Structure and Reactivity in Intramolecular Catalysis. Catalysis of Sulfonamide Hydrolysis by the Neighboring Carboxyl Group[1a]

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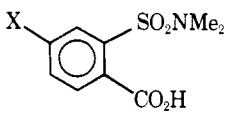
Abstract: This paper reports kinetic data for the intramolecular carboxyl-catalyzed hydrolysis of 26 sulfonamides in water and in some mixed aqueous solvents. The effective molarity of the carboxyl group is very high (up to ca. 10^8 M) but depends markedly on the structure of the sulfonamide. Substituent effects within a series of 4- and 5-substituted 2-carboxy-*N*,*N*-dimethylbenzenesulfonamides are interpreted in terms of nucleophilic catalysis with breakdown of the pentacovalent intermediate **18** rate determining. The role of nonbonded interactions in the initial state and in the transition state is discussed. By using X-ray structural data where available, strain effects have been elucidated for a series of sulfonamides in which the sulfonamide and carboxyl groups are held cis to each other. Striking differences from the corresponding carboxamide systems are attributed to differences in transition state geometries and steric effects. A "*gem*-dimethyl effect" is found in the hydrolysis of **14**. Relative rates within a series of compounds with a variable carbon chain between the sulfonamide and carboxyl groups reflect entropic factors. The results indicate a clear preference for the formation of a five-membered cyclic transition state. Solvent effects on thermodynamic parameters of activation are analyzed for some highly aqueous mixed solvents taking into account the unique solvent properties of water. In *t*-BuOH–H_2O effects originating from hydrophobic hydration give rise to mirror-image behavior of $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$.

Recent studies on intramolecular catalysis have provided considerable insight into the complex factors which determine the efficiency of enzyme-catalyzed reactions.[2] In model studies, special attention has been paid to the hydrolysis of esters,[3] phosphates,[4] and amides[5] since these substrates are of particular biological importance. Many of these results[6] have been discussed in connection with the related biological transformations in a scholarly review.[2b] Apart from their obvious biochemical interest, these investigations have revealed interesting mechanistic pathways in intramolecular catalysis.[7]

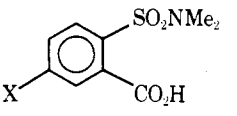
In our recent studies,[1,8] we have examined a relatively simple hydrolytic process: the cleavage of the S–N bond in sulfonamides catalyzed by a neighboring carboxyl group. Since the Hinsberg reaction was discovered,[9] the *inter*molecular acid-catalyzed hydrolysis of sulfonamides has been used frequently despite the severe conditions necessary.[10] It is assumed that hydrolysis proceeds via reversible protonation of the sulfonamide nitrogen atom,[10a,11] followed by a concerted displacement at sulfonyl sulfur with water acting as the nucleophile.[12] This mechanism is consistent with results obtained for other nucleophilic substitution reactions at sulfonyl sulfur.[12,13] In none of the cases studied so far, has a stepwise process, by way of a penta-coordinated intermediate, appeared to be involved as evidenced by, inter alia, Hammett ρ values[13] and Brønsted β values.[12]

Our previous results[8] have shown that intramolecular carboxyl-catalyzed sulfonamide hydrolysis is characterized by effective concentrations[2c] of the COOH group of the order of 10^8 M. We report here an analysis of several of the factors which affect the efficiency of the intramolecular reaction. Systems which have been examined include the sulfonamides **1–14.** Substituent effects on the rate of the pH-independent hydrolysis within the series **1–3** led us to propose an intermediate with a pentacoordinated sulfur atom on the reaction coordinate of the intramolecular catalyzed reaction. Sulfonamides **4–6** were selected to probe the steric requirements of the protonated leaving group in the apical position at sulfonyl sulfur. Compounds **4** and **5** place significantly different constraints on the direction of departure of the leaving group. As a result, either initial state or transition state strain becomes the dominant factor in determining the relative rates of hydrolysis. Factors such as steric strain[5c] and the degree of rotational freedom[14] affect the hydrolysis of the sulfonamides **7–14.** Very large differences in rate were found. The interpretation in terms of sulfonamide geometry was facilitated by the determination of crystal and molecular structures for several systems. Finally, rates and activation parameters for the hydrolysis of **7** and **11** in highly aqueous *t*-BuOH–H_2O demonstrate a remarkable sensitivity toward changes in hy-



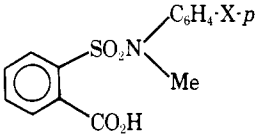
1

a, X = MeO
b, X = Me
c, X = H
d, X = F
e, X = NO_2



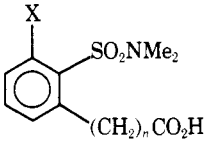
2

a, X = MeO
b, X = *t*-Bu
c, X = F
d, X = NO_2

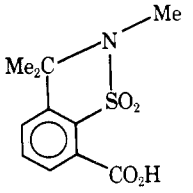


3

a, X = MeO
b, X = H
c, X = NO_2



4a, *n* = 0, X = Me
4b, *n* = 0, X = *t*-Bu
5a, *n* = 1, X = H
5b, *n* = 1, X = Me
5c, *n* = 1, X = *t*-Bu



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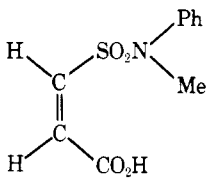

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Table I. First-Order Rate Constants (k_{obsd}) for Hydrolysis of Sulfonamides **1, 2,** and **3** at 75 °C

compd	X	pK_A[a]	medium	$k_{obsd} \times 10^5$, s^{-1}
1a	MeO	3.90	0.97 M HCl[b]	54.7
1b	Me	3.75	0.97 M HCl[b]	33.7
1c[c]	H	3.67	0.97 M HCl[b]	25.0
1d	F	3.55	0.97 M HCl[b]	24.3
1e	NO_2	3.04	0.97 M HCl[b]	3.1
2a	MeO	3.61	0.97 M HCl[b]	33.0
2b	*t*-Bu	3.75	0.97 M HCl[b]	41.0
2c	F	3.32	0.97 M HCl[b]	15.0
2d	NO_2	3.20	0.97 M HCl[b]	4.2
3a[d]	MeO	3.74	50% EtOD-D_2O (v/v), 0.356 M DCl[e]	1.45
3b[f]	H	3.63	50% EtOD-D_2O (v/v), 0.356 M DCl[e]	1.29
3c	NO_2	3.62	50% EtOD-D_2O (v/v), 0.356 M DCl[e]	0.25

[a] At 25.0 °C in 50% EtOH-H_2O (v/v) and ionic strength 1.0 M (NaCl). [b] Ionic strength 1.0 M (NaCl). [c] $\Delta H^{\ddagger} = 20.9 \pm 0.3$ kcal mol^{-1}; $\Delta S^{\ddagger} = -15 \pm 1$ eu, 25 °C. [d] $k(D_2O)/k(H_2O) = 1.31$ [e] Ionic strength 1.1 M (NaCl). [f] $k(D_2O)/k(H_2O) = 0.78$.

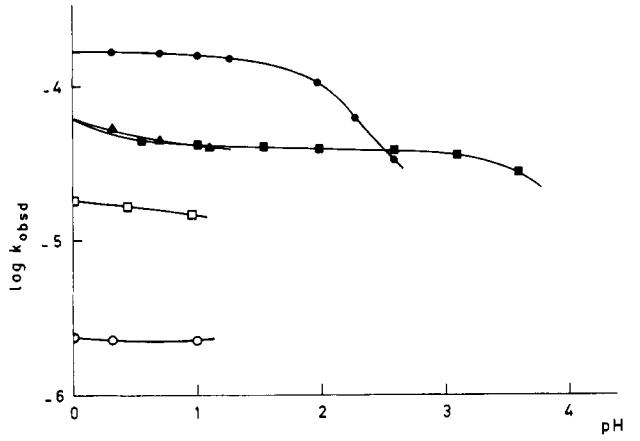
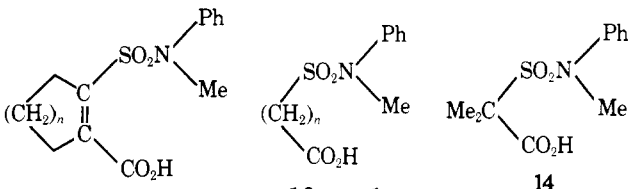


Figure 1. pH-rate profiles (k_{obsd} in s^{-1}) for hydrolysis of five sulfonamides: (□) **3a** in 50% (v/v) EtOH-H_2O at 75 °C; (●) log $k_{obsd} - 1$ vs. pH for **7** in H_2O at 40 °C; (▲) **9** in H_2O at 75.4 °C; (○) **10** in 50% (v/v) EtOH-H_2O at 75 °C; (■) **11** in H_2O at 49.5 °C.



8, $n = 1$
9, $n = 2$

10, $n = 1$
11, $n = 2$
12, $n = 3$
13, $n = 4$

14

drophobic hydration,[15] a feature which is also of particular interest with respect to enzyme-catalyzed reactions.[16]

Results

First-order rate constants (k_{obsd}) for the intramolecular COOH-catalyzed hydrolysis of the sulfonamides **1a–e, 2a–d,** and **3a–c** are listed in Table I, together with their pK_A values. Typical log k_{obsd}-pH profiles have been given previously for **1c** and **7**[8] and indicate intramolecular catalysis by the COOH group. Several such plots are shown in Figure 1. The curves fit eq 1

$$k_{obsd} = (k_{H_2O} + k_{H^+}[H^+])(1 + K_A/[H^+])^{-1} \quad (1)$$

for acidities below pH 7, where k_{H_2O} is the rate constant for the pH-independent hydrolysis of the undissociated substrate, k_{H^+} is the second-order rate constant for the specific-acid catalyzed hydrolysis of the undissociated substrate and K_A is the apparent dissociation constant of the carboxyl group.

