210 *Acc. Chem. Res.* **1981**, *14*, 210–217

Molecular Design of Tautomeric Compounds

VLADIMIR I. MINKIN,* LEW P. OLEKHNOVICH, and YURII A. ZHDANOV

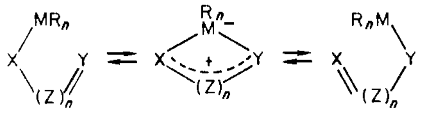
Department of Chemistry, Rostov on Don University, 344711 Rostov on Don, USSR

Received October 24, 1980

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 code[1] 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** ⇌ **1b**) of acidic moieties MR_n in which M is an atom to the right of carbon in the periodic table.



1a **1c** **1b** (1)

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

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.

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 ⇌ B. Equation

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

$$\Delta G^\ddagger_{25} < 25 \text{ kcal/mol} \tag{3}$$

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** ⇌ **1b** reaction.[15] in any event, the ΔG° problem (eq 2) can be removed by dealing with degenerate tautomeric reactions (A ≡ B, $\Delta G^\circ = 0$).

The general strategy followed in our work was to design molcules 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-

Vladimir I. Minkin was born in Rostov on Don in 1935. He received his Doctorate in Chemical Science in 1966 from Rostov on Don University where he is currently Professor of Chemistry. His research interests include intramolecular rearrangements, photochromism, and quantum organic chemistry.

Lew P. Olekhnovich was born in Rostov on Don in 1940. He received the Candidate degree from Rostov on Don University in 1968 where he is now Associate professor of Chemistry.

Yurii A. Zhdanov is Professor of Chemistry of Rostov on Don University and corresponding member of the Academy of Sciences of the USSR. He was born in Kalinin in 1919. His research interests are in carbohydrate chemistry, heterocyclic compounds, and tautomeric reactions.

---

[1] (a) P. O. Lowdin, *Adv. Quantum Chem.*, **2**, 213 (1965); (b) W. G. Cooper, *Int. J. Quantum Chem.*, **14**, 71 (1978).

[2] M. L. Huggins, *Angew. Chem.*, **83**, 155 (1971).

[3] G. Wilkinson and T. S. Piper, *J. Inorg. Nucl. Chem.*, **2**, 232 (1956).

[4] (a) A. N. Nesmeyanov and D. N. Kravtsov, *Dokl. Akad. Nauk SSSR*, **135**, 331 (1960); (b) A. N. Nesmeyanov, *J. Organomet. Chem.*, **100**, 161 (1975).

[5] I. F. Lutsenko, Yu. I. Baukov, V. L. Voss, and Z. S. Novikova, *Vestn. Moscow Univ., Ser. Khim.*, **18**, 504 (1977).

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

[7] C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, NY, 1969, Chapter 11.

[8] P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977).

[9] Yu. A. Zhdanov, V. I. Minkin, L. P. Olekhnovich, and E. H. Malysheva, *Zh. Org. Khim.*, **6**, 554 (1970).

[10] I. Fleming and D. Phillipides, *J. Chem. Soc. C*, 2426 (1970).

[11] T. Winkler, W. V. Philipsborn, J. Stroh, W. Silhan, and E. Zbiral, *J. Chem. Soc., Chem. Commun.*, 1645 (1970).

[12] V. I. Minkin, L. P. Olekhnovich, and Yu. A. Zhdanov, "Molecular Design of Tautomeric Systems", Rostov on Don University Publishing House. Rostov on Don, USSR, 1977.

[13] N. S. Zefirov and S. S. Trach, *Zh. Org. Khim.*, **12**, 697 (1976).

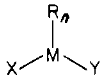
[14] E. L. Eliel, *Israel J. Chem.*, **15**, 7 (1976/1977).

[15] See for thorough discussion M. C. Flanigan and J. T. McIver in "Modern Theoretical Chemistry", Vol. 3, H. Schaefer, Ed., Plenum Press. New York, 1977, p 1.

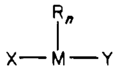
0001-4842/81/0114-0210$01.25/0

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 Exchenmoser[16] 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 rules[18] 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.



