

Molecular Design of Tautomeric Compounds

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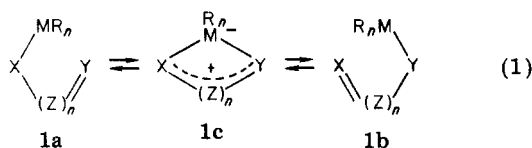
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There are good reasons for the special attention given to the phenomenon of tautomerism in organic chemistry. These include the important role of prototropic rearrangements within DNA base pairs in the determination of the genetic code¹ and the general influence that solution of the keto-enol equilibrium problem has had on contemporary understanding of acid-base and structure-reactivity relationships. Even the concept of the hydrogen bond emerged from the study of prototropic tautomerism.²

For some time it was believed that only the hydrogen ion, the simplest Brønsted acid, might be capable of rapid inter- or intramolecular exchange of its positions within a molecule. However, beginning in the early sixties it became known^{3,4} that a replacement of the mobile proton in some prototropic compounds by certain organometallic groups which could be regarded as Lewis acids gave rise to so-called "metallotropic"⁴ tautomeric compounds. At the present time several metallotropic systems (1) are known, including those with typical organometallic groups MR_n from Li to $SiR_1R_2R_3$ as mobile moieties. The work has been reviewed extensively.^{4b-6}

Our own interest in the field of tautomeric systems began with the question of whether it is possible to observe intramolecular tautomeric rearrangements (1a \rightleftharpoons 1b) of acidic moieties MR_n in which M is an atom



X, Y = O, S, NR...

$-Z_n-$ = CR, N, conjugated chain

MR_n = $CR_1R_2R_3$, COR, aryl, NO, NO_2 , PR_1R_2 , $PR_1R_2R_3^+$, POR_1R_2 , AsR_1R_2 , SR, SOR, SOR_1R_2

to the right of carbon in the periodic table.

Although irreversible rearrangements of this type are well-known (e.g., Chapman and Smiles rearrangements) and many examples of slow interconversions of type 1 isomers can be found in the literature,^{7,8} the rapidly and reversibly equilibrated, i.e., tautomeric, compounds of type 1 were not documented prior to 1970.⁹⁻¹² This Account aims to describe a general approach to the molecular design of type 1 tautomeric compounds and to present results that have been obtained so far.

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In order to elucidate which rearrangements can be considered to be tautomeric, some thermodynamic and kinetic criteria have to be introduced.¹²⁻¹⁴ They are summarized in eq 2 and 3 which show the free-energy limits for the tautomeric reaction $A \rightleftharpoons B$. Equation

$$\Delta G^\circ_{25} < 6 \text{ kcal/mol} \quad (2)$$

$$\Delta G^\ddagger_{25} < 25 \text{ kcal/mol} \quad (3)$$

2 relates to the sensitivity of current techniques for the observation of the minor tautomer in an equilibrium mixture. Equation 3 serves to differentiate tautomeric rearrangements from those slower rearrangements in which the lifetimes of the isomers are sufficiently long to permit the preparative separation of A and B. Obviously, the above criteria should be regarded as no more than approximate. Nevertheless, taken altogether, they form a reasonable basis for distinguishing tautomeric reactions within the entire domain of rearrangement reactions.

General Approach to the Construction of Tautomeric Reactions

Equation 3 presents the more difficult problem because it is easier to estimate on a good predictive level the total energies and entropies of the ground state than of the transition state for any 1a \rightleftharpoons 1b reaction.¹⁵ In any event, the ΔG° problem (eq 2) can be removed by dealing with degenerate tautomeric reactions ($A \rightleftharpoons B$, $\Delta G^\circ = 0$).

The general strategy followed in our work was to design molecules in which the geometric features of the 1c-like transition state were already present to a great extent in the ground states of 1a,b or in minor con-

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(6) *Adv. Organomet. Chem.*, **16** (1977).

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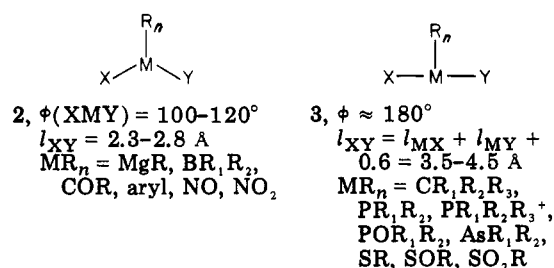
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formations accessible over low energetic barriers. Since the reactions of interest (eq 1) correspond to intramolecular nucleophilic substitution at the central atom M of the migrating group, the synthetic problem was to select and to adapt to the interacting sites (X, Y, M) those bridge chains Z whose sizes and conformations would be appropriate to the requirements of S_N2 and/or Ad_N-E_N -like transition states. The significance of such a correspondence between initial and transition states was first pointed out by Exchenmoser¹⁶ to account for steric constraints toward endocyclic methyl group transfers. The same idea was developed independently by Koshland.¹⁷ It was also incorporated into the Baldwin rules¹⁸ which provided explanations for the regularities in the orientation of ring-closure reactions.

Our detailed approach to the construction of type 1 tautomeric compounds involved the following considerations: (1) All typical nucleophilic substitutions are treated as addition-elimination (AdE) reactions, and the adduct is considered to lie on the reaction coordinate with a structure 1c appropriately close to that of the transition state. A very helpful theoretical model for the prediction of the preferred configuration of the central atom M in 1c is the Gillespie-Nyholm VSEPR theory. In accordance with its predictions, the 1c-type intermediates may be divided into two distinct groups depending on the M-X and M-Y bond arrangements. The first (2) contains bent X-M-Y fragments which are



present in bent, pyramidal, and tetrahedral 1c structures. Trigonal-bipyramidal, disphenoidal, and T-shaped 1c structures, which form the second group, favor the linear arrangement 3 because the most electronegative centers X and Y are placed at the axial positions.¹⁹⁻²² Both experimental^{20c,21c} and theoretical^{19,22} data indicate that the axial bonds of such structures are 0.2-0.3 Å longer than the equatorial bonds.

The closer the initial structure 1 to the geometrical requirements of structures 2 or 3 as appropriate, the lower should be the energy barrier for the $1a \rightleftharpoons 1b$ rearrangement.