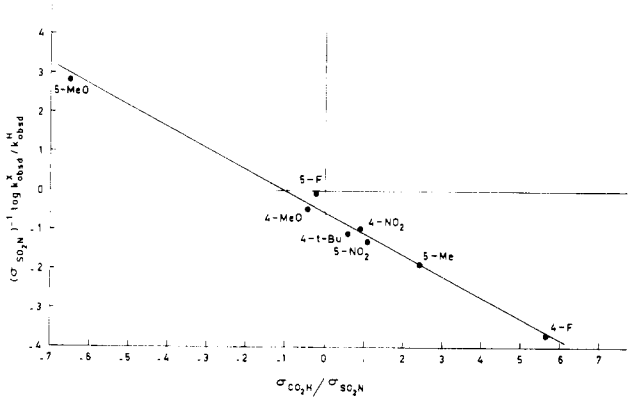


Figure 2. Extended Hammett plot of the rate data for the sulfonamides **1a–e** and **2a–d** (Table I) at 75 °C in 0.97 M HCl and ionic strength 1.0 M.

Previous work[8] has shown the absence of general acid catalysis in the hydrolysis of **7.**

Substituent effects within the series **1** and **2** were analyzed by using Jaffé's extended Hammett equation[17]

$$\log k^X/k^H = \rho_1\sigma_1 + \rho_2\sigma_2 \quad (2)$$

which has been used previously for intramolecular reactions.[3b,17c] In this case ρ_1 and ρ_2 refer to the effects of the substituent (X in **1, 2**) on the sulfonamide and CO_2H groups, respectively, and σ_1 and σ_2 are the appropriate substituent constants for X. (Thus, σ_{SO_2N} is σ_m^X for **1,** σ_p^X for **2,** etc.). Recast as the equation of a straight line, eq 2 becomes:

$$1/\sigma_{SO_2N} \log k^X_{obsd}/k^H_{obsd} = \rho_{SO_2N} + (\sigma_{CO_2H}/\sigma_{SO_2N})\rho_{CO_2H}$$

A plot of $(\sigma_{SO_2N})^{-1}$ log k^X_{obsd}/k^H_{obsd} vs. $\sigma_{CO_2H}/\sigma_{SO_2N}$ (Figure 2) gives $\rho_{SO_2N} = -0.58 \pm 0.01$ and $\rho_{CO_2H} = -0.54 \pm 0.02$ ($r^2 = 0.989$). Note that electron-donating substituents para to either the COOH or the sulfonamide group accelerate the reaction.

The pK_A values of compounds **1a–e** and **2a–d** are satisfactorily correlated by the simple Hammett relationship. For **1a–e,** pK_A's are linear in σ_p ($\rho = -0.79$; $r^2 = 0.987$), for **2a–d,** pK_A's correlate with σ_m ($\rho = -0.70$; $r^2 = 0.942$). Comparison with the pK_A of benzoic acid (4.21, H_2O, 25 °C)[18] demonstrates the electron-attracting properties of the sulfonamide function.

The rate data for **3a–c** illustrate the modest electronic effects on amine leaving ability in the *N*-aryl-substituted sulfonamides ($\rho = -0.76 \pm 0.10$). Table II summarizes pK_A's and k_{obsd}

Table II. First-Order Rate Constants (k_{obsd}) for Hydrolysis of the Sulfonamides **1c** and **4–6** at 75 °C in 0.97 M HCl and Ionic Strength[a] 1.0 M

compd	pK_A[b]	$k_{obsd} \times 10^5$, s^{-1}	k_{rel}[c]
1c	3.67	25.0	1
4a	3.80	0.105	4.2×10^{-3}
4b	4.34	0.40	1.6×10^{-2}
5a	4.88	0.33	1.3×10^{-2}
5b	5.13	2.3	9.2×10^{-2}
5c	5.33	5.6	2.2×10^{-1}
6	3.64	1.62	6.4×10^{-2}
6[d]	3.64	5.77	[e]

[a] NaCl. [b] At 25 °C in 50% (v/v) EtOH–H_2O and ionic strength 1.0 M (NaCl). [c] $k_{rel} = k_{obsd}/k_{obsd}$ (**1c**). [d] 1.04 M DCl in D_2O at 75 °C. [e] $k_{obsd}^{D_2O}/k_{obsd}^{H_2O} = 3.6 \pm 0.2$.

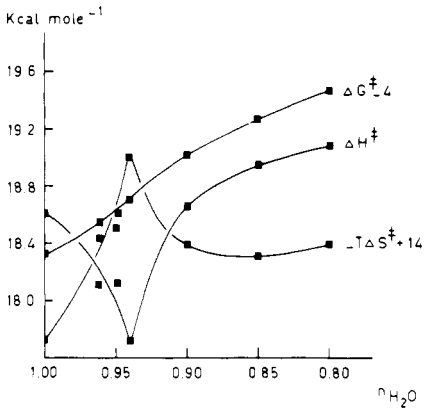


Figure 3. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the intramolecular carboxyl-catalyzed hydrolysis of **7** in *t*-BuOH–H_2O at 25 °C.

values for **4a–b, 5a–c,** and **6.** In the final column, the rate constants are expressed relative to that of **1c.** Table III lists pK_A's, rate constants, thermodynamic parameters of activation, and solvent deuterium isotope effects for the hydrolysis of **7–14,** in water and in some mixed aqueous solvent systems. Sulfonamide **7** is by far the most reactive of the structurally closely related sulfonamides **7–9:** the effective molarity of the carboxyl group has been estimated previously[8b] to be about 10^8. Since the reactivity of **7** prevented the experimental determination of its pK_A, this was derived from the log k_{obsd}–pH plot at 40 °C. The solvent dependence of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for the hydrolysis of **7**[1a] and **11** in highly aqueous *t*-BuOH–H_2O is portrayed in Figures 3 and 4, respectively. Relative rate constants within the series **10–13** are listed in Table IV. The k_{rel}^{cor} constants refer to rate constants corrected for the increase in rotational freedom from extending the carbon chain between the functional groups, assuming 4 eu per degree of rotational freedom, according to Page and Jencks.[19]

Since the rate of intramolecular COOH-catalyzed hydrolysis of sulfonamides depends critically on substrate geometry, crystal and molecular structures were determined for **7** (methyl ester), **8, 10,** and **11.** The most relevant bond lengths and bond angles are shown in Figure 5. In these studies, the methyl ester **15** derived from **7** was employed because of the high reactivity of the carboxylic acid. Full crystallographic details will be published elsewhere.

Finally, thermodynamic parameters for the acidity constants of **8** and **10–12** are listed in Table V. The data illustrate the interplay of enthalpy and entropy effects in the variation of the pK_A as a function of the structure of the sulfonamide.

Discussion

Mechanism. The acid-catalyzed hydrolysis of sulfonamides normally proceeds only under extreme conditions.[10] A major

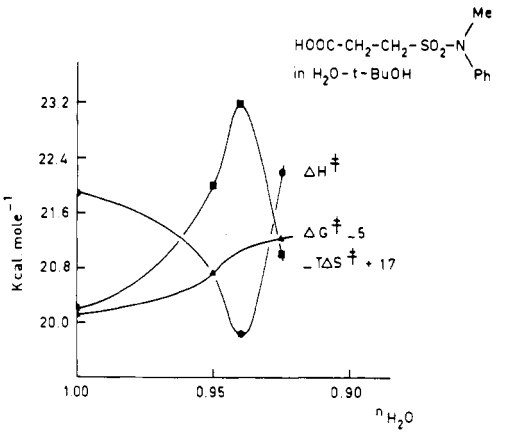


Figure 4. Plot of $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $-T\Delta S^{\ddagger}$ vs. n_{H_2O} for the intramolecular carboxyl-catalyzed hydrolysis of **11** in *t*-BuOH–H_2O at 25 °C.

