

available for the practical calculations of chemical reaction rates and thermochemical and structural interpretations of rate processes.

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Stereospecific Reactions of Nitrilium Ions and Analogous 1,3-Dipoles

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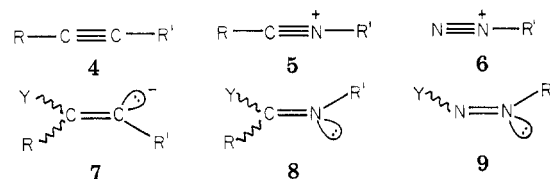
The quest for reaction pathways which are stereospecific and not merely stereoselective continues to intrigue the synthetic chemist. This is an area which is particularly susceptible to the tools of physical organic chemistry, since it is the structure of the transition state of the reaction (probed by means of kinetics, isotope effects, modeling, etc) which is important in determining the initial product formed. A rational approach to synthesis then depends to a large extent on an understanding of the factors which control transition-state structure.

The concept of stereoelectronic control of organic reactions has received a new impetus from the work of Deslongchamps.¹ These ideas are particularly useful when applied to the problem of which way a short-lived intermediate is likely to break down to products. It appears that the preferred mode of cleavage is determined by the necessity of having one (or more) electron pairs on an adjacent heteroatom arranged *antiperiplanar* to the leaving group to "assist" its departure. This important factor must now be routinely taken into account when determining the course of organic reactions (or in devising a successful synthetic scheme). The driving force for reaction in the stereoelectronically controlled direction may outweigh other factors (e.g., steric) in the transition state, leading to products with less stable (but desirable) geometries.

The question arises as to whether the same factors apply to the addition of nucleophiles to unsaturated systems and whether this can be reflected in the preferred geometries of the product(s). Thus addition to a protonated ketone (1, XZ = OH) could, in theory, lead

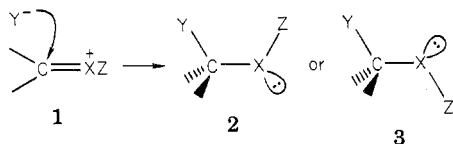
initially to **2** or **3** (or indeed any intermediate geometry). However, because of rapid C–O bond rotation, one can only surmise the stereochemistry of the initial addition from the way in which the adduct (**2** or **3**) further reacts.¹ The same problem arises in additions to the carbon–carbon double bond (1, XZ = CR₂) and the carbon–nitrogen double bond (1, XZ = NR₂); in each case the bond order of the C–X bond is decreased from two to one.

This problem is less severe in the addition of nucleophiles to alkynes **4**, nitrilium ions **5**, and diazonium ions **6**. Here just two geometries can arise when a



nucleophile is added, but again inversion of the carbanion (from addition to the alkyne **4**) or of the imino (in **8**) or azo (in **9**) nitrogen may be so rapid as to obscure stereospecificity. There are indications in the case of diazonium ion adducts² and nucleophilic addition to alkynes³ that the formation of one isomer may be preferred and, indeed, certain conditions (dependent on the nucleophile Y⁻ and the substituents) only one isomer of **7** and **9** is actually formed.

Our interest in this area stemmed from a study of displacement reactions at the carbon–nitrogen double bond. We were struck by the ease with which nitrilium ion intermediates (**5**) are formed in these reactions (see below). The step which determines the product is essentially the trapping of this nitrilium ion by a nucleophile. The marked stereospecificity noted in these trapping reactions has wide implications not only for our understanding of the factors which control transition-state geometry but also in the selective formation of reactive synthons of known stereochemistry.



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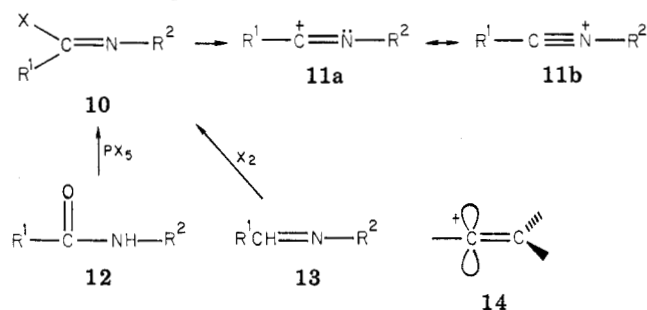
(1) P. Deslongchamps, *Pure Appl. Chem.*, **43**, 351 (1975); *Tetrahedron*, **31**, 2463 (1975); *Heterocycles*, **7**, 1271 (1977).

(2) H. Zollinger, *Acc. Chem. Res.*, **6**, 335 (1973).

(3) R. W. Strozler, P. Caramella, and K. N. Houk, *J. Am. Chem. Soc.*, **101**, 1340 (1979).

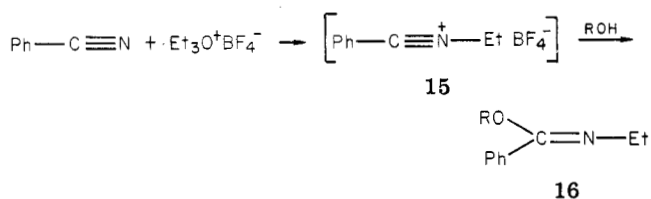
Nitrilium Ions

Generation. From *Imidoyl Halides*. Dissolution of imidoyl halides (10, X = halogen) in aqueous organic solvent mixtures at room temperature is usually sufficient to cause rapid ionization, giving the nitrilium ion 11. For example, when $R^1 = R^2 = \text{Ph}$ and $X = \text{Cl}$, $t_{1/2}$ for ionization at 25 °C in 1:1 dioxane–water is $<1 \text{ s}$.⁴ Electron-withdrawing substituents in R^1 or R^2 slow the rate of ionization, but this can be counteracted by increasing the aqueous content (or ionizing power) of the solvent. (The halides 10 are usually prepared from the corresponding amides 12 by using the halogenating



agents PX_5 , SOX_2 , or $\text{CX}_4/\text{Ph}_3\text{P}^{5,6}$ or by direct halogenation of the substituted imine 13.⁷) The ease of formation of nitrilium ions thus contrasts with the difficulty encountered in the ionization of vinyl halides to give the corresponding vinyl cations 14.⁸ This is undoubtedly attributable to the extra stabilization gained by donation into the vacant p orbital on carbon by the adjacent lone pair on nitrogen in the nitrilium ion 11. In fact the chemistry of imidoyl halides is dominated by the ease of this ionization—only under forcing conditions and in solvents of low ionizing power does the addition–elimination pathway compete^{9,10} (again in contrast to the vinyl halides).

