Steric Effects in the Intramolecular Carboxyl-Catalyzed Hydrolysis of Sulfonamides. Ab Initio Quantum Chemical Studies of the Pentacoordinated Sulfur Intermediate[1]

Teun Graafland,[2a] Wim C. Nieuwpoort,[2b] and Jan B. F. N. Engberts*[2a]

Contribution from the Department of Organic Chemistry and the Department of Chemical Physics, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands.
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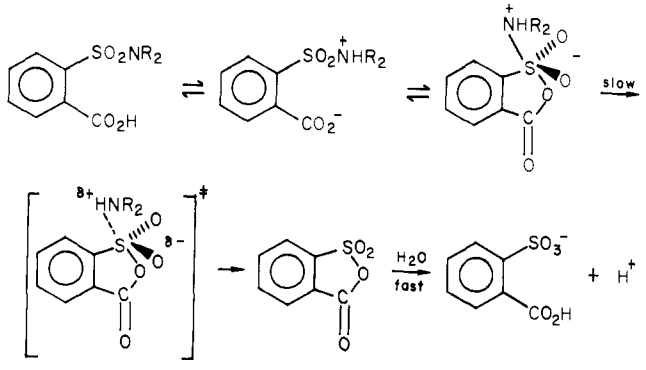
Abstract: This paper describes a semiquantitative analysis of the large differences in rate for the intramolecular carboxyl-catalyzed hydrolysis of the sulfonamides **1-5**. Ab initio molecular orbital calculations, using a double-ζ basis set of contracted Gaussian orbitals, provide further support for a stepwise nucleophilic substitution at sulfonyl sulfur involving a pentavalent sulfur intermediate. Calculations on the different conformations I-IV for this intermediate show a clear preference for a trigonal-bipyramidal structure I with apical bonds to the incoming nucleophile and the amine leaving group. Perturbation of the ideal bond angles for these groups is associated with substantial increases of the energy, implying well-defined geometrical constraints in the formation of the transition state for hydrolysis. The extremely slow hydrolysis of **4** is easily rationalized in terms of this theory. The preference for the formation of four- and five-membered rings rather than six-membered rings in this intramolecular process is also accommodated by the theoretical results. Finally, the results of the computations for V confirm the previously proposed destabilization of the transition state for hydrolysis of **2** and **3** by steric repulsion between the amine leaving group and "ortho" hydrogen atoms.

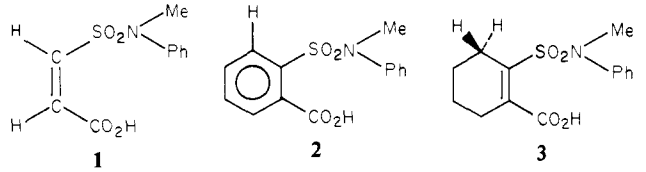
One of the still unresolved problems in sulfur chemistry involves the question of the mechanism of nucleophilic substitution at sulfonyl sulfur. At least two mechanisms have been considered:[3] (i) a concerted mechanism comprising synchronous bond formation and cleavage and (ii) a nonconcerted pathway involving a trigonal-bipyramidal sulfur intermediate. Although most authors prefer the concerted mechanism, Tillett[3g] gives preference to the two-step mechanism in spite of the absence of definite evidence.

Until now, pentacoordination is primarily connected with phosphorus chemistry. In the case of phosphoranes there exists a continuous range of conformations extending from ideal trigonal-bipyramidal geometries to rectangular pyramids.[4] Pentacoordination is less frequently encountered in sulfur chemistry. For example, a few sulfurane oxides belong to this class of pentavalent sulfur species.[5,6] Pseudopentacoordinated sulfuranes, in which one of the coordination sites is occupied by a lone electron pair, are much more common.[7] In these compounds the valence shell of the central sulfur atom has been expanded from eight to ten electrons. We also note that several of these structures have been proposed either as intermediates or as transition states in nucleophilic displacement reactions on sulfur.[3a,8]