2, $\phi(XMY) = 100–120°$
$l_{XY} = 2.3–2.8$ Å
$MR_n = MgR, BR_1R_2,$
COR, aryl, NO, NO_2



3, $\phi \approx 180°$
$l_{XY} = l_{MX} + l_{MY} +$
$0.6 = 3.5–4.5$ Å
$MR_n = CR_1R_2R_3,$
$PR_1R_2, PR_1R_2R_3{}^+,$
$POR_1R_2, AsR_1R_2,$
SR, SOR, SO_2R

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** ⇌ **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., $PR_1R_2R_3R_4$), 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** ⇌ **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** ⇌ **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

---

(16) L. Tenud, S. Farooq, J. Seibl, and A. Eschenmoser, *Helv. Chim. Acta*, **53**, 2059 (1970).

(17) (a) D. R. Storm and D. E. Koshland, *J. Am. Chem. Soc.*, **94**, 5805, 5815 (1972); (b) T. C. Bruice, *Annu. Rev. Biochem.*, **45**, 331 (1976).

(18) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734, 738 (1976); "Further Persrectives in Organic Chemistry", Elsevier Excerpta Medica, North-Holland. Amsterdam, 1978, p 85.

(19) I. Ugi and F. Ramirez, *Chem. Brit.*, **10**, 101 (1972).

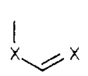
(20) (a) R. Hoffmann, J. M. Howell, and E. L. Muetterties, *J. Am. Chem. Soc.*, **94**, 3047 (1972); (b) A. Rauk, L. C. Allen, and K. Mislow, *ibid.*, **94**, 3035 (1972); (c) R. R. Holmes, *Acc. Chem. Res.*, **12**, 257 (1979).

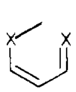
(21) (a) V. I. Minkin and R. M. Minyaev, *Zh. Org. Khim.*, **11**, 1993 (1975); (b) M. M. L. Chen and R. Hoffmann, *J. Am. Chem. Soc.*, **98**, 1647 (1976); (c) F. Perozzi and J. C. Martin, *Science (Washington, D.C.)* **191**, 154 (1976); (d) R. M. Minyaev and V. I. Minkin, *Zh. Struct. Khim.*, **18**,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

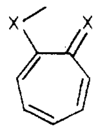
(22) (a) R. Gleiter and A. Veillard, *Chem. Phys. Lett.*, **37**, 33 (1976); (b) G. M. Schewzer and H. F. Schaeffer, *J. Am. Chem. Soc.*, **97**, 1393 (1975).

(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) MR_n = COR: 109.5° ($H^- + CH_2O$, 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° ($CH_3O^- + HCONH_2$, PRDDO: S. Sheiner, W. H. Lipscomb, and D. A. Kleier, *J. Am. Chem. Soc.*, **98**, 4770 (1976)); 103.5° ($H^- + CH_3CHClCHO$, ab initio, STO-3G: Nguyen Trong Anh and O. Eisenstein, *Nouv. J. Chim.*, 1, 161 (1977)). (b) MR_n = $CR_1R_2R_3$: 180° ($F^- + CH_3F$, ab initio, 4-31G: H. B. Schlegel, K. Mislow, F. Bernardi, and A. Bottoni, *Theor. Chim. Acta*, **44**, 245 (1977)); 171.5–180° ($F^- + CH_2RF$, ab initio, 4-31G: S. Wolfe, D. J. Mitchell, and H. B. Schlegel, unpublished results, R = H, F, OH, CH_3, CHO)). (c) MR_n = NO: 119° ($H^- + HNO$), 109° ($F^- + NOF$). MINDO/3: M. E. Kletsky, R. M. Minyaev, and V. I. Minkin, *Zh. Org. Khim.*, **16**, 686 (1980). (d) MR_n = NO_2: 130° ($HO^- + HNO_2$, MINDO/3: M. E. Kletsky, R. M. Minyaev, and V. I. Minkin, *Zh. Org. Khim.*, **16**, 686 (1980)). (e) MR_n = SR: 180° (HSSH + H^-, F^-, HS^-, ab initio, DZ: J. A. Pappas, *J. Am. Chem. Soc.*, **99**, 2926 (1977)); 180, 90° ($H^- + H_2S$, $F^- + ClFS$, CNDO/2: V. I. Minkin and R. M. Minyaev, *Zh. Org. Khim.*, **13**, 1129 (1977). 172° ($F^- + CH_3SF$, CNDO/2: G. H. Schmid and G. M. Hallman, *Int. J. Chem. Sulfur*, **8**, 607 (1976)). (f) MR_n = PR_1R_2: 180, 90° ($F^- + PClF$, CNDO/2: R. M. Minyaev, V. I. Minkin, and M. E. Kletsky, *Zh. Org. Khim.*, **14**, 449 (1978)). (g) MR_n = SOR: 180, 90° ($F^- + SOClF$, CNDO/2: R. M. Minyaev, V. I. Minkin, and M. E. Kletsky, *Zh. Org. Khim.*, **14**, 449 (1978)). (h) MR_n = $PR_1R_2R_3R_4$: 90° ($H^- + PH_4CH_3$, MINDO/3: R. M. Minyaev and V. I. Minkin, *Zh. Struct. Khim.*, **20**, 842 (1979)).

