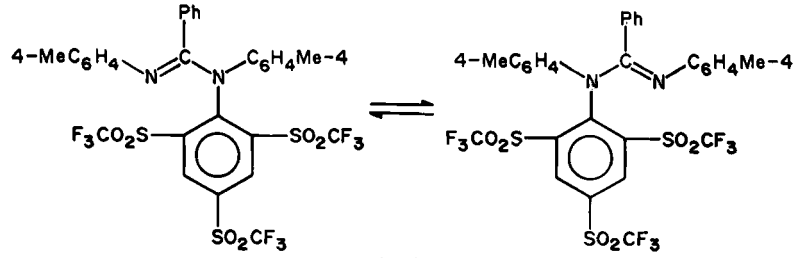

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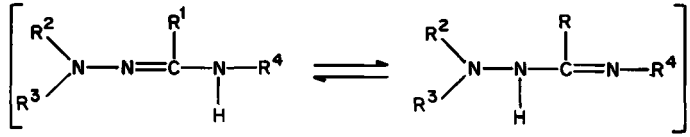
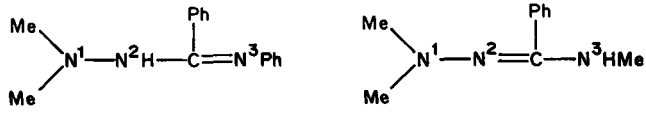
SCHEME 4



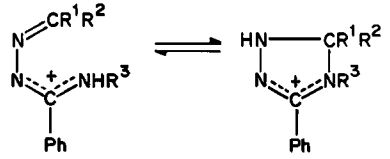
(85a) (85b)

nitrogen atoms. With this approach it becomes clear which amidrazones may tautomerize and equations 24–29 can be applied to predict this ability. It was shown (Section III.A.1) that in the equilibrium mixture the tautomer with the stronger electron-withdrawing group at the imino nitrogen atom predominates, and the equilibrium position depends on the difference between the σ values of the substituents at the two nitrogen atoms (Figures 6 and 7). Thus, amidrazone (**86**) exists exclusively in the hydrazide imide form[101], but if the N^3-phenyl group is replaced by an N^3-methyl group (**87**), apparently the exclusively formed tautomer[102] is the amidrazone.



(86) (87)

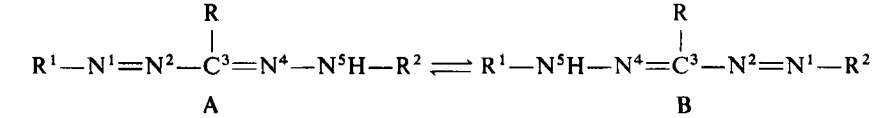
Another type of tautomerization was observed for N^1-alkenylidene amidrazone salts[107] (**88**). Using ^{13}C NMR spectroscopy it was found that they undergo ring-chain tautomerization **88a–88b**, and the equilibrium depends to a considerable degree on steric effects. The presence of a substituent at the N^2 nitrogen atom makes the cyclic form preferable; otherwise the chain form **88a** predominates. A substituent at the N^3 nitrogen atom has only little effect on the equilibrium.



(88a) (88b)

D. Tautomerism of Formazans

Unsymmetrically 1,5-disubstituted formazans (**89**) may exist in the two tautomeric forms A and B, where the N^1 and N^5 nitrogen atoms may be called 'azo' and 'hydrazo' nitrogen atoms, respectively.



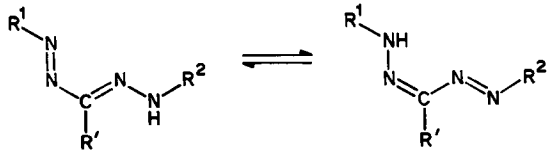
A B

(89)

The numbering of atoms in formazans is different from that of amidines. To show that owing to tautomerism the position of a substituent is not clearly defined, two locants for a substituent are given, the second (less probable) in parentheses; however, this system is not in general use. Numbering begins with the double-bonded terminal nitrogen atom, as shown in **89**.

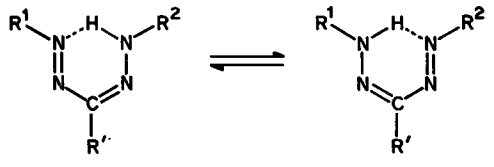
Formazans may formally exist in various configurational and conformational forms. Configuration at both C=N and N=N double bonds may be *syn* or *anti*, and conformational arrangements on single bonds also contribute to the variety of forms. Moreover, each geometrical form may exist as a mixture of two tautomers[62,108–111].

However, the data indicate that all atoms of the formazan group are practically coplanar, and that on both nitrogen–nitrogen bonds there is an *anti* configuration, or conformation, respectively. Thus mainly two geometrical forms are observed, the one (**90**) referred to as 'the open form'[111] and the second (**91**), with an intramolecular hydrogen bond forming a six-membered ring, referred to as the 'chelated form'[109,110].



A B

(90)

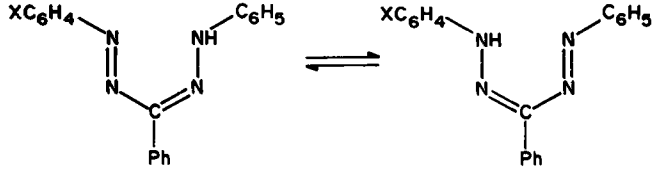


A B

(91)

In the treatment of structure–basicity relations and of tautomerism, the formazan group can be treated as an amidino group, where the system of conjugated double bonds is extended by an additional azo double bond at the amino nitrogen atom, and by a nitrogen atom at the imino nitrogen atom. Thus it could be expected that the general conclusions concerning the structure of the predominant tautomer in amidines were valid for formazans as well, and that in the equilibrium the tautomer containing at the double-bonded nitrogen atom the more electron-withdrawing group will predominate.

In several papers dealing with formazans the conclusions are just the opposite. It was shown that the more electron-withdrawing substituent is at the single-bonded hydrazo nitrogen atom[108,110,112]. However, it has to be pointed out that in these papers the structures, determined by ^1H or ^{13}C NMR spectroscopy, are referred to the structure of 1,3,5-triphenylformazan (**92**) containing a nitro group at one of the terminal phenyl rings, as determined by Fischer, Kaul and Zollinger[113]. The authors recorded the ^1H NMR spectra of three labelled formazans (**92**, X = H, OMe, 4-NO_2) which contained a ^{15}N atom bonded to an unsubstituted phenyl ring and the three corresponding unlabelled ones.



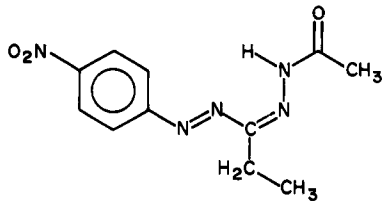
(92A) (92B)

Usually, in the ^1H NMR spectra of compounds containing a ^{15}NH group, the signal of the proton at the nitrogen atom is split into a doublet by the ^{15}N–^1H coupling. It was found that the NH signal in labelled *N*-phenyl- and *N*-(*p*-methoxyphenyl)formazans was a doublet, whereas for the *p*-nitro derivative and for unlabelled compounds the NH signal was a broad singlet. It was then concluded that in the case of the first two derivatives the proton is at the ^{15}N atom, i.e. the substituted phenyl ring is at the azo (N^1) nitrogen atom. From the lack of splitting in the other cases it was concluded that the *p*-nitrophenyl derivative exists practically as a single tautomer B, with the *p*-nitrophenyl group at the hydrazo nitrogen atom.

Interpretation of the NMR data is, however, not convincing. The presence or absence of ^1H–^{15}N coupling is not a reliable criterion for determining the structure of the formazan. It is well known that the absence of NH coupling is often a consequence of a high rate of proton exchange, and thus it cannot be taken as evidence of the C=N double-bond position. Neither was the possibility of hydrogen bonding between N^1 and N^5 nitrogen atoms considered. The spectra of formazans labelled at the second nitrogen atom was also not studied, and therefore there is no evidence that the NH coupling will be observed for a nitrogen atom bonded to a *p*-nitrophenyl group. Moreover, the splitting of the NH signal does not mean that the second tautomer which contains the hydrogen at the unlabelled

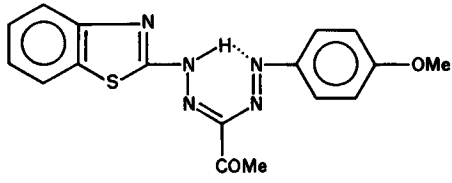
nitrogen does not exist in the mixture, because it may happen to be unobservable. Therefore the problem calls for reinvestigation using other techniques.

Support for the assumption that equilibria in formazans and amidines obey the same rules is provided by the paper of Buzykin and coworkers[111]. The authors determined the structure of 1-(4-nitrophenyl)-3-ethyl-5-benzoylformazan (**93**) by X-ray analysis[111] and found it to be in an 'open' form. The obtained bond lengths (N^1N^2:1.259(3) Å, N^4N^5:1.370(3) Å, N^2C^3:1.425(3) Å and C^3N^4:1.281(3) Å) show that the *p*-nitrophenyl group is at the double-bonded (azo) nitrogen atom. The ^{1}H NMR chemical shifts of some other *N*-acyl-*N'*-(4-nitrophenyl)-formazans, reported in the same paper, indicate that they also exist in the tautomeric form with the phenyl ring at the azo nitrogen atom, i.e. in the form expected on the basis of general considerations for amidines. Unfortunately, this paper was devoted mainly to conformational and configurational aspects and the authors did not note that their results may throw new light on the problem of tautomerization of formazans.



(93)

The X-ray-determined structure[109] of 1-(*p*-methoxyphenyl)-3-phenyl-5-(2-benzothiazolyl)-formazan (**94**) shows that in this case both nitrogen–nitrogen bond lengths (1.33(2) and 1.31(2) Å, respectively) are equal. The two C^3—N bonds, 1.34(3) and 1.39(2) Å, are slightly different similarly to the bonds between terminal nitrogen atoms and carbon atoms of the 2-thiazolyl and *p*-methoxyphenyl moieties, which are 1.37(3) and 1.43(2) Å, respectively. Thus it can be concluded that either the amounts of the two tautomers are equal, or that in this case the question of a predominant tautomer does not exist. The equalization of the bond lengths in the formazan group provides also confirmation for strong hydrogen bonding.



(94)

Tautomeric equilibria in the gas phase for 1(5)-phenyl-3-phenyl-5(1)-(2-benzthiazolyl)-formazans (**95**, X = S, $R^1 = 4\text{-}C_6H_4Y$, R = Ph) and 1(5)-phenyl-3-phenyl-5(1)-2-benzimidazolyl)-formazans (**95**, X = NR) were estimated on the basis of the peak distributions in their mass spectra[109] (Table 42). In addition to the two tautomeric forms involving the formazan group only, a third one (**95C**) was assumed[114]. It is noteworthy that the tautomer C was not differentiated from A, so there is no evidence of its amount.

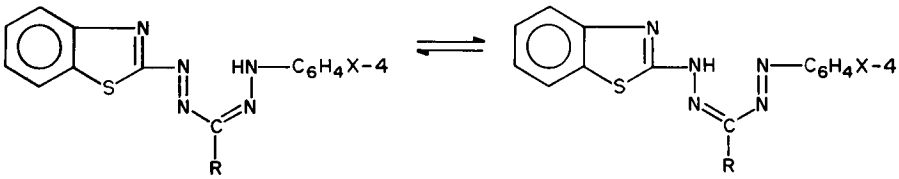
Tautomeric equilibria in 1(5)-phenyl-5(1)-(2-thiazolyl)-formazans (**95D** and **E**) were

TABLE 42. Tautomeric equilibria of 1(5)phenyl-3-phenyl-5(1)-(2-benzthiazolyl)-formazans (**95**), as estimated on the basis of their mass spectra[109]

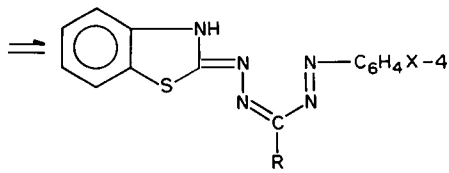
X	% (A + C)	% B
H	89.3	10.7
Me	90.6	9.4
NMe_2	91.9	8.1
OMe	89.6	10.4
Cl	93.6	6.4
Br	94.2	5.8
COOH	90.1	9.9

TABLE 43. Tautomeric equilibria of 1(5)-phenyl-5(1)-(2-thiazolyl)-formazans (**95D** and **E**) in $CDCl_3$ and DMSO solutions[110]

	% of B form	
X	$CDCl_3$	DMSO
OMe	0	2
Me	30	26
H	50	40
Br	40	36
NO_2	70	80



(**95A**) (**95B**)



(**95C**)

determined on the basis of the averaged chemical shifts in their ^{13}C NMR spectra[110] (Table 43).

IV. COMPLEX FORMATION

A. Complexes of Amidines

Complexes of amidines, depending on the bonding type, can be classified into three main groups. The first group comprises collision complexes with proton-donating compounds. The second group consists of complexes with metals or complexes with other ligands. The third group comprises boron complexes.

1. Collision complexes

Collision complexes are formed by hydrogen bonding of proton-donating molecules to the nitrogen atoms of the amidine. Vaes, Faubert and Zeegers-Huyskens[115] have found

that N^1,N^1-dimethyl-N^2-phenylformamidines (**26**, $R^x = XC_6H_4$), in carbon tetrachloride solutions, form complexes with ethanol and phenols, and that the formation of the hydrogen bond takes place on the imino nitrogen atom. For complexes with ethanol it was found that the differences $\Delta\nu$(OH) between the stretching O—H vibration frequencies in complexed and uncomplexed ethanol molecules correlate with the Hammet σ constants of substituents on the phenyl ring in the amidine molecule according to the relation

$$\Delta\nu(\mathrm{OH}) = 300 - 53.7\sum\sigma \qquad (r = 0.96)$$

Stability constants K also correlate with the σ values:

$$\log K = 0.74 - 0.48\sum\sigma \qquad (r = 0.98)$$

For complexes with substituted phenols, it was found that stability constants correlated with σ constants of substituents both on the phenyl ring in the N^1,N^1-dimethyl-N^2-phenylformamidine and on the phenol molecule according to the general equation 35, where σ_a and σ_b are σ values of the substituents in the two types of molecule.

$$\log K = \log K^\circ + \rho_a\sum\sigma_a + \rho_b\sum\sigma_b + B\sum\sigma_a\sum\sigma_b \qquad (35)$$

The stability constants of the 2:1 complexes were also calculated, and it was concluded that 'the second molecule of phenol seems to be bonded to the oxygen atom of the first phenol molecule rather than to the amino nitrogen atom'[115].

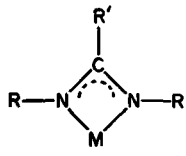
Mierzecki, Oszczapowicz and Kozakowski[116] have shown that amidines form complexes with chloroform molecules. Infrared studies of deuteriochloroform complexes with various formamidines have shown that complexes containing a larger number of molecules are also formed besides 1:1 complexes. In the IR spectra of these mixtures two new bands for the stretching ν(CD) vibrations appear, providing evidence for two kinds of complexes. As in such a system the only possible electron donors are amidine nitrogen atoms, it was concluded that both nitrogen atoms may be involved in the formation of 2:1 complexes.

In a further study[117] on 1:1 complexes of amidines with deuterated chloroform, the differences ($\Delta\nu$) between ν(C—D) stretching frequency in uncomplexed and complexed $CDCl_3$ molecules were determined for 75 N^1,N^1-dimethylamidines including dimethylformamidines (**26**), dimethylacetamidines (**27**), dimethylisobutyramidines (**44**) and dimethylpivalamidines (**45**). In the case of N^2-alkylamidines the two bands are well separated and the $\Delta\nu$ is as high as 50 cm^{-1}, while for N^2-phenylamidines it is lower but still discernible. It was found that $\Delta\nu$ correlates with the pK_a values of amidines as well as with the σ values of substituents at the phenyl ring in N^2-phenylamidines. For alkyl- and aryl-substituted formamidines (**26**) and acetamidines (**27**) a good, common correlation is obtained. For isobutyramidines (**44**) and pivalamidines (**45**) better results are obtained if correlations are calculated separately for N^2-alkyl and N^2-aryl substitutions. This was explained by differences in configuration of the C=N double bond. As was recently shown[47], N^2-phenylamidines containing an isopropyl (**44**) or *t*-butyl (**45**) group at the amidino carbon atom are, like all formamidines and acetamidines, in the *trans* configuration, but those containing aliphatic substituents at the imino nitrogen atom are *cis* isomers.

2. *Metal complexes of amidines*

Complexes of amidines with metals can be further classified according to the type of bonding between the amidine molecule and the metal ion. Three kinds of 1:1 complexes are possible: symmetrically chelated (**96**), unsymmetrically chelated (**97**) and *ortho*-metallated (**98**) ones. Metals can be complexed also by two (**99**) or three (**100**) amidine molecules. *Ortho*-metallated complexes (**98**) may form complexes with an additional

molecule of amidine[118]. If the amidine molecule takes part in complexing of two metal ions (bridging complexes), then the amidine may bridge either two identical (**101**) or two different (**102**) metal atoms.



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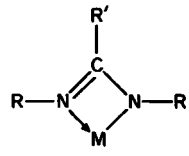

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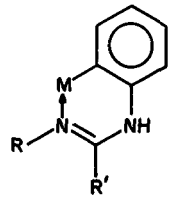

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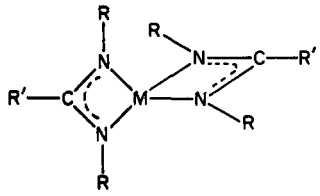

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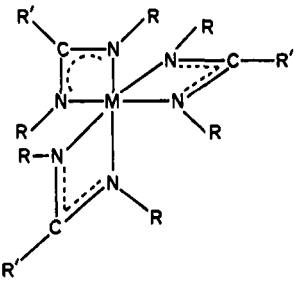

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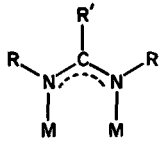

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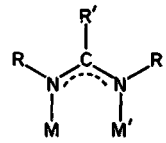


(102)

The various bonding modes of amidines to metals have attracted much interest. The amidino group in the majority of its complexes bonds as an *N,N'*-chelate[119-124] or *N,N'*-bridging[125-133] three-electron donor, although it is known to act as a monodentate one-electron ligand to transition metals[134]. Symmetrical chelate amidino groups have been assigned to a variety of tungsten[120,122-124], manganese[119-121], rhenium[121], platinum[135] and palladium[135] complexes. Unsymmetrical chelate groups, as found[126] in $[TaMeCl_2\{Pr^iNC(Me)NPr^i\}_2]$, are less well documented. *N,N'*-bridging amidino groups were found in molybdenum[125], rhenium[130] and silver–platinum[136] complexes. In addition to coordination to metals as monodentate and bidentate groups, amidines act also as nucleophilic reagents towards coordinated carbonyl and nitrile groups[118]. *N,N'*-Diphenylformamidines, acetamidines and benzamidines react thermally or photolytically[118] with rhenium carbonyls $Re(CO)_5X$ or $[Re(CO)_4X]_2$, where X = Cl or Br, to afford stable complexes $Re(CO)_4[RNC(R')NHR]X$ containing monodentate amidine ligands.

Several stereochemical problems of metal complexes with amidines are discussed in the literature. However, these are problems of complex chemistry rather than of amidines, and

therefore will not be discussed here in detail. In the complexes with one metal atom the question of the spatial arrangement of the ligands arises, particularly in the case of complexes with metal carbonyls. If two or three unsymmetrically *N,N'*-disubstituted amidine molecules are complexing one metal atom, the possibility of chiral compounds exists, where the metal atom is an asymmetry centre. For example, it was found that amidines react with $PhMo(CO)_3Cl$ to yield $Ph(CO)_2Mo$–amidinato chelate complexes, in which the molybdenum atom is an asymmetric center[137]. With optically active amidines pairs of diastereoisomers, and with racemic chiral amidines diastereoisomeric pairs of enantiomers are obtained, which can be separated. The [α] values for these complexes are very high (from + 6165 to − 3930 at 578 nm) and depend on the wavelength. Considerable differences in their CD spectra were found. The compounds epimerize by change of configuration at the Mo atom. It was shown[137,138] that the conformations of optically active substituents with respect to the Mo–amidinato complexes can be unambiguously determined by CD or ^1H NMR spectra.

With $C_5H_5Mo(CO)_3Cl$, optically active amidines $R^xN{=}CR^1{-}NHR$ form $C_5H_5(CO)_2Mo$–amidinato complexes which differ in configuration on the molybdenum atom[139]. Diastereoisomers can be separated by crystallization. In solutions epimerization occurs. Equilibrium between the isomers depends on temperature, solvent and on the kind of substituents.

In one case the absolute configurations of four diastereoisomers having the composition $(R''C_5H_4)Mo(CO)_2[(HCPhR){-}N{-}C(Ph){-}N{-}(HCPhR')]$ were established by X-ray diffraction methods[140].

a. Complex formation. Metal complexes of amidines are obtained by various methods, depending mainly on the constituents.

With metal salts in boiling ethanol amidines form[141] complexes of general formula $Me[(amidine)_2{\cdot}(H_2O)_2]$ where Me is Mn, Fe, Co, Ni or Cu. Copper acetate reacts with *N,N'*-bis(benzoyl)-pentasulphinamidine (HL) in benezene solution to give a Cu(OAc)L complex[142].

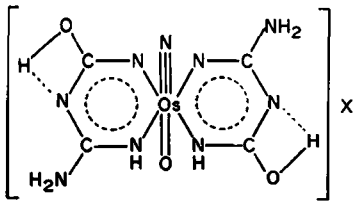
With $Os_3(CO)_{14}$ or $Os_3(CO)_{10}$(cyclooctene)$_2$, *N,N'*-dibenzyl- or *N,N'*-diisopropyl-formamidines react[143] to give different types of nonacarbonyl complexes $HOs_3(CO)_9$-($Pr^iNCHNPr^i$) and $HOs_3(CO)_9(PhCH_2NCH_2Ph)$, the difference being in the ability of the benzyl group to be *ortho*-metallated.

Ruthenium salts react in acetonitrile with pyrazole derivatives to give[144–146] amidine complexes, which were characterized by the IR and NMR spectra, and in some cases by X-ray analysis[146].

Dimethylgallium or molybdenum complexes react with pyrazole derivatives and *ortho*-aminophenol to give complexes of the type $Na^+[Me_2Ga(pyrazolyl)(o\text{-aminophenol})]$. This complex reacts with $NiBr_2$, $Re(CO)_4Cl$ or $(MeCN)_3Mo(CO)_3$ yielding the corresponding nickel, rhenium or molybdenum complexes[147]. Structures of some of the complexes were determined by X-ray diffraction method.

Nitrido complexes of osmium with amidines are formed in the reaction of $KOsO_3N$ with amidinoisourea sulphate in water at pH ~ 10, when a crystalline complex of the type $[OOsNL_2]OH{\cdot}H_2O$ (L = amidinoisourea) insoluble in common organic solvents is obtained (**103**). The structures of the complexes with various amidinoisoureas were determined[148] on the basis of the structures of ligands and IR characteristics of the complex.

In complexes of amidines with cobalt(III) it was found[149,150] that the complex (**104**) has a hexadentate ligand which involves a novel diamidine arrangement of an *N,N'*-disubstituted amidine and a trisubstituted amidine, each amidine group being coordinated through one nitrogen. The structures have been characterized by ^{13}C and ^1H NMR and IR spectra.



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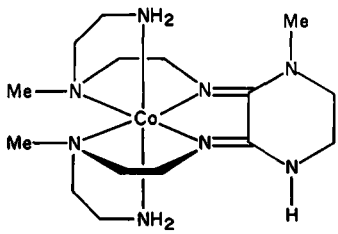


(104)

It was shown[151] that reactions of the iridium complex $[(Ph_3P)_2(CO)IrCl]$ with [M(RN=CH—NR')], where M is Cu or Ag, afforded the complex $[(Ph_3P)_2(CO)IrM(RN{=}CH{-}NR')]$ in which the formal iridium to metal donor bond is stabilized by a bridging formamidino group. The ease of complex formation and its stability depends on the metal and on the size of the group R. For small R groups the stability and the ease of complex formation is higher than for bulky R groups. For Ag complexes it was found that for small R groups two isomers were formed, the NR group being bonded to either Ir or Ag, but in the case of bulky R groups the NR group is always bonded to Ag.

Complexes of amidines with rhodium and mercury of the composition $[diene(RNC(R')NR^1)_2RhHgCl]$ are formed in almost quantitative yield in the reaction[133] of $[(diene)RhCl]_2$ with $[Hg(RNC(R')NR^1)_2]$. These complexes in the solid state are probably dimeric, while in solution they are definitely monomeric. NMR data show that the molecular configuration consists of the rhodium atom coordinated by a bidentate diene, and a bidentate amidino group, which bridges the Rh—Hg bond. The ^{13}C NMR data show that the complexes are fluxional. The process involves an interchange of the bridging and the chelating amidino groups via monodentate intermediates. The diene ligands do not exchange with free olefins, but the formamidino group can be rapidly replaced by a more acidic triazenido or amidino group.

b. Practical applications of amidine complexes. Metal complexes of amidines are applied for spectrophotometric determination of some metals, such as molybdenum[152], tungsten[153], niobium[154] and antimony[155]. The method is based on extraction from solution containing thiocyanate and metal ions as a complex with a derivative of *N,N'*-diphenylbenzamidine.

$Mo^{(V)}$ was detected by extraction from a solution containing amidine hydrochloride, thiocyanate and ascorbic acid as the 1:2:2 Mo–SCN–amidine complex into benzene, followed by absorbance measurements[156]. The method is sensitive and selective and free from interference by metal ions commonly associated with molybdenum in various ores and minerals. The applicability of the method has been confirmed by using it to determine Mo in steel samples, and the dust obtained from phosphate fertilizers.

A comparative study of the extraction of $Nb^{(V)}$ in benzene and chloroform showed that extractability and selectivity of the method are greatly affected by the nature of the solvent. In the determination of niobium, Mo interferes and has to be removed by prior extraction. Other metals do not interfere in benzene. The method was applied to the recovery of niobium from columbite.

Determination of tungsten[153] is based on reduction of $W^{(VI)}$ to $W^{(V)}$ and extraction of the resultant thiocyanate complexes with a benzene solution of amidine. The method is applied to steel alloys.

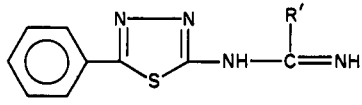
A method for the determination[155] of trace amounts of antimony in industrial waste water is based on reaction of Sb^{III} with iodine and extraction of the iodo complex with

amidine [HA] as Sb_2I_6HA complex. The method was applied for the recovery of Sb from water samples.

A method for the determination[157] of gold in low-grade ores is based on the extraction of Au from the ore with *N,N'*-diphenylbenzamidine into chloroform, and stripping the gold from the organic phase with thiourea and its determination in the aqueous phase. Another method[158] is based on extraction of $[AuX_4]$ where X = Cl, Br, I with amidines in benzene or chloroform as solvents. The method is simple, rapid, reproducible and free from the interference of almost all metal ions tested.

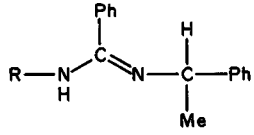
Complexes with magnesium of the type R—N=C(R')—$NRCO_2MgBr$ were found[159] to be useful reagents for the transfer of CO_2 to $R^2COCH_2R^3$ to give $R^2COCH_2(R^3)$-COOH in good yields.

Amidine complexes of the general formula $Me[(amidine)_2 \cdot (H_2O)_2]$, where Me is Mn, Fe, Co, Ni or Cu, were investigated as antifungal agents[141]. It was found that metal complexes with *N*-(5-phenyl-1,3,4-thiadiazol-2-yl)-acetamidines (**105**, R'=Me) and benzamidines (**105**, R' = Ph) are more fungitoxic than the free ligand, and that the fungiotoxicity of the complexes increases as the radius of the metal ion decreases.

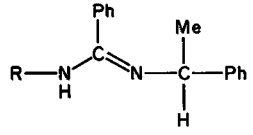


(105)

Metal complexes with optically active amidines were investigated as stereodifferentiating catalysts. It was found that optically active amidines (**106a** and **b**) or their Li derivatives with $[RhCl(cyclooctene)_2]_2$ after activation with molecular hydrogen give catalysts which hydrogenate unsaturated compounds such as cyclohexene, benzene or toluene, as well as prochiral substrates, such as various derivatives of cinnamic acid, with a high (75–100%) yield[160]. However, the good hydrogenation activity is in contrast to the low optical induction which gives values different from zero only in the hydrogenation of α-methylcinnamic alcohol.



(106a)



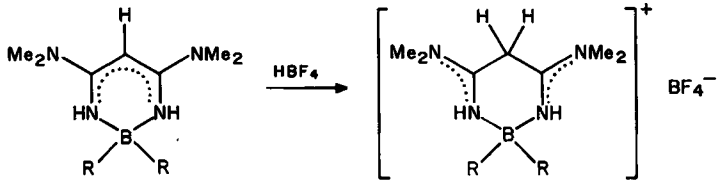
(106b)

3. *Boron complexes of amidines*

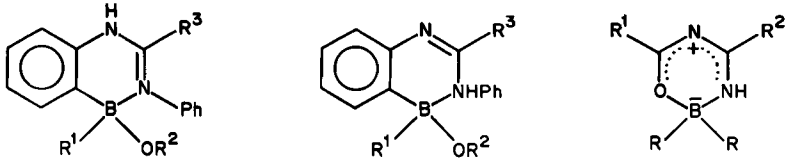
N,N,N',N'-Tetramethylmalonamidine reacts[161] with triethylborane, ethoxydiphenylborane or trimethoxyborane to give neutral chelating complexes **107**, which can be protonated with HBF_4 to form the salt **108**.

Intramolecular boron complexes[162] are formed in the reaction of 3,4-dihydro-4-boraquinazolines with acids or alcohols. These complexes may exist in two tautomeric forms **109a** and **109b**.

Dialkylboracylamidinates (**110**) were obtained[163] in the reaction of primary amides with nitriles and trialkylboranes in THF. The IR spectra showed that intermolecular hydrogen bonding occurs between the complex molecules.



(107) (108)

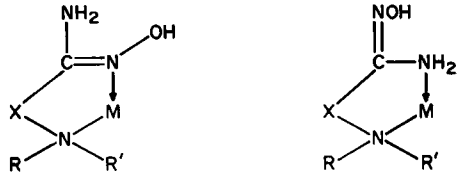


(109a) (109b) (110)

B. Complexes of Amidoximes

Owing to their practical applications amidoxime complexes with various metals are the subject of extensive studies. Their colour reactions with transition metals were already noted in the early days of coordination chemistry[53]. Analytical applications of amidoximes have been reviewed[7,53,164]. More recently the analytical applicability of amidoximes was investigated[165,166] for spectroscopic determination of $Hg^{(I)}$, $Hg^{(II)}$, $Cu^{(II)}$, $Mo^{(VI)}$, $Fe^{(II)}$, $Fe^{(III)}$, $Co^{(II)}$ and $Ni^{(II)}$.

The amidoxime group is capable of binding metal ions as such or in the form of the amidoximate anion, and can behave as a bidentate ligand through the amide nitrogen and oxime oxygen or nitrogen atoms. However, when the amidoxime ligand contains an additional —NRR′ donor site allowing a five-membered chelate ring via amine nitrogen to be formed, the second coordinating atom can be either the oxime nitrogen (**111**) or the amide nitrogen (**112**). In both modes of chelation the stabilities of the complexes would be expected to decrease with increasing N-methylation.

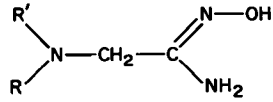


(111) (112)

(X = any group containing one or two carbons)

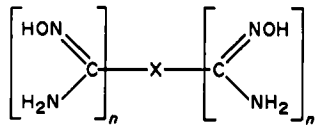
Complex formation equilibria between $Ni^{(II)}$ and 2-aminoacetamidoxime (**113**, HL) and its N-methylated derivatives was studied[167]. It was shown that the complexes $Ni(HL)^{2+}$, $Ni(HL)_2^{2+}$ and $Ni(HL)_3^{2+}$ are formed stepwise. Stability constants decrease with increasing N-substitution, the effect being more prominent for tris complexes than for bis

and mono complexes, clearly demonstrating the participation of the amine nitrogen atoms in the coordination.



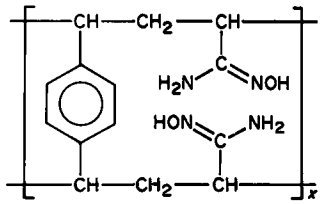
(113)

It was found[165] that some polyamidoximes (**114**) easily form complexes with such metals as $Cu^{(II)}$, $Co^{(II)}$, $Ni^{(II)}$, $Fe^{(II)}$, $Fe^{(III)}$, $Pd^{(II)}$, $Mo^{(VI)}$ and $U^{(VI)}$.



(X=any organic moiety)

(114)

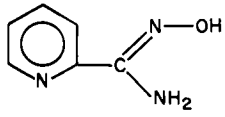


(115)

A divinylbenzene cross-linked poly-(acryloamidoxime) resin (**115**) was applied[168] for concentration of trace metals from aqueous solutions. The resin exhibits no affinity to alkali or alkaline earth metals, and therefore can be applied to samples at high electrolyte content, such as sea water. The order of decreasing selectivity is $Cu^{(II)}$, $Ni^{(II)}$, $Co^{(II)}$, $Zn^{(II)}$ and $Mn^{(II)}$. Similar resins were found suitable for the accumulation of uranium from sea water[169]. The method was also investigated using other poly-amidoxime resins[170–172].

A method[173] for the recovery of rare earth metals from aqueous solutions by extraction with organic solvents using amidoxime complexes in a continuous counter-current process was proposed.

Complexes of $Cu^{(II)}$, $Ni^{(II)}$, $Co^{(II)}$, $Fe^{(II)}$ and $Mn^{(II)}$ with pyridine-2-amidoxime[174] (**116**) and pyrazine-2-amidoxime[175] were prepared as potential biologically active compounds.

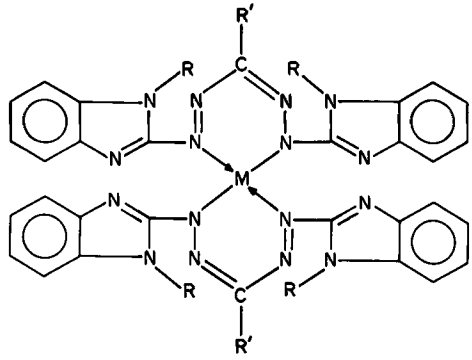


(116)

C. Complexes of Formazans

It was found that with Cu^{2+}[176], Ni^{2+}[176], Co^{2+}[177] and Zn^{2+}[178], symmetrical dibenzazolyl formazans form chelate complexes of the L_2M type (**117**). With tetrachlorides of elements of the IV group, molecular complexes of the type $LMCl_4$, L_2MCl_4 and $L(MCl_4)_2$ are formed[179]. Complexes of the L_2M type with $Zn^{(II)}$, $Cd^{(II)}$, $Ag^{(I)}$, $Pb^{(II)}$, $Mn^{(II)}$ and $Fe^{(II)}$ of similar structures are formed also with other 1,5-diarylformazans[60].

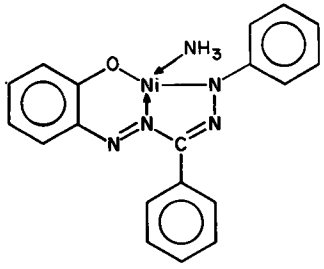
In complex formation with formazans other functional groups, in addition to the terminal nitrogen atoms, can be involved. A kinetic study[179] of the reaction of 1-(2-hydroxyphenyl)-3,5-diphenylformazan with nickel$^{(II)}$ has shown that complex formation occurs stepwise. An intermediate (**118**) was isolated which, in contrast to the more stable



(117)

isomeric form (**119**), contains a five-membered ring. The kinetics of the rearrangement of **118** to **119** was studied[180].

Similar complexes with 1-(2-hydroxy-4-nitrophenyl)-3-alkyl-5-(2-benzazolyl)formazans were investigated later[62], and the conclusions concerning the structure were in principle the same.



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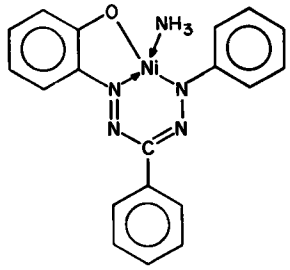

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V. ACKNOWLEDGEMENT

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VI. REFERENCES

1. J. Oszczapowicz and E. Raczyńska, *Polish J. Chem.*, **57**, 419 (1983).
2. J. Oszczapowicz and E. Raczyńska *J. Chem. Soc., Perkin Trans. 2*, 1643 (1984).
3. J. Oszczapowicz, E. Raczyńska and T. Pawlik, *Polish J. Chem.*, **58**, 117 (1984).
4. J. Oszczapowicz and J. Jaroszewska-Manaj, *J. Chem. Soc., Perkin Trans. 2*, submitted.
5. J. Oszczapowicz and M. Kumińska, in preparation.
6. O. Exner, *Collect. Czech. Chem. Commun.*, **31**, 3222 (1966).
7. J. Ševčik and F. Grambal, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, London, 1975, (a) p. 601, (b) p. 602.

8. B. Fernández, I. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans. 2*, 1416 (1974).
9. J. Oszczapowicz, J. Osek and R. Orliński, *Polish J. Chem.*, **54**, 1191 (1980).
10. J. Oszczapowicz, E. Raczyńska and R. Orliński, *Polish J. Chem.*, **55**, 2031 (1981).
11. J. Oszczapowicz and J. Osek, *Polish J. Chem.*, **57**, 93 (1983).
12. E. Raczyńska, J. Oszczapowicz and M. Walczak, *J. Chem. Soc., Perkin Trans. 2*, 1087 (1985).
13. Z. B. Kiro, Yu. A. Terenin, L. N. Nikolenko and B. I. Stepanov, *Zh. Org. Khim.*, **8**, 2573 (1972); *Chem. Abstr.*, **78**, 135210z (1973).
14. B. E. Zaitsev, L. B. Krasnova, S. I. Popov and T. A. Mikhailov, *Zh. Org. Khim.*, **22**, 1743 (1986); *Chem. Abstr.*, **107**, 6907a (1987).
15. G. Häfelinger, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, London, 1975, p. 17.
16. J. Oszczapowicz, R. Orliński and E. Hejchman, *Polish J. Chem.*, **53**, 1259 (1979).
17. J. Oszczapowicz, R. Orliński and H. Walczyńska, *Polish J. Chem.*, **53**, 2531 (1979).
18. J. Oszczapowicz and R. Orliński, *Polish J. Chem.*, **54**, 1901 (1980).
19. J. Oszczapowicz, E. Raczyńska and I. Barecka, *Polish J. Chem.*, **59**, 387 (1985).
20. E. Raczyńska and J. Oszczapowicz, *Tetrahedron*, **41**, 5175 (1985).
21. E. Raczyńska, J. Oszczapowicz and M. Wojtkowska, *Polish J. Chem.*, **59**, 945 (1985).
22. J. Oszczapowicz, W. Krawczyk, J. Osek and E. Raczyńska, *Polish J. Chem.*, **60**, 157 (1986).
23. J. Oszczapowicz and K. Ciszkowski, *J. Chem. Soc., Perkin Trans. 2*, 663 (1987).
24. J. Oszczapowicz and W. Krawczyk, *J. Chem. Soc., Perkin Trans. 2*, 21 (1989).
25. J. Oszczapowicz and K. Ciszkowski, *J. Chem. Res.*, in press
26. J. Oszczapowicz, W. Krawczyk and P. Łyżwiński, *J. Chem. Soc., Perkin Trans. 2*, 311 (1990).
27. J. Oszczapowicz, J. Jaroszewska-Manaj and B. Pojeć, in preparation.
28. D. D. Perrin, B. Dempsey and E. P. Serjeant, pK_a *Predictions for Organic Acids and Bases*, Chap. 5, Chapman and Hall, London, 1981.
29. B. V. Passet, G. N. Kul'bitskii, N. A. Kalashnikova and T. I. Voropaeva, *Zh. Org. Khim.*, **8**, 1246 (1972); *Chem. Abstr.*, **77**, 100964a (1972).
30. S. O. Chua, M. J. Cook and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 2*, 546 (1974).
31. H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
32. E. Lorz and R. Baltzly, *J. Am. Chem. Soc.*, **71**, 3992 (1949).
33. M. Charton, *J. Org. Chem.*, **30**, 969 (1965).
34. D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
35. R. W. Taft jr. and I. C. Lewis, *J. Am. Chem. Soc.*, **80**, 2436 (1958).
36. L. L. Popova, I. D. Sadekov and V. I. Minkin, *Reakts. Sposobn. Org. Soedin. (Tartu)*, **5**, 682 (1968); *Chem. Abstr.*, **70**, 67451m (1969).
37. V. A. Bren', V. I. Minkin, A. D. Garnovskii, E. V. Botkina and B. S. Tenaseichuk, *Reakts. Sposobn. Org. Soedin. (Tartu)*, **5**, 651 (1968); *Chem. Abstr.*, **70**, 77168p (1969).
38. L. L. Popova, I. D. Sadekov and V. I. Minkin, *Reakts. Sposobn. Org. Soedin. (Tartu)*, **6**, 47 (1969); *Chem. Abstr.*, **71**, 112279 (1969).
39. M. J. Cook, A. R. Katritzky and S. Nadji, *J. Chem. Soc., Perkin Trans. 2*, 211 (1976).
40. J. Ševčik, *Acta Univ. Palacki. Olomuc., Fac. Rerum Nat.*, **49**, 53 (1976).
41. B. Fernández, I. Perillo and S. Lamdan, *J. Chem. Soc., Perkin Trans. 2*, 1371 (1973).
42. I. Perillo, B. Fernández and S. Lamdan, *J. Chem. Soc., Perkin Trans. 2*, 2068 (1977).
43. O. Exner, *Collect. Czech. Chem. Commun.*, **41**, 1516 (1976).
44. R. W. Taft in *Steric Effects in Organic Chemistry*, M. S. Newman (Ed.), Chap. 13, Wiley, New York, 1951, p. 591.
45. J. Oszczapowicz, C. U. Regelman and G. Häfelinger, *J. Chem. Soc., Perkin Trans. 2*, 1551 (1990).
46. G. Häfelinger, J. Oszczapowicz and F. K. H. Kuske, in preparation.
47. Z. Kosturkiewicz, E. Ciszak and E. Tykarska, *J. Chem. Soc., Perkin Trans. 2*, submitted.
48. J. Oszczapowicz, unpublished results.
49. E. J. King, *Acid–Base Equilibria*, Pergamon Press, Oxford 1965, pp. 13 and 215.
50. J. D. Halliday, E. A. Symons and P. D. Binder, *Can. J. Chem.*, **56**, 1470 (1978).
51. E. V. Borisov, D. N. Kravtsov, A. S. Peregudov and E. I. Fedin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2151 (1980); *Chem. Abstr.*, **94**, 30064g (1981).
52. J. Ševčik, *Chem. Zvesti*, **26**, 49 (1972).
53. F. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962).
54. H. Gonçalves and A. Secches, *Bull. Soc. Chim. France*, 2589 (1970).

55. J. L. Bernal, M. Pedrero, V. Cerda and J. Cantallops, *Thermochim. Acta*, **98**, 19 (1986).
56. E. Martin, H. Kühmstedt, L. Lübeck, A. Peters and B. Kretschmer, *Pharmazie*, **40**, 365 (1985).
57. Y. C. Martin, *Quantitative Drug Design*, Marcel Dekker, New York, Basel, 1978.
58. C. Hansch and A. J. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979.
59. R. G. Pelova, A. T. Kozhukharova and G. D. Velinov, *Ukr. Khim. Zh.*, **48**, 325 (1982); *Chem. Abstr.*, **96**, 198966 (1982).
60. G. N. Lipunova, L. I. Sharova, E. P. Darienko, N. P. Bednyagina, G. I. Sigeikin and Yu. I. Aleksandrov, *Zh. Obshch. Khim.*, **53**, 178 (1983); *Chem. Abstr.*, **98**, 198134m (1982).
61. G. N. Lipunova, T. I. Krivonogova, N. V. Marina, A. D. Garnovskii and E. P. Darienko, *Zh. Obshch. Khim.*, **57**, 2780 (1987); *Chem. Abstr.*, **109**, 110326n (1988).
62. T. I. Krivonogova, E. P. Darienko and G. N. Lipunova, *Zh. Obshch. Khim.*, **53**, 1163 (1983); *Chem. Abstr.*, **99**, 194871x (1988).
63. D. C. Prevoršek, *J. Phys. Chem.*, **66**, 769 (1962).
64. D. C. Prevoršek, *Bull. Soc. Chim. Fr.*, 788 (1958).
65. F. L. Pyman, *J. Chem. Soc.*, **367**, 3359 (1923).
66. C. Chew and F. L. Pyman, *J. Chem. Soc.*, 2318 (1927).
67. A. G. Moritz, *Spectrochim. Acta*, **20**, 1555 (1964).
68. J. C. Grivas and A. Taurins, *Can. J. Chem.*, **37**, 795 (1959).
69. J. C. Grivas and A. Taurins, *Can. J. Chem.*, **39**, 414 (1961).
70. J. A. Gautier, M. Miocque, C. Fauran and A. Y. le Cloarec, *Bull. Soc. Chim. Fr.*, 478 (1971).
71. P. Reynaud, J. D. Brion and G. Menard, *Bull. Soc. Chim. Fr.*, 449 (1978).
72. R. B. Tinkler, *J. Chem. Soc. (B)*, 1052 (1970).
73. L. M. Jackman and T. Jen, *J. Am. Chem. Soc.*, **97**, 2811 (1975).
74. B. Clement and T. Kämpchen, *Chem. Ber.*, **119**, 1101 (1986).
75. W. G. Granik, *Usp. Khim.*, **52**, 669 (1983); *Chem. Abstr.*, **99**, 1005265u (1983).
76. M. Tisler, *Arch. Pharm. (Weinheim. Ger.)*, **45**, 621 (1960).
77. M. Tisler, *Tetrahedron Lett.*, 12 (1959).
78. H. Najer, R. Gludicelli and J. Mennin, *Bull. Soc. Chim. Fr.*, 2120 (1965).
79. H. Najer, J. Armand, J. Mennin and N. Voronina, *C.R. Acad. Sci.*, 4343 (1965).
80. E. Herbullez, B. Baekler, O. Espejo, H. Jindra, B. Wilhelm and J. Rabinovitz, *Helv. Chim. Acta*, **50**, 331 (1967).
81. J. Rabinovitz, *Helv. Chim. Acta*, **52**, 255 (1969).
82. P. Jakobsen and S. Treppendahl, *Tetrahedron*, **33**, 3137 (1977).
83. P. Jakobsen and S. Treppendahl, *Tetrahedron*, **37**, 829 (1981).
84. N. M. Mironovskaya, S. F. Dymova, I. L. Vladimirova and *N. N.* Melnikov, *Zh. Obshch. Khim.*, **48**, 2465 (1978).
85. E. D. Raczyńska, *J. Chem. Soc., Perkin Trans. 2*, 1189 (1986).
86. E. D. Raczyńska, *J. Chem. Res. (S)*, 258 (1988).
87. Th. J. Zielinski, M. R. Peterson, I. G. Csizmadia and R. Rein, *J. Comput. Chem.*, **3**, 62 (1982).
88. Th. J. Zielinski, R. A. Poirier, M. R. Peterson and I. G. Csizmadia, *J. Comput. Chem.*, **4**, 419 (1983).
89. Th. J. Zielinski and R. A. Poirier, *J. Comput. Chem.*, **5**, 466 (1984).
90. P. Baudet and D. Rao, *Helv. Chim. Acta*, **53**, 1011 (1970).
91. T. Ishida, Y. In, M. Shibata, H. Inoue and I. Yanagisawa, *Mol. Pharmacol.*, **31**, 410 (1987).
92. E. P. Ivakhnenko, E. I. Mikhailov, V. I. Minkin and L. P. Olekhnovich, *Zh. Org. Khim.*, **19**, 2624 (1983); *Chem. Abstr.*, **100**, 209031p (1984).
93. V. V. Negrebetskii, L. Ya. Bogel'fer, A. D. Sinitsa, V. A. Kal'chenko and V. S. Krishtal', *Zh. Obshch. Khim.*, **51**, 1485 (1981); *Chem. Abstr.*, **95**, 186385 (1981).
94. V. V. Negrebetskii, L. Ya. Bogel'fer, V. I. Kal'chenko, V. S. Krishtal', A. D. Sinitsa and L. N. Markovskii, *Zh. Obshch. Khim.*, **50**, 2133 (1980); *Chem. Abstr.*, **92**, 197779 (1980).
95. V. V. Negrebetskii, L. Ya. Bogel'fer, A. D. Sinitsa, V. I. Kal'chenko, V. S. Krishtal' and L. N. Markovskii, *Zh. Obshch. Khim.*, **52**, 40 (1982); *Chem. Abstr.*, **96**, 162847 (1982).
96. V. V. Negrebetskii, L. Ya. Bogel'fer, A. D. Sinitsa, V. I. Kal'chenko, B. S. Krishtal' and L. N. Markovskii, *Zh. Obshch. Khim.*, **52**, 1496 (1982); *Chem. Abstr.*, **97**, 463118m (1982).
97. I. E. Mikhailov, N. M. Ivakhnenko, L. P. Olekhnowich, V. I. Minkin and Yu. A. Zhdanov, *Dokl. Akad. Nauk SSSR, Ser. Khim.*, **263**, 366 (1982); *Chem. Abstr.*, **97**, 23023b (1982).

98. V. V. Negrebetskii, V. I. Kal'chenko, R. B. Rudyi and L. N. Markovskii, *Zh. Obshch. Khim.*, **55**, 271 (1985); *Chem. Abstr.*, **103**, 37540x (1985).
99. V. V. Negrebetskii, V. I. Kal'chenko, R. B. Rudyi and L. N. Markovskii, *Zh. Obshch. Khim.*, **55**, 1982 (1985); *Chem. Abstr.*, **105**, 97559m (1986).
100. I. E. Mikhailov, V. I. Minkin, L. P. Olekhnovich, V. N. Boiko, N. V. Ignat'ev and L. M. Yagupolski, *Zh. Org. Khim.*, **20**, 454 (1984); *Chem. Abstr.*, **101**, 71979r (1984).
101. R. F. Smith, D. S. Johnson, C. L. Hyde, T. C. Rosenthal and A. C. Bates, *J. Org. Chem.*, **36**, 1155 (1971).
102. R. F. Smith, D. S. Johnson, R. A. Abgott and M. J. Madden, *J. Org. Chem.*, **38**, 1344 (1973).
103. V. A. Khrustalev, K. N. Zelenin and V. P. Sergutina, *Zh. Org. Khim.*, **15**, 2280 (1979); *Chem. Abstr.*, **92**, 180607 (1980).
104. I. D. Cunningham and F. A. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 537 (1986).
105. G. Fodor and B. A. Phillips, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, London, 1975, pp. 93–94.
106. K. M. Watson and D. G. Neilson, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, London, 1975, pp. 514–515.
107. V. A. Khrustalev, V. P. Sergutina, K. N. Zelenin and U. V. Pinson, *Khim. Geterotsikl. Soedin.*, 1264 (1982); *Chem. Abstr.*, **98**, 16382k (1983).
108. L. V. Shmelev, Yu. S. Ryabokobylko, A. V. Kessenikh and V. M. Ostrovskaya, *Zh. Obshch. Khim.*, **57**, 1637 (1987); *Chem. Abstr.*, **108**, 166892r (1988).
109. N. A. Klyuyev, V. G. Zhil'nikov, G. G. Aleksandrov, I. I. Grandberg and G. N. Lipunova, *Zh. Org. Khim.*, **19**, 2615 (1983); *Chem. Abstr.*, **100**, 156139w (1984).
110. L. V. Shmelev, G. N. Lipunova, O. P. Sulim and N. P. Bednyagina, *Zh. Obshch. Khim.*, **56**, 2393 (1986); *Chem. Abstr.*, **107**, 58913u (1987).
111. B. I. Buzykin, L. P. Sysoeva, A. A. Espenbetov, Yu. T. Struchkov and Yu. P. Kitaev, *Zh. Org. Khim.*, **22**, 2277 (1986); *Chem. Abstr.*, **107**, 133786k (1987).
112. L. A. Fedorov, S. A. Sokolovskii, G. N. Lipunova, G. I. Sigeikin and L. I. Rusinova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 691 (1987); *Chem. Abstr.*, **108**, 21274f (1988).
113. P. B. Fischer, L. B. Kaul and H. Zollinger, *Helv. Chim. Acta*, **51**, 1449 (1968).
114. N. V. Serebriakova, G. N. Lipunova, N. P. Bednyagina and L. F. Lipatova, *Khim. Geterotsikl. Soedin.*, 1403 (1970); *Chem. Abstr.*, **74**, 138178k (1971).
115. J. Vaes, F. Faubert and Th. Zeegers-Huyskens, *Can. J. Chem.*, **53**, 604 (1975).
116. R. Mierzecki, J. Oszczapowicz and G. Kozakowski, *Polish J. Chem.*, **53**, 1139 (1979).
117. J. Oszczapowicz, J. Jaroszewska-Manaj, L. Skulski and K. Erbel, in preparation.
118. J. A. Clark and M. Kilner, *J. Chem. Soc., Dalton Trans.*, 389 (1984).
119. T. Inglis, M. Kilner, T. Reynoldson and E. E. Robertson, *J. Chem. Soc., Dalton Trans.*, 924 (1975).
120. T. Inglis and M. Kilner, *J. Chem. Soc., Dalton Trans.*, 930 (1975).
121. E. W. Abel and S. J. Skittral, *J. Organomet. Chem.*, **193**, 389 (1980).
122. W. H. de Roode, M. L. Beekes, A. Oskam and K. Vrieze, *J. Organomet. Chem.*, **142**, 337 (1977).
123. W. H. de Roode, D. G. Prins, A. Oskam and K. Vrieze, *J. Organomet. Chem.*, **154**, 273 (1978).
124. W. H. de Roode, J. Berke, A. Oskam and K. Vrieze, *J. Organomet. Chem.*, **155**, 307 (1978).
125. F. A. Cotton, T. Inglis, M. Kilner and T. Webb, *Inorg. Chem.*, **14**, 2023 (1973).
126. M. G. B. Drew and J. D. Wilkins, *Acta Crystallogr.*, **B31**, 2642 (1975).
127. W. Bradley and I. Wright, *J. Chem. Soc.*, 641 (1956).
128. L. Toniolo, T. Boschi and G. Deganello, *J. Organomet. Chem.*, **93**, 405 (1975).
129. W. H. de Roode and K. Vrieze, *J. Organomet. Chem.*, **145**, 207 (1978).
130. F. A. Cotton, W. H. Isley and W. Kaim, *Inorg. Chem.*, **19**, 2360 (1980).
131. F. A. Cotton and L. W. Shive, *Inorg. Chem.*, **14**, 2027 (1975).
132. L. Toniolo, G. Deganello, P. L. Sandrini and G. Bombieri, *Inorg. Chim. Acta*, **15**, 11 (1975).
133. P. I. Van Vliet, G. Van Koten and K. Vrieze, *J. Organomet. Chem.*, **188**, 301 (1980).
134. L. Toniolo, A. Immirizi, V. Croatto and G. Bombieri, *Inorg. Chim. Acta*, **19**, 209 (1976).
135. J. A. Clark and M. Kilner, *J. Chem. Soc., Dalton Trans.*, 2613 (1983).
136. A. F. M. J. van der Ploeg, G. van Koten and K. Vrieze, *Inorg. Chem.*, **21**, 2026 (1982).
137. H. Brunner, J. Lukassek and G. Agrifoglio, *J. Organomet. Chem.*, **195**, 63 (1980).
138. H. Brunner, G. Agrifoglio, R. Benn and A. Rufinska, *J. Organomet. Chem.*, **217**, 365 (1981).
139. H. Brunner, G. Agrifoglio, I. Bernal and M. W. Creswick, *Angew. Chem.*, **92**, 645 (1980).

140. M. W. Creswick and I. Bernal, *Inorg. Chim. Acta*, **74**, 241 (1983).
141. R. S. Srivastava, *Inorg. Chim. Acta*, **55**, L71 (1981).
142. B. A. Borykin, N. A. Skidan, A. V. Kharchenko, M. M. Kremler, I. V. Koval and S. I. Shaposhnikov, *Vopr. Khim. Khim. Tekhnol.*, **71**, 104 (1983); *Chem. Abstr.*, **101**, 203190p (1984).
143. A. J. Deeming and R. Peters, *J. Organomet. Chem.*, **202**, C-39 (1980).
144. C. J. Jones, J. A. Cleverty and A. S. Rothin, *J. Chem. Soc., Dalton Trans.*, 109 (1986).
145. A. Romero, A. Vegas and A. Santos, *J. Organomet. Chem.*, **310**, C-8 (1986).
146. M. D. Albers, A. F. S. Crosby, D. C. Liles, D. J. Robinson, A. Shaver and E. Singleton, *Organometallics*, **6**, 2014 (1987).
147. G. D. Gracey, S. J. Rettig, A. Storr and J. Tretter, *Can. J. Chem.*, **65**, 2469 (1987).
148. N. C. Ta and D. Sen, *J. Inorg. Nucl. Chem.*, **43**, 209 (1981).
149. G. H. Searle, S. F. Lincoln, S. G. Teague and D. G. Rowe, *Aust. J. Chem.*, **32**, 519 (1979).
150. G. H. Searle, *Aust. J. Chem.*, **33**, 2159 (1980).
151. P. I. Van Vliet, G. Van Koten and K. Vrieze, *J. Organomet. Chem.*, **182**, 105 (1979).
152. L. P. Chandrakar, R. Singh and R. Mishra, *Analyst (London)*, **112**, 1511 (1987).
153. A. Shukla, K. S. Patel and R. K. Mishra, *Anal. Chim. Acta*, **208**, 91 (1988).
154. K. S. Patel and K. H. Lieser, *Anal. Chem.*, **58**, 192 (1986).
155. A. Golwelker, K. S. Patel and R. K. Mishra, *Int. Environ. Anal. chem.*, **33**, 185 (1988).
156. R. M. Verma, K. S. Patel and R. K. Mishra, *Fresenius Z. Anal. Chem.*, **307**, 128 (1981).
157. K. S. Patel and K. H. Lieser, *Fresenius Z. Anal. Chem.*, **323**, 494 (1986).
158. K. S. Patel and K. H. Lieser, *Anal. Chem.*, **58**, 1547 (1986).
159. N. Matsumura, T. Ohba and M. Inoua, *Bull. Chem. Soc. Jpn.*, **55**, 3949 (1982).
160. H. Brunner and G. Agrifoglio, *Monatsh. Chem.*, **111**, 275 (1980).
161. K. Hartke, B. Krug and R. Hoffman, *Justus Liebigs Ann. Chem.*, 370 (1984).
162. V. A. Dorokhov, M. N. Bochkarieva, O. G. Bol'dyrieva, B. V. Rassadin and B. M. Mikhailov, *Izv. Akad. Nauk USSR*, 411 (1979); *Chem. Abstr.*, **90**, 203057e (1979).
163. V. A. Dorokhov, L. J. Lavrinovich, M. N. Bochkareva, V. S. Bogdanov and B. Mikhailov, *Zh. Obshch. Khim.*, **43**, 1115 (1973), Chem. Abstr., **79**, 66436j (1973).
164. A. I. Busev, T. N. Zholondkovskaya, L. S. Krysina and L. I. Korobkina, *Sovrem. Metody Anal. Mater.*, 153 (1969); *Chem. Abstr.*, **73**, 94224h (1970).
165. F. Borrull, J. Guasch, E. Casassas and V. Cerdá, *Polyhedron*, **5**, 1277 (1986).
166. V. Cerdá, E. Casassas and F. Borrul, *Ann. Quim. (B)*, **78**, 327 (1982).
167. H. Saarinen, M. Orama, T. Raikas and J. Korvenranta, *Acta Chem. Scand.*, **A37**, 631 (1983).
168. M. B. Colella, S. Siggia and R. M. Barnes, *Anal. Chem.*, **52**, 967 (1980).
169. L. Astheimer, H. J. Schenk, E. G. Witte and K. Schwochan, *Sep. Sci. Technol.*, **18**, 307 (1983).
170. M. Suzuki, T. Fuji, S. Tanaka, T. Hagaki and S. Kato, Proc. Eng. Found. Conf. Fundam. Adsorpt., 2nd 1986, p. 537; *Chem. Abstr.*, **107**, 100265m (1987).
171. H. Omichi, A. Katakai, T. Sugo, J. Okamoto, S. Katoh, K. Sakane, K. Sugasaka and T. Itagaki, *Sep. Sci. Technol.*, **22**, 1313 (1987).
172. H. Omichi, A. Katakai, T. Sugo and J. Okamoto, *Sep. Sci. Technol.*, **21**, 563 (1986).
173. J. L. Drobnick, P. R. Ktuesc and T. P. Chen, German Patent 2044574 (1971).
174. G. S. Sanyal, A. B. Modak and A. K. Mudi, *Indian J. Chem.*, **22A**, 307 (1983).
175. G. S. Sanyal and B. Modak, *Synth. React. Inorg. Met.-Org. Chem.*, **16**, 113 (1986); *Chem. Abstr.*, **104**, 6057 (1986).
176. N. P. Bednyagina and Yu. A. Rybakova, *Khim. Geterotsikl. Soedin.*, 426 (1965); *Chem. Abstr.*, **63**, 13239h (1965).
177. A. D. Garnovskii, O. A. Osipov, N. P. Bednyagina, L. I. Kuznetsova, R. I. Ogloblina, V. P. Kurbatov and L. S. Kostromina, *Zh. Obshch. Khim.*, **39**, 1920 (1969); *Chem. Abstr.*, **72**, 18035m (1970).
178. R. I. Ogloblina, N. P. Bednyagina and A. D. Garnovskii, *Zh. Obshch. Khim.*, **40**, 367 (1970); *Chem. Abstr.*, **72**, 139164m (1970).
179. V. T. Panyushkin, A. D. Garnovskii, D. A. Osipov, N. P. Bednyagina and K. I. Nikitina, *Zh. Obshch. Khim.*, **38**, 1161 (1968); *Chem. Abstr.*, **69**, 408632q (1968).
180. S. Balt, J. Meuldijk and W. E. Renkema, *Inorg. Chim. Acta*, **43**, 173 (1980).

CHAPTER 13

Electronic effects of amidino, guanidino and related groups

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I. INTRODUCTION

Previous articles by the present contributor in *The Chemistry of Functional Groups* series have dealt with the electronic effects of the sulphonio group[1], of the sulphinyl and sulphonyl groups[2], and of SOOH and related groups[3]. In the first two cases there was copious information in the literature from which to draw; in the last mentioned case there was very much less information available. The present case sees a further reduction in available information; only a handful of papers provides material relevant to the topic. This situation has emerged quite clearly from exhaustive work in *Science Citation Index* and a computerized search of the *Chemical Abstracts* data base, as well as from consultations with venerable authorities in physical organic chemistry.

Thus there appears to be no information about the electronic effect of the amidino group —C(=NH)NH_2, i.e. bonded to the probe moiety via its carbon atom, or of substituted amidino group —C(=NX)NYZ similarly bonded. There is, however, material on the amidinium group —$C(NH_2)_2^+$and on amidino groups bonded via the imino or the amino nitrogen atom. Guanidino and guanidinium groups have attracted some attention. Of related heterocyclic groups there appears to be information only on the behaviour of the imidazolyl substituent. The search for material on groups derived from imidates (otherwise iminoesters or iminoethers) $R^1C(=NR^2)OR^3$ has proved entirely fruitless.

The Chemistry of Amidines and Imidates, Volume 2
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It is difficult to account for the apparent lack of attention to amidino, guanidino and related substituents by most workers in physical organic chemistry, particularly when there is much interest in amidino groups as reaction centres (e.g. their acid–base behaviour[4]) and in the biological activities of amidines[5]. It may be that some workers are apprehensive about possible complications in the interpretation of results because of the structural problems of amidines, namely the geometrical isomerism at the C=N double bond, the restricted rotation about the C—N 'single' bond due to conjugation and the possibility of prototropic tautomerism, unless all three hydrogen atoms of the amidino group are replaced by other groups. Suitable choice of systems for study can reduce the impact of these potential problems.

The most substantial studies of the substituent effects of amidino and related groups involve the measurement of ^{13}C and ^{19}F chemical shifts and the greater part of this chapter will be concerned with such studies. A small number of other spectroscopic studies and of reactivity studies (kinetics and acid–base equilibria) provide some additional information. Many measurements of ^{1}H chemical shifts in these systems have been made[6]. Potentially these also will shed light on the electron distribution in the molecules and hence on substituent electronic effects. However, the correlation analysis of ^{1}H chemical shifts in terms of substituent constants is beset with problems, particularly for hydrogen atoms linked to a benzene ring. Also, ordinary carefully made measurements of ^{1}H chemical shifts are not really suitable for this purpose. There are marked effects of substrate concentration and of solvent, and the extrapolation of the chemical shifts to zero substrate concentration is often required in order to obtain data which may be suitable for correlation analysis. This topic is therefore not included in this chapter.

Much of the chapter will be devoted to the determination and discussion of appropriate sigma values. (Throughout this chapter substituent constants for benzene derivatives as originally defined by Hammett are set as 'σ', while substituent constants in general are represented by 'sigma'.) It will be assumed that the reader has a basic knowledge of the Hammett equation and its extensions, particularly the separation of substituent electronic effects into inductive and resonance components as developed by Taft and his colleagues. Two of the earlier articles referred to above[1,2] gave short introductory accounts of such matters. Some references to background material in linear free-energy relationships (correlation analysis) are provided in the present chapter[7–11].

As already indicated, some of the information about electronic effects concerns positively charged groups, i.e. amidinium and guanidinium substituents. This information will usually be expressed in terms of sigma values of various kinds. This is often done for charged substituents, but it must be pointed out that the inclusion of unipolar substituents in Hammett-type treatments, which are essentially based on the behaviour of *dipolar* substituents, is not a strictly valid procedure. There is a long history of anomalies, failures and warnings in connection with the attempt to include unipolar groups in the use of the Hammett equation and related treatments. An account of this was given in Reference 1. Thus the various types of sigma value for unipolar substituents must be regarded as having only a semi-quantitative or even just a qualitative significance. These quantities give merely an indication of the electronic behaviour of the groups in question under the given circumstances.

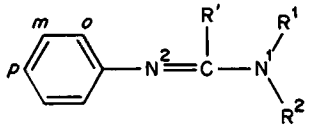
II. SUBSTITUENT CONSTANTS FROM NMR STUDIES

A. Inductive and Resonance Constants from ^{13}C NMR

Oszczapowicz and coworkers have measured substituent-induced chemical shifts in ^{13}C NMR spectra of N^2-phenyl-formamidines, -acetamidines and -guanidines[12]. (N^2 is the imino nitrogen atom.) While most of this study concerns the influence of various polar

substituents *m*-X or *p*-X in the N^2-C_6H_4X moiety and the elucidation of the cumulative substituent effect on the NMR shifts of various carbon atoms, about twenty compounds with X = H provide information on the electronic effects of a variety of formamidino, acetamidino, and guanidino groups, as transmitted to various positions in a benzene ring. The compounds studied have the great merit that they are trisubstituted with respect to the nitrogen atoms of the amidino group, i.e. there are no problems of prototropic tautomerism. Further, it seems probable that all the compounds involved are in the *trans* (*E*) configuration for the group at the imino nitrogen with respect to the amino nitrogen atom. The results have not been used by Oszczapowicz and coworkers[12] to derive sigma values, but they may be so analysed by utilizing appropriate equations based on other work.

The ^{13}C chemical shifts were measured in $CDCl_3$ solutions, with 200 mg of each substrate dissolved in 2 ml of solvent, and TMS as internal reference. The procedures necessary to obtain reliable results were followed and an accuracy of 0.04 ppm was claimed for the ^{13}C chemical shifts. The chemical shifts for C-3 and C-4 in the authors' Tables 1 and 2[12] have been converted into *meta*- and *para*-substituent chemical shifts, S_m and S_p respectively, by taking the ^{13}C chemical shift of benzene itself as 128.5 ppm. The values are displayed in Tables 1 and 2, for the structures **1** and **2** respectively. The structural



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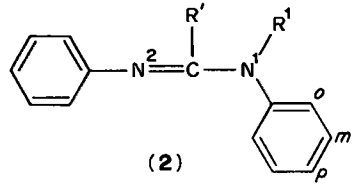

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representation, naming of compounds and groups, and numbering of entries are based on the paper of Oszczapowicz and coworkers[12] to facilitate comparison with the original data.

Values of S_m and S_p may be analysed in terms of σ_I and σ_R^0 by means of the dual substituent-parameter (DSP) equation of Taft and colleagues or the extended Hammett (EH) equation of Charton[13]. For this purpose the DSP equations 1 and 2 proposed by Bromilow and coworkers[14,15] are very convenient[16]. By solving equations 1 and 2 as a pair of simultaneous equations, values of σ_I and σ_R^0 may be calculated for any substituent for which the values of S_m and S_p have been determined, but have not been used in establishing the equations. Values of σ_I and σ_R^0 calculated on this basis for the various formamidino, acetamidino and guanidino groups are shown in Tables 1 and 2.

$$S_m = 1.6\sigma_I - 1.4\sigma_R^0 \quad (1)$$

$$S_p = 4.6\sigma_I + 21.5\sigma_R^0 \quad (2)$$

However, there is some doubt as to whether the DSP treatment is altogether satisfactory in respect of its forcing regressions through the origin, i.e. no intercept term is permitted[17]. The alternative EH equation permits such an intercept. For the purpose of analysing S_m and S_p for amidino groups, the present author has based EH equations on values of S_m and S_p (in $CDCl_3$ or CCl_4 as solvent) taken from Ewing' s critical compilation of ^{13}C substituent chemical shifts in monosubstituted benzenes[18]. Sixteen common substituents, comprising a wide range of electronic effects, were involved[19]. Equations 3 and 4 were derived by multiple linear regression. Values of σ_I and σ_R^0 calculated on the basis of equations 3 and 4 are shown in Tables 1 and 2.

TABLE 1. ^{13}C substituent chemical shifts and sigma constants for formamidino, acetamidino and tetramethylguanidino groups (structure **1**)

No.	Substituent	R′	R^1	R^2	S_m[a]	S_p[a]	σ_I[b]	σ_R^0[b]	σ_I[c]	σ_R^0[c]
1	N^1,N^1-dimethylformamidino	H	Me	Me	0.39	−6.16	−0.01	−0.29	0.03	−0.29
2	N^1,N^1-pentamethyleneformamidino	H	R^1R^2:	$(CH_2)_5$	0.40	−6.23	0.00	−0.29	0.03	−0.30
3	N^1,N^1-hexamethyleneformamidino	H	R^1R^2:	$(CH_2)_6$	0.41	−6.34	0.00	−0.30	0.03	−0.30
4	N^1,N^1-oxapentamethyleneformamidino	H	R^1R^2:	$(CH_2)_2O(CH_2)_2$	0.49	−5.62	0.07	−0.28	0.09	−0.28
5	N^1-methyl-N^1-phenylformamidino	H	Me	Ph	0.54	−5.23	0.11	−0.27	0.12	−0.27
6	N^1,N^1-dimethylacetamidino	Me	Me	Me	0.15	−7.22	−0.17	−0.30	−0.10	−0.31
7	N^1,N^1-tetramethyleneacetamidino	Me	R^1R^2:	$(CH_2)_4$	0.10	−7.22	−0.20	−0.29	−0.11	−0.31
8	N^1,N^1-pentamethyleneacetaminido	Me	R^1R^2:	$(CH_2)_5$	0.15	−7.22	−0.17	−0.30	−0.10	−0.31
9	N^1,N^1-oxapentamethyleneacetamidino	Me	R^1R^2:	$(CH_2)_2O(CH_2)_2$	0.27	−7.53	−0.12	−0.33	−0.06	−0.34
10	N^1-ethyl-N^1-phenylacetamidino	Me	Et	Ph	0.18	−6.96	−0.14	−0.29	−0.08	−0.31
11	N^1-methyl-N^1-phenylacetamidino	Me	Me	Ph	0.27	−6.75	−0.09	−0.30	−0.03	−0.31
12	N^1-methyl-N^1-*p*-tolylacetamidino	Me	Me	*p*-MeC_6H_4	0.25	−6.83	−0.10	−0.30	−0.05	−0.31
13[d]	N^1-methyl-N^1-*p*-anisylacetamidino	Me	Me	*p*-$MeOC_6H_4$	0.19	−6.84	−0.13	−0.29	−0.07	−0.30
15[d]	N^1-methyl-N^1-*m*-chlorophenylacetamidino	Me	Me	*m*-ClC_6H_4	0.32	−6.56	−0.06	−0.29	−0.01	−0.30
16	N^1,N^1-di-*n*-propylacetamidino	Me	n-Pr	n-Pr	0.14	−7.53	−0.19	−0.31	−0.11	−0.33
17	N^1,N^1-di-*n*-butylacetamidino	Me	*n*-Bu	*n*-Bu	0.15	−7.53	−0.18	−0.31	−0.11	−0.33
18	N^1,N^1-di-isopropylacetamidino	Me	*i*-Pr	*i*-Pr	0.10	−8.05	−0.22	−0.33	−0.14	−0.34
19	N^1,N^1-di-isobutylacetamidino	Me	*i*-Bu	*i*-Bu	0.15	−7.57	−0.18	−0.31	−0.11	−0.33
20	N^1,N^1-di-cyclohexylacetamidino	Me	*c*-Hex	*c*-Hex	0.10	−7.87	−0.22	−0.32	−0.14	−0.34
21	N^1,N^1,N^2,N^2-tetramethylguanidino	NMe_2	Me	Me	0.15	−8.78	−0.22	−0.36	−0.15	−0.38

[a] ^{13}C substituent chemical shifts calculated from results of Oszczapowicz and coworkers[12], taking the chemical shift for benzene as 128.5.
[b] Calculated from equations 1 and 2[14,15].
[c] Calculated from equations 3 and 4.
[d] The missing No. 14 was the *p*-bromo compound which was subject to uncertainty of assignment.

$$S_m = -0.2700 + 2.217(\pm 0.204)\sigma_I - 2.006(\pm 0.206)\sigma_R^0 \quad (3)$$

$$n = 16,\ R = 0.9625,\ s = 0.1835,\ \psi = 0.301$$

$$S_p = -0.2929 + 5.111(\pm 0.608)\sigma_I + 20.498(\pm (0.614)\sigma_R^0 \quad (4)$$

$$n = 16,\ R = 0.9957,\ s = 0.5482,\ \psi = 0.1027$$

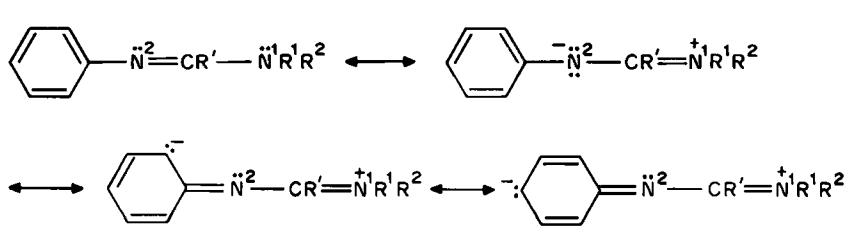
(n = number of data points; R = multiple correlation coefficient; s = standard error of estimate; ψ = Exner's statistic of goodness of fit[20,21]. The $\pm$ values in parentheses are standard errors of the regression coefficients[22].)