In a previous study of the intramolecular carboxyl-catalyzed hydrolysis of sulfonamides,[1a] we have presented strong evidence for the formation of a pentacoordinated sulfur intermediate (Scheme I). The main argument involved the *negative* ρ_{COOH} value (-0.54 ± 0.02) for hydrolysis of a series of aromatic sulfonamides with substituents in meta and para positions to the carboxyl function. This observation implies that the new sulfur-oxygen bond is already fully formed in the transition state of the slow step.[9] Consequently, the amine leaving group is expelled via breaking of a pd-hybridized bond in a trigonal-bipyramidal intermediate.[1a] Consistent with this theory, the rate of hydrolysis of the sulfonamides **2** and **3** is retarded as compared with that of **1** because expulsion of the amine leaving group is sterically hindered by the ortho hydrogen in **2** and both hydrogen atoms in β position to the sulfonyl group in **3**.[1a]

Scheme I





1 2 3

In view of these results, we aimed at a better insight into the geometrical constraints of the trigonal-bipyramidally positioned ligands in the proposed pentavalent sulfur intermediate in order to provide a more quantitative explanation for the large changes

(1) Part VI in the series on intramolecular-catalyzed sulfonamide hydrolysis. (a) Part IV: Graafland, T.; Wagenaar, A.; Kirby, A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1979**, *101*, 6981-6991; (b) part V: Graafland, T.; Kirby, A. J.; Engberts, J. B. F. N. *J. Org. Chem.* **1981**, *46*, 215-217. in press.

(2) (a) Department of Organic Chemistry; (b) Department of Chemical Physics.

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(4) Holmes, R. R. *Acc. Chem. Res.* **1979**, *12*, 257-265.

(5) (a) von Halasz, S. P.; Glemser, O. *Chem. Ber.* **1970**, *103*, 594-602; (b) von Halasz, S. P.; Glemser, O.; Feser, M. F. *Ibid.* **1971**, *104*, 1242-1246.

(6) (a) Perozzi, E. F.; Martin, J. C. *J. Am. Chem. Soc.* **1972**, *94*, 5519-5520; (b) Adzima, L. J.; Martin, J. C. *Ibid.* **1977**, *99*, 1657-1659.

(7) (a) Martin, L. D.; Perozzi, E. F.; Martin, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 3595-3602; (b) Martin, J. C.; Perozzi, E. F. *Science* **1976**, *191*, 154-159.

(8) La Rochelle, R. W.; Trost, B. M. *J. Am. Chem. Soc.* **1971**, *93*, 6077-6086.

(9) An analysis of the Brønsted β value for the incoming carboxylate nucleophile (Graafland, T.; Engberts, J. B. F. N., to be published) in the same series of aromatic sulfonamides provides additional support for the stepwise mechanism. We find that $\beta_{CO_2H} = -\rho_{CO_2H}/\rho_E = 0.72$, in which ρ_E in the ρ value for the acid dissociation constants. The magnitude of β_{CO_2H} is fully consistent with that expected for a completely formed O-S bond in the transition state of the slow step, compare ref 3f.

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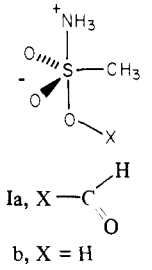
in reactivity observed in our sulfonamide systems. To this end we have performed a series of ab initio self-consistent field (SCF) molecular orbital (MO) calculations on the hypothetical species Ia and Ib. These species can be viewed as simplified models for



Ia, X = $-C(=O)H$

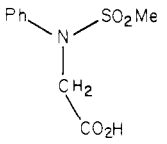
b, X = H

the assumed pentacoordinated sulfur intermediate shown in Scheme I. The main emphasis has been focused on the apical–apical relationship of the incoming group and the leaving group in the optimized geometry and on the kinetic consequences of geometric constraints affecting this relationship. The results of these studies fully support our previous mechanistic considerations and afforded additional quantitative insight into the factors influencing the efficiency of the intramolecular catalysis of sulfonamide hydrolysis.

Results and Discussion

Application of the same preference rules to pentacoordinated sulfur compounds[10] as those used for comparable phosphorus compounds[11] leads to the prediction that structures Ia and Ib are the most favorable ones of the possible structural alternatives. In these structures, the ring is attached via apical–equatorial (a–e) positions and the CSO_a angle is about 90°. The latter structural feature may well explain the relatively fast formation of four-membered rings containing phosphorus and sulfur in contrast with the situation for rings containing atoms of only first-row elements.[12] Two additional constraints that have been fulfilled in structures Ia and Ib are the preferential attachment of the incoming and leaving group in the apical positions[11] and the favorable binding of the more electropositive ligands to the equatorial sites.[13] The positive charge on the ammonium group places this moiety in the apical position as contrasted with the equatorial position of the neutral amino group in R_2NSOF_3.[14]