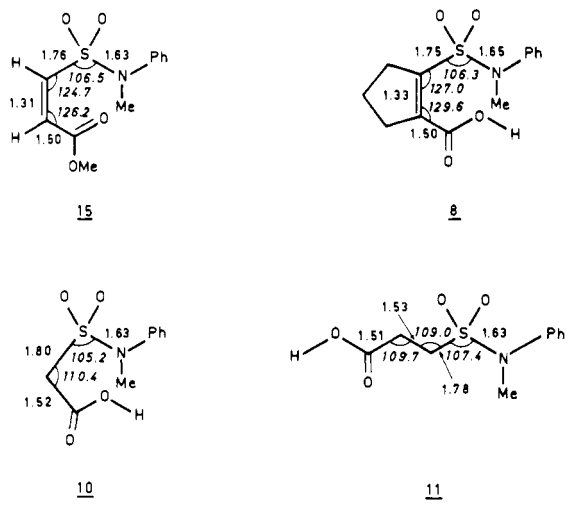


Figure 5. Bond lengths and bond angles in the sulfonamides **8, 10, 11,** and **15.**

reason for this lack of reactivity is the very low pK_A of the conjugate acids of this class of compounds[20] (in the region of −6, based on the H_0 scale). Since the reaction involves the protonated sulfonamide, strongly acidic media are required to obtain useful rates. There appears to be no doubt that protonation occurs on nitrogen,[21] although the sulfonyl oxygen atoms are presumed to be the preferred hydrogen-bond acceptor sites.[22] The alkylation of sulfonamides is apparently less site specific and may occur either on sulfonyl oxygen[23] or on nitrogen.[24]

The hydrolysis of sulfonamides **1–14** is catalyzed by the neighboring COOH group. This is evident from the pH–rate profiles (Figure 1), which show relatively very rapid pH-independent reactions in the region where the COOH group is fully protonated, and significant specific acid-catalyzed hydrolysis only in strong acid. (The measurements described in this paper were usually made in the pH-independent region between pH 0 and 1. Higher acid concentrations were avoided in order to reduce salt effects.[8]) The very high effective molarities of the carboxyl group (up to at least 10^8 M) and the observed solvent deuterium isotope effects (Table III and the footnotes in Table I) effectively rule out general acid–base catalysis mechanisms, and a mechanism involving nucleophilic catalysis by the carboxyl group seems certain.[7,8,25]

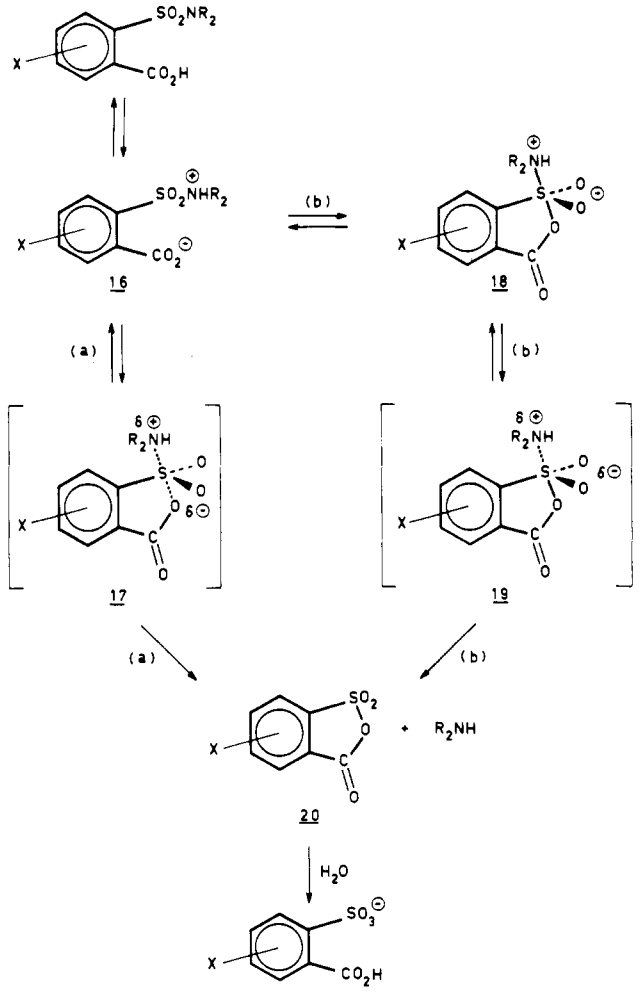
The first step is presumably a proton transfer or series of proton transfers, resulting in the rapid preequilibrium formation of the N-protonated zwitterion **16** (Scheme I). This opens the way for rate-determining nucleophilic displacement

Table III. pK_A's, Rate Constants, Thermodynamic Activation Parameters,[a] and Solvent Deuterium Isotope Effects for Hydrolysis of the Sulfonamides **7–14** in the Presence of 0.1 M HCl

compd	pK_A	solvent	t, °C	$k_{obsd} \times 10^5$, s^{-1}	$\Delta G^{\ddagger}$, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	k_{D_2O}/k_{H_2O}
7	2.01[b]	H_2O	75	2780	22.32	18.6	−12	1.36[b]
7		50% EtOH-H_2O (v/v)	75	1005	22.90	18.2	−16	
8	2.51[c]	50% EtOH-H_2O (v/v)	75	0.072				1.25
9	2.67[c]	H_2O	75	4.79	26.65	22.3	−14	1.21
9		50% EtOH-H_2O (v/v)	75	0.80				
10	2.49[c]	50% EtOH-H_2O (v/v)	75	0.226	29.38	29.0	−1	1.05
11	3.44[c]	H_2O	75	53.2	25.13	21.9	−11	1.29[b]
11		50% EtOH-H_2O (v/v)	75	4.5	27.75	21.0	−23	
11		t-BuOH-H_2O, $n_{H_2O} = 0.950$	75	14.7	25.71	20.7	−17	
11		t-BuOH-H_2O, $n_{H_2O} = 0.940$	75	10.4	26.06	19.8	−21	
11		t-BuOH-H_2O, $n_{H_2O} = 0.925$	75	9.15	26.21	22.2	−14	
11		50% MeCN-H_2O (v/v)	80	6.75				
11		50% dioxane-H_2O (v/v)	80	3.69				
12	3.90[c]	50% EtOH-H_2O (v/v)	75	0.0013	31.7	24.1	−26	
13	4.18[c]	50% EtOH-H_2O (v/v)	75	<0.0013				
14	2.78[c]	H_2O	75	17.4	26.41	26.2	−1	1.25[d]
14		50% EtOH-H_2O (v/v)	75	7.48	27.05	27.0	0	

[a] Extrapolated to 25 °C. [b] At 40 °C in H_2O. [c] At 50 °C in H_2O. [d] At 70 °C in H_2O.

Scheme I



of nitrogen from the protonated sulfonamide by carboxylate. An analysis of the effects of substituents on the rates of hydrolysis of compounds **1a–e, 2a–d,** and **3a–c** makes possible a rather detailed description of this displacement reaction.

We have interpreted our previous results[1,8] in terms of a concerted $S_N2(S)$ mechanism, consistent with earlier studies of nucleophilic substitution at sulfonyl centers.[12,13] For example, Williams and his co-workers[12] found that the transition state for the attack of phenolate anion on sultones is apparently symmetrical with regard to nucleophile and leaving group. The corresponding mechanism (a in Scheme I) for the reaction of our sulfonamides requires a transition state (**17**) with a significant negative charge on carboxylate oxygen. By separating the effects of ring substituents on the carboxylic acid and sulfonamide groups, we have been able to estimate the sign and magnitude of the charge at each center in the transition state, as compared with the initial state.[26] The ρ_{CO_2H} value obtained (−0.54 ± 0.02) is small but unmistakably negative, consistent with a *reduction* in electron density on the carboxyl group compared with the initial state COOH.

The simplest explanation of this result is that the new oxygen-sulfur bond is fully formed in the transition state: both the sulfonyl and the sulfonate anion[27] are more electronegative than the proton, so that the increased electron withdrawal would then be accounted for. The sulfur-nitrogen bond, on the other hand, is partially broken. Though it is not possible to estimate the ρ value for the leaving group very accurately (see data for compounds **3** in Table I), it is clearly negative and unlikely to be less than −1. This value is only a fraction of that for the protonation of anilines[28] ($\rho = -2.89$), so leaving group

Table IV. Relative Rate Constants within the Series **10–13** for Hydrolysis in 50% EtOH-H_2O (v/v) at 75 °C (0.1 M HCl)

compd	k_{rel}	k_{rel}^{cor} [a]
10	174	3.1
11	3460	462
12	1	1
13	<1	≈1

[a] See text.

Table V. Thermodynamic Parameters for Acidity Constants of the Sulfonamides **8** and **10–12** in H_2O at 25 °C

compd	pK_A (50 °C)	$\Delta G°$, kcal mol^{-1}	$\Delta H°$, kcal mol^{-1}	$\Delta S°$, eu
8	2.51	3.89	5.8	6.4
10	2.49	3.83	5.7	6.3
11	3.44	5.16	6.1	3.0
12	3.90	5.63	4.1	−5.2

nitrogen must carry a small partial positive charge in the transition state. The same conclusion applies to the sulfonyl center ($\rho_{SO_2N} = -0.58 \pm 0.01$).

The effects of substituents are thus consistent with a transition state in which all three centers—carboxyl, sulfonamide sulfur, and the leaving group nitrogen atom—are more electron deficient than in the initial state. The simplest transition state to fit these requirements is that for the breakdown of a pentacovalent addition intermediate (**19**): if S-O bond formation is complete, and S-N cleavage is not, the transition state for a concerted process would be so unsymmetrical as to be scarcely distinguishable from **19.**

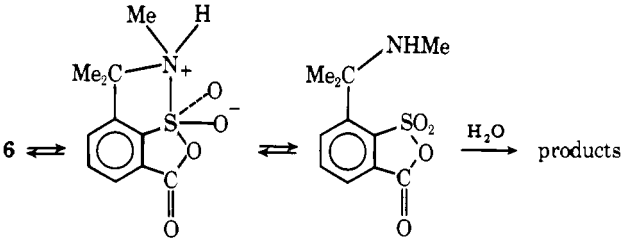
We therefore propose mechanism b (Scheme I), involving a pentacovalent intermediate (**18**), to account for intramolecular catalysis of sulfonamide hydrolysis by the carboxyl group, and discuss below steric and strain effects in terms of this mechanism. In fact these and other properties of the reaction, such as the solvent deuterium isotope effect, cannot be used to distinguish the two-step process from the concerted displacement mechanism.