From Nitriles. Alkylation or protonation of nitriles yields nitrilium ions which can be isolated as such (usually as salts with BF_4^- as counterion)¹¹ or reacted further with nucleophiles in situ. An example is the alkylation of benzonitrile with Meerwein's reagent to give 15, which on reaction with an alcohol gives a useful



route to imidates 16.¹² The Ritter reaction¹³ (of an alcohol or a diol with a nitrile in the presence of acid) probably follows a similar course.

From Isocyanides. Isocyanides 17 are weakly basic and undergo 1,1-addition to carbon, initiated by an

(4) A. F. Hegarty, J. D. Cronin, and F. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 429 (1975).

(5) P. Wolkoff, *Can. J. Chem.*, **53**, 1334 (1975).

(6) R. Appel, *Angew. Chem., Int. Ed. Engl.*, **14**, 801 (1975).

(7) H. Ulrich, "The Chemistry of Imidoyl Halides", Plenum Press, New York, 1968.

(8) P. J. Stang, Z. Rappoport, L. R. Subramanian, and M. Hanack, "Vinyl Cations", Academic Press, New York, 1979.

(9) R. Ta-Shma and Z. Rappoport, *J. Am. Chem. Soc.*, **98**, 8460 (1976).

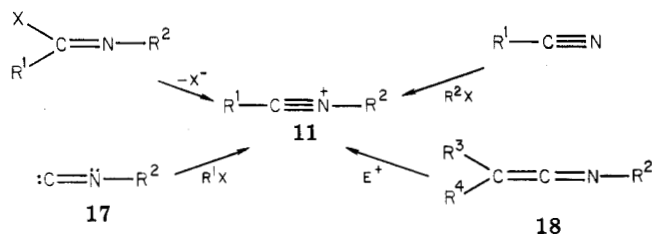
(10) A. F. Hegarty, M. T. McCormack, B. J. Hathaway, and L. Hulett, *J. Chem. Soc., Perkin Trans. 2*, 1136 (1977).

(11) H. Meerwein, *Chem. Ber.*, **89**, 209 (1956).

(12) R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

(13) L. I. Krimen and D. J. Cota, *Org. React.*, **17**, 213 (1969).

Scheme I

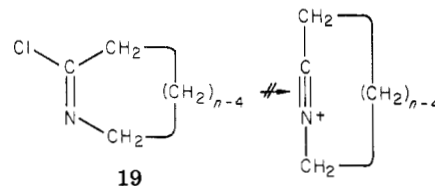


electrophilic step. Examples are the addition of acids HCl or HOAc ;¹⁴ metal ion catalyzed reactions of isocyanides also probably involve pseudo nitrilium ion species as intermediates (see Scheme I). This route has been relatively little explored but deserves attention both because of the resurgence of interest in isocyanide chemistry¹⁵ and the new facile routes to isocyanides (involving phase-transfer catalysis)¹⁶ which have become available.

From Ketenimines. Reaction of electrophiles with ketenimines 18 occurs at carbon to generate nitrilium ion species (which generally react further in situ). The driving force for proton abstraction by 18 emphasizes the stability of the nitrilium ion. Thus the ketenimine 18 ($R^2 = i\text{-Pr}$) removes a proton from water even in the presence of 1.0 M HO^- .¹⁷

Structure of Nitrilium Ions. There seems to be little doubt that the major contributing structure is 11b, which localizes the positive charge on nitrogen (rather than carbon) and thus forces the ion to adopt a linear configuration of R^1 , C, N, and R^2 . A low-temperature X-ray structure of a nitrilium ion (11, $R^1 = \text{Me}$, $R^2 = 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$) confirms the linear arrangement and the triple character of the carbon–nitrogen bond.¹⁸ Both CNDO/2 and ab initio calculations¹⁹ and NMR measurements²⁰ are in agreement with this. The charge distribution between carbon and nitrogen has also been probed by looking at the variation in the ease of formation of the ions 11 from the halides 10 as the substituents R^1 and R^2 are varied; the substituent on nitrogen (R^2) has the larger effect in determining nitrilium ion stability.⁴

Consistent with the linear (acetylene-like) structure of the nitrilium ion, cyclic halides of type 19 (where n



= 5 or 6) are quite unreactive, in contrast to the open-chain analogues.

The stability of simple nitrilium ions lies between the highly reactive vinyl cations 21 and iminium ions 20

(14) Y. Y. Lim and A. R. Stein, *Can. J. Chem.*, **49**, 2455 (1971).

(15) See, for example, "Isonitrile Chemistry", I. Ugi, Ed., Academic Press, New York, 1971; U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, **16**, 339 (1977).

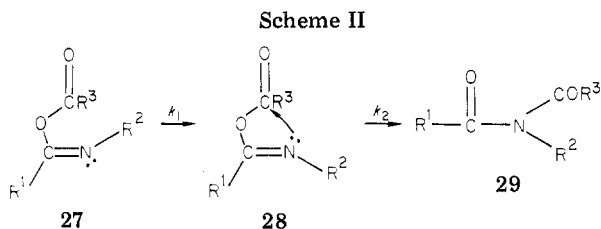
(16) W. P. Weber, G. W. Gokel, and I. K. Ugi, *Angew. Chem., Int. Ed. Engl.*, **11**, 530 (1972).