Rate constants and thermodynamic activation parameters for the intramolecular carboxyl-catalyzed hydrolysis of **1–5** are listed in Table I. The sulfonamides **1** and **5** are by far the most reactive



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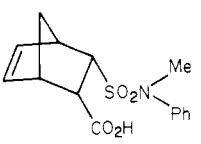

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systems. As mentioned before, the lower rates of hydrolysis of **2** and **3** will, at least in part, be caused by the approximate trigonal-bipyramidal geometry of the transition state, which implies appreciable steric repulsion between the leaving group and nearby protons in the phenyl and cyclohexenyl ring, respectively.[15] This steric repulsion will be particularly severe since puckering will

Table I. First-Order Rate Constants (k_{obsd}) and Thermodynamic Activation Parameters[a] for the Intramolecular Catalyzed Hydrolysis of the Sulfonamides **1–5**

compd	medium[c]	$10^5 k_{obsd}$,[d] s^{-1}	$\Delta G^{\ddagger}$, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
1[b]	H_2O	2780	22.32	18.6	−12
1[b]	50% EtOH–H_2O (v/v)	1005	22.90	18.2	−16
2[b]	50% EtOH–H_2O (v/v)	1.65			
3[b]	H_2O	4.79	26.65	22.3	−14
4	50% EtOH–H_2O (v/v)	$<5.10^{-4}$ [e]			
5	50% EtOH–H_2O (v/v)	4420	21.62	15.7	−20

[a] The thermodynamic activation parameters have been extrapolated to 25 °C. [b] Kinetic data from ref 1a. [c] All solvents contain 0.02–0.5 M HCl. The acidities represent pH values in the middle of the horizontal part of the pH–rate profile.[1a] [d] At 75 °C. [e] No hydrolysis after 3 months at 75 °C.

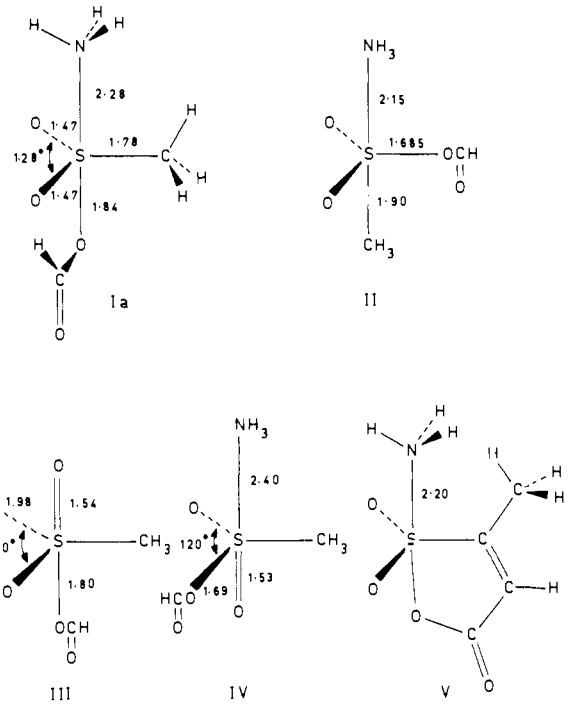


Figure 1. Optimized pentavalent sulfur species I–V. The optimized parameters are shown in the structures. Parameters not shown in II–IV are assumed to be identical with the corresponding values in Ia.

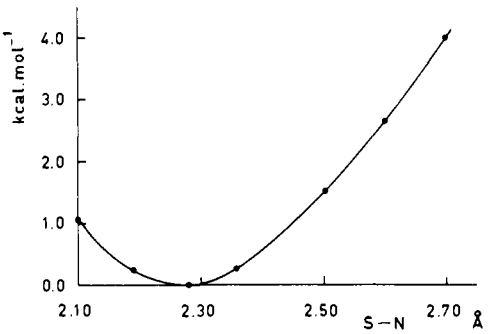


Figure 2. Plot of the total energy as a function of the S–N bond distance for structure Ia.

be almost prohibited in the five-membered ring formed after nucleophilic attack of the carboxylate group. Sulfonamide **4** is almost completely resistant toward hydrolysis under the same reaction conditions, the half-life of the reaction being greater than 1000 days. These and previous[1a] results strongly suggest that the large differences in relative rate of hydrolysis depend critically on geometric constraints involved in the formation of the trigonal-bipyramidal transition state. To scrutinize these constraints