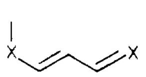
(24) there is also much experimental evidence for the formation of stable intermediates on the reaction coordinate in S_N2-type ion–molecule reactions in the gaseous phase. See, for example, AdE reactions at C_{sp^3} (W. N. Olmstead and J. I. Brauman, *J. Am. Chem. Soc.*, **99**, 4219 (1977)) and at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


4, j = 3

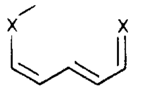

5, j = 5


6, j = 9

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


7, j = 5


8, j = 5


9, j = 7

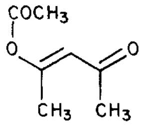
The simplest Z chain which is suitable for a type **3** MR_n group tautomeric rearrangement will correspond to the 1,7-sigmatropic system **9**, which maintains an all-cis configuration.

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

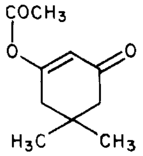
Tautomeric Rearrangements of Carbonic Acid Moieties

The first examples of these rearrangements were obtained with acyl derivatives of mercaptobenzaldimine[10] and naphthazarine[25] which may be referred to as type **5** systems. More detailed studies were then made on both degenerate[26-29] and nondegenerate[29,30] *O,O′*-acyl rearrangements of the corresponding derivatives of 1,3-diketones.

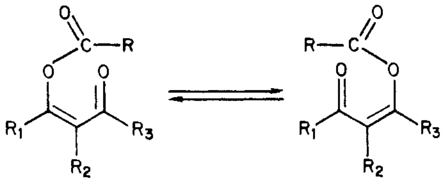
Acetylation of acetylacetone with acetyl chloride leads to an approximately 1:1 mixture of *E* (**10**) and *Z* (**12**, R = R_1 = R_3 = CH_3, R_2 = H) isomers.[26,27]



10



11



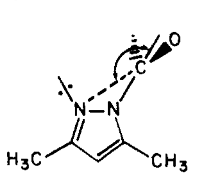
12a 12b

R = alkyl, aryl, OCH_3, NEt_2
R_1, R_3 = CH_3, C_6H_5, CF_3
R_2 = H, Cl, COOEt

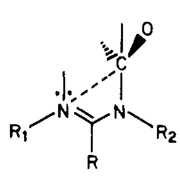
The ^1H NMR spectrum of compound **10** as well as that of the O-acetyldimedone **11** does not vary with temperature. On the other hand the NMR spectra of the *Z* isomers **12** show evidence of a rapid (k_{25} = 35 s^{-1}, $\Delta G^{\ddagger}_{25}$ = 15 kcal/mol) O,O′transfer of the acetyl group leading to isochronous behavior of the R_1 and R_3 methyl groups.[31] This finding is in full accord with the theoretical analysis of the problem.

With the exceptions of R = OCH_3 (k_{25} = 0.3 s^{-1}, $\Delta G^{\ddagger}_{25}$ = 18.1 kcal/mol) and NEt_2 (k_{25} = 6.5 × 10^{-5} s^{-1}, $\Delta G^{\ddagger}_{25}$ = 23.1 kcal/mol), the free energies of activation for the rearrangements **12a** ⇌ **12b** are not very sensitive to the electronic nature of substituents R, R_1–R_3 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.