(17) A. F. Hegarty and D. G. McCarthy, *J. Am. Chem. Soc.*, **101**, 1345 (1979); *J. Chem. Soc., Perkin Trans. 2*, 579 (1980).

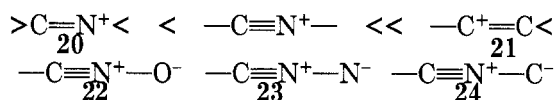
(18) A. K. Gjoystdal and C. Romming, *Acta Chem. Scand. B*, **31**, 56 (1977).

(19) G. Leroy, M. T. Nguyen, M. Sana, K. J. Dignam, and A. F. Hegarty, *J. Am. Chem. Soc.*, **101**, 1988 (1979).

(20) G. Olah and T. E. Kiovsky, *J. Am. Chem. Soc.*, **90**, 4666 (1968).

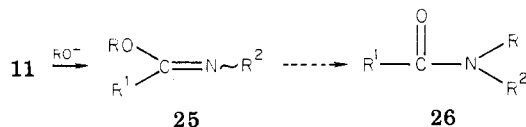


(but closer to the latter). The reactions of iminium ions with water can be slow enough to permit measurement using conventional techniques at 25 °C,²¹ whereas nitrilium ions react rapidly under these conditions.



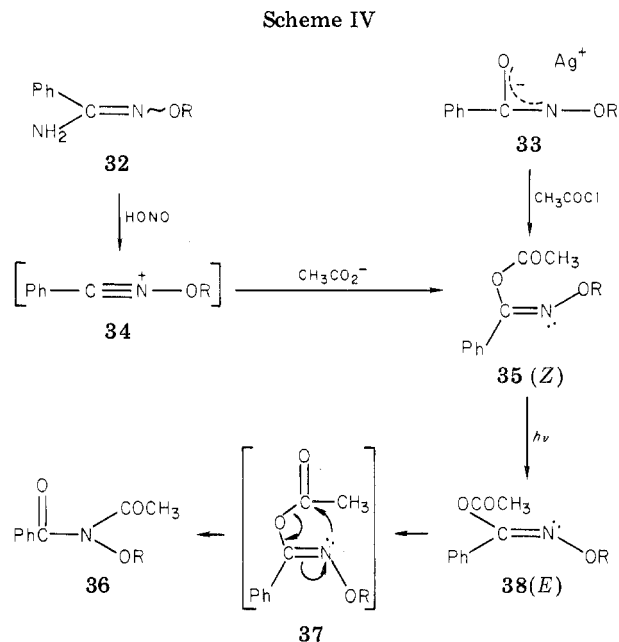
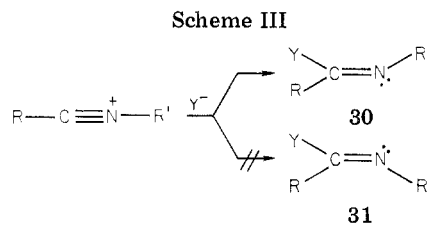
Substitution on nitrogen by a heteroatom can lead to a large increase in the stability of the nitrilium ion. Thus, for example, the 1,3-dipolar ions nitrile oxides **22**, nitrile imines **23**, and nitrile ylides **24** can be formally regarded as stabilized nitrilium ions and undergo analogous reactions (such as the addition of nucleophiles, below).

Stereospecific Reactions. While carrying out a number of displacement reactions on imidoyl halides **10** (where $\text{R}^2 = \text{NMeAr}$) with acetate ion (a reaction which can be shown to involve a nitrilium ion (**11**) as intermediate), we were surprised to find²² that the product was a relatively stable *O*-acetyl isoamide (**25**, $\text{R} = \text{Ac}$) rather than the expected *N*-acetyl amide (**26**, $\text{R} = \text{Ac}$). At that time stable acyclic *O*-acyl isoamides



(“isoimides”) were unknown; those reactions which might have yielded the *O*-acyl material (such as acylation of an amide) invariably gave the *N*-acyl amide **26** ($\text{R} = \text{Ac}$). Two plausible reasons could be advanced for the stability of **25** ($\text{R} = \text{Ac}$) formed by the trapping route: (a) the nucleophilicity of the imidoyl nitrogen could be much reduced because of the nature of the R^2 group or (b) the isoimide might be formed only as the *Z* isomer **27** (Scheme 2) in which the unfavorable trans arrangement of the acyl group and the lone pair on nitrogen precludes direct acyl transfer to nitrogen. The latter explanation proved to be correct. This was most notably shown by comparing the rates of conversion of the *O*-acyl (**27**) to *N*-acyl compound (**29**) at elevated temperatures with the rates of nitrogen inversion in the corresponding imidates (**25**, $\text{R} = \text{Me}$). The rates were essentially the same and responded in the same way to substituent variation, indicating that the rate-determining step was k_1 rather than k_2 .

The implications of this are quite general: *O*-acyl-isoamides can be readily prepared if nitrogen inversion is slowed by appropriate substitution and, more importantly, since none of the *E* isomer (**28**) is detected in the initial reaction, the trapping of the linear nitrilium ion **11** by acetate ion must be stereospecific. This



general conclusion (Scheme III) forms the central theme of this Account. As the nucleophile (Y^-) approaches carbon, the lone pair which is localized on nitrogen in the product (**30**) is formed trans to the incoming nucleophile (Scheme III). We have as yet discovered no exception to this rule and, in spite of careful searches, have been unable to observe any detectable quantity of the other product **31** (or of a product such as **29** which would have indicated a *cis* arrangement of the nucleophile and lone pair resulting from the initial coupling reaction).