(2) The next level of prediction is derived from quantum mechanical calculations of the reaction paths of selected model reactions. On this level it is possible to define in more detail the geometries associated with different migrating groups of the same type (e.g., NO and COR) and different nucleophiles (X, Y). Moreover, for certain migrating groups (e.g., $\text{PR}_1\text{R}_2\text{R}_3\text{R}_4$), qualitative arguments are not sufficient to distinguish the alternative type 2 and 3 arrangements. A number of calculations associated with studies of the minimum energy reaction path (MERP) for some simple reactions related to $1a \rightleftharpoons 1b$ transformations have been performed both on the semiempirical and ab initio levels.²³

A strong attractive potential for the approach of a nucleophile to the MR_n groups at the predicted angles is expected at sufficiently long M-Y distances.^{23,24} It is therefore reasonable to suggest that most of the energy barrier associated with the intramolecular nucleophilic (AdE) substitution $1a \rightleftharpoons 1b$ is due to the molecular distortion which brings the M and Y sites in 1a or the M and X sites in 1b together to provide the optimal X-M-Y configuration. This makes it possible to formulate the structural requirements that would enable a type 1 compound to exhibit the required low activation energy (eq 3).¹²

The initial structure must be constrained to a conformation which resembles the intermediate (transition state) structure, or it must be capable of adopting this favourable conformation via low-energy barrier rotation about single bonds or by polytopal rearrangement.

(3) Adherence to this condition imposes definite restrictions on the choice of the size and conformation of the moiety Z in compounds 1 so as to provide appropriate type 2 or 3 X-M-Y configurations dictated by the nature of the MR_n group. Since much structural information is available concerning bond lengths, bond angles, and rotational barriers of similar systems, the required structures may be derived readily. For example, systems 4-6 are quite appropriate for "allowed" 1,j-sigmatropic shifts of type 2 migrating groups MR_n ,

(23) The following values of the optimal angles of approaching nucleophile Y to the X- MR_n bond in 1a have been calculated for various model reactions: (a) $\text{MR}_n = \text{COR}$: 109.5° ($\text{H}^- + \text{CH}_2\text{O}$, ab initio, DZ: H.-B. Bürgi, J. M. Lehn, and G. Wipff, *J. Am. Chem. Soc.*, **96**, 1956 (1974); MINDO/3: M. E. Kletsky, R. M. Minyaev, and V. I. Minkin, *Zh. Org. Khim.*, **16**, 686 (1980); $99-111^\circ$ ($\text{CH}_3\text{O}^- + \text{HCONH}_2$, PRDDO: S. Sheiner, W. H. Lipscomb, and D. A. Kleier, *J. Am. Chem. Soc.*, **98**, 4770 (1976)); 103.5° ($\text{H}^- + \text{CH}_2\text{CHClCHO}$, ab initio, STO-3G: Nguyen Trong Anh and O. Eisenstein, *Nouv. J. Chim.*, **1**, 161 (1977)). (b) $\text{MR}_n = \text{CR}, \text{R}_2, \text{R}_2$: 180° ($\text{F}^- + \text{CH}_3\text{F}$, ab initio, 4-31G: H. B. Schlegel, K. Mislow, F. Bernardi, and A. Bottoni, *Theor. Chim. Acta*, **44**, 245 (1977)); $171.5-180^\circ$ ($\text{F}^- + \text{CH}_2\text{RF}$, ab initio, 4-31G: S. Wolfe, D. J. Mitchell, and H. B. Schlegel, unpublished results, R = H, F, OH, CH_3 , CHO). (c) $\text{MR}_n = \text{NO}$: 119° ($\text{H}^- + \text{HNO}$), 109° ($\text{F}^- + \text{NOF}$). MINDO/3: M. E. Kletsky, R. M. Minyaev, and V. I. Minkin, *Zh. Org. Khim.*, **16**, 686 (1980). (d) $\text{MR}_n = \text{NO}_2$: 130° ($\text{HO}^- + \text{HNO}_2$, MINDO/3: M. E. Kletsky, R. M. Minyaev, and V. I. Minkin, *Zh. Org. Khim.*, **16**, 686 (1980)). (e) $\text{MR}_n = \text{SR}$: 180° ($\text{HSSH} + \text{H}^-$, F⁻, HS⁻, ab initio, DZ: J. A. Pappas, *J. Am. Chem. Soc.*, **99**, 2926 (1977)); $180, 90^\circ$ ($\text{H}^- + \text{H}_2\text{S}$, F⁻ + ClFS, CNDO/2: V. I. Minkin and R. M. Minyaev, *Zh. Org. Khim.*, **13**, 1129 (1977)). 172° ($\text{F}^- + \text{CH}_3\text{SF}$, CNDO/2: G. H. Schmid and G. M. Hallman, *Int. J. Chem. Sulfur*, **8**, 607 (1976)). (f) $\text{MR}_n = \text{PR}, \text{R}_2$: $180, 90^\circ$ ($\text{F}^- + \text{PClF}$, CNDO/2: R. M. Minyaev, V. I. Minkin, and M. E. Kletsky, *Zh. Org. Khim.*, **14**, 449 (1978)). (g) $\text{MR}_n = \text{SOR}$: $180, 90^\circ$ ($\text{F}^- + \text{SOClF}$, CNDO/2: R. M. Minyaev, V. I. Minkin, and M. E. Kletsky, *Zh. Org. Khim.*, **14**, 449 (1978)). (h) $\text{MR}_n = \text{PR}_1\text{R}_2\text{R}_3\text{R}_4$: 90° ($\text{H}^- + \text{PH}_3\text{CH}_3$, MINDO/3: R. M. Minyaev and V. I. Minkin, *Zh. Struct. Khim.*, **20**, 842 (1979)).

(24) There is also much experimental evidence for the formation of stable intermediates on the reaction coordinate in S_N2 -type ion-molecule reactions in the gaseous phase. See, for example, AdE reactions at C_{sp^3} (W. N. Olmstead and J. I. Brauman, *J. Am. Chem. Soc.*, **99**, 4219 (1977)) and at carbonyl C_{sp^2} centers (O. I. Asubiojo and J. I. Brauman, *ibid.*, **101**, 3715 (1979)).

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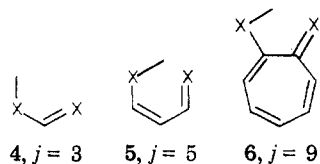
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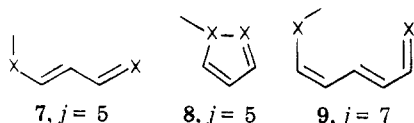
(21) (a) V. I. Minkin and R. M. Minyaev, *Zh. Org. Khim.*, **11**, 1993 (1975); (b) M. M. L. Chen and R. Hoffmann, *J. Am. Chem. Soc.*, **98**, 1647 (1976); (c) F. Perozzi and J. C. Martin, *Science (Washington, D.C.)* **191**, 154 (1976); (d) R. M. Minyaev and V. I. Minkin, *Zh. Struct. Khim.*, **18**, 274 (1977).

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(X = Y), whereas the systems 7 and 8 are predicted to be unfavorable for such rearrangements.