The values of σ_I and σ_R^0 as tabulated have been rounded-off at the second decimal place on the grounds that an accuracy of ± 0.04 ppm in the chemical shifts renders the third place of decimals of the calculated σ_I and σ_R^0 values unreliable. The accuracy of ± 0.04 ppm in the chemical shift gives a possible range of ± 0.02 for σ_I and ± 0.01 for σ_R^0. This must be borne in mind in the discussion of these substituent constants for the amidino groups. Overmuch significance must not be attached to small differences in σ_I or σ_R^0 respectively, even though the experimental data were obtained under standardized conditions in a single laboratory and have been analysed by the same procedures as above.

It will be seen from Table 1 that the different procedures of calculation yield σ_R^0 values which differ but slightly. However, the values of σ_I given by equations 3 and 4 tend to be more positive by several units in the second place of decimals than the corresponding values given by equations 1 and 2. In Table 2 the relationship for the alternative values of σ_I is reversed. Our discussion will be based on both sets of σ_I and σ_R^0 values, and we shall emphasize the features which do not depend too much on the set of values considered.

In Table 1 the most remarkable feature is the occurrence of definitely negative values of σ_I for the majority of the substituents. Inspection of any extended compilation of σ_I values shows that for most substituents σ_I is positive[23–25]. Small negative values may be shown by alkyl groups and by substituents involving silicon. Substituents bonded to the benzene ring through nitrogen commonly show appreciable or considerable positive values of σ_I. Thus for the NH_2 and NMe_2 groups, σ_I values are given as 0.12 and 0.06, respectively, by Ehrenson and coworkers[25], and as 0.17 for both groups by Charton[24]. The only substituents which often show substantial negative values of σ_I are negative unipolar (anionic) substituents, although the significance of such values is open to question in view of the uncertainty as to whether unipolar substituents conform to the same correlation equations as dipolar substituents (see the Introduction). However, σ_I values have recently been recorded for anionic substituents as follows[26]: $-CO_2^-$, -0.07; $NC-\bar{C}H$, -0.54; CH_3CON^-, -0.19; O^-, -0.89. (Values may be found in several compilations[23,24] often showing a numerical spread for any given substituent, but undoubtedly negative in many cases.)

The negative values of σ_I for most of the amidino groups in Table 1 are presumably attributable to the structure of the amidine involving a resonance hybrid **3**. There is



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evidence from dipole moment studies of strong mesomeric interaction between the amidino group and a benzene ring[27]. Also, NMR studies of the barrier to rotation about the $CR'—NR^1R^2$ bond indicate much double-bond character[28]. The participation of a canonical form in which negative charge is localized on N^2 can apparently lead to an electron-releasing inductive effect into the benzene ring.

For the formamidino groups Nos. 1–3, the inherent tendency of N^2 to attract electrons from the benzene ring is more or less neutralized by the effect of the above resonance. However, the introduction of an O atom into R^1R^2 in No. 4, or of Ph as R^2 in No. 5, imparts a more definite electron-attracting character as measured by σ_I. The introduction of Me as R' in the acetamido groups gives a distinct electron-releasing character to the substituents Nos. 6–9, in accord with the 'traditional' view of methyl itself being an electron-releasing group[29]. Here again the introduction of O into R^1R^2 (No. 9) or of Ph as R^2 (Nos. 10 and 11) moves σ_I in the positive direction. The effect on σ_I of introducing substituents into Ph as R^2 (Nos. 12, 13 and 15) is small, but is in qualitative accord with what might be expected from the usual electronic effects of *p*-Me, *p*-OMe and *m*-Cl. The introduction of longer chain and branched alkyl groups as R^1 and R^2 (Nos. 16–20) appears to make σ_I somewhat more negative. This may be a sign of electron-release increasing with chain length and branching, which is the traditional view of the behaviour of alkyl groups[29]. However, the effect could be steric in origin and due to bulky groups encouraging the bonds of N^1 to take up a planar sp^2 arrangement and thereby increasing the contribution of the charge-separated canonical forms in the above resonance hybrid. The tetramethylguanidino group (No. 21) has the most negative value of σ_I in Table 1. Presumably the two NMe_2 groups on the $—N=C\diagup\diagdown$ encourage the accumulation of negative charge on N^2.

There is relatively little variation with structure in the values of σ_R^0 in Table 1. At around -0.3 the resonance effects of these groups are clearly much less marked than those of NH_2 at -0.48 (Ehrenson and coworkers[25]) or -0.42 (Charton[24]) and NMe_2 at -0.52 (Ehrenson and coworkers[25]) or -0.44 (Charton[24]). They are more comparable with NHAc, for which a value of -0.25 is given by both the above sources. The difference between amino groups and amidino groups may be connected with the resonance donor effect of N^2 being due to the shifting of the double bond from $(N^2)=C$, rather than to the involvement of the lone pair of electrons which N^2 has in the ground state. Calculations of σ_R^0 values from ^{13}C substituent chemical shifts for several groups of the general form $—N=CXY$ find values of around -0.2 (X = H or Me, Y = Ph or OR; data from Ewing's compilation[18], analysed by equations 3 and 4). This appears to confirm that the resonance donor effect of $—\overset{\curvearrowleft}{N}=$ is weaker than that of $—\overset{\curvearrowleft}{N}R^1R^2$.

The values of σ_R^0 in Table 1 show some slight tendency to become more positive as σ_I becomes more positive, and to become more negative as σ_I becomes more negative. This seems a reasonable finding. The relationship is clearest towards the bottom of the Table and especially with the tetramethylguanidino substituent (No. 21), for which σ_I and σ_R^0 take the most negative values in the Table.

When a phenyl group is attached at N^2 as part of an amidino substituent which is exerting effects on the various positions of a phenyl group attached as probe at N^1, we see, so to say, the other side of the coin. The resonance hybrid structure invoked in the earlier part of the discussion implies that N^1 bears positive charge and is thus electron-attracting for the phenyl ring at N^1. Hence, as we see in Table 2, the formamidino and two acetamidino groups involved show considerable positive values of σ_I. At the same time the tendency of the lone pair on N^1 to be delocalized into the ring is greatly reduced by its involvement in the above resonance hybrid. The σ_R^0 values are therefore much less negative than those of NH_2 or NMe_2 quoted above. The parallel movement of the σ_I and σ_R^0 values which is hinted at by Table 2 is reasonable, but too much stress should not be laid on this in view of the paucity of results.

TABLE 2. ^{13}C substituent chemical shifts and sigma constants for formamidino and acetamidino groups (structure 2)

Substituent	R′	R^1	S_m[a]	S_p[a]	σ_I[b]	σ_R^0[b]	σ_I[c]	σ_R^0[c]
N^1-methyl-N^2-phenyl-formamidino	H	Me	0.88	−4.49	0.31	−0.28	0.27	−0.27
N^1-ethyl-N^2-phenyl-acetamidino	Me	Et	0.75	−1.85	0.33	−0.16	0.32	−0.16
N^1-methyl-N^2-phenyl acetamidino	Me	Me	0.84	−1.85	0.38	−0.17	0.35	−0.16

[abc]See footnotes in Table 1.

Ab initio calculations of charge distributions in monosubstituted benzenes have found a good linear relationship between *para* ^{13}C substituent chemical shifts and the total charge density at the *para* carbon atom[30]. (The situation is rather less clear for the *meta* disposition.) We may thus regard the *para* ^{13}C shifts as providing an overall measure of the electronic effects of the *para* substituents, without essaying a quantitative separation into inductive and resonance effects; cf. the original benzoic-acid-based Hammett σ values. It is worth looking at the S_p values in Tables 1 and 2 briefly in this simple way.

In Table 1 the upfield shifts (more negative values) shown by the values of S_p for the acetamidino groups (Nos. 6–11) compared with the formamidino groups (Nos. 1–5) indicate the electron-releasing properties of the methyl group attached to the amidino carbon atom. The electron-attracting effect of the Ph in producing a downfield shift is also clear; compare No. 5 with No. 1, and No. 11 with No. 6. The analogous effect of the ring O is seen in the formamidino series (compare No. 4 with No. 2 or 3), but the change in S_p is in the wrong direction in the acetamidino series (compare No. 9 with No. 7 or 8). The overall electronic effects of substituents in the N^1 phenyl ring are indicated qualitatively by the S_p values (compare Nos. 11–13 and 15), while a quite definite effect of chain lengthening and branching for R^1 and R^2 is shown by the S_p values of Nos. 16–20 compared with No. 6. As one might expect, the tetramethylguanidino group No. 21 is characterized by a pronounced upfield shift in S_p. The marked downfield shifts shown by the groups in Table 2 well indicate the much more electron-attracting character of the amidino groups bonded through N^1.

This type of explanation is rather limited and unrefined, particularly since it cannot be extended to the much smaller variations in S_m with structure, the values of which are also characterized by being of the wrong sign for any straightforward explanation in terms of electronic effects.

Oszczapowicz and coworkers[12] also record the ^{13}C chemical shifts for C-1 (*ipso*) and C-2 (*ortho*) carbon atoms, but these are not amenable to DSP or EH analysis, or indeed to any simple explanation in terms of electronic effects.

B. Substituent Constants from ^{19}F NMR and Miscellaneous Spectroscopic Studies

Heesing and Schmaldt[31] have measured the ^{19}F substituent chemical shifts for several *meta*- and *para*-guanidino- or guanidinium-substituted fluorobenzenes and have interpreted these by means of the DSP analysis proposed by Taft and his coworkers in 1963[32]. In accord with the practice of the nineteen-sixties and through much of the nineteen-seventies, the substituent chemical shifts were expressed as *shielding* parameters. Nowadays it is more usual to express the NMR magnitudes as *deshielding* parameters. We will bring Heesing and Schmaldt's data and analysis into accord with the modern

TABLE 3. ^{19}F substituent chemical shifts and sigma constants for guanidino and guanidinium groups in fluorobenzene

No.	Substituent	$S_m^{F\,a}$	$S_p^{F\,a}$	$\sigma_I{}^b$	$\sigma_R^{0\,b}$
1	Guanidino	−0.67	−11.53	−0.01	−0.37
2	*tert*-Butylguanidino	−1.02	−12.12	−0.06	−0.38
3	Phenylguanidino	0.00	−10.70	0.08	−0.36
4	Nitroguanidino	1.14	−3.94	0.25	−0.17
5	Guanidinomethyl	−0.99	−4.18	−0.05	−0.11
6	Guanidinium[c]	1.81	−2.27	0.34	−0.14
7	*tert*-Butylguanidinium[c]	1.28	−2.20	0.26	−0.12
8	Phenylguanidinium[c]	1.56	−2.75	0.30	−0.15
9	Guanidiniummethyl[c]	0.00	−1.99	0.08	−0.07

[a] ^{19}F substituent chemical shifts for fluorobenzenes in DMSO as solvent[31].
[b] Calculated from equations 5 and 6.
[c] The counter-ion was NO_3^-.

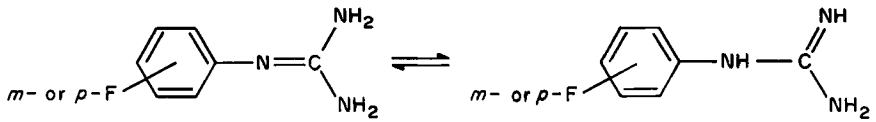
convention, which means changing the signs of the NMR shifts and of the coefficients in the DSP equations. Pertinent data are shown in Table 3. The σ_I and σ_R^0 values are as calculated by Heesing and Schmaldt[31] by using the equations of Taft and coworkers of 1963[32], which we will rewrite as equations 5 and 6[33], where S_m^F and S_p^F are the shifts relative

$$\sigma_I = 0.141\, S_m^F + 0.0845 \tag{5}$$

$$\sigma_R^0 = 0.0339\, S_p^F - 0.0339\, S_m^F \tag{6}$$

to fluorobenzene produced by the substituents in question in the *meta*- or *para*-position with respect to the fluorine atom. In Heesing and Schmaldt's study the shifts were measured in DMSO as solvent, whereas in the study by Taft and coworkers on which the above equations are based, so-called 'normal' solvents were used. The term 'normal' appears to embrace a wide range of solvents of the non-hydrogen-bonding, or not markedly hydrogen-bonding, type. Thus the NMR shifts, and the substituent constants derived therefrom, in Heesing and Schmaldt's work may well have been influenced by the choice of DMSO as solvent.

Another important consideration for the interpretation of Heesing and Schmaldt's results is the tautomerism of the compounds involved. The free bases in principle exhibit prototropic tautomerism, as in **4** for fluorophenylguanidine itself, with more complicated



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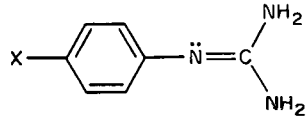
possibilities for the *N*-substituted derivatives. The authors do not refer to any information regarding the tautomeric equilibria in DMSO as solvent, and appear to attempt to interpret their results without involving themselves in details of tautomerism. In the related, immediately following, paper by Pies and Weiss[34], the guanidino substituent is represented as being attached to a phenyl ring through an amino nitrogen and not through the imino nitrogen, viz. —NH—C(=NH)NH_2. Other workers who have considered the

tautomerism of phenylguanidines appear to believe that the predominant form has the phenyl attached *via* the imino nitrogen atom, viz. —N=C(NH$_2$)$_2$[35–37]. There is in fact evidence from ^{15}N NMR studies that the principal tautomer for arylguanidines in DMSO is **5**[38]. We shall assume that this is the case for the compounds involving the guanidino substituent in Table 3, when the guanidino moiety is attached directly to a benzene ring.



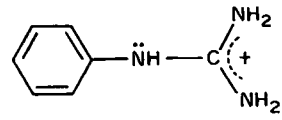
(5)

A guanidino group attached directly to a benzene ring must be supposed to be in extensive conjugation with that ring; cf. the amidino group as discussed in Section II.A. In the case of the parent guanidino group (No. 1 in Table 3) this conjugation appears to be sufficient to nullify the natural tendency of the nitrogen atom to draw electrons inductively from the benzene ring, so that in terms of σ_I the group is more or less electronically indifferent. Replacement of one H of an NH$_2$ group by *t*-Bu (No. 2) produces an appreciably more negative value of σ_I, while such replacement by Ph (No. 3) leads to an appreciably positive σ_I. These changes are in accord with what might be expected from the behaviour of the amidino groups as revealed in Section II.A. It should be noted that the σ_I value found in Section II.A for the tetramethylguanidino group is certainly much more negative than that of the guanidino group itself as shown by the ^{19}F study, indicating a considerable effect of replacing all four amino H atoms by methyl groups. However, the conjugative ability of the guanidino groups Nos. 1–3 in Table 3 as indicated by the σ_R^0 values is little affected by *t*-Bu or Ph substitution and is indeed very similar to that of the tetramethylguanidino group as shown in Table 1 of Section II.A, with $\sigma_R^0 \approx -0.37$. As would be expected, the replacement of H by NO$_2$ to obtain the nitroguanidino group (No. 4) produces a markedly positive σ_I value and a much less negative σ_R^0 value. In considering the electronic effect of the guanidinomethyl group (No. 5)we must consider the problem of tautomerism again. The guanidino moiety might be attached to the CH$_2$ via the imino or an amino N atom. Since extensive conjugation is blocked in either case, the question of tautomeric preference seems an open one. In the absence of definite information we will assume that the guanidinomethyl group is —CH$_2$N=C(NH$_2$)$_2$. On this basis the appreciably negative value of σ_I may be due to the restriction of the resonance of the guanidinomethyl group to **6**, thus localizing negative charge on the imino nitrogen atom, which cannot be passed by further conjugation into the benzene ring. A much less negative value of σ_R^0 than in Nos. 1–3 is only to be expected, and at −0.11 it is comparable with that of methyl itself[25].

$$—CH_2\ddot{N}=C(NH_2)_2 \leftrightarrow —CH_2\bar{\ddot{N}}—C(NH_2)_2^+$$

(6)

Discussion of the sigma values of the guanidinium groups is not complicated by the problem of tautomerism. However the parent base may be viewed, the phenylguanidinium ion is most simply **7**, with extensive possibilities of resonance. On the other hand, there is



(7)

the complication that the discussion of the sigma values of any unipolar substituent must be under the *caveat* that the treatment of charged substituents in the same systems of correlation analysis as dipolar substituents is a procedure of doubtful validity (see Introduction).

It is not surprising that the guanidinium substituents Nos. 6–8 show fairly strong electron-attracting properties as measured by σ_I. These seem slightly reduced by both *t*-Bu and Ph substitution. The σ_I values at *ca* 0.3 are somewhat lower than those usually found for unipolar substituents in which the positive charge is essentially localized on a group adjacent to the benzene ring, e.g. NMe_3^+, $\sigma_I = 1.07$[24]. In the guanidinium groups the positive charge is well dispersed over several atoms by resonance and the situation is perhaps analogous to an NMe_3^+ group which is slightly separated from the benzene ring by another moiety, e.g. $CH_2NMe_3^+$, for which σ_I is 0.39[24]. Separation of the guanidinium group itself from the ring by a CH_2 group (No. 9) reduces σ_I to 0.08; cf. 0.18 for $(CH_2)_2NMe_3^+$[24].

The guanidinium groups Nos. 6–8 show appreciably negative σ_R^0 values at about −0.14, indicating that the lone pair of electrons on the N atom attached to the benzene ring is able to be delocalized into the ring, in spite of the restraining influence of the positive charge and the possibility of delocalization in the opposite direction, with localization of the positive charge on the N atom. Naturally the σ_R^0 value becomes rather less negative when an insulating CH_2 group is placed between the benzene ring and the guanidinium group (No. 9).

The above discussion shows that the σ_I and σ_R^0 values of the guanidino and guanidinium groups based on ^{19}F substituent chemical shifts form a coherent body of data, which can be shown to be sensibly related to similar data for other groups. However, overmuch significance must not be attributed to the absolute values of σ_I and σ_R^0 given in Table 3. The equations relating ^{19}F substituent chemical shifts to σ_I and σ_R^0, which were used by Heesing and Schmaldt[31], were devised by Taft and coworkers quite early in the development of the correlation analysis of ^{19}F substituent chemical shifts[32]. We have adhered to them (in the form of equations 5 and 6) in the present account in order to follow exactly what Heesing and Schmaldt did, but it has been pointed out by Elguero and coworkers[39] that Taft and coworkers have several times changed the equations used to relate S_m^F and S_p^F to σ_I and σ_R^0. When the different equations are used to calculate σ_I and σ_R^0 for a given substituent, the same values are not necessarily obtained. The variations in σ_R^0 are usually no more than one or two units in the second place of decimals, but those in σ_I can amount to several such units. This is not an appropriate place to examine this matter in detail, which raises various questions, such as the properiety of using the DSP equation without permitting an intercept term (cf. the earlier discussion in Section II.A of the relationship of S_m and S_p for ^{13}C NMR to σ_I and σ_R^0). We content ourselves with the warning that the significance of values of σ_I and σ_R^0 based on ^{19}F NMR needs to be appraised in relation to the equations used.

Before we leave the work of Heesing and Schmaldt[31], it should be mentioned that indications of the substituent effects of guanidino and guanidinium groups were also obtained in other ways. Thus there is reference to earlier work on redox potentials of quinones, in which $E_{1/2}$ values were correlated with σ_p constants of substituents. The examination of 2-guanidino-1,4-naphthoquinone showed that the guanidino group exerted a considerable electron-releasing mesomeric (resonance) effect, comparable with that of the acetylamino group[40]. The guanidinium group showed a similar but weaker effect. These observations fit in well with the results which the authors later obtained from ^{19}F NMR studies as already described.

Heesing and Schmaldt[31] also studied the directing effect of the guanidinium group in nitration. They found only *ortho*- and *para*-nitro products, in the proportions of 28:72. The *meta* derivative, which in the nitration of substrates containing positively charged

TABLE 4. ^{35}Cl NQR substituent parameters κ for *N*-bonded groups[34] in chlorobenzene

Substituent	κ_o[a]	κ_m[a]	κ_p[a]	σ_m	σ_p	σ_I
$NHC(NH_2)_2^+$	0.938	0.494	0.282		0.38[b]	0.34[c]
NMe_2	0.336	−0.380	−0.550	−0.15[e]	−0.63[e]	0.17[d]
NHCOMe	0.667	0.343	0.056	0.12[e]	−0.09[e]	0.28[d]
NH_3^+	1.213	0.705	0.469	0.64[e]	0.49[e]	0.60[e]

[a]The units of κ are MHz.
[b]Mean value from Reference 48.
[c]Reference 31.
[d]Reference 24.
[e]Reference 23.

substituents is often formed predominantly or exclusively[41], could not be detected, and amounted certainly to less than 1% of the product. The reaction velocity was greatly reduced compared with that of benzene in competitive nitration. Thus the guanidinium group resembles the halogen substituents in respect of directing effect for electrophilic substitution: these are $+K$ (otherwise $+M$), $-I$ substituents (Ingold[42]). It was further found that the guanidiniummethyl group behaved rather similarly to an alkyl group. Nitration was somewhat faster than with the guanidinium group, and the *ortho*-nitro product now predominated, with an *ortho*: *para* ratio of 71:29. Again no *meta* product could be detected.

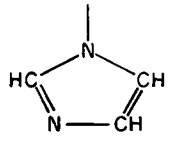
Finally, it must be mentioned that Heesing and Schmaldt[31] prepared a series of *N*-(chlorophenyl)guanidines and *N*-(chlorophenyl)guanidinium nitrates for ^{35}Cl NQR measurements by Pies and Weiss[34]. The ^{35}NQR study was not able to detect any systematic effect of the guanidino group on the charge distribution within the benzene system, but the guanidinium group was found to reduce the charge density in the phenyl ring by virtue of its inductive effect. NQR substituent parameters κ were derived for the guanidinium group and compared with those of other *N*-containing substituents. A selection of κ values is shown in Table 4. For the effect of substituents in the *meta*- or *para*-position there seems to be a rough parallelism between the value of κ and the ordinary benzoic-acid-based σ constants. This indicates that κ measures a resultant of inductive and resonance effects comparable with that operating on the ionization of benzoic acid. The κ values for *ortho*- substituents appear to show an enhanced contribution of the inductive effect relative to the resonance effect; there is a parallelism with σ_I values.

The paper by Elguero and coworkers[39] already mentioned in connection with ^{19}F NMR studies is concerned with the determination of σ_I and σ_R^0 parameters of *N*-substituted azoles. Imidazoles bear a structural relationship to amidines, etc. and may be deemed relevant to the present chapter. The variety of expressions relating ^{19}F substituent chemical shifts to σ_I and σ_R^0 which has been used by Taft and coworkers over the years led Elguero and coworkers to do their own calibration with eleven pairs of *meta*- and *para*-substituted fluorobenzenes involving substituents of well-established values of σ_I and σ_R^0. The NMR measurements were made with 0.5 M solutions in $CDCl_3$. The empirical equations which were derived on this basis were equations 7 and 8 (after some

$$\sigma_I = 0.151S_m^F - 0.003S_p^F + 0.019 \quad (7)$$

$$\sigma_R^0 = 0.032S_p^F - 0.035S_m^F - 0.012 \quad (8)$$

rearrangement and change of symbols to facilitate comparison with equations 5 and 6 above). For the 1-imidazolyl substituent **8**, σ_I was calculated as 0.513 and σ_R^0 as −0.155 from the S_m^F and S_p^F values of the appropriate 1-imidazolylfluorobenzenes. If we write the



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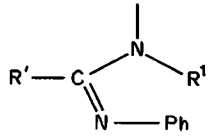
structures of the formamidino and acetamidino substituents of Table 2 as **9**, we can see the structural relationship to the 1-imidazolyl substituent **8** above. The amino N atom in the

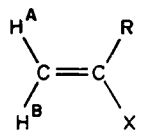


(9)

imidazolyl group will have a positive charge due to extensive delocalization of the lone pair into the imidazole ring, which is somewhat analogous to the delocalization into the amidino system of the amino lone pair in the acetamidines and formamidines. Thus it is not surprising that the 1-imidazolyl group is characterized by a substantial positive value of σ_I, in fact somewhat greater than the values for the substituents in Table 2. Similarly a modest value of σ_R^0 for 1-imidazolyl, comparable with the values for the analogous formamidino and acetamidino groups in Table 2, is reasonable, the values being much less than those characteristic of NH_2, NMe_2, etc. (values quoted in Section II.A).

From the values of σ_I and σ_R^0, Elguero and coworkers[39] derived a value of 0.358 for σ_p^0 by simple summation. This value is then compared with certain earlier estimates of σ_p for the 1-imidazolyl group[43]. These involved the correlation analysis of the effect of *para*-substituents on the asymmetrical stretching frequency (infrared) of the NH_2 group of aniline and on the proton chemical shift of the same group. The value of σ_p for the 1-imidazolyl group was 0.45 from infrared measurements and 0.24 from PMR. The duplicate values for other *N*-substituted azoles showed patchy agreement; some agreed quite well with each other and some agreed rather poorly. It may be that the correlation analysis carried out was in some respect(s) naïve. As far as 1-imidazolyl is concerned, the σ_p^0 value would be expected to be slightly more positive than σ_p. A value for σ_p of about 0.30 would be not unreasonable, i.e. within the range covered by the earlier estimates.

It was mentioned in the Introduction that the correlation analysis of ^1H NMR chemical shifts in terms of substituent constants is a matter of some difficulty for hydrogen atoms attached to the benzene ring. It has long been known that the study of PMR coupling constants in this respect might be more fruitful[44], although the matter does not seem to have been much developed in recent years[45]. A study bearing on the relationship of coupling constants to substituent constants was carried out by Knorr[46] some years ago. This is not concerned with aromatic compounds but with substituted ethylenes **10** and



(10)

their geminal coupling constants $^2J_{HH}$. An extensive survey of the dependence of $^2J_{HH}$ on the substituents R and X indicated that $^2J_{HH}$ was largely governed by the I_σ inductive effect (i.e. through-bonds effect). A correlation equation was developed and used as a basis for a σ_I^J scale. Values of σ_I^J for a large number of substituents were tabulated. These often do not agree very well with 'ordinary' σ_I values[24–26], but this is because σ_I^J supposedly measures a pure through-bonds effect, not mixed with a field effect as in the ordinary 'inductive' effect of physical organic chemistry. The only relevance of Knorr's[46] work to the present chapter is that a σ_I^J value of 0.60 is recorded for 1-imidazolyl; cf. 0.513 for σ_I given above[39].

III. SUBSTITUENT CONSTANTS FROM REACTIVITY STUDIES

A. Sigma Values from a Kinetic Study

In connection with a study of the deacylation rates of *para*-substituted benzoyl trypsins and chymotrypsins, Wang and Shaw[47] measured σ_p values for a number of substituents of biochemical interest, including amidino and guanidino substituents. The selected reaction was the alkaline hydrolysis of 4-nitrophenyl 4′-substituted-benzoates at pH 8.3 in 0.1 M veronal buffer containing 30% DMF. Measurements of rate constants k for several standard substituents gave a good Hammett plot, with a ρ value of 1.92. The σ_p values for the substituents of biochemical interest were then read off the Hammett plot at the appropriate values of $\log k$.

At a pH of 8.3 there is no doubt that all the substituents of biochemical interest were present almost entirely in protonated form. Indeed the solutions appear to have been made up with the substrates as hydrochlorides or hydrobromides. Once again we refer to our warning in the Introduction about the significance of Hammett treatments involving charged substituents. The derived σ_p values, presented in Table 5, must be regarded as giving only a rather general indication of the electronic behaviour of the substituents in the particular conditions.

The guanidinium groups (Nos. 1–3) all apparently show a rather feeble electron-releasing effect. This is not at all what would have been expected either *a priori* or from the values of σ_I and σ_R^0 as determined in the ^{19}F NMR studies described in Section II.B. These would suggest positive values of σ_p in the range 0.1 to 0.2. All that can be said about these discrepancies is that they may be connected with the very different conditions of medium and counter-ion. Also it should be noted that the Hammett line was established by reactions of an anionic reagent (OH^-) with a neutral substrate, whereas the reactions of the guanidine derivatives are those of an anionic reagent (OH^-) with a cationic substrate (the protonated form of the guanidine derivative). There is likely to be a considerable dependence of k (and hence of derived σ_p values) on substrate concentration and ionic

TABLE 5. Values of σ_p for various amidinium and guanidinium groups from a kinetic study[47]

No.	Substituent	σ_p
1	$NHC(NH_2)_2^+$	−0.02
2	$NHC(NHMe)(NH_2)^+$	−0.045
3	$NHC(NHMe)_2^+$	−0.06
4	$C(NH_2)_2^+$	0.65
5	$CH_2SC(NH_2)_2^+$	0.04
6	$CH_2SC(NHMe)(NH_2)^+$	−0.05
7	$CH_2SC(NHMe)_2^+$	−0.02

strength for the latter reactions. Extrapolation to 'infinite dilution' might give much higher values of k and positive values of σ_p.

The amidinium group (No. 4) certainly shows a not unreasonable σ_p value at 0.65. Such a value is fairly typical of positively charged substituents, with the positive charge close to the benzene ring, e.g. NH_3^+, *ca* 0.6; NMe_3^+, *ca* 0.9; SMe_2^+, *ca* 0.9[23]. It should be noted that $-C(NH_2)_2^+$ has the possibility of exerting an electron-attracting resonance effect. Thus the comparison with SMe_2^+ is not inappropriate, since this is commonly regarded as accepting electrons by π(pd) bonding with a benzene ring[1]. Attention to concentration and ionic strength effects on k might result in an even more positive value of σ_p for the amidinium group.

As to the small $\pm$ values for σ_p shown by the amidinium groups separated from the benzene ring by CH_2S (Nos. 5–7), all one can say is that such values are not unreasonable, bearing in mind the rapid fall-off in σ_p for groups such as NMe_3^+ when separated from the ring by methylene groups: NMe_3^+, 0.72; $CH_2NMe_3^+$, 0.44; $(CH_2)_2NMe_3^+$, 0.13; $(CH_2)_3NMe_3^+$, 0.02[23]. The possibility of moving the positive charge nearer the ring by conjugation involving S and the amidinium C atom should, however, be noted. Again it seems that σ_p values corrected as above would probably be somewhat more positive.

B. Sigma Values from pK_a Measurements

Koike[48] determined the pK_a values of a series of *para*-substituted phenylguanidinium ions in aqueous solution at 25 °C by UV spectrophotometric measurements. Among the substituents included were COOH, NH_2 and OH. In these cases the corresponding pK_a value for the ionization of the substituent was also measured as 3.76 (COOH), 3.68 (NH_3^+) and 9.05 (OH). Since the arylguanidines in question are very strong bases, the above pK_a values indicate the effect of the guanidinium substituent on the ionization of COOH, NH_3^+ and OH. In association with the appropriate ρ values and the pK_a values for the parent compounds, they may be used to calculate σ_p values for the $-NHC(NH_2)_2^+$ group. The values were found by Koike[48] to be 0.443, 0.377 and 0.317, respectively. In interpreting these it is necessary to point out that the ionization of the anilinium ion is of a charge type different from that of benzoic acid and phenol. Hence concentration and salt effects on pK_a values will be different. Bearing this in mind and the general limitations of sigma values for charged substituents, the mutual agreement of the above σ_p values is all that could be expected. The values are somewhat higher than might have been predicted from the ^{19}F studies described in Section II.B, and the guanidinium group seems to be much more electron-attracting than it appeared to be in the ester hydrolysis study described in Section III.A.

Koike also gives indications of the electron-attracting properties of the guanidinium group, now denoted as g^+, in an aliphatic system. The pK_a values of g^+CH_2COOH and $g^+(CH_2)_2COOH$ are given as 3.12 and 3.92 respectively, compared with acetic acid at 4.76; cf. 2.35 for $NH_3^+CH_2COOH$, 3.55 for $NH_3^+(CH_2)_2COOH$ and 4.03 for $NH_3^+(CH_2)_3COOH$. If it is assumed to be legitimate to interpret these values in terms of Taft's linear free energy–polar energy relationship[49] with $\rho^* = 1.72$, the corresponding values of σ^* and σ_I may be calculated and are shown in Table 6. For NH_3^+ and $NH_3^+CH_2$ the σ_I values agree with the literature[23]. The value of σ_I for g^+ is slightly higher than that based on the ^{19}F NMR studies (0.34), while that for g^+CH_2 is considerably higher than the ^{19}F NMR value (0.08).

A more recent paper by Rogana and coworkers[50] on the pK_a values of *meta*- and *para*-substituted benzamidinium ions permits a calculation of a σ_p value for the amidinium group $-C(NH_2)_2^+$. The pK_a value of the OH of *para*-hydroxyphenylbenzamidinium ion is given as 7.7. There is no doubt that at a pH corresponding to this pK_a value the amidine moiety would be fully protonated. (The pK_a value of the weakest amidine base

TABLE 6. Sigma values for positively charged groups from measurements of pK_a of substituted acetic acids XCH_2COOH[48]

Substituent XCH_2	σ^{*a}	Substituent X	$\sigma_I{}^b$
g^+CH_2	0.95	g^+	0.43
$g^+(CH_2)_2$	0.49	g^+CH_2	0.22
$NH_3{}^+CH_2$	1.40	$NH_3{}^+$	0.63
$NH_3{}^+(CH_2)_2$	0.70	$NH_3{}^+CH_2$	0.32
$NH_3{}^+(CH_2)_3$	0.42	$NH_3{}^+(CH_2)_2$	0.19

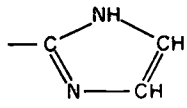
[a]Calculated from $\sigma^* = \Delta pK_a/\rho^*$, where $\Delta pK_a = pK_a(MeCOOH) - pK_a(XCH_2COOH)$ and $\rho^* = 1.72$ and $pK_a(MeCOOH) = 4.76$.
[b]Calculated from the equation $\sigma_I(X) = 0.45\sigma^*(XCH_2)$. (See Reference 49.)

studied, *p*-nitrobenzamidine, is 10.14.) By taking the ρ value for the ionization of phenols to be 2.11 and the pK_a value of the parent phenol to be 9.85 (following Koike[48]), σ_p for the amidinium group may be calculated as 1.02. This is rather higher than the value of 0.65 referred to in Section III.A. While one must be careful not to over-interpret this result, such a high value for the amidinium group would be quite reasonable, bearing in mind the possibility (already pointed out) of it being able to exert an electron-withdrawing resonance effect. If this were the case, then the calculated value of 1.02 would, in fact, have the status of a σ_p^- constant, as the sigma value for a conjugatively electron-withdrawing substituent determined from the ionization of a phenol; cf. the behaviour of NO_2, CN, SO_2Me, etc.[2].

Finally, we mention that the paper by Taylor and Wait[37] already cited in connection with the tautomerism of phenylguanidines has information on the σ_I values of imidazolyl groups. The pK_a values of a wide range of guanidinium ions $RNHC(NH_2)_2{}^+$ are correlated with the σ_I values of R though equation 9:

$$pK_a = 14.18(\pm 0.25) - 22.58(\pm 0.78)\sigma_I \qquad (9)$$
$$n = 16, \qquad r = 0.992, \qquad s = 0.51$$

(A similar equation was proposed by Charton[35] in 1965 on the basis of 8 data points.) Equation 9 was used by Taylor and Wait to determine the σ_I values of various heterocyclic groups, including imidazolyl groups. The value for 2-imidazolyl **11** was found to be 0.27, while that of 4(5)-imidazolyl **12** was 0.08. The σ_I value of 2-benzimidazolyl **13** was found to



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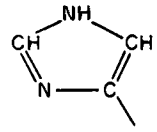

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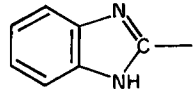

(13)

be 0.32. These values may be compared with that of 0.513 already given for 1-imidazolyl (Section II.B)[39]. It seems reasonable that the σ_I values for the carbon-bonded imidazolyl groups should be lower than the value for the nitrogen-bonded group, with σ_I for the attachment at C-2, situated between the two N atoms, being greater than that for C-4(5), which is adjacent to only one N atom. The more extended conjugation in the 2-benzimidazolyl group is not unreasonably associated with a slighly greater electron-

attracting effect. The introduction of a methyl group at the 1- or 4-position of 2-imidazolyl has only a trifling effect on σ_I, the value being given as 0.26 in both cases.

IV. ACKNOWLEDGEMENTS

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V. REFERENCES AND NOTES

1. J. Shorter, in *The Chemistry of the Sulphonium Group* (Eds. C. J. M. Stirling and S. Patai), Chap. 9, Wiley, Chichester, 1981.
2. J. Shorter, in *The Chemistry of Sulphones and Sulphoxides* (Eds. S. Patai, Z. Rappoport and C. J. M. Stirling), Chap. 10, Wiley, Chichester, 1988.
3. J. Shorter, in *The Chemistry of Sulphinic Acids, Esters and their Derivatives* (Ed. S. Patai), Chap. 17, Wiley, Chichester, 1990.
4. J. Oszczapowicz and W. Krawczyk, *J. Chem. Soc., Perkin Trans. 2*, 21 (1989) and references cited therein. See also the chapter by J. Oszczapowicz in the present volume.
5. R. J. Grout, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley, Chichester, 1975, pp. 258–281, and references cited therein.
6. J. Oszczapowicz, W. Krawczyk, J. Osek and E. Raczyńska, *J. Chem. Res. (S)*, 384; (*M*) 3975 (1985) and references cited therein.
7. J. Shorter, *Correlation Analysis of Organic Reactivity, with particular reference to multiple regression*, Research Studies Press, Wiley, Chichester, 1982.
8. N. B. Chapman and J. Shorter (Eds.), *Advances in Linear Free Energy Relationships*, Plenum Press, London, 1972.
9. N. B. Chapman and J. Shorter (Eds.), *Correlation Analysis in Chemistry: Recent Advances*, Plenum Press, New York, 1978.
10. O. Exner, *Correlation Analysis of Chemical Data*, Plenum Press, New York and SNTL, Prague, 1988.
11. R. I. Zalewski, T. M. Krygowski and J. Shorter (Eds.), *Similarity Models in Organic Chemistry, Biochemistry, and Related Fields*, Elsevier, Amsterdam, 1990 (in press).
12. J. Oszczapowicz, E. Raczyńska and J. Osek, *Magn. Reson. Chem.*, **24**, 9 (1986).
13. Expositions of the dual substituent-parameter equation and the extended Hammett equation in the articles by J. Shorter, in Reference 9, Chap. 4 and Reference 11, Chap. 2.
14. J. Bromilow, R. T. C. Brownlee, D. J. Craik and M. Sadek, *Magn. Reson. Chem.*, **24**, 862 (1986).
15. J. Bromilow, R. T. C. Brownlee, D. J. Craik, M. Sadek and R. W. Taft, *J. Org. Chem.*, **45**, 2429 (1980).
16. See, for example, Reference 3, p. 525.
17. See Reference 7, pp. 209–213.
18. D. F. Ewing, *Org. Magn. Reson.*, **12**, 499 (1979).
19. Values of σ_I and σ_R^0 were taken from S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973) for NMe_2, NH_2, OMe, Me, Ph, F, Cl, H, SOMe, $SiMe_3$, CF_3, SO_2Me, CN, COOMe, NO_2, COMe.
20. O. Exner, *Collect. Czech. Chem. Commun.*, **31**, 3222 (1966).
21. See also Reference 7, Chap. 7.
22. Equations 3 and 4 well reveal the limitations of the correlation analysis of ^{13}C substituent chemical shifts in terms of σ_I and σ_R^0. The goodness of fit as measured by R, or especially ψ, is really rather poor with equation 3, that for *meta*-substituents, although the value of s indicates that the equation is somewhat better as a summary of the data. On the other hand, the goodness of fit of equation 4 is considerably better, but the higher value of s indicates poor summarizing power. The reverse resonance effect corresponding to the negative sign of the coefficient of σ_R^0 in

equation 3 is not well understood (cf. equation 1). In recent years increasing doubts have been expressed concerning various aspects of the correlation analysis of ^{13}C substituent chemical shifts in terms of inductive and resonance parameters. See, for example, O. Exner and M. Buděšinský, *Magn. Reson. Chem.*, **27**, 27 (1989). As a basis for deriving approximate new values of σ_I and σ_R^0, the analysis still seems satisfactory.
23. O. Exner, in Reference 9, Chap. 10.
24. M. Charton, *Prog. Phys. Org. Chem.*, **13**, 119 (1981).
25. S. Ehrenson, R. T. C. Brownlee and R. W. Taft, *Prog. Phys. Org. Chem.*, **10**, 1 (1973).
26. I. G. Binev, T. M. Kolev and I. N. Juchnovski, *Can. J. Chem.*, **63**, 3149 (1985).
27. O. Exner, M. Buděšinský, D. Hnyk, V. Všetečka, and E. D. Raczyńska, *J. Mol. Struct.*, **178**, 147 (1988).
28. I. Wawer, *Magn. Reson. Chem.*, **27**, 577 (1989).
29. The electronic effects of alkyl groups are discussed at length by J. Shorter, in Reference 8, Chap. 2.
30. W. J. Hehre, R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.*, **12**, 159 (1976).
31. A. Heesing and W. Schmaldt, *Chem. Ber.*, **111**, 320 (1978).
32. R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 709, 3146 (1963).
33. The authors of Reference 31 actually use the simple symbol σ_R. This symbol is sometimes used to denote resonance parameters based on ordinary Hammett σ values. However, the DSP analysis of ^{19}F substituent chemical shifts was essentially founded on the use of σ_R^0 values, except for conjugatively electron-attracting substituents. None of the substituents with which we are concerned here is of this nature.
34. W. Pies and A. Weiss, *Chem. Ber.*, **111**, 335 (1978).
35. M. Charton, *J. Org. Chem.*, **30**, 969 (1965).
36. R. G. Button, J. P. Cairns and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1555 (1985).
37. P. J. Taylor and A. R. Wait, *J. Chem. Soc., Perkin Trans. 2*, 1765 (1986).
38. R. E. Botto, J. H. Schwartz and J. D. Roberts, *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 23 (1980).
39. J. Elguero, C. Estopa and D. Ilavský, *J. Chem. Res.* (*S*), 364; (*M*), 4237 (1981).
40. A. Heesing, U. Kappler and W. Rauh, *Justus Liebigs Ann. Chem.*, 2222 (1976).
41. P. B. D. de la Mare and J. H. Ridd, *Aromatic Substitution*, Butterworths, London, 1959.
42. C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, 2nd edn., Bell, London, 1969.
43. P. Bouchet, C. Coquelet and J. Elguero, *J. Chem. Soc., Perkin Trans. 2*, 449 (1974).
44. M. T. Tribble and J. G. Traynham, in Reference 8, Chap. 4.
45. D. F. Ewing, in Reference 9, Chap. 8.
46. R. Knorr, *Tetrahedron*, **37**, 929 (1981).
47. C.-C. Wang and E. Shaw, *Arch. Biochem. Biophys.*, **150**, 259 (1972).
48. H. Koike, *Nippon Kagaku Zasshi*, **83**, 917 (1962); *Chem. Abstr.*, **58**, 13301 (1963).
49. R. W. Taft, in *Steric Effects in Organic Chemistry* (Ed. M. S. Newman), Chap. 13, Wiley, New York, 1956. Taft's work is reviewed in Reference 8, Chap. 2.
50. E. Rogana, D. L. Nelson, L. F. F. Leite and M. Mares-Guia, *J. Chem. Res.* (*S*), 286; (*M*), 2963 (1985).

CHAPTER **14**

Radiation chemistry of amidines

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I. INTRODUCTION

Radiation chemistry is the study of the chemical effects produced in a system by the absorption of ionizing radiation. This definition includes the chemical effects due to radiation from radioactive sources, high-energy charged particles and short-wavelength (less than about 400 A)[1] electromagnetic radiation from accelerators. The principal characteristic of high-energy radiation is that it causes ionization in all materials. This makes a distinction between radiation chemistry and photochemistry[2,3]. Photochemistry deals with longer-wavelength electromagnetic radiations which have lower energy (less

The Chemistry of Amidines and Imidates, Volume 2
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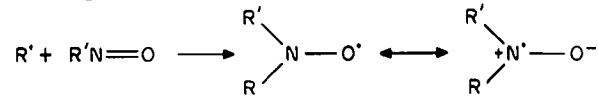
than about 30 eV). This relatively low energy leads in many cases only to the excitation of the molecules and does not produce ions. Usually, the energy of the particles and photons applied in radiation chemistry is much higher. The whole energy is not absorbed by a single molecule, as in photochemistry, but rather distributed over several molecules, along the track of the ionizing particle or photon. The high-energy photons and particles are not selective and may ionize, excite or dissociate any molecule lying in their path, while in photochemistry only some compounds may interact with the radiation, in accordance with the energy of the photons.

The high-energy photons or particles lose energy in successive events and produce ions and primary electrons, which in turn form several secondary electrons with lower energies[4]. The chemical effects of ionizing radiation occur almost exclusively through the secondary electrons, most of which have less than 100 eV. These electrons will cause ionization and excitation of the surrounding molecules and will lose energy until they reach thermal energies. In many solvents these thermal electrons polarize the solvent molecules and are bound in a stable quantum state to them; these electrons are called *solvated* electrons. On the average half of the absorbed energy is spent on ionization while the other half of the energy leads to excited molecules.

The study of radiation chemistry might be divided, from the experimental point of view, into two parts. The first is the study of unstable intermediates which have short lifetimes and thus cannot be studied by the usual methods of chemistry. The second part is the study of the final products of the radiolysis which are measured by common chemical techniques.

One way to make the short-lived intermediates amenable to study is to increase their lifetime, usually by irradiation in the solid state and/or at very low temperatures. Then, the intermediates can be detected at the end of the irradiation by ESR or optical absorption spectroscopy. The ESR of radicals in the solid state is done on single crystals, polycrystalline samples or frozen aqueous solution. In the case of polycrystalline samples or frozen aqueous solution the identification of the radicals from the ESR spectra is difficult in many cases and for better identification the ESR should be done on irradiated single crystals. Later, the method of spin trapping, developed for the liquid phase[5], was extended to polycrystalline solids. In this technique the polycrystalline solids are γ-irradiated and subsequently dissolved in a solution containing the spin trap. Most commonly it is aqueous solution and several spin traps were used[6].

Another method of making the lifetime longer in the liquid phase is by adding compounds which, upon addition of radicals, produce long-lived radicals; this method is called *spin trapping*[5]. In this method a diamagnetic spin-trap is used to convert radicals which are short-lived into long-lived radicals. For example, using nitroso compounds (as, e.g., *t*-nitrosobutane, *t*-NB) the short-lived radicals form long-lived nitroxide radicals (the spin-adduct) according to reaction 1[5].



(1)

More common in the liquid phase is pulse radiolysis[7]. In this technique, electron accelerators which can deliver intense pulses of electrons lasting a very short time (ns up to μs) are used. Each single pulse can produce concentrations of intermediates which are high enough to be studied by various methods, such as light absorption spectroscopy or electrical conductivity.

The yields of radiolysis products are always expressed by the *G* value, which is defined as the number of particles (molecules, radicals, ions) produced or consumed per 100 eV of energy absorbed in the system.

The units for the absorbed energy (dose) are the rad, defined by 1 rad = 100 erg g^{-1} = 6.243×10^{13} eV g^{-1}, and the Gray (Gy) defined by 1 Gy = 100 rad.

When radiolysing a solution, the radiation interacts mainly with solvent molecules, since the solution consists mainly of the latter and the radiation interacts with the molecules unselectively. Consequently, the radiation chemistry of a solution is the combination of the production of initial intermediates from the solvent, which will be the same as in pure solvents, and the reactions of those intermediates with the solute. The most common solvent is water.

The radiolysis of water produces hydrated electrons (e_{aq}^-, $G = 2.9$), hydrogen atoms ($G = 0.55$) and hydroxyl radicals ($G = 2.8$) which react with the molecules of the solutes. In addition, the radiolysis of aqueous solutions leads to formation of molecular products H_2O_2 ($G = 0.75$) and gaseous hydrogen ($G = 0.45$). Also produced are hydronium ions (H_3O^+, $G = 2.9$). In most cases the molecular products do not interfere with the reactions of the radicals. To study the reaction of one radical with the solute without interference from other radicals, scavengers for the other radicals should be added.

e_{aq}^- can be eliminated and even converted to the other radicals OH and H, by the addition of N_2O or H^+ to the system (equations 2 and 3, respectively). Therefore in aqueous N_2O saturated solutions, OH radicals are the predominant species (90%), while in acidic aqueous solution H and OH radicals exist, but not hydrated electrons. The small fraction ($\sim 10\%$) of hydrogen atoms in N_2O-saturated aqueous solution does not interfere significantly with the measurements of the reactions of OH radicals. In many cases H atoms and OH radicals react with solutes in a similar manner, e.g. by addition to a double bond or by hydrogen atom abstraction.

$$e_{aq}^- + N_2O \xrightarrow{H_2O} N_2 + OH^- + OH \qquad (k = 9 \times 10^9\ M^{-1}s^{-1}) \qquad (2)$$

$$e^- + H^+ \longrightarrow H \quad (k = 2.3 \times 10^9\ M^{-1}s^{-1}) \qquad (3)$$

The reaction of H atoms can be studied in acidic solution if the OH radicals are scavenged by *t*-butyl alcohol, in a very fast reaction, while hydrogen atoms react only very slowly with this alcohol (equations 4 and 5). The radical produced in reaction 4 is relatively unreactive and does not interfere with the study of the reaction of H atoms with the solute.

$$\dot{O}H + (CH_3)_3COH \longrightarrow H_2O + \dot{C}H_2C(CH_3)_2OH \qquad (k = 5 \times 10^8\ M^{-1}s^{-1}) \qquad (4)$$

$$H + (CH_3)_3COH \longrightarrow H_2 + \dot{C}H_2C(CH_3)_2OH \qquad (k = 1.7 \times 10^5\ M^{-1}s^{-1}) \qquad (5)$$

Hydrated electrons are obtained as predominant radicals by removing the OH radicals with *t*-butyl alcohol. The removal of both H and OH radicals is accomplished by isopropanol (equations 6 and 7).

$$H + (CH_3)_2CHOH \longrightarrow H_2 + (CH_3)_2\dot{C}OH \qquad (k = 7.4 \times 10^7\ M^{-1}s^{-1}) \qquad (6)$$

$$\dot{O}H + (CH_3)_2CHOH \longrightarrow H_2O + (CH_3)_2\dot{C}OH\ (86\%) + (CH_3)_2CH\dot{O}\ (1\%) + \dot{C}H_2CH(OH)CH_3\ (13\%) \quad (k = 1.9 \times 10^9\ M^{-1}s^{-1}) \qquad (7)$$

The various amidines for which radiation chemistry was studied are the purine and pyrimidine bases, the amino acids histidine and arginine, and derivatives of guanidine. Very few studies were done on the radiolysis of arginine and guanidines and this chapter will be devoted to the purine and pyrimidine bases and histidine.

II. RADIOLYSIS OF PYRIMIDINES IN THE SOLID STATE

A. Initial Processes and Ions

The real initial products are measured only when radiation-induced changes at very low temperatures (usually 4.2 to 20 K) are studied. At this low temperature ESR spectroscopy of irradiated pyrimidines shows only the cation and the anion of the original molecule. The

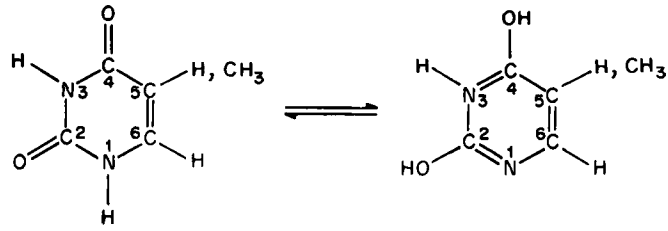
electron donated comes from the highest occupied molecular orbital (HOMO) and it is accepted into the lowest empty molecular orbital (LEMO). The orbitals are of π symmetry and thus the species formed are π^* anions and π cations. The probable reactions are

$$PH \rightsquigarrow PH^+ + e^- \tag{8}$$

$$PH + e^- \rightsquigarrow PH^-$$

where PH stands for a pyrimidine-derived molecule. At 4.2 K both cation and anion are detected simultaneously and it is assumed that electrons themselves do not exist as reactive chemical intermediates. In addition to the radiation chemistry of the pyrimidine nucleic acid bases, the radiation chemistry of 5-halogen substituted uracil has also been studied extensively due to the enhanced in vivo radiosensitivity of DNA in which a fraction of the thymine bases is replaced by 5-halouracils. For the different 5-halouracils it was found by calculation that the anion has π symmetry in the case of F and Cl, and σ symmetry for the case of I. For 5-bromourcil the two orbitals (π^* and σ^*) are nearly degenerate.

The cations are mainly formed by losing an electron from the N1 and C5 sites (Scheme 1), whereas the electron is attached to the anion mainly at C6. In addition to the diketo and dienol forms shown in Scheme 1, of course the enone with one OH group and one carbonyl group also exists. The data on the yields of the cations and anions have been proven somewhat unreliable, due to large variations found in G values. The yields obtained at 77 K range from about 0.2 to 0.8.



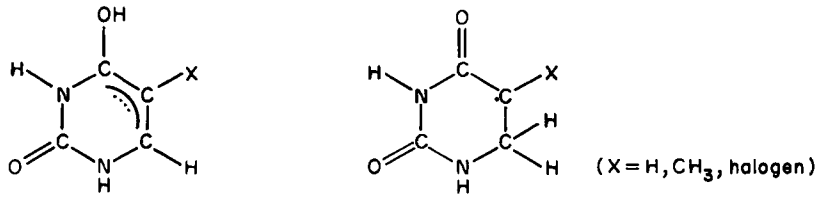
diketo form dienol form

SCHEME 1

Both π cations and π^* anions tend to regain the original charge state of the undamaged molecules. The cations are either deprotonated to form the P radical (the main route) or add an OH^- anion to produce the PHOH radical (a minor fraction). The anions are mainly protonated to PH_2, while to a lesser extent PH^- may lose an anion to produce a radical plus an anion,

$$PH^- \longrightarrow X^- + R^\cdot \tag{9}$$

For uracil, thymine and various 5-halouracils the protonation of the π^* anions involves two main sites, namely the C4 carbonyl group and the olefinic C6, to form the two radicals



I and II. Radical I has two resonative forms, with the unpaired electron either on C4 or on C6. Radical I has almost the same spin density at C6 as the anion and consequently it is ESR-spectroscopically nearly indistinguishable from the parent anion. However, radical II, is clearly distinguishable. In the case of cytosine the protonation cannot occur at C4, and occurs at C2 and C6.

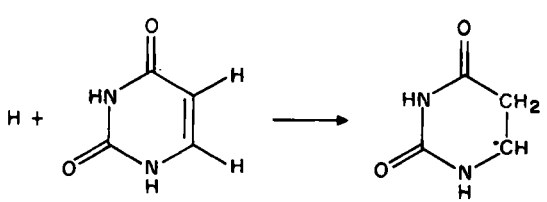
Anion elimination from the parent π^* anion (reaction 9) occurs only when the leaving group, X, is a very electronegative one, such as halide or NO_2^-, and even in these cases it is a very rare process in the solid state.

In the case of the π cations the dominant reactions re-establishing neutrality of the species are deprotonation and anion addition. The deprotonation usually occurs from the N1 position. However, if there is an alkyl substituent at either N1 or C5, the lost proton can come also from the alkyl group. Anion addition as an alternative route for neutralization of the π cation plays a significant role only in solid systems containing a large amount of water (glasses, frozen solutions) but not in the case of single crystals. The attached OH is connected to C6 leaving the unpaired electron on C5. More detailed information on the initial processes in the solid-state radiolysis of pyrimidines can be found in the extensive review of Bernhard[8] and in the less-detailed review by Hüttermann[9].

B. Initial Radicals

The initial cations and anions are observed only at low temperatures. Upon warming or when the irradiation is done at room temperature, the initial ions are not seen and instead the ESR spectra of the neutral radicals are observed. Irradiation of crystalline pyrimidine bases at room temperature leads to the formation of radicals mainly by addition and abstraction of hydrogen atoms. The H atoms are added mainly to the olefinic double bond C5—C6. The only effect of the amidine group is the activating effect, causing the two carbon atoms to be non-equivalent.

Thus, when a single crystal of uracil was γ-irradiated at room temperature ESR spectroscopy showed the presence of almost only the 6-yl radical (III), formed by the addition of a hydrogen atom to the C5 position[10]. A minor product is due to the 5-yl radical, formed by addition of an H atom at the C6 position (radical II). However, the concentration of this product is so low that in a later review paper[11] the same authors stated that the C6 addition product is absent in the case of uracil. Minor reactions involved also the addition of the H atom to the carbonyl group. Riesz and his coworkers[12a] studied room-temperature formation of the radicals by γ-irradiation of polycrystalline uracil by dissolving the latter after irradiation in aqueous solution containing the spin-trap *t*-nitrosobutane. They observed both radicals, with C6 addition (5-yl radical) being a minor product. Spalletta and Bernhard[12b], using the same technique of spin trapping of an irradiated polycrystaline sample, did not find in the case of uracil the 5-yl radical. Slifkin and coworkers[13] found for uracil powders irradiated by γ-rays at room temperature only the ESR spectra of radical III formed by H-atom addition to the C5 position.



6-yl radical
(III)

The 6-yl radical (III) can be converted into the 5-yl radical (II) by visible light of $\gamma > 400\,nm$[14]. The 5-yl radical decays slowly back to the 6-yl radical. This decay can be accelerated by raising the temperature. The same findings were found for 1-methyluracil where only the 6-yl radical (C5 addition) was found[15,16]. The 5-yl radical was obtained by illumination of the 6-yl radical with light of $\lambda > 435\,nm$ at 77 K. However, when crystals of 1-methyluracil·HBr were irradiated by X-rays at 77 K, the C6 addition product is also seen in the ESR spectra[17]. This phenomenon is clearer in the case of cytosine. While irradiated cytosine[18,19] shows only the spectrum of the C5 adduct (unless the single crystal is photobleached), the only H-adduct observed in irradiated cytosine·HCl crystals is the C6 addition radical[20]. This difference in the type of radical formed is explained as due to two different mechanisms of formation of the H-adduct in the solid state[21]. The first mechanism involves homolytic dissociation of atomic hydrogen from excited and superexcited molecules and subsequent addition of the hydrogen atom. This mechanism was termed the 'excitation path'. Another route to the formation of the H-adduct is the 'ionization path', a two-step process in which the first step is the formation of the molecule anion which is followed by protonation of the anion. The first process leads to the 6-yl radical (C5 addition) and it is the major one, if not the only one in apolar crystals. The second process is more prominent in polar crystals, e.g. pyrimidine·HX (X = halogen). Further evidence that the 6-yl radical is formed by the 'excitation path' is the finding that in 1,3-dimethyluracil, which is a completely non-hydrogen-bonding crystal and in which only van der Waals forces are present, the only H-adduct is the C5 adduct.

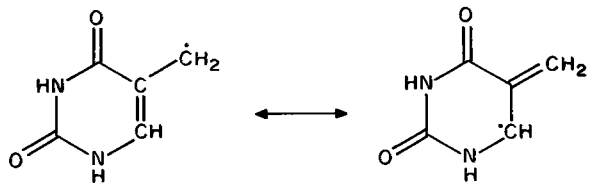
The observation that the 5-yl radical formed by illumination of the 6-yl radical in uracil, cytosine and similar compounds is decaying back to the 6-yl radical indicates that the C6 addition radical (5-yl) needs a specific environment in order to be stabilized in the crystal lattice, in contrast to the C5 addition radicals.

In the case of thymine the main radical formed is the C6 H-adduct (5-yl) radical[22,23]. The unpaired electron on the C5 interacts with the methyl group, connected to C5, and with the C6 methylene group by way of hyperconjugation. This interaction produces a very distinct ESR pattern of an octet with about 140 G total spread. The spin density on C5 in the 5-yl radical is approximately 0.70–0.75. The 6-yl radical was also found in single-crystal studies[24]. Kuwabara and coworkers[12a] found that for X-irradiated polycrystalline thymine dissolved in water containing *t*-nitrosobutane in the presence of oxygen, the major product is the H abstraction radical in which the H atom was abstracted from the methyl side-group and the C6 H-adduct is a minor product. However, this radical was not observed at all by Spalletta and Bernhard using the same technique, in spite of the fact that this radical is clearly present in the solid before dissolution. Riederer and collaborators[25] studied the reaction of H atoms produced by radiolysis or photolysis, with uracil and thymine in acidic glasses (H_2SO_4 and H_3PO_4). They used low solute concentrations in order to be sure that the radicals observed are due almost exclusively to the reaction of the mobile, thermally activated H atoms. In previous studies[26] of glasses with high concentrations the 'H-adduct' could also be produced by the protonation of the base anion. Hence this study is similar to the studies of bombardment of crystalline powders with H atoms[27]. Riederer and coworkers found[25] that in the case of uracil 50% of the radicals are from C5 addition and 50% from C6 addition, while in the case of thymine 70% of the hydrogen atoms add to C6 and only 30% of the H atoms form the 6-yl adduct. The different results for glasses and single crystals can be due either to the possibility that in single crystals the H-adduct radical is formed only by direct H addition to the double bond or to the different stabilization of the radicals in the glassy polar media.

Henriksen and Jones[26] studied the radical formation in thymine in frozen sulphuric acid glasses and found the only thymine radical to be the 5-thymyl radical. They also found that only a small fraction of the C6 H-adduct is formed by direct addition of the hydrogen atoms to the olefinic C5—C6 double bond. A convincing proof for the formation of the

5-thymyl radical, not from direct H-atom reaction, was found by an ESR study of the concentrations of both the H atoms and the 5-thymyl radical in H_2SO_4 glasses. The glasses containing thymine were irradiated at 77 K and then heated up to 105 K, which caused the hydrogen atoms to decay completely within 5 min followed by subsequent formation of the 5-thymyl radicals. Leaving the sample at 105 K for another 60 min hardly changed the yield of the 5-thymyl radicals. Subsequent warming to 140 K increased the 5-thymyl radicals almost fourfold although no H-atom signal was found after the first 5 min at 105 K. In glasses the main radiolysis is due to radiation absorbed in the H_2SO_4 glass rather than in thymine, and G values calculated assuming that energy was absorbed only in thymine were over 2000.

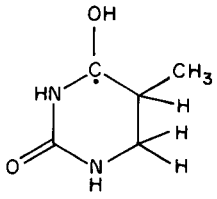
The observation that hydrogen-addition radicals were formed in pure anhydrous crystals of thymine[23,28] and uracil[29] proves that the bases themselves can act as hydrogen donors and there should be radicals from abstraction of hydrogen atoms. ESR studies show the existence at room temperature of the H-abstraction radicals in irradiated single crystals of several bases: thymine[28], uracil[29] and orotic acid[30], while for cytosine H-abstraction radicals were found only at 77 K, but not at room temperature. Two kinds of H-abstraction radicals were observed: (a) formed by abstraction from the ring N1 atom or (b) by abstraction from the methyl substituent, e.g. in thymine[22] or in N-methylated pyrimidines[16]. In the case of thymine the H-abstraction radical has two resonative forms and the spin density on the site of the abstraction is only about 0.60.



7 - yl radical

This radical is usually referred to as the 7-yl radical.

Due to the small mobility of the radicals in the solid phase, especially at low temperatures, the H-adduct radical and the H-abstraction radicals might be very close to each other and may form a radical pair with an electronic spin $s = 1$. Several radical pairs have been identified in 1-methyluracil[31,32] and in thymine[33,34]. Flossmann and coworkers[35] studied by ESR spectroscopy the radicals produced by X-ray radiolysis of single crystals of thymine and various thymine derivatives (thymine monohydrate—$T \cdot H_2O$, 5,6-dihydrothymine—TH_2, 1-methylthymine—mT and thymidine—dT) at 77 K and 300 K. They found six types of radicals. The anion radical was found only in $T \cdot H_2O$ at 77 K. For the other compounds the anion radical will be found only at lower temperatures. The 4-yl radicals, which is produced by hydrogen-atom addition to the carbonyl bond, was found only for dihydrothymine at 77 K. The 1-yl radical, formed by the abstraction of an H atom



4 - yl radical

from N1, was found only for anhydrous thymine. The 6-yl radical was found in T, TH_2 and mT. The 6-yl radical was converted into the 5-yl radical irreversibly by heat or by white light ($\lambda < 600$ nm). The 5-yl radical was found for all compounds at room temperature. The 7-yl radical was present at room temperature in all compounds except TH_2. In TH_2 the 7-yl radical does not have the allylic resonance stabilization and hence the hydrogen in the CH_3 side-group is bound more strongly than the other hydrogen atoms. The 7-yl radical was found to have the highest thermal stability and is stable up to 500 K. At room temperature the most prominent radicals in irradiated thymine were found to be the 5-yl and 7-yl radicals.

It is interesting to note that the thermal stability of thymine-derived radicals is different from that of other pyrimidines (uracil and cytosine). While in the latter two the 6-yl radical is thermally more stable, in the case of thymine the 5-yl radical is more stable.

C. Final Products

Slifkin and coworkers[13] studied the final products induced in crystalline uracil by ^{60}Co γ-rays, and also the electronic absorption spectra of γ irradiated and non-irradiated uracil powder after dissolution. After irradiation the complete spectrum shifts to a shorter wavelength by about 10 nm. Thus the long-wavelength maximum of the spectrum shifts from 258 to 250 nm and the short-wavelength maximum from 205 to 195 nm. This shift is consistent with the presence of a product having less π-electron delocalization than uracil—possibly a homodimer. No other pyrimidine or purine base has been found to produce this shift towards shorter wavelength upon irradiation. However, in the other bases a decrease in the absorbance of the irradiated sample relative to the non-irradiated compound was observed, similarly to uracil. After irradiation of 3.2 MGy the absorbance of uracil was decreased by about 40%, suggesting that a substantial fraction of the uracil was converted into a radiation product in the course of the dissolution. Thin layer chromatography (TLC) of the aqueous solution of the radiolysate shows only one product. Similarly, TLC of irradiated 6-methyluracil shows also one product while irradiated thymine (5-methyluracil) and 5,6-dimethyluracil did not show any radiation product. This comparison shows that product formation is prevented when the C5 of the uracil is methylated. The separated product does not show the strong band of cyclobutane which is expected from the dimerization of two uracil radicals.

The yield of the radicals as measured by ESR spectroscopy[36] follows the usual dose–yield curve[37]

$$I_D = I_\infty(1 - e^{-KD}) \tag{10}$$

where I_D is the intensity of radical signals as a function of the adsorbed dose D.

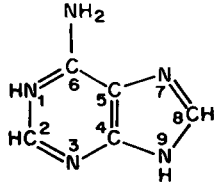
This curve is characteristic for the case where the radicals are not only formed by the radiation but are also destroyed by the radiation[38]. Slifkin and coworkers[13] found that equation 10 fits the data for uracil and, from the observation that there is no need for a second-order term, they concluded that there is no radical–radical interaction even at the high doses, explaining why there is no formation of a dimer. From the ESR measurement at a dose of 3.9 MGy only about 1% of the dry uracil is destroyed directly by γ-irradiation (G of radicals = 0.068) whereas the absorption after dissolution shows a 40% decrease ($G = 2.4$). Similar G values are found when aqueous solutions of uracil are irradiated, however in aqueous solution the decrease in absorption is due to radicals formed by radiolysis of the water molecules. The higher G value obtained from the absorption spectrometry of the dissolved irradiated uracil is probably due to excited uracil molecules, undetected by ESR but reactive with water molecules upon dissolution.

Neutron diffraction of dry uracil irradiated to 10 MGy shows that the irradiation causes only very little structural damage. This is an additional indication that a *cis–syn* dimer is not formed.

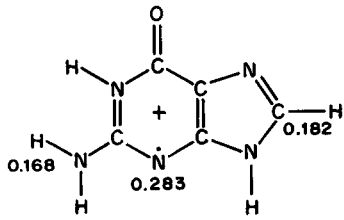
III. RADIOLYSIS OF PURINES IN THE SOLID STATE

There are only a few reports of single-crystal studies on irradiated purines, due to several reasons: (1) Purines are very sparingly soluble, making it difficult to grow good single crystals. (2) MO-INDO calculation of the spin density distribution for anions and cations of the purines shows a large degree of delocalization of the unpaired spin. The main fractions of the spin reside on atoms for which the expected hyperfine contribution is small or zero, making the ESR signals very weak. Higher radiation doses, compared to the case of pyrimidines, are necessary to produce even weak ESR signals. (3) The crystals are sometimes fragile and do not survive the cooling to liquid helium temperatures or do not last long under vacuum.

The results of these studies are not always conclusive and, in many cases, they are based on molecular orbital calculations combined with chemical intuition. The most recent reviews are those by Cadet and Berger[39]. Close and coworkers[40] and Cadet and coworkers[41]. The first, positive, structural identification was done by means of ENDOR (electron nuclear double resonance) for the adenine anion by Box and Budzinski[42], who identified a reduction product formed by irradiation at 4.2 K of single crystals of adenine dihydrochloride with unpaired spin density of approximately 0.3 on C8. Kar and Bernhard have used ENDOR to study adenine in a co-crystal of adenine and 5-bromouracil[43]. They found two products: an adenine with a spin density of 0.15 on C8 and 0.35 on C2, and a deprotonated cation where the hydrogen is abstracted from the NH_2 group at C6. Close and coworkers[44] found in an ESR study at 15 K, using an irradiated single crystal of guanine hydrochloride monohydrate, a structure which they associated with the guanine radical cation, with spin density of $g(C8) = 0.182$, $g(N3) = 0.283$ and $g(N10) = 0.168$. It is interesting to note that in guanine hydrochloride monohydrate (Gm) the N7 at pH ~ 7 is protonated, thus the formation of this radical cation must include also deprotonation.

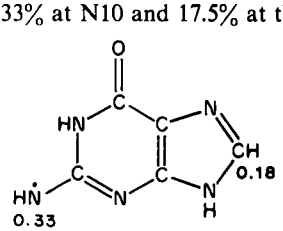


Adenine



Guanine radical cation

Close and coworkers[44] did not observe any decay product of the cation in their study, however, Hüttermann and Voit[45] and Hole and collaborators[46] found the decay product of the cation of guanine produced by radiolysis of 2'-deoxyguanosine-5'-monophosphate tetrahydrate. Hüttermann and Voit[45] proposed that the cation decays by deprotonation at N1, while the other group[46] disagreed with this assignment. From detailed ENDOR studies of a single crystal irradiated at 10 K, and INDO-MO calculations, they suggested that the cation decayed by a loss of proton from the side-chain NH_2 group N10. They found that the spin density is 33% at N10 and 17.5% at the C8.