(10) Pentacoordinated sulfur compounds exhibit a greater tendency to take up a regular trigonal-bipyramidal geometry than sulfuranes; see Kouteckỳ, V. B.; Musher, J. I. *Theor. Chim. Acta* **1974**, *33*, 227–238.
(11) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70–78.
(12) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183–278.
(13) Muetterties, E. L.; Mahler, W.; Schmutzler, R. *Inorg. Chem.* **1963**, *2*, 613–618.
(14) Glemser, O.; Mews, R. *Adv. Inorg. Chem. Radiochem.* **1972**, *14*, 333–390.
(15) This situation is not encountered in comparable carboxamide systems: Kirby, A. J.; Lancaster, P. W. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 1206–1214. Now the cyclohexenyl system hydrolyzes about 540 times faster than the maleamic acid analogue.

Table II. Relative Energies of the Pentavalent Sulfur Species I–IV

structure	ΔE, kcal mol^{-1} [a]
I	
II	25.4
III	79.1
IV	71.4

[a] Total energy relative to that of Ia (total energy = −830.33418 a.u.)

more quantitatively, we have carried out ab initio molecular orbital calculations,[16] using a double-ζ basis set of Roos and Siegbahn.[17,18] In this approach we assume that the pentavalent sulfur species Ia and Ib reasonably mimic the structural properties of the transition state since in the latter structure S–N bond breaking is far from complete.[1a] The geometrical structures that have been optimized (I–V)[19] are depicted in Figure 1. *The results of the calculations clearly indicate that the pentavalent sulfur species I in their optimized geometries represent energy minima* and, therefore, support the earlier conclusion[1a] that these species are true intermediates in the overall catalytic process.[20] Nevertheless, the energy minimum in the apical S–N bond in Ia is rather flat (Figure 2), consistent with the notion that we are dealing with a high-energy intermediate. This apical S–N bond (2.28 Å) is substantially longer than that found in spirodiaryldiamidosulfurane (1.90 Å) by Martin et al.[21] The other calculated bond lengths around the central sulfur atom agree nicely with those determined in X-ray studies of structurally related systems. Thus, the S–O(–COR) apical bond length is 1.83 Å in bis(2-carboxyphenyl)-sulfur dihydroxide dilactone,[22] which is almost identical with the corresponding bond length in Ia. The bond length of the equatorial S–C bond (1.78 Å) fits very well with the corresponding bond lengths in several sulfuranes and sulfurane oxides.[6,7,23] The equatorial S–O bonds are somewhat longer (1.47 Å) than those found in sulfurane oxides (1.42–1.44 Å),[23,24] but this may well be a consequence of the partial negative charge on the oxygen atoms of the sulfonyl moiety in Ia.

We have also examined three alternative structures (II–IV, Figure 1) in which the repulsion between the leaving group and the "ortho" substituents is absent for geometric reasons. However, their energies are much higher than that of Ia (Table II), thereby excluding them as possible alternatives. The unfavorable energy of II presumably reflects the preference of a methyl group to occupy the equatorial position. By contrast, equatorial bonding of the positively charged ammonium group leads to a large increase in energy (III), despite the shortening of the S–N distance. It has been suggested that apical bonding of these electronegative substituents is advantageous because of a better overlap with the pd-hybridized orbital on sulfur.[13] Most probably, structures III and IV are also destabilized by the apical position of the negatively charged oxygen atom of the relatively short sulfur–oxygen double bond.

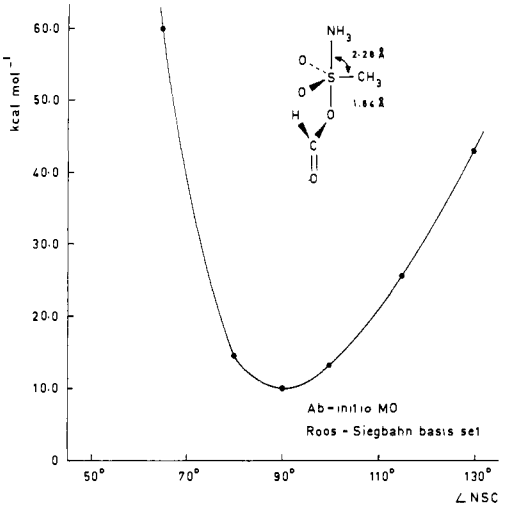


Figure 3. Plot of the total energy as a function of the angle NSC for structure Ia.

