The Thorpe–Ingold Effect in the Intramolecular Carboxyl-Catalyzed Hydrolysis of Sulfonamides[1a]

Jan Jager,[1b] Teun Graafland,[1b] Henk Schenk,[1c] Anthony J. Kirby,[1d] and Jan B. F. N. Engberts*[1b]

Contribution from the Department of Organic Chemistry, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands, Department of Crystallography, University of Amsterdam, Nieuwe Achtergracht 166, 1018 WV Amsterdam, The Netherlands, and The University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England. *Received April 20, 1983*

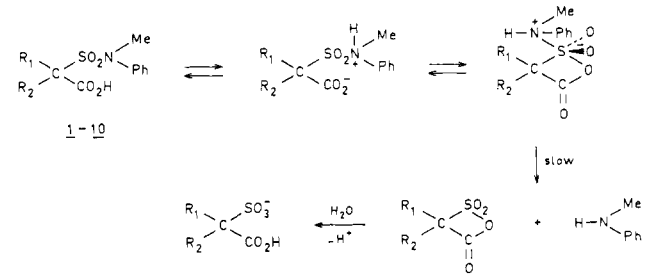
Abstract: Rate constants and thermodynamic activation parameters have been determined for the intramolecular carboxyl-catalyzed hydrolysis of a series of 1-mono- and 1,1-disubstituted carboxy-*N*-methyl-*N*-phenylmethanesulfonamides **1–10**. Alkyl and *gem*-dialkyl substituents favor the formation of the four-membered cyclic transition state. The effect increases with increasing number and size of the alkyl substituents and originates primarily from a decrease of $\Delta H^{\ddagger}$. X-ray structural data for four sulfonamides support an interpretation of the relative reactivities in terms of the Thorpe–Ingold effect. Two major factors are identified: (i) unfavorable non-bonding (van der Waals) interactions in the initial state which are partly relieved in the transition state and (ii) the decrease in ring strain during the activation process. Structural effects on the effective molarities are in accord with a mechanism involving intramolecular nucleophilic catalysis and in striking contrast with those in a related system involving intramolecular general base catalysis.

Studies of intramolecular processes are of considerable value in the elucidation of mechanistic aspects of many types of reactions and, perhaps still more important, in the quantitative analysis of the factors which determine the efficiency of enzymic catalysis.[2] The enormous rate enhancements commonly observed in intramolecular reactions[2d] allow the study of subtle aspects of reactions which normally only proceed under extreme conditions or with activated substrates. Our recent studies of the intramolecular carboxyl-catalyzed hydrolysis of sulfonamides have revealed dramatic rate enhancements which can be expressed in terms of high effective molarities (EM) of the carboxyl groups in the various substrates.[3] Several of the factors which determine these high EM's have been identified and analyzed. Furthermore, these studies have provided strong evidence for a mechanism involving nucleophilic substitution at sulfonyl sulfur via a pentavalent sulfur intermediate.[1a,3d]

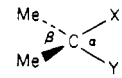
One of the most powerful methods for studying intramolecular-catalyzed reactions is by way of structure variation of the backbone which connects the substrate group and the catalytic group. In the present study we will examine the "*gem*-dialkyl effect" (also referred to as the "Thorpe–Ingold effect")[4] in a series of sulfonamides (**1**, $R_1 = R_2 = H$; **2**, $R_1 = H$, $R_2 = Me$; **3**, $R_1 = H$, $R_2 = Et$; **4**, $R_1 = H$, $R_2 = n\text{-}C_3H_7$; **5**, $R_1 = H$, $R_2 = i\text{-}C_3H_7$; **6**, $R_1 = H$, $R_2 = CH_2Ph$; **7**, $R_1 = H$, $R_2 = n\text{-}C_{16}H_{33}$; **8**, $R_1 = R_2 = Me$; **9**, $R_1 = R_2 = Et$; **10**, $R_1 = R_2 = n\text{-}C_3H_7$), which are all hydrolyzed by way of a four-membered cyclic transition state (Scheme I).[3d]

It has been recognized for many years that alkyl substitution promotes the formation or the "stability" of cyclic compounds.[4] This is demonstrated, for example, by the effect of *gem*-dimethyl substituents on the cyclization of alkanes to form cyclopentanes

Scheme I



or cyclohexanes in the gas phase.[5] The earliest explanation for such effects was given by Thorpe and Ingold,[4] who assumed that the *gem*-dimethyl groups would cause, by mutual repulsion, an increase in the angle β and a concomitant decrease in the angle α:



X-ray results have confirmed this effect, for instance, for malonic acid and dimethylmalonic acid.[6] If α is part of a small ring, this effect would result in ring stabilization. However, it has been shown that the effect is by no means confined to small rings[7] or to *gem*-dialkyl groups.[8] Therefore other explanations have been advanced. Bruice and Pandit[9] suggested restrictions in rotamer population in succinic acids to explain enhanced rates of ring closure upon *gem*-dialkyl substitution. The negative geminal effect on ring opening was explained in terms of steric hindrance to the approach of nucleophiles to the anhydride carbonyl group.[9] Similar arguments have been advanced to rationalize differences in rates of hydrolysis of some alkylated sultones.[8a] However, the very high rate enhancements observed in some systems upon alkyl substitution[8b] suggest that restrictions in rotamer population cannot be the sole origin of the *gem*-dialkyl effect. This is demonstrated, for example, by the high efficiency of the "trimethyl lock" in the

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Table I. First-Order Rate Constants and Thermodynamic Activation Parameters[a] for Hydrolysis of **1-10** in the Presence of 0.5 M HCl

compd	R_1	R_2	pK_a[b]	$k_{obsd} \times 10^5$,[c] s^{-1}	k_{rel}[c]	$k_{obsd} \times 10^5$,[d] s^{-1}	k_{rel}[d]	$\Delta G^{\ddagger}$,[e] kcal mol^{-1}	$\Delta H^{\ddagger}$,[e] kcal mol^{-1}	$\Delta S^{\ddagger}$,[e] eu
1	H	H	2.94	0.395	1	0.226	1	28.9	27.0	−6
2	H	Me	3.18	2.17	5.5	0.900	4.0	28.1	29.1	3.5
3	H	Et	3.24	2.19	5.5	0.712	3.2	28.0	28.3	1
4	H	*n*-Pr	3.34	1.94	4.9	1.03	4.6	27.6	25.0	−9
5	H	*i*-Pr	3.43	4.43	11.3	1.40	6.2	27.1	25.4	−6
6	H	CH_2Ph	3.43	1.26	3.2	0.665	3.0	28.2	27.4	−2
7	H	*n*-$C_{16}H_{33}$	3.55			1.37[f]	6.1			
8	Me	Me	3.57	17.4	44.1	5.00	22.1	26.4	26.2	−1
9	Et	Et	3.98	95.4	242	13.8	61.7	25.2	24.6	−2
10	*n*-Pr	*n*-Pr	3.82	133	335	13.6	60.3	25.0	24.4	−2

[a] Extrapolated to 25 °C. [b] At 50 °C in 1:1 (v/v) EtOH-H_2O, ionic strength 1.0 M (NaCl). [c] In H_2O at 75 °C (UV method). [d] In 1:1 (v/v) EtOH-H_2O at 75 °C (NMR method). [e] In H_2O. [f] UV method.

lactonization of some 3-(2-hydroxyphenyl)propionic acids.[10,11] In the sterically crowded "trimethyl acid" unfavorable non-bonding van der Waals interactions are partly removed and partly converted into bonding interactions upon going to the transition state.[12,13]

The *gem*-dialkyl effect in the formation of cyclohexane from hexane has been discussed by Allinger and Zalkov.[14] Two contributions were identified: (i) Upon formation of cyclohexane from hexane there arise six additional gauche interactions whereas on ring closure of an alkyl-substituted hexane there are less than six. Hence, there is a reduction of the enthalpy of cyclization upon alkyl substitution. (ii) Alkyl substituents restrict rotation in the acyclic form and thus increase $\Delta S^{\ominus}$. Consequently, six-membered-ring formation is favored by alkyl substitution by a decrease of both the $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ terms. These types of effects have recently been analyzed by molecular mechanics calculations.[15]

Here we analyze rates and thermodynamic activation parameters for hydrolysis of the sulfonamides **1-10**. Differences in terms of efficiency of intramolecular catalysis are expressed in effective molarities of the carboxyl group. Our analysis of the structure–reactivity relationship is supported by X-ray structural data obtained for four sulfonamide substrates.

Results and Discussion

First-order rate constants (k_{obsd}) and thermodynamic activation parameters for the hydrolysis of **1-10** are listed in Table I, together with the measured pK_a's of the carboxyl group of each compound.

We have described the evidence that the hydrolysis of compound **1** involves intramolecular nucleophilic catalysis, by way of a four-membered cyclic intermediate (Scheme I).[3d] In particular, the efficiency of catalysis is far greater than observed for related reactions involving intramolecular general acid–base catalysis,[2d] and the near-zero entropy of activation is inconsistent with the involvement of a second molecule in the transition state. The strain involved in the formation of the four-membered ring is clearly reflected in the increased enthalpy of activation for the reaction of **1** compared with that of the homologous $(CH_2)_2$ compound,[3d] which reacts by way of a five-membered cyclic transition state. This strain is expected to be relieved by alkyl substitution at the central carbon atom, as discussed above, and we find that the rate constants for the hydrolysis of compounds **1-10** increase with increasing number and size of alkyl substituents, further supporting the case for the nucleophilic mechanism.