Deprotonated guanine radical cation

Deprotonation of the NH_2 group was found also with adenosine, both with a pure crystal[47] and a cocrystal with 5-bromouracil[43]. Strand and collaborators[48] studied the free radicals induced by radiation in single crystals of guanine hydrochloride dihydrate (Gd) between 20 and 300 K, using ESR and ENDOR spectroscopy. They did not observe with Gd the radical cation observed by Close's group[44] for Gm. Although the radical cation was observed for Gm at a lower temperature (15 K), it was found[49] to be stable also at higher temperatures and decayed at 80 K with no apparent succesor radical. Strand and coworkers[48] explained this difference between Gm and Gd as due to different hydrogen bonding in the crystals of Gm and Gd. The radical cation can decay in three competitive reactions, two neutralizations and one deprotonation (equations 11–13):

$$G^+ + e^- \longrightarrow G^* \tag{11}$$

$$G^+ + e^- \longrightarrow G^* + G \tag{12}$$

$$G^+ \longrightarrow G'(-H) + H^+ \tag{13}$$

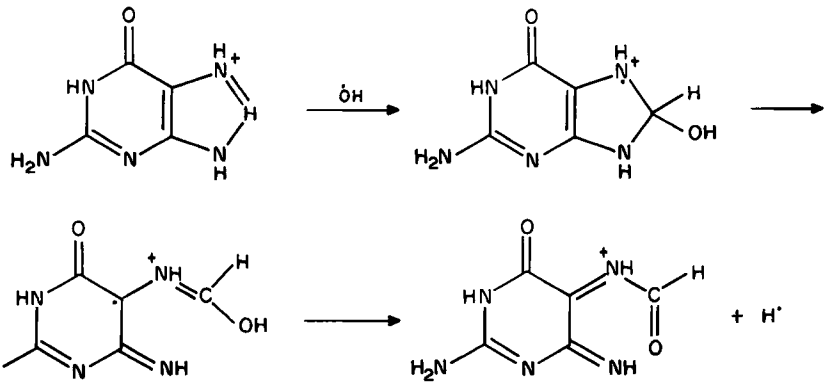
With Gd reactions 11 and/or 12 may dominate, while with Gm reaction 13 may dominate, leading to the observed deprotonated cation.

Nelson and coworkers[50] did not agree with this explanation, as they did not expect a large difference in the strength of the hydrogen bonds in the two systems. They suggested that the difference between Gm and Gd [and also 5'-guanosine monophosphate (GMP), in which the cation was also not found[51]] is due to differences in the decay rates rather than in the formation rates. They claimed that the protonated N7 radicals are formed in all three systems, but in Gd and GMP they are easily destroyed by the radiation and their equilibrium concentrations are too low to be detected. The difference between Gm on the one hand and Gd and GMP on the other is the hydrogen bond of the acceptor to HN7. The acceptor is the O atom of the OC6 group of another guanine in Gm and the O atom of water in Gd and in GMP. Thus in Gd and GMP the proton orginating from HN7 produces H_3O^+, which in turn reacts with an electron produced by further radiation to give $H + H_2O$. The H atom reacts with high efficiency with the deprotonated cation radical to re-form the parent molecule.

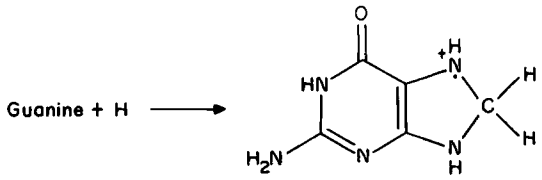
Hüttermann's group[48] found three radicals in low-temperature (20 K) irradiated guanine hydrochloride dihydrate. One of them is the C8 H-adduct found twenty years earlier by room-temperature irradiation[52]. A second radical was the O6-protonated anion radical, the same product as obtained by H-atom addition to the carbonyl bond (the unprotonated anion was not observed due to the fast protonation caused by O6 being a hydrogen-bond acceptor). They could not identify the third radical. Nelson and coworkers[50] extended the very low temperature studies for Gd and found it to be the C8 OH-adduct. Annealing of the sample to above 250 K for several hours led to the disappearance of the O6-protonated anion radical and the appearance of a new radical. The latter is a product of net hydrogen abstraction from N9 of the guanine base, by the O6-protonated anion radical.

At low temperatures the O6-protonated anion radical was found to exist in four different conformations, which coalesce into the most stable one at 180 K. The O6 protonated anion radical of Gm was found to have two conformations[49].

Close and collaborators[49] found in the case of Gm another radical, which is due probably to OH addition to C8. However, while in Gd this OH-adduct is stable, in Gm it undergoes further rearrangement and H-atom dissociation and only the rearrangement product is observed (Scheme 2). This radical decays at 160 K by reaction with another guanine base to form the C8 H-addition radical[53] (Scheme 3). This mechanism shows that the H-adduct might result from an oxidation process (addition of OH radical) and not only from reduction (protonation of the anion) or by addition of an H atom.

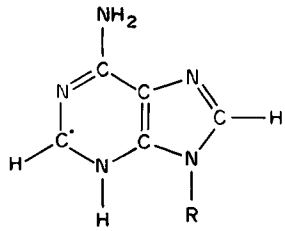


SCHEME 2

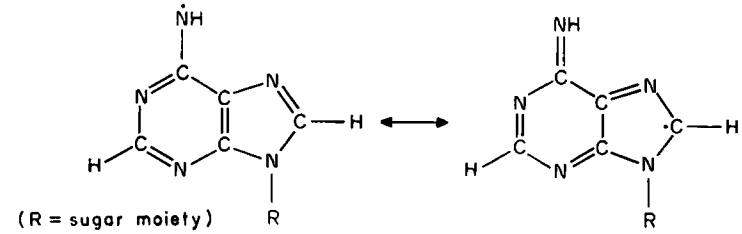


SCHEME 3

Close and Nelson[47] studied the ESR and ENDOR spectra of adenosine single crystals X-irradiated at 10 K and found two radicals, the N3 protonated anion radical (a) and the N10 deprotonated cation radical (b). The only radicals formed at room temperature are

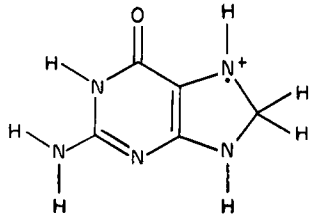


(a)

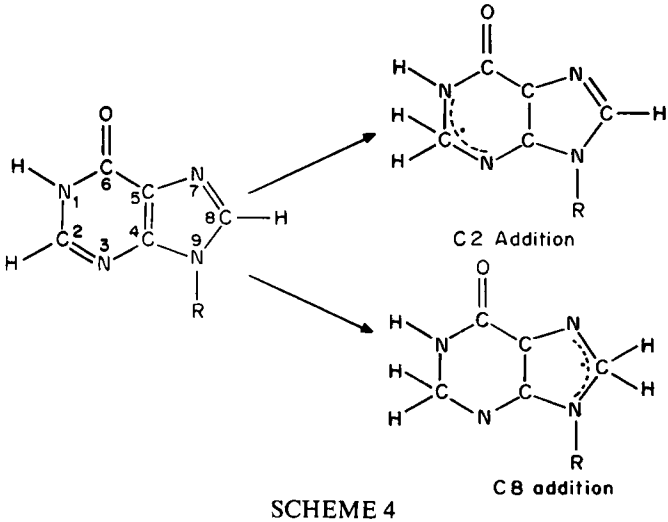


(b)

the hydrogen-addition radicals. The hydrogen atom is added to C8, producing a radical at N7 which is also protonated in the case of guanine.



In the case of polycrystalline adenine it was shown that ESR data are not sufficient to distinguish between H addition to C8 or to C2[54,55]. Schmidt and Borg[54] studied several polycrystalline N9-substituted adenine derivatives which were selectively deuterated at position C8 and/or in the hydrogen-bonding network. They concluded that the hydrogen atoms are mainly added to C8 and that the C2 adduct is only a minor product. Zehner and coworkers[56,57,11] extended this study to single crystals and used also heat and illumination to distinguish between the two radicals. They showed that for most adenine derivatives both a C8 adduct and a C2 adduct were formed. The C2 radical is usually less stable and needs a specific environment in order to be stabilized. Similar results of both C2 and C8 addition were also found for hypoxanthine[58] (Scheme 4).



SCHEME 4

Sieber and Hüttermann[59] studied the reaction of H atoms with purines in acid glasses. They found that H atoms produce C2- and C8-addition radicals in the case of adenine and C8-addition radicals with guanines.

IV. RADIOLYSIS OF AQUEOUS SOLUTIONS OF PYRIMIDINES

A. Initial Radicals

Several reviews were published in the last five years on the radiolysis of aqueous solutions of pyrimidine bases, among others by von Sonntag[60–63] and by Neta and

TABLE 1. Rate constants for the reactions of e_{aq}^-, OH and H with pyrimidine and purine bases ($\times 10^8\,M^{-1}s^{-1}$)

	e_{aq}^-	OH	H
Uracil	100	60	3
Thymine	170	60	7
Cytosine	130	45	1
Adenine	90	50	1
Guanine	130	90	—

Dizdaroglu[64]. Table 1 gives the rate constants for the reactions of the three main species, formed in the radiolysis of water, with three pyrimidine and two purine bases[65]. OH reacts with thymine and uracil with the same rate constant while the reducing radicals (e_{aq}^- and H) react above twice as fast with thymine. OH and e_{aq}^- react very fast with the pyrimidine bases while H atoms react about one to two orders of magnitude slower.

While many data on the radicals formed by radiolysis of solid bases were obtained by ESR, this technique is not so informative in the liquid phase, due to the shorter lifetime of the radicals in the latter. While spin-trapping can be used to produce longer-lived radicals, the ESR spectra of spin-trapped radicals do not provide as much information on the structure of the initial radicals as is obtained by direct observation. In some cases the spin-trapped radicals are sufficiently unreactive to be separated by chromatography[66]. In this way Riesz and his coworkers[66] identified the 5-OH adduct of uracil and distinguished between the *cis* and *trans* isomer.

Short-lived radicals of pyrimidines in irradiated aqueous solution were measured by direct ESR (without spin-traps) both by *in situ* radiolysis, within the spectrometer, and in steady-state experiments. In the pulse radiolysis *in situ* studies[67] the radicals produced by OH and by e_{aq}^- with pyrimidine bases have been identified and the rate constants of their reactions with oxygen and with thiols were measured.

These studies were extended by Novais and Steenken[68], who used *in situ* radiolysis ESR and determined the coupling constants of the radicals produced in aqueous solutions of uracil and thymine. They found that the splittings of the radicals measured in aqueous solution are very similar to those previously reported for the solid state. However, only the major hyperfine constants were measured accurately due to the low sensitivity of the method. The sensitivity can be increased by using steady-state studies[69–71], but then, due to lack of time resolution, often the secondary radicals cannot be differentiated from the primary radicals. Thus, for example, the C5 and C6 OH-adducts were not observed, but the secondary products formed by dehydration or oxidation were identified.

Both OH and H are electrophilic radicals and will add to double bonds of the pyrimidines. With uracil and thymine there is only one site for addition, i.e. the C5—C6 double bond. With cytosine the double bond N3—N4 is also a potential reaction site, but it was found that OH addition takes place predominantly at C5—C6 with a large preference for C5[72,73]. In uracil, OH and H both attack preferentially at the C5 position, but in thymine and its derivatives there is also considerable attack at the C6 position. Steenken and coworkers[74,75] showed that C5H-adduct radicals with the free electron at C6 have reducing properties and readily reduce tetranitromethane, quinones and riboflavin with rate constants $> 10^9\,M^{-1}s^{-1}$. The reducing properties are due to α-substitution of the carbon-centred 6-yl radical by nitrogen[76]. In basic media this radical undergoes a dehydration process, which converts it to an oxidizing radical. The 5-yl radicals (C5—OH adducts) have oxidizing properties and can oxidize *N,N,N',N'*-tetramethyl-*p*-phenylenediamine (TMPD) very fast, with rate constants in the order of

$10^9\,M^{-1}\,s^{-1}$. The 5-yl radical can also react with other reducing agents and it was monitored, e.g., in its reaction with ascorbate[77]. The C5 and C6 adducts have similar absorption spectra[78–80] and their yields are determined using their different redox properties. Recently the different spectra of the C5 and C6 adducts were measured[62]. The spectra of the OH-adducts differ from one another much more than those of the H-adducts. In the case of thymine and its derivatives, OH and H abstract also hydrogen atoms from the CH_3 side-group. At high pH when OH is converted to O^-, hydrogen abstraction becomes the predominant reaction. The allyl radical formed by abstraction of a hydrogen atom from the CH_3 group is neither a strong oxidant nor a strong reductant. Its yield has been determined by its reaction with oxygen yielding the peroxyl radical, which is an oxidant and reacts with TMPD in a reaction that can be monitored[74]. Table 2 gives the relative reactivities of the different sites in various pyrimidines towards OH and H. It can be seen from this table that H abstraction from a CH_3 group occurs only for C—CH_3 but not for N—CH_3.

The reducing 6-yl radical is converted by dehydration in basic pH to an oxidizing radical, which can also be formed directly by oxidizing a pyrimidine base with a strong oxidizing radical such as $SO_4^{\cdot-}$. The suggested mechanism is shown in Scheme 5.

This dehydration process does not occur for methyl-substituted N1 pyrimidines[75], a fact which agrees with a suggested mechanism.

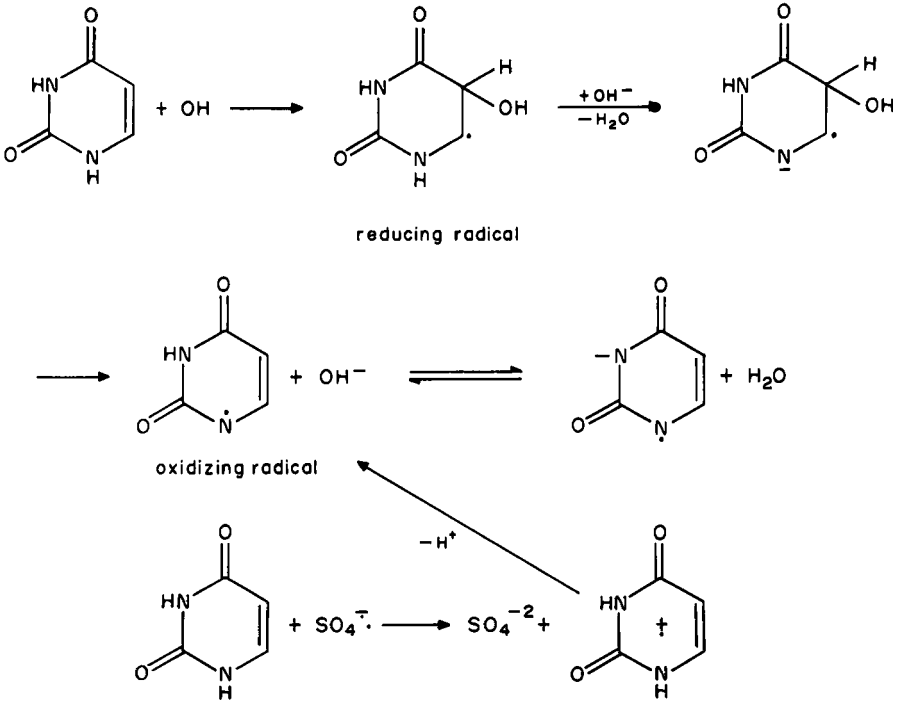
At acidic pH there is a proton-catalysed rearrangement of the C5—OH adduct into the C6—OH adduct and *vice versa*[81].

The major radical, the 6-yl radical, is readily oxidized by transition metal ions[82,83] as well as by organic oxidants. The primary product is an intermediate carbocation which is too short-lived to be observed in pulse radiolysis. However, its decay product, the isopyrimidine formed by deprotonation at N1, has been observed and its decay kinetics were followed[82] (Scheme 6). The isopyrimidines are formed also in disproportionation reactions of pyrimidine radicals.

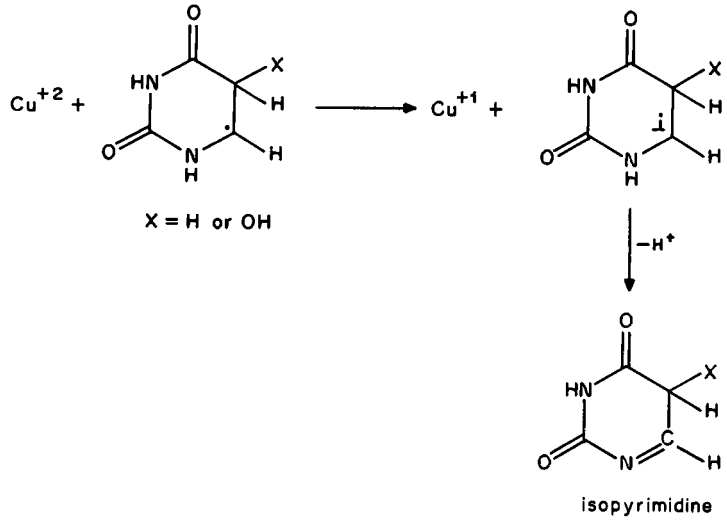
The pyrimidines react with the hydrated electron at a diffusion-controlled rate. The radical anions formed are protonated by H^+ or by water. The protonation by H^+ proceeds at diffusion-controlled rates for all pyrimidines, however concerning protonation by water there is a large difference between cytosine on the one hand and uracil and thymine on the other. The cytosine radical anion reacts very fast with water ($t_{1/2}$ = 210 ns[84]). The uracil and thymine are longer-lived in water with respect to protonation ($t_{1/2} \geqslant 40\,\mu s$[79]). Thus it is possible to study by pulse radiolysis the electron adduct (before protonation) of uracil and thymine, but not that of cytosine. In the accessible

TABLE 2. Relative reactivities of the various sites in pyrimidines for the attack of H atoms and OH radicals

Reactant	OH			H		
	C5	C6	CH_3	C5	C6	CH_3
Uracil	82	18	—	69	31	—
1,3-Dimethyluracil	80	20	—	71	29	—
Thymine	60	30	10	37	59	4
6-Methyluracil	88	12	little			
Cytosine	89	11	—			
1-Methylcytosine	92	8	—			
3-Methylcytosine	91	9	—			
5-Methylcytosine	65	22	13			

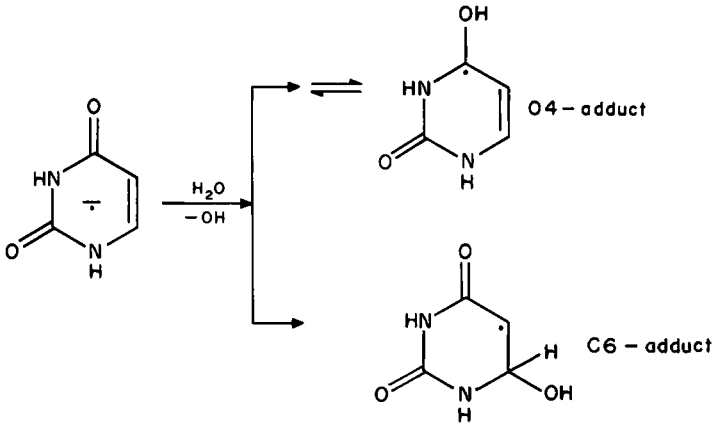


SCHEME 5



SCHEME 6

wavelength region it only shows the tail of an absorption whose maximum must be below 300 nm[85]. Protonation can occur at two sites, either at O4 or at C6. The absorption spectrum of the oxygen-protonated radical is very close to that of the radical anion, except that it has lower extinction coefficients. The protonation at O4 is very rapid while the C6 protonation is slow[68,86,87]. The protonation at O4 is reversible while the C6 protonation is irreversible. Consequently, if not destroyed by other reactions, all the electron adducts should lead to the C6 protonation product. Phosphate buffer was found to speed up both protonations (C6 and O4) and, of course, also the reversible O4 deprotonation. It was found that in the presence of high concentration of phosphate buffer the electron adducts are irreversibly protonated at C6 (Scheme 7). The O4 protonated radical, like the electron

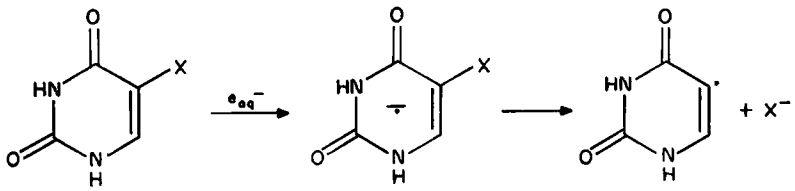


SCHEME 7

adduct, is a reducing radical and reacts rapidly with tetranitrometane (TNM) to give $C(NO_3)_3^{\cdot}$, which can be monitored. The C6-protonated radical, which is the same as the C6-H adduct, has oxidizing properties and does not react with TNM on the pulse-radiolysis time scale. The O4-protonated and the electron adduct can also transfer an electron to oxygen, quinones and to other pyrimidines having a higher electron affinity, such as orotic acid[92].

The electron adducts of 5-halouracils can undergo rapid dehalogenation[88,89]. This is the predominant process for the bromo and iodo derivatives while for 5-chlorouracil there is a competition between this process and the protonation reaction[90,91]. Rivera and Schuler[91] measured the decay of the radical anions of 5-halouracils, obtained by their reaction with e_{aq}^-, using their optical absorption at 330 nm. The 5-bromo and 5-iodouracil radical anions decay with very short half-lives (7.0 ± 0.5 and 1.7 ± 0.3 ns, respectively), which is in contrast with the much longer half-lives of the electron adducts of 5-chloro and 5-fluorouracil (4.9 and $> 15\,\mu$s).

The uracilyl radical produced in this reaction is very reactive and can add to another molecule of halouracil. In the presence of 2-propanol the uracilyl radical can abstract the secondary hydrogen of 2-propanol. The produced isopropanol radical can in turn abstract the bromine or iodine atom of the 5-halouracil, propagating a chain reaction[88,89] (Scheme 8). The much faster reaction of the electron adduct of cytosine (compared to uracil and thymine) is not yet understood. The rapid protonation by water suggests that it is likely to occur at O2 or at N3, which will agree with the reducing properties of the protonated radical. However, it is not reconciled with the high pK_a of the radical (> 12[61]). The pK_a of the electron adducts of uracil and thymine is near 7[85].



SCHEME 8

Busi and coworkers[108] measured the properties of the radiation-induced radicals of pyrimidine (and purine) bases. They studied the transient potential changes at the double layer of a dropping mercury electrode. Their conclusions are not independent but are based on previous results, such as, for example, that the radical produced by addition to C6 is already reduced at 0.0 V (vs standard calomel electrode). From the previous electrochemical properties they found for Ar-saturated solution at pH = 7 that G(U(5)OH) = 2.5, G(U(5)H) = 0.46, G(Th(5)OH) = 1.54, G(Th(5)H) = 0.36, G(U(6)OH) = 0.40, G(U(6)H) = 0.14, G(Th(6)OH) = 0.81 and G(Th(6)H) = 0.11. In this assignment G(U(5)OH) is the radiolytic yield of the radical formed by addition of an OH radical to C5 of uracil, yielding the 6-yl radical. Similarly G(Th(6)H) is the yield for the addition of a hydrogen atom to C6 of thymine. In thymine solution the yields obtained for H abstraction by ·OH and H reaction at the methyl groups are 0.55 and 0.13, respectively.

B. Final Products

Products of the γ-radiolysis of N_2O-saturated aqueous solutions are almost exclusively due to the reactions of OH radicals. Many studies were done on the products and the consumption of uracil in de-aerated or N_2O-saturated solutions. Shragge and Hunt[79] found that the G value of uracil consumption varies considerably with pH, with a pK of about 7. This pH dependence was explained later[74,96] as due to the OH^--catalysed C5—OH adduct eliminating water to become the uracil radical. This radical reforms the uracil molecule by H-atom abstraction from other products or impurities. The adduct itself, if not dehydrated, either recombines to dimers or disproportionates. Increasing the dose rate should increase the rate of the bimolecular reactions while not having any effect on the dehydration rate. Fujita[96] irradiated a N_2O-saturated aqueous solution of uracil with 4 μs pulses of electron beams with doses of either 5.7 Gy per pulse or 0.6 Gy per pulse. Measuring G(-uracil), he found that the pK for the consumption of uracil is $\sim$ 9.8 for the higher dose pulse and 7.9 for the lower dose pulse. This trend agrees with the lower pK ($\sim$ 7) found by Shragge and Hunt[79] for ^{60}Co γ-irradiation with a dose rate of 8.7×10^3 Gy h^{-1}. At the same pH (> 6) higher concentration of radicals (higher dose rate) leads to higher G(-uracil). This is due to the bimolecular reactions of OH-adducts (either combination or disproportionation) competing more favourably with the dehydration to uracil radicals. This effect of dose rate explains the variations in G(-uracil) found for N_2O-saturated solutions. Bhattacharyya and Mandal[130] and Infante and coworkers[131] obtained G(-uracil) $\sim$ 3 at pH $\sim$ 5.6 compared to 5.5 given in Table 3, due to their lower dose rates.

Bhattacharyya and Mandal[130] proposed the following scheme for N_2O-saturated solutions.

Addition to double bond

$$\begin{aligned} OH + U &\longrightarrow UOH \\ H + U &\longrightarrow UH \end{aligned} \qquad (14)$$

TABLE 3. Radiolysis products of aqueous solutions of pyrimidines

I. Uracil, deoxygenated solutions

Product	Ref. 94		Ref. 79		Ref. 95			
	pH = 6–7	pH = 12	pH = 5	pH = 8.1	pH = 2	pH = 4	pH = 6	pH = 8
G(-uracil)	3.75	2.92	4.4	1.9	2.68	4.25	5.51	2.11
cis-Uracil glycol	0.81	0.45	0.2	0.4				
trans-Uracil glycol	0.92	0.25	0.5	0.4	0.68	0.32	0.30	0.18
Isobarbituric acid	0.38	0.72	0.1	0.1	0.29	0.12	0.52	0.16
Dihydrouracil	0.05	—						
Formyl urea	0.34	0.18						
Alloxan	0.25	0.53						
Alloxantin	0.13	0.34						
5,6-Dihydro-6-hydroxy uracil (+ 5-hydroxy)	0.13	—	0.5	0.3	0.31	0.44	0.29	0.18
Dialluric acid	0.15	0.03						
Dimers	0.21	0.14	3.1	0.7	1.35	3.30	4.38	1.6

II_1. Uracil, N_2O saturated solutions[97], pH = 5.6

Product	
G(-uracil)	5.59
Dimers	4.00

II_2. Uracil N_2O/O_2 saturated solution[98]

Product	pH = 3	pH = 6.5	pH = 10.0
G(-uracil)	4.9	5.3	5.2
cis-Uracil glycol	0.6	0.9	1.4
trans-Uracil glycol	0.5	1.1	1.0
Isobarbituric acid	0	0.2	1.2
Formyl-5-hydroxyhydantoin	1.6	1.4	0.2
Dialuric acid	0.1	0.2	0.1
5-Hydroxyhydantoin	0.4	0.4	0.3

III. 1,3-Dimethyluracil (DMC), N_2O saturated[81]

Product	pH = 3	pH = 6.5	pH = 10.4
G(-DMC)	3.9	5.7	5.1
DMC glycol	1.5	0.85	0.8
1,3-Dimethylisobarbituric acid	0.15	0.1	$\leqslant$0.1
5-Hydroxy-5,6-dihydro-DMC	0.4	0.75	0.6
6-Hydroxy-5,6-dihydro-DMC	<0.1	0.2	<0.1
Dimers (in monomeric units)	1.7	3.6	3.2

IV. Thymine–N_2O saturated (DHT = 5,6 dihydrothymine)

Product	Ref. 93	Ref. 99 pH = 7.0	Ref. 100 pH = 6.3	Ref. 97 pH = 5.6
G(-thymine)	3.9	2.7	5.5	4.48
Thymine glycol	2.26	0.32	1.4	
5- or 6-Hydroxy-DHT	0.13	0.18	0.5	
5-Hydromethyluracil	0.22	0.27	0.2	
DHT	0.1	0.17	0.04	
Dimers	0.26	—	3.1	1.47

V. Thymine-aerated solution, pH = 4[101] (DHT = 5,6-dihydrothymine)

G(-thymine)	2.6
cis-Thymine glycol	0.12
trans-Thymine glycol	0.12
cis-6-Hydroperoxy-5-hydroxy-DHT	0.03
trans-6-Hydroperoxy-5-hydroxy-DHT	0.7
cis-5-Hydroperoxy-6-hydroxy-DHT	0.08
trans-5-Hydroperoxy-6-hydroxy-DHT	0.17
cis-6-Hydroperoxy-DHT	0.03
trans-6-Hydroperoxy-DHT	0.03
5-Hydroperoxy-DHT	0.06
Urea	0.08
Formyl urea	0.07
Formyl-pyruvil urea	0.46
5-Hydroperoxymethyl uracil	0.05
5-Hydroxymethyl uracil	0.02
5-Hydroxy-5-methylbarbituric acid + 5-Hydroxy-5-methylhydantoin	0.15

VI. Cytosine–N_2O saturated solutions[102]

G(-cytosine)	5.6
Uracil	0.02
Uracil glycol	0.15
5-Hydroxy cytosine	1.4
6-Hydroxy cylosine	0.07
Cytosine glycol	0.05
5,6-Dihydroxy cytosine	0.20
Dimers	3.2

VII. Cytosine, aerated solution[103]

G(-cytosine)	2.5
trans-1-Carbamoylimidazolidone-4,5-diol	0.6
4-Amino-1-formyl-5-hydroxy-2-oxoimidazoline	0.2
cis-Uracil glycol	0.03
trans-Uracil glycol	0.1
5-Hydroxyhydantoin	0.1
Oxaluric acid	0.2
Parabanic acid	0.03
Biuret	0.06
Formyl urea	0.06

VIII. 5,6-Dihydrothymine (DHT)[109]

Saturating gases	N_2O/O_2	O_2
G(-DHT)	4.1	2.0
trans-6-Hydroxy-DHT	0.2	0.09
cis-6-Hydroxy-DHT	0.22	0.10
trans-6-Hydroperoxy-DHT	0.29	0.13
cis-6-Hydroperoxy-DHT	0.61	0.30
5-Hydroxy-DHT	0.17	0.09
5-Hydroperoxy-DHT	0.38	0.24
Thymine	0.50	0.46
cis-5,6-Dihydroxy-DHT	0.52	0.23
trans-5,6-Dihydroxy	0.28	0.18
N-formyl-5-hydroxy-5-methylhydantoin	0.24	0.03

Disproportionation

$$2UOH \longrightarrow U(OH)_2 + U \tag{15}$$

$$2UOH \longrightarrow \underset{\text{C5-adduct}}{U(OH)^+} + \underset{\text{C6-adduct}}{U(OH)^-} \tag{16}$$

$$UH + UOH \longrightarrow UH^+ + UOH^- \tag{17}$$

$$UH^+ \xrightarrow{H_2O} U + H_3O^+ \tag{18}$$

$$UOH^+ \xrightarrow{H_2O} \begin{cases} U(OH)_2 + H_3O^+ & (19a) \\ \text{Isobarbituric acid} + H_3O^+ & (19b) \end{cases}$$

$$UOH^- \xrightarrow{H_2O} \begin{cases} U(OH)H + OH^- & (20a) \\ U + OH^- & (20b) \end{cases}$$

Dimerization

$$2UOH \longrightarrow (UOH)_2 \tag{21}$$

$$UOH^+ + UOH^- \longrightarrow (UOH)_2 \tag{22}$$

Assuming steady-state concentration of the various intermediates leads to the equation

$$G(\text{dimer}) = 2\left\{\frac{k(k_{17a} + k_{17b})}{k_{17b}{}^2(k_{16a} + k_{16b})}[G_{OH} - G(\text{-}U)]^2 D_r + \frac{k_{18}}{2(k_{18} + k_{19})} G_{OH}\right\}$$

where G_{OH} is the yield of OH in N_2O-saturated solution containing known concentration of uracil (since some of the hydrated electrons will still react with the uracil), and D_r is the dose rate. This equation may be written in a simplified form:

$$G(\text{dimer}) = K_1[G_{OH} - G(\text{-U})]^2 D_r + K_2 G_{OH} \tag{23}$$

Bhattacharyya and Mandal showed that their result together with previous ones[133,134] give a linear dependence between G(dimer) and $[G_{OH} - G(\text{-U})]^2 D_r$ as can be seen in Figure 1. Another pH effect is found in the low pH range. Idris Ali and Scholes[95] found that G(-uracil) decreased not only on increasing the pH, but also by decreasing it to pH = 2 (see Table 3). In this range the explanation is different and will be given in the next paragraph.

The formation of dimers has been observed in the uracil system, but it has not been possible to assign them a definite structure[97]. Idris Ali[97] used paper chromatography to isolate the radiation-induced dimeric products, and used mass spectrometry to characterize the dimers. However, due to insufficient separation, he could not identify clearly the dimers. Al-Sheikhly and von Sonntag[81] were able to identify dimers in the radiolysis of an aqueous solution of 1,3-dimethyluracil, which is easier for analysis than uracil. Mass spectral analysis indicates that the dimers were formed exclusively by the combination of two C5-OH adduct radicals or of a C5—OH adduct with a C5—H adduct. No dimer was found which involves any combination of a C6—OH adduct, either with itself or with a C5—OH adduct. Instead, a C6—OH adduct radical reacts with a C5—OH adduct radical by electron transfer, resulting in the formation of glycols and the original molecule.

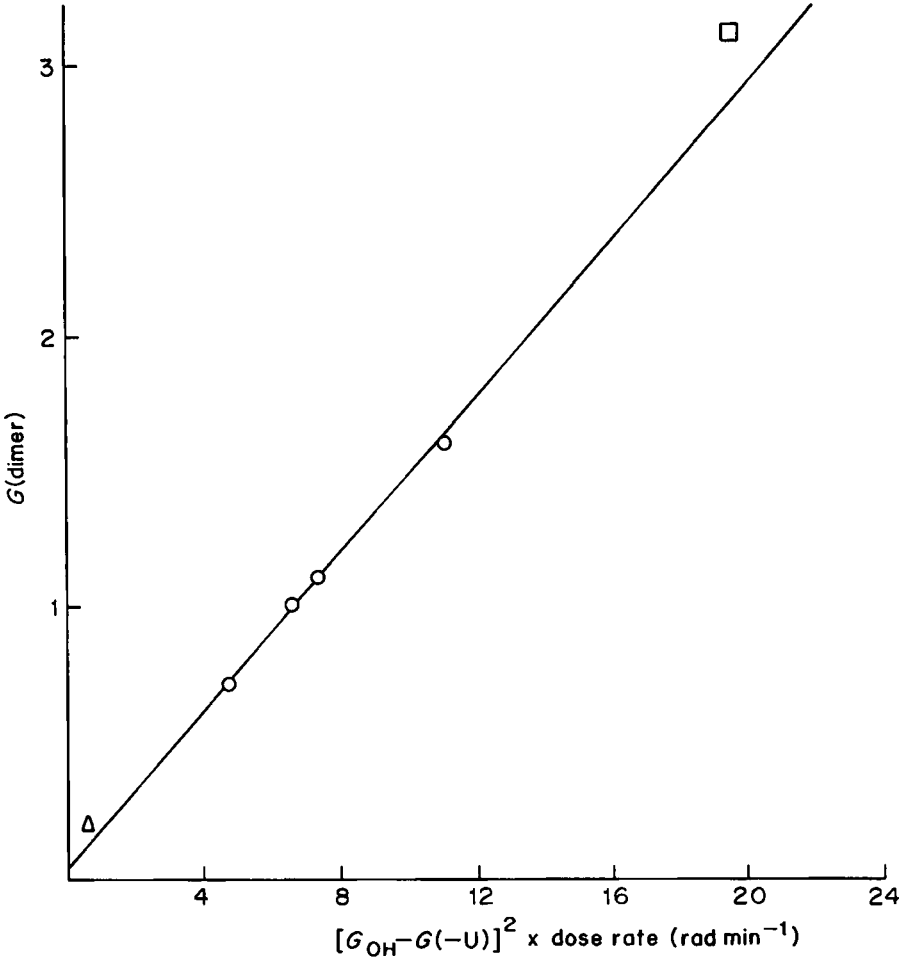
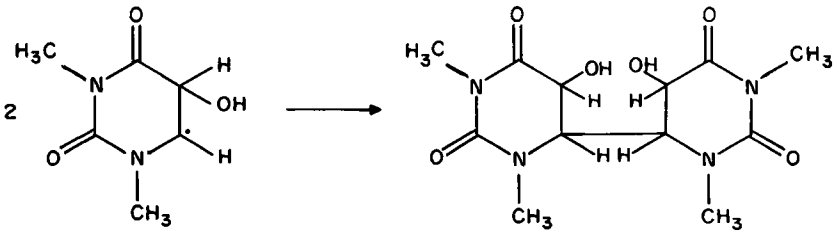


FIGURE 1. Plot of G(dimer) against $[G_{OH} - G(-U)]^2 \times D_r$. Reproduced by permission of Gordon and Breach from Reference 130.

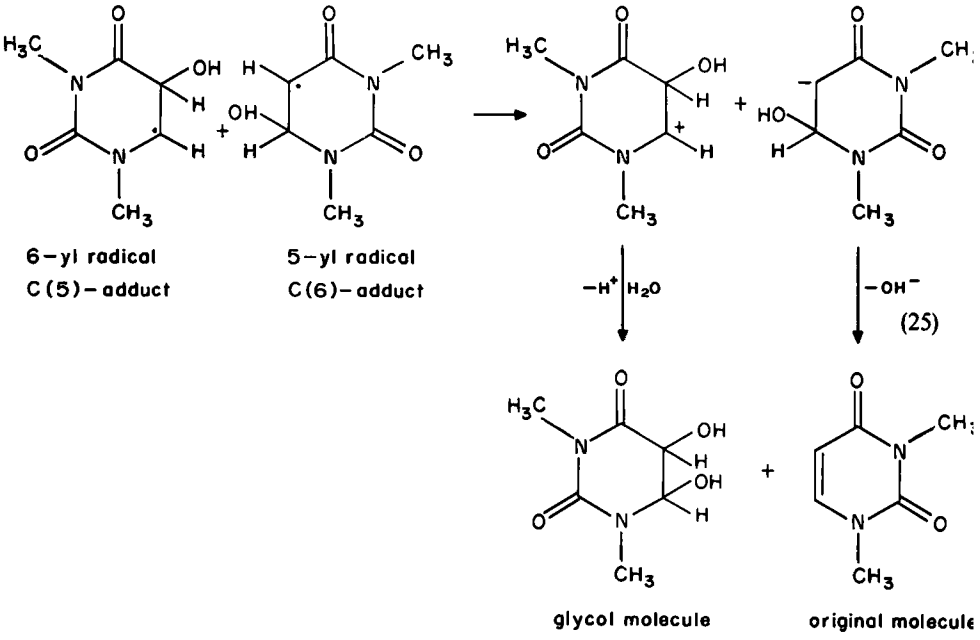
The net reaction is a disproportionation involving the transfer of an OH group. Idris Ali[97] used $^{14}C2$ labelled pyrimidines and found that the G values of dimeric products is 71% of the total decomposition of uracil, while it is only 33% of the total thymine destruction. The carbanion formed from the C5-adduct may lose the OH^- group or may also be protonated to form the hydrate, the latter appearing as a minor product. However, the carbanion may be formed also due to electron transfer from other substrates to the 5-yl radical.

In acidic solution G(-1,3-dimethyluracil) decreases as it does in the case of uracil, while the dimer yield is drastically reduced and that of the glycol increased with respect to neutral solutions. The reason for the decrease in G(consumption) with the decrease in the pH is a proton-catalysed isomerization of the 5-yl radical to the 6-yl radical, a reaction which occurs through the radical cations of the original molecules. This isomerization is



(24)

Electron transfer



6-yl radical C(5)-adduct

5-yl radical C(6)-adduct

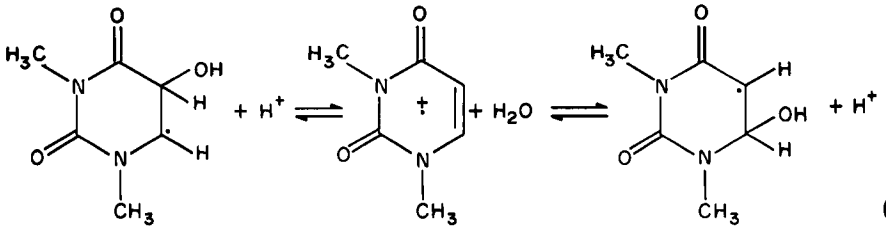
$-H^+$ H_2O

$-OH^-$

(25)

glycol molecule

original molecule



(26)

reversible and it is catalysed by H^+ ions, but is usually very slow. At pH < 3, instead of having 90% C(5)—OH adduct and only 10% C(6)—OH adduct (as in pH > 6), the fraction of the latter is considerably larger, leading to a decrease in the combination and an increase in the disproportionation (electron transfer) reaction of the radicals. Since the electron transfer leads to reformation of half of the parent molecules, the decrease in pH causes a decrease in G(consumption).

The intermediate radical cation is likely to be formed also in the reaction of strong oxidants, e.g. $SO_4^{\cdot-}$ with 1,3-dimethyluracil. Since the cation of 1,3-dimethyluracil cannot lose the positive charge by deprotonation, due to the methylation of both nitrogens, it must react with water to yield the OH^- adduct. It was found by Riederer and Hüttermann that in sulphuric acid glasses[104] the $SO_4^{\cdot-}$ leads to the production of the C6—OH.

Examination of Table 3 indicates that the data obtained in various laboratories differ considerably, even for *G*(consumption). For example, *G*(-thymine) changes from 2.7[99] to 5.5[100] (almost at the same pH). The spread in the yield of the products is even higher. For example, *G*(thymine glycol) in the radiolysis of N_2O-saturated aqueous solutions of thymine is between 0.32[99] and 2.26[100]. These results are probably due to the different dose rate used.

Consequently, it is difficult to draw conclusions by comparing studies from two laboratories. However, conclusions about the same system at different pH values are probably correct. One of the major problems of the analytical method was that the products were separated by gas chromatography. In order to separate such large polar molecules by GC, they first had to be modified into their trimethylsilyl derivatives. However, the derivation might lead to some changes in the molecules. For example, Dizdaroglu and Simic[100] studied the nature of OH-induced dimers of thymine by using GC-MS analysis of the trimethylsilyl derivatives of the products. The MS spectra suggested that the dimers are products of combination reactions of OH-adduct radicals. Some of the dimers have also been shown to dehydrate. However, it is not clear whether the dehydration was taking place during the combination or during the derivatization process, although probably the latter suggestion is correct. Thus, separation of the products by HPLC might be preferable.

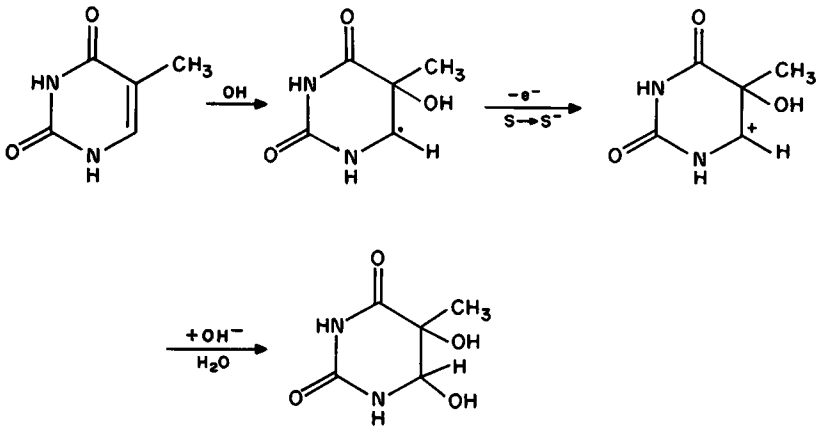
The dimers were found to be composed of two OH-adducts, but it was not determined whether these are C5—OH or C6—OH adducts. However, several peaks of the dimers indicated the formation of all three possible isomers: 5–5′, 6–6′ and 5–6. The number of dimer peaks observed in the GC was larger than three, possibly due to stereoisomers. In the presence of O_2 no dimeric products were observed, due to the rapid reaction of the OH-adducts with O_2 to give thymine peroxy radicals, which lead to a variety of monomeric products.

The fact that in the case of N_2O-saturated aqueous solution of cytosine[102] the number of dimer peaks is larger than 3 (at least 8) was also explained as due to stereoisomers. Since there are four optically active carbon atoms, there are six stereoisomers of each type of dimer. Dehydrated dimers have been found also in the case of cytosine. When irradiated samples of cytosine were treated with HCOOH before derivatization and GC-MS analysis, it was found that the normal dimers were absent and the yield of the dehydrated dimers increased, showing that the dehydration of the dimers is an acid-catalysed reaction.

Radiolysis of solutions containing oligo- and polynucleotides of thymine[105,106] shows the formation of dimers, resulting from combination reactions of OH-adduct and H-adduct radicals of thymine.

The electron adducts of pyrimidine bases also form dimers, most probably after protonation. Nishimoto and coworkers[107] observed the formation of the dihydrodimer in radiolysis of de-aerated aqueous solutions of thymidine in the presence of formate ions (to scavenge the OH radicals). They found *G*(-thymidine) = 2.97 and *G*(dimer) = 0.87. The main products are the two stereoisomers of 5,6-dihydrothymidine (56% from the consumed thymidine). The OH radical yields, with the formate ions, $CO_2^{\cdot-}$ and H_2O. The $CO_2^{\cdot-}$ radical anion in turn transfers an electron to the thymine molecule, as was proven by irradiation of an N_2O-saturated aqueous solution of thymidine in the presence of sodium formate. In this system all e_{aq}^- is converted to OH, which is converted to $CO_2^{\cdot-}$. This process is followed by one-electron reduction of the thymidine to the radical anion. The product distribution is almost identical with that in the de-aerated solution.

Nishimoto and coworkers[99] studied the effect of electron-affinic compounds on the radiolysis of thymine in de-aerated and N_2O-saturated solutions. The addition of electron-affinic compounds in the radiolysis depresses the thymine consumption in both de-aerated and N_2O-saturated solutions, while it increases in aerated solution. The radiolysis with varying concentration of misonidazole indicates that the depression of thymine decomposition is due to competition over the OH radical between the thymine and the electron-affinic compounds. In the presence of these compounds the formation of thymine glycol was promoted remarkably. The G value of thymine glycol increased in a sigmoidal form with the one-electron reduction potential of these compounds. This sigmoidal increase reaches the saturation values of 1.1 and 1.8 in de-aerated and N_2O-saturated solutions, respectively. These results are explained by the one-electron oxidation of the thymine–OH-adduct radical with the electron-affinic compound to the corresponding cation, which in turn undergoes solvolytic substitution to give thymine glycol. In the absence of the electron-affinic compounds the OH-adduct dimerize or disproportionate, in which case only one-half leads to the glycol. In equation 27 S stands for the electron-affinic compound and S^- is its anion.



(27)

Mandal and coworkers[110,111] measured the yield of the products in the radiolysis of uracil in aqueous solution by high-energy α-particles. This radiolysis, characterized by much higher linear energy transfer (LET of 19.9 eV per nm compared to 0.25 eV per nm for ^{60}Co γ-rays), produces much higher concentration of radicals. Due to this, many ions and radicals react back with their counterparts to reform the uracil molecule, thus leading to a lower G value for consumption of uracil, G(-U). Table 4 shows that G(-U) for α-particles is about 0.26–0.33 of G(-U) for ^{60}Co γ-rays. The decrease in the yield fits quite well the earlier measurements of free radical yields in α- and γ-radiolysis[112].

TABLE 4. Radiolytic yields of uracil by 37 MeV α-particles[110], pH = 5.6

Gas-saturated aqueous solution	G(-U)	$G(-U)_\alpha/G(-U)_\gamma$[a]	$G(\text{radicals})_\alpha/G(\text{radicals})_\gamma$[112]
Ar	0.73	0.26	0.25
O_2	0.7	0.26	0.26
N_2O	1.1	0.33	0.24

[a] $G(-U)_\gamma$ taken from Reference 60 and Reference 112.

When mixtures of thymine and tyrosine are irradiated by ionizing radiations, besides the dimers of thymine and tyrosine, there is also formation of a molecule with a link between thymine and tyrosine[113,114]. Similar crosslinks are formed between thymine and phenylalanine[115]. Similarly, when oligonucleotides are irradiated, crosslinking occurs between the pyrimidine bases. The crosslinking between thymine and tyrosine radicals is favoured over the thymine–thymine and tyrosine–tyrosine radical dimerization. Predominant formation of crosslinking between the molecules was observed also in pulse radiolysis studies, when it was found that the cross-combination rate constant is 4.8 $\times 10^8\,M^{-1}s^{-1}$ while the dimerization of thymine radicals has a rate constant of 3.2 $\times 10^8\,M^{-1}s^{-1}$ and the dimerization of tyrosine radicals, $2.4 \times 10^8\,M^{-1}s^{-1}$. No explanation is suggested for the deviation from the classical general rule that[116] the cross-combination rate constant is the geometric average of the combination rate constants of the pure radicals.

C. The Reactions of Secondary Radicals

In many cases the irradiated solutions contain other solutes besides the pyrimidine bases. For example, in biological fluids and tissues the concentration of NaCl is much higher than that of the nucleic acids. Consequently the OH radicals will react with Cl^- to form $HOCl^{\dot{-}}$ or $Cl_2^{\dot{-}}$, which will then react with the pyrimidine bases. The presence of chloride ions in irradiated acidic air-saturated aqueous solutions has been shown to increase the destruction yields of uracil and cytosine, to have no effect on G(-thymine) and to decrease the consumption of nucleotides and nucleosides[117–119]. At acidic pH (pH < 2) OH radicals react with Cl^- to give $Cl_2^{\dot{-}}$[120].

$$OH + Cl^- \longrightarrow HOCl^{\dot{-}} \tag{28}$$

$$OHCl^{\dot{-}} + H^+ \longrightarrow H_2O + Cl \tag{29}$$

$$Cl + Cl^- \longrightarrow Cl_2^{\dot{-}} \tag{30}$$

Ward and Kuo also measured the rate of reaction of $Cl_2^{\dot{-}}$, formed from the reaction of OH with Cl^- at acidic pH[121], with various bases, and their results are given in Table 5. It can be seen that the results for uracil and thymine agree quite well with the results of Patterson and coworkers[121]. However, for cytosine there is almost an order of magnitude difference. $Cl_2^{\dot{-}}$ does not add to the double bond, since no chlorine-containing organic compounds or molecular chlorine have been found in irradiated aqueous uracil in the presence of $H^{36}Cl$[118,119]. Rather, $Cl_2^{\dot{-}}$ abstracts an electron from the base molecule[124,125] and thus oxidizes the pyrimidine molecule:

$$Cl_2^{\dot{-}} + e^- \longrightarrow 2Cl^-$$

At neutral and basic pH, OH radicals do not yield $Cl_2^{\dot{-}}$ in the presence of Cl^- (due to the

TABLE 5. Rate constants for the reaction of $Cl_2^{\dot{-}}$ with pyrimidine/purine bases ($\times 10^7\,M^{-1}s^{-1}$)

Base	Ref. 119 pH = 2.7	Ref. 120 pH = 2.0	Ref. 122 pH = 6	Ref. 123 pH = 7
Uracil	4.1	3.5	3.7	28
Thymine	12	7.0		32
Cytosine	9.1	1.0		35
Guanine	8.1			
Adenine	<0.5			

slow rate of reaction 29), and at these pH values the reactions are due to OH or $HOCl^-$. The reaction of $Cl_2^{\dot{-}}$ at neutral and basic pH can be studied either by the reaction of $SO_4^{\dot{-}}$[122] formed in the radiolysis from the reaction of e_{aq}^- with $S_2O_8^-$, or by photolysis of Cl^- solutions[123]. Masuda and coworkers[123] explained their higher observed rate constants (Table 4) as due to the higher pH at which the measurements were conducted. This might be the case with cytosine for which $pK_a = 4.6$ for the first ionization step. However, for thymine and uracil the pK_a values are 9.94 and 9.5, respectively, and there should not be any difference between pH 2 and pH 7. Fendler and Patterson[126] suggested that irradiation of substrates in micellar solutions would provide a better approximation of the microenvironment involved in biological radiation processes than does pure water. Hence, Patterson and coworkers[121] measured the rate constants of $Cl_2^{\dot{-}}$ with some pyrimidine bases in the presence of micelle-forming surfactants, such as sodium lauryl sulphate (NaLS), cetyl (trimethyl) ammonium chloride (CTACl) and Igepal CO-730. For NaLS they found that the rate constants for uracil and thymine were unaffected, while for cytosine, 5-chlorouracil and cytidine this surfactant decreased the rate constants by a factor of two.

Several studies on the oxidation of pyrimidines by inorganic radicals were carried out using the strong oxidant $SO_4^{\dot{-}}$, formed in radiolysis of aqueous solutions containing $S_2O_8^{2-}$ ions. This is not a common solute and thus this reaction will not occur frequently. $SO_4^{\dot{-}}$ reacts very fast with pyrimidines ($k \sim 5 \times 10^9\ M^{-1}s^{-1}$)[127]. $SO_4^{\dot{-}}$ can either abstract electrons (oxidizing) or add to the double bond[128]. In the case of 1,3-dimethylthymine the adduct with $SO_4^{\dot{-}}$ was found to have a half-life of 15 μs[61]. There is no evidence for the adduct in the case of uracil or 1,3-dimethyluracil, but this may be due to the short half-life of the adduct ($t_{1/2} \leqslant 2\ \mu s$).

In the presence of Br^-, the OH radicals are converted to $Br_2^{\dot{-}}$ even at basic pH. $Br_2^{\dot{-}}$ is a weaker oxidant than $Cl_2^{\dot{-}}$. However, at basic pH the redox potential of the deprotonated pyrimidines is much lower and the electron transfer is quite efficient ($2 \times 10^8\ M^{-1}s^{-1}$ at pH 13 compared to $< 1 \times 10^7$ at pH 7)[129].

Bhattacharyya and Mandal[130] studied the degradation of uracil in aqueous solution by ^{60}Co γ-irradiation in the presence of N_2O or NO_3^-. They found that G(-U) in N_2O-saturated and Ar-saturated solutions are the same, indicating that e_{aq}^- and OH lead to degradation of uracil to the same degree. Addition of a low concentration of NO_3^- (0.5 mM) decreases G(-U) to about half. This is probably due to e_{aq}^- scavenged by NO_3^- to form NO_2, which is a very weak oxidant[132]. Although part of the electrons react with uracil, it is possible that the anion transfers an electron to NO_3^-.

$$U^{\dot{-}} + NO_3^- \longrightarrow U + NO_3^{2\dot{-}} \tag{31}$$

$$NO_3^{\dot{-}2} \longrightarrow NO_2^{\cdot} + O^{-2}$$

However, when the NO_3^- concentration is increased above 3 mM, the degradation yield is increased. For $[NO_3^-] > 5$ mM the degradation yield is the same as in the absence of NO_3^-. This was explained by Bhattacharyya and Mandal as due to electron transfer between the nitrate ion and the hydroxyl adduct:

$$\cdot UOH + NO_3^- \longrightarrow UOH^+ + NO_3^{\dot{-}2} \tag{32}$$

The UOH^+ ion leads more to degradation than UOH itself. If this suggestion is true, then at higher dose rates where almost all UOH adducts lead to degradation, this sensitization effect of NO_3^- should disappear. This explanation predicts the decrease in G(dimer) and increase in G(glycols) and G(barbituric acid) with the addition of NO_3^-. The results show a real decrease in G(dimer) but almost no increase in G(glycols) on the addition of 0.1 M NO_3^-. Bhattacharyya and Mandal[135-137] found that several metal ions increase the radiosensitivity of uracil in aqueous solution, e.g. Cu^{+2} and Fe^{+3}, while

TABLE 6. G values of various products in the γ-radiolysis of 2×10^{-3} M uracil in the presence of different metal ions[135-137]

G(product)	N_2O saturated pH = 5.5			Ar saturated pH = 5.5		Ar saturated pH = 1	
Metal ion	—	5×10^4 M Cu^{+2}	5×10^4 M Ni^{+2}	—	5×10^4 M Cu^{+2}	—	5×10^4 M Fe^{+3}
G(-uracil)	3.1	5.1	2.9	2.7	2.8	1.3	3.3
G(dimr)	1.5	0.5	1.5		0.36	0.5	0.5
G(*cis*-uracil glycol)	0.4	1.7	0.2		0.70	0.1	2.0
G(*trans*-uracil glycol)	0.5	0.7	0.5		0.30	0.2	0.3
G(hydroxydihydrouracil)	0.4	0.8	0.2		0.42	0.2	0.2
G(isobarbituric acid)	0.3	0.3	0.3		0.66		

Ni^{+2} does not do so. Cu radiosensitizes uracil only in the N_2O-saturated solution, but not in Ar-saturated ones, while Fe^{+3} radiosensitizes also in Ar-saturated solution. The concentration of metal ions was chosen so that the primary radicals from water radiolysis will react with uracil but not with metal ions. It is clearly seen from Table 6 that not only G(-uracil) increases in the presence of Cu^{+2} or Fe^{+3} but also the distribution of products is changed. The presence of Cu^{+2} or Fe^{+3} decreases drastically the yield of the dimer, which was the major product in the absence of the metal ions. Simultaneously there is an increase in the yield of the uracil glycols, mainly the *cis* isomer.

The metal ions react to oxidize the transient radical species:

$$\begin{aligned} UOH + M^{n+} &\longrightarrow UOH^+ + M^{(n-1)+} \\ UH + M^{n+} &\longrightarrow UH^+ + M^{(n-1)+} \\ U^- + M^{n+} &\longrightarrow U + M^{(n-1)+} \end{aligned} \tag{33}$$

While UH^+ is unknown to revert back to uracil, UOH^+ undergoes transformation to give glycols and isobarbituric acid. In N_2O-saturated solutions the main radical species is UOH and its presence will explain the observed results. In Ar-saturated solutions, UOH and UH (or U^-) are present in about the same concentration. However, in the case of Fe^{+3}, Fe^{+2} is produced by its reduction and the latter reacts with H_2O_2 in the Fenton reaction

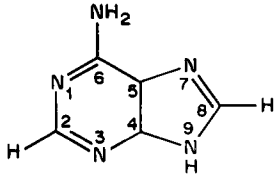
$$H_2O_2 + Fe(II) \longrightarrow Fe(III) + OH + OH^- \tag{34}$$

leading to further formation of OH radicals, which are responsible for the enhanced degradation of uracil.

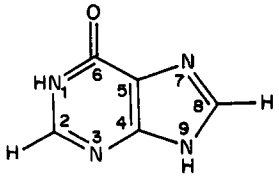
V. RADIOLYSIS OF AQUEOUS SOLUTIONS OF PURINES

A. Initial Intermediates

The radiolysis of purines (adenine and guanine) in solution has received considerably



adenine



guanine

less attention than that of pyrimidines. The main features were reviewed recently[138]. Both the hydrated electron and OH react very fast with the purine bases ($\sim 10^{10}\ M^{-1}\ s^{-1}$) while the hyderogen atom reacts two orders of magnitude slower (Table 1). The same high reactivity of e_{aq}^- and OH is observed also for purine nucleotides. On introduction of the phosphate group into the system (base + phosphate $\longrightarrow$ nucleotide) the OH reaction rate constant decreases by about 20% while the e_{aq}^- reacts more than two-fold slower with the nucleotides compared to the bases themselves. This rate-decreasing effect in the case of e_{aq}^- is probably due to electrostatic repulsion between the two negatively charged reactants.

Several studies were undertaken to elucidate the chemical nature and reaction of the electron adduct. Moorthy and Hayon[139] found for several purines and for purine nucleosides that the absorption spectra of the electron adducts change with pH in a way

that was interpreted as due to protonation equilibria of the e_{aq}^- adducts. They found that for adenosine at pH 11.5 and pH 5.9 there are different spectra of the e^- adduct. They concluded that at pH 5.9 the doubly protonated radical cation is present while at pH = 11.5 it is the monoprotonated (uncharged) radical AdH.

$$Ad + e^- \longrightarrow Ad^-$$

$$Ad^- + 2H^+ \longrightarrow AdH_2^+ \qquad (35)$$

Although Hissung and coworkers[140] observed different absorption spectra at pH 4.9 and at pH = 11.5, they demonstrated by conductivity measurements that at both pH values the uncharged monoprotonated radical is present. Thus it is clear that the two different spectra are not due to a deprotonation equilibrium but rather to some other reaction—probably a rearrangement of the adduct. Visscher's group[141] found that not only the spectrum but also the chemical properties are changed with the pH. Using optical absorbance and conductance detection with nanosecond resolution they showed that the direct electron adduct of adenine A^- is protonated by H_2O in less than 5 ns. The product thus formed is a strongly reducing radical which can reduce MV^{2+} (methyl viologen) and *p*-NAP (*p*-nitroacetophenone). The reduction of MV^{2+} is quantitative between pH 5 and 9. However, for pH values above 10 the situation is changed drastically, as can be seen in Figure 2, and above pH 12 the electron adduct is no longer reducing. Later, it was found that the unreducing rearranged adduct can also be formed at pH near to neutral by using

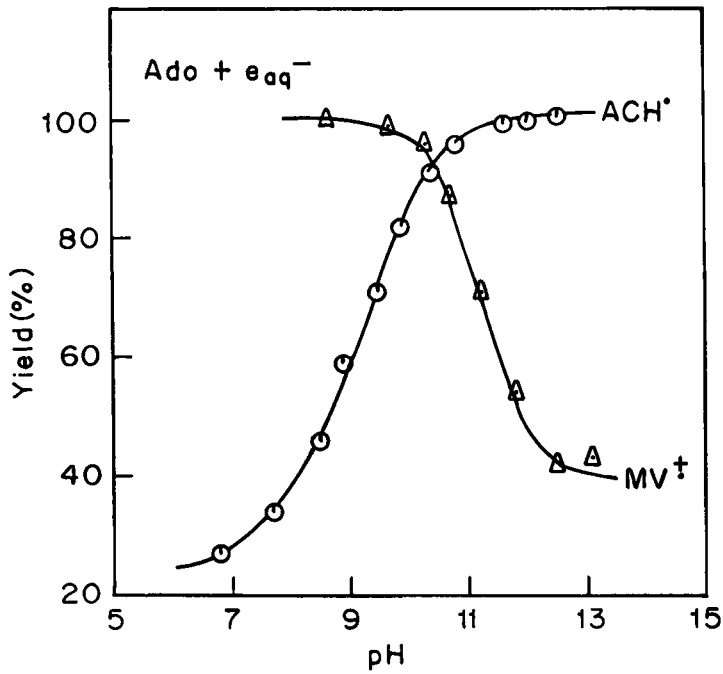
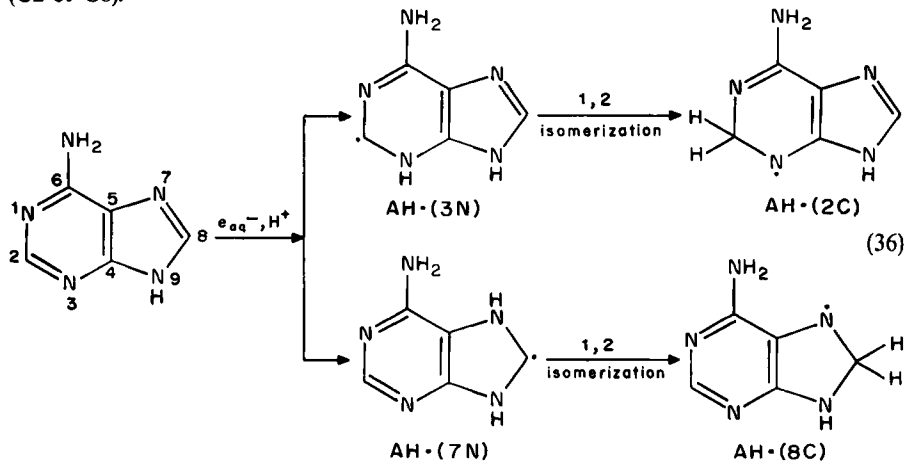


FIGURE 2. Dependence on pH of (a) the reducing equivalents as titrated by MV^{2+} (Δ) and (b) the yield of carbon-protonated electron adduct of adenosine (O). With (a), [adenosine] = 2.5 mM, 1 M *tert*-butyl alcohol, $[MV^{2+}] = 0.1$ mM; with (b), [adenosine] = 2 mM, [*tert*-butyl alcohol] = 0.5 M. ACH· is the same as AH·(C) in the text. Reprinted with permission from Moorthy and Hayon, *J. Am. Chem. Soc.*, **97**, 3345. Copyright (1975) American Chemical Society

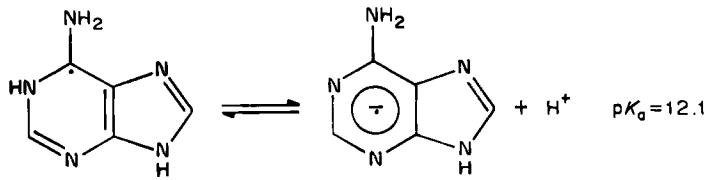
phosphate anions as catalysts[138]. Thus it was concluded that the phosphate ions catalysed the rearrangement similarly to OH^- anions, and this was demonstrated by the change both in the spectrum and in the reducing ability.

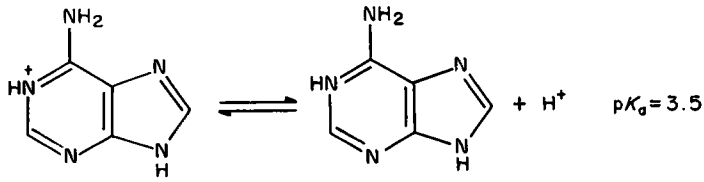
There is no proof for the structures of the two different species of the netural radical AG·. However, considering the solid state chemistry of purines and pyrimidines and the *in situ ESR* studies of pyrimidines in aqueous solutions, Steenken[138] suggested that the rearrangement is a 1,2-H atom migration. The two forms of AH·comprise one where the H atom is on the nitrogen atom (either N2 or N7) and the unpaired electron is on a carbon atom, while the other is a species in which the H atom was added to a carbon atom (C2 or C8).



(36)

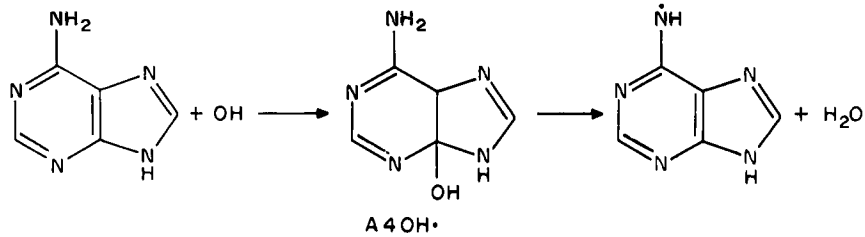
The C-protonated radicals have appreciably higher spin density on the electron-attracting nitrogens and hence have a lower tendency to give up an electron, i.e. to reduce other compounds. The strong reducing power of the N-protonated radical is due probably to the α-nitrogens stabilizing the ion produced by the oxidation of the AH·(N). The first protonation occurs almost exclusively on nitrogen, since protonation on carbon atoms is a much slower process due to high bond reorganization energy[142,143]. The rate of direct protonation at the carbon atoms was studied by measuring the rate of formation of AH·(C) between pH = 13 and 1 M OH^-, and in this range the rate constant was found to be constant ($3.6 \times 10^6\ s^{-1}$). This rate is about two orders of magnitude lower than for protonation on nitrogen ($\geqslant 1.4 \times 10^8\ s^{-1}$). In this pH range the radical is ionized. The rate of C protonation of the neutral radical was measured by monitoring the build-up of AH·(C) as a function of the concentration of the phosphate catalyst, and plotting it as a linear function of the phosphate concentration. The intercept gives the rate of self-C - protonation ($1.4 \times 10^4\ s^{-1}$), which is two orders of magnitude slower than the protonation of the anionic radical. The ratio of protonation at C2 and C8 is as yet unknown. The basicity of the electron adduct is much higher ($pK_a = 12.1$) than that of the parent compound (3.5).





Such large changes of basicity upon addition of an electron to heterocyclic systems have been found earlier for pyridine, pyrimidine, pyrazine and pyridazine[144,145].

The reactivity of the OH radical with 6-substituted purines was found to follow the $\sigma^+\rho^+$ Brown–Okamoto equation. The value of ρ^+ was found to be negative (-0.9), indicating that the transition state is polar. OH radicals are added to 6-substituted purines in at least two different places, leading to at least two different products. The products are the adducts of OH to C4 and to C8, which will be denoted by A4OH· and A8OH in the case of adenine. Both radicals undergo unimolecular decays: A4OH· is dehydrated while A8OH· undergoes ring opening[146]. In the dehydration, a carbon-centred radical is transformed into a nitrogen centred radical, this being a transformation of a weak oxidant to a strong oxidizing radical.

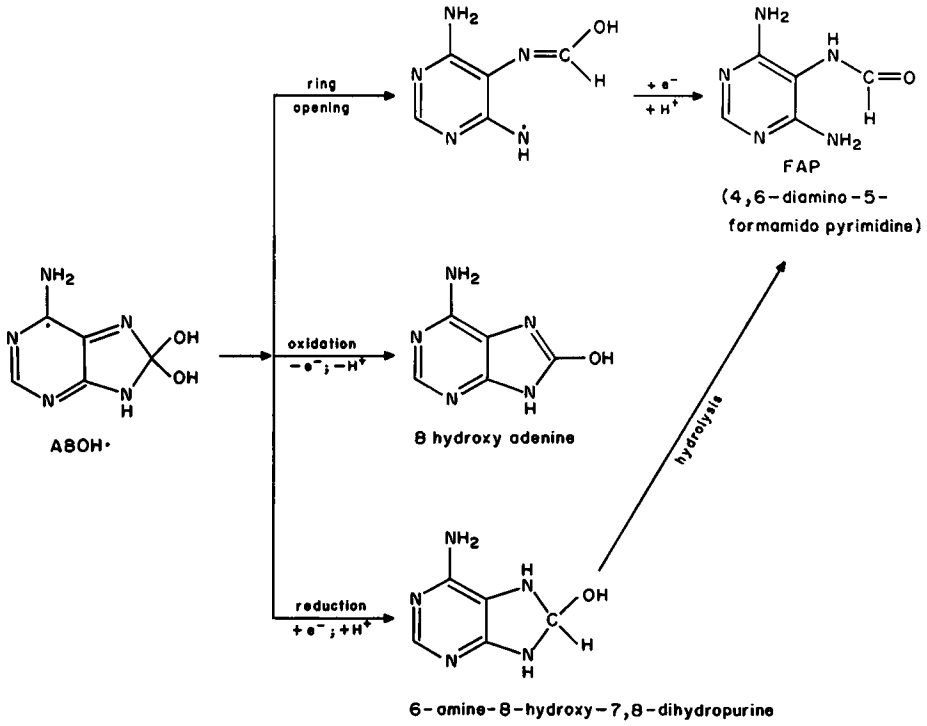


The dehydrated radical can oxidize TMPD (*N*,*N*,*N'*,*N'*-tetramethyl *p*-phenylenediamine) and the yield of $TMPD^+$ is used to calculate the yield of A4OH·, which is 30% of the yield of OH in the case of deoxyadenosine[146,147].

The ring-opening reaction of A8OH· is recognizable by the increase in the optical density at 350 nm[148]. This process can be suppressed quantitatively by small concentrations of oxidants, e.g. O_2[149], indicating that A8OH· is a strong reductant. This was further proved by showing that the addition of oxidants reduces the yield of the products of ring opening (5-formamido-6-amino pyrimidine derivatives—FAP). The A8OH· radical can also be reduced; besides being oxidized, however, the product of reduction is sensitive to hydrolysis, yielding the open-ring product. This is reasonable since the final product of the ring opening is formed by reduction of the opened-ring radical (Scheme 9).

In the case of adenine and adenosine at room temperature and pH 7, it is difficult to distinguish between the ring opening (build-up at 330 nm) and the dehydration (decrease at 400 nm) since both processes have similar rates. However, the processes can be distinguished by their different pH dependencies, by their different temperature dependence and by the effect of substituents. Substituents at N6 have higher influence on the dehydration reaction ($\rho^+ = -3.0$) than on the ring-opening reaction ($\rho^+ = -0.3$)[148]. The Hammet lines for the two processes intersect at the N6 substituent being NH_2, i.e. adenine and deoxyadenosine.

O'Neill and his coworkers[150–152] found that the reaction of OH with 2'-deoxyguanosine (G) leads to an oxidizing-type radical (50%) and to reducing radicals (50%) (while guanine is not sufficiently soluble in water to study its solutions). The oxidizing radical was found to be identical with that produced on reaction with $Br_2^{\cdot-}$. This is the



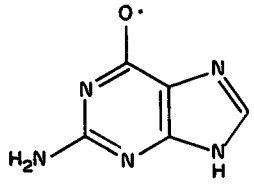
SCHEME 9

neutral radical *G*(-H) which is obtained by abstracting a hydrogen atom from guanosine.

$$G + Br_2^{\cdot -} \longrightarrow G^{\ddagger} + 2Br^-$$

$$G^{\ddagger} \longrightarrow G(\text{-H})\cdot + H^+$$

In the case of OH this radical is formed by addition of OH to C4 followed by elimination of a water molecule to give *G*(-H). This is similar to the case of adenine, except that in adenine the radical centre is on a nitrogen atom while in guanosine it is on an oxygen atom.



The reducing radical is the OH adduct to C5 and C8. The C8 adduct radical can be reduced or it may undergo ring opening, as described above for adenine. The C5 OH adduct is a reasonably strong reductant[152].