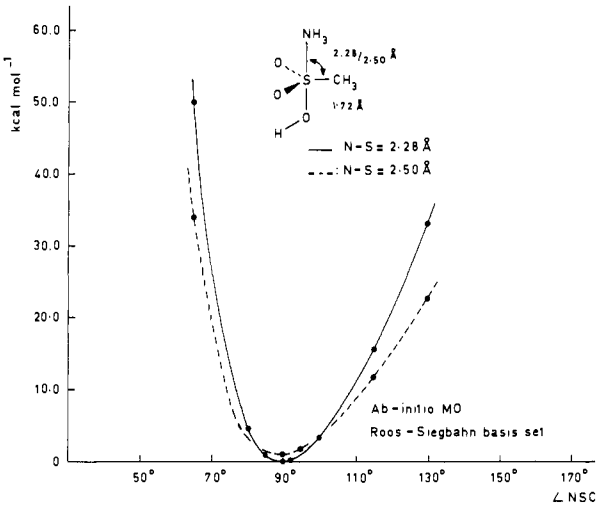


Figure 4. Plot of the total energy as a function of ∠NSC at two different N–S bond lengths for structure Ib.

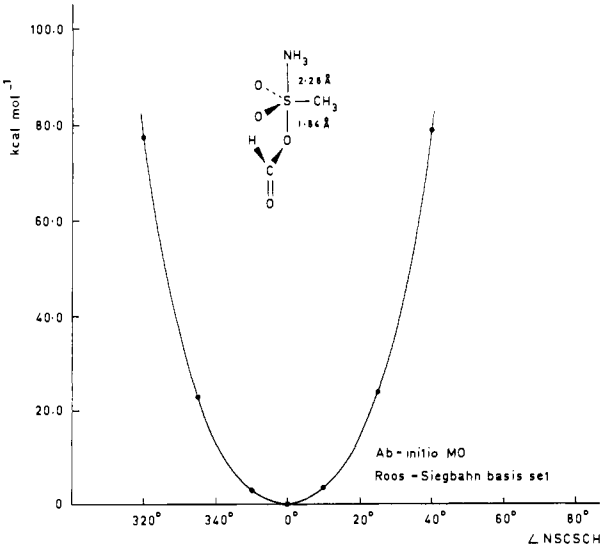


Figure 5. Total energy vs. dihedral angle NSCSCH for structure Ia.

Variation of the NSC angle in I is associated with remarkably large changes in energy despite the large S–N bond length (Figure 3). In this connection we emphasize that our computational method at the ab initio SCF level should be considered as a realistic

(16) Roothaan, C. C. J. *Rev. Mod. Phys.* **1951**, *23*, 69–89.
(17) Roos, B.; Siegbahn, P. *Theor. Chim. Acta* **1970**, *17*, 209–215. The basis set and the contraction scheme were those given in van Duynen, P. T.; Thole, B. T.; Broer, R.; Nieuwpoort, W. C. *Int. J. Quantum Chem.* **1980**, *17*, 651–671.
(18) Preliminary calculations at the STO-3G basis set level (lacking 3d polarization functions) afforded unrealistic bond lengths in the optimized structures.
(19) If the hydrogen atom (X) in Ib is replaced by the –COH group, the S–O apical distance is 1.84 Å; the other parameters are not changed.
(20) As correctly pointed out by one of the referees, the computational results refer to the gas phase in the absence of entropy effects. However, the concerted and nonconcerted mechanism considered in this work both comprise dipolar transition states that only differ in the timing of S–O bond formation. This situation warrants the suggestion that the main conclusions are also valid for the reaction in the liquid phase.
(21) Adzima, L. J.; Chiang, C. C.; Paul, I. C.; Martin, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 953–962.
(22) Kálmán, A.; Sásvari, K.; Kapovits, I. *Acta Crystallogr., Sect. B* **1973**, *29*, 355–357.
(23) Perozzi, E. F.; Martin, J. C.; Paul, I. C. *J. Am. Chem. Soc.* **1974**, *96*, 578–580.
(24) Kimura, K.; Bauer, S. H. *J. Chem. Phys.* **1963**, *39*, 3172–3178.