The final hydrolysis of the cyclic mixed anhydride (**20**) will be rapid:[29] compound **20,** X = H, for example, has a half-life of 40 s in 90% (v/v) dioxane-water at 25 °C.

Steric Interactions in Initial and Transition State. For the penta-coordinated intermediate **18,** it is highly likely that the entering carboxylate anion and the amine leaving group are bound via pd-hybridized bonds to a trigonal bipyramidal sulfur atom.[29] Inspection of molecular models also suggests that this apical-apical configuration is the most reasonable spatial arrangement. These models reveal that in the arenesulfonamides **1** and **2** the amine leaving group in the transition state **19** will experience considerable nonbonded interactions with ring substituents ortho to the sulfonyl group. This steric effect is probably the origin of the 238-fold decrease in the rate of hydrolysis upon substitution of the ortho hydrogen in **1c** by a methyl group (**4a,** Table II).[30] A similar phenomenon has been observed by Kice et al.[31] for the reverse process, i.e., nucleophilic attack on the sulfonyl group, in naphtho[1,8-*cd*]-1,2-dithiole 1,1,2,2-tetraoxide, where the ortho-hydrogen atom blocks the attack of an approaching nucleophile. In general, however, one should also consider the change in nonbonded interactions in the initial state when a bulky substituent is introduced in the molecule, since the overall effect on the Gibbs free energy of activation will reflect the differences between initial and transition state destabilization. Thus, the observation that **4b,** with an ortho *tert*-butyl group, is hydrolyzed about four times *faster* than **4a,** is readily explained by assuming that substrate destabilization now makes a more important contribution to $\Delta\Delta G^{\ddagger}$ [$= \Delta G^{\ddagger}$(**4b**) $- \Delta G^{\ddagger}$(**1c**)] than in the case of **4a.**

We now turn to the rates of hydrolysis of **5a-c** which demonstrate even more clearly the balance of substrate and transition state destabilization as a function of the bulk of a substituent ortho to the sulfonyl group. Sulfonamide **5a** is hydrolyzed ca. 75 times more slowly than **1c,** the principal reason being that now a six-membered transition state is involved which is energetically less favorable than a five-membered one (vide infra). In this series replacement of the ortho hydrogen by an ortho-methyl or ortho-*tert*-butyl substituent leads to progressively higher rate constants for hydrolysis (Table II). Consideration of molecular models clearly indicates that the apical S-N and S-O bonds in the pentacovalent intermediate are no longer situated in the plane of the aromatic ring. This preferred arrangement is associated with only minor nonbonded interactions between ortho substituents and the amine leaving group in the transition state of the slow step. Consequently, nonbonded in-plane interactions in the initial state now predominate, culminating in the highest rate of hydrolysis for the sulfonamide with the most bulky ortho substituent (**5c**). The rate enhancements caused by bulky ortho substituents in intermolecular nucleophilic displacement reactions in aryl sulfonyl chlorides have been rationalized along similar lines.[32] Another example is provided by the ready hydrolysis of 2,4-dimethylbenzenesulfonic acid to *m*-xylene.[33]

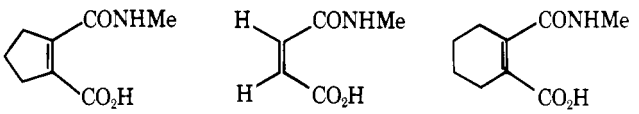
In sulfonamide **6** the leaving group is incorporated in a ring and itself occupies the ortho position. Steric hindrance to the leaving group is thus removed, at the expense of new constraints on the formation of the transition state for S-N bond cleavage, which will be close in structure to the fused tricyclic intermediate (**21**). These new constraints may account for the



21

15-fold decrease in k_{obsd} relative to the reaction for **1c.** But we note that the formation of the mixed anhydride may now be reversible, since intramolecular nucleophilic attack by the leaving methylamino group could compete, even at pH 1, with external attack by water. In fact if attack by the neighboring amino group were faster than attack by water, then the rate-determining step of the overall reaction would be the hydrolysis of the mixed anhydride. We note that the solvent deuterium isotope effect for hydrolysis of **6** in 1 M acid [$k(D_2O)/k(H_2O) = 3.6$] is quite different from the values observed for the other sulfonamides (Tables II and III). This is consistent with at least partly rate-determining hydrolysis of the mixed cyclic anhydride since less free amine will be present in D_2O. Furthermore, reaction rates now increase with acid concentration (0.1-1.0 M HCl). Therefore, we cannot usefully compare directly the rates of hydrolysis of **6** and **1c** because the rate-determining steps are most likely different.

Strain Effects in 7-10. Another feature of paramount importance in intramolecular nucleophilic catalysis, which influences particularly the hydrolysis of sulfonamides **7-9,** is ring strain. In all three compounds the carboxyl and sulfonamide groups are held cis to each other, but the unsubstituted compound **7** is hydrolyzed over 10^4 times more rapidly than the cyclopentene **8.** This factor is similar to that observed in the corresponding series of carboxamides,[5c] and a similar explanation applies: in the cyclopentene system the reacting groups



k_{rel}(39 °C): 1 2.4 × 10^4 1.3 × 10^7

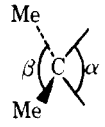
are held back, compared with the unsubstituted system, resulting in increased ring strain on cyclization to the 5,5-fused system. X-ray structures in both series (ref 5c and Figure 5) support this explanation. In the sulfonamides it is noteworthy that in both the methyl ester (**15**) derived from **7** and in **8** the -COO- group is rotated out of the plane of the C=C double bond, presumably as a result of steric interaction with the sulfonamide function. The angle of rotation is 75° for **15** and 71° for **8,** also consistent with the above suggestion. However, it is clear that there is also another large effect controlling the reactivity of the sulfonamide series, because the cyclohexenyl compound (**9**) is now also much less reactive than the unsubstituted derivative. Two factors may account for this difference (which makes **9** only 11 times more reactive than **8,** but still some 10^3 times less reactive than **7**). One is reduced strain in

the 5,6-fused system containing sulfur. However, this is probably not a dominant effect as suggested by the relative rates of hydrolysis in a series of corresponding mixed cyclic anhydrides (vide infra). The second effect is steric hindrance to the departure of the leaving group characteristic of the sulfonamide system. This factor is important in the benzenesulfonamides, as discussed above, and since the rates are rather similar, the effect of the ortho hydrogen in the aromatic series appears to be comparable with that of the two hydrogens of the methylene groups in the corresponding positions of the cyclohexenyl and (to a smaller extent) the cyclopentenyl compounds **9** and **8.** An inspection of molecular models suggests that this is reasonable, and the rate difference is almost entirely accounted for by the differences in the enthalpy of activation, as expected (Table III).

This steric hindrance, on the other hand, is entirely absent for the reaction of the unsubstituted compound **7,** which has no atoms in a position to interfere with the departure of the leaving group, and as a result is hydrolyzed hundreds of times more rapidly than **8** or **3b.**

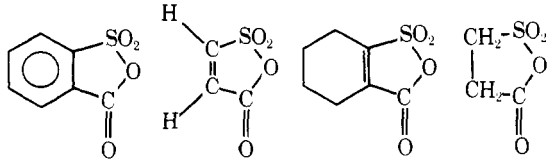
The strikingly different response of the rates of hydrolysis to the same changes in structure in the sulfonamide and carboxamide series thus depends also on the different geometries of the two transition states. The direction of departure of the leaving group from the tetrahedral intermediate in the carboxamide reaction is quite different from that from the pentacoordinated intermediate in the sulfonamide hydrolysis, and steric effects on this step are thus quite different also.

Resistance to ring formation is also revealed by the relatively slow hydrolysis of sulfonamide **10.** In this case, a four-membered cyclic anhydride is involved as an intermediate[34] and the substantial resultant ring strain is reflected in the enthalpy of activation which is increased by 8 kcal mol^{-1} compared with **11** [Table III; 1:1 (v/v) EtOH-H_2O]. Replacement of the methylene hydrogen atoms of **10** by two methyl groups results in a 33-fold rate enhancement (Table III, sulfonamide **14**). This "*gem*-dimethyl effect" is the expected consequence of the decrease in the bond angle α known to result from the introduction of two geminal methyl groups.[25,35] This angle must



decrease still further as the four-membered cyclic transition state is formed, and the deformation required is significantly reduced compared with the unsubstituted compound **10.** However, inspection of molecular models leads us to suggest that the effect will be partly compensated by nonbonded interactions between the almost eclipsed S-O and C-Me bonds in the transition state.

Quantitative predictions concerning differences in ring strain in the transition state for intramolecular carboxyl-catalyzed hydrolysis of sulfonamides are difficult to make at the moment. The availability of the rates of hydrolysis of the relevant cyclic mixed anhydrides (Scheme I) could be most helpful, but very few data are available. Rates of hydrolysis have been determined for **22,**[29] **23,**[36] **24,**[36] and **25**[29] in 90% (v/v) dioxane-H_2O



	22	**23**	**24**	**25**
$k_{obsd} \cdot 10^3$, s^{-1}:	16.7	32.8	6.3	19.1

at 25 °C and most likely pertain to nucleophilic attack on the anhydride carbonyl group.[29] The results show a rather modest dependence on strain in the five-membered ring, but the eclipsing of C-H bonds in **25** may partially compensate for angle-strain effects.