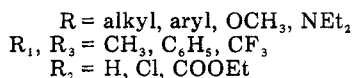
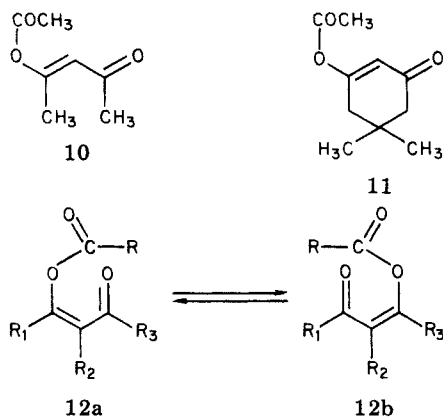
The simplest Z chain which is suitable for a type 3 MR_n group tautomeric rearrangement will correspond to the 1,7-sigmatropic system 9, which maintains an all-cis configuration.

We now consider some experimental results which demonstrate tautomeric rearrangements of various acidic moieties and support the approach described above.

Tautomeric Rearrangements of Carbonic Acid Moieties

The first examples of these rearrangements were obtained with acyl derivatives of mercaptobenzaldimine¹⁰ and naphthazarine²⁵ which may be referred to as type 5 systems. More detailed studies were then made on both degenerate²⁶⁻²⁹ and nondegenerate^{29,30} O,O'-acyl rearrangements of the corresponding derivatives of 1,3-diketones.

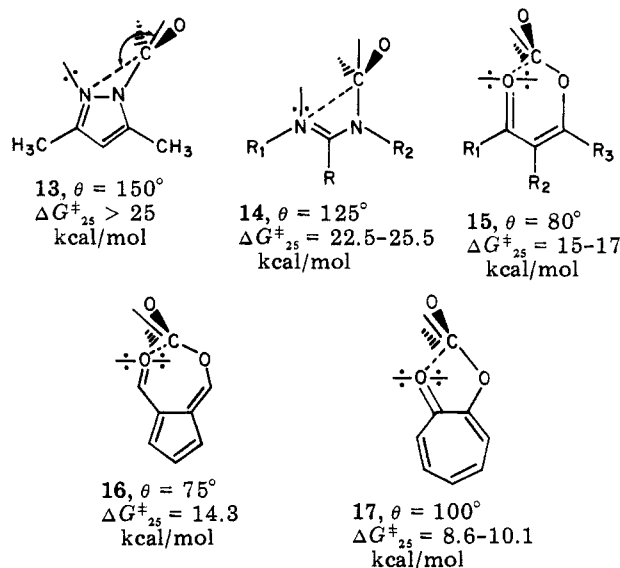
Acetylation of acetylacetone with acetyl chloride leads to an approximately 1:1 mixture of E (10) and Z (12, R = R₁ = R₃ = CH₃, R₂ = H) isomers.^{26,27}



The ¹H NMR spectrum of compound 10 as well as that of the O-acetyldimedone 11 does not vary with temperature. On the other hand the NMR spectra of the Z isomers 12 show evidence of a rapid ($k_{25} = 35 \text{ s}^{-1}$, $\Delta G^{\ddagger}_{25} = 15 \text{ kcal/mol}$) O,O'-transfer of the acetyl group leading to isochronous behavior of the R₁ and R₃ methyl groups.³¹ This finding is in full accord with the theoretical analysis of the problem.

With the exceptions of R = OCH₃ ($k_{25} = 0.3 \text{ s}^{-1}$, $\Delta G^{\ddagger}_{25} = 18.1 \text{ kcal/mol}$) and NEt₂ ($k_{25} = 6.5 \times 10^{-5} \text{ s}^{-1}$, $\Delta G^{\ddagger}_{25} = 23.1 \text{ kcal/mol}$), the free energies of activation for the rearrangements 12a \rightleftharpoons 12b are not very sensitive to the electronic nature of substituents R, R₁-R₃ but, rather, suggest that a stereochemical factor dominates. All of these tautomeric rearrangements were shown to be exclusively intramolecular in nature and were not significantly influenced by solvent effects.

Compounds 13-17 demonstrate a strong dependence of the migratory ability of the acetyl group on the angle of approach of the nucleophilic center to a carbonyl group within an appropriate molecular conformation.^{27,32-35}



There is a good correlation between the θ values and the free energies of activation for acetyl migration. Thus conformation 13 of a pyrazole derivative (cf. 8) is unfavorable for the MERP requirement ($\theta = 100-110^\circ$),^{23a} and intramolecular N,N'-acetyl migration does not occur,³⁶ but conformation 17 of tropolone deriva-

(31) The character and rate of degenerate 12a \rightleftharpoons 12b rearrangements do not depend on the ratio of Z and E forms in solution. These can be separated by column chromatography.^{26a}

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(35) The θ values ($\pm 5^\circ$) were evaluated from molecular models, having standard bond lengths and bond angles (J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory", McGraw-Hill, New York, 1970, p 110) at the most favorable conformation for nucleophile-carbonyl group interactions (13-17). These conformations and angles are in good agreement with our MINDO/3 calculations for compounds 14, 15, and 17. Experimental evidence in favor of the perpendicular arrangement of the acetyl group is presented in an X-ray study of the diacetate of naphthazarine (J. G. Rogrigues, F. H. Cano, and S. Garcia-Blanco, *Acta Crystallogr., Sect. B*, B33, 49 (1977)).

(36) At elevated temperatures (180-200 °C), intermolecular acyl transfer was detected (J. Castells, M. S. Merino, and M. Moreno-Manas, *J. Chem. Soc., Chem. Commun.*, 709 (1972)).

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(b) K. Hartke, D. Krampitz, and W. Uhde, *Chem. Ber.*, 108, 128 (1975);

(c) E. Wachsen and K. Hartke, *ibid.*, 108, 138, 683 (1975); 109, 1353 (1976); (d) K. Hartke and E. Wachsen, *Liebigs Ann. Chem.*, 730 (1976).