The largest difference in rate, a factor of 737 in water at 25 °C, is found between compounds **1** and **10**. The free energies of activation for the monosubstituted sulfonamides show a regular decrease with increasing bulk of the alkyl substituent (up to 1.8 kcal mol^{-1} for R = *i*-Pr). The only irregularity is observed for the monobenzyl-substituted compound (**6**), which is less reactive than expected. Possibly, the hydrogen-bonding network which stabilizes the polar transition state is disrupted more by a benzyl group than by a simple alkyl substituent.[16]

Table II. Selected Structural Features[a] and Reactivity of Sulfonamides **1**, **3**, **8**, and **9**

	R_1, R_2			
	H,H	H,Et	Me,Me	Et,Et
	Bond Angles, deg			
$R_1-C_2-R_2$			111.6	113.7
$S-C_2-C_1$	110.4	107.4	105.0	105.3
	Dihedral Angles, deg			
$S-C_2-C_1-O_1$	−85	−118	−83	−79
$S-C_2-C_1-O_2$	93	65	98	100
	Interatomic Distances, Å			
C_1-C_2	1.52	1.51	1.53	1.53
$S-C_2$	1.794	1.811	1.826	1.859
$S\cdots O_1$	2.72	2.67	2.62	2.58
	Relative Reactivities			
k_{rel} (H_2O, 75 °C)	1	5.5	44.1	242

[a] C_1, carbon of CO_2H; C_2, central carbon; O_1, hydroxyl oxygen of CO_2H; O_2, carbonyl oxygen of CO_2H.

The data in Table I demonstrate that the largest effects both on rates of hydrolysis and on the pK_a values are brought about by *gem*-dialkyl substitution. The decrease in $\Delta G^{\ddagger}$ originates predominantly from a decrease in $\Delta H^{\ddagger}$. This would suggest that relief of steric strain makes a significant contribution to the increase in the rate of hydrolysis upon alkyl substitution. In order to gain more insight into the changes in geometry of the sulfonamides upon alkyl substitution, X-ray structures were determined for **1**, **3**, **8**, and **9**. The most relevant data are shown in Table II. Inspection of these data reveals that the bond angles $S-C_2-C_1$ and bond lengths $S-C_2$ (which are involved in the four-membered cyclic transition state) exhibit a regular change upon alkyl substitution and correlate with the reactivity of the sulfonamides. As predicted by the Thorpe–Ingold rule,[4] the angle between the sulfonamido and carboxyl groups at the central carbon atom decreases upon alkyl substitution. The decrease amounts to 3.0° for a single alkyl group and 5.4° for two alkyl substituents. Rather surprising is the minor difference between the angles $S-C_2-C_1$

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(16) A rather similar irregularity has been observed previously: Bruice, T. C.; Bradbury, W. C. *J. Am. Chem. Soc.* **1965**, *87*, 4838, 4846, 4851. This case involves the rates of solvolysis of some 3-mono- and 3,3-disubstituted mono-*p*-bromophenyl glutarates. The feature was explained by invoking hydrophobic back-bonding of the phenyl substituent to the ester *p*-bromophenoxy group so as to increase the population of nonprofitable extended rotamers. This type of explanation does not apply for **6**, since hydrophobic back-bonding of the benzyl group with the *N*-phenyl group will hardly change the position of the sulfur atom with respect to the carboxyl group.

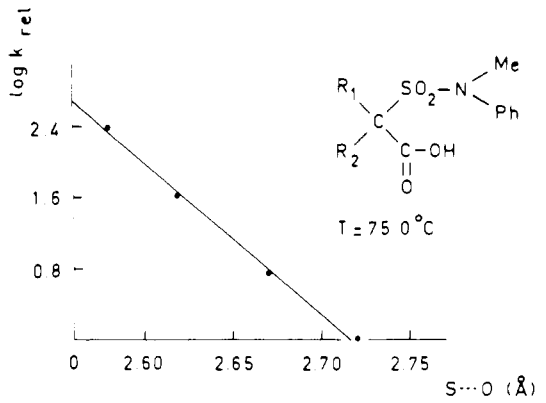
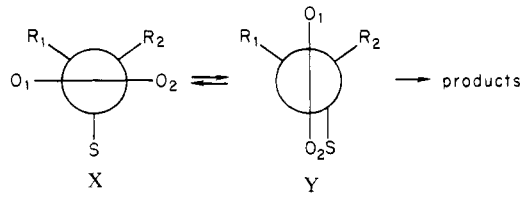


Figure 1. Plot of log k_{rel} vs. S···O_1 interatomic distance (data from Table II).

of sulfonamides **8** and **9**, although the rate of hydrolysis of **9** is much higher than that of **8**. This is remarkable, since the angle β between the two alkyl substituents at C_2 does show an increase (i.e., from 111.6 to 113.7°) upon going from **8** to **9**. Presumably, the S–C_2–C_1 angle has reached a minimum at 105° because of non-bonded repulsion between the sulfonamido and carboxyl groups.