Kaiser et al.[37] showed that five-membered ring sultones are hydrolyzed more than 10^4 times faster than the corresponding six-membered species, probably mainly as the result of larger ring strain. However, this result cannot be extrapolated to systems containing an additional carbonyl group (**22–25**) as is demonstrated by the fact that the formation of five-membered lactones occurs more readily than that of the six-membered analogues.[38,39]

Rotational Freedom. The rates of hydrolysis of sulfonamides **10–13** are of interest in that they illustrate another factor influencing the efficiency of intramolecular catalysis, namely, the degree of rotational freedom of the carboxyl with respect to the sulfonamide group. As the chain length increases, an increasing amount of rotational entropy will be frozen out when the substrates are converted into the transition state for hydrolysis (**19,** Scheme I). One can correct the rate constants (to give k_{rel}^{cor} values) for this factor, assuming a loss of 4 eu per degree of freedom as suggested by Jencks.[19] Both the uncorrected and corrected rate constants exhibit a maximum for the formation of the five-membered ring (Table IV). This preference has been noted before for several other ring-closure reactions,[14,38] but is not a general rule for ring systems containing a sulfonyl group.[37] It is likely that the formation of a six-membered ring intermediate (from **12**) with the favorable apical-apical positioning of the entering and leaving group, and involving a C-S-O (CO) angle of 90°, induces more strain than the formation of the corresponding intermediate from **11,** despite the eclipsed position of the C-H bonds in the latter compound. In the more flexible sulfonamide **13,** the entropic disadvantage of the four carbon chain leads to a further decrease of the rate of hydrolysis. In the next section it will be argued that effects of changes in rotational freedom do not necessarily show up in the entropies of activation of reactions in aqueous solution.

Solvent Effects and Hydrophobic Hydration. It now remains to consider the effect of the reaction medium on the hydrolysis process. The data in Table III indicate that the rate of the intramolecular catalyzed reaction falls considerably if the reaction medium is changed from water to a mixed aqueous solvent system. Since charge separation occurs upon formation of the transition state, these results are not unexpected. For enzymic reactions, however, solvent *polarity* is not the dominant factor.[2b] Biological reactions are intimately dependent on the unique solvent properties of water.[16,40] The unique hydrogen-bond regime found in aqueous solutions[41] gives rise to very specific solvation changes accompanying association equilibria and chemical transformations. One important example is hydrophobic hydration[41] which is the major cause of hydrophobic interactions.[42] Because highly aqueous *t*-BuOH-H_2O is one of the best solvent systems for investigating the effects of changes in hydrophobic hydration,[41,43] we have measured the changes in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ as a function of the mole fraction of water (n_{H_2O}) for the hydrolysis of **7**[1a] and **11** (Table III and Figure 4). For both substrates, $\Delta G^{\ddagger}$ increases continuously with decreasing n_{H_2O} but $\Delta H^{\ddagger}$ and $-T\Delta S^{\ddagger}$ show marked mirror-image behavior and pass through extrema around $n_{H_2O} = 0.94$. This type of behavior has been observed previously for several *inter*molecular acid and base catalyzed hydrolytic processes[44] and most likely reflects the maximum in hydrophobic interaction between substrate and *t*-BuOH around 6 mol % *t*-BuOH. A more thorough analysis requires the availability of the thermodynamic transfer parameters for the substrates.[44] We suggest that the minimum in $\Delta H^{\ddagger}$ for hydrolysis of **7** and **11** at the solvent composition of maximum

hydrophobic hydration also corresponds to a maximum in hydrogen-bond stabilization of the polar transition state.[42b]

Another important aspect of intramolecular catalyzed reactions in aqueous media involves the notion that the experimental $\Delta S^{\ddagger}$ values do not directly represent the intrinsic entropy loss associated with the loss of translational and rotational freedom in the transition state.[2b] In this respect, it is interesting to compare the activation parameters for hydrolysis of **7** with those of **11.** Although these systems are not fully comparable,[45] one could argue that the rate difference would be primarily reflected in different $\Delta S^{\ddagger}$ values as the result of the difference in flexibility of the two-carbon chains connecting the sulfonamide and carboxyl groups.[2c] However, the difference in $\Delta G^{\ddagger}$ in water as the solvent is primarily brought about by different *enthalpic* contributions (Table III). Therefore, we are led to suggest that the entropy loss involved in bringing together the sulfonamide and carboxyl groups in **11** is compensated by a gain in entropy as a result of partial desolvation. These effects, which are of course almost completely absent in **7**, "translate" an entropy loss into an increase in $\Delta H^{\ddagger}$ for the hydrolysis of **11.** A comparison of the enthalpies and entropies for the acidity constants of **8** and **10–12** (Table V) provides supporting evidence for these views. Whereas the entropies of dissociation of simple carboxylic acids[18] are usually in the range of −17 to −24 eu, the positive ΔS° for the ionization of **11** (+ 3 eu) is in agreement with the hypothesis that even in the conjugate base of **11** the full development of a hydration shell around the carboxylate function is hampered by the sulfonamide group.

Rather similar arguments have been used by Larsen,[46] who has calculated that dimerization of cyclopentadiene *in water* would lead to only a very small change in entropy, because of the favorable change in solvation entropy upon rearrangement of solvent molecules in the association process. Thus, the unfavorable change in translational entropy is now expressed in the experimental unfavorable change in solvation enthalpy. In this connection we note that the change in k_{obsd} for hydrolysis of **11** upon going from water to 50% (v/v) EtOH–H_2O is remarkably large ($k_{obsd}^{H_2O}/k_{obsd}^{EtOH-H_2O}$ ca. 11) compared with the corresponding ratio of rate constants for the sulfonamides with fixed geometries (**1c, 7, 9,** and **14**). This difference in solvent effect might also reflect the favorable desolvation entropy upon transferring the substrate into the transition state in water as the solvent.

Conclusions

The substance of this paper can now be summarized as follows. We have presented evidence that the acid-catalyzed hydrolysis of sulfonamides can be very efficiently catalyzed by a neighboring carboxyl group (effective molarity up to about 10^8 M). For the first time strong evidence has been obtained that nucleophilic substitution at sulfonyl sulfur occurs via a two-step mechanism, involving a pentacoordinated intermediate, rather than via synchronous nucleophilic attack and departure of the leaving group. This change in timing, as compared with *inter*molecular substitution reactions at sulfonyl sulfur studied previously, may find its origin in the combination of an intramolecular nucleophile and a poor leaving group in **1–14.**

The efficiency of the intramolecular catalysis is remarkably sensitive to nonbonded interactions in initial and transition states. In **4–5** there is a delicate balance of the two effects, but a dramatic decrease in rate is observed in those cases where there is severe hindrance to the leaving group in the transition state. The observed effects are consistent with the postulate, incorporated in the proposed mechanism, that there is an apical-apical alignment of the entering and leaving groups in the transition state, as part of a trigonal bipyramidal arrangement about the central sulfur atom.

In those unsaturated sulfonamides **7–9** in which the reacting groups are fixed cis to each other, the rates depend very strongly on the exact geometry of the carbon chain bringing the interacting groups together. The observed differences are explained in terms of ring strain modified by steric effects involving the leaving group. If the carbon chain allows rotational freedom (**10–14**), there is a well-defined maximum in catalytic efficiency for the sulfonamide hydrolysis by way of a five-membered cyclic transition state.

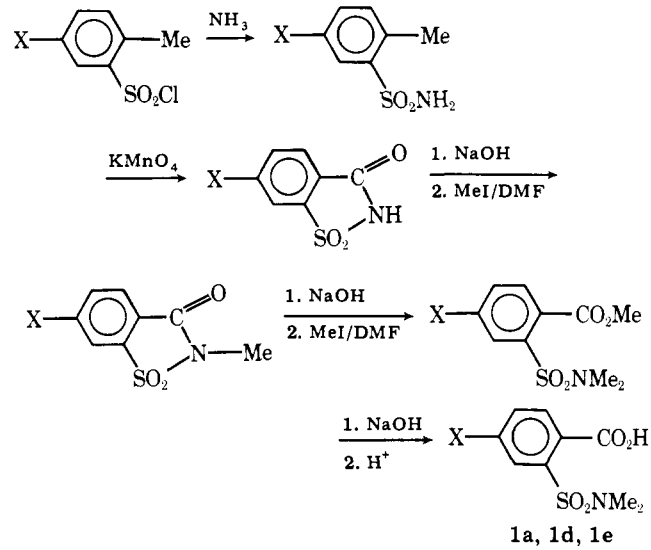
In general, structural effects on intramolecular carboxyl assisted sulfonamide hydrolysis are dramatically different from those for comparable carboxamide systems. Differences in reaction mechanism and transition-state geometry largely account for these observations.

The thermodynamic quantities of activation ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, but not $\Delta G^{\ddagger}$) for hydrolyses of **7** and **11** respond to changes in hydrophobic hydration in highly aqueous media. Solvent effects also demonstrate that the interpretation of thermodynamic activation parameters for intramolecular catalyzed reactions should take into account effects due to overlap of solvation spheres of reacting groups positioned in close proximity.