Table I
Rate Constants and Free Energies of Activation (25 °C) for *O,O'*-Acyl Migrations 17a \rightleftharpoons 17b

migrating group COR, R =	R ₁	R ₂	R ₃	k, s ⁻¹	ΔG^\ddagger , kcal/mol
CH ₃	H	H	H	2.3×10^5	10.1
OCH ₃	H	H	H	3.5×10^3	12.6
OCH ₃	CH ₃	H	H	8.2×10^3	12.2
CH ₃	CH ₃	CH ₃	CH ₃	1.2×10^6	9.2
OCH ₃	CH ₃	CH ₃	CH ₃	5.6×10^4	11.0
N(CH ₃) ₂	CH ₃	CH ₃	CH ₃	3.0×10^{-2}	19.5
C ₆ H ₄ OCH ₃ - <i>p</i>	CH ₃	CH ₃	CH ₃	1.0×10^4	12.0
OCH ₃	H	Br	H	72	14.9
OCH ₃	Br	H	Br	18	15.7
CH ₃	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	3.0×10^6	8.6
OCH ₃	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	1.0×10^4	12.0
N(CH ₃) ₂	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	3.8×10^{-1}	18.0
CF ₃	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	$> 5 \times 10^7$	< 7.0

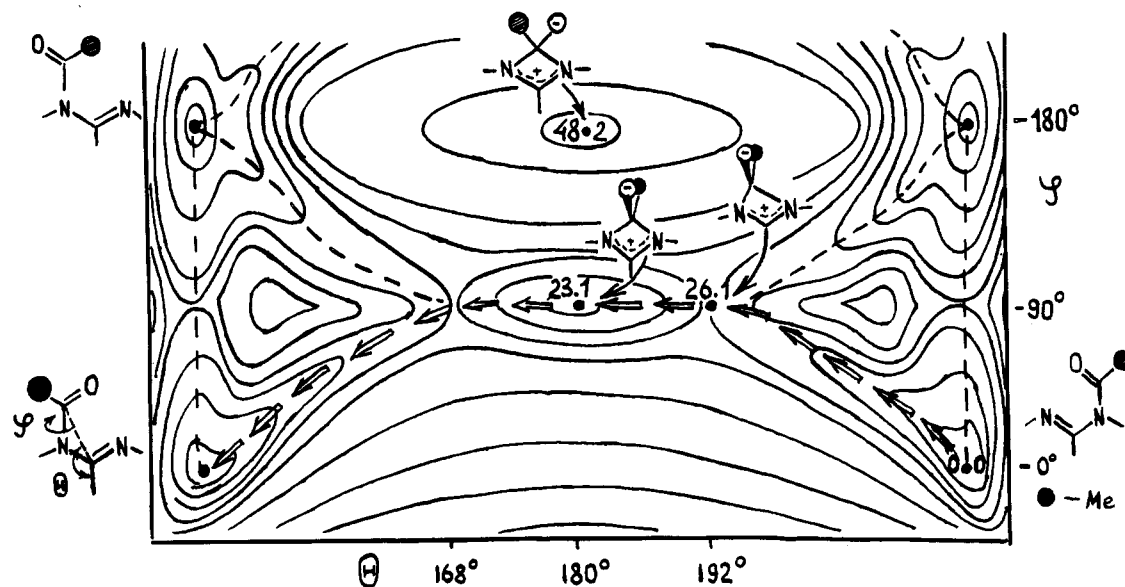
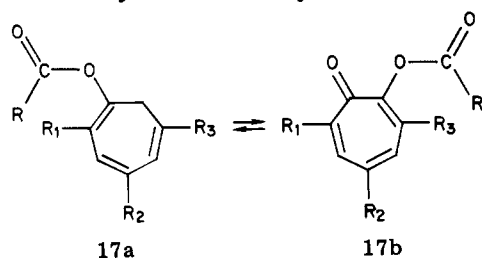


Figure 1. Potential-energy surface for the reaction 18a \rightleftharpoons 18b ($R_1 = R_2 = H$) as a function of angles θ and ϕ .

tives is very favorable for intramolecular nucleophilic substitution at a carbonyl carbon atom. This facilitates *O,O'*-rearrangement. Table I contains a brief summary of kinetic studies³⁷ of *O,O'*-acyl migrations in tropolone derivatives 17 by ¹H and ¹³C dynamic NMR.



As seen from Table I, substituents in the seven-membered ring affect significantly the energy barriers, but the latter are most sensitive to the structure of the migrating group. The migration frequency is decreased by almost eight orders of magnitude when the methyl group of compound 4 is replaced by the dimethylamino group of 6. This may be attributed to the great increase in the electronic density on the carbon atom of the carbamoyl group, which results in a strong decrease in its electrophilicity.

(37) V. I. Minkin, L. P. Olekhovich, Yu. A. Zhdanov, Z. N. Budarina, V. P. Metlushenko, and I. B. Orenstein, *Zh. Org. Khim.*, **13**, 777 (1977); (b) L. P. Olekhovich, N. I. Borisenko, Z. N. Budarina, V. P. Metlushenko, Yu. A. Zhdanov, and V. I. Minkin, *ibid.*, submitted for publication.

The acyl derivatives 12a and 17a possess usually the planar, lowest energy *s-trans* conformation.³⁸ Meanwhile the MERP conditions require the carbonyl group to be rotated into the orthogonal *s-cis* conformation, as shown in structures 15 and 17. The energy barrier between these conformations is associated with the low activation energy rotation about the C–O bond.^{38b} The value of this barrier contributes to the total energy barrier of the acyl-group transfer.

This is exemplified by the MINDO/3 scanning potential-energy surface for an acetyl group *N,N'* transfer in a model amidine derivative 18 ($R_1 = R_2 = H$)³⁹ (Figure 1).

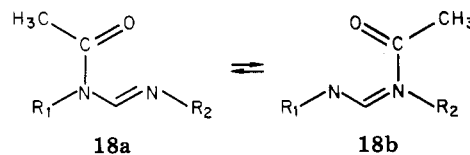


Figure 1 shows that prior to the *N=N'* transfer, the acetyl group rotates to the plane perpendicular to the amidine moiety. The energy barrier calculated is in good accordance with the experimental values of *N*-

(38) (a) J. P. Schaefer and L. L. Reed, *J. Am. Chem. Soc.*, **93**, 3902 (1971); (b) H. Nakanishi, H. Fujita, and O. Yamamoto, *Bull. Chem. Soc. Jpn.*, **51**, 214 (1978).

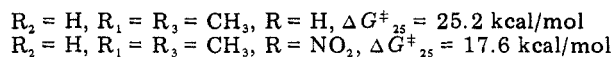
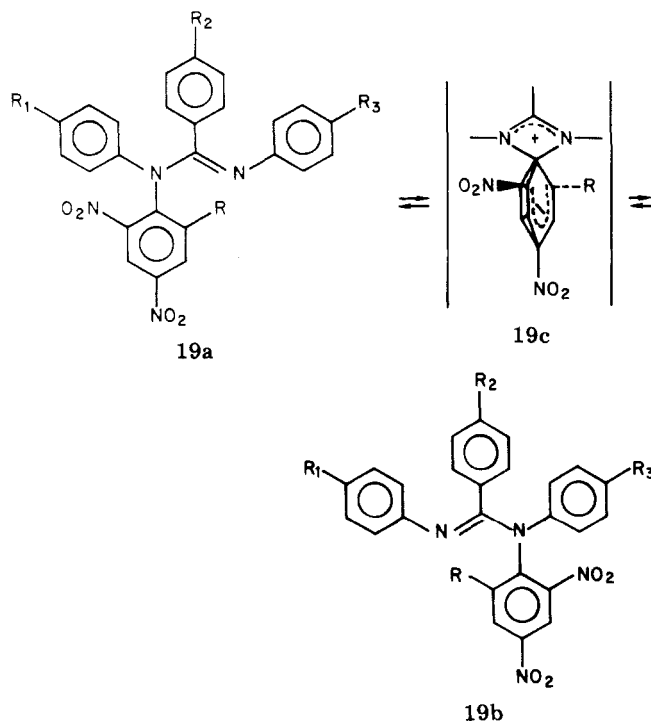
(39) R. M. Minyaev, M. E. Kletsky, B. Ya. Simkin, and V. I. Minkin, in press.