Interestingly, the S–C_2 bond length increases upon alkyl substitution, probably also as a result of non-bonded repulsion[17] between the alkyl and carboxyl groups and the bulky sulfonamido group. There is only a small concomitant increase of the length of the C_1–C_2 bond, most likely because of the smaller size of the carboxyl group compared with the sulfonamido group and the slightly larger force constant for a C–C bond than for a C–S bond.[18] Although deformation of bond lengths is generally difficult,[19] the increase of the C_2–S bond length by 0.065 Å going from **1** to **9** is equivalent to an increase in energy[18] of about 1.0–1.5 kcal mol^{-1}. The changes in the S–C_2–C_1 bond angle and the S–C_2 bond length directly affect the S···O_1 interatomic distance (Table II). This is the closest distance of approach of O_1 to the sulfur atom, attained when the carboxyl group is rotated into the S–C_2–C_1 plane, as it must be for reaction. A reduction in this distance in the ground state will facilitate the formation of the S–O_1 bond, insofar as the free energy of the ground state is raised by the increased non-bonding interactions between the carboxyl and sulfonamido groups, because these are relieved in the cyclic transition state. It is clear that there is no possibility of incipient S–O_1 bond formation in the ground state, because the preferred conformation (X) about the C_1–C_2 bond of **1**, **3**, **8**, and **9** is almost exactly perpendicular to that (Y) required for ring formation.



X Y

It is likely that structural changes that reduce the interatomic distances between reacting centers will generally lead to enhanced rates of formation of small (3-, 4-, and 5-membered) rings. One of us has shown previously that the hydrolysis of a series of maleamic acids, which involves formation of a five-membered cyclic anhydride, is facilitated by alkyl substitution.[20] In that case also X-ray structural evidence showed marked changes in bond angles, which had the effect of bringing the reacting amide and carboxyl groups closer together in the ground states for the more reactive compounds.[6] So it is of interest to look for specific correlations between reactivity and structural parameters.

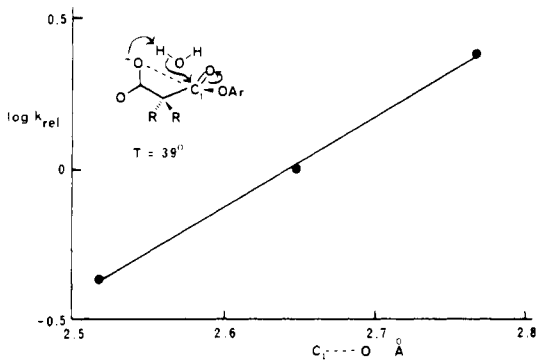


Figure 2. Plot of log k_{rel} vs. (minimum) C_1···O distance for a series of monoaryl malonates. Data from ref 6. In this case the crystallographic data are for the parent malonic acids, since the structures for the half esters are not available.

Table III. Effective Molarities for the Intramolecular Carboxyl-Catalyzed Hydrolysis of **1**–**10**

sulfonamide	α, deg	EM	EM[a] (ester)
1	110.4	5×10^5	25[b]
2		2×10^6	
3	107.4	2×10^6	
4		1×10^6	
5		2×10^6	
6		6×10^5	
7		6×10^5	
8	105.0	7×10^6	11[c]
9	105.3	2×10^7	0.3
10		4×10^7	

[a] From ref 6. [b] α(∠C_1–C_2–C_3) = 110°. [c] α(∠C_1–C_2–C_3) = 106.2°.

Remarkably, the simplest possible correlation, between the free energy of activation for hydrolysis and the interatomic distance S–O_1, is linear (Figure 1). In the absence of more, related data it is not possible to say whether the linearity of this plot is significant or fortuitous, though we note a similar linear relationship between log k_{hyd} for the cleavage of the C–OAr bond of a series of aryl tetrahydropyranyl acetals and the length of the bond being broken.[21] Most striking in the present case is the contrast between the plot of Figure 1 and the corresponding plot (Figure 2) for a related series of aryl malonate esters. The plot shown in Figure 2 shows a much lower sensitivity of reactivity to geometry and shows reactivity *decreasing* with decreasing interatomic distance (C_1···O). These differences clearly reflect the different mechanism of the hydrolysis of the malonate esters, which has been shown to involve intramolecular general base catalysis (Figure 2).[6] With crystallographic data now so readily accessible[22] this result suggests that correlations of the sort shown in Figures 1 and 2 may be worth investigating as a potential criterion of mechanism.