Experimental Section

Materials.[47] The sulfonamides used in this study were usually prepared according to standard procedures for which adequate descriptions can be found in texts on organic synthesis. Intermediates not described in the literature had correct elemental analyses and showed IR and NMR spectral data in good accord with the proposed structures. Detailed information on the synthesis of particular sulfonamides is available on request.

Sulfonamides **1a, 1d,** and **1e** were prepared by the following route:



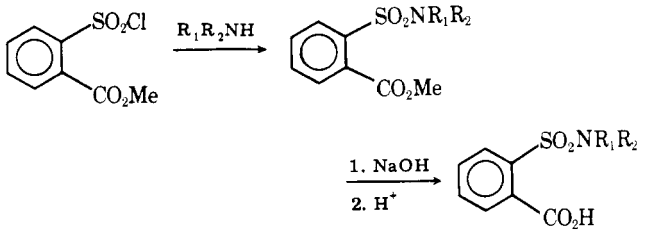
1a, 1d, 1e

2-Carboxy-5-methoxy-*N,N*-dimethylbenzenesulfonamide (1a): mp 114–116 °C; NMR ($CDCl_3$) 2.88 (s, 6 H), 3.90 (s, 3 H), 6.9–7.8 (m, 3 H), 8.9 (s, broad, 1 H). Anal. Calcd for $C_{10}H_{13}NO_5S$: C, 46.32; H, 5.05; N, 5.40; S, 12.37. Found: C, 46.5; H, 5.0; N, 5.4; S, 12.5.

2-Carboxy-5-fluoro-*N,N*-dimethylbenzenesulfonamide (1d): mp 111–113 °C; crystallized with 0.5 mol of benzene of crystallization; NMR ($CDCl_3$) 2.87 (s, 6 H), 7.13–7.80 (m, 3 H), 8.1 (s, broad, 1 H). Anal. Calcd for $C_9H_{10}FNO_4S + 0.5\ C_6H_6$: C, 50.34; H, 4.58; N, 4.90; S, 11.20; F, 6.64. Found: C, 50.2; H, 4.5; N, 5.1; S, 11.0; F, 6.6.

2-Carboxy-5-nitro-*N,N*-dimethylbenzenesulfonamide (1e): mp 168–172 °C; NMR (CD_3OD) 2.87 (s, 6 H), 7.50–8.67 (m, 3 H). Anal. Calcd for $C_9H_{10}N_2O_6S$: C, 39.42; H, 3.66; N, 10.21; S, 11.69. Found: C, 39.4; H, 3.6; N, 10.3; S, 11.7.

The sulfonamides **1c** and **3a–c** were prepared as follows:



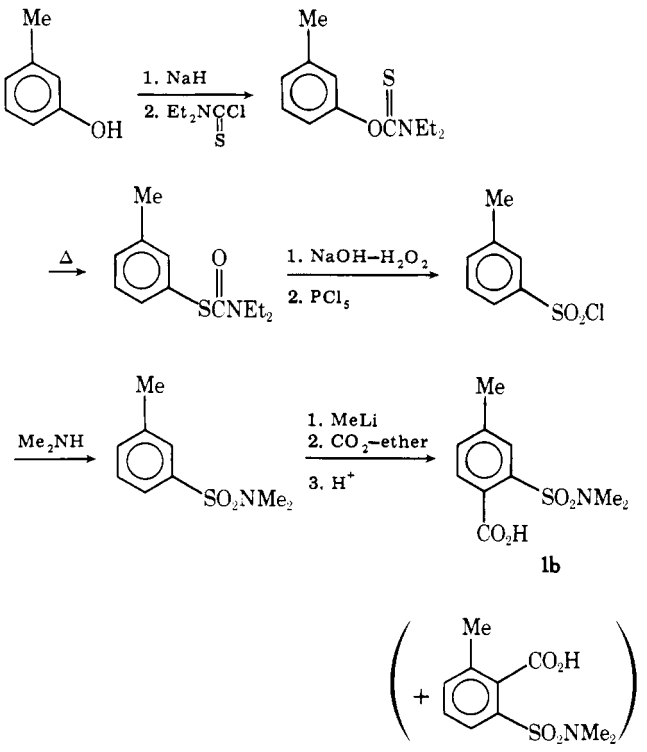
2-Carboxy-*N,N*-dimethylbenzenesulfonamide (1c): mp 98–103 °C (lit.[48] 98–102 °C).

2-Carboxy-*N*-*p*-methoxyphenyl-*N*-methylbenzenesulfonamide (3a): mp 118–120 °C; NMR ($CDCl_3$) 3.27 (s, 3 H), 3.75 (s, 3 H), 6.78–7.15 (m, 4 H), 7.33–7.68 (m, 4 H), 8.09 (s, 1 H). Anal. Calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.71; N, 4.36; S, 9.98. Found: C, 56.2; H, 4.8; N, 4.4; S, 10.0.

2-Carboxy-*N*-methyl-*N*-phenylbenzenesulfonamide (3b): mp 94–96 °C; NMR ($CDCl_3$) 3.33 (s, 3 H), 7.31 (s, 5 H), 7.40–7.80 (m, 4 H), 11.49 (s, 1 H). Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81; S, 11.01. Found: C, 57.5; H, 4.5; N, 4.8; S, 11.1. As reported previously,[49] the acid is difficult to crystallize. Upon distillation, the compound is partly converted into *O*-sulfobenzoic anhydride. The acid was obtained from the corresponding methyl ester (mp 92–93 °C; lit.[49] 93–94 °C).

2-Carboxy-*N*-methyl-*N*-*p*-nitrophenylbenzenesulfonamide (3c) was obtained by nitration (HNO_3–HOAc) of 2-carbomethoxy-*N*-methyl-*N*-phenylbenzenesulfonamide at 75 °C and subsequent hydrolysis in aqueous NaOH: mp 177–178 °C; NMR (CD_3OD) 3.23 (s, 3 H), 7.0–8.0 (m, 8 H). Anal. Calcd for $C_{14}H_{12}N_2O_6S$: C, 50.00; H, 3.60; N, 8.33; S, 9.53. Found: C, 50.0; H, 3.6; N, 8.4; S, 9.6.

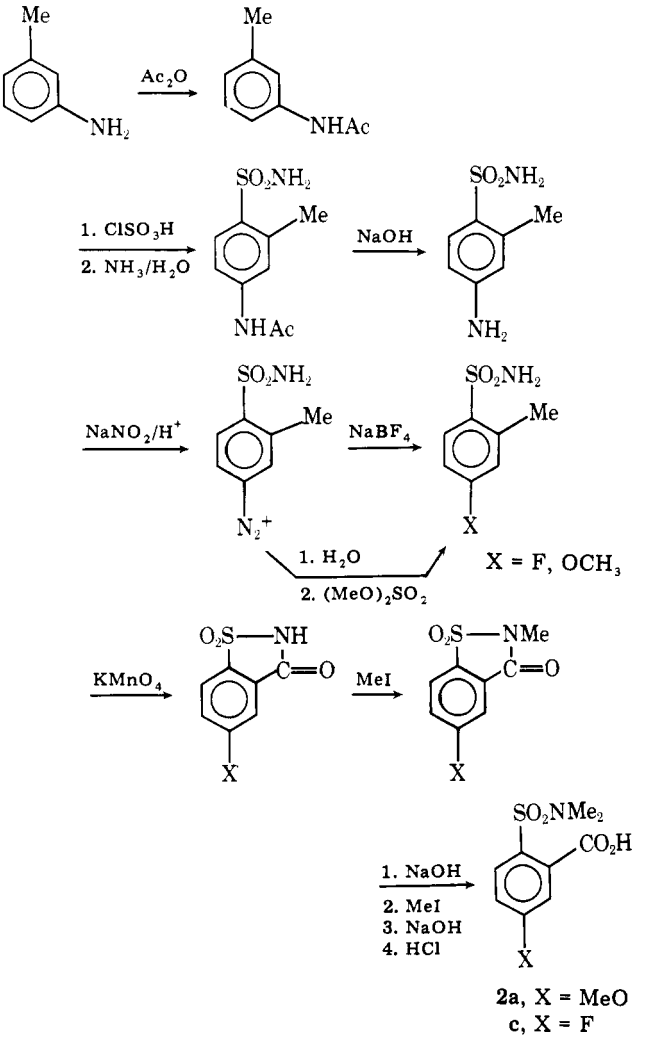
Sulfonamide **1b** was synthesized according to the following scheme:



The mixture of acids obtained in the last step was separated via conversion in the methylcarboxylates (CH_2N_2) and subsequent hydrolysis in 10% NaOH in 50% (v/v) EtOH–H_2O for 2 h at 70 °C. The hindered methyl ester of the undesired product is not hydrolyzed under these conditions, whereas **1b** is obtained in good yield after acidification of the reaction mixture.

2-Carboxy-5-methyl-*N,N*-dimethylbenzenesulfonamide (1b): mp 143–145 °C; NMR ($CDCl_3$) 2.50 (s, 3 H), 2.88 (s, 6 H), 7.25–7.80 (m, 3 H), 11.48 (s, 1 H). Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.38; H, 5.38; N, 5.75; S, 13.18. Found: C, 49.1; H, 5.4; N, 5.6; S, 13.2.