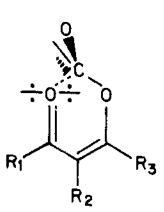
Compounds **13**–**17** demonstrate a strong dependence of the migratory ability of the acetyl group on the angle of approach of the nucleophilic center to a carbonyl group within an appropriate molecular conformation.[27,32-35]



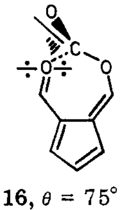
13, θ = 150°
$\Delta G^{\ddagger}_{25}$ > 25 kcal/mol

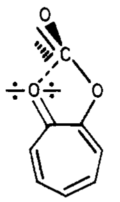


14, θ = 125°
$\Delta G^{\ddagger}_{25}$ = 22.5–25.5 kcal/mol



15, θ = 80°
$\Delta G^{\ddagger}_{25}$ = 15–17 kcal/mol


16, θ = 75°
$\Delta G^{\ddagger}_{25}$ = 14.3 kcal/mol


17, θ = 100°
$\Delta G^{\ddagger}_{25}$ = 8.6–10.1 kcal/mol

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 (θ = 100–110°),[23a] and intramolecular *N,N′*-acetyl migration does not occur,[36] but conformation **17** of tropolone deriva-

---

(25) J. C. Calder and D. W. Cameron, *J. Chem. Soc., Chem. Commun.*, 36 (1971).

(26) V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, V. V. Kiselev, M. A. Voronov, and Z. N. Budarina, *Dokl. Akad. Nauk SSSR*, **204**, 1363 (1972).

(27) 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).

(28) (a) A. Mannschreck and H. Dvorak, *Tetrahedron Lett.*, 547 (1973); (b) M. Kruszynski and G. Kupryszewski, *Polish J. Chem.*, **52**, 1183 (1978).

(29) V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, V. V. Kiselev, V. P. Metlushenko, and N. I. Borisenko, *Zh. Org. Khim.*, **10**, 2248 (1974); **11**, 1163 (1975).

(30) (a) K. Hartke, D. Krampitz, and W. Uhde, *Chimia*, **27**, 209 (1973); (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).

(31) The character and rate of degenerate **12a** ⇌ **12b** rearrangements do not depend on the ratio of *Z* and *E* forms in solution. These can be separated by column chromatography.[28a]

(32) V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, I. E. Mikhailov, and V. P. Metlushenko, *Zh. Org. Khim.*, **11**, 448 (1975); **12**, 1261 (1976).

(33) S. Masamune, A. V. Kemp-Jones, J. Green, and D. L. Rabenstein, *J. Chem. Soc., Chem. Commun.*, 283 (1973).

(34) V. I. Minkin, L. P. Olekhnovich, Yu. A. Zhdanov, Z. N. Budarina, and V. P. Metlushenko, *Tetrahedron Lett.*, 563 (1974).

(35) The θ values (±5°) 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)).

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

migrating group COR, R =	R_1	R_2	R_3	k, s^{-1}	$\Delta G^{\ddagger}$, 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
$C_6H_4OCH_3$-*p*	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	$CH_2C_6H_5$	H	$CH_2C_6H_5$	3.0×10^6	8.6
OCH_3	$CH_2C_6H_5$	H	$CH_2C_6H_5$	1.0×10^4	12.0
$N(CH_3)_2$	$CH_2C_6H_5$	H	$CH_2C_6H_5$	3.8×10^{-1}	18.0
CF_3	$CH_2C_6H_5$	H	$CH_2C_6H_5$	$>5 \times 10^7$	<7.0

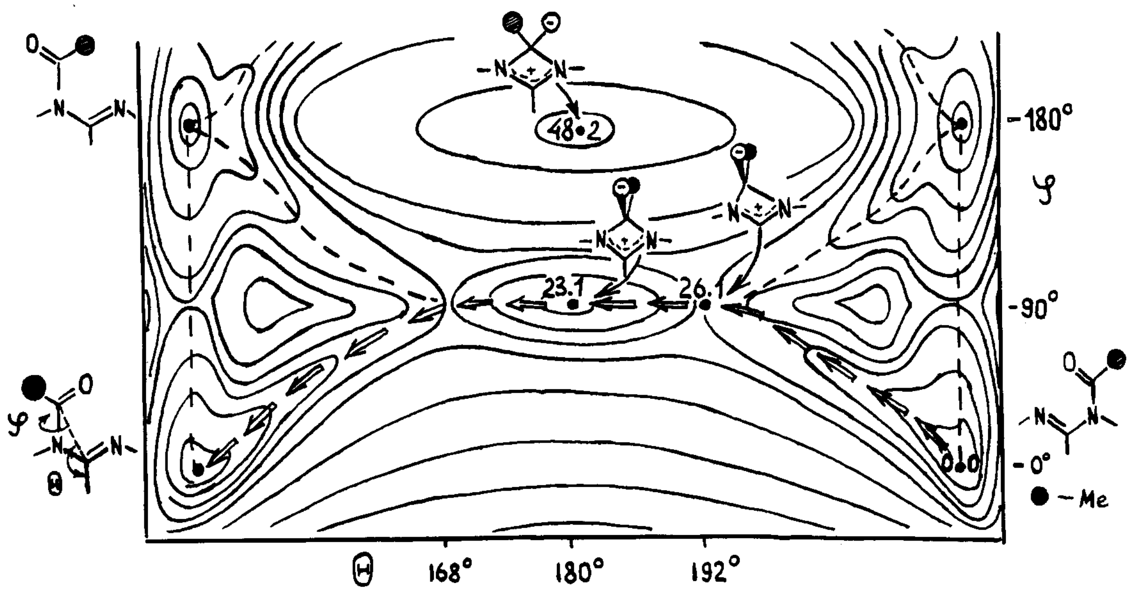
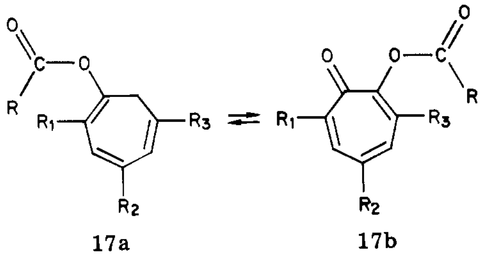