It seems clear that relative reactivities within the series **1**–**10** are not determined primarily by changes in unprofitable rotamer distribution.[9] There is no obvious reason why the conformation (X) about the C_1–C_2 bond favored in the solid state should not also be that preferred in solution. Decreasing the size of R_1 and R_2 should not, therefore, have a large effect on the rotamer distribution (particularly X ⇄ Y).

Taking into account the X-ray structural data for **1**, **3**, **8**, and **9**, we suggest that the increase in rate upon alkyl substitution at the central carbon atom of **1** can best be rationalized by invoking two major factors:[23] (a) unfavorable non-bonding (van der Waals)

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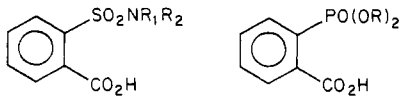
interactions in the *initial state*, which are partly relieved in the transition state, and (b) the decrease in ring strain in the *transition state*. Further support for steric crowding in the initial state is provided by the fact that attempts to synthesize the diisopropyl-substituted sulfonamide gave only the monoisopropyl compound (**5**). Apparently, introduction of a second isopropyl group at C_2 is severely hindered by strong non-bonded interactions with the sulfonamido and carboxyl groups.

Estimated effective molarities (EM's) for the carboxyl groups of compounds **1–10** are given in Table III. Since the corresponding intermolecular reactions are too slow to measure, accurate EM's cannot be calculated. A previous estimate[24] of the EM for the carboxyl group of sulfonamides (**11**) assumed the value (3×10^6 M) obtained for the similar reaction of the corresponding phosphonates (**12**). Various alternative assumptions all give



11 12

estimates in the region of 10^6 M, so we have based our estimates of EM for the reactions of **1–10** on this crude value (10^6 M) for the EM of the carboxyl group of **11**.[25] In three cases the EM values can be compared with those for the intramolecular general base catalyzed hydrolysis of the corresponding carboxylic esters.[6] The much larger values,[24] and the wide range of EM's observed for the reactions of the sulfonamides are in agreement with the previous conclusion[3] that the hydrolysis of the sulfonamides proceeds by intramolecular nucleophilic catalysis. In the intramolecular general base catalyzed reaction of the monoaryl malonates[6] a water molecule has to be incorporated in the transition state (Figure 2) between the ester and carboxyl groups.[26] It appears that this is less favorable the smaller the angle between them, so that the EM *decreases* in this case.

The EM values for the reactions of **1–10** are remarkably high for reactions which go through a four-membered cyclic transition state but are nevertheless consistent with direct nucleophilic attack by the carboxylate ion on sulfur. Previous ab initio MO calculations[1a] have shown that the optimum angle at S is ca. 81°, and this, together with the extra length of the C–S bond, accounts for the relative stability of four-membered rings containing sulfur.

Experimental Section

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

Synthesis. The synthesis of **1** has been reported previously.[3c]

1-(Ethylcarboxy)-*N*-methyl-*N*-phenyl-1-ethanesulfonamide (15). (Ethylcarboxy)-*N*-methyl-*N*-phenylmethanesulfonamide[3c] (3.0 g, 11.7 mmol) was dissolved in 25 mL of DMF. To this mixture 0.66 g (11.7 mmol) of KOH was added. Thereupon, 1.7 g (1 equiv) of methyl iodide, dissolved in 25 mL of DMF, was added. This mixture was stirred for 15 h at 60 °C. After the mixture was cooled to room temperature 75 mL of water was added, and the aqueous layer was extracted three times with 75 mL of chloroform. The combined $CHCl_3$ layers were extracted with 100 mL of water. After evaporation of the solvent a yellow oil was obtained. The oil was dissolved in 50 mL of carbon tetrachloride and extracted with 50 mL of water. The tetra layer was dried over $MgSO_4$, and after evaporation of the solvent the crude sulfonamide **15** (2.6 g, 83%) was obtained. NMR ($CDCl_3$): δ 1.3 (t, 3 H), 1.55 (d, 3 H), 3.35 (s, 3 H), 4.0 (q, 1 H), 4.2 (q, 2 H), 7.35 (m, 5 H).

1-Carboxy-*N*-methyl-*N*-phenyl-1-ethanesulfonamide (2). The crude sulfonamide (**15**) was dissolved in 25 mL of ethanol at 60 °C. Thereupon, the maximum amount of 1 N NaOH was added, which did not precipitate the ester. This mixture was stirred for 20 h at 60 °C. After the mixture was cooled to 0 °C, 50 mL of water and 75 mL of dichloromethane were added. After separation of the two layers, the aqueous layer was acidified with 2 N HCl solution until pH <1. The aqueous layer was extracted two times with 75 mL of dichloromethane. The combined dichloromethane layers were dried over $MgSO_4$. After evaporation of the solvent the crude acid was obtained. Crystallization from $CHCl_3$–pentane yielded pure 1-carboxy-*N*-methyl-*N*-phenyl-1-ethanesulfonamide (**2**) (1.9 g, 83%): mp 97.4–98.0 °C; NMR ($CDCl_3$) δ 1.6 (d, 3 H), 3.35 (s, 3 H), 4.0 (q, 1 H), 7.35 (m, 5 H), 10.4 (s, 1 H); IR (KBr) 1140 and 1345 (-SO_2-) and 1735 cm^{-1} (C=O). Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76; S, 13.18. Found: C, 49.23; H, 5.41; N, 5.71; S, 13.09.