B. Final Products

Van Hemmen and Bleichrodt[153] measured the yields of several products of the radiolysis of N_2O-saturated aqueous solution of adenine while Berger and Cadet[154]

TABLE 7. The yields (G values) of the various products from the γ-radiolysis of aqueous solutions of purines

I. Adenine in N_2O-saturated aqueous solution[153]

Product	G value
Adenine consumption	1.0
8-Hydroxyadenine	0.35
4,6-Diamino-5-formamidopyrimidine	0.2
6-Amino-8-hydroxy-7,8-dihydropurine	0.1

II. 2′-deoxyguanosine in N_2 and N_2O-saturated aqueous solutions[154]

Product	G value	
	N_2	N_2O
2′-Deoxyguanosine consumption	0.81	1.50
9-(2-Deoxy-β-D-erythropentopyranosyl)-2,4-diamino-5-formamidopyrimid-6-one	0.08	0.09
9-(2-Deoxy-α-D-erythropentopyranosyl)-2,4-diamino-5-formamidopyrimid-6-one	0.26	0.25
9-(2-Deoxy-α-D-erythropentopyranosyl) guanine	0.02	0.03
9-(2-Deoxy-β-D-erythropentopyranosyl) guanine	0.01	0.02
9-(2-Deoxy-α-D-erythropentofuranosyl) guanine	0.02	0.02
9-(2-Deoxy-α-L-threopentofuranosyl) guanine	0.02	0.03
9-(2-Deoxy-β-D-erythropento-1,5-dialdo-1, 4-furanosyl) guanine	0.07	0.08
5′,8-Cyclo-2′,5′-dideoxyguanosine	0.05	0.06
8-Hydroxy-2′-deoxyguanosine	—	0.24
Guanine	0.19	0.38

studied the products of the γ-radiolysis of 2′-deoxyguanosine (since, owing to its very low solubility in water, guanine itself could not be used) in N_2O- and N_2-saturated solutions. The results are given in Table 7.

The most striking results in this table are the low yields of consumption of the parent compounds. The G values of radicals in N_2O-saturated solution are $G(OH) = 6$ and $G(H) = 6$. Even assuming that the OH-adduct and the H-adduct react with each other to reform the purine parent molecule, and that all the remaining OH-adducts ($G = 5.4$) disproportionate leading half to the parent molecule and half to a product, the expected value would be $G(\text{consumption}) = 2.7$. This is in contrast to the observed values $G(\text{purine consumption}) \leqslant 1.5$ in Table 7. Van Hemmen and Bleichrodt[153] suggested that this is probably due to a reconstitution reaction of the adenine radicals. It is possible that some of the products can be reduced by the OH-adduct radicals; the OH radicals are oxidized to as yet unknown hydrates, which upon loss of water could regenerate the purines.

VI. RADIOLYSIS OF AQUEOUS SOLUTIONS OF MIXTURES OF PURINES AND PYRIMIDINES

Sevilla and coworkers[155] employed pulse radiolysis with optical detection to study the radiation chemistry of aqueous solutions of a dinucleoside phosphate, namely thymidine-5-phosphatedeoxyadenosine (TPdA). They observed initial formation of the adenosine electron adduct, which then transfer the electron to the thymine moiety. They calculated that the transfer from the purine residue to the pyrimidine is only partial. However,

Visscher and coworkers[156] pointed out an error in the calculations of Sevilla and coworkers[155], who treated the pyrimidine spectra as due to the thymidine anion radical T^-, while Visscher's group[156] noted that in phosphate-buffered solutions, as used in that study[155], the anion is very rapidly protonated since this reaction is catalysed by the phosphate ions. Considering that the radical is not T^- but really the C6 protonated thymidine monophosphate (TMP) radical leads to the conclusion that the electron is almost completely transferred to the pyrimidine base. Visscher and coworkers[156] studied the radical spectra in radiolysis of aqueous solutions of mixtures of adenosine-5'-monophosphate (AMP) with either thymidine-5'-monophosphate (TMP) or uridine-5-monophosphate (UMP) containing OH and H atom scavengers. The observed spectra can be explained only if it is assumed that there is an electron transfer from the purine electron adduct to the pyrimidine base.

Visscher and collaborators[156] used lower pH to increase the protonation of A^- to AH· and found no electron transfer to thymidine, and hence they concluded that it is the radical anion of adenine which is transferring an electron to thymidine. There is some competition between this transfer and the protonation of the anion radical, due to the low concentration of pyrimidine used in this study (in order to ascertain that the e_{aq}^- will react with the adenine moiety). For the cases of dinucleoside phosphates (dApT, ApU or dCpdA) the concentration of the pyrimidine is much higher and the competition by protonation can almost be neglected. The electron transfer was found to be a diffusion-controlled reaction with rate constants of $1.2 \times 10^{10}\,M^{-1}s^{-1}$ for TMP and $3.5 \times 10^{9}\,M^{-1}s^{-1}$ for UMP.

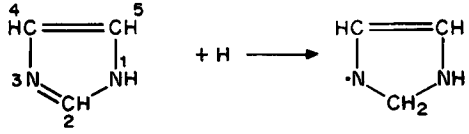
Gregoli and coworkers[157] observed electron transfer from purine anion to thymine moiety in AMP–TMP mixtures and DNA in frozen solution, by analysis of ESR spectra.

The observation that the electron is eventually located on the pyrimidines agrees with theoretical molecular orbital calculations[158a] and shows the affinity for electrons to be in the order thymine > cytosine > adenine > guanine.

VII. RADIOLYSIS OF IMIDAZOLE AND HISTIDINE

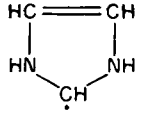
A. Solid State

Lamotte and Servoz-Gavin[158b] found by ESR a radical formed by X-ray radiolysis of imidazole and proposed that the ESR spectrum is due to a radical formed by hydrogen atom addition to C2 (equation 37). Blum and coworkers[159] argued that the radical formed



(37)

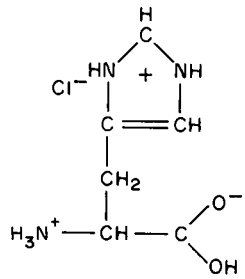
is due to hydrogen addition to N3. The ESR spectrum of the X-irradiated imidazole crystal shows a characteristic splitting of about 45G and three lines with an intensity ratio of 1:2:1. The authors attributed this large splitting to hyperfine coupling with two C4 and C5 protons. However, Bohme[160] showed that the N3 H-adduct cannot have such a large splitting and the radical formed is due to the C2 H-adduct radical. Lamotte and



Gloux[161,162] proved by ESR studies of single crystals of imidazole and of derivatives deuterated at various places, which were γ-irradiated at room temperature, that the radical observed is a π radical formed by the addition of one hydrogen atom to a carbon of the ring. They showed that the hydrogen which is added to form the radical comes from hydrogen atoms that are involved in the hydrogen-bonded chains in the crystal (imidazole forms one-dimensional intermolecular chains of hydrogen bonds). From ENDOR studies they determined all the proton hyperfine tensors, and hence the spin density distribution in the radical.

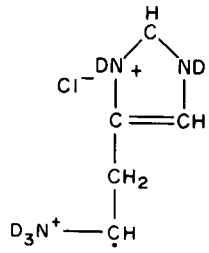
Miyagawa and coworkers[163] found that the H atom added to C2 to form the radical can be exchanged with a deuterium atom of a neighbouring molecule, and *vice versa*. The activation energy for this exchange was found to be 17.4 ± 2 kcal mol^{-1}.

Box and coworkers[164] studied the formation of free radicals in X-irradiated histidine hydrochloride single crystals. At 4.2 K, the most prominent component of the ESR spectrum has a four-line hyperfine pattern with an over-all splitting of approximately 37 G. In crystals partially deuterated, the absorption has a doublet hyperfine pattern. Two protons, one of which is exchangeable, account for these hyperfine characteristics. ENDOR measurements gave coupling tensors of the anisotropy which is typical of β-proton couplings, observed for a variety of anions formed by electron addition to carboxylic acid derivatives. The exchangeable proton has a significantly larger anisotropy than the nonexchangeable one. These observations are consistent with the interpretation that the absorption is due to the radical anion in which the unpaired electron is localized mainly on the carbon atom of the carboxyl group. In addition to the added electron the radical anion is abstracting a proton from a neighbouring molecules.

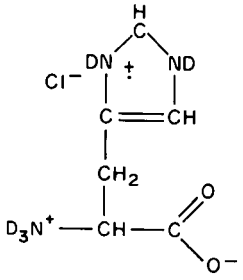


Histidine – HCl

In addition to the lines due to the radical anion, there are two other components in the ESR spectrum of X-irradiated (4.2 K) partially deuterated histidine hydrochloride single crystals. One is due to radical formed by decarboxylation (I) and the other originates from the imidazole cation of the histidine (II).



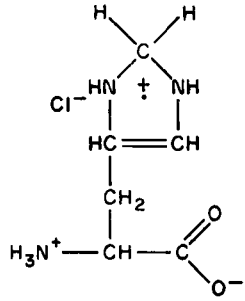
(I)



(II)

In the decarboxylation product, the unpaired electron is localized mainly on the carbon atom adjacent to the amino group. This radical is formed by oxidation of histidine–HCl followed by dissociation of CO_2, as has been found for other amino acids[165].

The radical produced by ionizing radiation from histidine–HCl at room temperature was identified as the hydrogen adduct[166,167]. The unpaired electron is delocalized in the

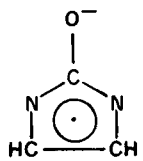


imidazole ring and experiences a large interaction with the CH_2 protons via hyperconjugation. The same radical was also observed[164] in crystals irradiated at 4.2 K and subsequently warmed to room temperature.

B. Aqueous Solutions

Samuni and Neta[167] studied the radical formed by the reaction of OH with imidazole by the *in situ* ratiolysis steady-state ESR technique.

The ESR spectra recorded at pH 9 and at pH 12, in N_2O-saturated aqueous solutions of imidazole, were found to be different. The spectrum at the higher pH showed splittings by two equivalent nitrogens, two equivalent protons and one additional proton. The obvious structure is that formed by the loss of hydrogen from the NH group. At the lower pH a completely different spectrum is obtained. The nitrogens are not equivalent; the hyperfine constants are 1.4 G and 2.6 G, the average of which is identical with that found for the two nitrogens at pH 12. Five different proton hyperfine constants were observed at pH 9. One of these constants is 26.4 G, which is characteristic for a proton and OH on the same carbon. Two others, 9.8 G and 16.3 G, can be reasonably assigned to allylic hydrogens and two, very low constants, 1.43 G and 0.35 G, are due to NH and OH protons. Thus this radical is due to the OH-adduct of imidazole. It was found that around pH 10 both radicals are present at similar concentrations. Both OH radical and imidazole dissociate and form different species at different pH values (OH or O^- and ImH or Im^+). However, the two observed radicals are not due to different reacting species since the pH in which equal yields of the two radicals were observed (pH = 10) is considerably different from the pH of either OH radical (11.8) or imidazole (7.0). Thus it is reasonable to assume that the two radicals are not due to different reacting species, but rather to one radical dissociating with pH to the second one. The most reasonable mechanism is addition of OH to the imidazole ring followed by a slow process of water elimination. This slow process is catalysed by

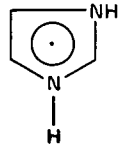


hydroxyimidazole radical

OH^- anions. At pH 13 and above, ESR lines of an additional radical were found by Samuni and Neta[167], who attributed them to the hydroxy imidazole radical produced by secondary reactions.

Rao and coworkers[168] studied by pulse radiolysis the optical spectra of the products of the reaction of e_{aq}^- and OH radicals with imidazole and histidine. The rate constants for the reaction with e_{aq}^- strongly depend on the pH ($\sim 2 \times 10^7$ and $4 \times 10^9\ M^{-1}s^{-1}$ at pH 11 and pH 6, respectively) due to the protonation of the nitrogen in the ring. The reaction of OH depends only slightly on the pH and the rate constants are in the range 5–$12 \times 10^9\ M^{-1}s^{-1}$; the higher the pH, the larger is the rate constant.

The reaction of e_{aq}^- with protonated imidazole (ImH_2^+, where ImH is the imidazole molecule) leads to a relatively strong transient absorption spectrum with maxima at 300 nm ($\varepsilon = 5600\ M^{-1}cm^{-1}$) and 360 nm ($\varepsilon = 2000\ M^{-1}cm^{-1}$). It was suggested that e_{aq}^- is added to the ring nitrogen to form the following radical, after protonation:



If, instead of imidazole, *N*-methylimidazole is irradiated, the formed radical has about the same extinction coefficients (increase of 10–20%) and a shift of 10 nm in the short wavelength peak. Similar results were found for histidine. The following absorption lines were found: 295 nm ($\varepsilon = 4700\ M^{-1}cm^{-1}$) and 370 nm ($\varepsilon = 1700\ M^{-1}cm^{-1}$). The decay rate of the electron adduct of histidine is three times slower than that of the imidazole electron adduct (8×10^8 compared to $21 \times 10^8\ M^{-1}s^{-1}$); both decayed by second-order kinetics.

Rao and coworkers[168] found that the OH-adduct of imidazole has two optical bands. However, the maxima at pH 4.4 [295 nm ($3300\ M^{-1}cm^{-1}$) and 400 nm ($1400\ M^{-1}cm^{-1}$)] are more separated that at pH 8.5 [310 nm ($5500\ M^{-1}cm^{-1}$) and 390 nm ($1200\ M^{-1}cm^{-1}$)]. The authors concluded that these findings indicate formation of more than one adduct radical and suggested that probably OH is added at both the C2 and C5 positions. However, as the O.D. at 310 nm as a function of pH shows a titration curve with pH = 6.1, the different spectra can be due to the protonated and non-protonated radicals. Similar results were found for the reaction of OH with histidine. The OH-adduct of imidazole decayed five times faster than the OH–histidine adduct (5.5 and $1.2 \times 10^9\ s^{-1}$), similarly to what was found for the e_{aq}^- adduct.

In the presence of both N_2O and O_2 it was found that the OH-adducts react with O_2 to give probably the peroxy radical, with a rate constant of $\sim 10^9\ M^{-1}cm^{-1}$.

Bansal and Sellers[169,170] employed polarographic and optical pulse radiolysis to study the radicals formed by OH attack on imidazole and histidine. This work, conducted independently and almost simultaneously with that of Rao and coworkers[168], gave very similar results concerning the optical spectra, with small differences of ~ 10 nm in λ_{max}. The acidities used were not the same; however, they are far enough from the pH values to expect the pH changes to be responsible for the different maxima of absorption. For example, OH–histidine at pH 3.5 was found by Rao's group to have maxima at 300 and 410 nm while Bansal and Sellers at pH 3.05 found $\lambda_{max} = 290$ and 400 nm. Similarly, for OH–imidazole at pH 9.9, Bansal and Sellers obtained 300 and 380 nm while Rao's group measured $\lambda_{max} = 310$ and 390 nm at pH = 8.5.

Both groups measured the reactions not only of imidazole and histidine but also of their methyl derivatives; Rao studied *N*-methylimidazole and *N*-methylhistidine while Bansal and Sellers studied 1- and 2-methylimidazole.

Bansal and Sellers studied also the rate of the base-catalysed water elimination from the OH-adduct occurring at pH > 11. They found that there is an increase in the absorption of the dehydrated radical after the OH-adduct peaks at 300 and 390 nm had decayed. This increase was found to be approximately first order and pH-dependent, and the authors suggested that it is due to a dehydrated radical produced by water elimination from another OH–imidazole adduct, which does not absorb at 300 or 390 nm. No such second buildup was found in the case of histidine.

Faraggi and Bettelheim[171] studied the reactions of hydrated electrons with histidine and two histidine dipeptides (β-alanyl-histidine and glycyl-histidine), by kinetic spectrophotometric pulse radiolysis. The rate constants were found to the pH-dependent. Below the pK value of the imidazole ring, the rate constants for the reaction of the hydrated electron with the histidyl peptides are similar to that with histidine ($3 \pm 1 \times 10^9\ M^{-1} s^{-1}$). Above the p$K$ value, the pH-dependent rate constants were lower for histidine than for the histidyl peptides (6×10^7 compared to $4–8 \times 10^8\ M^{-1} s^{-1}$). This indicates that at low pH values the main site of the e_{aq}^- reaction is the protonated ring, possessing the highest reactivity toward the hydrated electrons. The unprotonated ring reacts slowly with e_{aq}^- ($2 \times 10^7\ M^{-1} s^{-1}$[168]) and finally the e_{aq}^- reacts also with the carbonyl group in the peptides. Similar conclusions were obtained from the transient absorption spectra resulting from the reaction of e_{aq}^- with histidine and histidyl peptides. Below the pK of imidazole, the transient absorption spectra of the histidyl peptides are similar to that of histidine. In alkaline solution of glycyl–histidine it was found that the band characterizing the imidazole transient ($\lambda_{max} = 360$ nm) disappears with simultaneous appearance of a band at $\lambda_{max} \simeq 410$ nm. The latter band was suggested to be due to a de-aminated radical produced via an internal electron transfer from the carbonyl group[171].

D'Arcy and Sevilla[172] studied the reactions of hydrated electrons with peptides in neutral aqueous glasses at low temperature by ESR spectroscopy. They found that for dipeptides containing one histidine residue there is competition between de-amination of the amino acids and addition of the e_{aq}^- to the imidazole ring. 65–80% of the formed radicals are due to a primary de-amination process while 20–35% of the radicals are produced by protonation of the aromatic ring anion formed by the addition of e_{aq}^- to the ring. There is no large difference in the fraction of the de-amination irrespective of whether the histidyl group is at the C-terminal or at the N-terminal residue.

Kopoldova and Heneir[173] studied the yield of the various products of radiolysis of O_2-saturated aqueous solution of histidine. They found that the yield of the oxidative degradation of the histidine (imidazole) ring corresponds to $G \sim 4$, with many degradation products. The major products were asparagine and aspartic acids. OH also attacks at the main chain, as imidozolylpyruvic and imidazolylacetic acids were identified among the products.

Petryaev and coworkers[174] studied the yield of fragmentation products of imidazole in γ-irradiation of aqueous solutions. They found the main products to be ammonia and formamide. The G value of ammonia is more than twice that of formamide at pH 3–7. Both G values decrease with pH, reaching almost zero at pH $\geqslant 12$.

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IX. REFERENCES

1. J. H. O'Donnell and D. F. Sangster, *Principles of Radiation Chemistry*, Edward Arnold, London, 1970.

2. J. W. T. Spinks and R. J. Wood, *An Introduction to Radiation Chemistry*, 2nd edn., Wiley, Chichester, 1976.
3. A. J. Swallow, *Radiation Chemistry—An Introduction*, Longman, London, 1973.
4. A. Mozumder, *Adv. Radiat. Chem.*, **1**, 1 (1969).
5. E. G. Janzen, *ACC. Chem. Res.*, **4**, 31 (1971).
6. C. Lagercrantz and S. Forshult, *Nature*, **218**, 1247 (1968).
7. P. K. Ludwig, *Adv. Radiat. Chem.*, **3**, 1 (1972).
8. W. A. Bernhard, *Adv. Radiat Biol.*, **9**, 199 (1981).
9. J. Hüttermann, *Ultramicroscopy*, **10**, 25 (1982).
10. H. Zehner, W. Flossmann, E. Westhof and A. Muller, *Int. J. Radiat. Biol.*, **32**, 869 (1976).
11. E. Westhof, W. Flossmann, H. Zehner and A. Muller, *Faraday Discuss.*, **63**, (Radiation Effects in Liquids and Solids), 248 (1978).
12. (a) M. Kuwabara, Y. Lion and P. Riesz, *Int. J. Radiat. Biol.*, **39**, 465 (1981).
    (b) R. A. Spalletta and W. A. Bernhard, *Radiat. Res.*, **89**, 11 (1982).
13. P. Martel, B. M. Powell and M. Slifkin, *Radiat. Eff.*, **106**, 151 (1988).
14. W. Flossmann, E. Westhof and A. Muller, *J. Chem. Phys.*, **64**, 1688 (1976).
15. J. N. Herak and C. A. McDowell, *J. Chem. Phys.*, **61**, 1129 (1974).
16. W. Flossmann, J. Hüttermann, A. Muller and E. Westhof, *Z. Naturforsch.*, **28C**, 523 (1973).
17. W. Flossmann, E. Westhof and A. Muller, *Int. J. Radiat. Biol.*, **28**, 105 (1975).
18. W. Flossmann, E. Westhof and A. Muller, *Int. J. Radiat. Biol.*, **30**, 301 (1976).
19. J. B. Cook, J. P. Elliott and S. J. Wyard, *Mol. Phys.*, **13**, 49 (1967).
20. E. Westhof, W. Flossmann, H. Zehner and A. Muller, *Int. J. Radiat. Biol.*, **28**, 427 (1975).
21. W. Flossmann, H. Zehner and E. Westhof, *Int. J. Radiat. Biol.*, **36**, 249 (1979).
22. J. Hüttermann, *Int. J. Radiat. Biol.*, **17**, 249 (1970).
23. A. Dulcic and J. N. Herak, *Radiat. Res.*, **47**, 573 (1971).
24. T. Henriksen and W. Snipes, *Radiat. Res.*, **42**, 255 (1970).
25. H. Riederer, J. Hüttermann and M. C. R. Symons, *J. Phys. Chem.*, **85**, 2789 (1981).
26. T. Henriksen and W. B. G. Jones, *Radiat. Res.*, **45**, 420 (1971).
27. J. N. Herak and W. Gordy, *Proc. Natl. Acad. Sci. U.S.A.*, **55**, 1373 (1966).
28. A. Dulcic and J. N. Herak, *J. Chem. Phys.*, **57**, 2537 (1972).
29. H. Zehner, W. Flossmann, E. Westhof and A. Muller, *Mol. Phys.*, **32**, 869 (1976).
30. P. K. Horan and W. Snipes, *Radiat. Res.*, **41**, 24 (1970).
31. W. Flossmann, A. Müller and E. Westhof, *Mol. Phys.*, **29**, 703 (1975).
32. A. Dùlcic and J. N. Herak, *Mol. Phys.*, **26**, 605 (1973).
33. A. Dùlcic and J. N. Herak, *Biochim. Biophys. Acta*, **319**, 109 (1973).
34. R. Bergene and T. B. Melo, *Int. J. Radiat. Biol.*, **23**, 263 (1975).
35. W. Flossmann, H. Zehner and A. Muller, *Z. Naturforsch.*, **35C**, 20 (1980).
36. J. B. Cook and S. J. Wygard, *Mol. Phys.*, **11**, 357 (1966).
37. A. Muller, *Prog. Biophys. Mol. Biol.*, **17**, 99 (1967).
38. J. Rotblat and J. A. Simmons, *Phys. Med. Biol.*, 7, 489 (1963).
39. J. Cadet and M. Berger, *Int. J. Radiat. Biol.*, **47**, 127 (1985).
40. D. M. Close, W. H. Nelson and E. Sagstuen, in *Electronic Magnetic Resonance of the Solid State* (Ed. J. Weil), Canadian Society of Chemistry, Ottawa, 1987, p. 237.
41. J. Cadet, M. Berger and A. Shaw, in *Mechanism of DNA Damage and Repair* (Eds. M.G. Simic, L. Grossman and A. C. Upton), Plenum Press, New York, 1986, p. 69.
42. H. C. Box and E. E. Budzinski, *J. Chem. Phys.*, **64**, 1593 (1976).
43. L. A. Kar and W. A. Bernhard, *Radiat. Res.*, **93**, 232 (1983).
44. D. M. Close, E. Sagstuen and W. H. Nelson, *J. Chem. Phys.*, **82**, 4386 (1985).
45. J. Hüttermann and K. Voit, in *Electronic Magnetic Resonance of the Solid State* (Ed. J. Weil), Canadian Society of Chemistry, Ottawa, 1987, p. 286.
46. E. O. Hole, W. H. Nelson, D. M. Close and E. Sagstuen, *J. Chem. Phys.*, **86**, 5218 (1987).
47. D. M. Close and W. H. Nelson, *Radiat. Res.*, **117**, 367 (1989).
48. P. Strand, E. Sagstuen, T. Lehner and J. Hüttermann, *Int. J. Radiat. Biol.*, **51**, 303 (1987).
49. D. M. Close, W. H. Nelson and E. Sagstuen, *Radiat. Res.*, **112**, 283 (1987).
50. W. H. Nelson, E. O. Hole, E. Sagstuen and D. M. Close, *Int. J. Radiat. Biol.*, **54**, 963 (1988).
51. E. Sagstuen, E. O. Hole, W. H. Nelson and D. M. Close, *Free Radiat. Res. Commun.*, **6**, 91 (1989).
52. C. Alexander Jr. and W. Gordy, *Proc. Natl. Acad. Sci. U.S.A.*, **58**, 1279 (1967).
53. D. M. Close, E. Sagstuen and W. H. Nelson, *Radiat. Res.*, **116**, 379 (1988).
54. J. Schmidt and D. C. Borg, *Radiat. Res.*, **46**, 36 (1971).

55. J. Hütterman, *J. Magn. Reson.*, **17**, 66 (1975).
56. H. Zehner, W. Flossmann and E. Westhof, *Z. Naturforsch.*, **31C**, 225 (1976).
57. H. Zehner, E. Westhof, W. Flossmann and A. Muller, *Z. Naturforsch.*, **32C**, 1 (1977).
58. H. Zehner, E. Westhof, W. Flossmann and A. Muller, *Int. J. Radiat. Biol.*, **33**, 121 (1978).
59. K. Sieber and J. Hüttermann, *Int. J. Radiat. Biol.*, **55**, 331 (1989).
60. C. von Sonntag and H. P. Schuchmann, *Int. J. Radiat. Biol.*, **49**, 1 (1986).
61. C. von Sonntag, *Radiat. Phys. Chem.*, **30**, 313 (1987).
62. C. von Sonntag, *Free Radiat. Res. Commun.*, **2**, 217 (1987).
63. C. von Sonntag, *The Chemical Basis of Radiation Biology*, Taylor and Francis, London, 1987, p. 116.
64. P. Neta and M. Dizdaroglu, in *The Chemistry of Enones* (Eds. S. Patai and Z. Rappoport), Wiley, New York, 1989, p. 787.
65. G. V. Buxton, C. L. Greenstock, W. P. Helman and A. B. Ross, *J. Phys. Chem. Ref. Data*, **17**, 513 (1988).
66. K. Makino, M. Mossoba and P. Riesz, *J. Phys. Chem.*, **87**, 1074 (1983).
67. G. Nucifora, B. Smaller, R. Remko and E. C. Avery, *Radiat. Res.*, **54**, 35 (1973).
68. H. M. Novais and S. Steenken, *J. Am. Chem. Soc.*, **108**, 1 (1986).
69. P. Neta, *Radiat. Res.*, **49**, 1 (1972); **56**, 201 (1973).
70. K. M. Bansal and R. W. Fessenden, *Radiat. Res.*, **75**, 497 (1978).
71. J. Planinic, *Int. J. Radiat. Biol.*, **38**, 651 (1980).
72. S. Rustgi and P. Riesz, *Int. J. Radiat. Biol.*, **33**, 21 (1978).
73. A. Hissung and C. von Sonntag, *Z. Naturforsch.*, **33B**, 321 (1978).
74. S. Fujita and S. Steenken, *J. Am. Chem. Soc.*, **103**, 2540 (1987).
75. D. K. Hazra and S. Steenken, *J. Am. Chem. Soc.*, **105**, 4380 (1983).
76. E. Hayon and M. Simic, *J. Am. Chem. Soc.*, **95**, 1029 (1973).
77. S. V. Jovanovic and M. G. Simic, *J. Am. Chem. Soc.*, **108**, 5968 (1986).
78. L. M. Theard, F. C. Peterson and L. S. Myers Jr., *J. Phys. Chem.*, **75**, 3815 (1971).
79. P. C. Shragge and J. W. Hunt, *Radiat. Res.*, **60**, 233 (1974).
80. A. Hissung and C. von Sonntag, *Z. Naturforsch.*, **40C**, 925 (1985).
81. M. Al-Sheikhly and C. von Sonntag, *Z. Naturforsch.*, **38B**, 1622 (1983).
82. M. N. Schuchmann, M. Al-Sheikhly, C. von Sonntag, A. Garner and G. Scholes, *J. Chem. Soc., Perkin Trans. 2*, 1777 (1984).
83. S. N. Bhattacharyya and P. C. Mandal, *J. Chem. Soc., Faraday Trans. 1*, **79**, 2613 (1983); **80**, 1205 (1984).
84. A. Hissung and C. von Sonntag, *Int. J. Radiat. Biol.*, **35**, 449 (1979).
85. E. Hayon, *J. Chem. Phys.*, **51**, 4881 (1969).
86. S. Das, D. J. Deeble, M. N. Schuchmann and C. von Sonntag, *Int. J. Radiat. Biol.*, **46**, 7 (1984).
87. D. J. Deeble, S. Das and C. von Sonntag, *J. Phys. Chem.*, **89**, 5784 (1985).
88. G. E. Adams and R. L. Wilson, *Int. J. Radiat. Biol.*, **22**, 589 (1972).
89. K. Bhatia and R. H. Schuler, *J. Phys. Chem.*, 77, 1888 (1973).
90. B. D. Wagner and D. Schulte-Frohlinde, *Ber. Bunsenges. Phys. Chem.*, **79**, 589 (1975).
91. E. Rivera and R. H. Schuler, *J. Phys. Chem.*, **87**, 3966 (1983).
92. H. Loman and M. Ebert, *Int. J. Radiat. Biol.*, **18**, 369 (1970).
93. G. A. Infante, E. J. Fendler and J. H. Fendler, *Radiat. Res. Rev.*, **4**, 301 (1973).
94. G. A. Infante, P. Jirathana, E. J. Fendler and J. H. Fendler, *J. Chem. Soc., Faraday Trans. 1*, **70**, 1162 (1974).
95. K. M. Idris Ali and G. Scholes, *J. Chem. Soc., Faraday Trans. 1*, **76**, 449 (1980).
96. S. Fujita, *Int. J. Radiat. Biol.*, **42**, 205 (1982).
97. K. M. Idris Ali, *Radiat. Res.*, **20**, 84 (1979).
98. M. N. Schuchmann and C. von Sonntag, *J. Chem. Soc., Perkin Trans. 2*, 1525 (1983).
99. S. Nishimoto, H. Ide, T. Wada and T. Kagiya, *Int. J. Radiat. Biol.*, **44**, 585 (1983).
100. M. Dizdaroglu and M. G. Simic, *Int. J. Radiat. Biol.*, **46**, 241 (1984).
101. R. Teoule and J. Cadet, *J. Chem. Soc., Chem. Commun.*, 1269 (1971); *in Effects of Ionizing Radiation on DNA* (Eds. J. Hüttermann, W. Kohnlein, R. Teoule and A. J. Bertinchamps), Springer, Berlin, 1978, p. 171.
102. M. Dizdaroglu and M. G. Simic, *Radiat. Res.*, **100**, 41 (1984).
103. M. Polverelli and R. Teoule, *Z. Naturforsch.*, **29C**, 16 (1974).

104. H. Riederer and J. Hüttermann, *J. Phys. Chem.*, **86**, 3454 (1982).
105. M. Dizdaroglu and M. G. Simic, *Radiat. Phys. Chem.*, **26**, 309 (1985).
106. L. R. Karam, M. G. Simic and M. Dizdaroglu, *Int. J. Radiat. Biol.*, **49**, 67 (1986).
107. S. Nishimoto, H. Ide, K. Nakamichi and T. Kagiya, *J. Am. Chem. Soc.*, **105**, 6740 (1983).
108. F. Busi, V. Concialini, O. Tubertini and M. D'Angelantonio, *Radiat. Phys. Chem.*, **34**, 857 (1989).
109. J. Cadet, *Z. Naturforsch.*, **35b**, 1579 (1980).
110. S. N. Bhattacharyya, P. C. Mandal and S. Aditya, *Radiat. Eff. Express*, **1**, 201 (1988).
111. S. N. Bhattacharyya and P. C. Mandal, *Radiat. Eff.*, **91**, 9 (1985).
112. A. O. Allen, *The Radiation Chemistry of Water and Aqueous Solutions*, Van Nostrand, New York, 1961, p. 11.
113. M. G. Simic and M. Dizdaroglu, *Biochemistry*, **24**, 233 (1985).
114. S. A. Margolis, B. Coxon, E. Gajewski and M. Dizdaroglu, *Biochemistry*, **27**, 6353 (1988).
115. M. Dizdaroglu and M. G. Simic, *Int. J. Radiat. Biol.*, **47**, 63 (1985); *Radiat. Phys. Chem.*, **26**, 309 (1985).
116. S. W. Benson, *The Foundations of Chemical Kinetics*, McGraw-Hill, New York, 1960, p. 154.
117. J. F. Ward and I. Kuo, *Radiat. Res.*, **31**, 651 (1967).
118. J. F. Ward and I. Kuo, *Adv. Chem. Ser.*, **81**, 368 (1968).
119. J. F. Ward and I. Kuo, *Int. J. Radiat. Biol.*, **15**, 293 (1969); *Int. J. Radiat. Biol.*, **18**, 381 (1970).
120. G. G. Jayson, B. J. Parsons and A. J. Swallow, *J. Chem. Soc., Faraday Trans. 1*, **68**, 1597 (1973).
121. L. K. Patterson, K. M. Bansal, G. Bogan, G. A. Infante, E. J. Fendler and J. H. Fendler, *J. Am. Chem. Soc.*, **94**, 9028 (1972).
122. O. P. Chawla and R. W. Fessenden, *J. Phys. Chem.*, **79**, 2693 (1975).
123. T. Masuda, T. Kimura, E. Kadoi, T. Takahashi, K. Yamauchi and M. Kondo, *Radiat. Res.*, **24**, 165 (1983); T. Takahashi, K. Yamauchi and T. Masuda, *Bull. Chem. Soc. Jpn.*, **58**, 223 (1985).
124. K. M. Bansal and R. W. Fessenden, *Radiat. Res.*, **75**, 497 (1978).
125. D. M. Sevilla, D. Suryanavayana and K. M. Morehouse, *J. Phys. Chem.*, **85**, 1027 (1981).
126. J. H. Fendler and L. K. Patterson, *J. Phys. Chem.*, **74**, 4608 (1970).
127. H. P. Schuchmann, D. J. Deeble, G. Olbrich and C. von Sonntag, *Int. J. Radiat. Biol.*, **51**, 441 (1987).
128. M. J. Davies and B. C. Gilbert, *J. Chem. Soc., Perkin Trans. 1*, 1809 (1984).
129. S. V. Jovanovic and M. G. Simic, *J. Phys. Chem.*, **90**, 974 (1986).
130. S. N. Bhattacharyya and P. C. Mandal, *Radiat. Eff.*, **91**, 9 (1985).
131. G. A. Infante, P. Jirathana, E. J. Fendler and J. H. Fendler, *J. Chem. Soc., Trans. Faraday Soc. 1*, **70**, 1162 (1974).
132. Z. B. Alfassi, R. R. Huie and P. Neta, *J. Phys. Chem.*, **90**, 4156 (1986).
133. P. C. Shragge, A. J. Varghese, J. W. Hunt and C. L. Greenstock, *Radiat. Res.*, **60**, 250 (1974).
134. R. Teoule, *Radiational Research*, Proc. Sixth Int. Congress Radiat. Res. May 13–19, 1979, Tokyo, Springer-Verlag, p. 400.
135. S. N. Bhattacharyya and P. C. Mandal, *Indian J. Phys.*, **58A**, 339 (1984).
136. S. N. Bhattacharyya and P. C. Mandal, *J. Chem. Soc., Faraday Trans. 1*, **79**, 2613 (1983).
137. S. N. Bhattacharyya and P. C. Mandal, *Int. J. Radiat. Biol.*, **43**, 141 (1983).
138. S. Steenken, *Chem. Rev.*, **89**, 503 (1989).
139. P. M. Moorthy and E. J. Hayon, *J. Am. Chem. Soc.*, **97**, 3345 (1975).
140. A. Hissung, C. von Sonntag, D. Veltwisch and K. D. Asmus, *Int. J. Radiat. Biol.*, **39**, 63 (1981).
141. K. J. Visscher, M. P. de Haas, H. Loman, B. Vojnovic and J. Warman, *Int. J. Radiat. Biol.*, **52**, 745 (1987); K. J. Visscher, M. Hom, H. Loman, H. J. W. Spoedler and B. J. Verberne, *Radiat. Phys. Chem.*, **32**, 4 (1988).
142. M. Eigen, *Angew. Chem.*, **75**, 489 (1963).
143. J. W. Alberg, *Ann. Rev. Phys. Chem.*, **31**, 227 (1980).
144. P. Neta, *Radiat. Res.*, **52**, 471 (1972).
145. T. Rakowsky and J. K. Dohrmann, *Ber. Bunsenges. Phys. Chem.*, **83**, 495 (1979).
146. A. J. S. C. Vieira and S. Steenken, *J. Am. Chem. Soc.*, **109**, 7441 (1987).
147. P. O'Neill, P. W. Chapman and D. G. Papworth, in *Free Radicals in Biology and Medicine*, Harwood, Chur, 1985, p. 62.
148. A. J. S. C. Vieira and S. Steenken, *J. Phys. Chem.*, **91**, 4138 (1987).
149. J. J. van Hemmen, *Int. J. Radiat. Biol.*, **27**, 403 (1975)
150. P. O'Neill and P. W. Chapman, *Int. J. Radiat. Biol.*, **47**, 71 (1985).

151. P. O'Neill and S. E. Davies, *Int. J. Radiat. Biol.*, **49**, 937 (1986).
152. P. O'Neill, *Radiat. Res.*, **96**, 198 (1983).
153. J. J. van Hemmen and J. F. Bleichrodt, *Radiat. Res.*, **46**, 444 (1971).
154. M. Berger and J. Cadet, *Z. Naturforsch.*, **40b**, 1519 (1985).
155. M. D. Sevilla, R. Failor, C. Clark, C. Holroyd and M. Pettei, *J. Phys. Chem.*, **80**, 353 (1976).
156. K. J. Visscher, H. J. W. Spoelder, H. Loman, A. Hummel and M. L. Hom, *Int. J. Radiat. Biol.*, **54**, 787 (1988).
157. S. Gregoli, M. Olast and A. Bertinchamps, *Radiat. Res.*, **70**, 255 (1977); **77**, 417 (1979); **89**, 238 (1982).
158. (a) B. Rakvin and J. N. Herak, *Radiat. Phys. Chem.*, **22**, 1043 (1983).
(b) B. Lamotte and P. Servoz-Gavin, *Proc. Tihany Symp. Radiat. Chem., 2nd Tihany, Hungary, 1966*, 223 (1967).
159. T. Blum, A. R. McGhie, A. Kawada and M. M. Labes, *J. Chem. Phys.*, **53**, 4097 (1970).
160. U. R. Bohme, *J. Chem. Phys.*, **55**, 3614 (1971).
161. P. Gloux and B. Lamotte, *Mol. Phys.*, **24**, 23 (1971).
162. B. Lamotte and G. Gloux, *J. Chem. Phys.*, **59**, 3365 (1973).
163. T. Maekawa, J. G. Webster and I. Miyagawa, *Radiat Res.*, **78**, 371 (1979).
164. F. Q. Ngo, E. E. Budzinski and H. C. Box, *J. Chem. Phys.*, **60**, 3373 (1974).
165. J. Y. Lee and H. C. Box, *J. Chem. Phys.*, **59**, 2509 (1973); H. C. Box and E. E. Budzinski, *J. Chem. Phys.*, **55**, 246 (1971).
166. H. C. Box, H. G. Freund and K. T. Lilga, *J. Chem. Phys.*, **46**, 2130 (1967).
167. A. Samuni and P. Neta, *J. Phys. Chem.*, **77**, 1629 (1973).
168. P. S. Rao, M. Simic and E. Hayon, *J. Phys. Chem.*, **79**, 1260 (1975).
169. K. M. Bansal and R. M. Sellers, in *Fast Processes in Radiation Chemistry and Biology* (Eds. G. E. Adams, E. M. Fielden and B. D. Michael), Wiley, London, 1975, p. 259.
170. K. M. Bansal and R. M. Sellers, *J. Phys. Chem.*, **79**, 1775 (1975).
171. M. Faraggi and A. Bettelheim, *Radiat. Res.*, **71**, 311 (1977).
172. J. B. D'Arcy and M. D. Sevilla, *Radiat. Phys. Chem.*, **13**, 119 (1979).
173. J. Kopoldova and S. Heneir, *Z. Naturforsch, C*, **32C**, 482 (1977).
174. E. P. Petryaev, A. E. Pavlov and O. I. Shadyro, *Khim. Vys. Energ.*, **17**, 552 (1983) [*High Energy Chem. (Engl. Transl.)*, **17**, 434 (1983)].

CHAPTER 15

Catalysis by amidines

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I. INTRODUCTION

In this chapter catalysis by derivatives of formamidine (**1**), guanidine (**2**) and imidic acid (**3**) is reviewed. Such compounds may act as bases and nucleophiles. Protonation yields the corresponding derivatives of **4–6**. Depending on the substitution pattern of the derivatives of **1–3** new acidic hydrogens are created upon mono-protonation. Some of these may be bonded to nitrogen or oxygen remote from the basic atom being protonated. These features suggest that such compounds may act as bifunctional (polyfunctional) acid–base catalysts[1–3]. Their geometries indicate that they may function as bifunctional acid–base catalysts in various 1,3-hydron[4] transfer reactions. One of the hydron transfers could be catalyzed by the other one. Such catalysis is considered to be of great importance in, e.g., enzyme catalysis. Derivatives of **1–3** have been designed as models of enzyme catalysis.

The imino-nitrogens in **1–3** may also act as nucleophiles and, upon the nucleophilic

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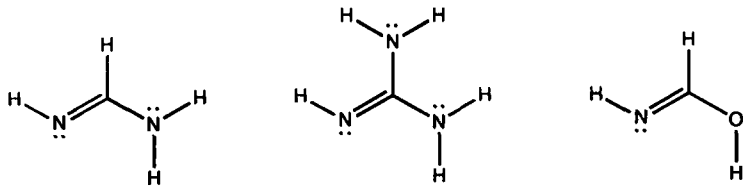

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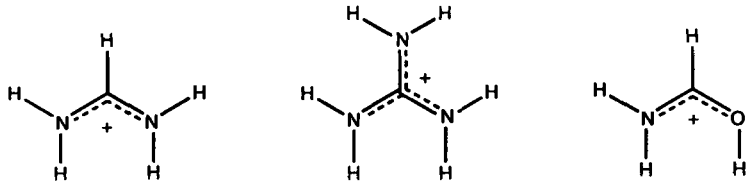


(4) (5) (6)

attack, acidic hydrogens are created which may catalyze the nucleophilic attack on suitable substrates like esters, etc., by interaction with, e.g., oxygens.

Although imidazoles are related to amidines and play important roles in the catalysis by many enzymes, their catalysis is not reviewed here.

The present review emphasizes the bifunctional aspects of the catalysis of derivatives of compounds **1–3** but does not completely ignore that they may operate as monofunctional acid–base catalysts. In most applications of compounds **1–3** as catalysts it is not mechanistically clear whether the catalysis is of bi- or monofunctional nature. We are here particularly reviewing results of studies aimed at elucidating mechanisms of catalysis.

II. BIFUNCTIONAL CATALYSIS

A. Two-hydron Transfers

1. Allylic rearrangements involving transfers from and to carbons and nitrogens

According to Woodward and Hoffmann, suprafacial 1,3-sigmatropic shifts are symmetry forbidden[5]. As a consequence, uncatalyzed 1,3-sigmatropic shifts are high barrier processes. There have been attempts to circumvent this symmetry forbiddenness, e.g. by

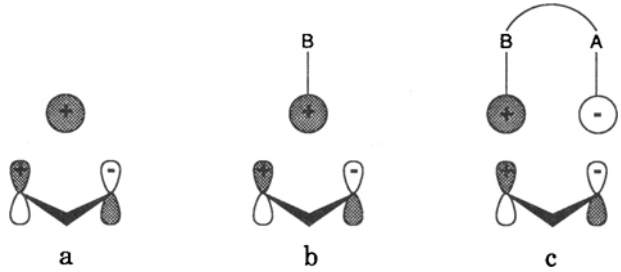
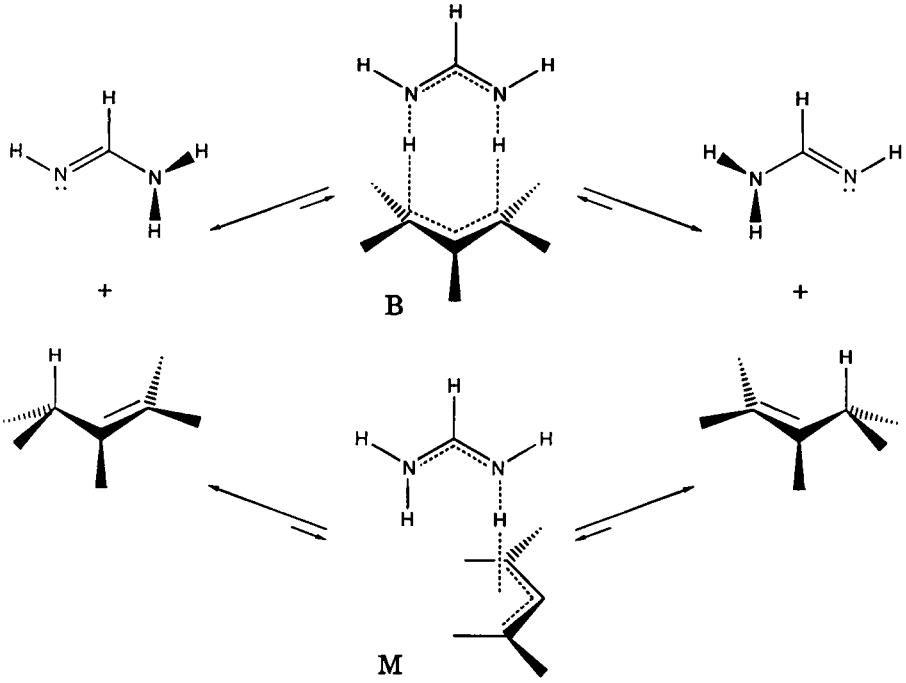


FIGURE 1. Illustration of interactions in important orbitals involved in (a) uncatalyzed, (b) monofunctionally catalyzed and (c) bifunctionally catalyzed 1,3-hydron transfer reactions

using amidines as catalysts and 'open up' an allowed pseudo-pericyclic rearrangement route as illustrated in Figure 1[6-15].

Secondary amidines have the potential possibility to perform 1,3-hydron transfer in propenes in a bifunctional manner besides a monofunctional mechanism as shown in Scheme 1.

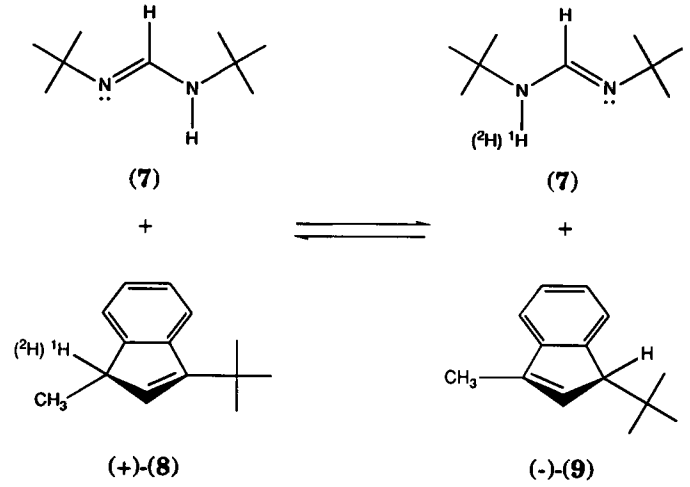


SCHEME 1

If an amidine acts in a bifunctional manner, i.e. the catalysis takes place through a cyclic transition state (cf. the B-transition state in Scheme 1), deuterium labelling in the proper positions of either substrate or catalyst would result in products with the deuterium in the base or the substrate, respectively. This predicted experimental outcome of bifunctional catalysis is quite different from that expected if the amidine is operating as a monofunctional catalyst, i.e. with an M-like transition state (Scheme 1). In monofunctional catalysis a deuterium-labelled catalyst will stay labelled when operating on an unlabelled substrate and *vice versa*. Of course, more complex experimental results could be found than the two extreme types discussed above, e.g. if the M and B routes and/or other exchange reactions compete with each other.

The first study of the detailed mechanism of secondary amidine catalyzed 1,3-hydron transfer was performed with *N,N'*-di-*t*-butylformamidine (**7**) with racemic and optically active 3-*t*-butyl-1-methylindene (**8**) in benzene, dioxane and dimethyl sulfoxide (DMSO) using GLC and polarimetry[6]. The rearrangement of **8** to 1-*t*-butyl-3-methylindene (**9**) was found to be highly stereospecific in benzene and dioxane, i.e. (+)-**8** rearranges into (−)-**9** as shown in Scheme 2.

The stereospecificity determined using polarimetry and a high-precision equilibration method at 60 °C was found to be > 99.96% and > 99.90% in benzene and dioxane, respectively. Thus the 1,3-hydron transfer proceeds in a suprafacial manner consistent



SCHEME 2

with a bifunctional mechanism. However, the same stereochemistry has previously been found by Bergson and coworkers and by Cram and coworkers for monofunctional amine-catalyzed rearrangements in the present and other indene systems[16-20].

In DMSO, on the other hand, the 7-catalyzed rearrangement of **8** is nearly nonstereospecific.

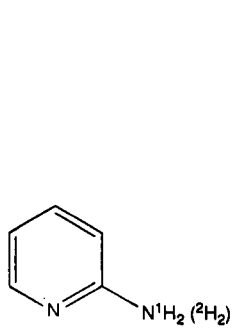
To obtain further information about the 7-catalyzed rearrangement of **8**, isotope labelling experiments were designed. A benzene solution of pure racemic **^{2}H-8** (0.1 M) and **7** (1.0 M) was reacted for 16 hours at 25.0 °C. The reaction mixture was quenched and analyzed by GLC, which showed that 12.5% had isomerized to **9**. Preparative GLC isolation of nonisomerized material and analysis of the deuterium content by mass spectrometry showed that 44.2% of the deuterium were exchanged with protium[6].

Also, when pure (+)-**^{1}H-8** (0.1 M) was reacted with **7**, deuterium-labelled at the nitrogen, at 25 °C, rapid exchange of the starting material accompanied the highly stereospecific isomerization. This interference of exchange with the rearrangement made it difficult to conclude about the detailed mechanism of the rearrangement. The exchange was suggested to proceed via ion-pairs or through a concerted reaction as discussed below. Possible conformational equilibria and dimerization of the catalyst were also discussed.

The bifunctional and monofunctional routes of formamidine-catalyzed 1,3-hydron transfer of propene have been studied quantum chemically by the CNDO/2 MO method. Application of this crude method indicated that the transition state for monofunctional catalysis (M) has considerably higher energy than that for the bifunctional route (B) (cf. Scheme 1)[7,8].

To avoid possible steric problems with **7** that may cause the exchange reactions to be faster than the rearrangement, catalysis by 2-aminopyridine (**10**) was investigated. Thus **$^1H_2$-10** and its isotopomer *N,N*-**$^2H_2$**-2-aminopyridine (**$^2H_2$-10**) have been studied as catalysts for 1,3-hydron transfer reactions of the substrates **11** and **13**[9].

β-9-Fluorenylstyrene (**11**) was rearranged into 9-*β*-phenylethylidenefluorene (**12**) and 1-methylindene (**^{1}H-13**) and 1-deuterio-1-methylindene (**^{2}H-13**) to 3-methylindene (**^{1}H-14**) and 1-deuterio-3-methylindene (**^{2}H-14**), respectively. Based upon this observed absence of $^1H/^2H$ exchange in the reactions, compound **10** was concluded to act as a monofunctional catalyst and not as a bifunctional one.



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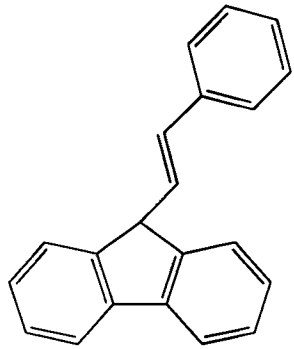

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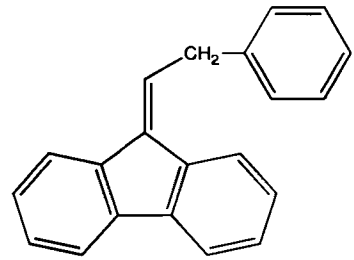

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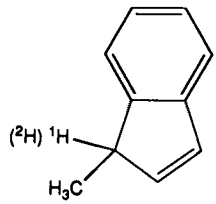
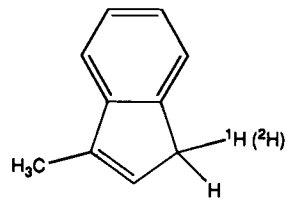




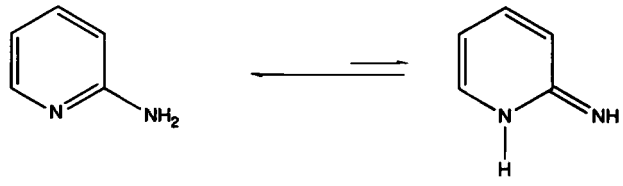
The activation parameters, the isotope effect and rate dependence on the base concentration for the **10**-catalyzed rearrangement of ^{1}**H-13** to ^{1}**H-14** have been measured. The deuterium isotope effect showed that the hydron abstraction is rate limiting.

It is not clear why the M-route is the preferred one but a number of possible reasons have been analyzed. Compound **10** is in tautomeric equilibrium with the amidine **15** (Scheme 3) but **10** is strongly favored in the equilibrium, at least in water ($\Delta G = 7.3$ kcal mol^{-1}). Therefore, protonation with 2-aminopyridinium ion to yield **10** is expected to be preferred over the route yielding **15**. Thus this thermodynamics might contribute in favoring the monofunctional route.

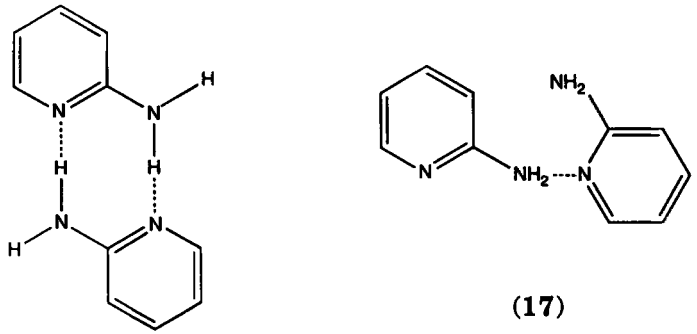
Amidines may form cyclic and linear dimers in solution. The cyclic dimers (**16**) are expected to be much weaker catalysts than the linear dimers (**17**) which are predicted to be catalytically more active than the monomers. The rate dependence of the rearrangement of ^{1}**H-13** on the concentration of ^{1}**H$_2$-10** indicates that linear dimers contribute substantially to the catalysis. Another reason for why the experimental results contrast those found theoretically is that the substrates resemble cyclopentadiene rather than propene and thus have a more delocalized carbanion. All these facts are expected to favor monofunctional rather than bifunctional catalysis.

2-Aminopyridine (**10**) has been reported to be a bifunctional acid–base (tautomeric) catalyst for the mutarotation of the aldohexose tetramethylglucose (TMG) by Swain and Brown[21,22]. However, this result has been questioned by Rony and Neff, who concluded that **10** is not to be considered a tautomeric catalyst of that reaction[23–25].

With the aim to favor the bifunctional route the following reaction system was developed[10,11]. The bicyclic secondary amidine (**18**) was synthesized. This catalyst shows symmetry with respect to the tautomeric equilibrium (Scheme 4) and has well-defined stereochemistry. In the cyclic dimers (**19**) the nitrogen lone pairs are occupied by hydrogen bonds and therefore these dimers are not expected to be catalytically active. The linear dimers (**20**) are presumably not catalytically active for steric reasons. Thus **18** was designed to favor the B-route (Scheme 1) and also for making it possible to pull protons from rather weak carbon acids. 1,3,3-Triphenylpropene (**21**) and benzene were chosen as substrate and

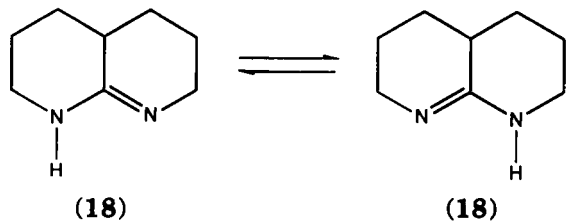


(10) (15)

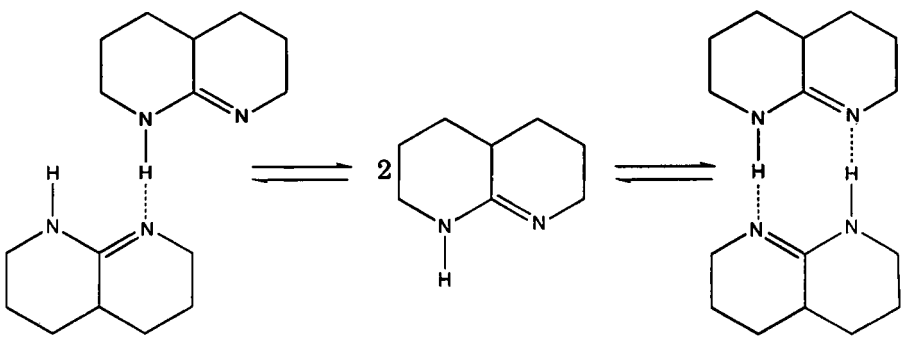


(16) (17)

SCHEME 3



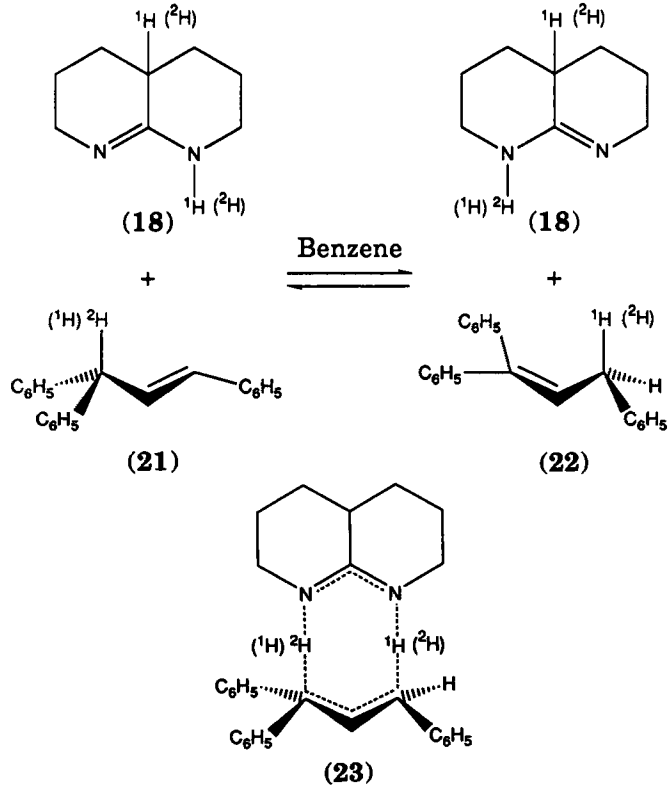
(18) (18)



(20) (18) (19)

SCHEME 4

solvent, respectively[10]. The amidine $^1H_2$-**18** was found to catalyze the rearrangement of ^{2}H-**21** into 1,1,3-triphenylpropene (**22**) in benzene at 75 °C. The reaction mixture was initially 1 M in the catalyst $^1H_2$-**18** and 0.05 M in the substrate ^{2}H-**21** (Scheme 5). After *ca* 1 hour the reaction mixture was quenched and the mixture of isomeric propenes was isolated. Analysis by GLC showed that 40% of ^{2}H-**21** had rearranged to **22**. The propenes were separated by preparative GLC and analyzed by ^{1}H NMR spectroscopy. Within experimental error the fraction containing **21** consisted solely of the deuterated starting material ^{2}H-**21** whereas the fraction containing **22** was largely (93%) the nondeuterated compound ^{1}H-**22**.



SCHEME 5

In a separate experiment employing ^{2}H-**22** and $^1H_2$-**18** it was shown that exchange of the carbon-bonded deutron with the amidine proton was much slower than the rate of catalyzed isomerization of ^{2}H-**21** to **22**.

These results indicated for the first time that the rearrangement is bifunctionally rather than monofunctionally catalyzed and might involve an activated complex such as **23**. In **23** the two hydrons are transferred concertedly[10].

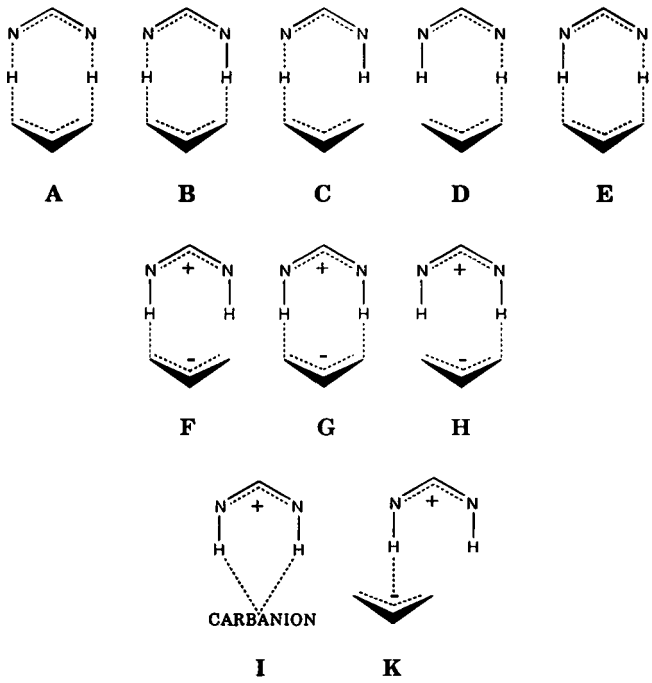
In a recent paper a full report has been provided on the ^{2}H-labelling experiments and kinetic deuterium isotope effects for this bifunctional catalysis. A detailed understanding of the reaction mechanism and its transition states have emerged[11].

To avoid misinterpretations caused by unexpected isotope effects, the following 'mirror'

isotope experiment was carried out. A mixture which initially was 0.49 M in the ^{2}H-labelled catalyst ($^2H_2$-**18**) and 0.06 M in the nonlabelled substrate (^{1}H-**21**) in benzene was reacted at 75 °C and quenched and analyzed as above. The isolated product mixture consisted of 23% **21** and 77% **22**. The product **22** was composed of 42% ^{2}H-**22** and 58% ^{1}H-**22**. No trace of $^2H_2$-**22** could be detected by ^{1}H NMR. Similar experiments were carrried out at 25 °C. At this temperature the bifunctionality was less pronounced and also some $^1H/^2H$ exchange of the starting material **21** was observed.

These labelling experiments show conclusively that at least a substantial fraction of this amidine-catalyzed rearrangement is bifunctional in nature. However, the results also clearly show considerable interference from isotope exchange and/or monofunctionally catalyzed rearrangements.

In the light of these results, a number of transition-state structures for the rearrangements and exchange reactions were considered (Scheme 6).



SCHEME 6

In addition to structure **A** (cf. structure **23**), in which there is a concerted transfer of the two hydrons from and to carbons and nitrogens, transition states **B–E**, involving nonconcerted 1,3-hydron transfers, are possible representations. In structure **B** the 3-hydrogen of the carbon acid is in transit but the NH binds only to the C-1 with an asymmetric hydrogen bond. In **C**, on the other hand, the 3-hydron is being transferred but no NH···C bond has developed in the transition state. Structure **D** depicts a transition state in which the 3-hydron of the propene has been transferred completely to nitrogen and the other hydron originally bonded to N is in transit. In transition state **E** a hydrogen bond remains between C-3 and the NH group, while the other N-hydron is in transit.

Any of the transition states **A**–**E** could be thought of as being possible rate-limiting transition state for the rearrangement. The transition states **B**–**E** may lead to ion-pair intermediates such as **F**–**H** (Scheme 6). The observed exchange is possibly the consequence of exchange within such ion-pairs via transition states of type **I**. Monofunctionally catalyzed rearrangement may also involve intermediates of the type **F**–**G** and a transition state such as **K**. Hence, in addition to the possibility that the exchange and rearrangement processes are independent reactions, they could be coupled, e.g. stepwise processes employing common transition states and intermediates.

An obvious source of further mechanistic information is kinetic deuterium isotope effects[26]. However, the knowledge of the relationships between transition state structures and such isotope effects for concerted two-hydron transfer reactions is limited. Deuterium isotope effects were measured at 25 °C. A quench-extraction capillary GLC procedure was used to obtain accurate kinetics. Complications due to exchange and reversibility of the rearrangement were avoided by running the rearrangement for only about 4%. The results are summarized in Table 1[11].

For the interpretation of these isotope effects the nature of the amidine catalyst **18** (cf. Scheme 4) was investigated. The NH ^{1}H NMR chemical shift was measured as a function of the concentration of **18**. The data showed that **18** is considerably dimerized and from these data the dimerization constant for **18** and the monomer concentrations at various amidine concentrations were calculated. These results in combination with the knowledge of the dependence of the rearrangement rate constant on the concentration of **18** formed the basis of the conclusion that the catalyst for the rearrangement is monomeric **18**.

The data in Table 1 excluded the concerted two-hydrogen transfer mechanism. The main evidence against such a mechanism was the observed large difference between k_{1H^2H}/k_{1H^2H} (6.56) and k_{1H^2H}/k_{1H^2H} (1.19). A concerted transfer is expected to yield $k_{1H^1H}/k_{2H^1H} \approx k_{1H^1H}/k_{1H^2H}$ if the transition state is symmetric with respect to the hydron transfers (cf. **23** in Scheme 5 and **A** in Scheme 6).

Instead, it was concluded, on the basis of the pronounced difference between these isotope effects, that the abstraction of the 3-hydron from **21** is rate limiting. The second hydron is not transferred simultaneously but it may assist the abstraction of the 3-hydron from **21** by hydrogen bonding (cf. **B** and **C** in Scheme 6), thereby giving rise to a secondary isotope effect. Also, the other isotope effects in Table 1 are consistent with such a mechanistic picture and thus suggest a stepwise mechanism.

In summary, the stepwise mechanism gets support from the similarly of pK_a values of **21** and **22** and the asymmetry of the two hydron transfers in combination with the accompanying hydrogen exchange reaction. It seems plausible that the rearrangement employs one or more ion-pair intermediates and that transition state **B** or **C** is rate limiting and that **D** or **E** is populated in the hydronation of the intermediate preceding **22**. It seems likely that an ion-pair with two hydrogen bonds (cf. **G** in Scheme 6) is on the reaction coordinate. Ion-pairs were assumed to participate in the exchange reactions (cf. **I** in Scheme 6).

A more detailed analysis of the isotope effects favored a stepwise mechanism with two rate-limiting transition states, e.g. **B** and **E** (or **C** and **D**). But **E** or **D** are minor contributors.

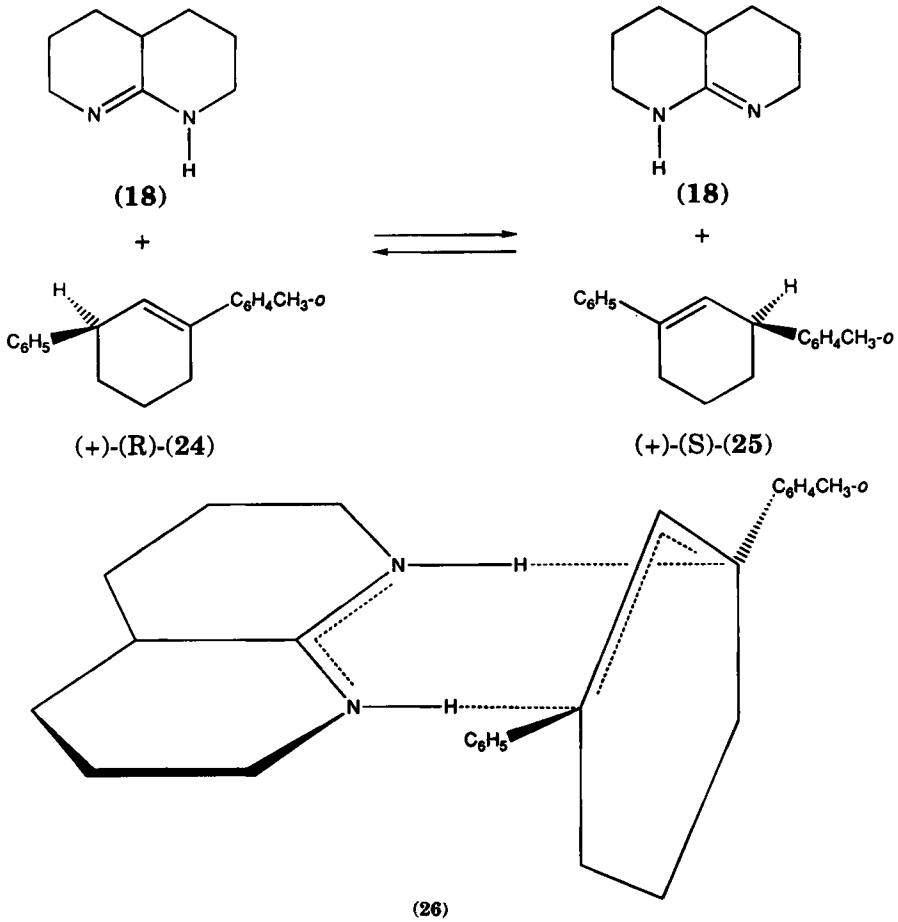
TABLE 1. Deuterium kinetic isotope effects at 25.00 °C for the Scheme 5 reaction system[a]

k_{1H^1H}/k_{2H^1H}	k_{1H^1H}/k_{1H^2H}	k_{1H^1H}/k_{2H^2H}	k_{1H^2H}/k_{2H^2H}	k_{2H^1H}/k_{2H^2H}
6.56	1.19	7.08	5.94	1.08

[a]The first superscript refers to the substrate and the second to the catalyst.

So far all amidine catalyzed 1,3-hydron transfers from carbon to carbon seem to make use of stepwise mechanisms but, under favorable conditions, bifunctional mechanisms are employed. Why are stepwise processes the low-energy pathways rather than concerted mechanisms in which the two hydrons are transferred simultaneously from carbon to nitrogen and from nitrogen to carbon? It is known that in monofunctional catalysis by, e.g., amines there is a barrier towards protonation of the carbanion by the aminium ion in the intermediate. Therefore, it seems reasonable to assume that there also should be a barrier for monofunctional protonation of the substituted allyl anions by amidinium ions. In the rate-limiting transition state neither the allyl anion nor the amidinium ion is fully developed. As a consequence, concerted two-hydron transfer is predicted to have a considerably higher barrier than each of the stepwise processes[11].

Recent high level *ab initio* calculations of formamidine catalyzed 1,3-hydron transfer of propene indicate an asymmetric transition state structure (cf. **B** in Scheme 6) and an intermediate which is essentially composed of an allyl anion hydrogen bonded by two hydrogen bonds to the amidinium ion (cf. **G** in Scheme 6)[27].



SCHEME 7

The stereochemistry of the reversible 1,3-hydron transfer of 3-phenyl-1-(2-tolyl) cyclohexene (**24**) to 1-phenyl-3-(2-tolyl)cyclohexene (**25**), catalyzed by **18** (Scheme 7), has been studied in benzene using a novel method. The stereospecificity was determined by reversibly rearranging partially-resolved **24** with **18** and by comparing *only* the specific rotation of the starting material **24** with that of **24** recovered after about $4t_{1/2}$. Since a large fraction of recovered **24**-molecules had been converted to **25** one or more times, the specific rotation of these molecules is affected by the stereospecificity of the reaction. A novel method, in which a reversible reaction is regarded as a series of irreversible processes, has been used to calculate the fraction of **24**-molecules that has been **25** one or more times, and with these results an accurate lower limit for the stereospecificity of the 1,3-hydron transfer was determined to be $> 98.4\%$[12].

The absolute stereochemistry of this 1,3-hydron transfer, i.e. if it takes place mainly suprafacially or antarafacially, was determined using resolved **24** and **25**. Since (+)-(*R*)-**24** is found to rearrange mainly into (+)-(*S*)-**25**, and since their absolute stereochemistries were determined, it was clear that the reaction takes place mainly suprafacially and possibly via structures like **26**.