Figure 1. Potential-energy surface for the reaction 18a ⇌ 18b (R_1 = R_2 = H) as a function of angles θ and ϕ.

tives is very favorable for intramolecular nucleopholic substitution at a carbonyl carbon atom. This facilitates O,O′-rearrangement. Table I contains a brief summary of kinetic studies[37] of *O,O′*-acyl migrations in tropolone derivatives 17 by ^1H and ^{13}C dynamic NMR.

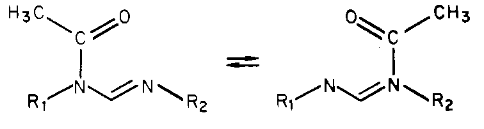


17a 17b

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 electrophility.

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).



18a 18b

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,-

---

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

[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).

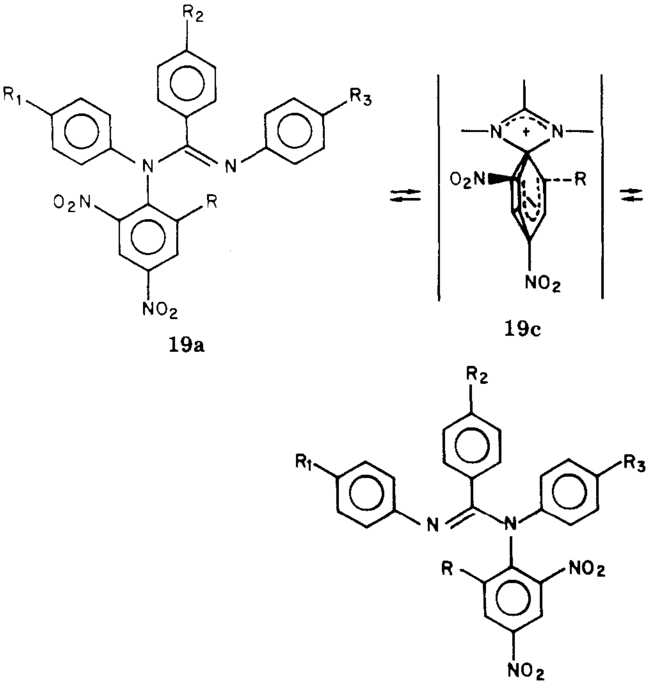
[39] R. M. Minyaev, M. E. Kletsky, B. Ya. Simkin, and V. I. Minkin, in press.

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** ⇌ **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 derivatives[42] (**19a–c**). Crossover experiments have established that these are intramolecular rearrangements.



19a

19c

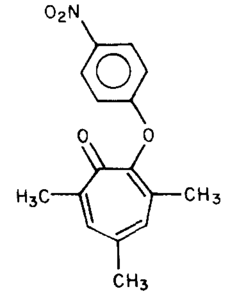
19b

R_2 = H, R_1 = R_3 = CH_3, R = H, $\Delta G^{\ddagger}_{25}$ = 25.2 kcal/mol
R_2 = H, R_1 = R_3 = CH_3, R = NO_2, $\Delta G^{\ddagger}_{25}$ = 17.6 kcal/mol

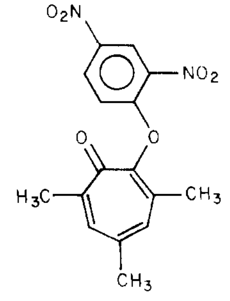
In similar compounds the energy barriers for 2,4-dinitrophenyl migration were found to be approximately the same as those for acyl group migration. However, the 2,4,6-trinitrophenyl group was found to migrate 5 × 10^5 times more rapidly than the acetyl group in the *N,N*′-diarylbenzamidine system.[32] 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.