1-Carboxy-*N*-methyl-*N*-phenyl-1-propanesulfonamide (3). For the alkylation of **15** with ethyl iodide and the saponification of the ester, a similar procedure was followed as described for **2**. Crystallization from $CHCl_3$–pentane yielded **3** (overall yield 1.0 g, 35%): mp 114.0–115.5 °C; NMR ($CDCl_3$) δ 1.0 (t, 3 H), 2.05 (q, 2 H), 3.3 (s, 3 H), 3.9 (t, 1 H), 7.3 (m, 5 H), 10.8 (s, 1 H); IR (KBr) 1140 and 1350 (-SO_2-) and 1710 cm^{-1} (C=O). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44; S, 12.46. Found: C, 51.21; H, 5.73; N, 5.52; S, 12.31.

1-Carboxy-*N*-methyl-*N*-phenyl-1-butanesulfonamide (4). For the alkylation of **15** with *n*-propyl iodide and the saponification of the ester a similar procedure was followed as described for **2**. The acid (1.4 g, 45%) could not be obtained as crystalline material. **4**: MS, M^+ 271 ($C_{12}H_{17}NO_4S$); NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.3 (m, 2 H), 2.0 (m, 2 H), 3.35 (s, 3 H), 4.0 (t, 1 H), 7.3 (m, 5 H), 10.5 (s, 1 H); IR (Nujol) 1140 and 1350 (-SO_2-) and 1725 cm^{-1} (C=O).

1-Carboxy-2-methyl-*N*-methyl-*N*-phenyl-1-propanesulfonamide (5). For the alkylation of **15** with 3 equiv of isopropyl iodide and the saponification of the ester, the same procedure was followed as for **2**. The acid (1.6 g, 49%) was crystallized from $CHCl_3$–pentane. **5**: mp 83.4–83.7 °C; NMR ($CDCl_3$) δ 1.05 (d, 6 H), 2.55 (m, 1 H), 3.35 (s, 3 H), 3.85 (d, 1 H), 7.3 (m, 5 H), 10.95 (s, 1 H); IR (KBr) 1145 and 1350 (-SO_2-) and 1700 cm^{-1} (C=O); MS, M^+ 271 ($C_{12}H_{17}NO_4S$).

1-Carboxy-2-phenyl-*N*-methyl-*N*-phenyl-1-ethanesulfonamide (6). For the alkylation of **15** with benzyl bromide and the saponification of the ester, a similar procedure was followed as for **2**. The acid (2.0 g, 55%) could not be obtained as crystalline material. **6**: MS, M^+ 319 ($C_{16}H_{17}NO_4S$); NMR ($CDCl_3$) δ 3.25 ("s", 2 + 3 H), 4.25 (t, 2 H), 7.2 (m, 10 H), 11.0 (s, 1 H); IR (Nujol) 1145 and 1360 (-SO_2-) and 1730 cm^{-1} (C=O).

1-Carboxy-*N*-methyl-*N*-phenyl-1-heptadecanesulfonamide (7). The alkylation of **15** with cetyl iodide was carried out as described for **2**. The workup procedure was as follows. The solvent was evaporated after cooling of the mixture. The product was crystallized once from absolute ethanol and was used immediately for saponification. This was carried out as described for **2**. During the reaction a precipitate was formed, which was filtered off. The filtrate was acidified with 2 N HCl solution until pH <1 and the acid precipitated. The acid (0.4 g, 23%) was filtered off and dried in the air. The mass spectrum showed that the acid was contaminated with ca. 7% of the ester. **7**: MS, M^+ 453 (93%, $C_{25}H_{43}NO_4S$) and M^+ 481 (7%, $C_{27}H_{47}NO_4S$); NMR (CD_3CD_2OD) δ 0.9–2.0 (m, 33 H), 3.35 (s, 3 H), 3.85 (m, 1 H), 5.1 (s, 1 H), 7.3 (m, 5 H); IR (KBr) 1150 and 1350 (-SO_2-) and 1725 cm^{-1} (C=O).