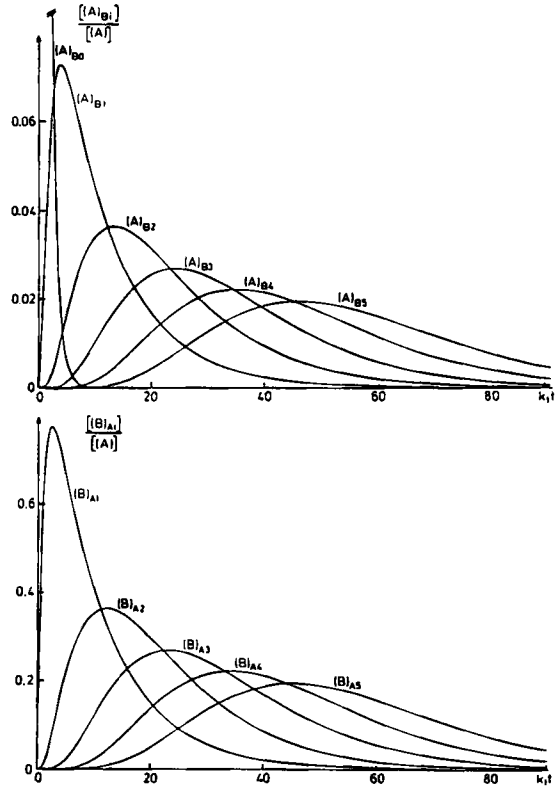


FIGURE 2. Dependence of $[(A)_{Bi}]/[(A)]$ and $[(B)_{Ai}]/[(A)]$ on k_1t for reversible first-order or pseudo-first-order reactions having $K = k_1/k_{-1} = 10$. The curves make up a universal representation of all such reactions with $K = 10$ in the sense that the curve set is independent of the absolute values of k_1 and k_{-1}

In the novel method employed reversible reactions:

$$(A) \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (B)$$

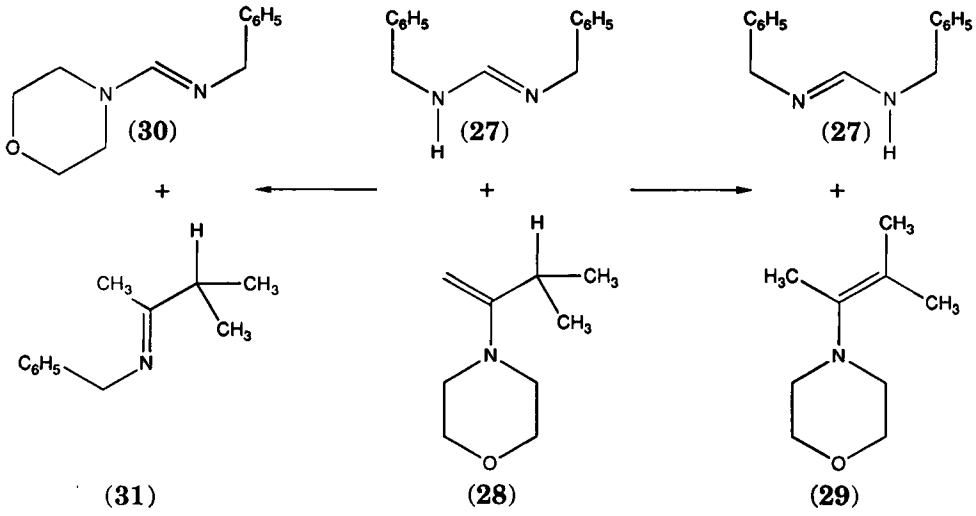
were regarded as a series of irreversible processes, i.e.

$$(A)_{B0} \xrightarrow{k_1} (B)_{A1} \xrightarrow{k_{-1}} (A)_{B1} \xrightarrow{k_1} (B)_{A2} \cdots$$
$$\xrightarrow{k_{-1}} (A)_{Bi-1} \xrightarrow{k_1} (B)_{Ai} \xrightarrow{k_{-1}} (A)_{Bi} \xrightarrow{k_1} (B)_{Ai+1}$$
$$\xrightarrow{k_{-1}} \text{etc.}$$

$(A)_{B0}$-molecules [(A)-molecules that have been (B) zero times] are, of course, irreversibly transformed into $(B)_{A1}$-molecules [(B)-molecules that have only been (A) once] and these, in turn, into $(A)_{B1}$. $(A)_{Bi}$ and $(B)_{Ai}$ denote those (A)- and (B)-molecules that have been (B) or (A) i times, respectively. This transformation has a formal resemblance with nonbranched radioactive decay, but the rate constants alternate between k_1 and k_{-1}. Solutions of the linear differential equations describing the time dependence of the $(A)_{Bi}$- and $(B)_{Ai}$-molecules and features of these solutions were reported for the general case $K = k_1/k_{-1} \neq 1$ as well as for the special case $K = 1$. These results were used for accurate determination of the stereospecificity of reversible first- and pseudo-first-order reactions. Figure 2 gives an universal representation of all such reactions with $K = 10$[28,29].

This novel model has recently also been applied to chromatography in which molecules are transferred reversibly between mobile and stationary phases. An improved stochastic theory of chromatography emerged and a main result was the derivation of an extended van Deemter equation[30].

The possibility of having bifunctional catalysis of 1,3-hydron transfers from carbon to carbon in some enamines by an amidine has also been investigated. Thus *N,N'*-dibenzylmethaneimidamide (**27**) has been reacted with 4-(1-isopropylvinyl) morpholine (**28**). The 1,3-hydron transfer of **28** to **29** (Scheme 8) is expected to be facilitated by the partial delocalization of the nitrogen lone pair into the olefinic moiety of the enamine. However, instead of observing basic tertiary amidine nitrogen abstraction of the enamine



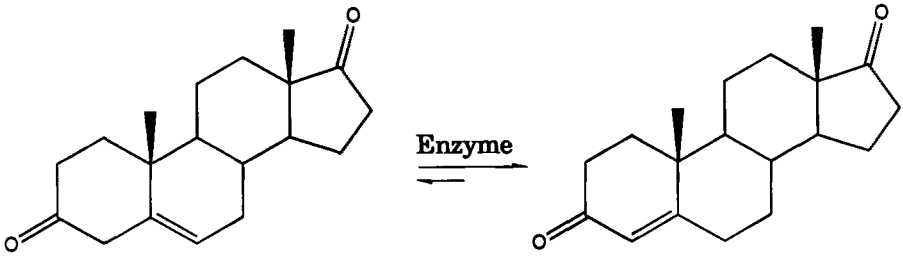
SCHEME 8

hydron and transfer of the nitrogen hydron of the amidine to the olefinic carbon of the enamine, formation of tertiary amidine (**30**) and imine (**31**) resulted. The reaction is further discussed in Section III[31].

Pyridoxamine derivatives have been prepared with acetamidine, guanidine and *N,N,N'*-trimethylethylenediamine covalently attached to the pyridine ring via flexible alkyl- or alkylthio-side chains. These compounds react readily with pyruvic acid in methanol with zinc(II) to afford ketimines, which more slowly isomerize to aldimines in a process that parallels transamination. The isomerization is suggested to be catalyzed by the basic side-chain groups (cf. Section IV)[32].

2. Enolizations and allylic rearrangements involving transfers from and to carbons, nitrogens and oxygens

Many enzyme-catalyzed reactions involve hydrogen bonding between the substrate and the active site in the enzyme and the transfer of one or more hydrons between the species, e.g. isomerization of deconjugated steroid ketones catalyzed by a group of enzymes called Δ^5-3-ketosteroid isomerases. One of these enzymes, isolated from the bacterium *Pseudomonas testosteroni*[33–40], exerts a molecular turnover number of 8.7×10^6/(minute and dimer unit) in the isomerization of androst-5-ene-3,17-dione (**32**) to **33**.



(32) **(33)**

This may be considered a remarkable catalytic activity, since molecular turnover numbers greater than 5×10^6 have not often been observed in enzyme catalysis[40]. The isomerization has also been found to proceed through an intramolecular suprafacial 1,3-hydron transfer[37,41,42]. Although this reaction has been extensively studied, the structure of the active surface of the enzyme and the detailed mechanism of the hydron transfers seem to be obscure and the object of some controversy[42–50].

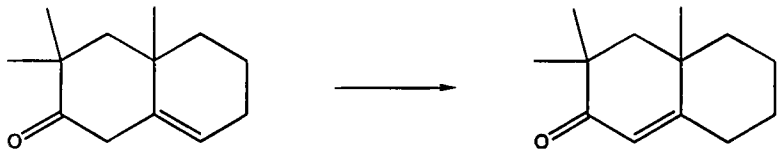
The 1,3-hydron transfer in this reaction also poses problems of special interest, namely the timing of the transfers. Are the two hydrons transferred simultaneously in the same elementary reaction step or do the transfers proceed by a stepwise mechanism? If the high isomerization rate may partly be explained by a concerted 1,3-hydron transfer, how do the transfers depend on each other?

Several attempts have also been made to elucidate the mechanisms operating in acid- and/or base-catalyzed isomerizations of β,γ-unsaturated ketones[42,51–67]. Simultaneous 1,3-hydron transfers have been postulated for the enolization catalyzed by monocarboxylic acids[57], without decisive experimental evidence for such mechanisms.

Kergomard and coworkers[56,59–61,66] have studied the isomerization of β,γ-unsaturated steroid ketones in benzene solution with a variety of potential bifunctionally active catalysts, such as mono- and dicarboxylic acids, phenol–tertiary amine complexes and phosphinic acids. One of the goals of these studies was to design and test bi- and multifunctional catalysts for the isomerization. Indeed, several such catalysts were found and, contrary to what was stated above, dicarboxylic acids, such as tetrafluorosuccinic acid in benzene, were found to lead to reactions that were faster and of lower kinetic order

than those catalyzed by monocarboxylic acids of similar acid strength. When the reaction was catalyzed by monocarboxylic acids, these investigations revealed that two molecules of carboxylic acid were present in the rate-limiting step of the allylic isomerization. It was proposed that this step corresponded to the γ-protonation of the dienol[68], although no experimental results, such as kinetic isotope effect measurements, were published in favor of such a proposal.

For the purpose of detailed mechanistic studies the bicyclic ketone (**34**) was recently designed. It is similar to the A- and B-ring part of a β,γ-unsaturated ketosteroid with dimethylated C-2 position. Synthetic routes to racemic and optically pure **34** has been developed[13,14].

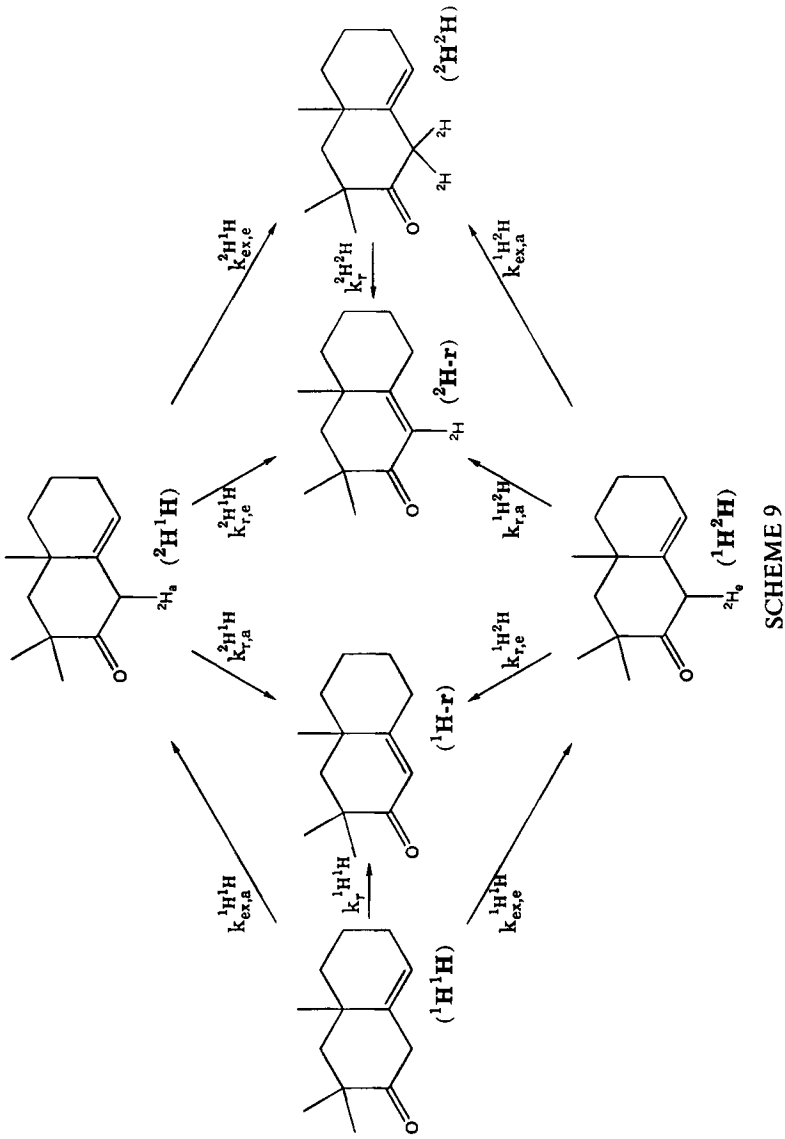


(34) **(35)**

The ketone **34** was found to undergo hydrogen exchange at the α-position as well as isomerization to its conjugated isomer (**35**), when **34** was reacted with bifunctional catalysts such as formamidines and acetic acid. As shown in Scheme 9 the $^1H/^2H$ exchange and isomerization of **34** may result in a product mixture of six detectable components. By a combination of ^1H NMR and GLC analysis, it was possible to calculate the mole fraction of each component in such mixtures. The $^1H/^2H$ exchange at the C-2 position in **34** will produce three different ketones and, together with the unexchanged starting material, this will give the four variants of **34**: $^1H^1H$, $^2H^1H$, $^1H^2H$ and $^2H^2H$. The first capital in each of these symbols relates to the C-2 hydrogen axial to the π-system of the C—C double bond (C-2a-H) (H_a), and the second capital to the corresponding equatorial C-2 hydrogen (C-2e-H) (H_e). If it is assumed that the axial hydrogen is positioned on the same side of the ring plane as the C-6-CH_3 group in **34** (β-side), then these hydrogens may be referred to as the β- and α-hydrogens, respectively. A conformational analysis performed with **34**, by ^1H and ^{13}C NMR and molecular mechanics, did not, however, unequivocally define the C-2a hydrogen as the β-hydrogen.

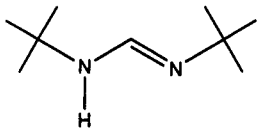
The isomerization of **34** may proceed from all of these nondeuterated, partially deuterated or fully deuterated variants of **34**. As a first approximation, this will give two conjugated ketones, **^1H-r** and **^2H-r**, with protium and deuterium at the C-2 positions, respectively. However, ketone **35** may exist as six isotopomers, since the isomerization of **34** may theoretically proceed by incorporation of either protium or deuterium at the γ-position on each side of the ring plane in **34**. With available analytical techniques, it was not possible to differentiate between the latter structures; only the isotopic substitution pattern at the C-2 position was determined.

Together with isotope labelling and isotope effects the rearrangement of **34** to **35** has the potential for elucidation of detailed mechanisms of catalysis. The action of the catalysts acetic acid, formamidines **7** and **36**, and pyridinium chloride were studied. Acetic acid and **7** were found to catalyze the exchange of C-2 hydrogens in **34** faster than **34** was rearranged to **35** (**^1H-r**). The following experiment was carried out with **7**: An evacuated and sealed-off NMR-tube with a reaction mixture being 0.8 M of **34** and 0.034 M in the catalyst **7** in (^2H)chloroform was placed in a thermostat bath at 25 °C. The ^1H NMR spectrum obtained immediately after the preparation of the mixture showed that no rearrangement to **^1H-r** had taken place but that the N-bonded protium of **7** had been exchanged for deuterium in (^2H)chloroform. Even after 1.5 h essentially no rearrangement product ($\leq$ 1 mol% of **^1H-r**) could be detected but a large fraction of the C-2 protium in **34**

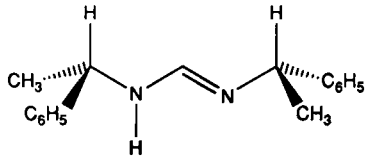

^2H_a ($^2H^1H$)
^2H_e ($^1H^2H$)
($^1H^1H$)
($^2H^2H$)
(^1H-r)
(^2H-r)
$k_{ex,a}^{1H^1H}$
$k_{ex,e}^{1H^1H}$
$k_r^{1H^1H}$
$k_{r,a}^{2H^1H}$
$k_{r,e}^{2H^1H}$
$k_{r,a}^{1H^2H}$
$k_{r,e}^{1H^2H}$
$k_r^{2H^2H}$
$k_{ex,e}^{2H^1H}$
$k_{ex,a}^{1H^2H}$

SCHEME 9

had been exchanged for ^2H. In about 47 mol% of the **34**-molecules both protiums at the C-2 position were exchanged, and in 42 mol% of the molecules only one of these two protiums. After long reaction times, considerable rearrangement to ^{1}**H-r** was observed and at equilibrium no trace of the starting material could be detected by GLC.

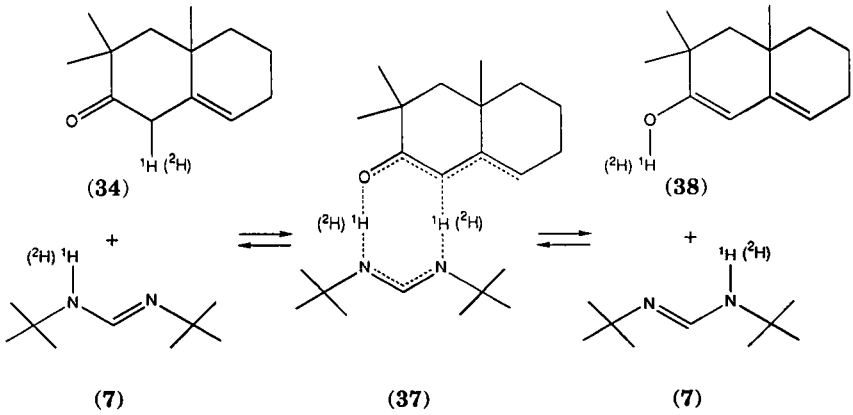


(7)



(36)

The examples of amine-catalyzed isomerization of β,γ-unsaturated ketones found in the literature suggest that a dienolate anion or an iminium ion is involved in such reactions[54,55,62,63,65,67], although this does not necessarily imply that the formamidine-catalyzed $^1H/^2H$ exchange utilizes such intermediates. In view of the effectiveness of this catalyst, the structural complementarity of the catalyst and the substrate, and the fact that extensive $^1H/^2H$ exchange was obtained with only minor concomitant allylic isomerization, a bifunctional concerted mechanism may possibly be in operation. It is possible that the abstraction of the C-2 bonded hydrogen by the imine-N of **7** is assisted by bonding between the N—H group of **7** and the carbonyl-oxygen of **34**. Both hydrons may be in transit (Scheme 10) in the transition state (**37**) and dienol (**38**) is formed as an intermediate. Deuterium could thus be introduced at the 2-carbon of **34** by employing the reverse reaction and amidine **7** labelled with ^2H at the nitrogen. Apart from their mechanistic implications, these results gave a convenient synthetic route to β,γ-unsaturated ketones isotopically labelled at the α-carbon.



(7) **(37)** **(7)**

SCHEME 10

When acetic acid was used both as solvent and catalyst, the paths for exchange and isomerization seemed to compete with each other on almost equal terms. A solution containing 0.35 M of **34** in (O—^2H)acetic acid was reacted at 25 °C for 50 hours. The analysis of the ^1H NMR spectrum of the solution showed that 39 mol% of **34** had rearranged to the α,β-unsaturated ketone, of which approximately 1 mol% contained ^2H at the C-2 position. Moreover, this rearrangement was found to be accompanied by

extensive $^1H/^2H$ exchange at the 2-carbon of **34**. The mixture contained 28 mol% of **34** substituted with ^2H at the C-2e position and approximately 3 mol% of **34** with ^2H at the C-2a position, and in 5 mol% both protiums at the C-2 position had been exchanged for ^2H.

The above results led to studies of the outcome of monofunctional catalysis by hydrochloric acid. A 0.11 M ^2HCl-solution in (O-^2H)acetic acid was prepared by adding a small amount of acetyl chloride to (O-^2H)acetic acid, and the substrate **34** (0.14 M) was added. The investigation of the reaction mixture by ^1H NMR after reaction at 25 °C for approximately 80 minutes showed only the presence of the product α,β-unsaturated ketone (**^{1}H-r**) and no trace of **34**. Interestingly, no trace of (**^{2}H-r**) could be detected, indicating that no exchange of the C-2 hydrogens of **34** had taken place prior to the rearrangement to the conjugated isomer. The results sharply contrasted with those obtained with acetic acid but were in accordance with results obtained by Malhotra and Ringold, using Δ^5-3-ketosteroids and hydrochloric acid[42,52]. Thus, the results seemed to constitute support for the operation of a bifunctional exchange mechanism also with acetic acid, similar to the one postulated for the amidine (cf. Scheme 10).

The formamidine **36** was also found to catalyze the $^1H/^2H$ exchange at the C-2 position of **34** at a rate that was faster than the rate at which **34** was rearranged to its conjugated isomer. Amidine **7** seemed to be the most effective of all catalysts tested in this respect. The inability of these catalysts to produce fast allylic isomerization could possibly be due to their steric requirements. However, it is not clear why **36** caused a larger fraction of allylic isomerization than **7**.

The stereoselectivity $[^2H^1H]/[^1H^2H]$ for exchange at the C-2 position in **34** was more pronounced with acetic acid and opposite to that with the sterically more crowded formamidines (Table 2). Based on investigations in other systems, it has been suggested that stereoselectivity of the $^1H/^2H$ exchange is to be expected for the diastereotopic hydrogens positioned at the α-carbon vicinal to a carbonyl group. It has been proposed that this stereoselectivity is mainly due to steric hindrance of hydron abstraction, to stereoelectronic control or to steric interactions in alternative transition states[69-85]. By stereoelectronic control of proton abstraction is meant that a more favorable orbital overlap between the π-system of the carbonyl group and one of the C—H σ-orbitals is obtained during the abstraction. According to this theory, an axial-positioned C_α-hydrogen will be more easily abstracted than an equatorial C_α-hydrogen in a cyclohexanone derivative[71-85].

The stereoselectivities $[^2H^1H]/[^1H^2H]$ found for the $^1H/^2H$ exchange of **34** were not easily interpreted. The spatial orientation of the C-2 hydrogens in **34** could not be unequivocally defined according to a conformational analysis. This results indicated that both β- and α-hydrogens at C-2 may take up axial positions in different conformations of **34**.

The mechanism of acetic acid catalyzed enolization of **34** and the rearrangement to **35** have been further studied by isotope effects and reaction order with respect to acetic acid in benzene. The $^1H/^2H$ exchange of **34** in benzene was shown to be first order in (O-^2H)acetic acid and thus indicated that monomeric acetic acid catalyzes the enolization. The rearrangement to **35**, on the other hand, was found to be second order in acetic acid monomer. The primary deuterium kinetic isotope effects found for the enolization of **34** in neat acetic acid were $2.7^{+1.0}_{-0.7}$ for the O—H—O transfer and $9.0^{+1.3}_{-1.11}$ for the C—H—O transfer. The results suggest that two hydrons are in transit in the rate-limiting enolization transition state[13,14].

3. *Hydrogen exchange of carbon acids*

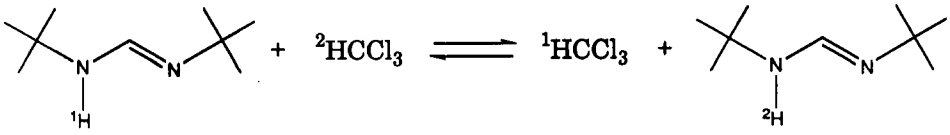
Amidinium ions (and guanidinium ions) cover a large interval of pK_a values. Some amidines and guanidines are strong enough bases to pull hydrons at reasonable rates from

TABLE 2. The product composition of quenched reaction mixture in the $^1H/^2H$ exchange and isomerization of **34** catalyzed by mono- or bifunctional catalysts in various solvents at 25 °C[a]

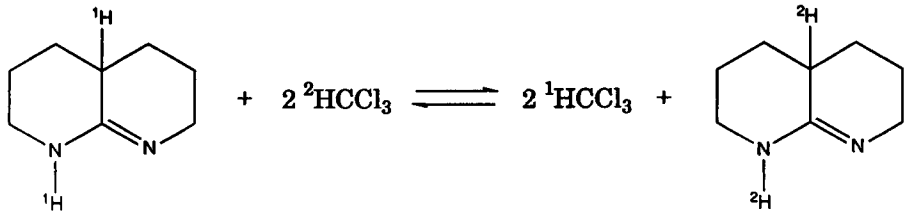
Catalyst[b]	Solvent	[Catalyst] / [Substrate][c]	Time (h)	$^1H/^2H$ exchange in **34** (mol%)				Isomerization (mol%)	
				$^1H^1H$	$^2H^1H$	$^1H^2H$	$^2H^2H$	^1H-r	^2H-r
^{2}H-7	C^2HCl_3	0.0425	1.5	9.7	19.5	22.7	47.1	< 0.5	< 0.5
^{2}H-36	C^2HCl_3	0.342	24.0	26.9	20.0	23.4	16.6	8.4	4.7
CH_3COO^2H	CH_3COO^2H	129.0	50.0	24.7	28.4	2.8	5.0	37.9	1.2

[a]The $^1H/^2H$ exchange in **34** refers to the exchange of the C-2 hydrogens ($^1H^1H$). The symbols used are defined in Scheme 9.
[b]The catalysts were labelled with ^2H in the acidic O—H and N—H positions.
[c]The initial concentration of the substrate was 0.35 M in each experiment except in the experiment **^{2}H-7**/C^2HCl_3 where it was 0.08 M.

not too weak carbon acids. Thus *N,N'*-di-*t*-butylformamidine (^{1}**H-7**) reacts rapidly with neat (^{2}H)chloroform yielding (^{1}H)chloroform and ^{2}**H-7**. This reaction has been used synthetically to make ^{2}**H-7** with 99.7 ± 0.2% of ^{2}H in the N—H group[13,14]. Similarly the bicyclic amidine **18** reacts rapidly with $^2HCCl_3$ yielding hydrogen exchange.

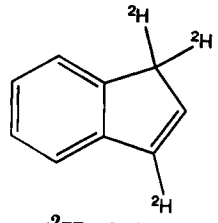


(^{1}**H-7**) (^{2}**H-7**)



(^{1}**H-18**) (^{2}**H$_2$-18**)

However, not only the N-bonded hydrogen in **18** is exchanged but also the α-hydrogen exchanges. The latter reaction is acid–base catalyzed. Small quantities of acid are produced by side reactions (cf. Section III.A.3). Compound ^{2}**H$_2$-18** with high isotopic purity has been synthesized by this reaction[11,86,87]. To avoid the contamination of acidic impurities, neat trideuterated indene (^{2}**H$_3$-39**) has been used as a deuterium pool.

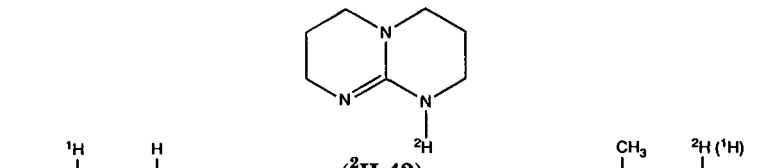


(^{2}**H$_3$-39**)

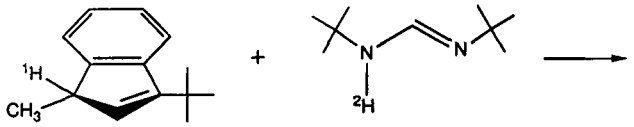
Compound ^{2}**H$_3$-39** is easily accessible from base-catalyzed ^{1}H/^{2}H exchange of indene (**39**) with ^2H_2O. All three deutrons are available for exchange through combination of methylene hydrogen exchange and base-catalyzed 1,3-hydron transfers. With ^{2}**H$_3$-39** the rate of exchange of the N-bonded hydrogens in **18** is much faster than the rate of exchange of the α-hydrogens. $(C^2H_3)_2CO$ has also been used as a deuterium pool.

The mechanistic studies of the **18**-catalyzed rearrangement of 1,3,3-triphenylpropene (**21**) into 1,1,3-triphenylpropene (**22**) have revealed that **21** and **22** also undergo ^{1}H/^{2}H exchange (cf. Section II.A.1)[11]. Similarly, hydrogen exchange has been found to accompany rearrangements of 3-phenylbutene (**40**) to 1-phenylbutene (**41**) and of 3-methylcyclohexene to 1-methylcyclohexene catalyzed by the N-^{2}H labelled guanidine (^{2}**H-42**).

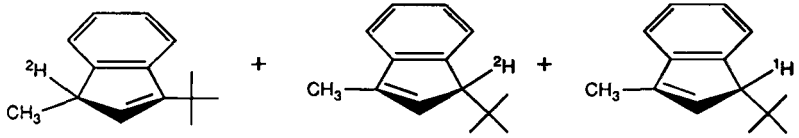
Hydrogen exchange catalyzed by *sec*-amidines has been found to take place with retention of the configuration of the carbons exchanging their hydrogens. The rearrangements of **8** to **9** and of **24** to **25** catalyzed by ^{2}**H-7** and ^{2}**H$_2$-18**, respectively, have been found to take place suprafacially and so do accompanying exchange reactions[6,15].



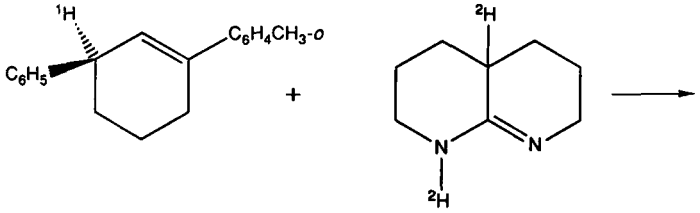
(40) (41)



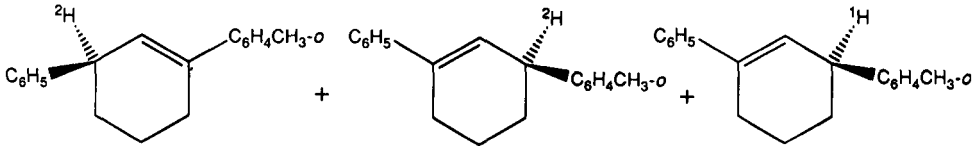
(¹H-8) (²H₂-7)



(²H-8) (²H-9) (¹H-9)

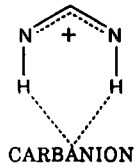


(¹H-24) (²H₂-18)



(²H-24) (²H-25) (¹H-25)

The mechanism for *sec*-amidine catalyzed hydrogen exchange of carbon acids has not been studied in detail, but it seems likely that ion-pairs are intermediates and transition states like **43** are involved[6,11].



(43)

Large isotope effects, originally attributed to tunneling, have been measured by Caldin and Mateo in hydrogen-transfer reactions of (4-nitrophenyl)nitromethane with bases containing the imine group in non-polar solvents[88-90]. For example, an isotope effect of $k_{1H}/k_{2H} = 45$ was measured in toluene with tetramethylguanidine (**BH**).

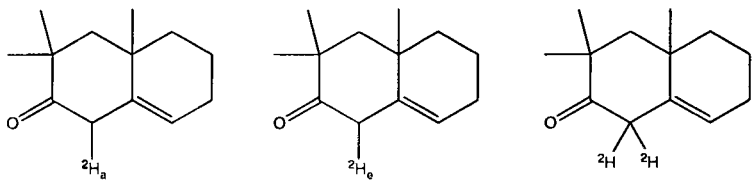
$$ArC^2H_2NO_2 + B^1H \longrightarrow ArC^2HNO_2^- \ldots\ldots {}^2HB^1H^+$$

However, it has been pointed out that the kinetics are complex since the ion-pair initially formed from the deuterium substrate gives several other ion-pairs as a result of isotopic scrambling; these also return to the substrate resulting in exchange. If these factors are not taken into consideration, an overestimation of the magnitude of the isotope effect will result since protonation competes favorably with deuteration of the anion in the ion-pair[91-96]. This is an example that reaction branching may cause extreme kinetic isotope effects[97,98].

β,γ-Unsaturated ketones of the type **34** undergo base-catalyzed rearrangement to their α,β-unsaturated isomers.

(34) (35)

When ^{2}**H-7** was used as catalyst it was found that α-hydrogen exchange was much faster than rearrangement, yielding ^{2}**H**^{1}**H** and ^{1}**H**^{2}**H** in about equal amounts besides ^{2}**H**^{2}**H**[13,14].

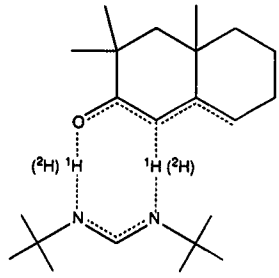


(^{2}**H**^{1}**H**) (^{1}**H**^{2}**H**) (^{2}**H**^{2}**H**)

Cyclic transition states of the type **37** leading to and from enol intermediates have been proposed to be involved in this unusual exchange (cf. Section II.A.2).

4. Epimerizations involving transfers from and to nitrogens and oxygens

Almost forty years ago Swain and Brown reported their discovery of the unusual catalytic activity of 2-pyridinone (**44**) and its tautomer 2-hydroxy pyridine (**45**), a derivative of imidic acid, in the epimerization of α-tetramethylglucose (**46**) to β-tetra-



(37)

methylglucose (**47**) in benzene[1,2,21–25,99–104]. The extraordinary efficiency of this catalyst in relation to its weak basic and acidic properties was the basis for the formulation of the bifunctional mechanism shown in Scheme 11.

The reaction system has recently been quantitatively reinvestigated with the use of microcalorimetry, and some new features have been revealed[105]. Not only the thermodynamics but also the dynamics of the system have been measured with this technique. Tetramethylglucose, previously assumed to be monomeric and complexed with **44**, were found to be highly dimerized at concentrations commonly used in kinetic investigations. The equilibrium constant for its self-association and that of **44** and the complexation constants for the tetramethylglucose:**44** complexes were measured together with the thermodynamic parameters for the equilibria. The heats of reaction (ΔH^0) for these reactions show that the association complexes involve two hydrogen bonds and that they are therefore cyclic, as previously assumed. Also, the rate of epimerization, together with its small heat of reaction, was measured microcalorimetrically. These studies have led to a revised free-energy diagram for the system (Figure 3).

The unusual (enzyme-like) catalytic activity of **44** compared with several monofunctional catalysts spanning a large pK_a interval formed the basis for the suggestion by Swain and coworkers that the first step in the epimerization—formation of the aldol complex (**49**) in Scheme 11—is bifunctionally catalyzed and the two hydrons are transferred concertedly between N and O, and O and O, respectively, as indicated by the transition state structure **48**.

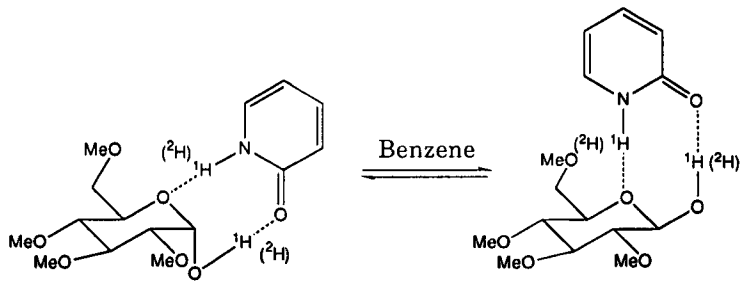
Various transition-state structures have been formulated, depending on the number of hydrogens and their degree of transfer and coupling to heavy-atom motion. Making use of isotope effects, answers to the following questions have been searched: Does the multiple hydron transfer occur in an elementary reaction, i.e. are the hydrons transferred simultaneously, as suggested, or by a stepwise mechanism? To what extent are the hydron transfers coupled to heavy-atom motion in the transition state? Is tunneling important in the reactions?[99–101,106,107]

Rate constants for the epimerization were obtained with high accuracy using optically active **46** and polarimetry. The primary deuterium isotope effects were extracted from the positively curved plot of the specific rate of epimerization vs the mole fraction of ^2H in the pool of OH and NH hydrogens (Figure 4).

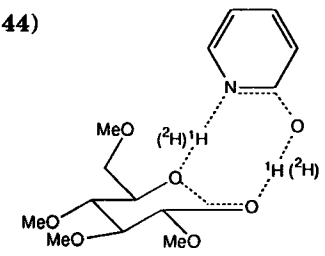
The following values were obtained: $k_{1H^1H}/k_{2H^2H} = 3.66 \pm 0.09$, $k_{1H^1H}/k_{2H^1H} = 1.5$ and $k_{1H^1H}/k_{1H^2H} = 2.4$. The secondary deuterium isotope effect 1.14 ± 0.02 was measured by using **1-^{2}H-46**.

The interpretation of the primary isotope effects of this complex reaction has been assisted by calculations using the Bebovib-IV program with assumed vibrational force constants as input. The results suggest that two hydrogens are in transit in the rate-controlling transition state and that each of them has a fractionation factor of about 0.5.

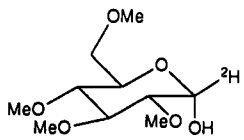
(44) (45)



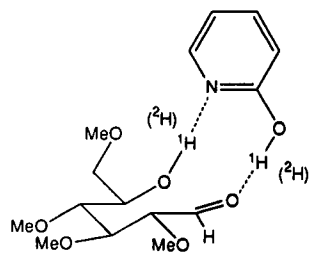
(46:44) (47:44)



(48)



(1-^{2}H-46)



(49)

SCHEME 11

These results, together with the calculations, favor a transition state structure in which the simultaneous hydron transfers are coupled with considerable heavy-atom motion (i.e. cleavage of the ring C—O bond). The tunnel corrections to the isotope effects were found to be negligible. The calculations also showed that, to a quite close approximation, the isotope effect for the dideuterated species is the product of the isotope effects for the two monodeuterated species in consistency with the experiments. Thus, the results uphold the principle behind the rule of the geometric mean despite strong coupling in the transition

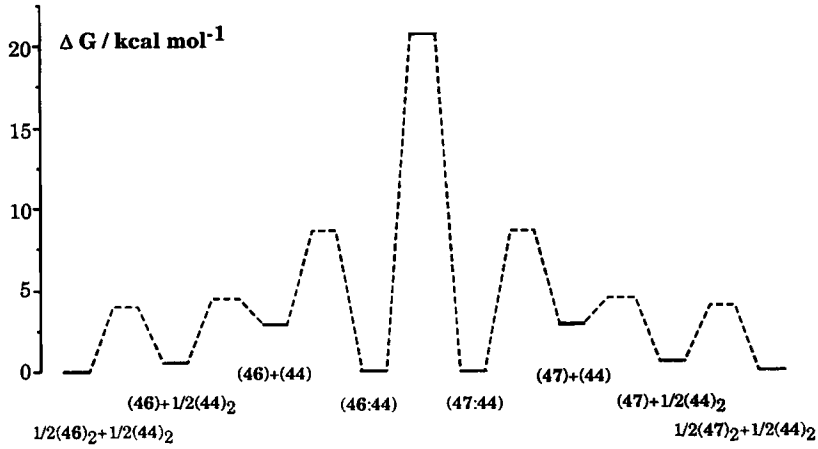


FIGURE 3. Free-energy profile of the **44**; **46**; **47**-system in benzene at 25 °C. The free energy of $\frac{1}{2}(\mathbf{46})_2 + \frac{1}{2}(\mathbf{44})_2$ has arbitrarily been set to zero

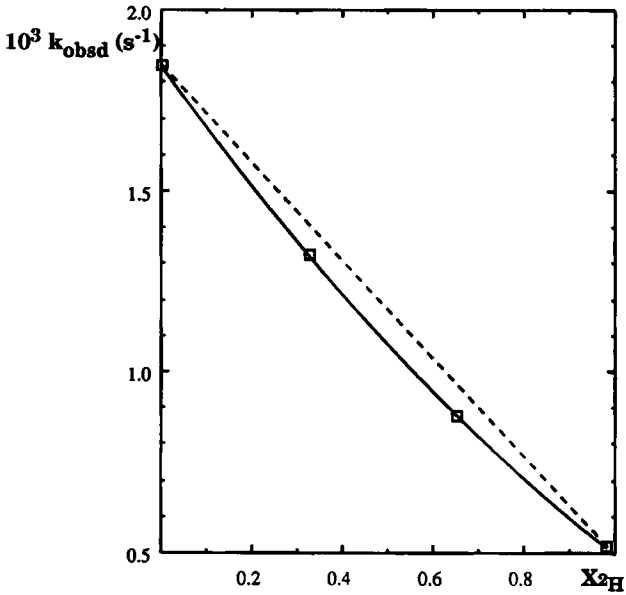


FIGURE 4. Plot of k_{obsd} vs $X_{^2H}$, the mole fraction of ^2H in the mobile hydrogen pool in benzene, at 24.98 ± 0.03 °C. The points are experimental values. The solid and dashed lines have been simulated with the pairs of fractionation factors 0.65, 0.42 and 1.00, 0.27, respectively

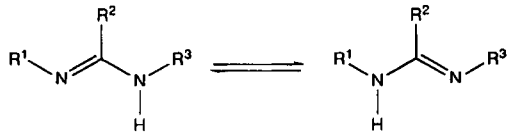
state. Another result of the calculations was that computed k_{1H^1H}/k_{2H^2H} values are relatively insensitive to the extent of hydron transfer.

The two hydrogens in transit could, in the transition state, either be governed by a barrier, as assumed in the calculations, or, following Kreevoy and coworkers, be transferred without any energy of activation[108-110].

2-Aminopyridine (**10**) has been reported to be a bifunctional acid–base (tautomeric) catalyst for the mutarotation of **46** (**47**) by Swain and Brown[21]. However, this result has been questioned by Rony and Neff who concluded that **10** is not to be considered a tautomeric catalyst of that reaction[25].

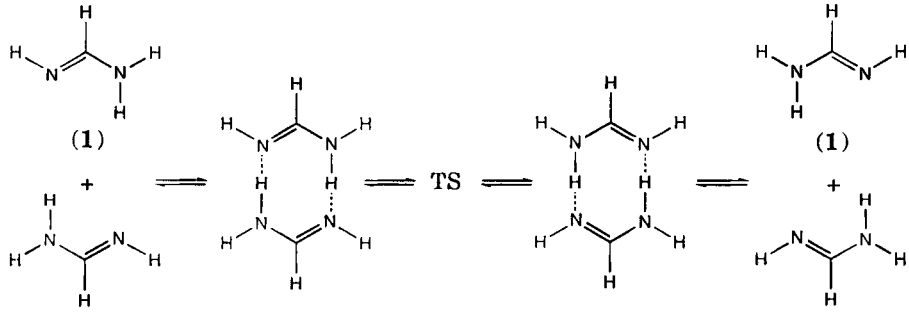
5. *Identity reactions involving transfers from and to nitrogens*

Amidines may tautomerize, i.e. **50** isomerize to **51**. Such reactions may be acid or base catalyzed. They may be self-catalyzed by catalysis of either the mono- or the bifunctional type. For the latter type the tautomerization takes place within amidine dimer and involves two-hydron transfers. Reactions involving transfer of two hydrons, in which one of the hydron transfers is assisted by the other one, are common in enzyme and other catalysis[1-3]. There has been a large number of mechanistic studies of such reactions and a major tool has been $^1H/^2H$ isotope effects[106,107,111-116]. Besides experimental studies of the interplay of the two hydrons being transferred, theoretical studies of model systems have been carried out[117-122] to assist the interpretation of observed isotope effects and to investigate the predictive power of simple vibrational models[120-122].



(50) **(51)**

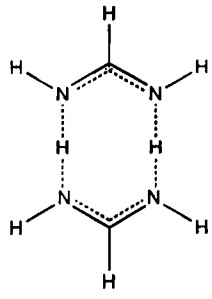
The potential energy surface for the bifunctionally catalyzed tautomerization of **52** has recently been studied in detail theoretically by *ab initio* calculations[120-122].



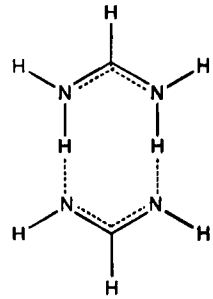
(1) **(52)** **(52)** **(1)**

Gaussian-type orbital basis sets of increasing size and precision, namely STO-3G, 3-21G, 6-31G, 6-31 + G and 6-31G*, have been used. Symmetry-restricted geometry optimization was performed using various optimization techniques. Four stationary points have been located: monomer (**1**), dimer (**52**), transition state (TS) (**53** or **54**, identified as a first-order saddle point) and, at the 6-31G* level, an intermediate (**55**). All

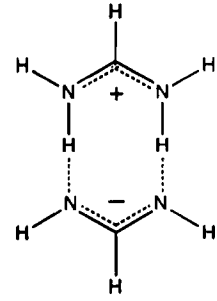
stationary points were characterized by their force-constant matrices, calculated using analytical differentiation methods.



(53)



(54)



(55)

The variation of transition state structure and energy with basis set is shown in Figure 5 and Table 3, respectively.

Thus at the STO-3G level a highly symmetrical transition state with D_{2h} symmetry was obtained. This is consistent with the general conception of such reactions[117,120]. In contrast, at the split valence level of theory a less symmetrical transition state was formed showing C_{2v} symmetry where the two hydrogens were closer to one of the two amidine subunits than to the other. No transition state structure of D_{2h} symmetry (the two hydrogens exactly midway between the two amidine subunits) could be found. At the 3-

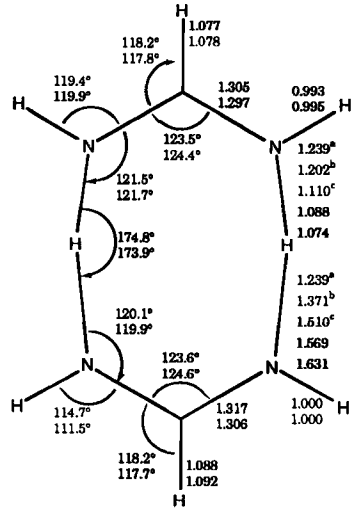


FIGURE 5. Calculated equilibrium geometries. Bond lengths are given in Å. The values with superscript correspond to (a) STO-3G, (b) 3-21G and (c) 6-31G. Of the values without reference the upper one corresponds to the 6-31 + G and the lower one to the 6-31G* level of theory[121]

TABLE 3. Energies, relative to the dimer (52) and the imaginary frequencies for the transition states

Basis set	$E_{2(1)} - E_{(52)}$ (kcal mol^{-1})	$E_{TS} - E_{(52)}$ (kcal mol^{-1})	Imag. freq. (cm^{-1})
STO-3G	11.7	9.0	1311i
3-21G	19.9	16.0	1494i
6-31G	14.3	19.4	432i
6-31 + G	12.8	19.4	146i
6-31G*	11.2	25.4[a]	

[a]At this level of theory, the structure with C_{2v} symmetry is a local minimum, not a transition state.

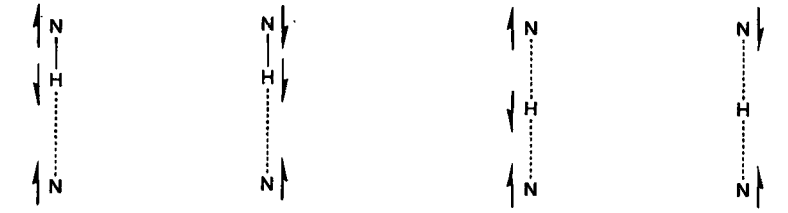
21G level, the structure with D_{2h} symmetry (earlier reported as a transition state) was shown to have two imaginary frequencies, as was also the case for the D_{2h} structure at the 6-31G* level.

When introducing polarization functions the computed C_{2v} structure turned out to be a local minimum instead of a transition state. This indicates that there is an ion-pair-like intermediate of C_{2v} symmetry on the reaction path of the two-proton transfer reaction. Thus there must be two transition states, both of C_1 or C_s symmetry, one before and the other after the intermediate. These transition states were not localized. It is interesting to note that systems which were assumed previously to use concerted two-hydron transfer pathways may make use of stepwise mechanisms involving intermediates even in the absence of solvent.

Electron correlation has been taken into account in MP2/6-31G* calculations. The results suggest that the inclusion of electron correlation effects will not change the symmetry of the potential energy surface. The two-hydron transfer within the formic acid dimer have transition states with D_{2h} symmetry at all the above levels of calculation.

Deuterium isotope effects on the two-hydron transfers have been calculated using the vibrational frequencies obtained from the STO-3G-potential energy surface and the Bebovib-IV program. The results deviated from predictions based on common simple vibrational models.

Scheme 12 shows the stretching modes of an one-hydron transfer reaction. The initial state is a weakly hydrogen-bonded linear complex, and the TS is linear and symmetrical. The N—H stretch corresponds to the decomposition mode (unsym. stretch) in the

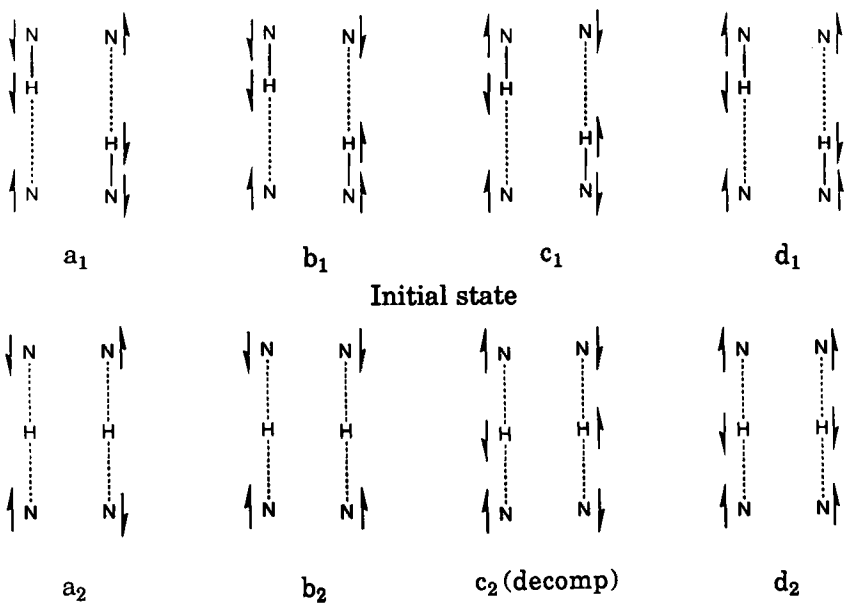


SCHEME 12

transition state. The H-bond stretch, which is almost isotopically insensitive, corresponds to the isotopically insensitive symmetrical stretch of the TS. If it is assumed that the sum of the frequencies for the bending vibrations is equal for the initial and transition states, respectively, we may conclude that the isotope effect (k_{1H}/k_{2H}) for the hydron transfer is dominated by the zero-point energy (ZPE) difference for the N–^{1}H and N–^{2}H stretching vibrations of the initial state[26].

For a concerted two-hydron transfer reaction having a TS with D_{2h} symmetry, one might at a first glance predict a $k_{1H^1H}/k_{2H^2H} = (k_{1H}/k_{2H})^2$ using assumptions similar to those for the one-hydron transfer above, i.e. isotope effects for two one-hydron transfers have been multiplied.

However, a deeper analysis still using a simple model yields a different answer. Scheme 13 shows the stretching modes of a two-hydron transfer. The initial state is a weakly hydrogen-bonded complex and the TS has D_{2h} symmetry. There are four stretching modes for each state. The (H-bond)$_2$ stretches a_1 and b_1, which are essentially isotope insensitive, correspond to the insensitive stretches a_2 and b_2 of the TS. The (N–^{1}H)$_2$ stretches c_1 and d_1, on the other hand, correspond to c_2 and d_2 of the TS, where c_2 corresponds to the decomposition mode. Thus for the two-hydron transfer we may conclude that k_{1H^1H}/k_{2H^2H} is dominated not only by the zero-point energies (ZPE) of the (N–^{1}H)$_2$ and (N–^{2}H)$_2$ stretching vibrations c_1 and d_1 of the initial state, but we also have to take into account the corresponding difference for d_2 of the TS. However, if we assume that the frequency for d_1 is equal to that of d_2, and again ignore any difference in sums of bending frequencies of the initial and transition states respectively, we find that k_{1H^1H}/k_{2H^2H} is dominated by just the difference in ZPE of (N–^{1}H)$_2$ and (N–^{2}H)$_2$ of c_1. The frequency difference is likely to be close to the corresponding frequency difference for the one-hydron transfer case above. Therefore one expects that k_{1H^1H}/k_{2H^2H} for a two-hydron transfer is approximately equal to k_{1H}/k_{2H} for a one-hydron transfer and thus not equal to $(k_{1H}/k_{2H})^2$. Furthermore, we



SCHEME 13

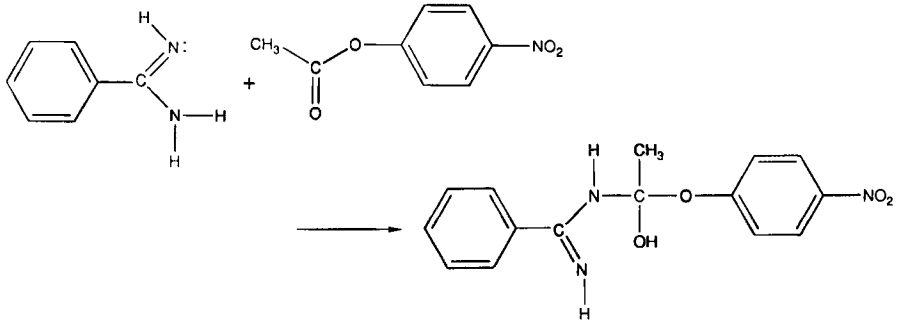
predict by this simple model for a concerted two-hydron transfer via a D_{2h} TS that k_{1H^1H}/k_{1H^2H} ($= k_{1H^2H}/k_{2H^1H}$) is approximately equal to $(k_{1H}/k_{2H})^{1/2}$. However, it has not been easy to see how accurate are the approximations made above.

The calculated isotope effects from the STO-3G potential energy surface are dominated by the zero-point energy contribution. The effect due to the stretching vibrations of the initial state is to a small extent counteracted by stretching vibrations of the transition state. The bending vibrations appear to play a dominant role in reducing the magnitude of the isotope effect for the two-hydron transfer reaction to a value expected for a one-hydron transfer reaction[121].

Recent high-level calculations of the tautomerization of the formic acid dimer also show the decisive role of the bending vibrations in determining isotope effects[122].

B. Acid-catalyzed Nucleophilic Addition

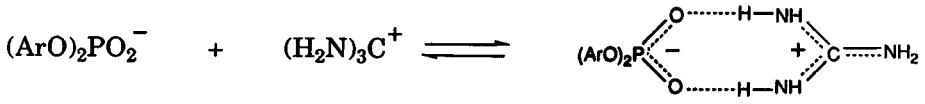
Benzamidine has been shown to react with *p*-nitrophenyl acetate in chlorobenzene in a second-order process. n-Butylamine, a nucleophile with a basicity similar to that of benzamidine, reacts with *p*-nitrophenyl acetate in chlorobenzene by means of a third-order process, the rate of which is little affected by the presence of large amounts of a tertiary amine. Benzamidine reacts at least 15,000 times faster than n-butylamine monomer. This reactivity of benzamidine with the ester in the aprotic solvent is attributed to the bifunctional nature of the nucleophile which can concertedly attack the carbonyl carbon of the ester and deliver a proton to the carbonyl oxygen, thereby forming the tetrahedral intermediate without creation of zwitterions[123].



In lactate dehydrogenase, several arginines appear to function in catalysis and in binding of coenzyme and substrate. The effect of association with guanidinium ion on the rate of reaction of a carboxylate anion has been investigated with the monophenyl ester of succinic acid which hydrolyzes by a pH-independent pathway between pH 4.5 and 9 involving intramolecular nucleophilic attack of the succinate carboxylate anion. Guanidinium ions were found to inhibit the hydrolysis, presumably by complexation as shown in Scheme 14[124].

SCHEME 14

In contrast, guanidinium ions have been found to catalyze nucleophilic attack at phosphate monoanion. The importance of the association equilibrium in Scheme 15 is stressed.



SCHEME 15

The catalysis could be due either to nucleophilic attack by guanidine, which is a strong base, or to guanidinium ion catalysis of attack by hydroxide[125].

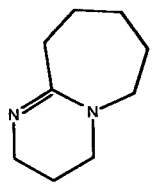
III. MONOFUNCTIONAL CATALYSIS

A. One-hydron Transfers

1. Rearrangements

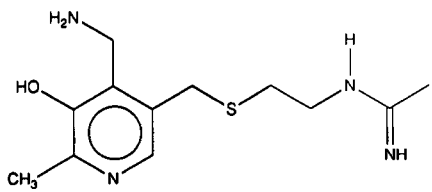
In Section II.A.1 catalysis by secondary amidines, which have the potential to act as bifunctional catalysts by making use of two-hydron transfers was reviewed. These catalysts may also operate as monofunctional catalysts and the interference of such catalysis was also reviewed in Section II.A.1; e.g. 2-aminopyridine (**10**) acts as a monofunctional catalyst of 1,3-hydron transfers in allylic systems.

The tertiary amidine (**56**), which has not the possibility to act in a bifunctional manner, has been found to be an efficient catalyst for the rearrangement of the indene **8** to **9**[6]. This monofunctional catalysis is highly stereospecific in benzene. The stereospecificity was determined to be $>99.996\%$ and the 1,3-hydron transfer takes place suprafacially. In DMSO, on the other hand, the isomerization with **56** is nearly nonstereospecific.

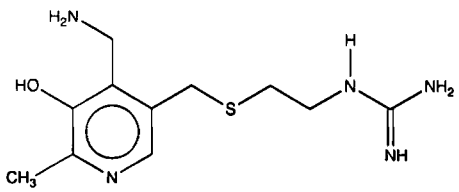


(**56**)

Recently transaminase and racemase activity of pyridoxal/pyridoxamine enzyme analogs with acetamidine, guanidine and *N,N,N'*-trimethylethylenediamine covalently attached to the pyridine ring via flexible allyl- or alkylthio-side chains **57** and **58** have been studied.



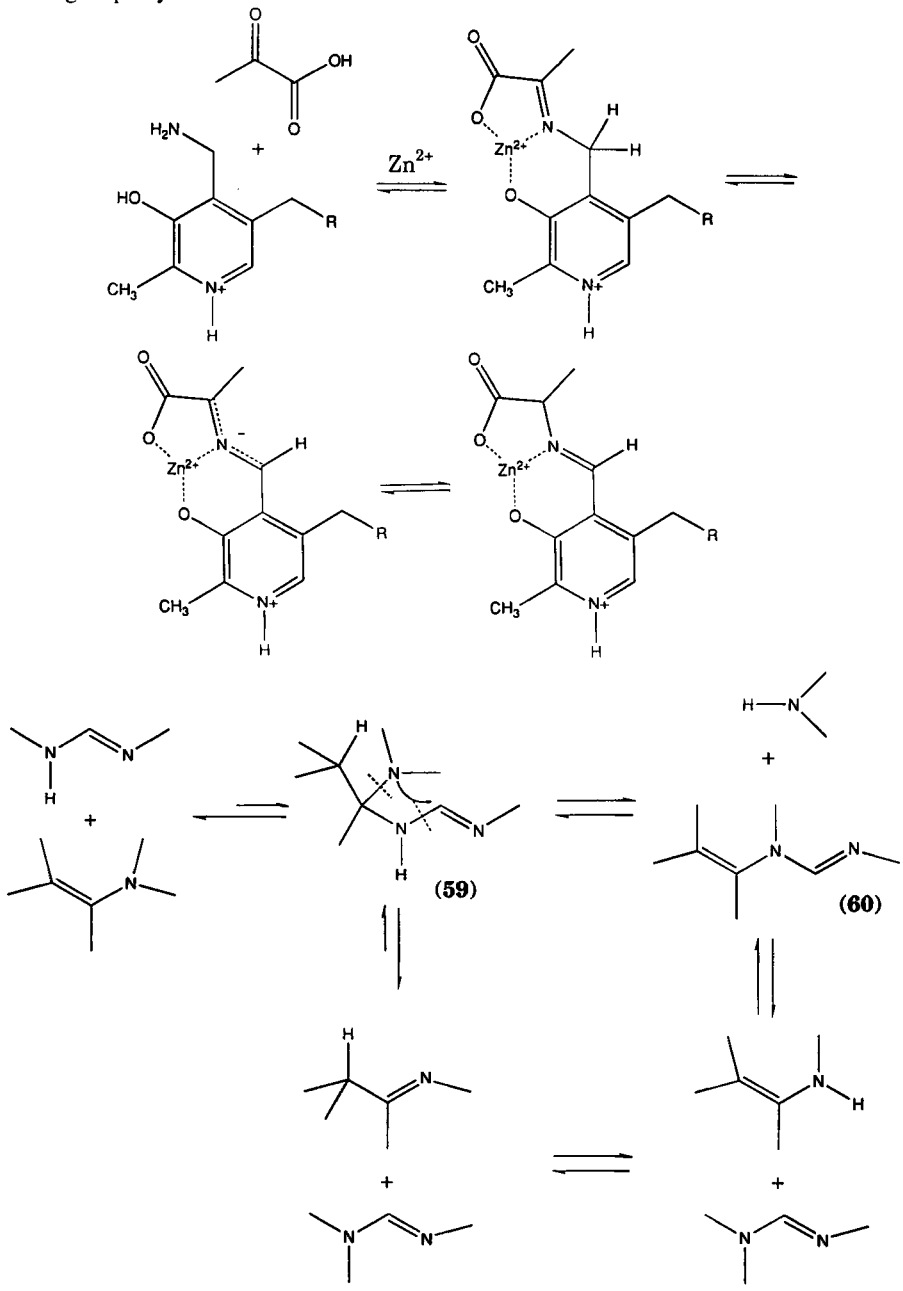
(**57**)



(**58**)

These compounds react readily with pyruvic acid in methanol in the presence of zinc(II) to afford ketimines, which more slowly isomerize to aldimines in a process that parallels

transamination. It has been suggested that the isomerization is catalyzed by the basic side chain groups by a bifunctional mechanism[32].



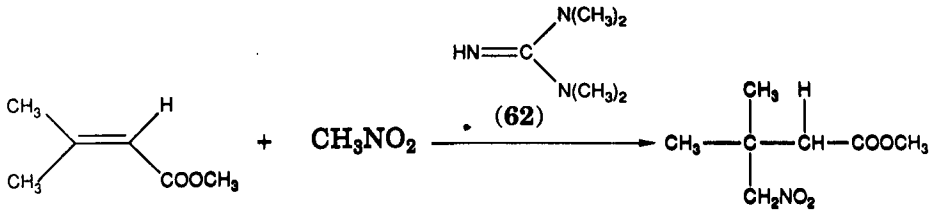
SCHEME 16

In Section II.A.1, results of the reaction of secondary amidine with enamines were reviewed[31]. As shown in Scheme 8, a novel rearrangement took place instead of an expected bifunctionally catalyzed 1,3-proton transfer. Imines and tertiary amidines were produced. Apparently the amine parts of the enamine and the *sec*-amidine were exchanged. The stability of imines over enamines should be an important driving force for this reaction. Several reaction mechanisms could be formulated that make use of amidineaminals and/or enamidines as intermediates (Scheme 16).

In an amidineaminal, one of the amine residues of an aminal has been replaced with an amidine residue. Compound **59** could be formed by addition of amidine to enamine, possibly employing the bifunctional character of the amidine. Elimination of *sec*-amidine from **59** results in the enamidine **60**, which in a subsequent step could react with the secondary amine to yield, after tautomeric rearrangement, the observed products. Another possible route to products could be a direct formation from **59** in a concerted reaction where bonds are formed and broken as indicated in structure **59**. Acid as well as base catalysis could be of importance in these reactions[31].

2. *Addition reactions*

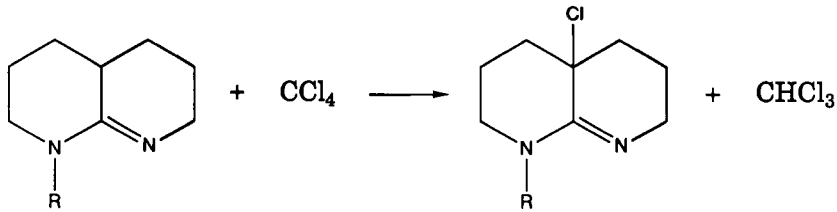
Attempts to prepare the γ-nitroester (**61**) by means of the usual Michael catalysts failed to give any results. This fact may be ascribed to steric hindrance due to the two methyl groups at the β-position of the acceptor. Pollini and coworkers were able to prepare **61** under Michael conditions by use of tetramethylguanidine (**62**). The catalyst **62** has been used in several Michael additions. The detailed mechanism has not been elucidated[126].



(61)

3. *Halogenation reactions*

Recently a reaction of amidines with carbon tetrachloride (CCl_4) was discovered giving α-chlorinated amidines and chloroform (Scheme 17). The reaction was investigated for the bicyclic amidines 2,10-diazabicyclo[4.4.0]dec-1-ene (**18**), 2-methyl-2,10-diazabicyclo[4.4.0]dec-1-ene (**63**), 1,8-diazabicyclo[5.4.0]undec-7-ene (**56**) and 1,5-

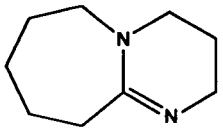


(18) R = H
(63) R = Me

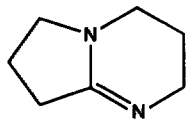
(64) R = H
(65) R = Me

SCHEME 17

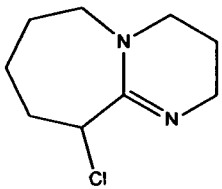
diazabicyclo[4.3.0]non-5-ene (**66**). Amidines **18**, **63** and **56** gave the monochlorinated amidines **64**, **65** and **67**, while **66** gave a mixture of mono- and dichlorinated amidines **68** and **69**. These reactions involve amidine catalysis and the α-chlorinated amidines are useful for synthetic purposes. For example, hydrolysis of **64**, **65** and **67** gave new bicyclic and spirolactams which, on further hydrolysis, may be transformed into α-amino acids[86,127].



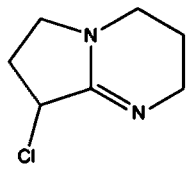
(56)



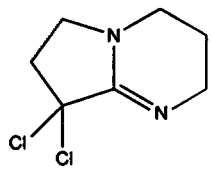
(66)



(67)

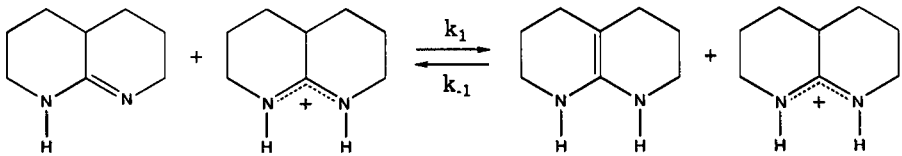


(68)

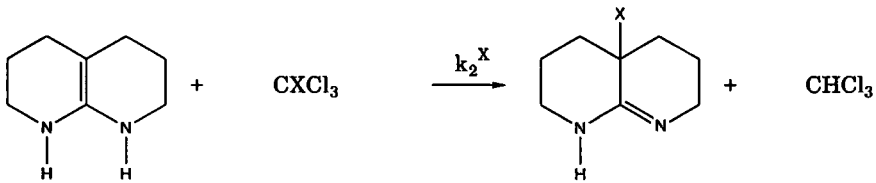


(69)

The mechanism of the halogenation reaction has been studied in detail using amidine **18** as substrate and bromotrichloromethane ($CBrCl_3$) as reagent in benzene[87,128]. This reaction proceeds at rates convenient for detailed kinetic studies by HPLC. The results obtained from this investigation show that the α-bromination of **18** is acid-catalyzed and of nonchain type, in contrast to the chain reactions of amines with CCl_4. The acid which catalyzes the bromination of **18** seems to be formed in a side reaction by a radical chain mechanism. Kinetic results and measured hydrogen isotope effects and reaction branching indicate that the ketene aminal tautomer **70** is an intermediate in the α-bromination. The



(18) **(70)**



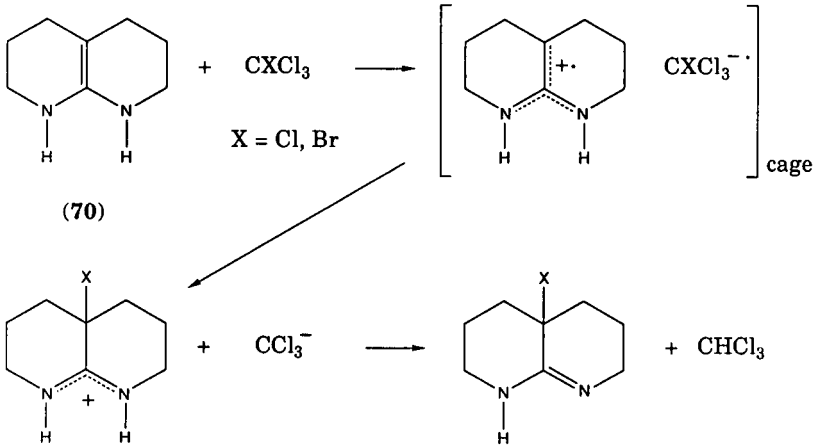
(70) **(71)** X = Br **(72)** X = Cl

X = Cl, Br

SCHEME 18

reaction with $CBrCl_3$ probably occurs via a redox reaction within the solvent cage. Schemes 18 and 19 summarize the mechanistic results obtained with $CBrCl_3$ and CCl_4.

In the first step an amidine molecule abstracts an α-hydron from an amidinium ion produced by addition of acid or added as amidinium bromide. In this reaction a ketene aminal (**70**) and a new amidinium ion are formed. In the next step **70** reacts with $CXCl_3$ and an α-halogenated amidine along with $CHCl_3$ were formed.



SCHEME 19

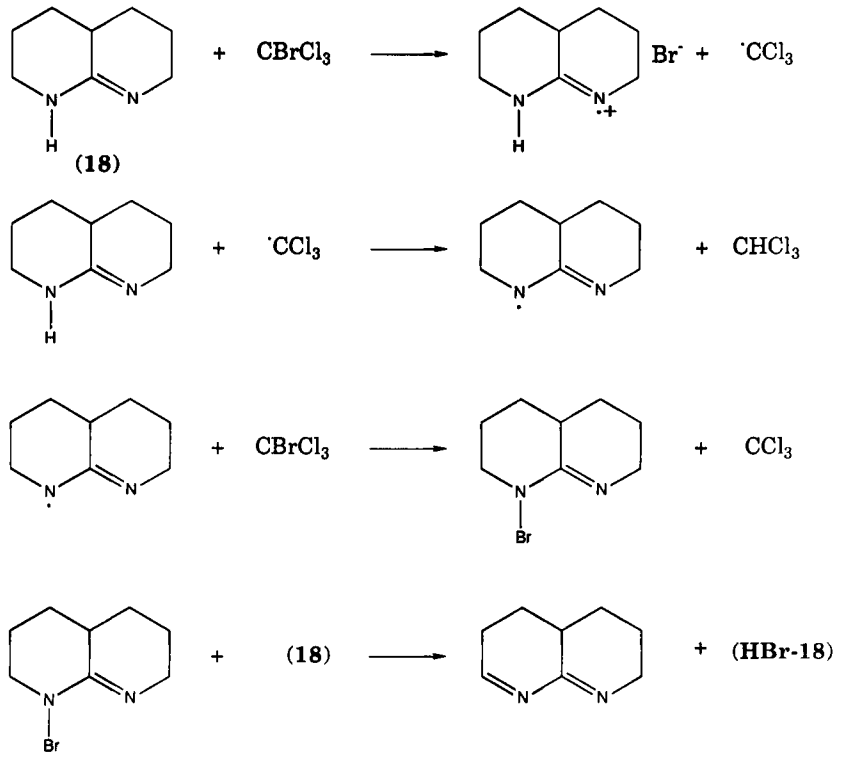
The kinetics of the acid-catalyzed reaction of **18** with CCl_4 in benzene, methylene dichloride and dimethylformamide (DMF), and with $CBrCl_3$ in DMF, have been investigated. The kinetics of the reaction of DBU (**56**) with CCl_4 in DMF and DMSO has also been studied. The reaction of **18** with CCl_4 and DMF is first-order in [**18**], close to zero-order in [CCl_4] and close to pseudo-first-order in [acid], indicating rate-limiting formation of the ketene aminal **70**. In contrast, in the nonpolar solvents the rate of reaction is found to be limited by the reaction of the tautomer **70** with CCl_4, which is much lower than in DMF. This change of rate-limiting step is also observed for the reaction of **18** in benzene when $CBrCl_3$ is exchanged for CCl_4, and is most likely induced by a much faster reaction of tautomer **70** with $CBrCl_3$ than with CCl_4. The results support a nonchain one-electron-transfer mechanism for the halogenation step, with formation of an intermediate radical-ion pair (cf. Scheme 19).

In Scheme 20 is shown a sequence of reactions leading to production of acid that may catalyze α-halogenation. Hydrolysis of the amidine function in **64** (Scheme 21) followed by an intramolecular substitution gave the azaspirolactam (**73**) and the methyl-substituted amidine (**65**) gave the isomers **74** and **75** in the ratio 22:78, respectively. Similarly α-chlorinated DBU (**67**) gave the bicyclic azalactam (**82**) (Scheme 22). The azalactam and the azaspirolactams may be hydrolyzed yielding novel diamino acids.

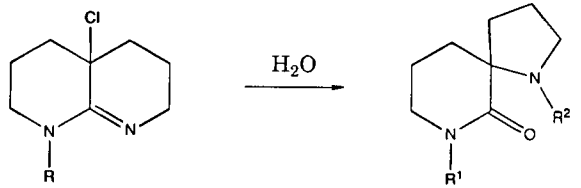
The reaction of enamines with bromotrichloromethane which involve the intermediacy of trichloromethyl anions have also been studied.