N'-acetyl and -aroyl migrations in the series of *N,N'*-diarylbenzamidines.³²

The same sequence of molecular motions is calculated for *N,N'* rearrangement in *N*-nitro- and -nitrosoamidine derivatives.^{23c,d} Thus the overall reaction coordinate for the process **1a** \rightleftharpoons **1b** contains both rotation and bond shift. The overall reaction proceeds via an asymmetric reaction path (see ref 40).

Tautomeric Rearrangements of Aryl Groups

The steric requirements for nucleophilic substitution at a carbonyl carbon and for S_NAr substitution are quite similar.⁴¹ Therefore structures 4–6 with an activated aryl moiety attached, might be expected to exhibit tautomeric properties. We have been able to observe by NMR *N,N'* transfer of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl groups in a series of benzamidine derivatives⁴² (**19a–c**). Crossover experiments have es-



ablished that these are intramolecular rearrangements.

In similar compounds the energy barriers for 2,4-dinitrophenyl migration were found to be approximately the same as those for acyl group migration. However, the 2,4,6-trinitrophenyl group was found to migrate 5×10^5 times more rapidly than the acetyl group in the *N,N'*-diarylbenzamidine system.³² A variety of compounds with a common formula (**19**) have been studied, and the influence of substituents R_1 – R_3 on the energy barriers of rearrangements has been shown to be less significant than that of R.

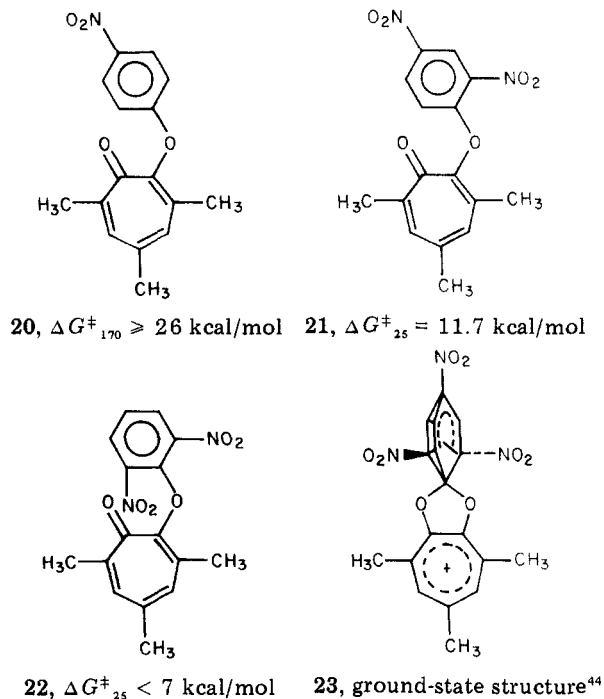
(40) (a) L. Salem, *Acc. Chem. Res.*, **4**, 322 (1971); (b) S. Wolfe, H. B. Schlegel, I. G. Csizmadia, and F. Bernardi, *J. Am. Chem. Soc.*, **97**, 2020 (1975).

(41) (a) J. F. Bunnett and R. F. Zahler, *Chem. Rev.*, **49**, 362 (1951); (b) E. Buncel, A. R. Norris, and K. E. Russell, *Q. Rev. Chem. Soc.*, **22**, 123 (1968); (c) M. G. S. Strauss, *Chem. Rev.*, **70**, 667 (1970).

(42) (a) V. I. Minkin, L. P. Olekhovich, Yu. A. Zhdanov, I. E. Mikhailov, Z. N. Budarina, and N. M. Ivanchenko, *Dokl. Akad. Nauk SSSR*, **219**, 357 (1974); (b) V. I. Minkin, L. P. Olekhovich, Yu. A. Zhdanov, I. E. Mikhailov, V. P. Metlushenko, and N. M. Ivanchenko, *Zh. Org. Khim.*, **12**, 1271 (1976).

Although the possible formation of an intermediate σ complex (**19c**) seems quite reasonable, by analogy with the similar structures postulated as intermediates in 1,3 rearrangements (e.g., the Smiles, Chapman, Stevens, Newman–Kwart rearrangements),⁴³ unequivocal evidence for **19c** could not be obtained. However, in the more sterically favorable tropolone system, such compounds could not only be observed but also be isolated to provide the first examples of the previously unknown dipolar Meisenheimer spiro complexes.⁴⁴

Compounds **20–23** show an interesting trend in both the dynamic behavior and the structure depending on the number of nitro groups in the migrating aryl moiety.^{37a,42a}



While the 4-nitrophenyl derivative **20** lies outside the limits for a tautomeric rearrangement (eq 3) and coalescence of the 3- and 7-methyl group peaks is observed in the ^1H NMR spectrum only at $>170^\circ$, O,O' migration of the 2,6-dinitrophenyl group could not be frozen out on the ^1H and ^{13}C NMR time scales even at -100°C . Thus, according to their NMR spectra, both **22** and **23** have effective C_{2v} symmetry. However, in contrast to **20–22**, **23** is a deeply colored compound, and its electronic absorption spectrum (two long-wave bands in the regions of 400 and 500 nm) is characteristic of an anionic Meisenheimer complex.^{41b,c} Therefore the compound **23** which is formed by the reaction of picryl chloride with the sodium salt of the substituted tropolone represents a stable dipolar spirocyclic σ complex. This conclusion was confirmed by the structure of compound **23**⁴⁵ as determined by X-ray crystallography and shown in Figure 2. The high value of its dipole moment (5.2 D) reflects substantial charge separation in the dipole structure **23**.

(43) M. S. Newman, *Acc. Chem. Res.*, **5**, 354 (1972).

(44) By using a flash-photolysis technique, a formation of the open structure isomer of **23** and its rapid relaxation to the spirocyclic ground-state form was observed (N. V. Volbushko, V. A. Krikov, and Z. N. Budarina, unpublished results).