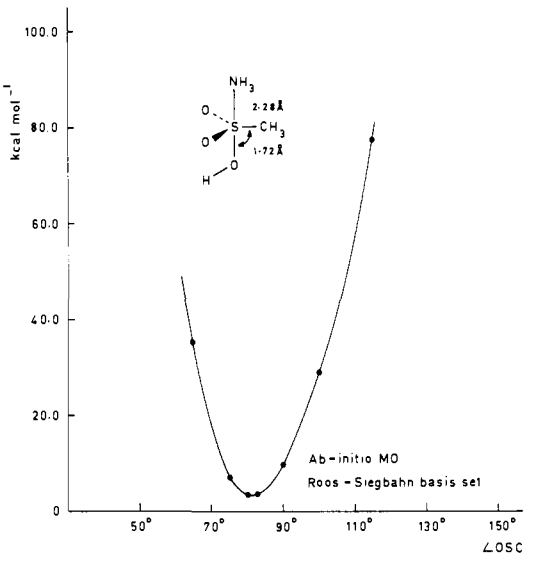


Figure 6. Total energy vs. ∠OSC for Ib.

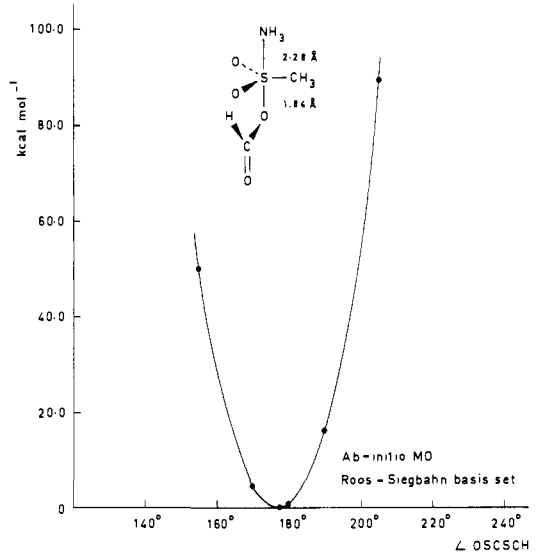


Figure 7. Total energy vs. dihedral angle OSCSCH for Ia.

tool even for substantially stretched bonds since an isodesmic reaction is involved.[25] As depicted in Figure 4, almost identical energy diagrams were obtained for Ib. The very steep slope for NSC angles smaller than 90° apparently results from nonbonded interactions between the ammonium and methyl groups. Even an increase of the NSC angle from 90 to 100° leads to an increase in energy of 3.3 kcal mol^{-1}; this illustrates the pronounced preference for the trigonal-bipyramidal geometry. As shown in Figure 4, stretching of the S–N bond length to 2.50 Å does not seriously affect the angular dependence of the total energy.

Movement of the ammonium group perpendicular to the NSC plane is also accompanied by substantial changes in energy (Figure 5) with a sharp minimum at a dihedral angle (NSCSCH) of 0°. We conclude from the above results that already a small displacement of the leaving group from its preferred position in the transition state for intramolecular catalyzed hydrolysis will be energetically unfavorable and, therefore, will have kinetic consequences. A similar sensitivity toward the positioning of the incoming nucleophile (mimicked by the –OCOH moiety) is found. This is shown by the steep angular potentials for variation of the OSC angle (Figure 6) and for variation of the OSCSCH dihedral

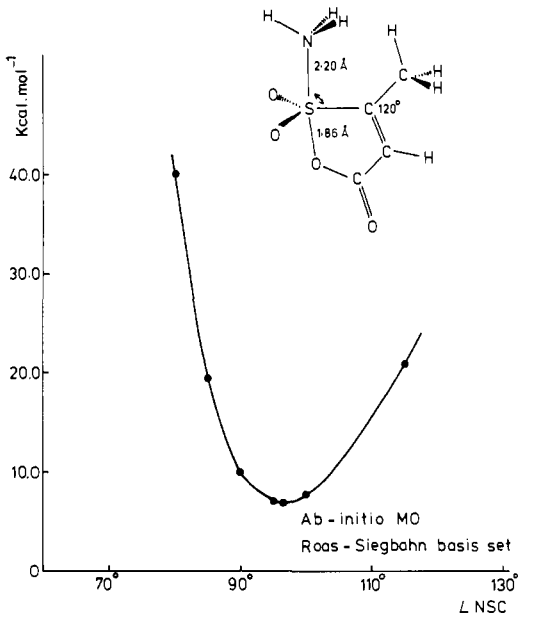


Figure 8. Total energy vs. ∠NSC for V.