IV. MISCELLANEOUS REACTIONS

A new method for the rapid preparation of methyl esters from vegetable oils and fats using tetramethyl guanidine as catalyst has been developed. The method produced the methyl esters in quantitative yields and did not result in isomerization of the fatty acids[129].



SCHEME 20

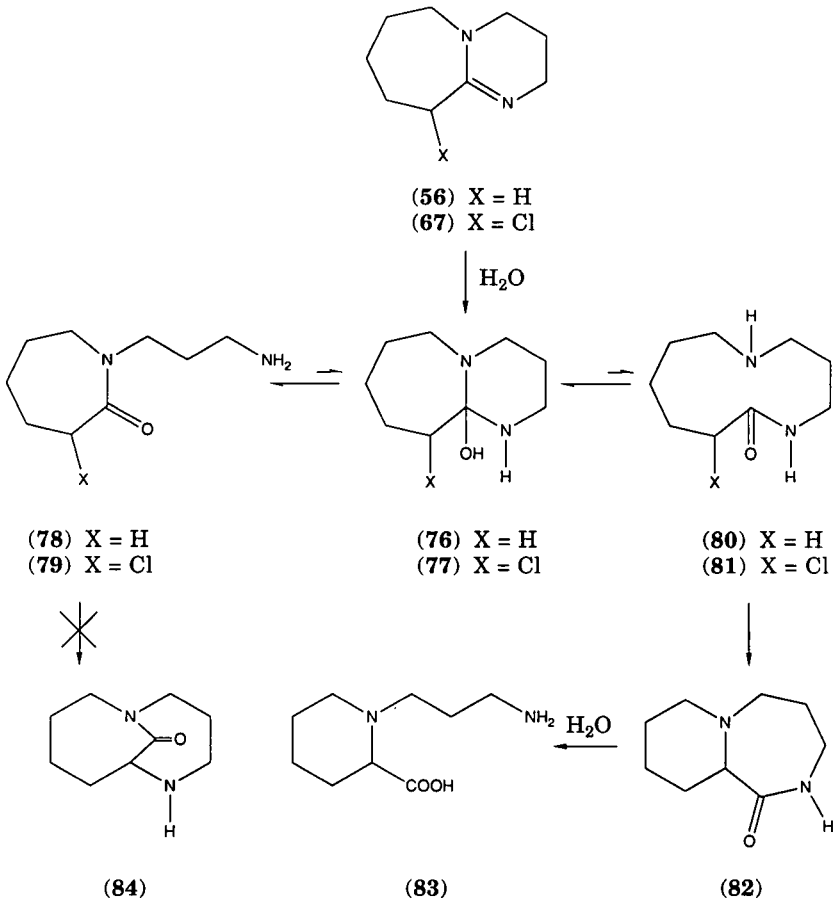


(64) R = H
(65) R = Me

(73) $R^1 = R^2 = H$
(74) $R^1 = H$, $R^2 = Me$
(75) $R^1 = Me$, $R^2 = H$

SCHEME 21

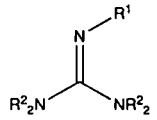
On hydrolytic polymerization of ε-caprolactam, semicyclic compounds containing terminal amidine groups are formed in addition to linear and cyclic oligomers of ε-aminocaproic acid. In contrast to other amidine compounds (e.g. amidine hydrochlorides) these are very reactive and can take part in several reactions during the polymerization. The first member of the polymeric homologous series, *N*-[1-azacycloheptene-(1)-yl-(2)]-ε-aminocaproic acid, can also initiate the polymerization of caprolactam with simultaneous formation of its polymeric homologous. Compounds containing terminal $—NH_3^+$



SCHEME 22

groups are formed in traces only. The amidine carboxylic acids can react with each other resulting in simultaneous disappearance of the amidine and carboxyl groups[130].

An improved preparation of vinyl iodides by using strong, fully substituted, guanidine bases (**85**, **86** and **62**) has been reported. The iodides are formed by oxidation of ketone hydrazones by iodine in the presence of base. Three factors were found to be responsible for the improved yields: (1) absence of water, (2) the use of **85**, **86** and **62**, and (3) inverse addition[131].



(**85**) $R^1 = t$-Bu, R^2 = Me
(**86**) $R^1 = R^2 = i$-Pr
(**62**) R^1 = H, R^2 = Me

Optically active amidines in complexes with rhodium have been used for hydrogenation of prochiral olefins[132]. Also, other transition metal complexes with amidines in asymmetric catalysis have been studied[133].

The guanidine exchanged forms of faujasites have been prepared by ion exchanging NaX and NaY zeolites with guanidine–HCl solution. The catalytic activity of guanidine–NaX and guanidine–NaY were tested. The high activity of guanidine–NaX is discussed[134].

N-Aryltetramethylguanidines catalyze the formation of polyurethane foams by a novel exchange reaction involving the CN double bond of the guanidines and the isocyanate groups of the polyisocyanate. The catalyst sites were transferred to the growing polymer network, achieving a rapid catalytic buildup of the foam. The guanidine catalysts, viz. 2-phenyl-1,1,3,3-tetramethylguanidine and 2,2'-(methylene-di-*p*-phenylene) bis [tetramethylguanidine] had a better catalytic activity in polyurethane foam formation than either Et_3 N or tetramethylbutanediamine[135].

The selectivity and kinetics of epoxy resin–bisphenol A reaction catalyzed by certain guanidine derivatives[136], the mechanism of the effect of chloroformamidinium chlorides in the production of isocyanates[137], the sulfur vulcanization of *cis*-1,4-polybutadiene in the presence of diphenylguanidine[138] and the inhibitory effect of a series of alkylguanidine hydrochlorides against trypsin catalysis have also been investigated[139].

The N-terminal α-helical region of phospholipase A_2 is an important part of the enzyme for catalytic activity and lipid binding. Semisynthetic analogs of ε-amidinated phospholipase A_2 have been prepared and studied[140].

V. REFERENCES

1. R. P. Bell, *The Proton in Chemistry*, 2nd ed., Chapman and Hall, London, 1973.
2. W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, 1969.
3. A. Fersht, *Enzyme Structure and Mechanism*, 2nd ed., Freeman, New York, 1985.
4. J. F. Bunnett and R. A. Y. Jones, *Pure Appl. Chem.*, **60**, 1115 (1988).
5. R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim/Bergstrasse, 1971.
6. P. Ahlberg and F. Ladhar, *Chem. Scr.*, **1**, 31 (1973).
7. H. M. Niemeyer and P. Ahlberg, *J. Chem. Soc., Chem. Commun.*, 799 (1974).
8. H. M. Niemeyer, O. Goscinski and P. Ahlberg, *Tetrahedron*, **31**, 1699 (1975).
9. K. Janné and P. Ahlberg, *Acta Chem. Scand., Ser. B*, **30**, 245 (1976).
10. K. Janné and P. Ahlberg, *J. Chem. Soc., Chem. Commun.*, 1040 (1976).
11. P. Ahlberg, K. Janné, S. Löfås, F. Nettelblad and L. Swahn, *J. Phys. Org. Chem.*, **2**, 429 (1989).
12. M. Ek and P. Ahlberg, *Acta Chem. Scand., Ser. B*, **38**, 211 (1984).
13. H. Bivehed, Ph. D. Thesis, Acta Universitatis Uppsaliensis, Abstracts of Uppsala Disertations from the Faculty of Science, **802**, Uppsala, Sweden, 1985.
14. H. Bivehed and P. Ahlberg, to be published.
15. M. Ek, Ph. D. Thesis, Acta Universitatis Uppsaliensis, Abstracts of Uppsala Disertations from the Faculty of Science, **692**, Uppsala, Sweden, 1983.
16. G. Bergson and A.-M. Weidler, *Acta Chem. Scand.*, **17**, 1798 (1963).
17. G. Bergson, *Chem. Scr.*, **8**, 145 (1975) and references cited therein.
18. J. Almy, R. T. Uyeda and D. J. Cram, *J. Am. Chem. Soc.*, **89**, 6768 (1967).
19. D. J. Cram, *Fundamentals of Carbanion Chemistry*, Academic Press, New York, 1965.
20. J. Almy, D. C. Garwood and D. J. Cram, *J. Am. Chem. Soc.*, **92**, 4321 (1970).
21. C. G. Swain and J. F. Brown, *J. Am. Chem. Soc.*, **74**, 2534 (1952).
22. C. G. Swain and J. F. Brown, *J. Am. Chem. Soc.*, **74**, 2538 (1952).
23. P. R. Rony, *J. Am. Chem. Soc.*, **90**, 2824 (1968).
24. P. R. Rony, W. E. McCormack and S. W. Wunderly, *J. Am. Chem. Soc.*, **91**, 4244 (1969).
25. P. R. Rony and R. O. Neff, *J. Am. Chem. Soc.*, **95**, 2896 (1973).
26. L. Melander and W. H. Saunders, Jr., *Reaction Rates of Isotopic Molecules*, Chap. 2, Robert E. Krieger Publishing Company, Malabar, Florida, 1987.

27. P. Svensson, N.-Å. Bergman and P. Ahlberg, to be published.
28. P. Ahlberg and M. Ek, *J. Chem. Soc., Chem. Commun.*, 624 (1979).
29. M. Ek and P. Ahlberg, *Acta Chem. Scand., Ser. B*, **38**, 203 (1984).
30. A. Gut and P. Ahlberg, *Chem. Scr.*, **18**, 248 (1981).
31. P. Ahlberg and M. Ek, *Chem. Scr.*, **10**, 47 (1976).
32. J. A. Chmielewski, Ph. D. Thesis, Columbia University, New York, 1988.
33. R. M. Pollack, P. L. Bounds and C. L. Bevins in *The Chemistry of Enones* (Eds. S. Patai and Z. Rappoport), Wiley, London, 1989.
34. (a) P. Talalay and V. S. Wang, *Biochim. Biophys. Acta*, **18**, 300 (1955)
(b) F. S. Kawahara, S. F. Wang and P. Talalay, *J. Biol. Chem.*, **237**, 1500 (1962).
35. A. M. Benson, R. Jarabak and P. Talalay, *J. Biol. Chem.*, **246**, 7514 (1971).
36. F. Vincent, H. Weintraub and A. Alfsen, *FEBS Lett.*, **22**, 319 (1972).
37. P. Talalay and A. M. Benson, *The Enzymes*, Vol. 6 (Ed. P. D. Boyer), Academic Press, New York, 1972, p. 591.
38. A. M. Benson, A. J. Suruda, R. Shaw and P. Talalay, *Biochim. Biophys. Acta*, **348**, 317 (1974).
39. H. Weintraub, F. Vincent, E. E. Beaulieu and A. Alfsen, *Biochemistry*, **16**, 5045 (1977).
40. F. H. Batzold, A. M. Benson, D. F. Covey, C. H. Robinson and P. Talalay, *Adv. Enzyme Regul.*, **14**, 243 (1976).
41. K. R. Hanson and I. A. Rose, *Acc. Chem. Res.*, **8**, 1 (1975).
42. S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **87**, 3228 (1965).
43. J. B. Jones and D. C. Wigfield, *Can. J. Chem.*, **45**, 5294 (1967).
44. J. B. Jones and D. C. Wigfield, *Can. J. Chem.*, **46**, 1459 (1968).
45. J. B. Jones and D. C. Wigfield, *Can. J. Chem.*, **47**, 4459 (1969).
46. H. Weintraub, A. Alfsen and E. E. Beaulieu, *Eur. J. Biochem.*, **12**, 217 (1970).
47. J. B. Jones and K. D. Gordon, *Biochemistry*, **12**, 71 (1973).
48. W. F. Benisek and A. Jacobson, *Bioorg. Chem.*, **4**, 41 (1975).
49. A. Viger and A. Marquet, *Biochim. Biophys. Acta*, **485**, 482 (1977).
50. H. J. Carrel, J. P. Glusker, D. F. Covey, F. H. Batzold and C. H. Robinson, *J. Am. Chem. Soc.*, **100**, 4282 (1978).
51. W. R. Nes, E. Loeser, R. Kirdani and J. Marsh, *Tetrahedron*, **19**, 299 (1963).
52. S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1538 (1963).
53. S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **86**, 1997 (1964).
54. H. C. Volger and W. Brackman, *Recl. Trav. Chim. Pays-Bas*, **84**, 1017 (1965).
55. Y. Mialhe and R. Vessière, *Bull. Soc. Chim. Fr.*, 4181 (1968).
56. A. Kergomard and M. F. Renard, *Tetrahedron Lett.*, 2319 (1970).
57. A. Kergomard and M. F. Renard, *Tetrahedron*, **28**, 2111 (1972).
58. (a) D. S. Noyce and M. Evett, *J. Org. Chem.*, **37**, 394 (1972).
(b) D. S. Noyce and M. Evett, *J. Org. Chem.*, **37**, 397 (1972).
59. A. Fauve, A. Kergomard and M. F. Renard, *Tetrahedron*, **29**, 2903 (1973).
60. A. Fauve, A. Kergomard and M. F. Renard, *Tetrahedron Lett.*, 607 (1973).
61. A. Kergomard, L. Q. Xáng and M. F. Renard, *Tetrahedron*, **32**, 1989 (1976).
62. D. L. Whalen, J. F. Weimaster, A. M. Ross and R. Radhe, *J. Am. Chem. Soc.*, **98**, 7319 (1976).
63. T. Okuyama, A. Kitada and T. Fueno, *Bull. Chem. Soc. Jpn.*, **50**, 2358 (1977).
64. P. B. D. de la Mare and R. D. Wilson, *J. Chem. Soc., Perkin Trans. 2*, 157 (1977).
65. S. K. Perera, W. A. Dunn and L. R. Fedor, *J. Org. Chem.*, **45**, 2816 (1980).
66. A. Fauve and A. Kergomard, *Tetrahedron*, **37**, 1697 (1981).
67. R. C. Mease and J. A. Hirsch, *J. Org. Chem.*, **49**, 2925 (1984).
68. B. Capon in *The Chemistry of Enones* (Eds. S. Patai and Z. Rappoport), Wiley, London, 1989.
69. G. Lamaty in *Isotopes in Organic Chemistry*, Vol. 2 (Eds. E. Buncel and C. C. Lee), Elsevier, Amsterdam, 1976, p. 33.
70. J. Toullec, *Adv. Phys. Org. Chem.*, **18**, 1 (1982).
71. H. J. Ringold and S. K. Malhotra, *J. Am. Chem. Soc.*, **84**, 3402 (1962).
72. E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).
73. R. R. Fraser and P. J. Champagne, *J. Am. Chem. Soc.*, **100**, 657 (1978).
74. G. A. Abad, S. P. Jindal and T. T. Tidwell, *J. Am. Chem. Soc.*, **95**, 6326 (1973).
75. P. Metzger, A. Casadevall and E. Casadevall, *Tetrahedron Lett.*, 2027 (1973).
76. P. Metzger and E. Casadevall, *Tetrahedron Lett.*, 3341 (1973).
77. G. B. Trimitsis and E. M. Van Dam, *J. Chem. Soc., Chem. Commun.*, 610 (1974).

78. A. A. El-Anani, C. C. Greig and C. D. Johnson, *J. Chem. Soc., Chem. Commun.*, 1024 (1970).
79. S. P. Jindal and T. T. Tidwell, *Tetrahedron Lett.*, 783 (1971).
80. T. T. Tidwell, *J. Am. Chem. Soc.*, **92**, 1448 (1970).
81. F. G. Bordwell and R. G. Scamehorn, *J. Am. Chem. Soc.*, **90**, 6749 (1968).
82. S. P. Jindal, S. S. Sohoni and T. T. Tidwell, *Tetrahedron Lett.*, 779 (1971).
83. A. F. Thomas, R. A. Schneider and J. Meinwald, *J. Am. Chem. Soc.*, **89**, 68 (1967).
84. P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon Press, Oxford, 1983.
85. O. S. Tee, J. A. Altmann and K. Yates, *J. Am. Chem. Soc.*, **96**, 3141 (1974).
86. S. Löfås and P. Ahlberg, *J. Chem. Soc., Chem. Commun.*, 998 (1981).
87. S. Löfås and P. Ahlberg, *J. Am. Chem. Soc.*, **107**, 7534 (1985).
88. E. F. Caldin and S. Mateo, *J. Chem. Soc., Chem. Commun.*, 854 (1973).
89. E. F. Caldin and S. Mateo, *J. Chem. Soc., Faraday Trans. 1*, **71**, 1876 (1975).
90. E. F. Caldin and S. Mateo, *J. Chem. Soc., Faraday Trans. 1*, **72**, 112 (1976).
91. O. Rogne, *J. Chem. Soc., Chem. Commun.*, 695 (1977).
92. O. Rogne, *Acta Chem. Scand., Ser. A*, **32**, 559 (1978).
93. O. Rogne, *J. Chem. Soc., Faraday Trans. 1*, **74**, 1254 (1978).
94. A. Thibblin and P. Ahlberg, *J. Am. Chem. Soc.*, **101**, 7311 (1979).
95. A. J. Kresge and M. F. Powell, *J. Am. Chem. Soc.*, **103**, 201 (1981).
96. R. P. Bell, *The Tunnel Effect*, Chapman and Hall, New York, 1980.
97. P. Ahlberg and S. Bengtsson, *Chem. Scr.*, **6**, 45 (1974).
98. A. Thibblin and P. Ahlberg, *Chem. Soc. Rev.*, **18**, 209 (1989).
99. K. B. Schowen, Ph.D. Thesis, Massachusetts Institute of Technology, Massachusetts, 1964.
100. R. L. Schowen, *Prog. Phys. Org. Chem.*, **9**, 275 (1972).
101. K. B. Schowen, L. McKay and J. Nisly, *Bull. Soc. Chim. Belg.*, **91**, 384 (1982).
102. A. Kergomard, L. Q. Xáng and M. F. Renard, *Tetrahedron*, **32**, 1983 (1976).
103. V. Fiandanese and F. J. Naso, *J. Chem. Soc., Perkin Trans. 2*, 1047 (1977).
104. A. M. Kjaer, H. Nielsen, P. E. Sörensen and J. Ulstrup, *Acta Chem. Scand., Ser. A*, **34**, 281 (1980).
105. K.-Å. Engdahl, H. Bivehed, O. Bohman, U. Obenius and P. Ahlberg, *Chem. Scr.*, **18**, 176 (1981).
106. K.-Å. Engdahl, H. Bivehed, P. Ahlberg and W. H. Saunders, Jr., *J. Chem. Soc., Chem. Commun.*, 423 (1982).
107. K.-Å. Engdahl, H. Bivehed, P. Ahlberg and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **105**, 4767 (1983).
108. M. M. Kreevoy, T. Liang and K.-C. Chang, *J. Am. Chem. Soc.*, **99**, 5207 (1977).
109. M. M. Kreevoy and T. M. Liang, *J. Am. Chem. Soc.*, **102**, 3315 (1980).
110. M. M. Kreevoy and B. A. Ridl, *J. Phys. Chem.*, **85**, 914 (1981).
111. R. D. Gandour and R. L. Schowen, *Transition States of Biochemical Processes*, Plenum Press, New York, 1978.
112. J. D. Hermes and W. W. Cleland, *J. Am. Chem. Soc.*, **106**, 7263 (1984).
113. J. G. Belasco, W. J. Albery and J. R. Knowles, *Biochemistry*, **25**, 2529 (1986).
114. J. G. Belasco, W. J. Albery and J. R. Knowles, *Biochemistry*, **25**, 2552 (1986).
115. W. J. Albery, *J. Phys. Chem.*, **90**, 3773 (1986).
116. H. H. Limbach, J. Henning, D. Gerritzen and H. Rumpel, *Faraday Discuss. Chem. Soc.*, **74**, 822 (1982).
117. Y.-T. Chang, Y. Yamaguchi, W. H. Miller and H. F. Schaefer, III, *J. Am. Chem. Soc.*, **109**, 7245 (1987).
118. M. J. Field and I. H. Hiller, *J. Chem. Soc., Perkin Trans. 2*, 617 (1987).
119. T. J. Zielinski and R. A. Poirier, *J. Comput. Chem.*, **5**, 466 (1984).
120. P. Svensson, N.-Å. Bergman and P. Ahlberg, *Z. Naturforsch., Teil A*, **44**, 473 (1989).
121. P. Svensson, N.-Å. Bergman and P. Ahlberg, *J. Chem. Soc., Chem. Commun.*, 82 (1990).
122. P. Svensson, N.-Å. Bergman and P. Ahlberg, *J. Chem. Soc., Chem. Commun.*, 862 (1990).
123. F. M. Menger, *J. Am. Chem. Soc.*, **88**, 3081 (1966).
124. B. L. Knier and P. Haake, *Tetrahedron Lett.*, 3219 (1977).
125. B. Springs and P. Haake, *Tetrahedron Lett.*, 3223 (1977).
126. G. P. Pollini, A. Barco and G. De Giuli, *Synthesis*, 1, 44 (1972).
127. S. Löfås and P. Ahlberg, *J. Heterocycl. Chem.*, **21**, 583 (1984).
128. S. Löfås and P. Ahlberg, *J. Chem. Soc., Perkin Trans. 2*, 1223 (1986).
129. U. Schuchardt and O. C. Lopes, *J. Am. Oil Chem. Soc.*, **65**, 1940 (1988).

130. Z. Csürös, I. Rusznák, G. Bertalan, L. Trézl and J. Körösi, *Makromol. Chem.*, **137**, 17 (1970).
131. D. H. R. Barton, G. Bashiardes and J.-L. Fourrey, *Tetrahedron Lett.*, **24**, 1605 (1983).
132. H. Brunner and G. Agrifoglio, *Monatsh. Chem.*, **111**, 275 (1980).
133. H. Brunner, G. Agrifoglio and I. Creswick, *Angew. Chem.*, **92**, 645 (1980).
134. Z. Pudzik, S. Kowalak and Z. Wanierowicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **23**, 1037 (1975).
135. H. Ulrich, H. E. Reymore, Jr. and A. A. R. Sayigh, *J. Polym. Sci., Polym. Chem. Ed.*, **13**, 2031 (1975).
136. P. N. Son and C. D. Weber, *J. Appl. Polym. Sci.*, **17**, 2415 (1973).
137. Z. Csürös, R. Soos, I. Bitter and E. Karpati-Adam, *Period. Polytech., Chem. Eng.*, **16**, 315 (1972).
138. V. M. Kharchevnikov, S. N. Korchernkin and V. V. Lomakina, *Issled. Obl. Fiz. Khim. Reziny*, 43 (1972).
139. T. Inagami and S. S. York, *Biochemistry*, **7**, 4045 (1968).
140. G. J. M. Van Scharrenburg, W. C. Puijk, G. H. De Haas and A. J. Slotboom, *Eur. J. Biochem.*, **133**, 83 (1983).

CHAPTER **16**

Electrochemistry of amidines

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I. INTRODUCTION

Two general observations may be formulated from a consideration of electrochemical investigations of amidines and related compounds before and after the review by Lund[1] in the previous volume of this series. First, in recent years far more attention has been paid to the electrochemical study of cyclic amidines and, in particular, of biologically active compounds which may be treated as amidines. And, second, in the last decade there has

The Chemistry of Amidines and Imidates, Volume 2
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been an unsurge of interest in the use of non-aqueous, formally aprotic solvents. According to the first observation a great part of this chapter is devoted to the electrochemistry of cyclic amidines, guanidines and biological molecules. The latter class of compounds needs some comment. Amidines are known as important medical and biochemical agents; the amidine moiety can be identified in numerous cyclic derivatives of biological interest. Consequently, the electrochemistry of these compounds is a very important part of biochemistry. The growing significance of cyclic amidines in organic electrochemistry may be estimated on the basis of a continuous flow of specialist publications beginning in the middle 1960s. The magnitude of the available literature and the complexity of the effects involved can be seen from monographs[2-8]. Therefore, only selected compounds will be discussed in this chapter, i.e. mainly pyrimidines and purine bases. It is noteworthy that some of the amidines presented here are important components of nucleic acids and their properties are of general interest. However, due to the large number of investigators and the wide variety of literature sources involved, no claim is made for completeness in this review.

Electrochemical investigations of heteroaromatic compounds including the amidine moiety, e.g. imidazoles, triazoles, etc., have been recently reviewed by Baumgärtel and Retzlaw[7] and in this field only later literature since 1980 is covered in our chapter. On the other hand, recent studies of the electrochemical behaviour of simple, non-cyclic amidines are scarce. There is no separate section on amidines in *Encyclopedia of Electrochemistry of the Elements*, although it was anticipated for volume XV[9]. More information on the electrochemistry of hydrazones, oximes, formazans, etc. have been given in a recent Russian review[10] but access to this work will be limited because of the language. Thus, for non-cyclic amidines this chapter covers the period from approximately 1973 to the end of 1989.

A comparison of the aqueous and non-aqueous electrochemistry of amidines shows the fundamental role of the experimental environment related to solvation of reactants, their protonation, influence on different equilibria, and accompanying reactions. These general principles of the electrochemistry of amidines are discussed in Section II. They include effects of reactant, solvent, pH and substituents on the half-wave potentials, as well as tautomeric equilibria of amidines. Electrosynthesis of amidines is presented in Section III, and their electrochemical behaviour in cathodic and anodic processes in Section IV. Discussion of reaction mechanisms is usually emphasized as a main topic of interest for organic chemists.

The investigations, interesting rather from the electrochemical point of view and important for practical applications of electrode reactions, and especially the adsorption phenomena, will not be discussed in detail. However, some applications of electrochemical processes of amidines are mentioned in the Epilogue (Section V).

The following abbreviations for non-aqueous solvents and supporting electrolytes are used: DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulphoxide; ACN, acetonitrile; EtOH, ethanol; MeOH, methanol; Py, pyridine; TEAP, tetraethylammonium perchlorate; TEAF, tetraethylammonium tetrafluoroborate; TBAP, tetrabutylammonium perchlorate; TBAI, tetrabutylammonium iodide; TBAB, tetrabutylammonium bromide. The quoted potentials are expressed versus an aqueous saturated calomel electrode (SCE), unless otherwise noted.

II. GENERAL ASPECTS

A. Relationships Between Electroactivity and Structure

Only some amidines and related compounds can be reduced or oxidized at electrodes and there is no general scheme describing the electrochemical behaviour of the amidines

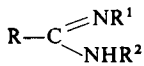
group. The overall reduction process usually involves a saturation of double bonds and a cleavage of C—N (e.g. in benzamidines), N—N (e.g. in tetrazolium cations) or N—O (e.g. in amidoximes) bonds. In other words, the electroactivity of an amidine is a general property of the whole molecule and depends on its constitution as well as on properties of the medium used. The first aspect is discussed in this section in relation to the half-wave potential, $E_{1/2}$, as the most convenient parameter for measurements.

For a simple one-electron (1e) reduction not accompanied by any preceding and succeeding chemical step, the correlations between $E_{1/2}$ values and electron affinities (EA) of a reactant have been well established in the literature (cf. work by Parker[11] and references cited therein):

$$E_{1/2} = \mathrm{EA} - C - \Delta\Delta G^{\circ}_{\mathrm{solv}} \qquad (1)$$

where $\Delta\Delta G^{\circ}_{\mathrm{solv}}$ denotes the difference in free energies of solvation of a reactant and its radical anion, whereas constant C is characteristic of the reference electrode. On the other hand, linear correlations of $E_{1/2}$ values with the energies of the lowest unoccupied molecular orbital, E_{LUMO}, can be predicted on the basis of molecular orbital theory[7,12]. Of course, half-wave potentials proper for 1e oxidation processes fulfil analogous relationships with ionization potentials and E_{HOMO}. In order to obtain meaningful regressions of this type it is best to use reversible $E_{1/2}$ values determined in non-proton-donating media, i.e. under conditions for a simple 1e step. Table 1 shows results of calculations performed in our department[13] for several amidines by the MNDO method[14,15] and also some experimental data for the reduction in DMF[16,17]. It is evident that LUMO energies (given in a conventional scale) decrease with the change of aliphatic amidines to aromatic ones and with the increase in the number of phenyl substituents. The results obtained can elucidate the limited scale of electrochemical data for simple amidines. It should be added, however, that the behaviour in aqueous solutions is more complex because polarographic waves correspond to irreversible, many-electron transfers accompanied by protonation and other chemical steps. In general, protonation of the amidine group facilitates reduction resulting in $E_{1/2}$ values at more positive potentials than those proper for the reduction under aprotic conditions.

TABLE 1. LUMO energies[13] and reduction potentials of simple amidines in DMF solutions at a mercury cathode



R	R^1	R^2	E_{LUMO}	$-E^{\circ}_{\mathrm{red}}$ [a]
H	H	H	1.162	
H	Ph	Ph	0.109	[b]
Me	H	H	0.993	
			−5.445[c]	
Me	Ph	H	0.263	
Me	H	Ph	0.312	
Ph	H	H	−0.159	1.78
Ph	Ph	H	−0.160	1.73
Ph	Ph	Ph	—	1.60

[a] Peak potentials (vs Ag/Ag^+) in DMF–TBAI[16].
[b] Not reducible in DMF–TEAP[17].
[c] Calculated for monoprotonated compound.

Taking into account that E_{LUMO}, as well as $E_{1/2}$ values, are dependent on all characteristics of the molecule, the electrode reactions of some amidine derivatives, in which only a substituent is reduced or oxidized, are occasionally reported in this review.

B. Medium Effects

It is well known that in aprotic conditions many organic substances are cathodically reduced in two reversible 1e steps. If the first of them is not accompanied by any chemical reactions, the $E_{1/2}$ value of a given compound measured in a series of non-proton-donating solvents can be compared with the difference of free solvation energies $\Delta\Delta G^0_{solv}$ according to equation 1 (for details, see References 18 and 19). Unfortunately, reliable comparisons for amidines are impossible so far because their investigations in non-aqueous solvents are limited only to DMF and ACN.

The situation becomes more complex in protolytic media. Now, any one or more of three parameters—the half-wave potential, the limiting current and the number of polarographic waves—depend on acidity of the solution electrolysed, most often expressed as pH or a corresponding acidity function. All these changes result from the effect of acidity on acid–base equilibria and on the rate of chemical reactions accompanied by an electron transfer step.

For a system in which fast protonation precedes the cathodic reduction, the $E_{1/2}$ potential is practically pH-independent at pH < pK, but is shifted towards more negative values at higher pH. In this case a plot of $E_{1/2}$ against pH includes two linear parts with the intersection corresponding approximately to pK. Emphasis is made, however, that such a picture can be observed when (1) only one polarographic wave is recorded in the whole pH region under study, and (2) the double layer effect on the acid–base equilibria can be neglected.

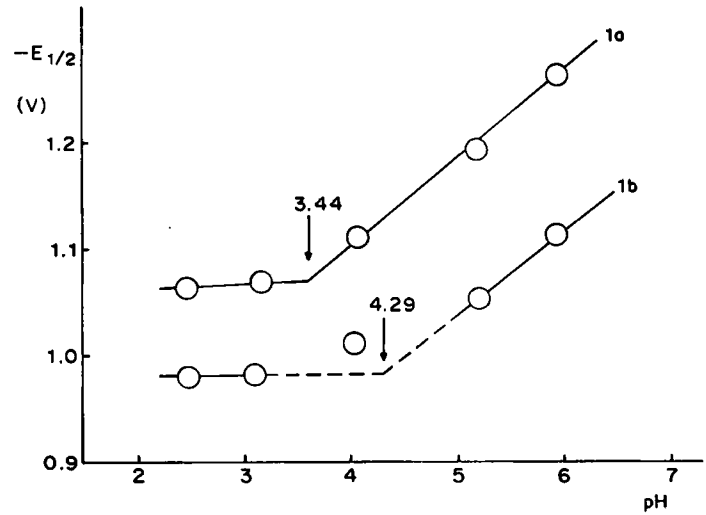
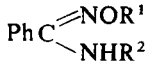


FIGURE 1. Dependences of half-wave potentials for the reduction of benzamidoximes (1) in aqueous ethanol on pH. Values of pK_a are given. Experimental data are from Reference 20. For numbering of reactants see text

An example of such behaviour is the reduction of benzamidoximes (1) at a dropping mercury electrode[20]. In 50 vol% ethanol these compounds are reduced to amidines, and, as can be seen from Figure 1, the corresponding half-wave potentials are pH-dependent. The observed intersections on the $E_{1/2}$–pH plots correspond really to the pK_a values of the protonated forms; the latter ones were determined by potentiometric titration.



(1a) $R^1 = Et$, $R^2 = H$

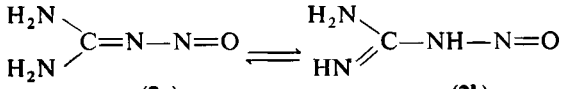
(1b) $R^1 = H$, $R^2 = CH_2Ph$

(1)

The slope of the $E_{1/2}$–pH dependence indicates how many electrons are involved in the overall electrode process. The behaviour presented in Figure 1 is very simple, but, in cases of more complex equilibria of protonation, more linear sections can be observed in the plots under discussion, as will be specified for individual amidines in further sections.

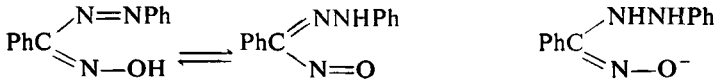
C. Tautomeric Equilibria

Tautomerism exhibited by amidines can influence their electrochemical behaviour, and thus polarographic methods can be used for a study of such equilibria. Unfortunately, only a limited number of cases is a direct investigation possible, when the two tautomeric forms show different waves (or peaks). Of course, the necessary condition for such behaviour is a sufficiently large difference in $E_{1/2}$ values of both forms. Usually, in protic media tautomeric equilibria depend strongly on pH and separated waves can be observed only within a narrow pH range. This is the case for the reduction of nitrosoguanidine (2) at a mercury electrode in acidic aqueous solutions. It was suggested[21] that two waves observed at pH < 8 correspond to tautomeric forms **2a** and **2b**, which are additionally protonated. The wave found at more positive potentials corresponds to the form **2a** which is reduced to guanidine. On the other hand, **2b** is reduced to aminoguanidine (cf. Section IV.D). It can be added here that a separation of polarographic waves for the reduction of nitroguanidine (3) in alkaline solutions due to the coexistence of both tautomeric forms was observed earlier and confirmed by UV spectra as well as by HMO calculations[22].



(2a) (2b)

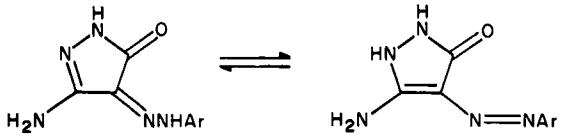
When one tautomer dominates under the experimental conditions it is possible to identify this form indirectly. For example, the azo form of phenylazobenzaldoxime (**4a**) was postulated in aqueous 40% methanolic solutions on the basis of the observed polarographic behaviour[23], namely the successive reduction of azo and oxime groups. Two 2e waves found in acidic media were identical with the waves proper for the reduction of azobenzene and benzaldehyde oxime, respectively[23]. On the other hand, in alkaline media (pH > 9.0) only the first wave was observed due to the formation of an anion (**4c**) which is less readily reduced.



(4a) (4b) (4c)

The occurrence of different tautomeric forms in some heterocyclic compounds poses a problem in considering a given compound as an amidine. Spectroscopic as well as polarographic studies of 3-amino-4-arylazo-2-pyrazolin-5-ones (5) indicated[24] that these

compounds existed in the hydrazone form (**5a**) in the solid state, but in aqueous 30% ethanolic solutions in the azo form (**5b**), which has no amidine grouping.



(**5a**) (**5b**)

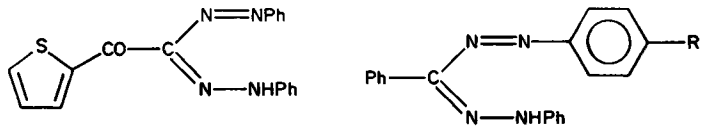
Hydroxypyrimidines coexist also in two tautomeric forms and only one of them has the amidine group; this problem will be considered in Section IV.G.1.

D. Substituent Effects

Effects of a substituent nature on half-wave potentials have been discussed qualitatively in many papers on electrochemical behaviour of amidines, but polarographic Hammett and Hammett-type equations have been used successfully only in a few cases. In general, linear correlations of $E_{1/2}$ values against the substituent constants, σ, have been well established in organic electrochemistry; earlier results were reviewed by Zuman[25,26] and some recent problems have been discussed elsewhere[19]. It is well known that the necessary condition for such relationships is that the same common mechanism operates for all members of a reaction series. This is the case, e.g., for a simple, reversible process, when a half-wave potential has a thermodynamic meaning. Unfortunately, for electrochemical studies of numerous amidine systems, in particular in aqueous solutions, $E_{1/2}$ values correspond to irreversible, many-electron processes where the overall mechanism is complicated by a sequence of electron transfers and chemical steps. Then, half-wave potentials have so complex a nature that the Hammett equation should be considered only as a local rule for a limited number of compounds and strong deviations are quite conceivable.

A comprehensive study of substituent effects for the electroreduction of substituted benzamidines in aqueous buffers containing 50% ethanol was described by Ševčik[27]. For six *N,N'*-diphenylbenzamidines with *meta*- and *para*-substituted phenyl groups at the imino nitrogen atom, a good correlation between Hammett σ constants and $E_{1/2}$ values of the first reduction wave at pH = 5 was found[27], with a reaction constant $\rho = 0.22$ V per σ unit. The considered $E_{1/2}$ values correspond to an irreversible 2e wave which is independent of pH (full protonation of the imino N atom occurs prior to the electron transfer).

More investigations have been devoted to formazans. For the oxidation of 3-thenoyl-1,5-diarylformazans (**6**) in ACN solutions two irreversible steps have been found[28], producing a radical cation and a dication, respectively. Half-wave potentials for both processes obtained at a rotating Pt anode have been related[28] to σ_p^+ constants of Brown and Okamoto[29], as is shown in Figure 2. Acceptable correlations have been observed[28]



(**6**) (**7**)

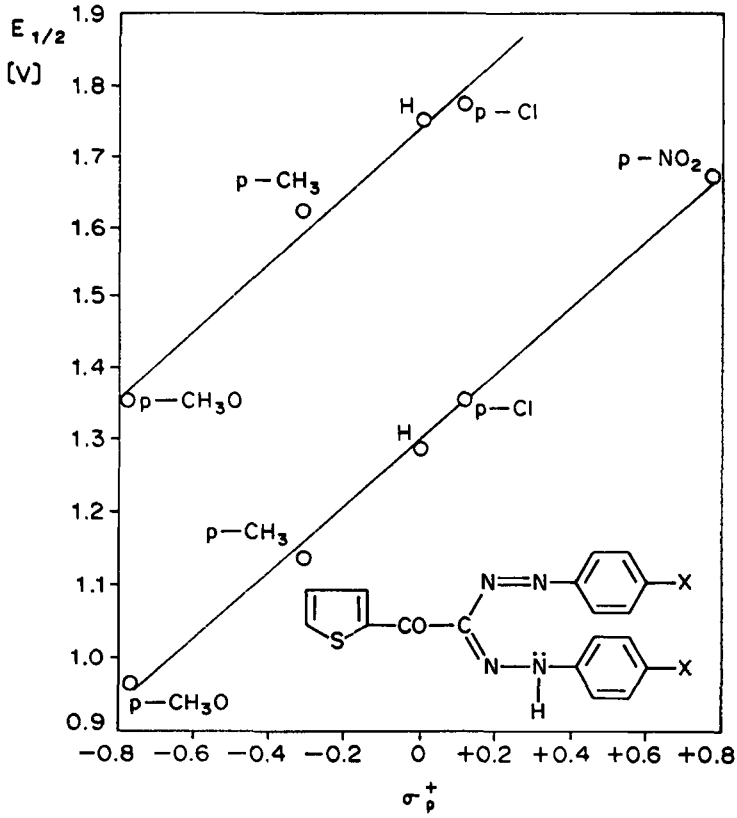


FIGURE 2. Half-wave potentials for the oxidation of 3-thenoyl-1,5-diarylformazans in ACN as dependent on Brown's substituent constants σ_p^+. The lower and upper lines correspond to the first and second electron transfer, respectively. Reprinted with permission from *Tetrahedron*, **30**, Laćan, Tabaković and Čeković, Electrochemical Syntheses of Heterocyclic Compounds. Copyright (1974) Pergamon Press PLC

(correlation coefficients $r = 0.998$ and $r = 0.992$, with $\rho = 0.44$ and $\rho = 0.48$ for the first and second step, respectively) although two alternative pathways have been suggested after a radical cation formation (see Section IV.B).

In other studies of formazans, the authors[30,31] did not use the Hammett equation and, in general, relationships of this type are poor. However, for a limited number of compounds the obtained results (taken from the original papers) can be interpreted on the basis of correlation analysis. For the irreversible oxidation of 1,3,5-triphenylformazans (7) in ACN at a rotating-disc Pt electrode[31] the following relationship has been obtained by us:

$$E_{1/2} = 0.66 + 0.18\sigma_p^+ \qquad (2)$$

with correlation coefficient $r = 0.990$ ($E_{1/2}$ values are given vs Ag/Ag^+ in ACN). Using a planar regression with Taft's inductive (σ_I) and mesomeric (σ_R) constants taken from

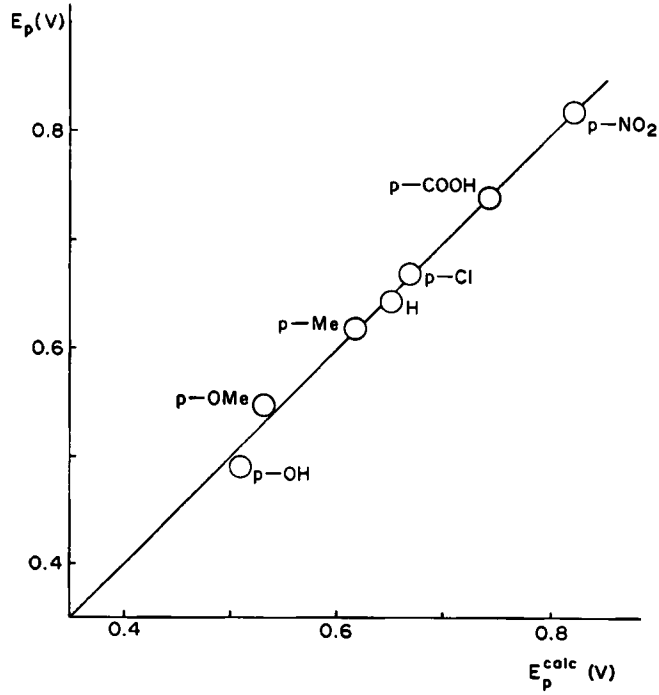


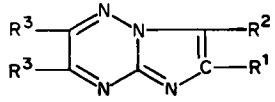
FIGURE 3. Plot of peak potentials for the oxidation of 1,3,5-triphenylformazans (7), taken from Reference 31 versus values calculated from the two-parameter equation 3. The theoretical line is shown

Reference 32, a statistically significant correlation is found (equation 3),

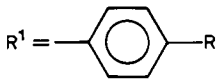
$$E_{1/2} = 0.24(\pm 0.02)\sigma_I + 0.31(\pm 0.02)\sigma_R + 0.65(\pm 0.01) \quad (3)$$

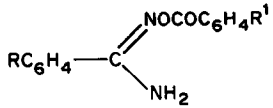
with the correlation coefficient of planar regression $R = 0.995$ (the numbers in parentheses denote 95% confidence intervals of regression coefficients). The plot of equation 3 is shown in Figure 3.

Simple correlations between $E_{1/2}$ and σ_p can also be obtained for the results[33] of the oxidation of 1,2,4-triazines (8), but points for R = Cl slightly deviate to lower $E_{1/2}$ values (cf. Table 10 in Section IV.D).



(8)
(8a) R^3=Me
(8b) R^3=Ph
R=H, Me, Cl, Br, NO_2





(9)

For the polarographic reduction of 25 *O*-benzoylbenzamideoximes (9) in 50% aqueous ethanol at pH 0.9–5.18, a planar regression of $E_{1/2}$ values with two σ_p constants for R and

R^1 positions was suggested[34]. However, a careful inspection of the results presented indicates that points for compounds with R = NMe_2 and NO_2 deviate even for a simple one-parameter Hammett equation for a series with a constant R^1 (= H, OMe or Cl). It should be added that there is a mistake[34] in the sign of the σ_p value for NMe_2. The observed deviations can be easily explained taking into account a change in the reaction mechanism. The reduction of the nitro group precedes the hydrogenolysis of the N—O bond in the acyloximino group[34] and, on the other hand, the dimethylamino group is additionally protonated[34], which causes a shift of $E_{1/2}$ to more positive values. Nevertheless, for 15 compounds with substituents other than NMe_2 and NO_2 a two-parameter regression, as well as a Hammett equation based on the additivity rule, is not statistically significant. Moreover, the substitution at the R^1 position by an electron-donor substituent (OMe) and an electron-acceptor one (Cl) causes a change of $E_{1/2}$ potentials into the same positive direction (150–200 mV) This reflects the complex nature of the half-wave potentials in contrast to the simple thermodynamic parameter, i.e. the pK_a values of **9**, which correlates far better with σ_p constants[34].

So far, polarographic Hammett equations have been discussed only, because applications of linear free-energy relationships to amidines with aliphatic substituents were not applied in the literature. However, in some cases the Taft equation seems to be useful as well. For example, the dependence of half-wave potentials (taken from Reference 20) for the reduction of amidoximes (**1**, R^1 = H, R^2 = Me, Et, Ph and CH_2Ph) in 50% ethanol at pH 4.03 on Taft σ^* constants is shown in Figure 4. It should be mentioned, however, that a similar correlation for results measured[20] at other pH values is less satisfactory.

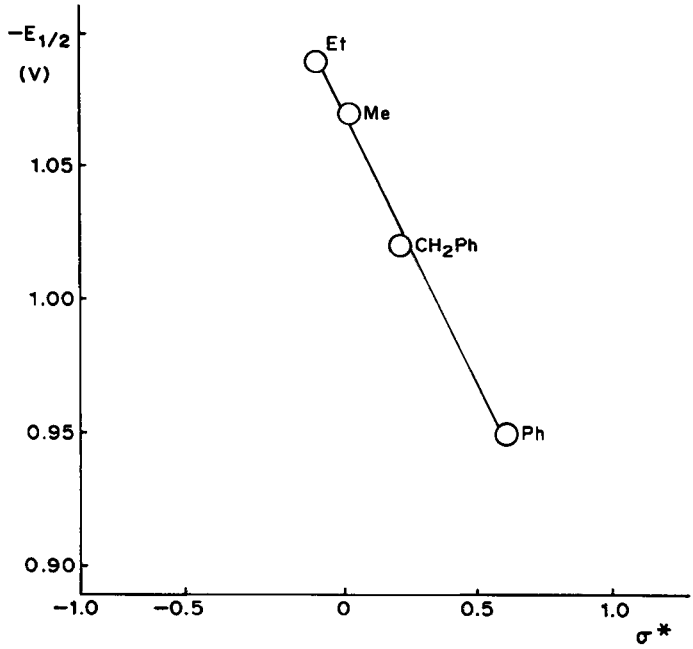
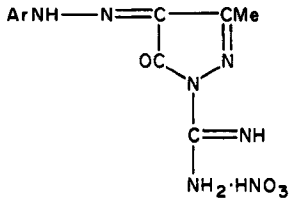


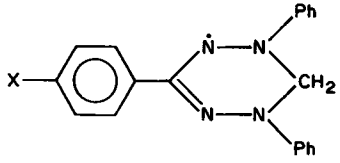
FIGURE 4. Relationship between $E_{1/2}$ values taken from Reference 20, for the reduction of benzamidoximes (**1**) and Taft's σ^* constants; the correlation coefficient is $r = 0.998$

An interesting application of correlation analysis has been proposed by Malik and coworkers[35] for the reduction of 4-arylhydrazono-1-guanidinium-3-methyl-2-pyrazoline-5-ones nitrate (**10**) in aqueous methanol. Half-wave potentials for irreversible 4e, $4H^+$ transfer correlate with substituent constants for *para*- and *meta*-substituted compounds. Moreover, by taking into account correlations for *ortho* derivatives obtained on the basis of steric substituents, E_S, a common straight line has been found[35] for all compounds with the reaction constant $\rho = 0.16$ V per σ unit. It should be mentioned, however, that the electrode process under consideration is a reduction of the hydrazono group. Malik and coworkers[35] also found that the reaction constant, ρ, depended on the size of the supporting electrolyte, but $E_{1/2}$ was independent of electrolyte concentration. For the irreversible process of interest the above result was interpreted[35] in terms of a change in the double-layer structure.



(**10**)

Analysis of substituent effects on half-wave potentials is more certain for 1,3,5-triphenylverdazyl free radical (**11**), which can be reversibly reduced to an anion and oxidized to a cation at a mercury electrode[36,37] in some non-aqueous solvents. Thus, values of $E_{1/2}$ have a thermodynamic meaning. The application of the Hammett equation for a series of five substituted verdazyl radicals (Table 2) indicated that the substituent effect was stronger for oxidation process (greater values of ρ) than for the reduction. Such behaviour was interpreted in terms of a greater coplanarity of the verdazyl cations. Positive values of ρ are quite conceivable: an increase in electron-donor properties of a



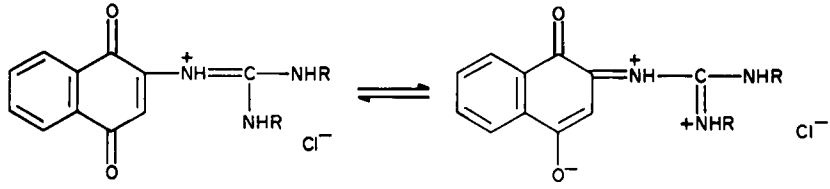
(**11**)
(**11a**) X=H

TABLE 2. Reaction constants and correlation coefficients of the Hammett equation for a series of 1,3,5-triphenylverdazyl radicals (**11**) and half-wave potentials for the unsubstituted compound **11a**[36,37]

	Oxidation			Reduction		
Solvent	ρ (V per σ unit)	r	$E_{1/2}$ (V)	ρ (V per σ unit)	r	$-E_{1/2}$ (V)
ACN	0.10	0.984	0.180	0.08	0.995	0.760
DMF	0.11	0.978	0.215	0.08	0.977	0.760
MeOH	0.12	0.982	0.160	−0.04	0.912	0.270

substituent facilitates the oxidation ($E_{1/2}$ is shifted to smaller values) and an increase in electron-acceptor properties of a substituent facilitates the reduction ($E_{1/2}$ is shifted in a more positive direction). On the other hand, the negative sign of the reaction constant for the reduction in methanol was explained[36] taking into account the strongest solvation of anions and free radicals by methanol. In our opinion, the observed change in the $E_{1/2}$ shift with substituents to the opposite direction in methanol is probably caused by a protonation of verdazyl anions which increases for compounds with electron-donor substituents. This is equivalent to a change in the overall mechanism.

An interesting application of a polarographic Hammett equation was suggested[38] for the evaluation of the substituent constant for guanidine ($\sigma_p = -0.63$) and guanidinium ($\sigma_p = -0.12$) groups on the basis of half-wave potentials for 2-guanidino-1,4-naphthoquinone and its hydrochloride (**12**) using the $E_{1/2}$ vs σ_p plot for 2-ureido-1,4-naphthoquinones and other 2-substituted naphthoquinones. The result obtained indicates the electron-donating properties of the guanidinium group, in spite of its charge. Such behaviour was discussed[38] in terms of the resonance structure **12b**.



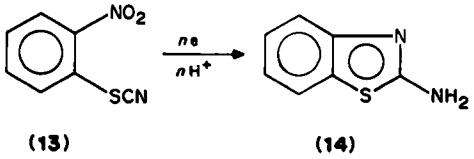
(12a) R = *tert*-Bu (12b)

In conclusion, it may be emphasized once more that for irreversible, many-electron processes of amidines at electrodes, the use of the Hammett equation is restricted to a local series of reactants and media, due to the complex nature of the mechanisms reflected by $E_{1/2}$ values. Fortunately, recent observations of a simple, one-electron reduction of benzamidines in DMF solutions[16] have given a great hope for further applications of the Hammett equation in the electrochemistry of amidines.

III. ELECTROCHEMICAL PREPARATION OF AMIDINE COMPOUNDS

It has been well documented that ionic and radical intermediates, produced during electrolysis in aprotic media, can further react, first of all with nucleophilic and electrophilic species present in a solution, giving a final product with a high yield and selectivity. However, only a few reports on electrosynthesis have been devoted to compounds with the amidine grouping. Some of them, in which starting materials are amidines, will be discussed in the next section. Here, the main attention will be paid to processes in which only the products have the amidine group.

A number of early investigations were devoted to reductive cyclization, as in the following examples[39,40]. In acidic aqueous ethanol the cyclization of *o*-nitrothiocyanatobenzene (**13**) at a mercury electrode[39] results, among other products, in 2-aminobenzothiazole (**14**) and 2-aminobenzothiazole-3-oxide (**15**). Yields of products

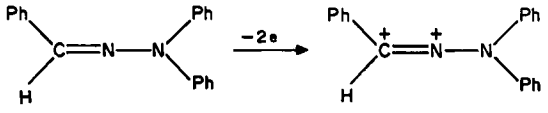


(13) (14) (15)

−*E* (V)	Yield (%) 14	15
0.6	4	81
1.4	31	50

depend on pH and the potential applied. In aqueous ethanol at pH 4.5 the cathodic cyclization of 2-nitro-2′-isothiocynatobiphenyl yielded 6-mercaptodibenzo[*d*,*f*]-(1,3)-diazepin-5-oxide (93%)[40].

Anodic electrosyntheses have been studied more intensively in recent years. Electrochemical oxidation of benzaldehyde diphenylhydrazone (**16**), at a platinum electrode in ACN in the presence of pyridine, results[41] in substituted pyridinium cation (**17**) with a good yield (80%).



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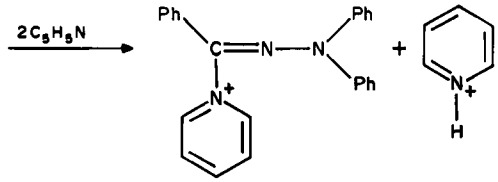


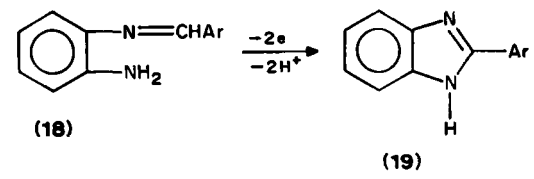
(17)

A number of reports were related to anodic oxidative cyclization producing N-heterocycles. Anodic synthesis of 1,3-imidazoles **19** and **21** from Schiff bases at a platinum electrode in an acetonitrile solution containing TEAP and pyridine was elaborated[42]. Schiff bases used as a starting material showed two oxidation steps under the experimental conditions, and potentials applied for the preparative oxidation were a little higher than $E_{1/2}$ of the first step (Table 3). A detailed study by convolution potential sweep voltammetry for oxidation of **18a** indicated[42] a first-order rate-determining step for the overall cyclodehydrogenation process. The mechanism suggested involves the reversible formation of unstable radical cations which further yield imidazolyl radicals (**22**) by cyclization and deprotonation, but the order of the latter two reactions remains unknown[42]. Radicals **22** are then oxidized, either directly at an electrode, or by a solution electron-transfer, and the final product **19a** is formed after deprotonation.

TABLE 3. Anodic synthesis of 1,3-imidazoles in ACN–TEAP containing pyridine[42]

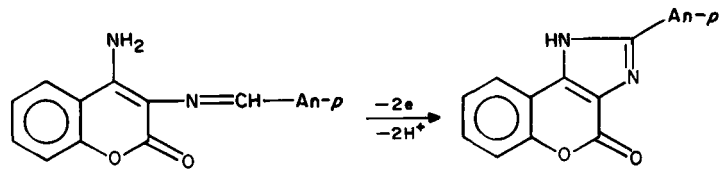
Starting material	$E^a_{1/2}$ (V)	$E^a_{1/2}$ (V)	E^b (V)	Yield (%)
18a	0.68	1.20	0.9	85
18b	0.85	1.30	1.0	78
18c	0.72	1.30	1.0	65
18d	1.20	1.71	1.3	80
20	0.83	1.06	0.95	82

[a] Half-wave potentials obtained at a rotating-disc Pt electrode.
[b] Applied potential of electrolysis.



(18) (19)

18 and 19	Ar
a	p-An
b	p-HOC$_6$H$_4$
c	3-MeO-4-HO-C$_6$H$_3$
d	p-O$_2$NC$_6$H$_4$



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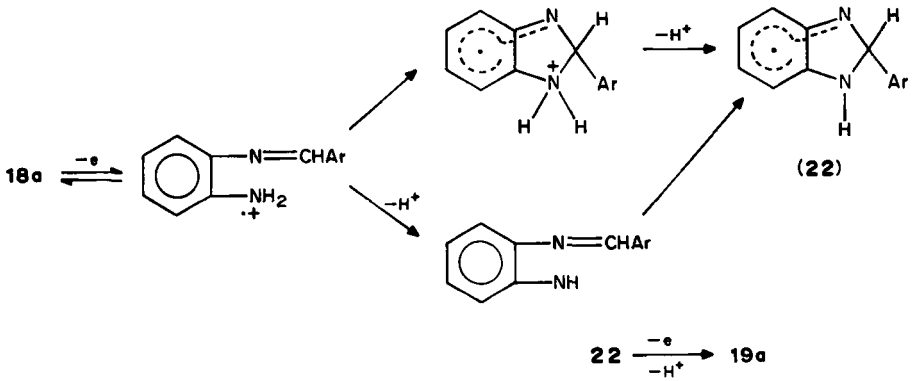


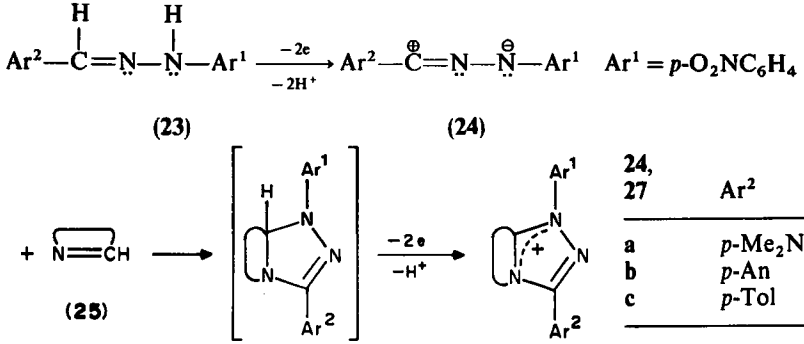
Cyclic amidines were also prepared[43,44] in a process of 1,3-dipolar addition of some N-heterocycles to diarylnitrilimines (**24**) produced in an anodic oxidation of nitrophenylhydrazones (**23**). Thus, 1-(*p*-nitrophenyl)-3-(*p*-*N*,*N*-dimethylaminophenyl)-1,2,4-triazolo[4,3-*a*]pyridinium perchlorate (**27**) and analogous compounds were obtained (Table 4) in a 4e process after addition of pyridine, isoquinoline, quinoline and their methyl

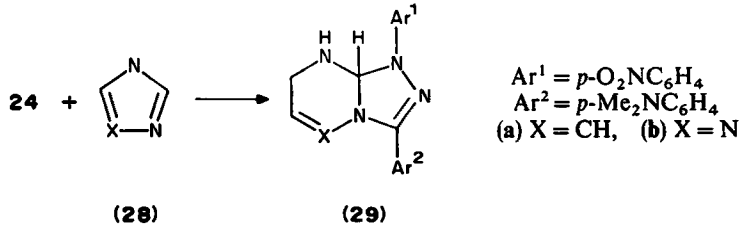
TABLE 4. Dipolar cycloaddition of N-heterocycles to nitrilimines (**24a**) generated at a Pt electrode in ACN–TEAP[44]

Heterocycle	E^a(V)	n^b	Product	Yield (%)
Pyridine	0.70	4	**27a**	62
Quinoline	0.60	4	**27a**	60
Isoquinoline	0.70	4	**27a**	58
Imidazole	0.60	2	**29a**	80
1,2,4-Triazole	0.70	2	**29b**	36

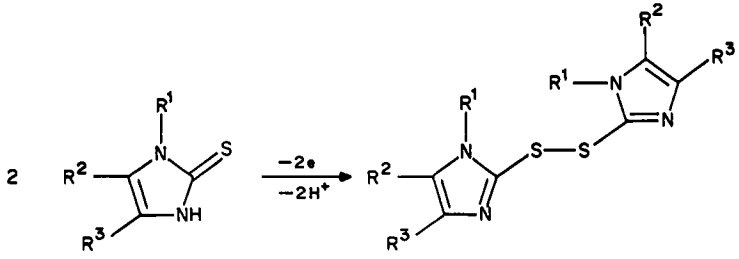
[a]Applied potential.
[b]Number of electrons (F mol^{-1}).

derivatives[44]. On the other hand, the use of imidazole (**28a**) and 1,2,4-triazole (**28b**) yielded, in a 2e process, **29a** and **29b**, respectively.

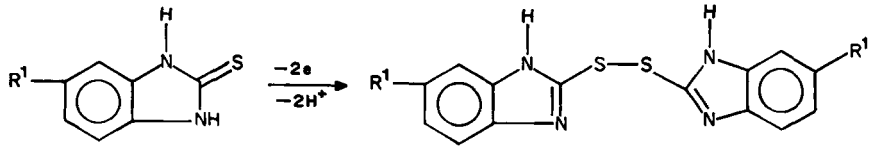




Electrochemical syntheses of imidazolyl and benzimidazolyl disulphides (**31** and **33**, respectively), which are important as reagents and intermediates in the production of pharmaceutics, have been recently reported[45]. The anodic oxidation of the corresponding imidazole-2(3*H*)-thiones **30** and **32** has been performed at a platinum electrode in solutions of ethanol containing aqueous 2 M HCl.



R^1	R^2	R^3	Yield (%)
H	H	H	54
H	Ph	Ph	72
Me	H	H	90

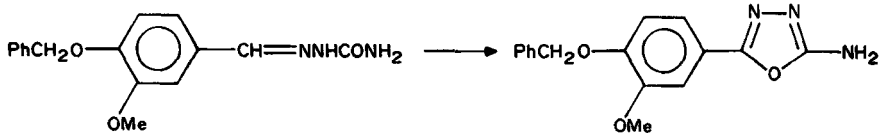
2 

(32) (33)

R^1	Yield (%)
H	77
Me	80[a]

[a]Mixture of isomers.

Very recently an interesting method of indirect anodic oxidation has been applied[46] with the use of organic mediators for syntheses of N-heterocycles, some of them with the amidine group (Table 5). The main idea of this method is the generation at a platinum



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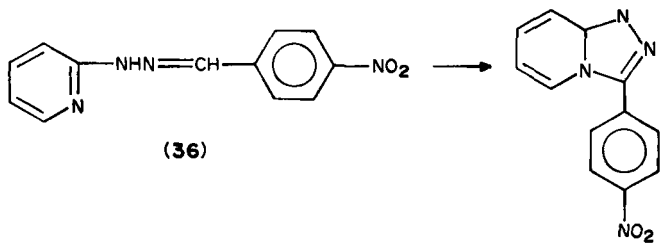


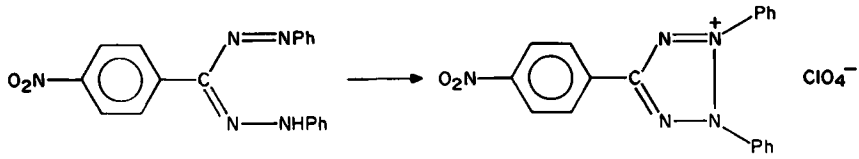
(36) (37)

TABLE 5. Synthesis of N-heterocycles with the amidine group by indirect anodic oxidation in the presence of tris-(4-bromophenyl)amine[46]

Starting material	E_p^a (V)	E^b (V)	Product	Yield (%)	Current yield (%)
34	1.3	1.1	**35**	81	58
36	1.4	1.1	**37**	60	81
38	1.3	1.1	**39**	78	95

[a]Peak potentials.
[b]Applied potential of electrosynthesis.

electrode of radical cations of tris-(4-bromophenyl)amine which oxidize the starting azomethines **34**, **36** and **38**, giving the cyclic compounds 2-amino-5-(3-methoxy-4-benzyloxy)phenyl-1,3,4-oxadiazole (**35**), 3-*p*-nitrophenyl-*s*-triazolo[4,3-*a*]pyridine (**37**) and 2,3-diphenyl-5-(*p*-nitrophenyl)tetrazolium perchlorate (**39**). The electrosynthesis has been performed in solutions of ACN containing TEAP at the potential characteristic of the oxidation of the mediator, which is far lower than the potential of the direct anodic oxidation of the starting azomethines (Table 5). The growing interest in electrocatalysis in recent years is certain to result in further investigations in this field.



(38) (39)

IV. ELECTROCHEMICAL PROPERTIES

A. Amidines

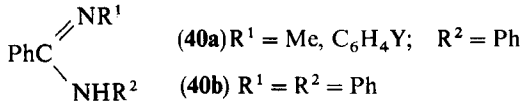
Only benzamidines, which are the most readily reducible (see Section II.A), have been studied electrochemically in recent years. Half-wave potentials for the reduction in various media of some typical examples are given in Table 6. Ševčik investigated[27] the reduction of *N,N'*-disubstituted benzamidines (**40**) at a mercury electrode in buffered aqueous ethanol. Two diffusion-controlled 2e waves were observed, in contrast to earlier results for unsubstituted benzamidine[1,47] which is reduced in one 4e step. The first, more positive wave was observed[27] at pH 3–9 and was irreversible. Values of $E^{I}_{1/2}$ conform to the Hammett equation (cf. Section II.D) and the inflection points on $E_{1/2}$ vs pH plots give pK values in accordance with photometric results. The second, reversible, 2e wave appears at pH 4 and its height increases with pH up to pH > 10, when it begins decreasing. The products of the macroelectrolysis of *N,N'*-diphenylbenzamidine (**40b**) at pH 4.85 were identified as benzalaniline (**41**) and aniline (**42**) after an electrolysis at a potential corresponding to a limiting current of the first wave, and primary and secondary amines

TABLE 6. Reduction potentials of some benzamidines

PhC(=NR¹)NHR²			1st step	2nd step	
R^1	R^2	Medium	$-E^{I}_0$ (V)	$-E^{II}_0$ (V)	Reference
H	H	DMF–TBAI	1.78[a]	1.85[a]	16
Ph	H	DMF–TBAI	1.73[a]	1.88[a]	16
Ph	Ph	DMF–TBAI	1.60[a]	2.37[a]	16
Ph	Ph	H_2O–EtOH	1.26[b]	1.47[c]	27
Me	Ph	H_2O–EtOH	1.24[b]	1.28[c]	27

[a]Peak potentials vs Ag/Ag^+.
[b]Half-wave potentials vs SCE, pH 5.
[c]Half-wave potentials vs SCE, pH 6.

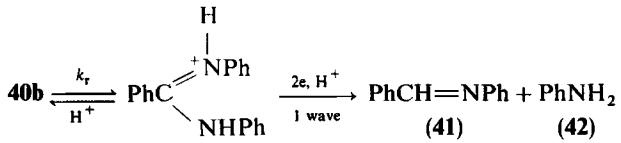
after a reduction at a potential proper for the second wave. The proposed mechanism for symmetrical disubstituted benzamidines starts with fast protonation; the rate constants, k_r, were estimated.



(40a) $R^1 = Me, C_6H_4Y; \quad R^2 = Ph$

(40b) $R^1 = R^2 = Ph$

(40)



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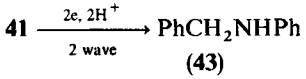
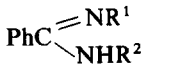
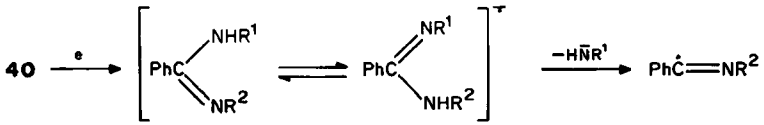


(43)

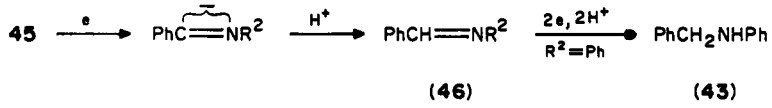
An important step forward in the electrochemistry of amidines has been made recently by Hess and Bluemcke[16] who have reported that benzamidines (**40b–40d**) can be reduced in DMF containing TBAI in two simple steps. Coulometric measurements supported the view that only one electron is transferred in the first step, forming a radical anion (**44**). The formation of a more stable imine radical (**45**) in the next step by the reductive loss of ammonia or a primary amine (in the form of an anion) has been confirmed by a study on further reactions with CO_2; the proper products were isolated by chromatography and identified. The formation of benzalaniline (**46**, $R^2 = Ph$) and *N*-benzylaniline (**43**) during macroelectrolysis was also shown[16]. The half-wave potentials obtained are collected in Table 6. The authors[16] have emphasized preparative applications of the process under investigation which can be used for a cathodic generation of imino radicals and dianions. Moreover, in our opinion, the finding of conditions for a simple 1 e step in the reduction of benzamidines opens new vistas in studying reactivity–structure relationships, tautomeric equilibria, etc.



(40b) $R^1 = R^2 = Ph$
(40c) $R^1 = R^2 = H$
(40d) $R^1 = Ph, R^2 = H$

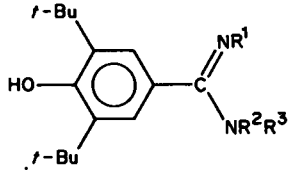


(44) (45)



(46) (43)

The anodic oxidation of 4-hydroxy-3,5-di-*tert*-butyl benzamidines (**47**) in ACN containing TBAP at a platinum disc electrode has been reported[48] very recently, but the hydroxy group is oxidized in this case. For some amidines (**47**) which are soluble in ACN, three anodic peaks have been found[48]. In slightly alkaline media (after addition of 0.01 M tetrabutylammonium hydroxide) all compounds of interest were soluble and gave two anodic peaks. The first of them was reversible and was related to the 1e oxidation of the hydroxyl group with formation of a stable phenoxyl radical. In more alkaline solutions a new irreversible wave appeared at 0.6 V which probably corresponded to the oxidation of a dianion formed after deprotonation of a nitrogen atom[48].



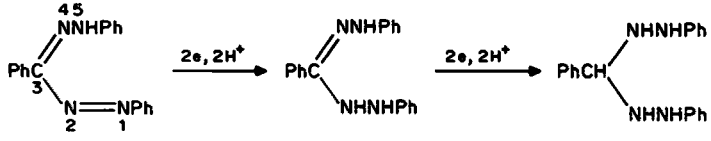
(47)

$R^1 = R^2 = Ph, Me, C_3H_5, C_6H_{11}; R^3 = H$
$R^1 = R^2 = R^3 = Me$
$R^1 = Me, R^2 = Ph, R^3 = H$

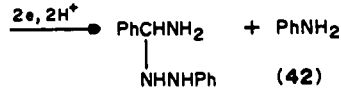
A quasi-reversible oxidation of acetamidine (**48**) at a pyrolytic graphite electrode in aqueous solutions at pH 1.35–6.84 has been recently reported[49]; **48** was postulated as a product of the oxidation of 8-methylxanthine and a cyclic voltammogram of **48** at pH 2.3 has been reproduced[49], but no details have been given.

B. Amidrazones, Hydrazidines, Formazans

Amidrazones and hydrazidines have not been investigated to any great extent electrochemically within the last 15 years, but more reports have been published on behaviour of formazans. Let us remember first that earlier studies in buffered aqueous solutions showed the general pathway[1,10,47] for the reduction of 1,3,5-triphenylformazan (**49**) to 1,5-diphenylbenzhydrazidine (**50**).



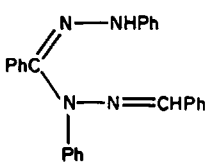
(49) (50)



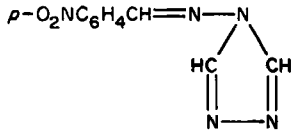
(42)

The first reports on the reduction in aprotic media appeared in the mid-1970s and gave no details on the reaction mechanism. Polarographic reduction of benzhydrazidine (**51**) in DMF containing TEAP showed[50] two waves at -1.92 and -2.44 V; the first one corresponded to the 1e process. For the reduction of **52** in DMF at a potential of the

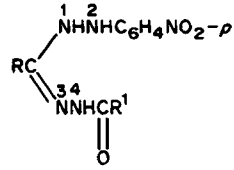
second wave, a cleavage of the N—N bond with a preceding deprotonation and the formation of a dianion was postulated[51].



(51)



(52)



(53)

The polarographic reduction of 2-aryl-acylhydrazidines (53) in DMF containing TEAP[52] occurs in three or four diffusion-controlled, irreversible waves (Table 7). The overall process involves a transfer of at least 8 electrons. Unfortunately, the reduction of nitro and hydrazo groups are found sometimes at similar potentials[52] and an interpretation of the observed waves is impossible.