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]

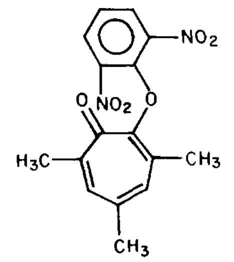
Compounds **20–23** show an interesting trend in both the dynamic behavior and the structure depending on the number of nitro groups in the migrating aryl moiety.[37a,42a]



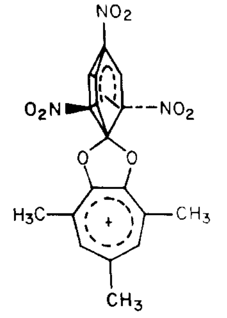
20, $\Delta G^{\ddagger}_{170} \geqslant 26$ kcal/mol



21, $\Delta G^{\ddagger}_{25} = 11.7$ kcal/mol



22, $\Delta G^{\ddagger}_{25} < 7$ kcal/mol



23, ground-state structure[44]

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°, 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**.

---

(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. Olekhnovich, 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. Olekhnovich, Yu. A. Zhdanov, I. E. Mikhailov, V. P. Metlushenko, and N. M. Ivanchenko, *Zh. Org. Khim.*, **12**, 1271 (1976).

(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. Olekhnovich, and V. I. Minkin, *Zh. Struct. Khim.*, **21**, 83 (1980).

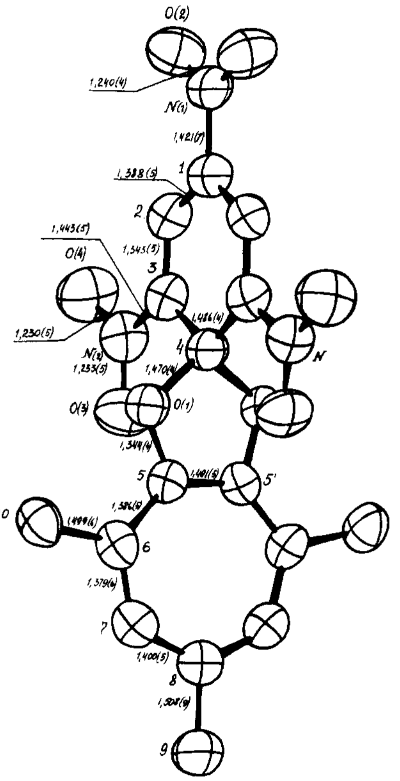


Figure 2. Structure of the dipolar spirocyclic σ complex **25** as determined by X-ray diffraction.

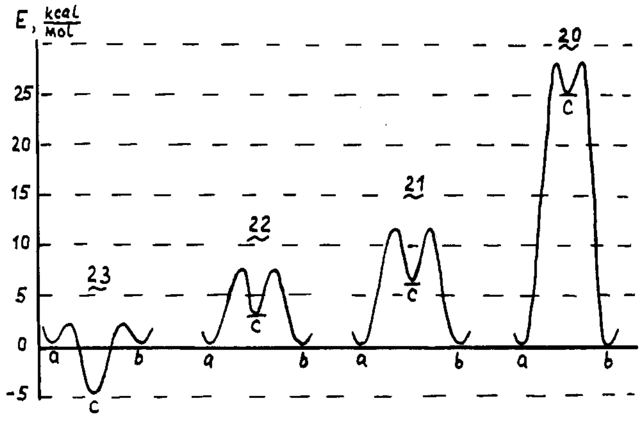


Figure 3. Potential-energy profiles for the type **1a** ⇌ **1b** intramolecular substitution reaction of compounds **20–23**. The middle minimum corresponds to the dipolar spirocyclic σ complex. The relative energies of the a, b, and c type structures have been determined from the **24a** ⇌ **24c** type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

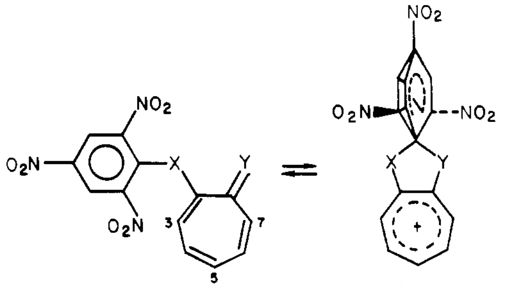
Figure 3 illustrates pictorially the static and dynamic properties of compounds **20–23** and reveals dependence of the activation energies and relative stabilities of the tropolone ether and spiro σ complex isomeric structures on the positive charge at the ipso carbon of the aryl substituent.