angle (Figure 7). Figure 6 shows an energy minimum at an OSC angle of 81° instead of 90°, presumably as a result of coulombic repulsion between the negatively charged oxygen atoms. The minimum at 81° is in line with the experimental observation that formation of four- and five-membered rings is favored compared with that of six-membered rings in intramolecular COOH-catalyzed sulfonamide hydrolysis.[1a] It also explains the relatively high effective molarity of the COOH group for the formation of the four-membered cyclic transition state.[1a,12]

In order to make a rough estimate of the nonbonded interaction between the leaving group and an "ortho" hydrogen atom, we also calculated the changes in energy associated with variation of the NSC angle for the cyclic structure V (Figure 8). The S–N bond length (2.20 Å) was optimized for a structure in which the α-methyl group was omitted. With this bond length, the energy was computed for NSC angles varying from about 80 to 120°. A well-defined minimum was found in the energy profile at 96.5°. This bending of the leaving group out of the "ideal" apical position almost certainly reflects the presence of the "ortho" hydrogen atom in V. Combined with the data from Figure 3 the repulsion energy is estimated to be 4.6 kcal mol^{-1} larger for a structure with an NSC angle of 90° instead of 96.5°. Therefore, the present results fully support the notion[1a] that the major reason for the differences in rate of hydrolysis of **1** as compared with those of **2** and **3** is steric hindrance experienced by the leaving group in the transition state. As expected, this difference between **1** and **3** is primarily reflected in the different enthalpies of activation (Table I). A dramatic example of the kinetic effect of perturbation of the ideal transition-state geometry is provided by sulfonamide **4** (Table I). In the transition state for intramolecular catalyzed hydrolysis both the nucleophile and the leaving group are incorporated in the five-membered ring. This excludes an apical–apical arrangement of both reactive groups, thereby reducing the rate of hydrolysis many orders of magnitude. Another factor that may contribute to the low rate of hydrolysis is intramolecular attack by the leaving amino group on the mixed cyclic anhydride.[1a] However, this back-reaction becomes less likely at higher acidities[1a] and suffers, of course, from the same geometrical constraints.

Sulfonamide **5** appears to be the most hydrolytically reactive sulfonamide system investigated until now. The effective molarity of the carboxyl group[12] may well be above 10^{11} M and illuminates the kinetic advantage of a proper positioning of the reacting functionalities within the same molecule.[26]

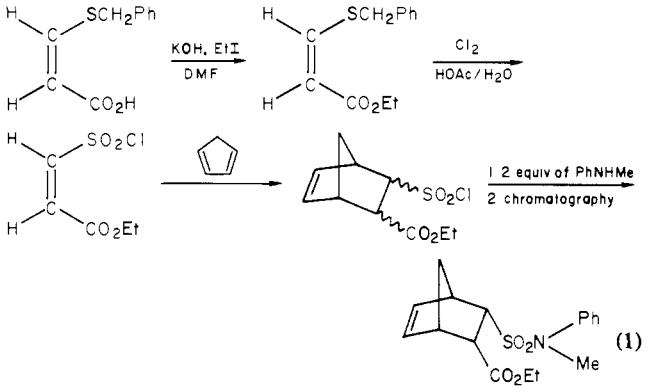
(25) (a) Hehre, W. J.; Ditchfield, R.; Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4796–4801; (b) Radom, L.; Pople, J. A.; von R. Schleyer, P. *J. Am. Chem. Soc.* **1972**, *94*, 5935–5945.

(26) (a) Jencks, W. P. *Adv. Enzymol.* **1975**, *43*, 219–410; (b) Page, M. I. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 449–459.

Experimental Section

Materials.[27] The sulfonamides **1-3** were synthesized as reported previously.[1a] Compound **4** was prepared according to standard procedures[28] starting from the ethyl ester of *N*-phenylglycine.