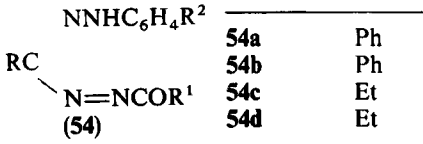
TABLE 7. Half-wave potentials[a] and limiting currents for the reduction of hydrazidines and formazans in DMF–TEAP[52]

Hydrazidines (53)	R = R¹ = Ph		R = Et, R¹ = Me		R = Et, R¹ = Ph	
Wave	$-E_{1/2}$ (V)	i (μA)	$-E_{1/2}$ (V)	i (μA)	$-E_{1/2}$ (V)	i (μA)
1	0.96	0.50	0.35	0.25	0.31	0.60
2	1.26	0.55	0.64	0.30	0.84	0.70
			0.84	0.25		
3	1.84	2.10	1.44	0.40	2.14	3.85
4	2.81	1.50	2.04	2.80	—	—

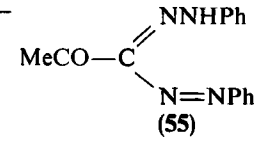
Formazans:	54a		54b		54c		54d	
Wave	$-E_{1/2}$ (V)	i (μA)	$-E_{1/2}$ (V)	i (μA)	$-E_{1/2}$ (V)	i (μA)	$-E_{1/2}$ (V)	i (μA)
1	0.53	0.60	0.30	0.40	0.42	0.50	0.37	0.60
2	1.28	0.60	0.90	0.70	0.92	0.65	0.80	0.75
3	2.46	1.20	1.55	0.80	2.15	4.40	2.12	4.20
4	2.60	1.00	2.03	1.60	—	—	—	—
5	—	—	2.58	2.05	—	—	—	—

Formazans:	49		55	
Wave	$-E_{1/2}$ (V)	i (μA)	$-E_{1/2}$ (V)	i (μA)
1	0.79	0.60	0.78	0.50
2	1.64	0.70	1.68	0.75
3	1.81	0.50	2.20	0.71
4	2.59	1.45	2.38	0.82
5	—	—	2.58	1.43

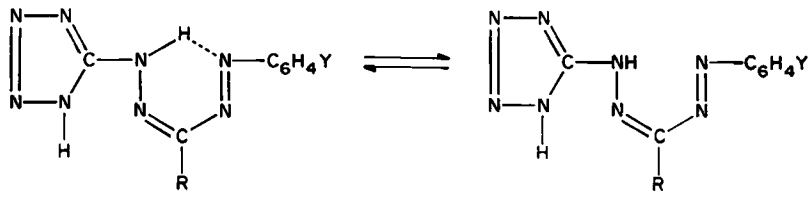
[a] $E_{1/2}$ values expressed vs Hg pool.



	R^1	R^2	R^3
54a	Ph	Ph	H
54b	Ph	Ph	4-NO_2
54c	Et	Me	4-NO_2
54d	Et	Ph	4-NO_2

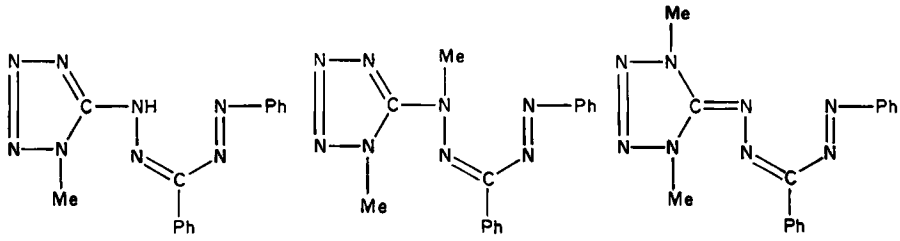


(54) (55)



(56a) (56b)

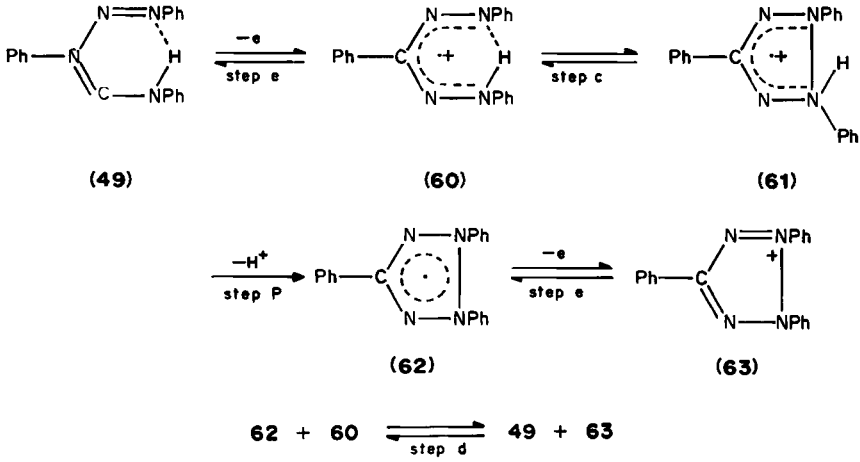
The reduction in the same media[52] of triphenylformazan (**49**), 1-acyl-5-arylformazans (**54**) and 1,5-diphenyl-3-acetylformazan (**55**) involves more complications. Three to five waves were observed (Table 7) and also some additional anodic peaks on cyclic voltammograms. Nevertheless, a comparison of results indicated[52] that the first reduction step of **49**, **55** and **54a** corresponded to the reduction of the azo group, which occurs at a more positive potential for **54a** due to the strong electron-withdrawing properties of the benzoyl group. The overall reduction process of **54b–54d** consumes about 10 electrons, which is in agreement with predictions: 2e + 4e + 4e for the reduction of the azo-, the hydrazo- and the nitro groups, respectively. The reduction of *N*-tetrazolylformazans (**56–59**) also gives three or four irreversible waves[30] corresponding approximately to a transfer of one electron each. The formation of radicals was confirmed by ESR measurements; however, spectra with more than 20 lines were not identified[30]. The most interesting observation was the splitting of the first wave of some aryl formazans into two waves. This behaviour was interpreted[30] on the basis of the formation of a quasi-aromatic chelate structure (**56a**) due to intramolecular hydrogen bonding. The more positive wave corresponds to the structure **56a** and is of a surface nature, in contrast to a more negative diffusion wave which corresponds to the structure **56b**. In general, *N*-tetrazolylformazans (**56–59**) are more readily reducible than **49**, in accordance with predictions based on the electron-acceptor properties of the tetrazole substituent and on calculations of LUMO energy[30].



(57) (58) (59)

Irreversible voltammetric reduction of substituted 3-cyano-1,5-diphenylformazans in benzonitrile containing TBAP has been recently described[53].

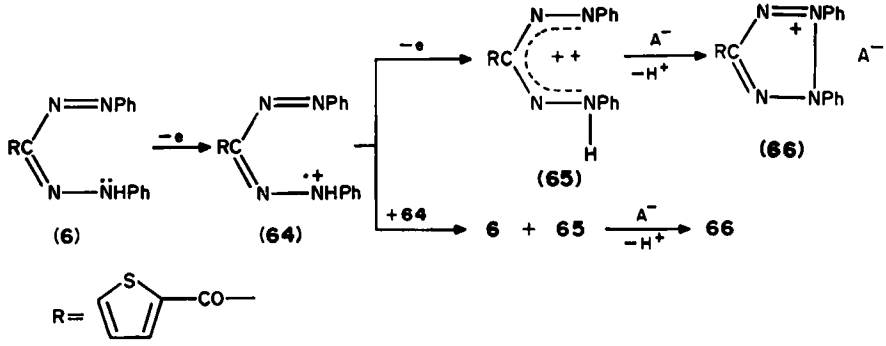
The oxidation of some compounds under discussion was also reported. It has been well known for many years[1,47] that 1,3,5-triphenylformazan can be readily oxidized to the 2,3,5-triphenyltetrazolium salt which, in turn, can be polarographically reduced. However, the detailed mechanism in aprotic media was not elucidated until the works of Tabaković and coworkers[28,54]. Two electrons are transferred in the overall oxidation process of formazan (**49**) at a platinum electrode in ACN containing TEAP, as confirmed by coulometry[54]. Two anodic peaks appear on cyclic voltammograms at 0.93 and 1.4 V, the second one, however, being very small. Both peaks are irreversible even for a sweep rate of $50\,V\,s^{-1}$; this means that the next chemical step is fast. The second peak corresponds, presumably, to oxidation of a formazan molecule protonated by protons which are liberated during the first step. The latter conclusion was confirmed[54] by measurements at a rotating disc electrode. After addition of perchloric acid, it was observed[54] that the first wave decreased and the second one increased. On the other hand, the addition of a base (4-cyanopyridine) caused the reverse behaviour. Moreover, experiments with a rotating ring-disc electrode supported the view that no long-lived intermediates existed and the structure of the final product **63** was confirmed by elemental analysis and IR spectra. Finally, it was concluded that an e–c–P–e–(d) mechanism was operative[54], i.e. oxidation of **49** to a radical cation (**60**) (step e), its cyclization (step c), deprotonation of the cyclic radical cation (**61**) which is the rate-determining step (step P). At the end the second electron is transferred from the tetrazolinyl radical (**62**), either directly (step e) or in the reaction (d).



A similar analysis of the reverse process, the reduction of 2,3,5-triphenyltetrazolium perchlorate to **49**, indicated[54] the opposite pathway, i.e. an e–P–c–e mechanism. One irreversible reduction peak is normally observed; however, it was shown[54] that in super-dry ACN, in the presence of activated alumina, the tetrazolinyl radical (**62**) was stable and one 1e reversible peak appeared in cyclic voltammograms. Substituent effects on potentials proper for the oxidation of **10** in ACN[54] were considered in Section II.D.

Two irreversible anodic steps were also observed earlier[28] for 3-aroyl-1,5-diarylformazans. However, the detailed mechanism of oxidizing 3-thenoyl-1,5-diphenylformazan (**6**) in ACN containing TEAP is more complicated than that discussed above for **49**. In experiments with a rotating disc electrode it was found[28] that the function $i/\omega^{1/2}c$ (where i means the limiting current, c the formazan concentration and ω the angular velocity) depended on $\omega^{1/2}$, in contrast to measurements performed in nitro-

benzene, as well as to the behaviour found previously[54] for **49**. It clearly indicates that the radical cation (**64**) is stable in nitrobenzene, but in ACN the chemical disproportionation of **64** to the original formazan **6** and a dication (**65**) occurs, especially at slower sweep rates in cyclic voltammetry. The disproportionation of radical cations was also supported in an elegant way by macroelectrolysis performed up to 1.1e transfer from a molecule: this process yielded 50% of the parent formazan (**6**) and 35% of the final product (**66**). The second, alternative pathway includes further electrochemical oxidation to a dication and a ring closure by nucleophilic addition, forming the corresponding tetrazolium salt (**66**) with supporting electrolyte anions, A^-. Substituent effects on $E_{1/2}$ values of **6** and its derivatives were discussed in Section II.D. A change of the substituents also influences the ratio of limiting currents for the first and second peak on cyclic voltammograms; e.g. for **6** disubstituted at both phenyls the ratio changes from i_1/i_2 1.14 to 3.72 for *p*-OMe and *p*-Cl substituents, respectively.



The application of the reactions discussed above to the electrochemical preparation of tetrazolium salts, which are used as biological staining agents, by anodic oxidation of formazans and the electrochemical synthesis of formazans in the opposite process (Table 8) has been elaborated[28,54].

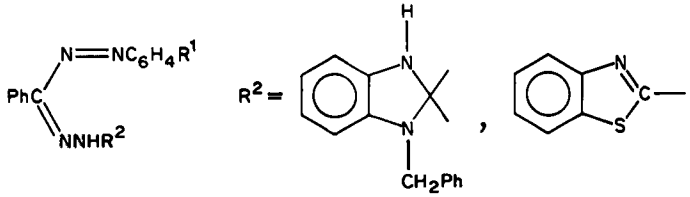
Probably, a similar mechanism governs the oxidation of formazans (**67**) with heterocyclic substituents. Two diffusion-controlled, irreversible waves were observed[31] for the oxidation of **67** in ACN containing $LiClO_4$, in contrast to oxidation of 1,3,5-

TABLE 8. Electrochemical syntheses based on formazan-tetrazolium salt systems in acetonitrile

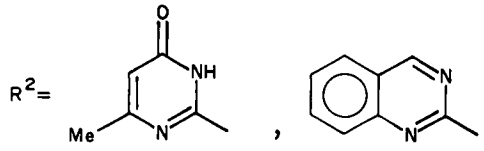
Starting material								
	R^1	R^2	Medium	Electrode	E^a (V)	Product	Yield (%)	Reference
49	—	—	TEAP	Pt anode	1.2	**63**	100	54
49	—	—	TEAF	Pt anode	1.2	**63**	97	54
67	4-Me	4-Tol	TEAP	Pt anode	2.0	*b*	91	28
67	4-Me	Ph	TEAP	Pt anode	1.1	*b*	100	54
67	H	4-Tol	TEAP	Pt anode	1.2	*b*	100	54
6	—	—	TEAP	Pt anode	2.0	**66**	95	28
6	—	—	TEAF	Pt anode	1.5	**66**	83	28
63	—	—	TEAP	Pt cathode	−0.45	**49**	95	54

[a] Applied potential.
[b] The corresponding tetrazolium perchlorate.

triphenylformazan (**49**) with a substituted phenyl group at the $N_{(5)}$ atom, which gives[31] only one 2e wave (Table 9). Moreover, the first wave of **67** is a little higher than the second one, and the sum of limiting currents for both waves is approximately equal to the limiting current of **49**. The above behaviour was interpreted[31] in terms of formation of intermediates after 1e transfer. However, Troepol'skaya and Budnikov pointed out[10] that protonation of the N-heterocyclic fragments of **67** by protons liberated during the oxidation can also be responsible for the observed behaviour. In our opinion, one should also consider residual water in $LiClO_4$ used as a supporting electrolyte (there are no details on its drying).



(67) **(67a)** **(67b)**



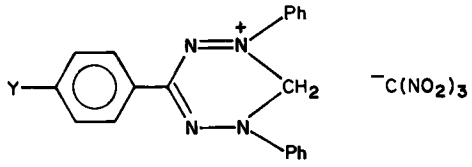
(67c) **(67d)**

TABLE 9. Half-wave potentials[a] and limiting currents for the oxidation of formazans at a platinum electrode in ACN–$LiClO_4$[31]

		1st wave		2nd wave	
Formazan	R^1	$E_{1/2}^{I}$ (V)	i (μA)	$E_{1/2}^{II}$ (V)	i (μA)
67a	H	0.31	—	0.93	—
	p-NO_2	0.40	—	1.04	—
67b	H	0.63	25.0	1.38	22.0
	p-OMe	0.54	24.0	0.98	21.0
	o-OMe	0.59	25.0	1.03	22.5
	p-Me	0.49	23.0	1.05	21.0
	o-Me	0.54	25.0	1.32	21.5
	p-Cl	0.63	24.0	1.41	20.0
	p-NO_2	0.76	23.0	1.44	21.0
	o-NO_2	0.73	24.0	1.46	21.5
67c	H	0.69	21.0	1.60	21.0
	p-OMe	0.66	22.5	1.34	22.0
	p-NO_2	0.74	23.0	1.63	20.0
67d	H	0.86	—	1.64	—
	p-Me	0.80	—	1.50	—
	p-NO_2	0.94	—	1.65	—
49	—	0.65	50.0		

[a] $E_{1/2}$ values are given vs Ag/Ag^+ in ACN.

1,3,5-Triphenylverdazyl free radicals (**11**), cyclic analogues of formazans, were reversibly reduced to anions and oxidized to cations[36,37]. Their substituent as well as solvent effects on $E_{1/2}$ values were discussed earlier (see Table 2 in Section II.D). On the other hand, the reduction of trinitromethide-verdazyl salts (**68**) in ACN containing TEAP yielded two reversible 1e waves[36] with $E_{1/2}$ values identical with half-wave potentials proper for the oxidation and the reduction of verdazyl radicals (**11**), respectively. Very recently, the temperature dependence of half-wave potentials for the 1,3,5-triphenylverdazyl radical (**11a**) has been measured and the entropy changes during the oxidation (ΔS_r^{ox}) and reduction (ΔS_r^{red}) have been obtained[55]. It has been found that ΔS_r^{red} values in a few aprotic solvents are linearly related to solvent acceptor numbers, AN[56], describing an anion solvating-tendency, whereas ΔS_r^{ox} values depend on the solvent basicity scale of Kamlet and Taft (cf. Reference 57 and references cited therein).

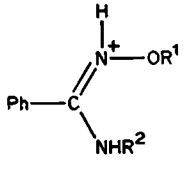


(**68**)

C. Amidoximes

The electroreduction of amidoximes has been investigated only in aqueous solutions and alcohol–water mixtures, because polarographic reduction is facilitated by preliminary protonation. (This is a general tendency for oximes[47], e.g. aliphatic α-amino-oximes cannot be reduced in DMF in contrast to protic solvents, where a protonation of the amino group occurs prior to the electron transfer[58]). The general mechanism for the reduction of benzamidoximes to benzamidine proposed earlier by Lund[1,47] (i.e. in acid solutions, prior protonation and a subsequent 2e, $2H^+$ process with a cleavage of the N—O bond, while in neutral media a decrease of the wave, which disappears at pH > 10) was confirmed and further extended within the last 15 years.

Mollin and coworkers[20] have shown by IR and H^1-NMR spectroscopy that protonation of substituted benzamidoximes takes place mainly at the N atom of the oxime group, forming **69**. Dependences of $E_{1/2}$ values corresponding to the reduction of **69** on pH have been discussed in Section II.B, and substituent effects in Section II.D. The reduction is facilitated by alkyl and aryl substituents at R^1 as well as R^2 positions. In two cases ($R^1 = C_4H_9$ and CH_2Ph) higher, in part catalytic, waves were observed[20]. In less acid media a second wave appears, which corresponds to the further reduction of benzamidine. The height of the second wave at pH 5.94 is nearly twice that of the first one, as expected for a 4e process for the reduction of benzamidine, but it is far higher at pH 5.22; the latter observation has not been explained[20].

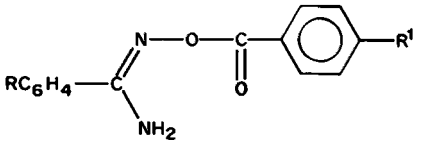


R^1 = H, Me, Et, Bu, CH_2Ph

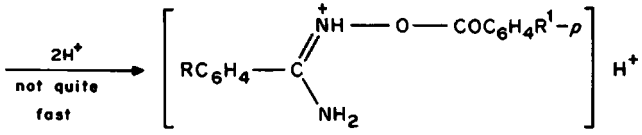
R^2 = H, Me, Et, Ph, CH_2Ph, C_6H_{11}

(**69**)

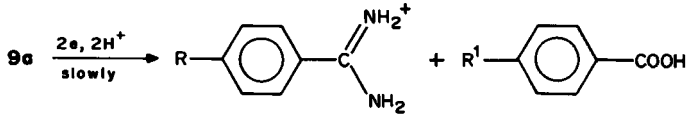
A similar irreversible 2e reduction to amidines, preceded by protonation, was also suggested[34] for *O*-benzoylbenzamidoximes (**9**) on the basis of coulometric experiments and consideration of the pH dependence of the $E_{1/2}$ values. However, $E_{1/2}$ vs pH plots have shown that the mechanism is more complicated for compounds with R = NMe_2, due to additional protonation of the dimethylamino group. On the other hand, in nitro derivatives the reduction of the NO_2 group precedes the cleavage of the N—O bond.



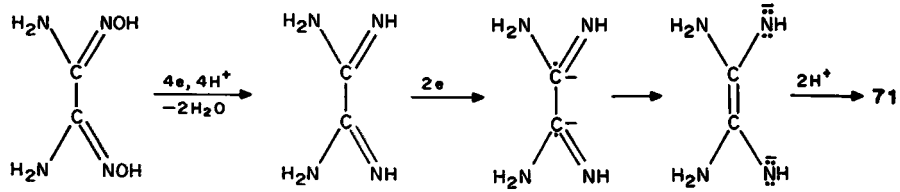
(**9**)



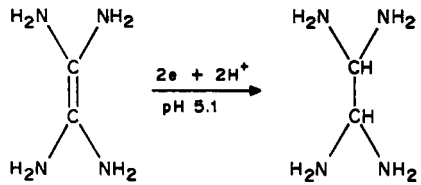
(**9a**)



Several electroanalytical techniques have been applied[59] to a wide range study of ethane diamidoxime (**70**). Two diffusion-controlled and completely irreversible reduction waves have been found. The first one expected for a protonated compound (pK = 3.06) has been observed in acidic media, and the second one (8e, $8H^+$) at pH 4.2–7.9. The overall reduction yields tetraaminoethylene (**71**) at pH 1.7 and tetraaminoethane (**72**) at pH 5.1.

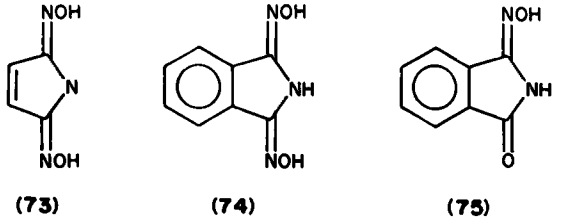


(**70**)

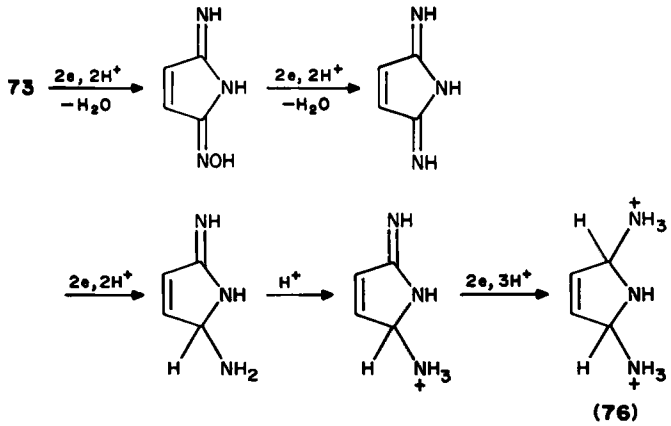


(**71**) (**72**)

The reduction of the cyclic dioxime (73) has been reported by Forteza and Cerdá[60], who studied previously the cyclic amidoximes 74 and 75. Four pH-dependent waves have been found for 73. The first one, observed in acidic media, corresponds to an 8e process and was attributed to the formation of the diammonium salt 76. The second 2e wave was related to hydration of the ethylene bond. In alkaline solutions the mechanism is changed, since it is difficult to form a dianion from a neutral molecule of dioxime. Nevertheless, the third 2e wave (pH > 7) and the fourth one (~ 8e, pH > 11) also correspond to the reduction of the oxime to the amino group. Some additional details of the mechanism were also suggested[60].

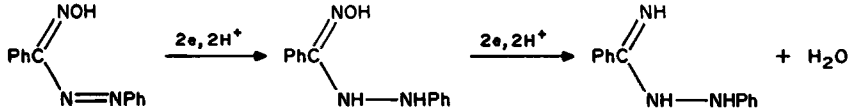


(73) (74) (75)

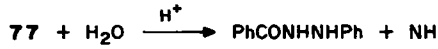


(76)

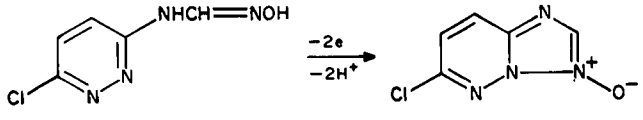
For the reduction of phenylazobenzaldoxime in aqueous methanol, successive reductions, first of the azo and then of the oxime group, were suggested[23,61] in acidic media where two diffusion-controlled, irreversible 2e waves were observed (cf. Section II.C). Comparison with the reduction of azobenzene and of benzaldehyde oxime supported the mechanism proposed. On the other hand, the possible reduction of the hydrazo to the amino group was rejected, since no wave proper for the reduction of benzamidoxime was found[23].



(77)



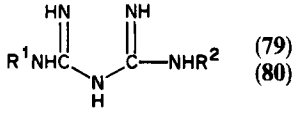
The anodic oxidation at a Pt electrode of 3-hydroxyiminomethyleneamino-6-chloropyridazine (**78**), which can be regarded as a substituted formamidoxime, gives in ACN containing TEAP two, irreversible voltammetric peaks ($E_{1/2}$ = 1.04 and 1.4V)[62]. The coulometry at a potential of the first peak indicates a number of electrons $n \approx 2$. Anodic intramolecular cyclization carried out at a platinum gauge yields (28%) the triazoles derivative (**78a**) and three other unknown products[62].



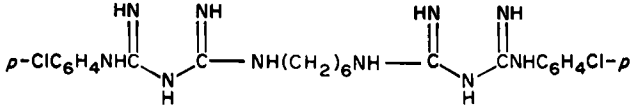
(**78**) (**78a**)

D. Guanidines

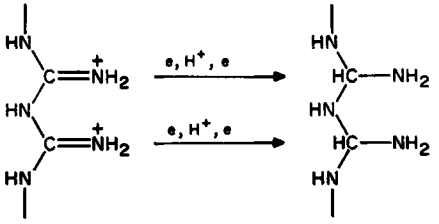
Some biguanides (i.e. imidodicarbonimidic diamides), important because of their pharmaceutical use, e.g. proguanil (**79**), phenforminin (**80**) and chlorhexidine (**81**), have been investigated[63–65] in water–DMF mixtures at mercury electrodes. Biguanides consist of two guanidine groups with a common nitrogen atom and in general can form a delocalized π-electron system. However, studies by different polarographic techniques indicated[63–65] that the reduction occurred in the monoprotonated species with the two localized azomethine double bonds. Polarographic activity was observed only for compounds with chlorophenyl groups. The observed irreversible, quasi-diffusion waves with some kinetic character were influenced by hydrogen evolution, so that the number of electrons transferred could not be determined directly. Nevertheless, for the overall process of one biguanide group 4e and $4H^+$ are needed for the reduction of two C=N double bonds to amino groups. On the other hand, it was found for **79** that only 1e is transferred in the potential-determining step, and only one proton is transferred prior to this step. It has been assumed that the electroreduction starts with adsorption of the



(**79**) $R^1 = p\text{-}ClC_6H_4$-, $R^2 = CHMe_2$
(**80**) $R^1 = PhCH_2CH_2$, $R^2 = H$

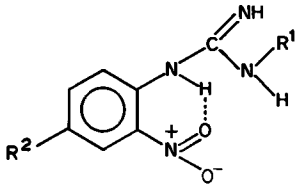


(**81**)

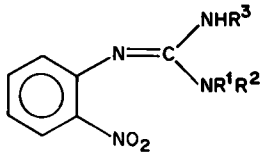


monoprotonated species and then further heterogeneous protonation occurs. For proguanil (**79**) the rate constant of this protonation at the electrode is $k_d = 5.3 \times 10^{11}$ mol $l^{-1} s^{-1}$ and $pK = 8.0$ under the experimental conditions[64]. Finally, simultaneous reduction of both azomethine bonds was assumed[64,65] as the most probable mechanism, although other possibilities were also considered.

Polarographic and cyclic voltammetric reduction of 2-nitrophenylguanidines (**82–83**) in ACN or DMF containing TEAF at a mercury electrode showed[66] similar behaviour for all compounds, but only 4-methyl-2-nitrophenylguanidine (**82a**) was studied in detail[66]. Two reduction waves (or peaks) were observed corresponding to a 1e (reversible at fast scan rates $> 20\,V\,s^{-1}$) and a 4e step, respectively. Both of them had a kinetic character due to preceding fast chemical reactions.

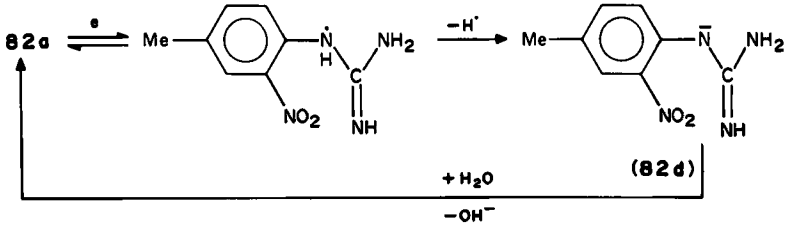


	R^1	R^2
(**82a**)	H	Me
(**82b**)	Et	H
(**82c**)	H	H

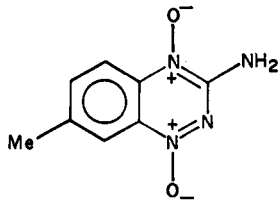


	R^1	R^2	R^3
(**83a**)	Et	Et	H
(**83b**)	Et	H	Et
(**83c**)	Et	Et	Et

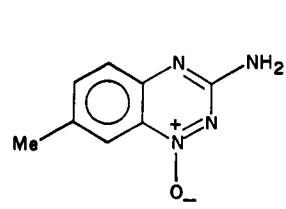
The first reduction step is preceded by cleavage of an intramolecular hydrogen bond. Addition of tetraethylammonium hydroxide indicated that a reaction between the parent molecule and its anion (**82d**) formed during the first reduction step, precedes the second electron transfer. Moreover, anions (**82d**) are adsorbed at the electrode, giving an additional peak in cyclic voltammograms. Anions (**82d**) also react with the added water re-forming the parent molecule:



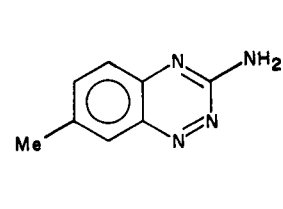
After chromatographic separation the following products of the controlled potential electrolysis of **82a** in ACN were identified by IR and UV/vis spectra: 3-amino-7-methyl-1,2,4-benzotriazine-1,4-dioxide (**84**), 3-amino-7-methyl-1,2,4-benzotriazine-1-oxide (**85**), 3-amino-7-methyl-1,2,4-benzotriazine (**86a**), 3-amino-7-methyl-1,4-dihydro-1,2,4-benzotriazine (**86b**), 4-methyl-2-nitroaniline (**87**) (yield 15–20 wt%) and an oligomeric organomercury compound (35–45%) resulting in melamine (**88**) after decomposition. The results indicated[66] that ring closure yielding **84**, **85** and **86** occurred in parallel with the elimination of the carbodiimide residue from the guanidine substituent, resulting in **87** and an organomercury compound. Moreover, **84**, **85** and **87** are electroactive at more positive



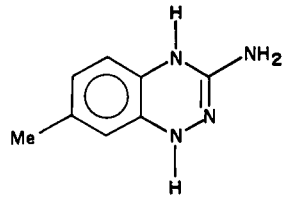
(84) (5%)



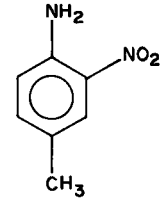
(85) (15%)



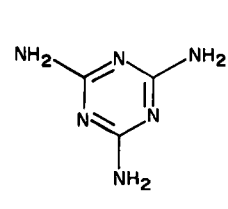
(86a)



(86b)

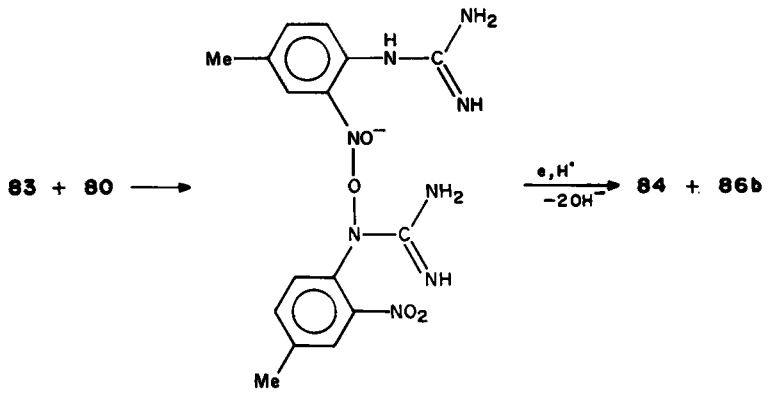


(87)



(88)

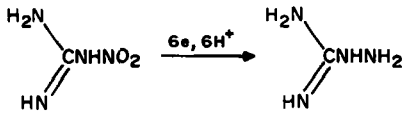
potentials than that corresponding to the reduction of parent **80a**. Finally, the proposed c–e–c–e mechanism includes the disruption of the hydrogen bond (the first chemical step), the formation of an anion (**83**) and its reaction with the parent molecule resulting in the intermediate (**89**), followed by cleavage of the N—O bond in the N—O—N grouping of **89** and the cyclization to **84** and **86b**. Further reduction of **84** yields, successively, **85** and **86**.



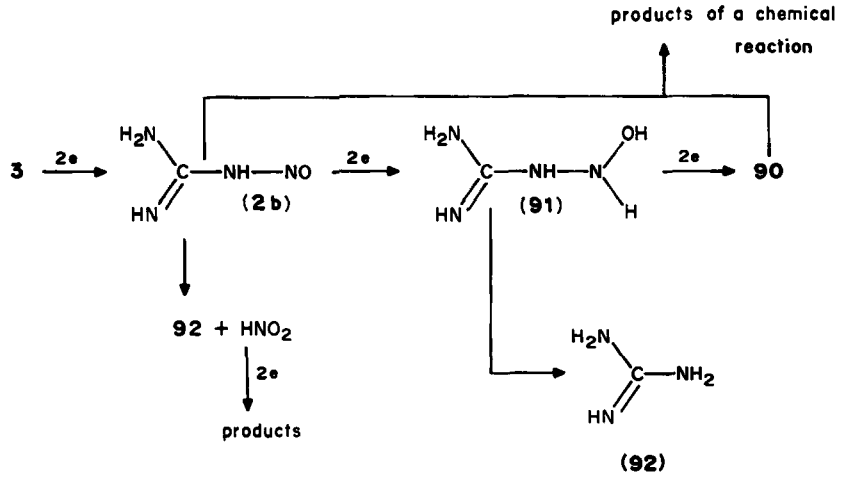
(89)

The reduction of nitroguanidine to aminoguanidine (**90**) in acidic aqueous media was performed previously at a mercury electrode, but a more detailed mechanism has been reconstructed[67] on the basis of investigations at a copper electrode in H_2SO_4 solutions. Potentiometric electrolysis at potentials 0.3–0.6 V yields guanidine (**92**) as the main product in a 4e process. On the other hand, at potentials corresponding to those of hydrogen evolution, aminoguanidine (**90**) is formed in a 6e process (yield $\approx 60\%$ at -0.9 V). The suggested pathway[67] includes **2** and **91** as intermediates. The chemical decomposition of nitrosoguanidine (**2**) to **92** and HNO_2 with a further reduction of the

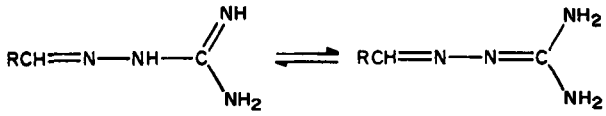
acid was considered[67] as less important in the process discussed. The reduction of **2** at a mercury electrode in buffered aqueous solutions occurs probably in a similar manner. In acid media (pH 1–5) two polarographic waves were obtained[21]. The first one corresponds to the 2e process of guanidine (**92**) formation and the second to a 4e process yielding aminoguanidine (**90**). In alkaline solutions only one 2e wave was observed. The existence of two waves in acidic media was explained[21] in terms of two tautomeric forms of **9**, as was discussed in Section II.C.

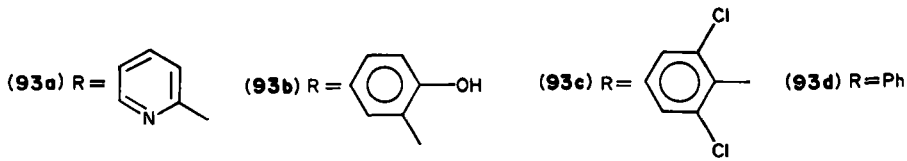


(90)

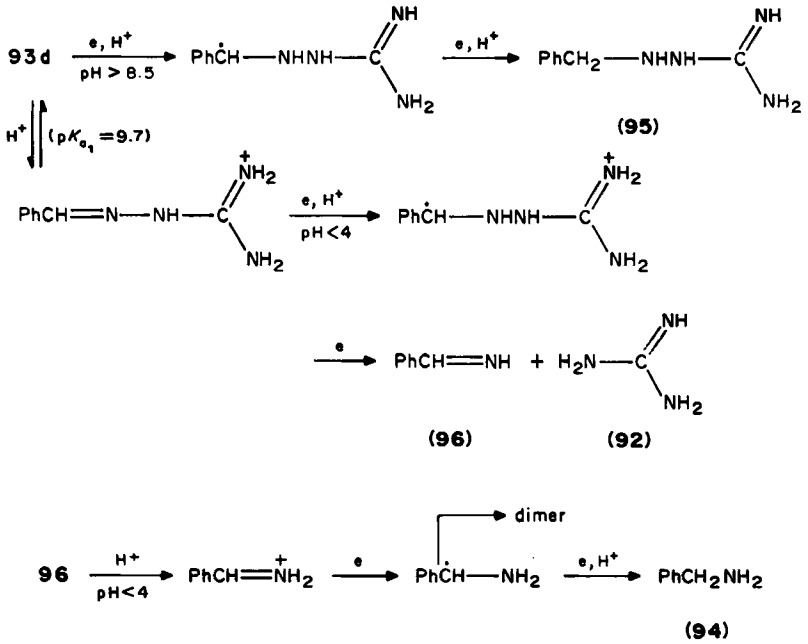


Among guanidines, a number of compounds with guanylhydrazone group was electrochemically reduced to guanylhydrazines (a similar reaction is familiar under homogeneous conditions). In most investigated cases, for **93a**[68], **93b**[69] and **93c**[70], in buffered aqueous solutions and in mixtures with DMF, only one, irreversible wave was obtained, corresponding to the 2e, $2H^+$ process. Two tautomeric forms (amidine and azine) are feasible for guanylhydrazones:



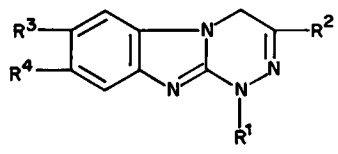


However, for the polarographic reduction of pyridine-2-carbaldehyde guanylhydrazone (**93a**) in acidic (pH < 3.3) and alkaline (pH > 8.4) media only the azine form was postulated[68]. The polarographic behaviour is additionally complicated by protonation of the amidino group and by surface phenomena. Adsorption of **93d** was postulated[71] and in all cases a maximum was observed in acid media. Nevertheless, in the presence of surface active substances all waves[35,68-71] had diffusion character. The reduction mechanism was investigated in detail[71] for benzylideneaminoguanidine (**93d**). The 2e wave was observed in alkaline DMF–water mixtures and the 4e wave in acid media, as supported by macroelectrolysis. Guanidine (**92**) and benzylamine (**94**) were identified[71] as products of the reduction in acid solutions, but 2-(phenylmethyl)hydrazinecarboxyimidamide (**95**) in alkaline media. Then, a simple reduction of the C=N bond was ascertained in alkaline media. On the other hand, in acid solutions, cleavage of the N—N bond with the formation of benzylimine (**96**) as the first step and then a reduction of the double bond in **96** was assumed[71]. The corresponding mechanism indicates[71] the amidine structure for **93d**.



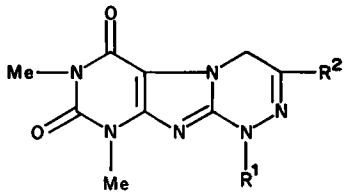
One, irreversible 4e wave was observed[35] for the polarographic reduction of 4-arylhydrazono-1-guanidinium-3-methyl-2-pyrazoline-5-one nitrate (**10**), in which also the hydrazono group was reduced in aqueous–methanol solutions (cf. Section II.D). $E_{1/2}$ values for the reduction of 2-guanidino-1,4-naphthoquinones in water–EMF and water–ethanol mixtures were measured[38].

The guanidine group appears in a number of heterocyclic compounds, derivatives of 1,2,4-triazine, which are important as luminophores, herbicides and inhibitors of acidic corrosion. Thus, their redox properties are of interest and the oxidation of 80 triazine derivatives (**8, 97–99**) at a rotating platinum elctrode in ACN was investigated by Beylis and coworkers[33,72]. The process is irreversible and only in some cases are anodic peaks well-defined. Nevertheless, values of peak and half-wave potentials were collected[33,72]. From the typical examples, presented in Table 10, it is evident that compounds belonging

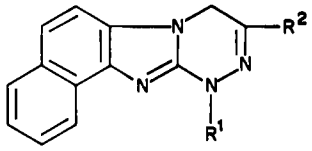


(97)

(97a) $R^3 = R^4 = H$
(97b) $R^3 = R^4 = Me$



(99)



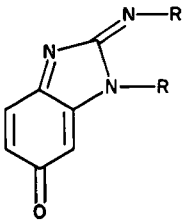
(98)

TABLE 10. Peak potentials for the oxidation of some triazine derivatives at a rotating Pt electrode in ACN–$LiClO_4$

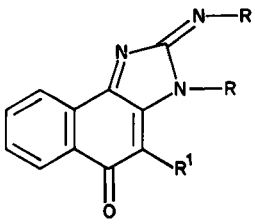
Compound	R^1	R^2	E_p (V)	E_p^2 (V)	Reference
97a	H	Me	1.03		72
	H	Ph	1.04		
	H	*p*-Tol	1.00		
	H	*p*-An	0.95		
	H	*p*-ClC_6H_4	1.05		
	H	*p*-$O_2NC_6H_4$	1.22		
	Me	Ph	0.42	0.72	
	Ph	Ph	1.08		
	COPh	Ph	1.00	1.61	
97b	Me	Ph	0.92		72
98	H	Me	0.66	1.42	33
	H	*t*-Bu	0.69		
	Me	Ph	0.78	1.42	
	n-Pr	Ph	0.77	1.40	
	Ph	Ph	0.85	1.42	
	Ph	*p*-Tol	0.82	1.35	
	COMe	Ph	0.94		
99	H	Ph	0.98		33
	Me	Ph	0.96		
	Ph	*p*-$O_2NC_6H_4$	1.10		
8a	Ph	H	1.56		33
	p-Tol	H	1.49		
	p-ClC_6H_4	H	1.62		
	p-BrC_6H_4	H	1.65		
	p-$O_2NC_6H_4$	H	1.88		
	Ph	Ph	1.42		
8b	Et	H	1.58		33
	Ph	H	1.60		
	p-Tol	H	1.54		
	p-$O_2NC_6H_4$	H	1.92		
	Me	Me	1.40		
	Ph	Ph	1.48		
	Ph	Me	1.44		
	Me	Me	1.40		

to a series of triazines (**98**) are more readily oxidizable than derivatives of triazino[3,4-*a*]benzimidazole (**97**) due to a more extended π-electron system in the naphthoimidazoles. The oxidation of compounds from a series of imidazo[1,2-*b*]-1,2,4-triazines (**8**) is, in turn, the most difficult. Substituent effects are also operating, e.g. the highest E_p values were observed for the oxidation of nitro derivatives. On the other hand, effects of methyl and phenyl groups are more complex, as was discussed elsewhere[33,72].

Half-wave potentials (vs silver chloride electrode) for the reduction of imidazole derivatives **100** and **101** possessing the guanidine group were measured[38] in DMF–water mixtures at pH 7.



(100)



(101)

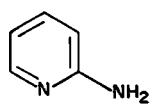
	R	R^1	$-E_{1/2}$ (V)
(**100**)	CMe_3	—	0.38
(**101**)	CMe_3	H	0.53
(**101**)	CMe_3	Br	0.50

It can be also mentioned that guanidinium perchlorate adsorption at a mercury electrode was studied in aqueous solutions[73].

E. Cyclic Amidines

1. 2-Aminopyridines and related compounds

Polarographic half-wave potentials of some 2-aminopyridines can be found in a review[7]. However, deeper insight into electrochemical mechanisms was not provided until recent studies in which 2-aminopyridine (**102**) was used as a model compound for more complex systems, in particular that of biological importance. Oxidation of **102** in aqueous solutions pH 3.2–10.3 at a pyrolitic graphite electrode[74] consumes 2e per molecule, yielding *trans*-2,2'-azopyridine (**105**), as confirmed by IR and NMR spectra, as well as by its electrochemical behaviour. Only one anodic peak was observed[74] without any cathodic response at sweep rates slower than $0.4\ V\ s^{-1}$, and another, quasi-reversible couple of peaks (corresponding to the oxidation of **104** to **105** in the following scheme), characteristic of the product. The reactant is strongly adsorbed at the electrode. The inflection point in the E_p vs pH plot indicates that at pH < 6.8 a monocation (**102a**) exists in solutions. At higher pH the value of dE_p/dpH is equal to 22 mV, which was interpreted in terms of either a tautomeric equilibrium or formation of the anion (**102b**). The suggested pathway for the oxidation includes the formation of the unstable radical (**103**), which dimerizes to **104** and undergoes further oxidation to **105**. A similar oxidation of amino to azo groups is also characteristic of other heterocyclic amines.



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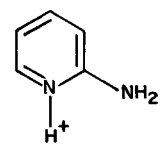
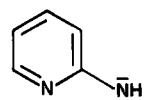
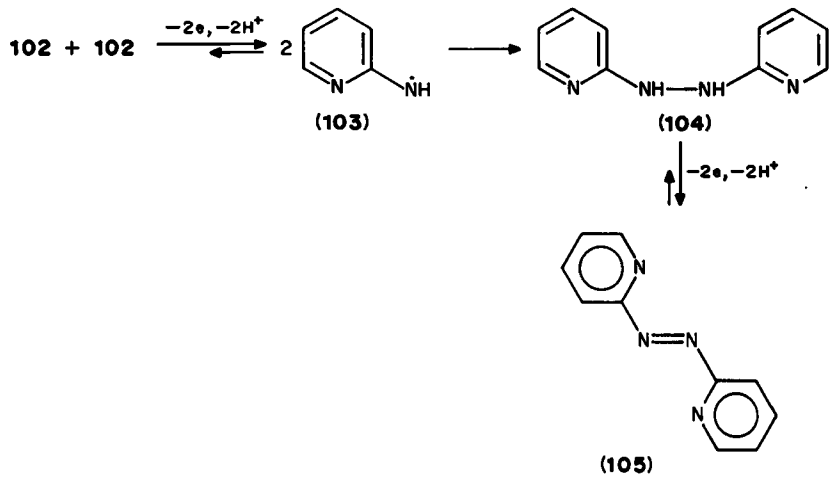


(102a)



(102b)



The reduction of 2,2′-azopyridine (**105**) at glassy carbon and pyrolytic graphite electrodes[75] yields **104** under cyclic voltammetric conditions, but **102** in controlled-potential electrolysis (in contrast to the 2e, $2H^+$ reduction of azobenzene). Peak potentials for the reduction of *cis*-2,2′-azopyridine in acidic media were about 25 mV more positive than those observed with the *trans* isomer, but they were practically identical at higher pH[75].

A number of pyridine derivatives with the amidine grouping have been used as starting materials for electrosyntheses. The anodic oxidative cyclization of benzaldehyde-2-pyridylhydrazone (**106a**) and related compounds (**106**) at a platinum electrode in ACN containing TEAP has been extensively studied[62,76] by Tabaković and coworkers. The oxidation of **106a** yields 3-phenyl-*s*-triazolo[4,3-*a*]pyridine (**107**) and other products, depending on the medium, as shown in Table 11. The best yields of **107** were obtained in acidic media; they reached 83–92% for 4-nitropyridine derivatives of **106**. At a rotating-disc electrode two anodic waves were observed[76] for the oxidation of **106a**, at 0.82 and 1.62 V, respectively; it was supposed that the second one corresponded to oxidation of a

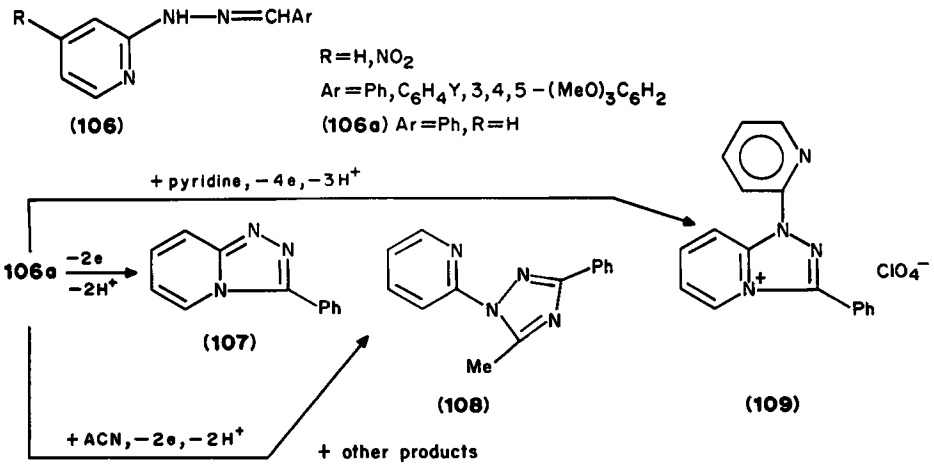
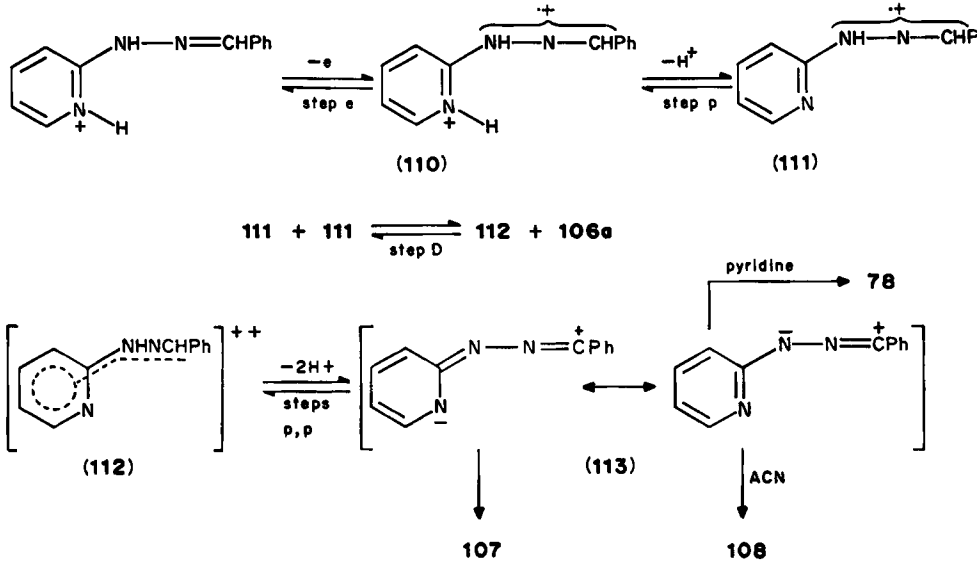


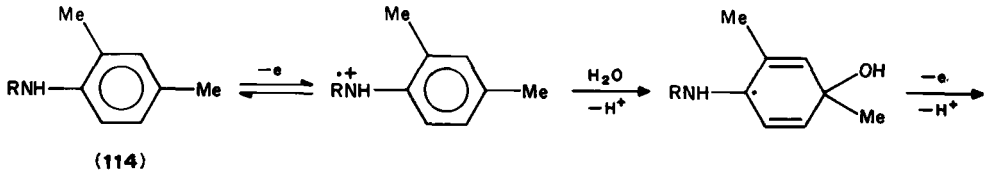
TABLE 11. Yields of main products of benzaldehyde-2-pyridylhydrazone oxidation[76]

Medium	Applied potential (V)	107 (%)	108 (%)	109 (%)
ACN	1.4	62	10	—
ACN + $HClO_4$	1.4	72	25	—
ACN + Py	1.0	26	—	45

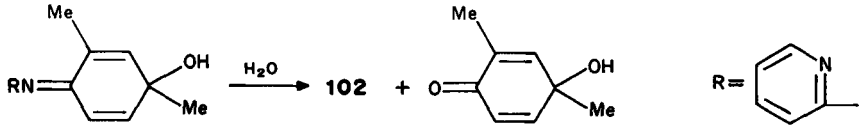
protonated molecule of **106a**. Detailed studies by various electroanalytical techniques indicated an e–D–c–p–p mechanism for **106a**, where the rate-determining step (D) is a homogeneous electron-transfer in a reaction of disproportionation. The first, reversible step of the protonated reactant yields a radical dication (**110**), which then forms a radical cation (**111**). Two radical cations result in a parent molecule (**106a**) and a dication (**112**) in a disproportionation reaction. Further deprotonation of **112** yields the nitrile imine (**113**) which is reasonable in the light of the observed products. Some related compounds were also used as starting materials for electrosyntheses by means of an organic mediator (cf. Section III).



Selective anodic cleavage of the C—N bond, unusual for secondary amines, has been reported[77] in the case of *N*-2-pyridyl-2,4-dimethylaniline (**114**). The oxidation in H_2SO_4 at Ti/MnO_2 and Ti/RuO_2 anodes yielded selectively 2-aminopyridine (**102**) and also 2,4-dimethyl-*p*-quinol (**115**), which was further oxidized. It was shown[77] that a redox system (e.g. MnO_2/MnO) fixed at an electrode surface can act as a heterogeneous catalyst giving a high current efficiency and selectivity of the product. In the mechanism suggested[77] the radical cation is formed in the first step. The nucleophilic addition of water and the second electron transfer yield quinolimine (**116**), which hydrolyses to the final products.

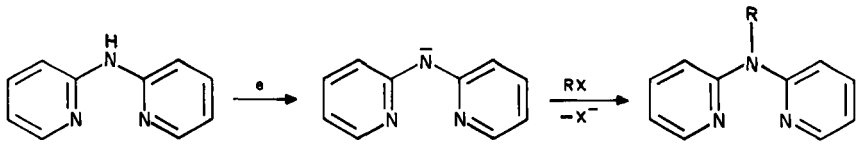


(114)



(116) (115)

Conditions for the selective alkylation of the 2,2'-dipyridylamine anion (**117**) generated at a platinum cathode in ACN containing TBAB has been recently found[78].

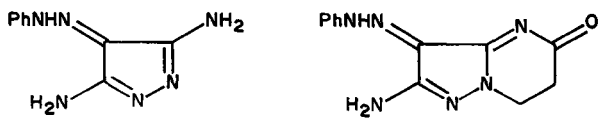


(117)

R	X
Me	I
Allyl	Br
$PhCH_2$	Cl

2. *Aminopyrazoles*

The electrochemistry of aminopyrazoles has not been investigated extensively and is not mentioned in the published review[7]. In the more recent literature the polarographic reduction of 4-phenylhydrazono-3,5-diaminopyrazole (**118**), 3-phenylhydrazono-2-amino-3,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidin-5-one (**119**), and 4-phenylhydrazono-3-amino-2-pyrazolin-5-one (**5**, Ar = Ph) in aqueous ethanol at pH 2–9 were investigated[79]. However, the observed 4e waves correspond to the reduction of the hydrazone group with a cleavage of the N—N bond. Nevertheless, only **118** and **5** can be reduced at pH > 9 and this fact was attributed[79] to their structure which facilitates protonation of the hydrazonic nitrogen at higher pH.



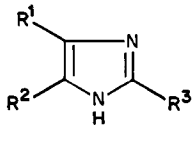
(118) (119)

The $E_{1/2}$ potentials for the reduction of a series of 3-amino-4-arylazo-2-pyrazolin-5-ones (**5**) were obtained in aqueous EtOH[24]. But it must be stressed that these compounds exist in the hydrazo form (**5a**) with the amidine group present only in the solid state, as has been discussed in Section II.C.

3. *Imidazoles and 1,2,4-triazoles*

The electrochemical behaviour of imidazoles and 1,2,4-triazoles was reviewed[7] and only subsequent works are reported in this section.

Polarographic investigations of a number of nitroazoles were stimulated by their physiological activity (related to redox properties) and their potential pharmacological applications as antimicrobial and radiotherapeutic agents. In aqueous solutions at pH 7.4 for a series of nitroimidazoles (**120–122**) and nitrotriazoles (**123**) only one reduction wave was observed[80], although two waves were found in earlier reports. The observed process corresponds to reduction of the nitro group and has only a secondary significance for the electrochemistry of amidines. However, in the reduction of these compounds in aprotic media the formation of radical anions in a 1e transfer can be observed and thus the considered process is characteristic of the whole molecules.



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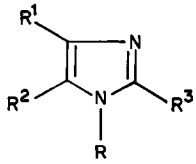
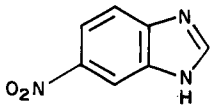
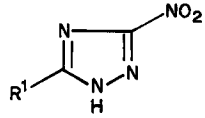


(121)



(122)



(123)

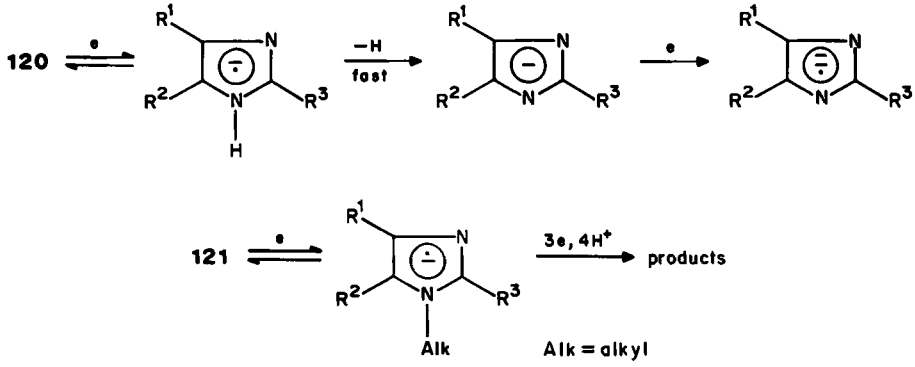
For a series of nitroazoles (**120**, R^1 or $R^3 = NO_2$), **122** and **123** studied in ACN[81,82], two cathodic 1e waves were observed and only the second one was reversible (Table 12). EPR signals were found for the electrolysis at potentials corresponding to the plateau of the

TABLE 12. Half-wave potentials[a] for the reduction of nitroimidazoles in ACN–TBAP and hyperfine splitting constants at the nitro group of products[82]

Imidazole	R	R^1	R^2	R^3	Product[b]	$-E^{I}_{1/2}$ (V)	$-E^{II}_{1/2}$ (V)	a_{NO_2} (G)
120	—	NO_2	H	H	R^{2-}	0.82	2.23	15.52
121	Me	NO_2	H	H	$R^{\cdot-}$	1.75	2.98	13.23
121	Et	NO_2	H	H	$R^{\cdot-}$	1.74	3.02	13.60
120	—	NO_2	H	Me	R^{2-}	0.93	2.39	15.59
121	Me	NO_2	H	Me	$R^{\cdot-}$	1.75	2.95	14.78
121	Me	H	NO_2	H	$R^{\cdot-}$	1.53	2.75	12.70
121	Et	H	NO_2	H	$R^{\cdot-}$	1.67	2.97	14.88
121	Me	H	NO_2	Me	$R^{\cdot-}$	1.51	2.85	13.53
120	—	H	H	NO_2	R^{2-}	0.71[c]	2.37	14.65
121	Me	H	H	NO_2	$R^{\cdot-}$	1.49	2.54	11.60
121	Et	H	H	NO_2	$R^{\cdot-}$	1.45	2.54	11.75

[a] $E_{1/2}$ values expressed vs Hg pool.
[b] $R^{\cdot-}$ and R^{2-} denote radical anion and radical dianion, respectively.
[c] Value 1.05 in Ref. 81.

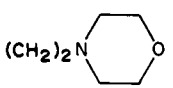
second wave only. The structure of EPR spectra indicated that an unpaired electron interacted with all magnetic nuclei of the molecule with the exception of only one proton. Thus, fast cleavage of the N—H bond was considered before the second electron transfer. Comparison with a series of *N*-alkylimidazoles (**121**) supported the above mechanism[82]. For **121** (R = Me, Et) the first wave was reversible, and EPR spectra as well as the colour of solutions indicated the formation of stable radical anions. The second wave was higher and had a maximum, and no paramagnetic final products were found.



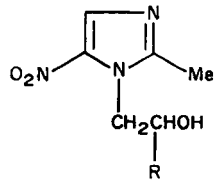
As indicated in Table 12, *N*-alkylimidazoles (**121**) are reducible with far more difficulty than **120**, while hyperfine splitting constants a_{NO_2} in ESR spectra are similar. On the basis of hs constants, it was evaluated that 60% and 45–50% of the spin density is disposed in the nitro group in radical dianions and anions, respectively.

A similar mechanism was also established[83] in DMSO at a platinum electrode. 5-Nitroimidazoles, which are not substituted at a nitrogen atom (Table 13), yield three cathodic waves, but substituted compounds yield only two waves. It was proved, using voltammetry, pulse polarography and rotating-disc measurements, that the first, diffusion-controlled wave is reversible; the corresponding standard rate constants were also measured (Table 13). Pulse voltammetric experiments indicated that the radical anion product undergoes a consecutive chemical step, and thus no anodic peaks were observed on cyclic voltammograms at scan rates $< 1\,V\,s^{-1}$. 5-Nitroimidazoles substituted at a nitrogen atom showed reversible behaviour even at slow scan rates. A detailed inspection of voltammetric behaviour indicated that for β-hydroxyethyl substituted compounds (**124**) the radical anions undergo a slow chemical reaction of the first order, with rate constants

TABLE 13. Half-wave potentials and standard rate constants for the first step of reduction of imidazoles in DMSO-LiCl[83]

Imidazole	R^3	R	$-E_{1/2}$ (V)	$10^2 k_s$ ($cm\,s^{-1}$)
121				
$R^1 = H$, $R^2 = NO_2$	H	Me	1.150	≈1.51
	Me	$(CH_2)_2SO_2CH_2CH_3$	1.060	2.14
	H		1.060	2.01
124a	—	H	1.080	2.16
124b	—	CH_2Cl	1.076	2.27

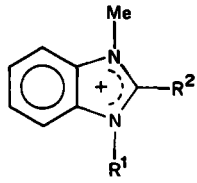
equal to 0.11×10^{-3} and $0.06 \times 10^{-3}\,s^{-1}$ for metronidazole (**124a**) and ornidazole (**124b**), respectively[83].



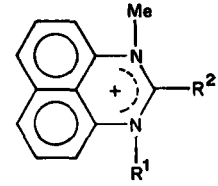
(**124**)

(**124a**) R = H
(**124b**) R = CH_2Cl

The polarographic reduction of *N*-phenylbenzimidazolium cations (**125a**) as well as related compounds **126**–**128** has been investigated in DMF–water mixtures containing TEAP[84,85] (adsorption pre-waves were observed in pure aqueous solutions). Two le waves were found for some compounds (Table 14). The first one corresponds to the formation of free radicals which can dimerize, probably giving a dimer with mercury, or can undergo further reduction, yielding the corresponding dihydro compounds. However, only one 2e wave was observed[84,85] for compounds that formed less stable radicals in the first electron transfer, especially perimidinium (**126c**) and benzimidazolium (**125d**) cations with 2-phenyl substituents (Table 14). Such a substitution increases the electrophilic properties of radicals which are reducible at more positive potentials than the parent molecules[85].



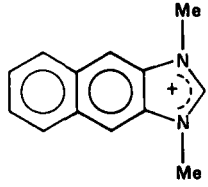
(**125**)



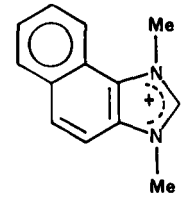
(**126**)

125	R^1	R^2
a	Ph	H
b	*p*-$MeOC_6H_4$	H
c	Me	H
d	Me	Ph

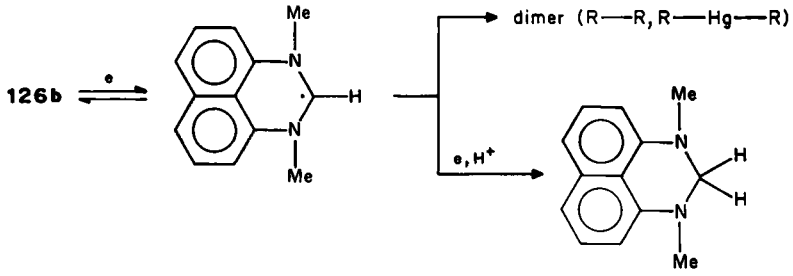
126	R^1	R^2
a	Ph	H
b	Me	H
c	Me	Ph
d	Me	Me



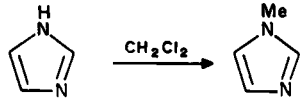
(**127**)



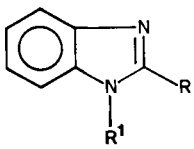
(**128**)



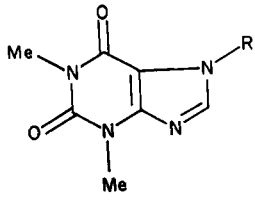
An interesting application of the cathodic reduction at a platinum electrode in CH_2Cl_2 solutions containing TBAB was suggested[86] for N-methylation of imidazole and other NH acids, as well:



N-aminobenzimidazole (**129a**) and other *N*-aminobenzazoles, among them amino derivatives of theophylline (**130a**), have been oxidized at a platinum electrode in ACN containing TEAP[87]. In general, only one 1e anodic peak was observed in the cyclic voltammograms (Table 15) and the absence of a cathodic peak was interpreted[87] in terms of a fast dimerization of the radical cations formed. For aminobenzimidazoles **129a** and **129b** (R = H, Me) small cathodic peaks appeared at − 1.35 to − 1.4 V corresponding to the



129	R^1
a	NH_2
b	NMe_2



130	R
a	H
b	NH_2
c	NMe_2

TABLE 14. Polarographic reduction potentials of imidazolium, naphthoimidazolium and perimidinium cations in DMF–water mixtures[a,84,85]

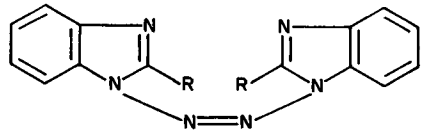
Compound	$-E^{I}_{1/2}$(V)	$-E^{II}_{1/2}$(V)
125a	1.50	1.81
125b	1.50	1.86
125c	1.85	—
125d	1.78	—
126a	1.35	1.68
126b	1.42	1.78
126c	1.38	—
126d	1.64	1.79
127	1.42	1.76
128	1.75	—

[a]Supporting electrolyte TEAP; 10% or 50% DMF.

TABLE 15. Peak potentials for the cyclic voltammetry of *N*-aminobenzazoles at a Pt electrode in ACN–TEAP and basicity constants measured potentiometrically in ACN[57]

Azole	R	E_p^I(V)	E_p^{II}(V)	pK_a
Benzimidazole	—	1.62	—	13.22
129a	H	1.44	—	12.83
	Me	1.46	—	14.24
	NH_2	0.94	1.78	15.60
	NHMe	0.90	1.78	15.83
	NMe_2	0.81	1.78	15.67
	Cl	1.54	—	9.04
129b	H	1.38	—	12.40
130b	NH_2	1.40	—	7.20
130c	NMe_2	1.56	—	6.30

reduction of the dimers 1,1′-azobenzimidazoles (**131**). Basicity constants for the investigated compounds were also estimated in ACN. The process of protonation occurs probably at the N atom of the heterocyclic fragments[87], but there is no correlation between pK_a and E_p values (Table 15). Accepting a minimum π-electron conjugation between the amino group and the heterocyclic system, it was suggested that during the oxidation process an electron is abstracted from the π orbital of the heterocyclic moiety.

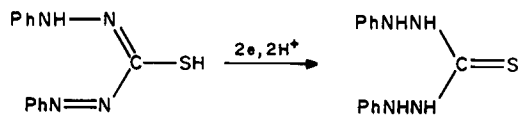


(**131**) R=H, Me

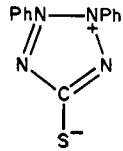
F. Thiamidines

In this section the electrochemical behaviour of some compounds with HN=C(NH_2)—S— grouping is presented in short. Usually, the introduction of a sulphur atom does not change the general pattern of electrode reactions, i.e. in most cases the electroactive centre for the oxidation is the amino group and in reductions the hydrogenation of unsaturated N=N and/or C=N bonds occurs. A more detailed, quantitative discussion of the effect of the S atom does not seem to be possible at present, because of the varied conditions (medium, electrodes) of the measurements described in the literature.

1,5-diphenyl-3-mercaptoformazan (**132**), well known as an analytical reagent, dithizone, is reducible in alkaline media[88] yielding 1,5-diphenylthiocarbazide (**133**). **132** can also be



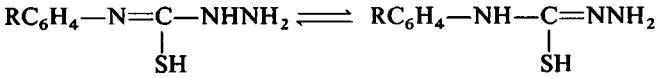
(**132**) (**133**)



(**134**)

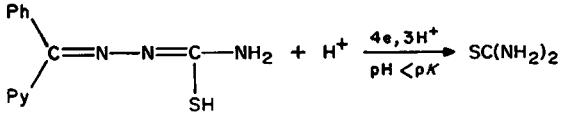
oxidized[89] at a mercury electrode giving the mesoionic dehydrodithizone (**134**). More recent investigations of the latter compound in aqueous methanol indicated[90] that its reduction proceedes indeed, through a dithizonate anion as an intermediate.

Polarographic reduction of arylthiosemicarbazides (**135**) in alkaline aqueous media gave irreversible 2e waves corresponding to reduction of the C=N bond, but without its cleavage[91].

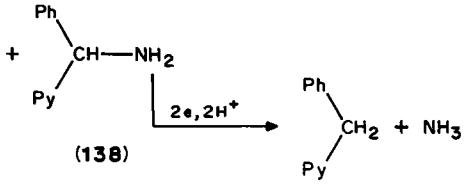


(135)

The cleavage of the S—C bond during the reduction of 2-benzoylpyridine thiosemicarbazone (**136**) at a mercury electrode, suggested in earlier work[205], has recently been found[92] to be non-existent. Investigation in buffered aqueous–ethanolic media indicated an irreversible 4e process yielding thiourea (**137**) and 2-(aminobenzyl)pyridine (**138**), which can be further reduced at more negative potentials. An additional adsorption peak was also found[92] by differential pulse polarography.

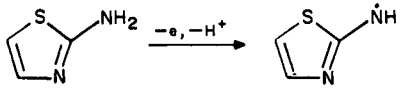


(136) (137)

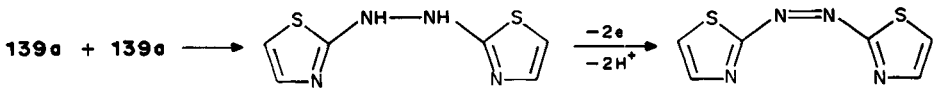


(138)

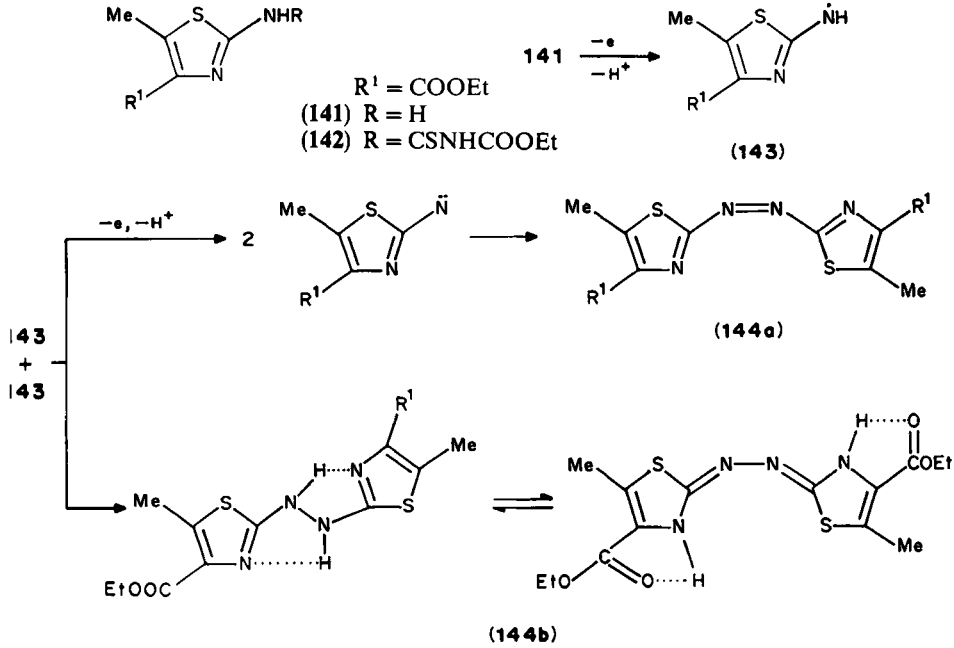
The anodic oxidation of 2-aminothiazole (**139**) and 2-aminobenzothiazole (**140**) have been recently studied[93,94] in buffered organic solvent–water mixtures at pyrolytic graphite electrodes. In both these cases a single anodic peak has been found corresponding to a 2e, $2H^+$ process. However, during the controlled potential electrolysis additional cathodic and anodic peaks, forming an irreversible redox couple related to the final product, have been observed. The mechanism suggested[93,94], on the basis of electrochemical as well as spectroscopic investigations, includes the formation of free radicals in the first step, their dimerization to a hydrazo compound and further oxidation to an azo compound, e.g. for 2-aminothiazole:



(139) (139a)



Oxidation of 4,5-disubstituted 2-aminothiazoles (**141** and **142**) in ACN containing $LiClO_4$ has been investigated earlier[95,96] using a rotating platinum disc electrode. For both the reactants, free radicals (**143**) formed in the first step can dimerize yielding the corresponding disulphide from **142** and, in the case of **141**, the dimeric azo compounds, **144a** and **144b**, which have been identified as the final products.