The sulfonamides **2a** and **2c** were prepared by the following sequence of reactions:

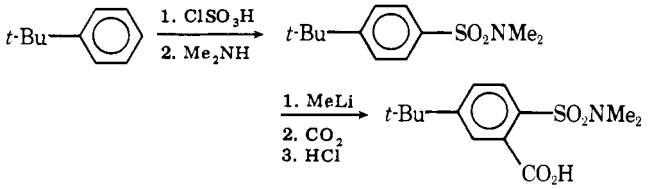


2a, X = MeO
c, X = F

2-Carboxy-4-methoxy-*N,N*-dimethylbenzenesulfonamide (2a): mp 123–125 °C (from $CHCl_3$–CCl_4; from benzene the sulfonamide crystallized with 0.5 mol of benzene of crystallization); NMR ($CDCl_3$) 2.82 (s, 6 H), 3.88 (s, 3 H), 6.87–8.00 (m, 3 H), 7.5 (s, 1 H). Anal. Calcd for $C_{10}H_{13}NO_5S$: C, 46.32; H, 5.05; N, 5.40; S, 12.37. Found: C, 45.9; H, 4.9; N, 5.4; S, 12.3.

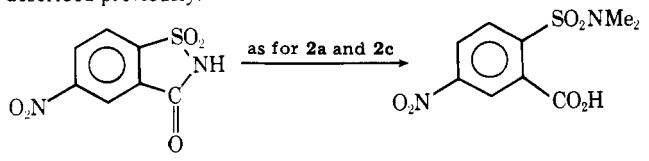
2-Carboxy-4-fluoro-*N,N*-dimethylbenzenesulfonamide (2c): mp 129–130 °C; NMR ($CDCl_3$) 2.85 (s, 6 H), 7.0–8.1 (m, 3 H), 9.53 (s, 1 H). Anal. Calcd for $C_9H_{10}FNO_4S$: C, 43.72; H, 4.08; F, 7.68; N, 5.67; S, 12.97. Found: C, 43.8; H, 4.0; F, 7.6; N, 5.6; S, 13.0.

The sulfonamide **2b** was prepared as follows:



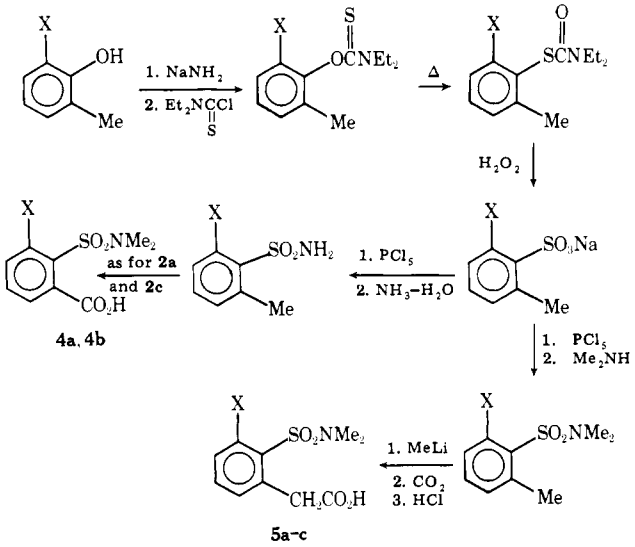
4-*tert*-Butyl-2-carboxy-*N,N*-dimethylbenzenesulfonamide (2b) had mp 60–65 °C (from EtOH–H_2O) and contained 1 mol of water of crystallization: NMR ($CDCl_3$) 1.34 (s, 9 H), 2.83 (s, 6 H), 7.63–7.81 (m, 3 H). Anal. Calcd for $C_{13}H_{21}NO_5S$: C, 51.47; H, 6.98; N, 4.62; S, 10.57. Found: C, 51.5; H, 7.0; N, 4.8; S, 10.7.

Sulfonamide **2d** was obtained starting from the saccharin derivative described previously:[50]



2-Carboxy-4-nitro-*N,N*-dimethylbenzenesulfonamide (2d): mp 152–155 °C; NMR (CD_3OD) 2.93 (s, 6 H), 8.00–8.67 (m, 3 H). Anal. Calcd for $C_9H_{10}N_2O_6S$: C, 39.42; H, 3.66; N, 10.21; S, 11.69. Found: C, 39.4; H, 3.6; N, 10.2; S, 11.8.

The series of sulfonamides **4a–b** and **5a–c** were synthesized according to the sequences:



2-Carboxy-6-methyl-*N,N*-dimethylbenzenesulfonamide (4a): mp 142–144 °C; NMR ($CDCl_3$) 2.65 (s, 3 H), 2.85 (s, 6 H), 7.33 (m, broad, 3 H), 8.33 (s, broad, 1 H). Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.38; H, 5.38; N, 5.75; S, 13.18. Found: C, 49.2; H, 5.3; N, 5.7; S, 13.3.

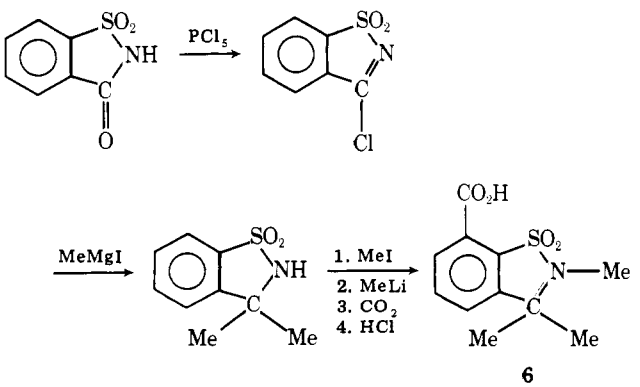
2-Carboxy-6-*tert*-butyl-*N,N*-dimethylbenzenesulfonamide (4b): mp 179–181 °C; NMR ($CDCl_3$) 1.60 (s, 9 H), 2.70 (s, 6 H), 7.01–7.97 (m, 3 H), 10.67 (s, 1 H). Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71; N, 4.91; S, 11.24. Found: C, 55.0; H, 6.7; N, 4.9; S, 11.1.

2-Methylcarboxy-*N,N*-dimethylbenzenesulfonamide (5a): mp 152–153 °C; NMR ($CDCl_3$) 2.66 (s, 6 H), 4.00 (s, 2 H), 7.13–7.50 (m, 4 H), 8.1 (s, broad, 1 H). Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.38; H, 5.39; N, 5.75; S, 13.19. Found: C, 49.1; H, 5.3; N, 5.8; S, 13.2.

2-Methyl-6-methylcarboxy-*N,N*-dimethylbenzenesulfonamide (5b): mp 149–150 °C; NMR ($CDCl_3$) 2.66 (s, 3 H), 2.69 (s, 6 H), 4.12 (s, 2 H), 7.0–7.5 (m, 3 H), 10.1 (s, 1 H). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44; S, 12.46. Found: C, 51.5; H, 5.9; N, 5.5; S, 12.4.

2-*tert*-Butyl-6-methylcarboxy-*N,N*-dimethylbenzenesulfonamide (5c): mp 178–180 °C; NMR ($CDCl_3$) 1.58 (s, 9 H), 2.53 (s, 6 H), 4.14 (s, 2 H), 7.0–7.7 (m, 3 H), 10.06 (s, broad, 1 H). Anal. Calcd for $C_{14}H_{21}NO_4S$: C, 56.17; H, 7.07; N, 4.68; S, 10.71. Found: C, 56.3; H, 7.1; N, 4.6; S, 10.6.

Sulfonamide **6** was prepared according to the following procedure:



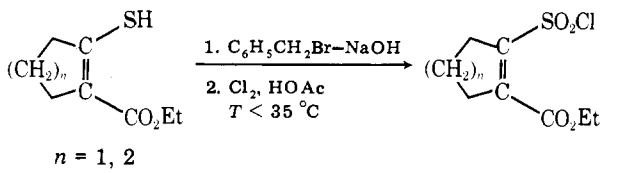
2,3,3-Trimethyl-7-carboxybenzisothiazolin 1,1-Dioxide (6): mp 294–295 °C (dec); NMR (CD_3OD) 1.51 (s, 6 H), 2.83 (s, 3 H), 7.67–8.23 (m, 3 H). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49; S, 12.56. Found: C, 51.8; H, 5.1; N, 5.5; S, 12.4.

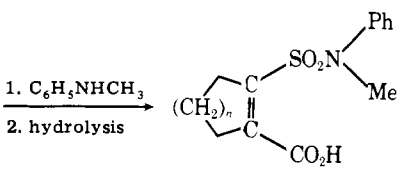
The synthesis of **7** has been outlined before.[8b] Details will be given for the final two steps of the synthesis since these are crucial in the preparation.

***cis*-2-Carboxymethyl-*N*-methyl-*N*-phenylethenesulfonamide.** A solution of *trans*-2-carboxymethyl-*N*-methyl-*N*-phenylethenesulfonamide (8 g, 31.4 mmol, mp 52–53 °C) and benzophenone (1.8 g, 10 mmol) in 1300 mL of dry benzene was irradiated by using a Hanau Q700 high pressure mercury lamp. The solution turned red-brown and a tarry material was deposited on the glass wall. As soon as the cis/trans ratio reached 1:1 (NMR; after 1–3 days), irradiation was stopped, the solution filtered, and the solvent removed in vacuo. Chromatography over silica gel (60–120 μm) using dichloromethane as eluent gave unreacted benzophenone as the first fraction. Then dichloromethane containing 2% (v/v) ether was used as the eluent. The next fraction gave starting material and, subsequently, the desired *cis*-sulfonamide (1.96 g, 25%). This material was further purified by bulk distillation and crystallization from petroleum–ether (40–60°C): mp 49–50 °C; NMR ($CDCl_3$) 3.20 (s, 3 H), 3.63 (s, 3 H), 6.10 (d, J = 11 Hz, 1 H), 6.38 (d, J = 11 Hz, 1 H), 7.15 (m, 5 H). The NMR spectrum is readily distinguished from that of the starting material: 3.20 (s, 3 H), 3.70 (s, 3 H), 6.42 (d, J = 15 Hz, 1 H), 7.13 (d, J = 15 Hz, 1 H), 7.13 (m, 5 H). Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.74; H, 5.14; N, 5.49; S, 12.56. Found: C, 51.8; H, 5.1; N, 4.5; S, 12.5.