Of course this stereospecificity can only be shown with certainty if nitrogen inversion in **30** is slower than the addition step involved in the formation of **30**. We have therefore principally used substrates where the group R' is a substituent capable of slowing inversion of the imidoyl nitrogen (i.e., $\text{R}' = \text{OR}$, SR , NR_2 , $-\text{N}=\text{CR}_2$). This is critical since the product first formed (**30**) may not be (and indeed usually is not) the more stable isomer thermodynamically.

O-Acyl Isoamides. A large number of *O*-acylated acyclic amides have now been prepared by using appropriate *N*-substitution to slow the inversion of nitrogen (Scheme IV). A particularly interesting example is the *N*-alkoxy material **35**. This is formed as the pure *Z* isomer **35** by trapping the nitrilium ion **34**;²³ the latter is uncharacteristically difficult to form from the corresponding halide but is readily obtained by diazotization of the amidoxime **32**. The *Z* isomer (**35**) is quite stable toward prolonged heating (in line with the configurational stability of oximes). However, on irradiation **35** is converted to a (~1:1) mixture of *Z* (**35**) and

(21) J. L. Hogg and W. P. Jencks, *J. Am. Chem. Soc.*, **98**, 5643 (1976).

(22) A. F. Hegarty and M. T. McCormack, *J. Chem. Soc., Chem. Commun.*, 168 (1975); *J. Chem. Soc., Perkin Trans 2*, 1701 (1976).

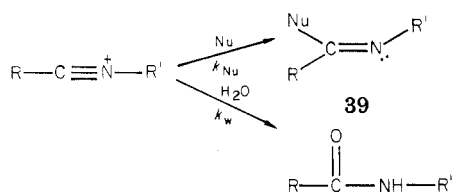
(23) D. G. McCarthy and A. F. Hegarty, *J. Chem. Soc., Perkin Trans 2*, 1080 (1977).

E (38) isomers. The *E* isomer 38, which can be isolated, rearranges (a 1,3-acyl group migration via a four-membered cyclic transition state) under very mild conditions to the *N*-acyl isomer 36.²⁴

Although it has been postulated that acylation of an amide (like alkylation and protonation) would occur preferentially under kinetic control on oxygen rather than nitrogen,²⁵ only *N*-acyl products have been observed. However, acylation of silver salts of amides 33 gives the *Z*-*O*-acyl isomer 35 quantitatively; thus the steps in the entire sequence of amide acylation (initial attack at oxygen to give the *Z* isomer, nitrogen inversion, and *O*→*N* intramolecular acyl group transfer) are clear. An intermolecular pathway for conversion of *O*-acyl to *N*-acyl amides has also been described;^{26a} this involves pyridine acting as a nucleophilic catalyst (an acyl group carrier).

Simple *N*-aryl isoimides (27, R³ = aryl or alkyl group) have now also been prepared, but it appears that when R² is, say, Ph, then the *O*→*N* acyl group migration occurs too rapidly at room temperature to permit their isolation. However even these isoimides can be readily formed and studied in situ by trapping of *N*-alkyl or *N*-aryl nitrilium ions.^{26b} Interestingly when R² = Ph or *p*-NO₂C₆H₄, the rate-determining step changes from nitrogen inversion (*k*₁, Scheme II) to intramolecular acyl group migration (*k*₂, Scheme II) as the nature of the migrating group (R³) is changed (as shown by sharp changes in the slopes of Hammett plots).

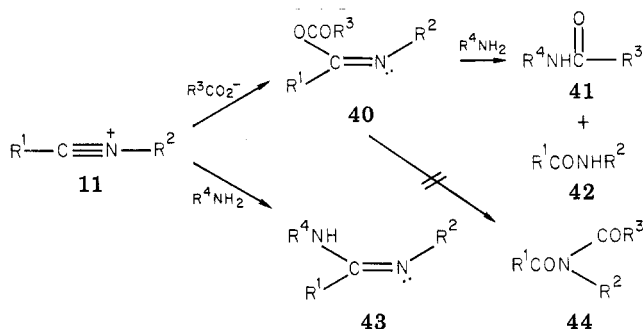
Selectivity of Nitrilium Ions. Unlike arenediazonium ions,² simple nitrilium ions do not have sufficient stability to permit the examination of their reactivity with various nucleophiles directly. However, this can be done indirectly using nitrilium ions generated in situ from the corresponding imidoyl halides 10. These reactions were carried out in aqueous solution and the relative amounts of product formed by trapping of the ion with an added nucleophile (Nu) compared with that formed by attack by water to give *k*_{Nu}/*k*_w values. The overall result is that the nitrilium ion



shows a low sensitivity to the nature of the nucleophile (while maintaining high stereospecificity), with *k*_{Nu}/*k*_w being in the range 100–120 for substituted acetates and 720 (N₃⁻), 460 (HO⁻), 322 (Cl⁻), 100 (CN⁻), and 36 (F⁻) using 11 (R = Ph; R' = NMePh). Neutral nucleophiles fall into a separate class: for amine nucleophiles (which yield amidines 39, Nu = NR₂, as products) *k*_{Nu}/*k*_w values are in the range 1–10.^{27,28}