Finally, it can be added that derivatives of 2-amino-1,3,4-thiadiazoles (e.g. 2-benzoylamino-5-cyanomethyl-1,3,4-thiadiazole[97,98]) are not electroactive in aqueous and organic–aqueous solutions (although 2,5-diphenyl-1,3,4-thiadiazole can be reduced under similar conditions), unless they possess some reducible or oxidizable groups[97,98].

G. Amidines of Biological Interest

1. Pyrimidines

Pyrimidine (**145**) is often treated as the prototype compound for the purine series; the cathodic reduction of purines occurs in the pyrimidine ring. Earlier studies on this subject have been reviewed[2-8]. In aqueous solutions within the pH range 0.5 to 13, five polarographic waves of **145** have been observed. The half-wave potentials of these waves are pH-dependent according to the relations below[7]:

$$-E^{I}_{1/2} = 0.576 + 0.105\,\text{pH} \quad (4)$$

$$-E^{II}_{1/2} = 1.142 + 0.011\,\text{pH} \quad (5)$$

$$-E^{III}_{1/2} = 0.680 + 0.089\,\text{pH} \quad (6)$$

$$-E^{IV}_{1/2} = 1.600 + 0.005\,\text{pH} \quad (7)$$

$$-E^{V}_{1/2} = 0.805 + 0.079\,\text{pH} \quad (8)$$

Some intermediate reduction products were not isolated, but were examined polarographically, coulometrically and spectrophotometrically[99]. The electrochemical reduction pathway which was suggested, based on the results of these studies, is as follows. The first wave, which is formed at low pH (0.5 to 5), can be explained by the following scheme (where R denotes **145**):

(145)

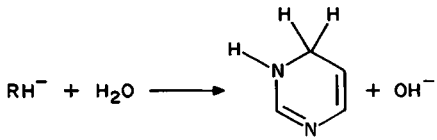
$$R + H_3O^+ \rightleftharpoons RH^+ + H_2O$$

$$RH^+ + e \rightleftharpoons RH^\cdot$$

$$2RH^\cdot \xrightarrow{\text{dimerization}} HR{-}RH$$

The second wave (pH 3 to 5) has been considered to result from the reduction of the radical $RH^\cdot$ with subsequent stabilization of the resulting anion, RH^-, by water forming 3,4-dihydropyrimidine (**146**). The third wave, recorded within the pH region from 5 to 8, corresponds to the overall process. Two remaining waves observed at pH 7 to 8 and at pH 9 to 13 were attributed to reduction of **146** and **145**, respectively, to tetrahydropyrimidines.

$$RH^\cdot + e \rightleftharpoons RH^-$$



(146)

$$\mathbf{145} + 2e + 2H_3O^+ \longrightarrow \mathbf{146} + 2H_2O$$

The cathodic process of **145** in non-aqueous media, such as DMF and ACN (for details see References 2 and 7), starts with a reversible 1e transfer

$$R + e \rightleftharpoons R^{\cdot -}$$

The resulting radical anion, $R^{\cdot -}$, is very unstable. Cyclic voltammograms of pyrimidine in ACN solutions containing TEAP as supporting electrolyte show no anodic peak corresponding to the oxidation of $R^{\cdot -}$ at scan rates below $3\ V\ s^{-1}$. Even at a sweep rate of $60\ V\ s^{-1}$ the ratio of anodic to cathodic peak current was found to be far from unity[100]. It seems evident that formation of dimers is the preferred pathway of stabilization of $R^{\cdot -}$ under aprotic conditions. During the cathodic reduction of **145** in DMF the corresponding ESR spectrum was recorded; this was unequivocally assigned to the radical anion of 4,4′-bis-pyrimidine[101]. In our opinion, the kinetics of this dimerization should be strongly affected by the nature of the supporting electrolyte cations, M^+, due to ion association phenomena in $R^{\cdot -}{-}M^+$ systems. To our knowledge, however, no experimental results on this subject are available in the literature.

Electrochemical processes of **145** in acetonitrile containing proton-donating agents, HA, such as phenol, have also been investigated[102]. Under these conditions the following reactions have been suggested:

$$R + HA \rightleftharpoons (R\cdots HA \rightleftharpoons RH^+ + A^-)$$

$$RH^+ + e \rightleftharpoons RH^\cdot$$

$$2RH^\cdot \xrightarrow{\text{dimerization}} HR{-}RH$$

We think, however, that such a mechanism needs some comments. Let us mention that the hydrogen-bonded adduct, R···HA, was not detected in the bulk of the solution. In other words, it can be formed only in the field of the double layer of an electrode. What is the effect of the potential gradient on the formation of R···HA? Does this adduct really dissociate in the field of an electrode forming RH^+? Up to now, it has not been possible to give a detailed explanation of this problem.

An important step forward was made by Malinski and coworkers[103] who investigated the electrochemical behaviour of 2-hydroxypyrimidine (**147**) and related compounds in DMSO. The existence of a keto–enol equilibrium should be considered, but in the solvent under study the molecules are predominantly in the keto form (cf. Reference 103 and references cited therein). Formally, the keto form of **147** has no amidine group; however, the redox behaviour of this compound is important in elucidating the reduction mechanism of cytosine (**148**), which is one of the important components of both DNA and RNA. Thus, it will be convenient to discuss at first the reduction of **147**, which was examined using many electroanalytical techniques. In general, the reduction pathway is similar to those described for pyrimidine. The primary and most remarkable difference between the cathodic behaviour of **147** and **145** is the ability of the substituted compound, **147**, to serve as a proton source. Therefore, it is interesting to note that **147** is a proton donor for neutralization of the radical anion formed as a result of a fast 1e transfer. Of course, the electrode processes for this reduction are diffusion controlled. However, a diffusion current constant I_d decreases visibly with increasing concentration of **147**. This is mainly due to the differences between the rates of protonation of the radical anion and the dimerization step. At high concentrations, protonation by the parent molecule is suggested to be the predominant factor, whereas at low concentrations this protonation is low and mainly dimerization occurs[103]. As a result of this concurrence, fundamental characteristics of the recorded polarographic waves are clearly dependent on the concentration of the compound under study (Table 16).

(147)

A part of the free radical formed on protonation can be further reduced. The resulting anion is also capable of abstracting a proton from the molecule of **147**, similarly to what was described above. Of course, in these *father–son* processes* 2-hydroxypyrimidine anions are produced. They are not reducible at a mercury cathode within the available potential range, but can take part in a Hg(I)/Hg(0) redox couple, involving formation of sparingly soluble mercury salts. As a consequence, three anodic polarographic waves can be observed ($E_{1/2}$ between -0.1 and -0.3 V).

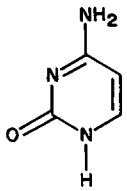
Similar anodic effects were also described for mercaptopyrimidines, e.g. 2-mercaptopyrimidine (**149**)[105] and dimercaptopyrimidines[106]; they have been attributed to the precipitation of corresponding Hg(I) salts. Moreover, **149** gave the pH-dependent cathodic waves with characteristics quite similar to those described above for the pyrimidine reduction.

*The term "father–son reaction" was first suggested to describe the situation where the principal product of the reaction then reacts with the original reactant of interest[104]. In our case, for instance, **147** and its radical anion can be regarded as "father" and "son", respectively.

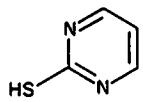
TABLE 16. Polarographic data of 2-hydroxypyrimidine (147) in DMSO–TBAP[103]

c^a (mM)	$-E_{1/2}$ (V)	$I_d{}^b$	n^c
→0	1.67	1.69	1.00
2	1.64	0.77	0.99

[a]Concentration of 147.
[b]$I_d = i_g/(cm^{2/3}t^{1/6})$ where i_g is the limiting current, and m and t denote the rate of mercury flow in a dropping mercury electrode and the drop time, respectively.
[c]The number of electrons transferred in the electrochemical process, n, was calculated based on the I_d value.



(148)

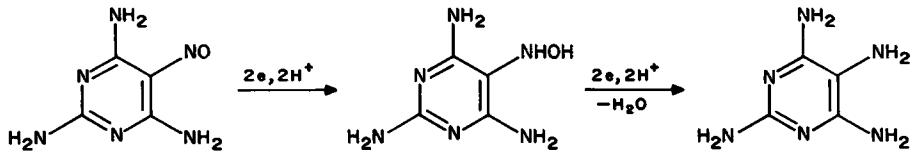


(149)

Very recently the electrochemical properties of 2,4,6-triamino-5-nitrosopyrimidine (150), a compound of pharmaceutical significance, have been studied using a dropping mercury electrode[107]. Within the pH range 4–14 a single diffusion-controlled cathodic wave has been observed; the changes in $E_{1/2}$ with pH may be expressed as follows:

$$-E_{1/2} = 0.20 + 0.055\,\text{pH} \tag{9}$$

The overall process was found to correspond to a 4e, $4H^+$ transfer, and is connected with the reduction of the nitroso group. However, on the basis of the shape of cyclic voltammograms, step-wise addition of electrons was suggested. Consequently, the hydroxylamino derivative (151) can be assumed as an intermediate, whereas 2,4,5,6-tetraaminopyrimidine (152) was identified as the final product.



(150) (151) (152)

Now, we focus our attention on the cathodic processes of cytosine (148), which is a typical cyclic amidine. The electroreduction of 148 has been studied extensively in aqueous solutions[108–113]. It is well established that the 3,4 N=C double bond is initially reduced in the 2e step. The resulting 3,4-dihydro species is rapidly deaminated to produce 2-hydroxypyrimidine, which is further reduced according to the reaction sequence described above. Consequently, a 2-hydroxypyrimidine dimer has been isolated and identified[113] after a controlled potential electrolysis (−1.45 V) of 148 at a Hg pool cathode.

More recently, the cathodic behaviour of **148** has been examined in DMSO solutions[103,114]. Characteristics of the polarographic wave were found to be visibly dependent on the reactant concentration; the half-wave potentials of $E_{1/2}$ -2.42 and -2.37 V, were estimated for infinite dilution and at a concentration of 2 mM, respectively (0.1 M TBAP was used as electrolyte). This result and characteristic changes of the I_d values with the concentration of cytosine indicate the occurrence of a *father–son* process quite similar to that in the case of **147**.

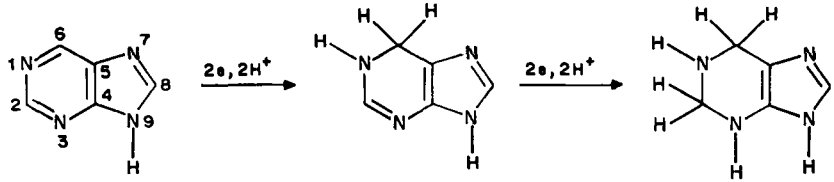
2. *Purines and purine bases*

Purine (**153**, note exceptional numbering according to IUPAC), and its derivatives react in many cases analogously to pyrimidine, or more precisely, the electrochemical reduction of purines is restricted to the pyrimidine system. Earlier works on the electrochemistry of these compounds have been extensively reviewed[2-8]; therefore, we note only that **153** forms two polarographic waves in aqueous media, both of which are pH-dependent (within the pH range 0 to 11):

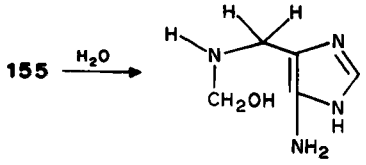
$$-E^{I}_{1/2} = 0.697 + 0.083\,\text{pH} \tag{10}$$

$$-E^{II}_{1/2} = 0.902 + 0.080\,\text{pH} \tag{11}$$

Based on the results of numerous electrochemical and spectroscopic experiments, 1,6-dihydropurine (**154**) was identified as the product of wave I. Wave II yields 1,2,3,6-tetrahydropurine (**155**) which hydrolyzes, forming **156**. The imidazole system is not reducible under polarographic conditions. Note that this observation is consistent with the reactivity of purines with hydrated electrons. As can be seen from the excellent review of Steenken[115], the purines have a very intrinsic reactivity with e_{aq} and this property is endowed by the electron-deficient pyrimidine ring.



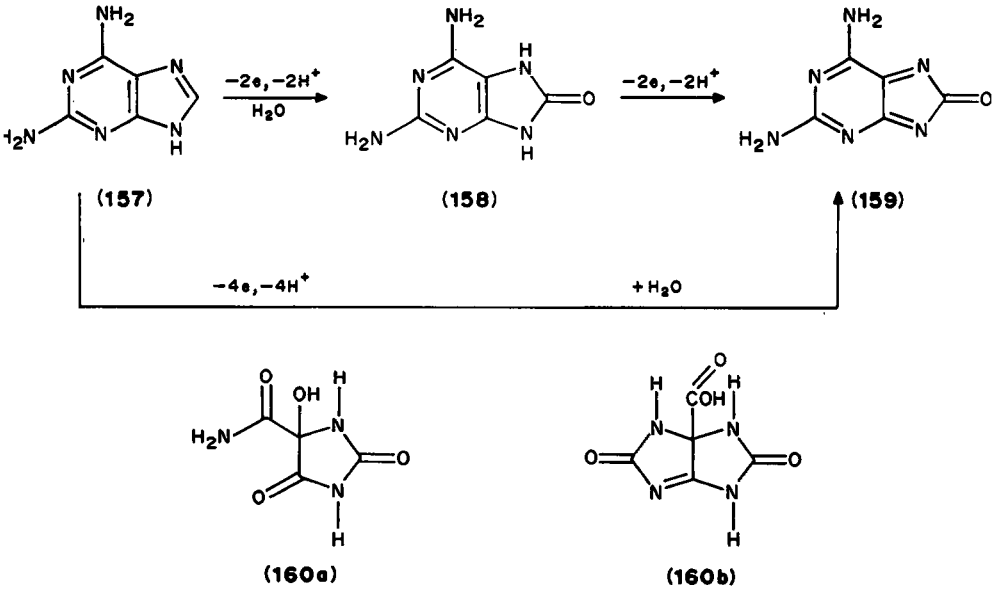
(153) (154) (155)



(156)

Purines may also be oxidized electrochemically[116-126]. By way of example, the anodic oxidation of 2,6-diaminopurine (**157**) was studied in detail on pyrolytic graphite[127]. Electrochemical, spectroelectrochemical and gas chromatographic/mass spectrometric experiments indicate that the oxidation pathway depends on potential. At less positive potentials **157** is initially oxidized in a 2e, $2H^+$ process to the keto form of 2,6-diaminopurinol (**158**), which is immediately further oxidized to 2,6-diaminopurinol-

diimine (**159**) in a 2e, $2H^+$ process. At more positive potentials a 4e, $4H^+$ process forms the diimine **159**. The latter is not stable and decomposes in a series of reactions (hydrolysis and elimination of NH_3) giving 5-hydroxyhydantoin-5-carboxamide (**160a**) and 2,4,6,8-tetraaza-3,7-dioxo-4-ene-bicyclo[3.3.0]oct-4-ene-1-carboxylic acid (**160b**) as final products. More recent experimental evidence indicated[128] that the 2e oxidation of **158** proceeded in two 1e steps. The mechanisms suggested to explain the results observed are also discussed in Reference 129.



Some information on the cathodic reduction of purine in non-aqueous media is also available. Santhanam and Elving[130] examined the redox properties of purine itself and its 6-substituted derivatives including adenine (6-aminopurine) in DMF. They postulated that neutral molecules are reducible due to prior reduction of hydrogen ions, background electrolyte cations or residual water, undergoing a 1e transfer to form the corresponding free radical anion. The latter dimerizes, as indicated by the lack of an anodic peak, after a potential scan reversal during cyclic voltammetric experiments. Recent studies of Malinski and coworkers[131] have shown that adenine (**161**) is reduced in DMSO containing 0.1 M TBAP at the potential -1.58 V. Differential pulse and cyclic voltammograms in the reverse scan showed an anodic peak at $E = -1.08$ V. More precise experiments with recording of thin-layer spectra during controlled potential electroreduction support a mechanism involving radical generation in a 1e transfer followed by protonation and dimerization; the dimer may be oxidized at a high overpotential:

$$\mathrm{Ad} \overset{+e}{\rightleftharpoons} \mathrm{Ad}^{\cdot -} \overset{+H^+}{\rightleftharpoons} \mathrm{AdH}^{\cdot} \longrightarrow \tfrac{1}{2}(\mathrm{AdH})_2$$

In this scheme Ad denotes the molecule of adenine.

The electrochemical reduction of **161** in aqueous media has been examined extensively at various types of electrodes and the results of these studies have been reviewed[2,3,132,133]. The following conclusions from these studies are particularly important. First, investigations have revealed adenine to be reducible only when protonated at the $N_{(1)}$ nitrogen

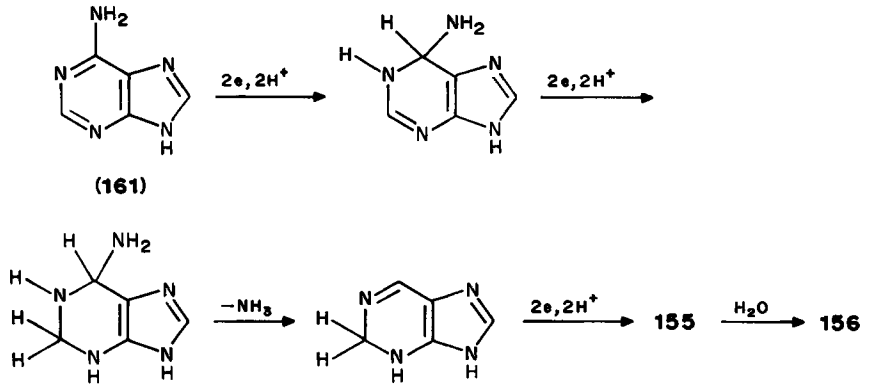
atom[2,110,134–136]; the reduction has not been observed above pH 5.5. The polarographic wave occurs close to the background electrolyte decomposition, and its half-wave potential is pH-dependent according to the following equation:

$$-E_{1/2} = 0.975 + 0.090\,\text{pH} \tag{12}$$

Controlled-potential coulometry and large-scale electrolysis show that 6e are consumed. The pH change during coulometric measurements in unbuffered solutions indicates that five or six hydrogen ions are consumed during the electrochemical process. Second, the reduction product at pH 1.4 is essentially superimposable on that of the product for the purine reduction at the potential of its second wave. Actually, the macroscale electrolysis at a mercury pool cathode produces **155** in 1 M HCl[137] as well as in solutions of the pH range 1.3 to 2.3[138]. Hence the electrochemical reduction occurs in the pyrimidine subsystem and is connected with the elimination of the amino group.

All these observations are fully consistent with the results of the pioneer work of Smith and Elving[139]. According to these authors the first (potential-controlling) step involves hydrogenation of the 1,6-double bond, i.e. the reduction of the amidine moiety. Further processes follow, being the reduction of the 2,3-double bond, the deamination of the 6-position, further reduction of the regenerated 1,6-double bond and finally hydrolytic cleavage at the 2,3-position.

The chemical steps, i.e. deamination and hydrolysis, are slower than the electrochemical ones. The overall mechanism of electrochemical processes may be represented by Scheme 1. It should be noted that electroreduction of some substituted derivatives of adenine was also studied (for reviews see References 2 and 7); the reduction pathway seems to be very similar to that of **161**.



SCHEME 1

The electrochemical behaviour of adenosine (**162**) is similar, in principle, to that of **161** itself[140]. Attachment of the ribose moiety decreases the reducibility; the half-wave potential of **162** becomes more negative with increasing pH, according to the following equations:

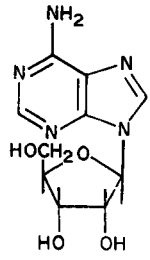
$$-E_{1/2} = 1.040 + 0.070\,\text{pH}; \qquad \text{at pH 2.0 to 4.5} \tag{13}$$

and

$$-E_{1/2} = 1.180 + 0.041\,\text{pH}; \qquad \text{at pH 4.5 to 6.0} \tag{14}$$

In proton-donating media polarograms exhibit a diffusion-controlled 4e wave due to

reduction of the 1,6 and 2,3 C=N double bonds in the protonated molecule. In aprotic conditions (DMSO–0.1 M TBAP) a 1e transfer was observed. The radical anion dimerizes after protonation[131].



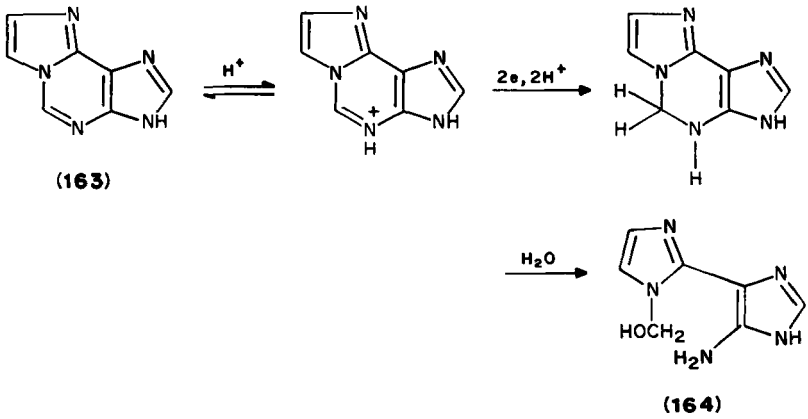
(162)

Recently, the participation of adenine reduction has been identified during a study[141] of the cathodic processes of coenzyme NAD^+ (nicotinamide adenine dinucleotide). In acidic media NAD^+ produces two polarographic waves: the first consists of a 1e reduction to a free radical $NAD^\cdot$ which reacts to give the dimer NAD–NAD[141,142]. The second step is connected with the reduction of the adenine system; this conclusion has been confirmed by spectrophotometric measurements and enzymatic assessment of the products of macro-scale electrolysis on a Hg pool cathode. It is noteworthy that electrochemical reactions of adenine nucleosides and nucleotides have also been studied[140,143]. The product of AMP (adenosine monophosphate) reduction was characterized by HPLC and spectroscopic measurements and was identified as a corresponding dihydroadenine nucleotide[143].

Adenine and its derivatives are strongly adsorbed at an aqueous solution/mercury interface. The relative extent of adsorption of **161** and NAD^+ from a solution of pH 4.8 (0.5 M McIlvaine buffer) has been measured as a function of potential by an inverse normal pulse polarography. **161** shows its maximum adsorption between -0.25 and -0.45 V[144]; in solution of pH 5.0 (in the same buffer) a maximum at -0.43 V has been reported[145]. **162** is strongly adsorbed at approximately -0.6 V, which probably involves an uncharged portion of the molecule. At more negative potentials the species are gradually desorbed and may be readsorbed via the protonated portion of the molecule[140]. Moreover, the inverse stripping voltammetry of twelve adenine nucleotides and seven nicotinamide adenine nucleotide coenzymes was performed in sodium phosphate buffer at a dropping mercury electrode using high scan rates (10 to 100 $V\,s^{-1}$). The stripped phase formed at $+0.15$ V consists of sparingly soluble mercurous salts and/or the corresponding mercuric surface complexes[146]. The adsorption of flavin adenine nucleotides at a platinum electrode has been recently studied[147].

Interesting results have been published[148] on the electrochemical reduction of ε-adenine (**163**). Within the pH range from 2 to 9.5 this compound forms a single, diffusion-controlled, 2e cathodic wave. The absorption spectrum of the reduced species was found to be similar to that of 5-amino-2,3-bis-imidazole (**164**), so that the most probable reduction site seems to be the 2,3 C=N double bond. The reduction mechanism for **163** shown in Scheme 2 has been suggested. The cathodic reductions of ε-adenosine and of ε-NAD^+ have also been analysed[148].

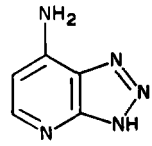
Only scanty information is available on the redox properties of 8-aza-adenine (**165**). In aqueous solutions the reduction pathway is similar to that of adenine: it occurs in the pyrimidine nucleus and takes place after elimination of the amino group in a dehydro compound which is suggested to be 3,4-dihydro-8-azapurine[138]. In liquid ammonia **165** forms two cathodic peaks; the first is very broad, while the second is close to the reduction



(163) (164)

SCHEME 2

wall and corresponds to the reduction of the medium used. No oxidation peak was present on the voltammogram. The mechanism of the electrochemical process was not elucidated[149].



(165)

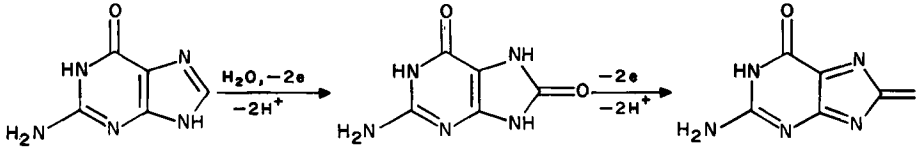
Electrochemical reactions of guanine (**166**) have been studied to some extent. Dryhurst and Pace[150] found that the anodic oxidation at pyrolytic graphite in 1 M CH_3COOH gave a mixture of guanidine, parabanic acid, CO_2 and, probably, 5-guanidinohydantoin (**167**). Afterwards, Yao and Musha[151] reported that **166** is oxidized anodically at a glassy carbon electrode in 1 M H_2SO_4 giving allantoin, NH_3, urea, guanidine, oxaluric and parabanic acids. Both papers[150,151] suggested a mechanism involving intermediates, but without a great deal of supporting evidence for the formation and identity of such species.

Reliable identification of products and intermediates have been reported by Goyal and Dryhurst[152]. These authors have found that **166** is oxidizable at pyrolytic graphite over a wide pH range in aqueous solutions. An oxidation peak is pH-dependent and its potential is described by the equation at a sweep rate of 5 mV s^{-1}. Controlled-potential coulometry

$$E_p = 0.99 - 0.047\,\text{pH}; \qquad \text{at pH 3.3 to 10.3} \tag{15}$$

at a peak potential between pH 3.0 and 9.0 showed that 4 electrons per molecule were transferred. Using a combination of thin-layer spectroelectrochemistry and gas chromatography–mass spectrometry to trap and identify intermediates and products, it was established that **166** was initially oxidized in a 2e, $2H^+$ process to give 8-oxyguanine (**168**) which, being more easily oxidized, was immediately further transformed in a 2e, $2H^+$ process to an unstable quinonoid diimine (**169**). Then, a series of hydration and other chemical reactions occurred leading to the final products: 2,5-diimino-4-imidazolone (**170**)

and 5-guanidinohydantoin (**167**). It is interesting to note that **168** is also oxidized by the peroxidase/H_2O_2 system. Electrochemical, kinetic and spectral data indicate that for this process the chemical reaction pathway is identical to that observed under the electrochemical conditions[152].



(166) (168) (169)

(170) (167)

The anodic oxidation of 6-thioguanine (**171**) proceeds by a pathway which involves the thio group as well as the purine ring. Cyclic voltammograms recorded at a rough pyrolytic graphite electrode showed two oxidation peaks, I and II; the first is present due to an adsorption-controlled process. From pH 1.7 to 7.4 at scan rate 5 mV s^{-1}

$$E_p^I = 0.53 - 0.037\,\text{pH} \tag{16}$$

and within the pH range from 8.0 to 10.0

$$E_p^I = 0.76 - 0.076\,\text{pH} \tag{17}$$

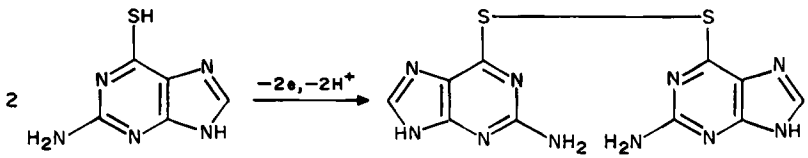
The potential of the second peak can be described as a function of pH by the following equations:

$$E_p^{II} = 1.11 - 0.032\,\text{pH}; \quad \text{at pH 1.7 to 4.0} \tag{18}$$

$$E_p^{II} = 1.28 - 0.065\,\text{pH}; \quad \text{at pH 4.0 to 10.0} \tag{19}$$

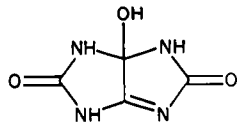
$$E_p^{II} = 1.36 - 0.082\,\text{pH}; \quad \text{at pH 10.0 to 12.5} \tag{20}$$

Experimental results (cyclic voltammetry, controlled-potential electrolysis, coulometry, UV/vis spectroscopy and mass spectrometry) indicate that the oxidation mechanism depends visibly on applied potentials. At a less positive potential (peak I) the —SH group is oxidized forming a dimeric product **172**. At more positive potentials (peak II) the process under consideration corresponds to the overall 10e, $10H^+$ transfer and then the oxidation involves both the thio group and the purine system. In this case 1-hydroxy-2,4,6,8-



(171) (172)

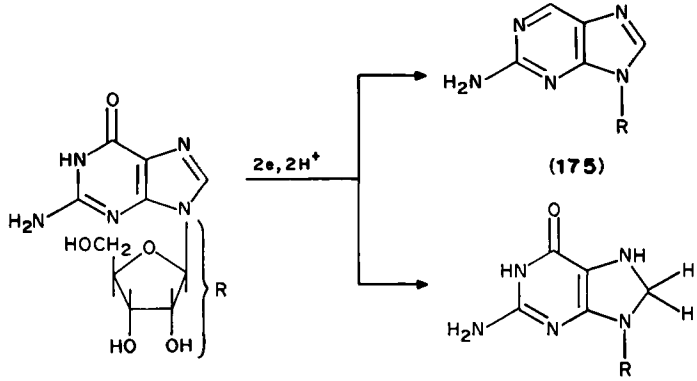
tetraaza-3,7-dioxo-bicyclo[3.3.0]oct-5-ene (**173**) and 5-guanidinohydantoin (**167**) were identified as the final products. However, it was not possible to obtain indirect evidence of the pathway for a process leading to these compounds[129,153].



(**173**)

It should be pointed out that **166** is not reducible under normal polarographic conditions[154,155]. It is known, however, that the guanine moiety may be reduced in nucleosides and nucleotides at potentials approximately -1.8 to -1.9 V. Dihydroguanine derivatives generated during this process may be electrooxidized at *ca* -0.2 V in buffered aqueous media at a mercury electrode[3,155]. Such a picture was observed on the cyclic voltammetric curves of guanosine (**174**), but the influence of the reactant concentration, scan rate, switching potential, pH and the nature of the supporting electrolyte was very complex, indicating that adsorption/desorption phenomena play an important role in the processes under study[155]. Quantitative investigations on the adsorption stage and association of **174**[156], its methylated derivatives[157,158] and guanosine phosphates[159] at a mercury electrode have been carried out in various buffer solutions by phase-sensitive a.c. voltammetry.

It was suggested that the 7,8 C=N double bond in the guanine system is reduced at mercury cathodes[160]. Very recently identification of the electroreduction products has been reported[161]. For this purpose a macroscale controlled-potential electrolysis of **174** in acetate buffer (pH 6.0) with ammonium formate was performed. In other experiments the authors attempted the reduction of **174** in DMSO by the use of borohydride and compared the voltammogram of the product of this chemical reduction with that of electroreduced guanosine. Identical products were found in both experiments. Analyses of the NMR spectrum of chemically reduced **174** revealed that two products were formed: one of them was attributed to 9-ribosyl-2-aminopurine (**175**), the other was identified as 7,8-dihydroguanosine (**176**). Thus, rather surprisingly (although intuitively expected in Reference 160) the electroreduction of **174** may really proceed in the imidazole ring. Certainly, this is a unique pathway for the electroreduction of the purine derivatives.



(**174**) (**175**) (**176**)

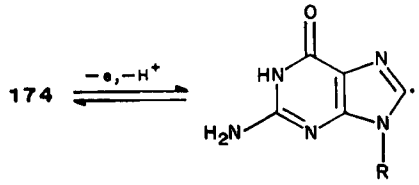
It should be emphasized in this context that highly original and very interesting results have been reported by Subramanian and Dryhurst[162]. Studying the oxidation of **174** in aqueous phosphate buffer solutions (pH 2–11) at a pyrolytic graphite anode, they found that cyclic voltammograms show up to three pH-dependent anodic peaks. Their potential characteristics were as follows (sweep rates and pH regions are given in parentheses):

$$E_p^{I} = 1.16 - 0.050\,pH \qquad (5\,mV\,s^{-1};\ pH\ 4\text{–}11) \tag{21}$$

$$E_p^{II} = 1.24 - 0.035\,pH \qquad (200\,mV\,s^{-1};\ pH\ 2\text{–}11) \tag{22}$$

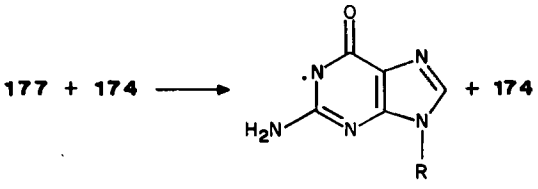
$$E_p^{III} = 1.28 - 0.011\,pH \qquad (200\,mV\,s^{-1};\ pH\ 2\text{–}8) \tag{23}$$

Having scanned these oxidation peaks several reduction peaks were observed on the reverse scan. Moreover, on the second anodic sweep, two new oxidation peaks appeared at less positive potentials than peak III. This complex picture was additionally influenced by adsorption phenomena. More precise experiments indicate clearly that **174** is really adsorbed at the surface of an electrode. This being the case the interpretation of experimental results becomes very difficult indeed. Nevertheless the authors[162] have shown convincingly that the primary electro-oxidation step involves a 1e, $1H^+$ transfer leading to a free radical (**177**) with the unpaired electron being located at the $C_{(8)}$ position:

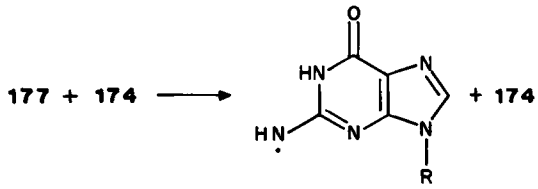


(177)

This radical reacts with guanosine and H_2O yielding other radicals, which then undergo a series of chemical and electrochemical processes giving novel guanine di- and tri-nucleosides. One of these, 8-(8-guanosyl)-1-(1-guanosyl)guanosine (**181**), is formed in the sequence of reactions shown in Scheme 3. Similarly, additional reasonable routes to form other guanine oligonucleosides were also suggested[162].



(178)



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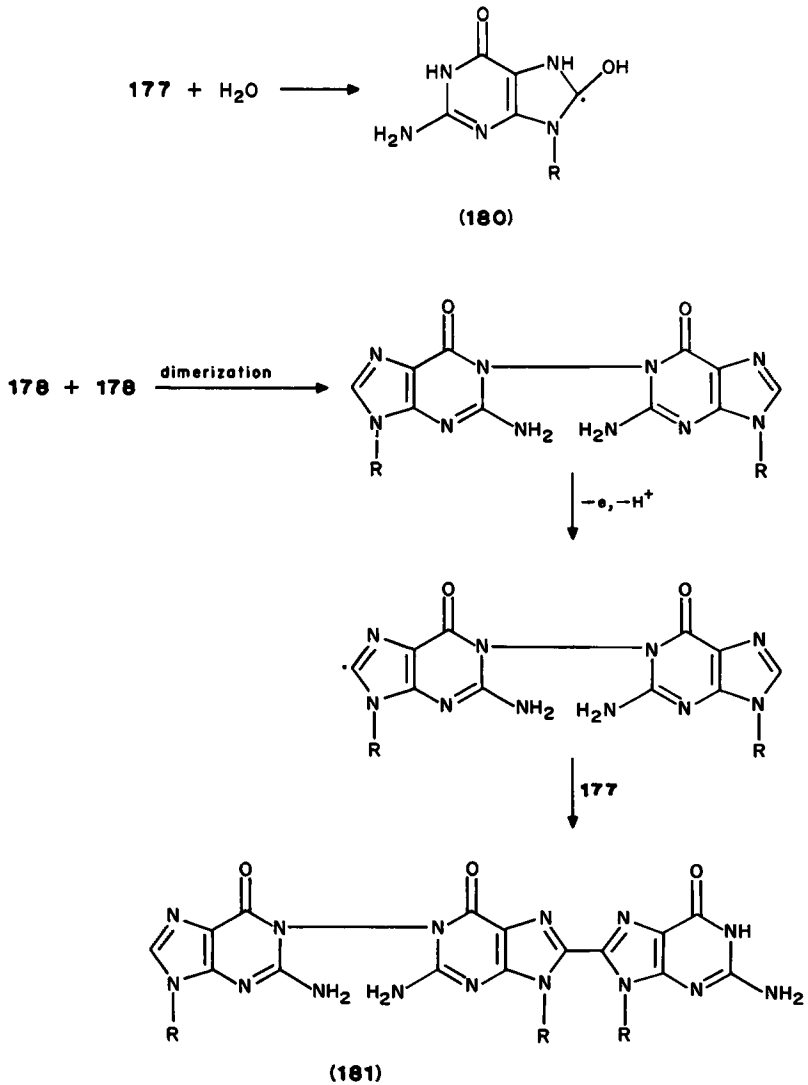


SCHEME 3

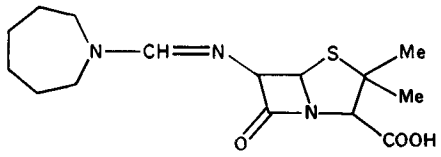
V. EPILOGUE

It can be seen from this chapter that electrochemical data have been accumulated and used mainly for the explanation of the mechanism of the reduction and oxidation of amidines. Numerous compounds of this group are of biological and pharmaceutical interest, and in several publications the electroanalytical point of view is accentuated. Yao and coworkers[154] have found that adenine, adenosine, guanine and guanosine can be oxidized

at a glassy carbon electrode in aqueous solutions at different potentials. The bases and their nucleosides were strongly adsorbed on the surface of the electrode, but at pH values below 4 good linear dependences were observed. The differences between the peak potentials of each of the purine bases were most pronounced at pH 2–4; consequently, it was possible to conduct experiments in mixtures of the bases and their nucleosides. The method was recommended as simple and rapid, since no prior separation is required.

Furthermore, Paleček[163] has applied a cathodic stripping voltammetry to determine purine derivatives. The method was based on a slow accumulation of the sparingly soluble salts with Hg at the electrode surface and their subsequent cathodic stripping. It was found that some purine derivatives can be detected at concentrations as low as 10^{-8} M; the limit of adenine detection was even 2×10^{-9} M.

Electroanalytical methods, mainly polarography, were applied for the quantitative determination of some important pharmaceutics, e.g. proguanil (**79**) and chlorohexidine (**81**, in the form of Hibitane tablets)[63], cimetidine[164], guanabenzoacetate (Wytensin, which is a derivative of **93c**)[70], as well as other amidines discussed in the previous section (**70**[59], **97–101**[72,33], **93d**[71], **3**[165]). The use of guanylhydrazones (**93a–93b**) as ligands for the polarographic determination of metal ions was also suggested[68,69]. Electrochemical detection combined with chromatographic methods was used in numerous papers, in particular, for guanidines and biological amidines[166–168]. Recently, differential pulse voltammetry has been applied[169] for anodic determination of 6-mercaptopurine and 6-thioguanine. Quite recently, Chodkowski and coworkers found[170] that amidopenicillines, Selexidin (**182**) and its pivaloyloxymethyl ester—Selexid, give catalytic polarographic



(182)

waves which can be used for their quantitation. A suitable medium is phosphate buffer in which **182** can be best determined in concentrations of 0.04–0.20 mg cm^{-3} at pH 8.20, and Selexid in concentrations of 10–50 $\mu g\, cm^{-3}$ at pH 7.0.

The development of electrode reactions is highly dependent on the nature of the electrode–solution interface. Most of these processes are still performed using metallic or carbon electrodes. However, modifications of the surface may result in the enhancement of particular properties of the working electrode which can be exploited in electroanalytical chemistry. Many times the acceleration of the rate of heterogeneous electron transfer at modified electrodes was observed. For example, cytochrome *c* is very slowly reduced at various bare electrodes, but modification of the surface by purine and its derivatives facilitates visibly the electron transfer. For this purpose a silver electrode was modified by the deposition of bis(4-pyridyl)disulphide and purine[171]. Purine and its derivatives, among them adenine and guanine[172], as well as 6-mercaptopurine[173,174], were found to be effective as new promoters for rapid electron transfer of cytochrome *c* at a modified gold surface. The effectiveness of other purinyl compounds has also been reported[175–181] Moreover, a film of ethylene-bis-biguanidine silver(III) on platinum has been electrodeposited from an aqueous $HClO_4$ solution and the electrochemical route for the generation and electrocatalytic activity of this film towards oxygen evolution was presented[182].

The use of metal phthalocyanines as catalysts in the electroreduction of molecular oxygen is a subject of growing interest[183–185]. Catalytic activity was usually considered in terms of redox processes involving the central ion[186,187]. Recent results[188] have indicated that in the case of adsorbed layers of iron phthalocyanine and iron naphthalocyanine on a gold and a stress-annealed pyrolytic graphite electrode, O_2 reduction is really associated with redox processes involving the metal ion through the Fe(II)/Fe(III) couple. However, in the case of iron tetrasulphonaphthalocyanine the existence of such a mechanism seems to be questionable.

In recent years more and more attention has been paid to the electrochemistry of the amidinato complexes of transition metal ions. Cathodic reactions of the biguanide complex of Co(III)[189] and silver(III) complexes of ethylene dibiguanide[190] in water are quite simple; polarographic processes of the latter indicated that formation of bivalent and monovalent states of silver occurred.

More recently, redox properties of dirhodium(II) complexes with *N,N*-diphenylbenzamidine were studied in CH_2Cl_2 and ACN solvents (0.1 M TBAP) and three reversible processes were observed[191]. Also, dipalladium complexes with the same ligand were found to be oxidizable at a platinum electrode in CH_2Cl_2, 0.1 M TBAP[192].

$$Rh_2(ligand)_4 \overset{e}{\rightleftharpoons} [Rh_2(ligand)_4]^-$$

$$Rh_2(ligand)_4 \overset{-e}{\rightleftharpoons} [Rh_2(ligand)_4]^+$$

$$[Rh_2(ligand)_4]^+ \overset{-e}{\rightleftharpoons} [Rh_2(ligand)_4]^{2+}$$

Chemical and electrochemical oxidation of dinuclear *p*-tolyl formamidinato Rh(I)[193], as well as Ni(II) and Pd(II)[194] complexes were studied in detail in dichloromethane solvent. The cyclic voltammograms show the first reversible 1e transfer for each compound. The second step is reversible for palladium, but irreversible for nickel complexes. The rhodium complexes display a series of sequential redox changes for which the complete elucidation of the relevant pathways is complicated, mainly because of the chemical irreversibility of some processes.

Electrochemical behaviour of a series of formamidinato rhenium(I) complexes in CH_2Cl_2, ACN, and acetone solvents is described[195]. As previously, the anodic reaction is connected with oxidation of the metal, namely with a rhenium(I)/rhenium(II) redox change. Nevertheless, the reversible oxidation potentials were found to be a linear function of the Hammett σ constants proper for substituents in the ligand.

The next problem is connected with the coordination chemistry of nucleic acids which are involved in a variety of interactions with metal ions in biological systems[196]. Of course, the elucidation of the reaction mechanisms between complicated macromolecular assemblies and cations is a very difficult task, and therefore one tries to elucidate the problem on the basis of results obtained for simpler models. Hence, the complexation of purine bases has been studied in detail by means of a variety of electrochemical methods, and the data accumulated in the literature are very ample, indeed. The use of electroanalytical techniques is very convenient in these cases; the stoichiometry and the stability constants can be calculated from the changes in the diffusion current and half-wave potential of a given metal cation upon changes in the ligand concentration[197]. Since electrochemical processes of purines are not observed in these measurements, the literature on their complexation is not reviewed here. It is noteworthy that the complexation of Cu(II), Fe(III), Fe(II) and Ni(II) by adenine and adenosine has been studied recently in DMSO[131]. One of the results of these studies was to find that adenine stabilizes copper in

its + 1 oxidation state, and therefore the reduction of Cu(II) ions in the presence of excess adenine proceeds in two 1e steps. A similar mechanism was observed in aqueous solutions (pH < 5) and some physicochemical properties of the intermediate species Cu(I)–adenine were identified[198]. Stabilization of the copper(I) ions by adenine was also found in a medium of sulphuric acid[199]. It should be added here that the stereodynamic Cu(I)/Cu(II) redox changes are the most important factors in this type of complex which, in many cases, constitute a valid model for blue copper proteins[200].

Biological activity of cyclic amidines is sometimes considered in terms of their redox properties. By way of example, polarographic and voltammetric data for purine, adenine, guanine and some of their derivatives[201] as well as quinoline derivatives with the guanidine dihydrochloride group[202] have recently been correlated with the current pictures of carcinogenity. Also, the effectiveness of some nitroimidazoles and nitrotriazoles as radiosensitizing agents in cancer therapy was discussed in relation to their electrochemical potentials[80,83].

Finally, considering electrochemical properties of amidines, some other practical aspects should not be omitted. It is well known that benzimidazole is extensively applied as a corrosion inhibitor for copper and its alloys. It has been found very recently that a compact film of benzimidazolato copper(I) is formed on the Cu surface when the electrode is immersed in a stirred benzimidazole solution and cyclic voltammetry applied. This polymer film inhibits anodic processes very effectively[203]. Among other applications the use of substituted derivatives of oxopyrimidine in zinc electrodeposition in order to obtain bright coatings was reported[204]. Although this finding was considered in terms of the adsorption phenomena, its full explanation still remains unknown.

VI. ACKNOWLEDGEMENT

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VII. REFERENCES

1. H. Lund, in *The Chemistry of Amidines and Imidates* (Ed. S. Patai), Wiley–Interscience, London, 1975, p. 241.
2. P. J. Elving, in *Topics in Electrochemistry and Bioenergetics* (Ed. G. Milazzo), Vol. 1, Wiley, London, 1976, p. 182.
3. G. Dryhurst, *Electrochemistry of Biological Molecules*, Academic Press, New York, 1977.
4. D. C. Sawyer (Ed.), *Electrochemical Studies of Biological Systems*, American Chemical Society, 1977.
5. K. M. Kadish (Ed.), *Electrochemical and Spectrochemical Studies of Biological Redox Components*, American Chemical Society, 1982.
6. G. Milazzo and M. Blank (Eds.), *Bioelectrochemistry*, Vol. 1, Plenum Press, New York, 1983.
7. H. Baumgärtel and K. J. Retzlaw, in *Encyclopedia of Electrochemistry of the Elements* (Eds. A. J. Bard and H. Lund), Vol. XV, M. Dekker, New York, 1984, p. 168.
8. G. Dryhurst, in *The Comprehensive Treatise on Electrochemistry* (Eds. S. Srinivasan, Y. A. Chizmadjev, J. O'M. Bockris, B. E. Conway and E. Yeager), Vol. 10, Plenum Press, New York, 1985.
9. A. J. Bard and H. Lund (Eds.) *Encyclopedia of Electrochemistry of the Elements*, Vol. XV, M. Dekker, New York, 1984.
10. T. V. Treopol'skaya and G. K. Budnikov, *Elektrokhimiya Azometinov*, Nauka, Moscow, 1989 (in Russian).
11. V. D. Parker, *Adv. Phys. Org. Chem.*, **19**, 131 (1983).
12. R. O. Loutfy and R. O. Loutfy, *Can. J. Chem.*, **54**, 1454 (1976).
13. S. Filipek, unpublished result.
14. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 489 (1977).
15. M. J. S. Dewar, M. L. McKee and H. S. Rzepa, *J. Am. Chem. Soc.*, **100**, 3607 (1978).

16. U. Hess and C-O. Bluemcke, *Z. Chem.*, **28**, 144 (1988).
17. J. S. Jaworski, unpublished result.
18. M. K. Kalinowski and T. M. Krygowski, *Croat. Chem. Acta*, **58**, 107(1985).
19. J. S. Jaworski and M. K. Kalinowski, in *Similarity Models in Organic Chemistry, Biochemistry, and Related Fields* (Eds. R. I. Zalewski, T. M. Krygowski and J. Shorter), Elsevier, Amsterdam, 1991, p. 387.
20. J. Mollin, F. Grambal, F. Kašpárek, T. Kučerová, J. Lasovský and N. Truong Son, *Chem. Zvesti*, **33**, 458 (1979).
21. V. N. Nikulin, V. N. Klochkova and L. A. Pavlichenko, *Zh. Fiz. Khim.*, **53**, 2969 (1979).
22. W. Kemula, M. K. Kalinowski, T. M. Krygowski, J. A. Lewandowski and A. J. Walasek, *Bull. Acad. Pol. Sci., Sér. Sci. Chim.*, **18**, 455 (1970).
23. A. S. Shawali, H. M. Sammour and B. A. Akrawi, *Indian J. Chem.*, **13A**, 1285 (1975).
24. H. M. Fahmy, M. H. Elnagdi and L. I. Ibrahim, *Indian J. Chem.*, **19B**, 644 (1980).
25. P. Zuman, *Substituent Effects in Organic Polarography*, Plenum Press, New York, 1967.
26. P. Zuman, *The Elucidation of Organic Electrode Processes*, Academic Press, New York and London, 1969.
27. J. Ševčik, *Acta Palacký Univ. Olomouc. Fac. Rerum Natur.*, **53**, 37 (1977).
28. M. Laćan, I. Tabaković and Ž. Čeković, *Tetrahedron*, **30**, 2911 (1974).
29. H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80**, 4979 (1958).
30. V. P. Shchipanov and A. I. Zabolotskaya, *Izv. Vuzov. Khim. i Khim. Tekhn.*, **20**, 1520 (1977).
31. V. F. Gryazev, E. S. Karavayeva, I. N. Borukhova and N. P. Bednyagina, *Khim. Geterosikl. Soedin.*, 1274 (1982).
32. O. Exner, in *Advances in Linear Free Energy Relationships* (Eds. N. B. Chapman and J. Shorter), Plenum Press, London and New York, 1972, p. 1.
33. Yu. I. Beylis, M. V. Povstyanoy, V. P. Kruglenko, G. I. Procenko, V. I. Fedortchenko and E. M. Belash, *Zh. Obshch. Khim.*, **49**, 879 (1979).
34. F. Grambal and J. Lasovský, *Chem. Zvesti*, **33**, 621 (1979).
35. W. U. Malik, R. N. Goyal and R. Jain, *J. Electroanal. Chem.*, **105**, 349 (1979).
36. O. M. Polumbrik, G. F. Dvorko, N. G. Vasil'kevich and V. A. Kuznetsov, *Org. React. (Tartu)*, **9**, 357 (1972).
37. O. M. Polumbrik, N. G. Vasil'kevich and V. A. Kuznetsov, *Org. React. (Tartu)*, **10**, 981 (1973).
38. A. Heesing, U. Kappler and W. Rauh, *Justus Liebigs Ann. Chem.*, 2222 (1976).
39. J. Hlavaty, J. Volke and O. Manoušek, *Coll. Czech. Chem. Commun.*, **40**, 3751 (1975).
40. J. Hlavaty, J. Volke and O. Manoušek, *J. Electroanal. Chem.*, **61**, 219 (1975).
41. G. Barbey and C. Caullet, *Tetrahedron Lett.*, 1717 (1974).
42. M. Laćan, V. Rogić, I. Tabaković, D. Galijaš and T. Solomun, *Electrochim. Acta*, **28**, 199 (1983).
43. I. Tabaković and S. Crljenak, *Heterocycles*, **16**, 699 (1981).
44. W. Jugelt, L. Grubert and V. Paulss, *Z. Chem.*, **25**, 443 (1985).
45. F. Freeman, M. C. Keindl, H. N. Po, E. Brinkman and J. A. Masse, *Synthesis*, 714 (1989).
46. J. Gunić, I. Tabaković and Ž. Saničanin, *Electrochim. Acta*, **35**, 225 (1990).
47. H. Lund, in *The Chemistry of the Carbon–Nitrogen Double Bond* (Ed. S. Patai), Wiley–Interscience, London, 1970, p. 505.
48. V. T. Abayev, A. A. Bumber, N. P. Belenko and O. Yu. Okhlobystin, *Zh. Obshch. Khim.*, **59**, 1863 (1989).
49. R. N. Goyal and A. Kumar, *Indian J. Chem.*, **28A**, 949 (1989).
50. L. A. Taran, B. I. Buzykin, O. Yu. Mironova, N. G. Gazetdinova and Yu. P. Kitaev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 166 (1983).
51. Yu. M. Kargin, V. Z. Latypova, M. Yu. Kitaeva, A. A. Vafina and R. M. Zaripova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2410 (1984).
52. L. P. Sysoeva, T. V. Troepol'skaya, B. I. Buzykin and Yu. P. Kitaev, *Zh. Org. Khim.*, **11**, 1525 (1975).
53. G. M. Abou-Elenien, S. O. Abd Allah, N. A. Ismail and W. M. Hosny, *J. Indian Chem. Soc.*, **65A**, 253 (1988).
54. I. Tabaković, M. Trkovnik and Z. Grujić, *J. Chem. Soc., Perkin Trans. 2*, 166 (1979).
55. J. S. Jaworski, *J. Electroanal. Chem.*, **300** (1991) in press.
56. V. Gutmann, *The Donor–Acceptor Approach to Molecular Interactions*, Plenum Press, New York, 1978.

57. Y. Marcus, M. J. Kamlet and R. W. Taft, *J. Phys. Chem.*, **92**, 3613 (1988).
58. T. V. Troepol'skaya, G. A. Vagina, B. I. Morozov and Yu. P. Kitaev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 512 (1983).
59. V. Cerdá, R. Jara and R. Forteza, *J. Electroanal. Chem.*, **195**, 335 (1985).
60. R. Forteza and V. Cerdá, *Bull. Soc. Chim. France*, 97 (1984).
61. A. S. Shawali, H. M. Sammour and B. A. Akrawi, *Fresenius Z. Anal. Chem.*, **269**, 29 (1974).
62. I. Tabaković, M. Trkovnik and D. Galijaš, *J. Electroanal. Chem.*, **86**, 241 (1978).
63. F. Tomas Vert, F. Vicente Pedros, J. Martinez Calatayud and V. Peris Martinez, *Talanta*, **30**, 977 (1983).
64. F. Vicente and C. Sanz, *Electrochim. Acta*, **29**, 1659 (1984).
65. F. Vicente Pedrós, C. Sanz Box and J. Trijueque Monge, *J. Electroanal. Chem.*, **182**, 413 (1985).
66. P. Pazdera, M. Studničková, I. Ráčková and O. Fischer, *J. Electroanal. Chem.*, **207**, 189 (1986).
67. V. N. Nikulin, V. N. Klochkova and L. A. Pavlichenko, *Zh. Fiz. Khim.*, **51**, 1727 (1977).
68. M. Roman Ceba, A. Sanchez Misiego, J. J. Berzas Nevado and A. Espinosa Mansilla, *Ann. Chim.*, **72**, 255 (1982).
69. F. Salinas, A. Sanchez Misiego, J. J. Berzas Nevado, A. Espinosa and P. Valiente, *Ann. Chim.*, **75**, 163 (1985).
70. H. Hoffmann and A. Zeller, *Fresenius Z. Anal. Chem.*, **326**, 446 (1987).
71. H. Hoffmann and A. Zeller, *Fresenius Z. Anal. Chem.*, **330**, 56 (1988).
72. Yu. I. Beylis, M. V. Povstyanoy, E. V. Logachev and A. V. Shikarev, *Zh. Obshch. Khim.*, **46**, 426 (1976).
73. V. V. Damaskin, S. L. Diyatkina and V. V. Kras'ko, *Elektrokhimiya*, **19**, 96 (1983).
74. R. N. Goyal and A. Kumar, *J. Electroanal. Chem.*, **242**, 209 (1988).
75. R. N. Goyal, *Indian J. Chem.*, **27A**, 858 (1988).
76. S. Crljenak, I. Tabaković, D. Jeremić and I. Gaon, *Acta Chem. Scand.*, **B37**, 527 (1983).
77. B. Wermeckes and F. Beck, *Electrochim. Acta*, **34**, 1595 (1989).
78. V. A. Dorokhov, T. K. Baryshnikova, M. F. Gordieev, M. E. Niyazymbetov and V. A. Petrosyan, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1708 (1989).
79. M. Z. El-Sabee, M. H. Elnagdi and G. M. Habashy, *J. Prakt. Chem.*, **318**, 658 (1976).
80. S. C. Leach, R. D. Weaver, K. Kinoshita and W. W. Lee, *J. Electroanal. Chem.*, **129**, 213 (1981).
81. V. A. Lopyriev, L. I. Larina, T. N. Rakhmatulina, E. F. Shibanova and T. I. Vakul'skaya, *Dokl. Akad. Nauk SSSR*, **242**, 142 (1978).
82. T. I. Vakul'skaya, L. I. Larina, O. B. Nefedova, L. P. Petukhov, M. G. Voronkov and V. A. Lopyrev, *Khim. Geterotsikl. Soedin.*, 1398 (1979).
83. D. Barety, B. Resibois, G. Vergoten and Y. Moschetto, *J. Electroanal. Chem.*, **162**, 335 (1984).
84. A. V. Lizogub and A. F. Pozarskiy, *Khim. Geterosikl. Soedin.*, 110 (1979).
85. A. V. Lizogub, A. F. Pozarskiy and V. I. Sokolov, *Zh. Obshch. Khim.*, **46**, 680 (1976).
86. M. E. Niyazymbetov, T. K. Baryshnikova, V. A. Petrosyan, M. F. Gordeev and V. A. Dorokhov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2874 (1987).
87. A. F. Pozarskiy, V. V. Kuz'menko, A. A. Bumber, S. Petrov, M. I. Terekhova, N. L. Tchikina and I. M. Nanavyan, *Khim. Geterosikl. Soedin.*, 221 (1989).
88. L. Tomcsanyi, *Anal. Chim. Acta*, **70**, 411 (1974).
89. L. Tomcsanyi, *Anal. Chim. Acta*, **88**, 371 (1977).
90. B. A. Abd-el-Nabey and A. M. Kiwan, *J. Electroanal. Chem.*, **105**, 365 (1979).
91. W. U. Malik, J. S. Upadhyaya, R. Jain and M. P. Sharma, *J. Indian Chem. Soc.*, **59**, 1057 (1982).
92. M. A. Gomez Nieto, M. D. Luque de Castro and M. Valcarcel, *Electrochim. Acta*, **27**, 435 (1982).
93. R. N. Goyal, Ashwani Minocha and A. P. Nautiyal, *J. Electroanal. Chem.*, **200**, 119 (1986).
94. R. N. Goyal, *Indian J. Chem.*, **26A**, 656 (1987).
95. G. Cauquis, H. M. Fahmy, G. Pierre and M. H. Elnagdi, *Electrochim. Acta*, **24**, 391 (1979).
96. G. Cauquis, H. M. Fahmy, G. Pierre and M. H. Elnagdi, *J. Heterocycl. Chem.*, **16**, 413 (1979).
97. H. M. Fahmy, N. F. Abdel Fattah and M. R. H. Elmoghayar, *J. Chem. Soc., Perkin Trans. 2*, 1 (1988).
98. M. Abdel Azzem, M. A. Aboutabi, N. F. Abdel Fattah and H. M. Fahmy, *Indian J. Chem.*, **28A**, 864 (1989).
99. P. J. Elving, J. S. Pace and J. E. O'Reilly, *J. Am. Chem. Soc.*, **95**, 647 (1973).
100. J. C. M. Hennig, *J. Phys. Chem.*, **44**, 2139 (1966).
101. E. van't Land and D. van der Meer, *Recl. Trav. Chim. Pays-Bas*, **92**, 409 (1973).

102. J. E. O'Reilly and P. J. Elving, *J. Am. Chem. Soc.*, **93**, 1871 (1971).
103. T. Malinski, J. E. Bennett and T. E. Cummings, *Bioelectrochem. Bioenerg.*, **16**, 371 (1986).
104. P. J. Elving, *Can. J. Chem.*, **55**, 3392 (1977).
105. A. Izquierdo, E. Bosch and M. D. Prat, *Electrochim. Acta*, **27**, 1465 (1982).
106. A. Izquierdo, E. Bosch and J. Guiteras, *Anal. Quim.*, **B84**, 366 (1988).
107. T. A. Arkhipova and I. A. Avrutskaya, *Elektrokhimiya*, **25**, 787 (1989).
108. E. Paleček and B. Janik, *Arch. Biochem. Biophys.*, 98, 527 (1962).
109. B. Janik and E. paleček, *Arch. Biochem. Biophys.*, **105**, 225 (1964).
110. G. Dryhurst and P. J. Elving, *Talanta*, **16**, 825 (1969).
111. B. Czochralska and D. Shugar, *Experientia, Suppl.*, **18**, 251 (1971).
112. D. L. Smith and P. J. Elving, *J. Am. Chem. Soc.*, **84**, 2741 (1962).
113. J. W. Webb, B. Janik and P. J. Elving, *J. Am. Chem. Soc.*, **95**, 991 (1973).
114. T. Wasa and P. J. Elving, *J. Electroanal. Chem.*, **142**, 213 (1982).
115. S. Steenken, *Chem. Rev.*, **89**, 503 (1989).
116. H. A. Marsch and G. Dryhurst, *J. Electroanal. Chem.*, **95**, 81 (1979).
117. M. Z. Wrona and G. Dryhurst, *Biochim. Biophys. Acta*, **570**, 371 (1979).
118. M. Z. Wrona, J. L. Owens and G. Dryhurst, *J. Electranal. Chem.*, **105**, 295 (1979).
119. R. N. Goyal, A. Brajter-Toth and G. Dryhurst, *J. Electroanal. Chem.*, **131**, 181 (1981).
120. R. N. Goyal, M. Z. Wrona and G. Dryhurst, *Bioelectrochem. Bioenerg.*, **7**, 433 (1980).
121. A. Brajter-Toth, R. N. Goyal, M. Z. Wrona, T. Lacava, N. T. Nguyen and G. Dryhurst, *Bioelectrochem. Bioenerg.*, **8**, 413 (1981).
122. R. N. Goyal, A. Brajter-Toth and G. Dryhurst, *Bioelectrochem. Bioenerg.*, **9**, 39 (1982).
123. G. Dryhurst, *Bioelectrochem. Bioenerg.*, **14**, 251 (1985).
124. W. U. Malik, R. N. Goyal and M. Rajeshwari, *J. Electroanal. Chem.*, **221**, 155 (1987).
125. A. A. Rostami and G. Dryhurst, *J. Electroanal. Chem.*, **223**, 143 (1987).
126. P. Subramanian and G. Dryhurst, *J. Electroanal. Chem.*, **262**, 281 (1989).
127. D. Astwood, T. Lippincott, M. Deysher, C. N. D'Amico, E. Szurley and A. Brajter-Toth, *J. Electroanal. Chem.*, **159**, 295 (1983).
128. D. Astwood, C. N. D'Amico, T. Lippincott and A. Brajter-Toth, *J. Electroanal. Chem.*, **198**, 283 (1986).
129. K. J. Volk, T. Peterson, K. McKenna, P. J. Kraske and A. Brajter-Toth, in *Redox Chemistry and Interfacial Behaviour of Biological Molecules* (Eds. G. Dryhurst and K. Niki), Plenum Press, New York, 1988, p. 309.
130. K. S. V. Santhanam and P. J. Elving, *J. Am. Chem. Soc.*, **96**, 1653 (1974).
131. T. Malinski, J. R. Fish, C. N. Mikulski and N. M. Karayannis, in *Redox Chemistry and Interfacial Behaviour of Biological Molecules* (Eds. G. Dryhurst and K. Niki), Plenum Press, New York, 1988, p. 247.
132. E. Paleček, in *Topics of Electrochemistry and Bioenergetics* (Ed. G. Milazzo), Vol. 5, Wiley, London, 1983, p. 65.
133. H. W. Nürnberg, in Reference 5, p. 183.
134. B. Janik and P. J. Elving, *Chem. Rev.*, **68**, 295 (1968).
135. P. Valenta, H. W. Nürnberg, and D. Krznarić, *Bioelectrochem. Bioenerg.*, **3**, 418 (1976).
136. D. Krznarić, P. Valenta, H. W. Nürnberg and M. Branica, *J. Electroanal. Chem.*, **93**, 41 (1978).
137. S. Kwee and H. Lund, *Acta Chem. Scand.*, **26**, 1195 (1972).
138. L. Kittler and H. Berg, *J. Electroanal. Chem.*, **16**, 251 (1968).
139. D. L. Smith and P. J. Elving, *J. Am. Chem. Soc.*, **84**, 1412 (1962).
140. B. Janik and P. J. Elving, *J. Am. Chem. Soc.*, **92**, 235 (1970).
141. B. Czochralska, E. Bojarska, P. Valenta and H. W. Nürnberg, *Bioelectrochem. Bioenerg.*, **14**, 503 (1985).
142. B. Czochralska, E. Bojarska and K. Pawlicki, in *Redox Chemistry and Interfacial Behaviour of Biological Molecules* (Eds. G. Dryhurst and K. Niki), Plenum Press, New York, 1988, p. 281.
143. H. Klukanová, M. Studničková, J. Kovář, J. Turánek and V. Kahle, *Bioelectrochem. Bioenerg.*, **15**, 317 (1986).
144. M. A. Jensen, W. T. Bresnahan and P. J. Elving, *Bioelectrochem. Bioenerg.*, **11**, 299 (1983).
145. J. Fleming, *J. Electroanal. Chem.*, **75**, 421 (1977).
146. H. Klukanová, M. Studničková and J. Kovář, *Bioelectrochem. Bioenerg.*, **12**, 279 (1984).
147. B. I. Podlovthenko, R. P. Petukhova and E. Yu. Pisarevskaya, *Elektrokhimiya*, **25**, 1401 (1989).

148. E. Bojarska and B. Czochralska, *Bioelectrochem. Bioenerg.*, **16**, 287 (1986).
149. M. Herlem and G. Van Amerongen, *Anal. Lett.*, **13**, 545 (1980).
150. G. Dryhurst and G. F. Pace, *J. Electrochem. Soc.*, **117**, 1259 (1970).
151. T. Yao and S. Musha, *Bull. Chem. Soc. Jpn.*, **52**, 2307 (1979).
152. R. N. Goyal and G. Dryhurst, *J. Electroanal. Chem.*, **135**, 75 (1982).
153. P. J. Kraske and A. Brajter-Toth, *J. Electroanal. Chem.*, **207**, 101 (1986).
154. T. Yao, T. Wasa and S. Musha, *Bull. Chem. Soc. Jpn.*, **50**, 2917 (1977).
155. L. Trnková, M. Studničková and E. Paleček, *Bioelectrochem. Bioenerg.*, **7**, 643 (1980).
156. Y. M. Temerk and M. M. Kamal, *Bioelectrochem. Bioenerg.*, **8**, 671 (1981).
157. Y. M. Temerk and M. M. Kamal, *Bioelectrochem. Bioenerg.*, **11**, 457 (1983).
158. Y. M. Temerk and M. M. Kamal, *Bioelectrochem. Bioenerg.*, **12**, 205 (1984).
159. Y. M. Temerk, M. M. Kamal, M. E. Ahmed and Z. A. Ahmed, *Bioelectrochem. Bioenerg.*, **16**, 497 (1986).
160. B. Janik, *Z. Naturforsch.*, **B24**, 539 (1969).
161. M. Studničková, L. Trnková, J. Zetěk and Z. Glatz, *Bioelectrochem. Bioenerg.*, **21**, 83 (1989).
162. P. Subramanian and G. Dryhurst, *J. Electroanal. Chem.*, **224**, 137 (1987).
163. E. Paleček, *Anal. Biochem.*, **103**, 129 (1980).
164. A. Sanchez-Perez, J. Hernandez-Mendez and J. E. Fuentes de Frutos, *J. Assoc. Off. Anal. Chem.*, **68**, 1060 (1985); *Chem. Abstr.*, **103**, 166234z (1985).
165. J. L. Da Ros and M. Taillan, *Int. Jahrestag.-Fraunhofer-Treib-Explosivst*, 655 (1984); *Chem. Abstr.*, **103**, 125938p (1985).
166. J. T. Stewart, *J. Pharm. Sci.*, **75**, 413 (1986).
167. D. Perrett, *Biochem. Soc. Trans.*, **13**, 1067 (1985).
168. J. Henderson, Jr. and C. A. Griffin, *J. Chromatogr.*, **298**, 231 (1984).
169. J. Zima, J. Barek and H. Patel, *Anal. Lett.*, **22**, 435 (1989).
170. J. Chodkowski, A. Chrzanowski and D. Gralewska-Ludwicka, *Chem. Anal. (Warsaw)*, **34**, 329 (1989).
171. I. Taniguchi, M. Iseki, H. Yamaguchi and K. Yasukouchi, *J. Electroanal. Chem.*, **175**, 341 (1984).
172. I. Taniguchi, M. Iseki, K. Toyosawa, H. Yamaguchi and K. Yasukouchi, *J. Electroanal. Chem.*, **164**, 385 (1984).
173. I. Taniguchi, N. Higo, K. Umekita and K. Yasukouchi, *J. Electroanal. Chem.*, **206**, 341 (1986).
174. I. Taniguchi, in *Redox Chemistry and Interfacial Behaviour of Biological Molecules* (Eds. G. Dryhurst and K. Niki), Plenum Press, New York, 1988, p. 113.
175. M. J. Eddowes and H. A. O. Hill, *J. Chem. Soc., Chem. Commun.*, 771 (1977).
176. P. M. Allen, H. A. O. Hill and N. J. Walton, *J. Electroanal. Chem.*, **178**, 69 (1984).
177. H. A. O. Hill, D. J. Page and N. J. Walton, *J. Electroanal. Chem.*, **208**, 395 (1986).
178. J. Haladjian, P. Bianco and R. Pilard, *Electrochim. Acta*, **28**, 1823 (1983).
179. J. Haladjian, R. Pilard, P. Bianco, L. Asso, J. P. Galy and R. Vidal, *Electrochim. Acta*, **30**, 695 (1985).
180. R. Dhesi, T. M. Cotton and R. Timkovich, *J. Electroanal. Chem.*, **154**, 129 (1983).
181. T. M. Cotton, D. Kaddi and D. Lorga, *J. Am. Chem. Soc.*, **105**, 7462 (1983).
182. K. Das, R. Banerjee, A. Das and S. Dasgupta, *Bull. Electrochem.*, **5**, 477 (1989).
183. J. A. R. van Veen, J. F. van Baar, C. J. Kroese, J. G. F. Coolgem, N. de Wit and H. A. Colijn, *Ber. Bunsenges. Phys. Chem.*, **85**, 693 (1981).
184. S. Zecevic, B. Simic-Glavaski, E. Yaeger, A. B. P. Lever and P. C. Minor *J. Electrochem. Soc.*, **196**, 339 (1985).
185. E. Yaeger, *J. Mol. Catal.*, **38**, 5 (1986).
186. J. A. R. van Veen and C. Vesser, *Electrochim. Acta*, **34**, 221 (1979).
187. F. Coowar, O. Contamin, M. Savy and G. Scarbeck, *J. Electroanal. Chem.*, **246**, 119 (1988).
188. C. Hinnen, F. Coowar and M. Savy, *J. Electroanal. Chem.*, **264**, 167 (1989).
189. A. K. De, P. K. Saha and P. K. Das, *Indian J. Chem.*, **16A**, 1042 (1978).
190. B. Chakravarty, *J. Inorg. Nucl. Chem.*, **41**, 757 (1979).
191. J. C. Le, M. Y. Chavan, L. K. Chau, J. L. Bear and K. M. Kadish, *J. Am. Chem. Soc.*, **107**, 7195 (1985).
192. C.-L. Yao, L.-P. He, J. D. Korp and J. L. Bear, *Inorg. Chem.*, **27**, 4389 (1988).
193. P. Zanello, F. Laschi, A. Cinquantini and P. Piraino, *Inorg. Chim. Acta*, **155**, 49 (1989).
194. F. A. Cotton, M. Matusz, R. Poli and X. Feng, *J. Am. Chem. Soc.*, **110**, 1144 (1988).

195. P. Zanello, A. Cinquantini, F. Laschi, R. Rossi, A. Duatti, A. Marchi and L. Magon, *Polyhedron*, **7**, 195 (1988).
196. H. Pezzano and F. Podo, *Chem. Rev.*, **80**, 365 (1980).
197. K. Burger, *Bioelectrochem. Bioenerg.*, **20**, 33 (1988).
198. R. Bilewicz, S. Głodowski and Z. Kublik, *J. Electroanal. Chem.*, **274**, 201 (1989).
199. J. E. Simão, M. M. Lopes and M. Hutchings, *Portugal. Electrochim. Acta*, **6**, 191 (1988).
200. P. Zanello, *Comments Inorg. Chem.*, **8**, 45 (1988).
201. P. Kovacic, P. W. Crawford, M. D. Ryan and V. C. Nelson, *Bioelectrochem. Bioenerg.*, **15**, 305 (1986).
202. P. W. Crawford, W. O. Foye, M. D. Ryan and P. Kovacic, *J. Pharm. Sci.*, **76**, 481 (1987).
203. G. Xue, J. Ding, P. Wu and G. Ji, *J. Electroanal. Chem.*, **270**, 163 (1989).
204. L. A. Taran and V. S. Gromakov, *Elektrokhimiya*, **24**, 376 (1988).
205. G. Dusinski, *Die Pharmazie*, **8**, 897 (1953).

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This author index is designed to enable the reader to locate an author's name and work with the aid of the reference numbers appearing in the text. The page numbers are printed in normal type in ascending numerical order, followed by the reference numbers in parentheses. The numbers in *italics* refer to the pages on which the references are actually listed.

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