2-Carboxy-*N*-methyl-*N*-phenyl-2-propanesulfonamide (8). For the alkylation of **15** with 4 equiv of methyl iodide and 2 equiv of KOH and the saponification of the ester, a similar procedure was followed as described for **2**. The acid **8** (2.2 g, 73%) was crystallized from $CHCl_3$–pentane. **8**: mp 92.6–93.0 °C; NMR ($CDCl_3$) δ 1.6 (s, 6 H), 3.35 (s, 3 H), 7.3 (m, 5 H), 11.0 (s, 1 H); IR (KBr) 1120 and 1340 (-SO_2-) and 1700 cm^{-1} (C=O). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44; S, 12.46. Found: C, 51.16; H, 5.80; N, 5.31; S, 12.60.

3-Carboxy-*N*-methyl-*N*-phenyl-3-pentanesulfonamide (9). The alkylation of **15** with 3 equiv of ethyl iodide and the saponification of the ester were carried out as described for **2**. The acid (2.3 g, 69%) was crystallized from CCl_4–pentane. **9**: mp 92.0–92.7 °C; NMR ($CDCl_3$) δ 0.95 (t, 6 H), 2.15 (q, 4 H), 3.3 (s, 3 H), 7.35 (m, 5 H), 10.6 (s, 1 H); IR (KBr) 1155 and 1350 (-SO_2-) and 1700 cm^{-1} (C=O). Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91; S, 11.24. Found: C, 54.59; H, 6.74; N, 4.98; S, 11.21.

4-Carboxy-*N*-methyl-*N*-phenyl-4-heptanesulfonamide (10). The alkylation of **15** with 3 equiv of *n*-propyl iodide and the saponification of the ester were carried out as described for **2**. The acid **10** (0.9 g, 25%)

(23) Differences in pK_a's for the various sulfonamides can be only partly responsible for the different rate constants. Since differences in polar effects for the various alkyl groups can be neglected to a first approximation, we suggest that the varying pK_a's reflect different solvation behavior of the anions. Assuming a β value for the carboxyl group of 0.72,[1a] the difference in pK_a of 0.88 between **1** and **10** would be reponsible for a difference in rate constant of a factor of only 4 (the observed k_{rel} is 737). Therefore, this effect does not seriously affect the explanation in terms of strain in the initial and transition state.

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was crystallized from $CHCl_3$–pentane. **10**: mp 105.5–106.0 °C; NMR ($CDCl_3$) δ 0.9 (t, 6 H), 1.3 (m, 4 H), 2.0 (m, 4 H), 3.3 (s, 3 H), 7.35 (m, 5 H), 7.9 (s, 1 H); IR (KBr) 1150 and 1350 (-SO_2-) and 1695 cm^{-1} (C=O). Anal. Calcd for $C_{15}H_{23}NO_4S$: C, 57.48; N, 7.40; N, 4.47; S, 10.23. Found: C, 57.12; H, 7.35; N, 4.54; S, 10.52.

pK_a Measurements. The pK_a's of the sulfonamides have been determined by potentiometric titration in 1:1 (v/v) EtOH–H_2O at an ionic strength of 1.0 M (NaCl). Employing the procedure given by de Ligny et al.,[27] we substracted a quantity δ from the meter readings to afford corrected pK_a values in order to account for the differences in the pH scale in water and the mixed aqueous solution. The general method for the determination of the pK_a was as follows. Carboxylic acid (ca. 40 mg) was dissolved in ca. 50 mL of 1:1 EtOH–H_2O at an ionic strength of 1.0 M (NaCl) at 50.0 °C. In order to exclude CO_2 absorption of the solvent all measurements were carried out under a N_2 atmosphere. The pH of the solution was measured by a KCl electrode and reproduced on a recorder. The pH meter and the recorder were calibrated by means of two buffer solutions of pH 4.0 and 7.0. Thereupon, a constant flow of a 0.1 N NaOH solution was added until pH >10, while the change of the pH with time was followed by the recorder. The pK_a of the carboxylic acid could be calculated directly from the sigmoid curve obtained. All measurements were carried out in duplicate or in triplicate. The reproducibility was within 0.03 pK_a unit.

Kinetic Measurements. The rates of hydrolysis were determined by following the decrease in absorption at a suitable wavelength in the UV spectrum (method A) or by following the decrease and the increase of the *N*-phenyl (or *N*-methyl) peak of the sulfonamide and the amine, respectively, in the NMR spectrum (method B). The accuracy of method A is higher than that of method B. Because of the low solubility of **7**, the rate of hydrolysis could only be measured in 1:1 (v/v) EtOH–H_2O. Usually the k_{obsd} values obtained by method B are a factor of 1.5–2 smaller than those determined by method A. Most likely, the relatively high concentration of the substrate (ca. 0.4 M) brings about a change in the properties of the reaction medium which leads to this difference.

Method A. The rates of hydrolysis were determined by monitoring the change in absorbance at 234 nm. The procedure was given previously.[3] Initial concentrations were ca. 4×10^{-5}–10^{-4} M. The k_{obsd} values were reproducible to within 2%.