(45) N. G. Furmanova, Yu. T. Struchkov, O. E. Kompan, Z. N. Budarina, L. P. Olekhovich, and V. I. Minkin, *Zh. Struct. Khim.*, **21**, 83 (1980).

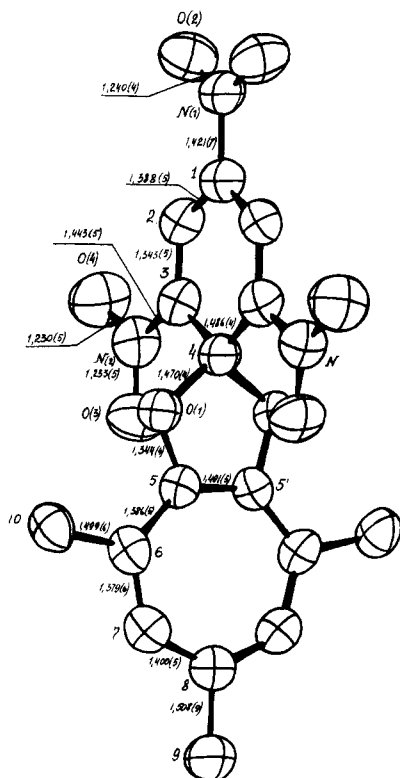


Figure 2. Structure of the dipolar spirocyclic σ complex 25 as determined by X-ray diffraction.

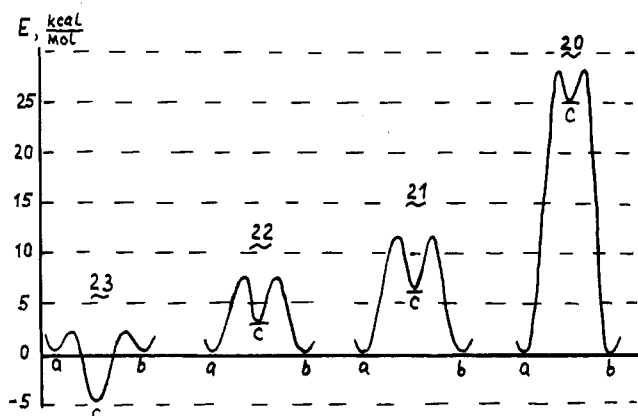


Figure 3. Potential-energy profiles for the type $1a = 1b$ intramolecular substitution reaction of compounds 20–23. The middle minimum corresponds to the dipolar spirocyclic σ complex. The relative energies of the a, b, and c type structures have been determined from the $24a = 24c$ type equilibria (compound 23) and estimated on the basis of the ΔG^\ddagger_{25} value for compound 22. Similar ΔE values are suggested for compounds 20 and 21.

Figure 3 illustrates pictorially the static and dynamic properties of compounds 20–23 and reveals dependence of the activation energies and relative stabilities of the tropolone ether and spiro σ complex isomeric structures on the positive charge at the ipso carbon of the aryl substituent.

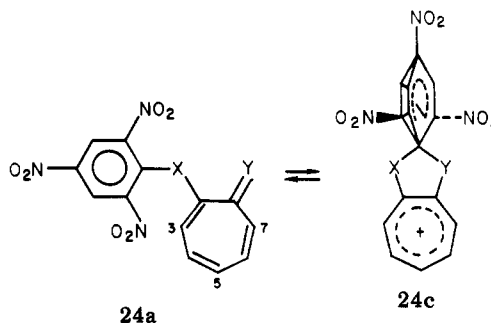
The X-ray structural data for 22 are also very instructive.⁴⁵ As already noted, this compound undergoes extremely rapid ($K_{25} > 10^7 \text{ s}^{-1}$) intramolecular O,O' rearrangement of the 2,6-dinitrophenyl moiety. The reason for its high mobility is the extraordinarily short $C=O \cdots C_{1(Ar)}$ intramolecular distance in the stable s-cis conformation with the two rings lying in mutually orthogonal planes. This $O \cdots C_1$ distance (2.45 Å) is 0.55 Å smaller than the sum of the van der Waals radii and

Table II

compound	solid-state structure (X-ray) ⁴⁵⁻⁴⁷	%	
		24c in benzene, 25 °C	24c in DMF, 25 °C
X = Y = O	24a, 24c (two crystal forms)	0	20
X = Y = O (3-Me)		0	55
X = Y = O (3,5,7-Me ₃)	24c	100	100
X = O, Y = S	24a	0	0
X = O, Y = NMe	24c	100	100
X = NMe, Y = S	24c	100	100
X = Y = NMe	24c	100	100

indicates a strong attraction between these two sites. The stable conformation of compound 22 is thus quite close to those of the transition state or intermediate structures expected for such reactions.

Alkyl and aralkyl substituents at the 3 and 7 positions of the seven-membered ring introduce a small buttressing effect which facilitates aryl migration. This follows from the data of Table I and from the existence of two separable valence isomers of the O-(2,4,6-trinitrophenyl)tropolone 24 (X = Y = O).⁴⁶ Both the



open (24a) and closed (24c) forms are observed in solution at equilibrium. Polar solvents shift the equilibrium to the right. Some representative data on this equilibrium are given in Table II.⁴⁵⁻⁴⁸

Addition-Rearrangement-Elimination Mechanism of Tautomeric Migrations

For the case of intermediate structures having a trigonal-bipyramidal derived geometry, there is an important additional mechanistic possibility which was first recognized by Westheimer.⁴⁸

There are two topologically nonequivalent equatorial and axial positions in these structures. Only the latter are appropriate for both an entering and a leaving nucleophile because of preference of axial attack and axial departure pathways for bond-making and bond-breaking and because of the principle of microscopic reversibility. For the reactions under consideration, this requires incorporation of the migrating group into a type 9 chain, for which difficult synthetic problems are encountered. However, it is possible to meet the demand of the principle of microscopic reversibility in a three-step reaction. In such a case the entering nu-

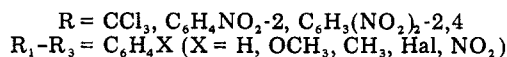
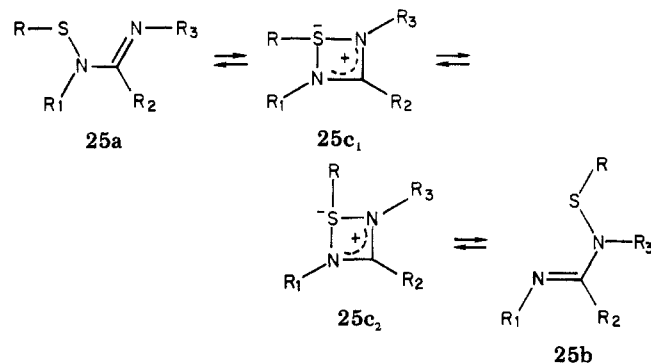
(46) The X-ray measurement of the open isomeric 24a structure (X = Y = O) has been completed and found to be similar to that of compound 22. The $C=O \cdots C_{Ar}$ distance was found to be 2.519 Å (N. G. Furmanova, L. P. Olekhovich, V. I. Minkin, Yu. T. Struchkov, O. E. Kompan, and Z. N. Budarina, *Zh. Org. Khim.*, submitted for publication.