The X-ray structural data for **22** are also very instructive.[45] As already noted, this compound undergoes extremely rapid ($K_{25} > 10^7$ 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 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.

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

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]



24a **24c**

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 reversibiity in a three-step reaction. In such a case the entering nu-

---

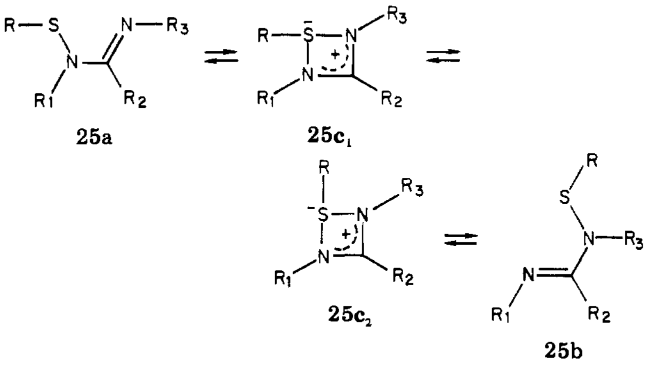
(46) The X-ray measurement of the open isomeric **24a** structure (X = Y = O) has been completed and found to be similar to that of compound **22**. The $C{=}O\cdots C_{Ar}$ distance was found to be 2.519 Å (N. G. Furmanova, L. P. Olekhnovich, V. I. Minkin, Yu. T. Struchkov, O. E. Kompan, and Z. N. Budarina,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

(47) L. P. Olekhnovich, 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 rearrangement[49] (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 ($\Delta G^{\ddagger}_{25}$ = 17–20 kcal/mol) of arenesulfenyl groups in the amidine derivatives **25**.[51]

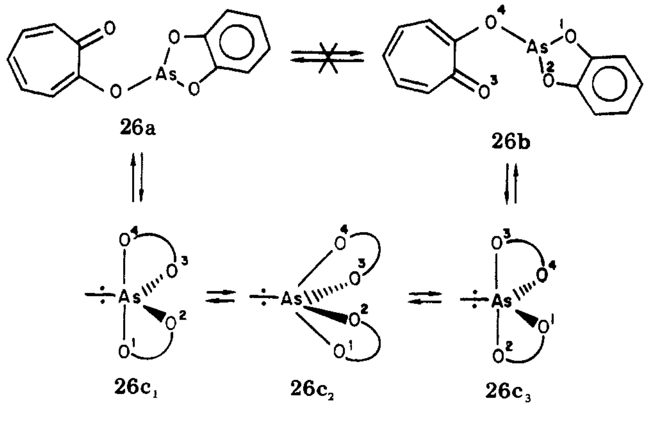


25a 25c$_1$ 25c$_2$ 25b

$R = CCl_3, C_6H_4NO_2\text{-}2, C_6H_3(NO_2)_2\text{-}2,4$
$R_1\text{-}R_3 = C_6H_4X$ (X = H, OCH$_3$, CH$_3$, Hal, NO$_2$)

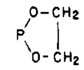
Because of the steric requirements of the T-shaped transition-state structure at dicoordinated sulfur,[23e,52] the geometry of an amidine system is unfavorable for the concerted intramolecular rearrangement **25a** ⇌ **25b**. However, a nonconcerted mechanism via **25c** is found to be plausible on the basis of CNDO/2 calculations[23e] which predict a simple in-plane rearrangement mode **25c$_1$** ⇌ **25c$_2$** for the topomerization of the T-shaped structure. The intramolecular nature of sulfenyl 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-benzodioxaarsole **26a**.[53] The ^{13}C NMR spectrum of this compound 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 ($\Delta G^{\ddagger}_{-70}$ < 6.5 kcal/mol).[54]