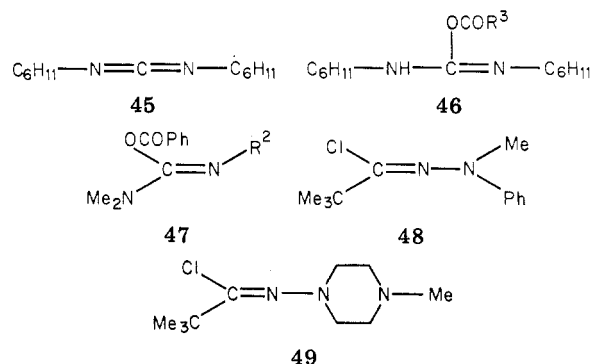
Peptide Synthesis. The observation that acetates react unexpectedly 10–100-fold faster than amines with nitrilium ions suggested that the latter could be used

as highly selective reagents for peptide synthesis. Thus in the presence of an equimolar concentration of an amine and a carboxylate ion the major product formed on reaction with the nitrilium ion 11 will be 40. The *O*-acyl material can be further favored by pH control; by using a pH (usually 5–7) between that of R³CO₂H and R⁴NH₃⁺, one may realize essentially quantitative formation of 40 (at the expense of the amidine 43) in



the presence of both reactants. Once the *O*-acyl material is formed, this behaves as a “normal” ester for intermolecular acyl transfer, reacting with an amine (R⁴NH₂) ca. 10⁵-fold faster than with any unreacted carboxylate ion, yielding the amide (or peptide) 41.²⁹

It is an advantage to use a substituent R² on the nitrilium ion (such as NMePh) which will slow nitrogen inversion (and thus intramolecular acyl transfer). By preventing the formation of unreactive *N*-acyl byproducts (44), this overcomes the main disadvantage previously experienced in attempts to use reactive *O*-acyl amides as dehydrating agents. Thus the most widely used reagent for promoting the coupling step in use today is dicyclohexylcarbodiimide (DCC, 45,³⁰ and a



reactive intermediate, 46, has been proposed (although never isolated) on reaction of 45 with a carboxylic acid. Not surprisingly 46 undergoes relatively rapid intramolecular acyl transfer to nitrogen. However, by using stereospecific addition to an amino-substituted nitrilium ion and by incorporating an appropriate substituent on nitrogen (R² = NMeC₆H₃(NO₂)₂) we have been able to isolate an analogue, 47, which can be stored indefinitely at room temperature and whose crystal structure clearly shows the *trans* arrangement of the benzoate group and the lone pair on the imidoyl nitrogen.^{31,32}

(24) D. G. McCarthy and A. F. Hegarty, *J. Chem. Soc., Perkin Trans 2*, 1085 (1977).

(25) B. C. Challis and J. A. Challis in “The Chemistry of Amides”, J. Zabicky, Ed., Interscience, London, 1970, Chapter 13.

(26) (a) B. C. Challis, J. A. Challis, and I. R. McDermott, *J. Chem. Soc., Perkin Trans 2*, 634 (1979). (b) K. Brady and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 121 (1980).

(27) A. F. Hegarty and K. Brady, unpublished results.

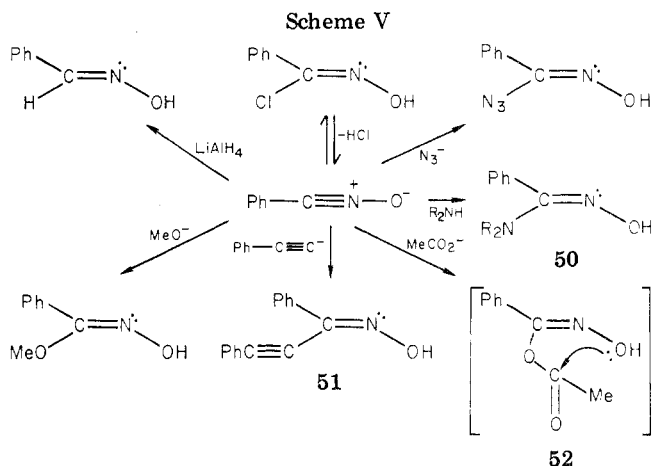
(28) Compare with: C. D. Ritchie, *Acc. Chem. Res.*, 5, 348 (1972).

(29) A. F. Hegarty and D. G. McCarthy, *J. Am. Chem. Soc.*, 102, 4537 (1980).

(30) M. Bodanszky, Y. S. Klausner, and M. A. Ondetti, “Peptide Synthesis”, 2nd ed., Wiley-Interscience, New York, 1976.

(31) A. F. Hegarty, M. T. McCormack, G. Ferguson, and P. Roberts, *J. Am. Chem. Soc.*, 99, 2015 (1977).

(32) A. F. Hegarty, M. T. McCormack, K. Brady, G. Ferguson, and P. J. Roberts, *J. Chem. Soc., Perkin Trans. 2*, 867 (1980).



The use of nitrilium ions (or their precursors, the imidoyl halides), appropriately substituted, has several other advantages in peptide synthesis. The reaction is best carried out under very mild conditions (usually pH 6–8); one can use “unprotected” amino acids (those in which neither the carboxylate or amino function is blocked) in certain cases, making use of the differential reactivity noted above; the byproduct **42**, when separated, can be reconverted to the starting imidoyl halide by means of a halogenating agent and thus recycled; racemization of component amino acids can be reduced to very low levels by incorporating a large group (such as *tert*-butyl in **48** and **49**) attached to carbon. The natural reaction medium for these condensations is an aqueous or aqueous–organic solvent mixture which promotes the formation of the nitrilium ion; the water-soluble reagent **49** (which gives a byproduct **42** with $R^1 = t\text{-Bu}$, $R^2 = -\text{N}(\text{CH}_2\text{CH}_2)_2\text{NMe}$, which can be readily removed by extraction with a weak acid)³³ is therefore particularly useful.

1,3-Dipoles

As mentioned above, 1,3-dipoles can be written in one canonical form (**22–24**) which is formally a substituted nitrilium ion. Some 1,3-dipoles (such as the nitrile oxides) are relatively stable, and we have been able to measure directly their reactivity in aqueous solution. Although the 1,3-dipolar cycloaddition is well-known,³⁴ these also undergo a useful series of reactions with nucleophiles at carbon, a reaction analogous to that of simple nitrilium ions. We have found that all of these reactions are quite stereospecific,^{35–37} the results for addition to benzonitrile oxide are summarized in Scheme V; included are examples of oxygen, nitrogen, and carbon nucleophiles and hydride donors.