(47) L. P. Olekhovich, N. G. Furmanova, V. I. Minkin, Yu. T. Struchkov, O. E. Kompan, Z. N. Budarina, and O. V. Eruzheva, *Zh. Org. Khim.*, submitted for publication.

(48) F. H. Westheimer, *Acc. Chem. Res.*, 1, 168 (1968).

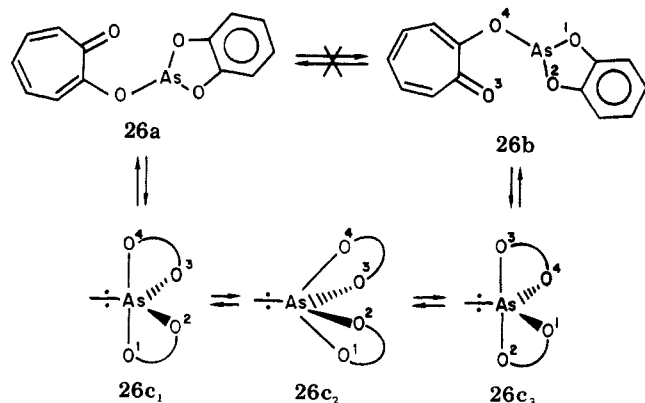
cleophile (Y in 1a) approaches from an axial position and the leaving group (X) occupies an equatorial position in intermediate 1c at this stage (Ad). The intermediate thus formed undergoes polytopal rearrangement⁴⁹ (R) which leads to interchange of the positions of these groups. The leaving group (X) may then be eliminated (E) from the axial position. A detailed examination of such addition-rearrangement-elimination (AdRE) mechanisms has been given by Mislow.⁵⁰

The key steps of these reactions are associated with polytopal rearrangements of the intermediates. Such a mechanism has been proposed to account for the tautomeric 1,3 shifts ($\Delta G^*_{25} = 17\text{--}20$ kcal/mol) of arenesulfonyl groups in the amidine derivatives 25.⁵¹



Because of the steric requirements of the T-shaped transition-state structure at dicoordinated sulfur,^{23e,52} the geometry of an amidine system is unfavorable for the concerted intramolecular rearrangement 25a \rightleftharpoons 25b. However, a nonconcerted mechanism via 25c is found to be plausible on the basis of CNDO/2 calculations^{23e} which predict a simple in-plane rearrangement mode 25c₁ \rightleftharpoons 25c₂ for the topomerization of the T-shaped structure. The intramolecular nature of sulfonyl shifts has been demonstrated by crossover experiments.⁵¹

Evidence in favor of an AdRE mechanism has been found recently in investigations of tautomeric rearrangement of (2'-tropolonyl)-1,3,2-benzodioxasole 26a.⁵³ The ¹³C NMR spectrum of this compound



(49) For determination of polytopal rearrangements, see E. L. Muetterties, *Acc. Chem. Res.*, **3**, 266 (1970).

(50) K. Mislow, *Acc. Chem. Res.*, **3**, 321 (1970).

(51) L. P. Olekhovich, V. I. Minkin, I. E. Mikhailov, N. M. Ivanchenko, and Yu. A. Zhdanov, *Dokl. Akad. Nauk SSSR*, **33**, 874 (1977); *Zh. Org. Khim.*, **15**, 1355 (1979).

(52) E. Ciufarelli and F. Griselli, *J. Am. Chem. Soc.*, **92**, 6015 (1970).

(53) V. I. Minkin, L. P. Olekhovich, V. P. Metlushenko, N. G. Furmanova, I. Bally, and A. T. Balaban, *Tetrahedron*, in press.

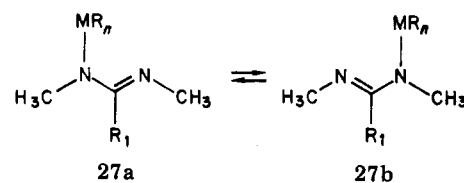
Table III
Tautomeric Rearrangements 27a \rightleftharpoons 27b

MR _n	R ₁	ΔG^+ , kcal/mol (t, °C)	ref
	C ₆ H ₅	17 (25)	57
⁺ S(C ₆ H ₅) ₂ (SbF ₆ ⁻)	C ₆ H ₅	T _c = 120°	56
⁺ P(C ₆ H ₅) ₃ (Cl ⁻)	C ₆ H ₅	13.9 (0)	56
⁺ P(C ₆ H ₅) ₃ (Cl ⁻)	CHCl ₂	16 (25)	57
⁺ P(C ₆ H ₅) ₃ (Br ⁻)	C ₆ H ₅	17.2 (77)	11
P(=O)(OEt) ₂	C ₆ H ₅	22.8 (172)	57
P(=NC ₆ H ₅)(OEt) ₂	C ₆ H ₅	22.6 (166)	57
⁺ As(C ₆ H ₅) ₃ (Br ⁻)	C ₆ H ₅	10 (-90)	56

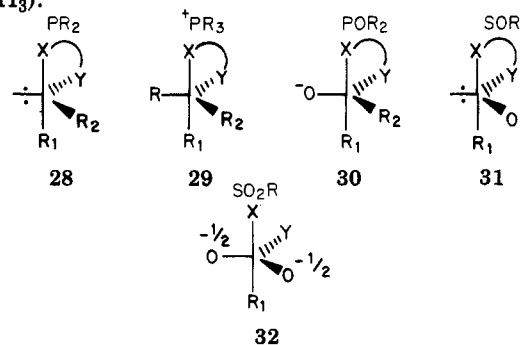
contains only seven peaks even at -70 °C, which indicates the existence of an effective symmetry plane in 26 on the NMR time scale and therefore very rapid O,O'-arsinyl moiety migrations ($\Delta G^*_{-70} < 6.5$ kcal/mol).⁵⁴

The reason for such a low energy barrier was elucidated by X-ray determination of the molecular structure of 26a. The As...O₄ distance in the ground-state conformation 26a was found to be 1.2 Å shorter than the van der Waals contact (3.4 Å), which indicates a very strong attraction of these centers within a molecule. A stable conformation of the latter is quite close to a pyramidally distorted disphenoid 26c₁ with the approaching nucleophile O₄ in the axial position. The conformation is well suited to the steric demands of the 26a \rightleftharpoons 26c₁ \rightleftharpoons 26c₂ \rightleftharpoons 26c₃ \rightleftharpoons 26b reaction pathway, including the Berry pseudorotation⁵⁵ via pyramidal transition-state structure 26c₂.