***N*-Phenyl-*N*-(methylsulfonyl)glycine (4)**: mp 151.0-152.7 °C; NMR ($CDCl_3$) 3.07 (s, 3 H), 4.50 (s, 2 H), 7.42 (s, 5 H), 8.20 (s, 1 H). Anal. Calcd for $C_9H_{11}NO_4S$: C, 47.15; H, 4.84; N, 6.11; S, 13.99. Found: C, 47.03; H, 4.83; N, 6.13; S, 14.13. The ethyl ester of compound **5** was prepared according to eq 1.[28,29]



6

2-*endo*-(Ethylcarboxy)-3-*endo*-(*N*-methyl-*N*-phenylsulfonamido)bicyclo[2.2.1]hept-5-ene (6): mp 81.2-82.6 °C; NMR ($CDCl_3$) 1.1-1.6 (m, 5 H), 3.0-3.5 (m, 3 H), 3.35 (s, 3 H), 3.9-4.3 (m, 1 H), 5.9-6.1 (m, 1 H), 6.4-6.6 (m, 1 H), 7.1-7.6 (m, 5 H). Anal. Calcd for $C_{17}H_{21}NO_4S$: C, 60.87; H, 6.31; N, 4.18; S, 9.56. Found: C, 61.17; H, 6.24; N, 4.21; S, 9.47. The X-ray structure[30] of **6** confirmed the endo position of both substituents at the ring.

2-*endo*-Carboxy-3-*endo*-(*N*-methyl-*N*-phenylsulfonamido)bicyclo[2.2.1]hept-5-ene (5). The preparation of the sodium salt of **5** was carried out as previously described[1a,31] for **1** and the salt was used as such in the kinetic measurements.

Kinetic Measurements. The kinetic data for hydrolysis of **4** and **5** have been determined by using the UV and NMR methods outlined in earlier studies.[1a]

Ab Initio Calculations. The closed-shell SCF ab initio calculations[16] were carried out by using Roos and Siegbahn's double-ζ contracted Gaussian basis set[17,18] with one 3d polarization function on sulfur. The orbital exponent for this polarization function was 0.54.[32] It has been shown that for compounds in which the sulfur atom is surrounded by electron-withdrawing groups, geometries can only be properly described by including sulfur d orbitals.[33] The molecular structure of Ib was optimized by sequentially varying the bond lengths to sulfur and the equatorial OSO angle. The sequence followed was[34] (1) S-O_e bond lengths, (2) OSO bond angle, (3) S-N bond length, (4) S-O_a bond length, (5) S-C bond length. Further iteration was not necessary. In Ia only the S-O_a and the S-N bond lengths were optimized, assuming that the equatorial bond lengths are less sensitive for the change in structure.[7] In order to save computer time, bond lengths and angles not involving the central sulfur atom were not optimized and standard values were taken from the literature.

All calculations were performed on a CDC Cyber 170/760 computer, using the program BIGMOL.[16,35]

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(27) Melting points were determined by using a Mettler FP1 apparatus. ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R24B high-resolution spectrometer. Me_4Si (δ 0) was used as an internal standard. IR spectra were taken on a Perkin-Elmer 257 spectrophotometer. Elemental analyses were performed by H. Draayer, J. Ebels, J. Hommes, and J. E. Vos of the analytical section of the Department.

(28) Details are available on request.

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(34) As indicated by one of the referees, the protocol followed for Ib does not allow for a structural deformation along the coordinates for Berry pseudo-rotation (BPR). However, on the basis of the data for II-IV listed in Table II, we suggest that high energies are involved in structural perturbations which result from BPR for Ib.

(35) The program has been written by B. T. Thole and P. T. van Duynen (University of Groningen) and has been especially designed to perform calculations on large molecules.

Methylation of Lithioisobutyrophenone in Weakly Polar Aprotic Solvents. The Effect of Aggregation[1]

L. M. Jackman* and B. C. Lange

Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802. *Received January 30, 1981*

Abstract: The ratios (C/O) of C- and O-methylation of lithioisobutyrophenone in dioxolane and in dimethoxyethane have been determined over a wide temperature range and in the presence and absence of LiCl. Comparison of these results with those of earlier NMR studies has established that ion-pair aggregates are the true reactants. The effects of crown ethers, [2.1.1]cryptand, and hexamethylphosphoric triamide on both C/O and ^{13}C chemical shifts confirm these findings. The influence of the leaving group structure on rates and C/O has been established. Direct ESR evidence for the formation of a radical anion in the reaction of lithioisobutyrophenone with methyl *p*-nitrobenzenesulfonate is presented.

Enolate ions are ubiquitous intermediates in organic chemistry and are involved in many reactions of great synthetic utility. The factors controlling reactivity and product orientation in the reactions of these ambident anions with electrophiles have received wide attention.[2] Their behavior in aprotic solvents of high ionizing power (class C solvents[3]) is reasonably well understood[2,4] in terms

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