In each case it is seen that the entering nucleophile and the lone pair on nitrogen are trans. Consequently the OH group is forced into a position cis to the nucleophile and is thus correctly placed for further intramolecular reaction (which occurs with the acetate adduct **52** and the phenylacetylene adduct **51**). The method therefore presents a useful route for the syn-

thesis of oximes of known configuration and can be applied with confidence to the elucidation of oxime structure.

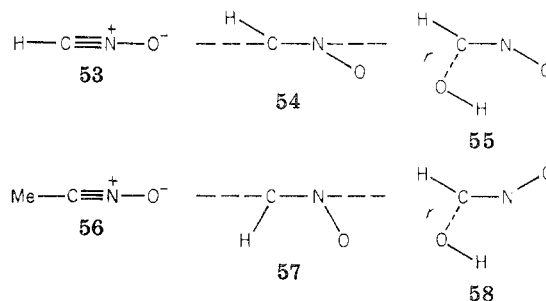
Although other 1,3-dipoles have not been examined in the same detail as the nitrile oxides, it is likely from the isolated examples available that the same clear stereospecificity exists.³⁵

In using the technique for the assignment of structure, one must take care to ensure that the *kinetic* rather than the more stable isomer (*thermodynamically*) is actually isolated. This is less critical with oxime isomers which possess high barriers to inversion. However the amidoximes **50** undergo relatively ready interconversion from the *Z* isomer (shown) to the *E* isomer when the amine is secondary ($R = \text{alkyl or aryl}$).³⁸

Theoretical Studies

It is of interest to discover whether the various methods available for predicting the energy of the transition state can be used to calculate the preferred configuration. An important question which also remains unanswered is the energy difference for the pathways resulting from addition of the nucleophile with unfavorable stereochemistry. Since no detectable quantities of the second isomer have as yet been found, we have not been able to measure these energy differences experimentally (although data on the reverse reaction do give an estimate).

The studies to date^{19,38} have concentrated on the addition of nucleophiles to the 1,3-dipoles fulminic acid (**53**) and acetonitrile oxide (**56**). Both of these are



linear in the ground state (as shown by *ab initio* calculations)¹⁹ but are relatively easily deformed. However it is markedly easier to bend the atoms about the nitrilium ion in a *trans* fashion (**54**) rather than in a *cis* mode (**57**). The transition state is reached relatively early on the reaction coordinate when the distance r (between the carbon of the nitrilium ion and the oxygen of the nucleophile, hydroxide ion) is 2.20 Å. At this stage the nitrile oxide has taken up the configuration **55** (with the CNO angle of 143°) observed in the product. No other energy minima are observed on the potential-energy hypersurface, so that an arrangement such as **58** (with $r = 2.20$ Å) does not even provide local stabilization. The calculated energy difference between the two arrangements is therefore very large indeed (>40 kcal mol⁻¹) in the transition state.

Thus the configuration of the product is clearly determined at the transition state; the approach of the nucleophile induces the 1,3-dipole to bend (*trans*) as the lone pair becomes localized on nitrogen.

(33) A. F. Hegarty, D. G. McCarthy, and G. Harnett, unpublished results.

(34) R. Huisgen, *J. Org. Chem.*, **41**, 403 (1976).

(35) K. J. Dignam, A. F. Hegarty, and P. L. Quain, *J. Org. Chem.*, **43**, 388 (1978).

(36) K. J. Dignam, A. F. Hegarty, and P. L. Quain, *J. Chem. Soc., Perkin Trans. 2*, 1457 (1977).

(37) K. J. Dignam and A. F. Hegarty, *J. Chem. Soc., Chem. Commun.*, 862 (1976).

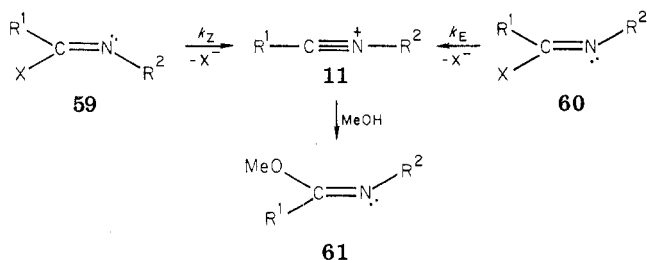
(38) K. J. Dignam and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1437 (1979).

As the nucleophile passes the transition state ($r < 2.0$ Å) a second minimum of higher energy does appear on the hypersurface with the oxygen trans to the incoming nucleophile, and the calculations predict that when bond formation is complete, the energy difference between the two configurations is small (although separated by a high energy barrier in the case of oximes). This is in line with experimental results that show that even though the reaction is tightly stereospecific, the least stable isomer may be formed.

The addition of water³⁹ to **53** or to **56** shows up a further interesting point. As the transition state is reached a corridor is opened on the hypersurface so that the proton can slide from one oxygen to the other. The latter process occurs without an energy barrier. Although the reaction can therefore be regarded as a cycloaddition between the 1,3-dipole (a potential 4π donor) and the H-O bond of water, it is clear that this is not the factor which determines the stereochemistry of the oxime product. Bending of the 1,3-dipole in the decisive direction occurs very early on the reaction coordinate, while there is essentially *no* interaction between the oxygen of the nitrile oxide and the incoming water nucleophile.