Analogous AdRE mechanistic schemes can be suggested for recently reported^{56,57} intramolecular 1,3 rearrangements of a number of phosphorus-containing migrants, diphenylsulfonio and triphenylarsonio groups in amidine derivatives of type 27 (Table III). Inter-



mediates 28-30 are expected to be formed and rearranged in the course of these reactions (X = Y = NCH₃).



(54) Estimated on the basis of approximate equality of the chemical shift values for similar carbon nuclei in 26a and 2-acetoxy- and 2-methoxytropone; see J. F. Bagli and M. St-Jacques, *Can. J. Chem.*, **56**, 578 (1978).

(55) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).

(56) K. Hartke and H.-M. Wolff, *Chem. Ber.*, **113**, 1394 (1980).

(57) V. V. Negrebetsky, L. Ya. Bogelfer, V. I. Kalchenko, V. S. Krystal, A. D. Sinita, and L. N. Markovsky, *Zh. Obsch. Khim.*, **50**, 2133 (1980).

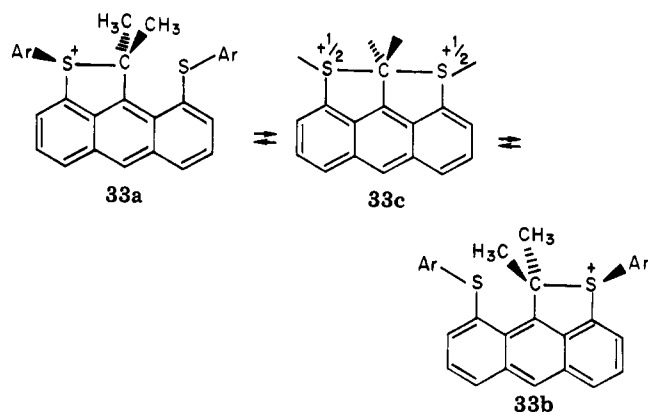
A strong preference for an O^- ligand to occupy the equatorial position due to its low apicophilicity is taken into account in drawing structures **30–32**.^{20,21,58,59} In the case of the sulfinyl and sulfonyl migrating groups, the typical permutational model (Berry pseudorotation) requires an O^- ligand in intermediates **31** and **32** to be situated transiently at an axial position. The energy difference between corresponding permutational isomers is expected to be not less than 15–20 kcal/mol in favor of initial structures **31** and **32**.⁶⁰ This may be considered as the likely explanation for the nontautomeric behavior of type **27** amidine derivatives with $MR_n = SOPh$ and SO_2Ph .⁶¹

The most striking stereochemical consequence of the AdRE mechanism of tautomeric migrations is retention of configuration at the central atom of the migrating group.^{48,50} If such an atom is a chiral or a prochiral center, this prediction can be checked experimentally.

Alkylotropic Migrations

The problem of tautomeric intramolecular migration of alkyl groups remains to be solved. All known alkyl-transfer reactions have been found to be intermolecular.^{8,62} Because carbon cannot form a long-lived pentacoordinate hypervalent intermediate,⁶³ an AdRE process is impossible. Therefore, the only possibility for the observation of an intramolecular alkyl group migrations would appear to be in the use of compounds with an all-cis conjugated chain **9**, whose conformation is suitable for an eight-membered cyclic transition state. Such a structure has been realized by Martin⁶⁴ in the 1,8-bis(arylthio)anthracene-9-carbynyl cations **33**.

The rate constant of the **33a** \rightleftharpoons **33b** process is of the order of 10^2 s^{-1} at 25°C . Although, strictly speaking, this reaction does not involve alkyl group migrations,



it reproduces all the specific features of an intramolecular nucleophilic substitution at a carbon sp^3 center.

Concluding Remarks

The results discussed in this Account illustrate the usefulness of the mechanistic approach to the molecular design of new tautomeric systems. Only one type of reaction mechanism (associative nucleophilic substitution) and its steric requirements have been considered, so that the structural rules that have been developed apply only to this specific, albeit important, type of reaction. Probably these rules would have to change if additional reaction mechanisms (dissociative, radical, ion radical, ion pair) were operative. However, this will not affect the main principle of structural design which requires close correspondence between transition-state and initial-state structures for a low-energy barrier reaction. Following this key concept has already led to the design of new tautomeric systems in which heavy acidic moieties migrate as rapidly as 10^6 – 10^9 s^{-1} at room temperature and to the discovery of unusual nonclassical structures representing superstabilized intermediates of such rearrangements. New syntheses and new reactions can be predicted by intelligent use of the principles involved.

We are continuing with the investigation of these aspects of tautomeric rearrangements, which obviously serve as useful models for group transfer reactions of synthetic interest.

The work described in this Account could not have been performed without the contributions of our colleagues whose names appear in the appropriate literature citations. Part of this paper was written during a visit by V.I.M. to Queen's University, Kingston, Ontario, Canada, where the hospitality of Professor Saul Wolfe and his helpful comments were appreciated.

(58) S. Trippett, *Pure Appl. Chem.*, **40**, 595 (1974); *Phosphorous Sulfur*, **1**, 89 (1976).

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(60) R. M. Minyaev, I. D. Sadekov, and V. I. Minkin, *Zh. Obsch. Khim.*, **47**, 2011 (1977).

(61) N. M. Ivanchenko, I. E. Mikhailov, and L. P. Olekhovich, unpublished results.

(62) J. F. King and M. J. McGarrity, *J. Chem. Soc., Chem. Commun.*, 1140 (1979).

(63) (a) C. A. Maryanoff, F. Ogura, and K. Mislow, *Tetrahedron Lett.*, 4095 (1975); (b) T. El Gomati, I. Gasteiger, D. Lenoir, and I. Ugi, *Chem. Ber.*, **109**, 836 (1976); (c) T. Vergnani, M. Karpf, L. Hoesch, and A. S. Dreiding, *Helv. Chim. Acta*, **58**, 2524 (1975); (d) for a recent claim concerning a structure with a pentavalent pentacoordinate carbon, see, however, T. R. Forbus and J. C. Martin, *J. Am. Chem. Soc.*, **101**, 5057 (1979).

(64) J. C. Martin, and R. J. Basalay, *J. Am. Chem. Soc.*, **95**, 2572 (1973).