Method B. The rate of hydrolysis was determined by monitoring the disappearance and the appearance of the *N*-phenyl (*N*-methyl)peak of the sulfonamide and of *N*-methylaniline, respectively, in the NMR spectrum as a function of time. The NMR tube was filled with 40 mg of the sulfonamide and 0.4 mL of the 1:1 (v/v) EtOH–H_2O solution (containing 0.5 N HCl) and sealed. The sulfonamide was dissolved by stirring and heating, whereupon the tube was placed immediately in a thermostated Haake F3 oil bath (±0.05 °C). At least three NMR spectra were taken per half-life. The period necessary for recording one NMR spectrum was about 1.5 min, which could be neglected in view of the long half-lives of the reactions. The concentration of unreacted sulfonamide could be calculated from the intensities of the two *N*-phenyl peaks (which are singlets in 1:1 (v/v) EtOH–H_2O). The k_{obsd} value could be obtained from the slope of the plot of ln [sulfonamide] vs. time. Measurements were taken up to at least 85% conversion of the sulfonamide into the sulfonic acid and *N*-methylaniline. The k_{obsd} values were reproducible to within 3–4%.

Solvents. The water used in the kinetic measurements was demineralized and distilled twice in an all-quartz distillation unit. The ethanol was of the highest grade available (Merck).

Thermodynamic Activation Parameters. For all sulfonamides the temperature dependence of the rate constant for hydrolysis (k_{obsd}) was determined at at least four temperatures over a temperature range of at least 14° within the range 50–70 °C (method A). Since the reproducibility of the k_{obsd} values was within 2%, the estimated errors are 0.02 kcal mol^{-1} in $\Delta G^{\ddagger}$, 0.3 kcal mol^{-1} in $\Delta H^{\ddagger}$, and 1 eu in $\Delta S^{\ddagger}$. For method B, the reproducibility of the k_{obsd} values was in all cases 4%.

X-ray Structural Determinations. Full details for the sulfonamides **1**, **3**, **8**, and **9** will be published elsewhere.[28]

Registry No. 1, 7117-20-6; **1** ethyl ester, 87712-30-9; **2**, 87712-31-0; **3**, 87712-32-1; **4**, 87712-33-2; **5**, 87712-34-3; **6**, 87712-35-4; **7**, 87712-36-5; **8**, 72519-81-4; **9**, 75599-75-6; **10**, 87712-37-6; **15**, 87712-38-7.

Supplementary Material Available: Tables with bond lengths, bond angles, and dihedral angles for the sulfonamides **1**, **3**, **8**, and **9** (4 pages). Ordering information is given on any current masthead page.

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Correlation of Nonadditive Kinetic Effects with Molecular Geometries. Structure and Reactivity of Alkyl- and Cycloalkenylpyridines[1]

Jeffrey I. Seeman,*[2a] Jimmy W. Viers,*[2b] John C. Schug,*[2b] and Michael D. Stovall[2b]

Contribution from the Philip Morris Research Center, Richmond, Virginia 23261, and the Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061. *Received April 8, 1983*

Abstract: The hypothesis that ground-state geometries can be used to quantify chemical reactivity is examined by evaluating a variety of geometrical parameters and steric congestion models for the methylation of a wide series of alkylpyridines. The ground-state minimum energy conformations of these pyridines were determined by using MINDO/3 semiempirical all-valence electron calculations. Nonadditive kinetics were observed for a series of 2,3-dialkylpyridines compared with the analogous 2,5-dialkylpyridines; correlations are found between the nonadditive portion of the rates of alkylation of these pyridines and both the N–C_2–C_{2_α} angle and d_{NH}, the distance between the pyridine nitrogen and the closest C_{2_α}-hydrogen atom. Long-range buttressing effects on reactivity were quantified by geometry modeling of the reactivity of 3,5-dialkylimidazo[1,2-*a*]pyridines. Steric substituent constants, $S°$, were derived on the basis of the Brønsted relationship for the pyridines bearing at least one C_{2_α} substituent. A geometric accessibility factor for the nitrogen in pyridines was developed and correlated with $S°$. This accessibility factor represents the free solid angle about a point 1.75 Å from the pyridine nitrogen along the C_4–N axis and in the pyridine ring plane. Another model based on overlapping van der Waals radii of substituents was evaluated; this latter model had previously been developed by Sternhell to predict the energy barriers for an intramolecular process, namely biphenyl ring–ring rotation. It was shown that the model works equally well for the intermolecular alkylation reaction. The relationships between nonadditive kinetics, buttressing effects, and the various steric substituent parameters and models are discussed in detail.

The correlation of molecular structure with chemical reactivity is a fundamental objective in organic chemistry. For the last forty years, the Hammett equation has played a well-deserved central role in determining structure–reactivity relationships for a wide

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