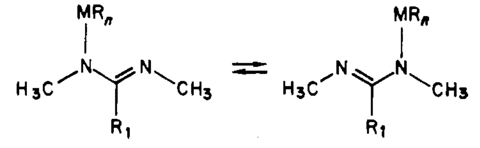
26a 26b 26c$_1$ 26c$_2$ 26c$_3$

Table III
Tautomeric Rearrangements 27a ⇌ 27b

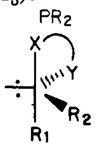
MR$_n$	R$_1$	ΔG‡, kcal/mol (*t*, °C)	ref
	C_6H_5	17 (25)	57
$^+S(C_6H_5)_2(SbF_6^-)$	C_6H_5	T_c = 120°	56
$^+P(C_6H_5)_3(Cl^-)$	C_6H_5	13.9 (0)	56
$^+P(C_6H_5)_3(Cl^-)$	$CHCl_2$	16 (25)	57
$^+P(C_6H_5)_3(Br^-)$	C_6H_5	17.2 (77)	11
$P(=O)(OEt)_2$	C_6H_5	22.8 (172)	57
$P(=NC_6H_5)(OEt)_2$	C_6H_5	22.6 (166)	57
$^+As(C_6H_5)_3(Br^-)$	C_6H_5	10 (−90)	56

The reason for such a low energy barrier was elucidated by X-ray determination of the molecular structure of **26a**. The As···O$_4$ 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 **26c$_1$** with the approaching nucleophile O$_4$ in the axial position. The conformation is well suited to the steric demands of the **26a** ⇌ **26c$_1$** ⇌ **26c$_2$** ⇌ **26c$_3$** ⇌ **26b** reaction pathway, including the Berry pseudorotation[55] via pyramidal transition-state structure **26c$_2$**.

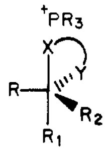
Analogous AdRE mechanistic schemes can be suggested for recently reported[56,57] intramolecular 1,3 rearrangements of a number of phosphorus-containing migrants, diphenylsulfonio and triphenylarsonio groups in amidine derivatives of type **27** (Table III). Intermediates **28**–**30** are expected to be formed and rearranged in the course of these reactions (X = Y = NCH$_3$).



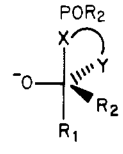
27a 27b



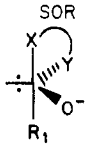
28



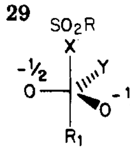
29



30



31



32

---

[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. Olekhnovich, 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. Olekhnovich, V. P. Metlushenko, N. G. Furmanova, I. Bally, and A. T. Balaban, *Tetrahedron*, in press.

[54] Estimated on the basis of approximate equality of the chemical shift values for similar carbon nuclei in **26a** and 2-acetoxy- and 2-methoxytropones; 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. Sinitsa, and L. N. Markovsky, *Zh. Obsch. Khim.*, **50**, 2133 (1980).

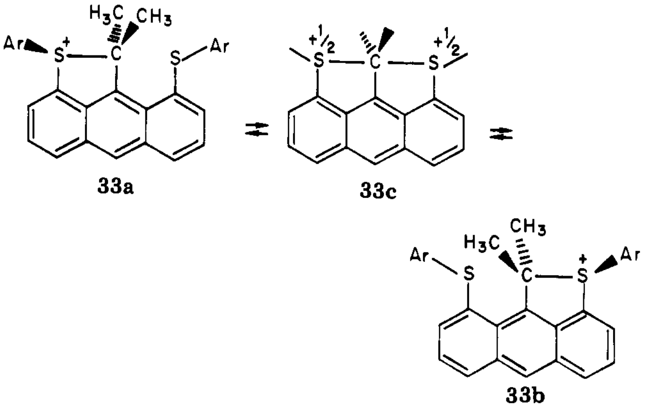
A strong preference for an O^- ligand to occupy the equatorial position due to its low apicophility is taken into account in drawing structures **30**–**32**.[20,21,58,59] In the case of the sulfinyl and sulfonyl migrating groups, the typical permutational model (Berry pseudorotation) requires an O^- ligand in intermediates **31** and **32** to be situated transitorily 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 Martin[64] in the 1,8-bis(arylthio)anthracene-9-carbynyl cations **33**.

The rate constant of the **33a** ⇌ **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.



33a **33c** **33b**

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 changed 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).

(59) C. A. Deakyne and L. C. Allen, *J. Am. Chem. Soc.*, **98**, 4076 (1976).

(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. Olekhnovich, 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).