Reverse Reaction

The marked stereospecificity noted in the addition of nucleophiles to nitrilium ions should also be apparent in the reverse reaction—loss of an atom or group leading to nitrilium ion formation. Thus we would predict that the *Z* isomer **59** (where the lone pair is trans to the leaving group) would react more rapidly than the *E* isomer **60**. The same effect should also be noticed in



the formation of 1,3-dipoles from isomeric substrates. Since we have been unable to estimate the energy barrier for the unfavorable pathway experimentally using the addition reaction, study of the reverse reaction might prove an attractive method of overcoming this difficulty.

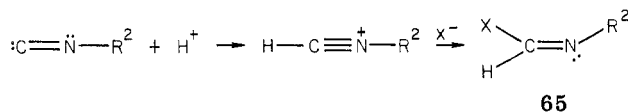
However there are several problems in applying this method. Thus it has not been possible to isolate simple imidoyl halides ($R^1 = \text{alkyl or aryl}$) as *E* and *Z* isomers; the evidence points to these being stable in the *Z* form **59** ($X = \text{Cl or Br}$),^{40,41} and NMR data at low temperatures suggest that in any event nitrogen inversion is rapid in these systems.²⁰ Attempts have also been made to isolate isomeric chlorides in systems substituted on nitrogen (e.g., $R^2 = \text{NMePh, NMeC}_6\text{H}_4\text{NO}_2$, etc.) to slow interconversion between **59** and **60**. However, again just a single isomer results (shown by X-ray¹⁰ in

(39) M. T. Nguyen, M. Sana, G. Leroy, K. J. Dignam, and A. F. Hegarty, *J. Am. Chem. Soc.*, **102**, 573 (1980).

(40) J. P. DeClercq, G. Germain, and M. Van Meerssche, *Acta Crystallogr., Sect. B*, **31**, 2894 (1975).

(41) O. Exner, V. Jehlicka, G. Barbaro, and A. Dondoni, *Collect. Czech. Chem. Commun.*, **42**, 833 (1977).

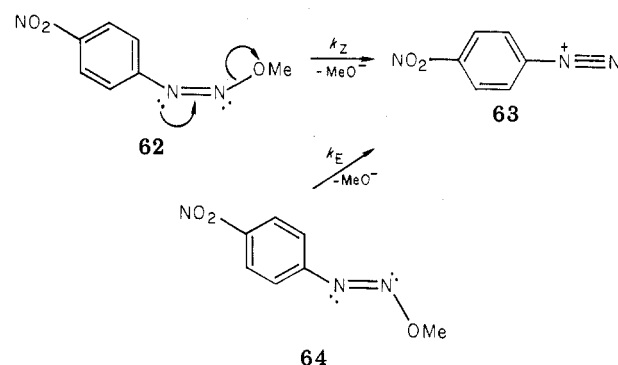
Scheme VI



one case to be *Z* (**59**, $R^1 = t\text{-Bu}$, $X = \text{Br}$, $R^2 = 2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3\text{NMe}$), and equilibration between **59** and **60** (for example, photochemically) before loss of halide ion was not successful. It also appears that the 1,3-dipole precursor **59** ($R^1 = \text{Ph}$, $R^2 = \text{OH}$) has the reactive *Z* structure, and although there are unconfirmed reports of an unreactive isomer in the literature,⁴² the structure of the latter (which might be **60**, $R^1 = \text{Ph}$, $R^2 = \text{OH}$) was not unequivocally demonstrated. Isomeric nitrolic acids (**59**, **60**, $X = \text{NO}_2$) are known and do appear to undergo loss of NO_2^- at markedly different rates.

The best example to date comes from the work of Johnson⁴³ who has isolated several pairs of isomeric *O*-alkylhydroxamoyl chlorides (**59**, **60**, $R^1 = \text{Ph}$, $R^2 = \text{O-alkyl}$, $X = \text{Cl}$). These undergo unimolecular loss of chloride ion under forcing conditions to give the nitrilium ion **11** ($R^1 = \text{Ph}$, $R^2 = \text{O-alkyl}$). The *Z* isomer is far more reactive, with k_Z/k_E being typically 450. Interestingly both chlorides yield a single product **61** on trapping the nitrilium ion with methanol. If this rate difference is also reflected in the transition state for the formation of adducts from nitrilium ion reactions, then it is easy to see why none of the product resulting from the unfavorable stereochemistry in the transition state has been detected.

Good evidence has also recently become available⁴⁴ for the corresponding reactions leading to arenediazonium ions **63**, where k_Z/k_E can be estimated as 10^5 .



The measurement of such a large rate difference involves some extrapolation but is certainly within an order of magnitude of the correct value; this provides another analogy between nitrilium and diazonium ion reactions.

Coordinated Isocyanides

Although the stereochemistry of 1,1-addition of HX to isocyanides without added catalysts has not been investigated, it is likely that it takes the course outlined in Scheme VI. Thus when X^- is AcO^- , the products formed (such as acetic anhydride) are consistent with the formation of an isomide type intermediate (**65**, X

(42) C. Grundmann and P. Grünanger, "The Nitrile Oxides", Springer-Verlag, Berlin, 1974.

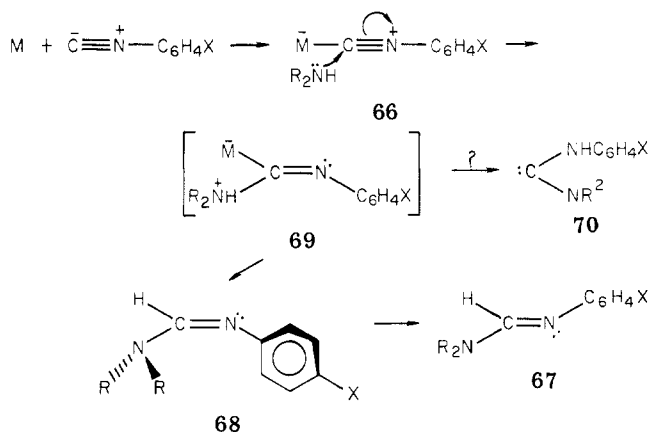
(43) J. E. Johnson, personal communication; see also J. E. Johnson, E. A. Nalley, Y. K. Kunz, and J. R. Springfield, *J. Org. Chem.*, **41**, 252 (1976), but note that the structural assignments for the (*E*-) and (*Z*-) hydroxamoyl chlorides should be reversed.

(44) T. J. Broxton, *Aust. J. Chem.*, **32**, 1031 (1979); **31**, 1519 (1978).

= AcO⁻). A stable isolable α -adduct is reported in one case (65, X = OAc, R² = *p*-MeOC₆H₄C(Me)=N⁻).⁴⁵ Since this R² substituent would slow nitrogen inversion (and thus intramolecular acyl group migration) it is likely that the product has the (expected) configuration shown (65).

A more interesting question concerns the very wide range of reactions which can be carried out at isocyanides coordinated to metal atoms or metal ions.⁴⁶ These can be divided into two classes: those in which the isocyanide ligand is released from the metal following reaction and those in which the modified ligand remains coordinated to the metal. It has been found that the group 1B and 2B metals (Cu, Ag, Zn, Cd, and Hg in various oxidation states) catalyze the former reaction involving 1,1-addition of alcohols, amines, and thiols to isocyanides (no reaction occurs in the absence of the catalyst).

The coordinated isocyanide 66 might be formally regarded as having nitrilium ion character. We were



interested to see if the same stereospecificity could be induced in these reactions. The usual reaction conditions employed involve heating at ca. 100° for several hours;⁴⁷ however, we have found that secondary amines undergo 1,1-addition to isocyanides under very mild conditions, viz., at -15 °C, catalyzed by Ag⁺.⁴⁸ Because of the mild reaction conditions the kinetic products are isolated and were shown to be the *Z* formamidine 68. These are strained (NMR evidence shows that they exist in the perpendicular configuration 68 in which rotation about the N-C and N-aryl bonds is blocked at room temperature)⁴⁹ and isomerize readily at 30 °C or in the presence of acid to the *E* isomer 67 (where rapid C-N bond rotation is observed at room temperature).

Concluding Remarks

It is clear that reactions in which nitrilium ions are intermediates show a very high degree of stereospecificity. They share this with pseudonitrilium ions such

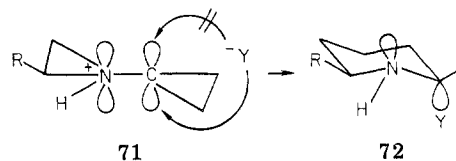
as those 1,3-dipoles in which nitrogen is the central atom and with coordinated isocyanides. Although not directly studied, nitriles and ketenimines are good candidates for similar stereospecific reactions.

Since the "imine" adducts obtained in these reactions are often thermodynamically unstable with regard to an inversion of configuration at nitrogen, this latter process can now be studied directly. To date this has been applied to the isomerization of amidines⁴⁹ and amidoximes;³⁷ in both cases the importance of acid catalysis was demonstrated.

The pronounced preference to bend in a particular direction demonstrated by 1,3-dipoles when a nucleophile approaches is exactly analogous to the bending observed in the much studied 1,3-dipolar cycloaddition. This is in spite of the fact that no interaction is observed between the incoming nucleophile and the third atom of the 1,3-dipole. This analogy between the cycloaddition and reaction with nucleophiles clearly deserves further study.

What of the extension to other systems? The diazonium ion reactions do show a close analogy in both the formation of azo adducts and also now⁴⁴ in the reverse reaction. It is likely that those reactions in which trans azo adducts have been observed² (in the reaction of diazonium ions with amines or aromatic substrates) represent either thermodynamic control (the *cis* adduct being labile) or result from rapid nitrogen inversion subsequent to adduct formation.

Rapid inversion of the heteroatom tends to obscure the clear demonstration of stereospecificity in many cases (as mentioned at the outset). However iminium ions (1, ⁺XZ = ⁺NR₂) do appear to show the same clear preference which we have observed for nitrilium ions. A particularly elegant example of this comes from the work of Stevens⁵⁰ on the synthesis of ladybug defense agents. "Remarkable" stereoselectivity is observed in the key step which involves attack on the iminium ion 71 to give a single product 72 which involves a trans



arrangement of the nucleophile and the forming lone pair on the nitrogen and minimizes the steric interaction of the group R in the transition state. Rapoport has also generated iminium ions (on the mild reaction of an α -amino acid with a halogenating agent), and these show stereoselection in cyclizations leading ultimately to alkaloids.⁵¹ These examples are encouraging, and we look forward to the demonstration (and use in synthesis) of clear stereospecificity in the reactions of other triply and doubly bonded systems with nucleophiles.

I am deeply indebted to the skillful work and enthusiasm of my research group (whose names appear in the references) and to the National Board for Science and Technology who supported part of the work described.

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(51) R. T. Dean and H. Rapoport, *J. Org. Chem.*, **43**, 4183 (1978).

(45) I. Hagedorn, *Angew. Chem.*, **75**, 304 (1963).

(46) A. Vogler in "Isocyanide Chemistry", I. Ugi, Ed., Academic Press, New York, 1971, Chapter 10.

(47) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and H. Yoshioka, *Tetrahedron Lett.*, 521 (1967); T. Saegusa, Y. Ito, S. Kobayashi, N. Takeda, and K. Hirota, *ibid.*, 1273 (1967); "Isocyanide Complexes of Metals", L. Malatesta and F. Bonati, Eds., Wiley, New York, 1969.

(48) A. F. Hegarty and A. Chandler, *Tetrahedron Lett.*, 885 (1980).

(49) A. F. Hegarty and A. Chandler, *J. Chem. Soc., Chem. Commun.*, 130 (1980).