Sodium Salt of *cis*-2-Carboxy-*N*-methyl-*N*-phenylethenesulfonamide (7). A solution of *cis*-2-carboxymethyl-*N*-methyl-*N*-phenylethenesulfonamide in a mixture of 25 mL of 1 M Na_2CO_3, 25 mL of 1 M $NaHCO_3$ and 8 mL of methanol (pH ca. 9.2) was stirred for 21 h at 40 °C. Water (50 mL) was added to the mixture. After extraction with ether (three 25-mL portions), the water layer was acidified to pH 1 with dilute H_2SO_4 at 0 °C. The solution was immediately extracted with three 25-mL portions of dichloromethane. The combined organic layers were dried by stirring over $MgSO_4$ for 3 min. Then 10 mL of water was added. Under vigorous stirring 0.1 N NaOH was added to the two-phase system until the pH in the aqueous layer was 7.0 (pH meter). The aqueous layer was separated and evaporated to dryness. The colorless sodium salt was washed with acetone. The yield varies from 40 and 70%. NMR (D_2O): 3.15 (s, 3 H), 6.10 (d, J = 11.5 Hz, 1 H), 6.84 (d, J = 11.5 Hz, 1 H), 7.33 (s, 5 H). The salt usually contains ca. 18% of the trans isomer, presumably resulting from base-catalyzed cis–trans isomerization [NMR (D_2O): 3.13 (s, 3 H), 6.53 (d, J = 15.5 Hz, 1 H), 6.95 (d, J = 15.5 Hz, 1 H), 7.32 (s, 5 H)], but this does not interfere with the kinetic studies since **7** is so much more rapidly hydrolyzed than the trans isomer.[8b] All attempts to obtain a pure sample of the acid **7** failed because of rapid decomposition (to give *N*-methylaniline as one of the products) of the oil which is formed after careful acidification of the sodium salt and removal of the solvent in vacuo.

The sulfonamides **8** and **9** were prepared as follows:[51]



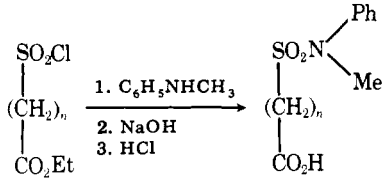


The deprotection of the ethyl ester was carried out with NaOH in EtOH–H_2O in the case of **8** and by the method of Jung,[52] using trimethylsilyl iodide, in the case of **9**.

2-Carboxy-*N*-methyl-*N*-phenylcyclopentene-1-sulfonamide (8): mp 120–128 °C; NMR (CD_3COCD_3) 1.8–2.2 (m, 2 H), 2.4–3.1 (m, 4 H), 3.35 (s, 3 H), 7.35 (s, 5 H), 9.9 (s, 1 H). Anal. Calcd for $C_{13}H_{15}NO_4S$: C, 55.50; H, 5.37; N, 4.98; S, 11.40. Found: C, 55.4; H, 5.3; N, 4.9; S, 11.3.

2-Carboxy-*N*-methyl-*N*-phenylcyclohexene-1-sulfonamide (9): mp 145–150 °C; NMR (CD_3COCD_3) 1.5–2.5 (m, 8 H), 3.35 (s, 3 H), 7.35 (s, 5 H), 9.7 (s, 1 H). Anal. Calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.80; N, 4.74; S, 10.86. Found: C, 56.9; H, 5.7; N, 4.7; S, 10.9.

The sulfonamides **10–13** were prepared from the corresponding ethyl chlorosulfonylcarboxylates:



n = 1–4 **10–13**

For n = 1, the starting material was prepared according to Veillefosse,[53] for n = 2 by chlorination of the isothiourea salt of ethyl acrylate,[54] for n = 3 and 4 by oxidative chlorination of the ethyl ω-mercaptocarboxylate (compare the synthesis of **8** and **9**).

Carboxy-*N*-methyl-*N*-phenylmethanesulfonamide (10): mp 118.6–119.0 °C; NMR (CD_3COCD_3) 3.40 (s, 3 H), 4.05 (s, 2 H), 7.4 (m, 5 H), 11.2 (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, 47.3; H, 4.9; N, 6.1; S, 13.9.

2-Carboxy-*N*-methyl-*N*-phenylethanesulfonamide (11) has been reported previously:[1a] NMR (CD_3COCD_3) 2.6–2.9 (m, 2 H), 3.2–3.6 (m, 2 H), 3.35 (s, 3 H), 7.4 (m, 5 H).

3-Carboxy-*N*-methyl-*N*-phenylpropanesulfonamide (12): mp 93.8–94.9 °C; NMR (CD_3COCD_3) 1.8–2.7 (m, 4 H), 3.0–3.3 (m, 2 H), 3.30 (s, 3 H), 7.35 (m, 5 H), 10.2 (s, 1 H). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44; S, 12.46. Found: C, 51.4; H, 5.9; N, 5.4; S, 12.6.

4-Carboxy-*N*-methyl-*N*-phenylbutanesulfonamide (13): mp 85.5–85.7 °C; NMR ($CDCl_3$) 1.5–2.0 (m, 4 H), 2.2–2.6 (m, 2 H), 2.8–3.2 (m, 2 H), 3.30 (s, 3 H), 7.3 (s, 5 H), 10.8 (s, 1 H). Anal. Calcd. for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16; S, 11.82. Found: C, 53.2; H, 6.3; N, 5.1; S, 11.7.

Sulfonamide **14** was obtained by methylation of $C_6H_5(CH_3)NSO_2CH_2CO_2Et$ in the presence of KOH in dimethylformamide followed by hydrolysis in EtOH–H_2O in the presence of NaOH.

2-Carboxy-*N*-methyl-*N*-phenyl-2-propanesulfonamide (14): mp 83–89 °C; NMR ($CDCl_3$) 1.65 (s, 6 H), 3.40 (s, 3 H), 7.2–7.6 (m, 5 H), 10.75 (s, 1 H). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.35; H, 5.88; N, 5.44; S, 12.46. Found: C, 51.0; H, 5.9; N, 5.5; S, 12.4.

Kinetic Measurements. The water used in the kinetic measurements was demineralized and distilled twice in an all-quartz distillation unit. Deuterium oxide (Reactor Centrum Nederland) was 99.94 ± 0.05% D_2O. The organic cosolvents were all of the highest grade available. 1,4-Dioxane was distilled under nitrogen just before use. The solvent mixtures were all made up by weight.

The UV and NMR kinetic methods for determining the rates of hydrolysis have been described in previous studies.[1a,8] The rates of hydrolysis of **1–7, 9** (in H_2O), **11** (in H_2O and in t-BuOH–H_2O), and **14** (in H_2O) were determined by following the change in absorbance at a suitable wavelength in the UV spectrum (usually at 235 nm; at 224 nm for **11**). Thermodynamic activation parameters were calculated from rates measured at four different temperatures over a temperature range of at least 15 °C. The k_{obsd} values were reproducible to within 2%. Estimated errors in $\Delta H^{\ddagger}$ are ca. ± 0.2 kcal mol^{-1} and in $\Delta S^{\ddagger}$ ca. ±1 eu. The rates of hydrolysis of **8, 9** (EtOH–H_2O), **10, 11** (EtOH–H_2O, CH_3CN–H_2O, and dioxane–H_2O), **12, 13,** and **14** (EtOH–H_2O) were determined by using the NMR method. In these cases the disappearance of the substrate N-phenyl peak and the appearance of the product N-phenyl peak was recorded as a function of time. The reproducibility of these k_{obsd} values is ±5%, the estimated errors in $\Delta H^{\ddagger}$ are ±0.3 kcal mol^{-1} and in $\Delta S^{\ddagger}$ ± 1.5 eu.

pK_A Measurements. The pK_A's of **8–14** (in H_2O) were determined by standard potentiometric titration methods. The thermodynamic quantities given in Table V were obtained from K_A values at four to five temperatures in the range 30–60 °C. The estimated errors in $\Delta G°$ are ± 0.01 kcal mol^{-1}, in $\Delta H°$ ± 0.2 kcal mol^{-1}, and in $\Delta S°$ ± 0.5 eu. The pK_A's of **1–6** were also measured by potentiometric titration and refer to solutions (under a nitrogen atmosphere) in 50% (v/v) EtOH–H_2O and ionic strength 1.0 M (NaCl) at 25 °C. These pK_A's were obtained by using a pH meter calibrated with an aqueous standard buffer solution. By employing the procedure given by De Ligny et al.,[55] a quantity δ was subtracted from the meter readings to afford corrected pK_A values (listed in Tables I and II) in order to account for the differences in the pH scale in water and the mixed aqueous solution. The applied corrections were: δ 0.18 for **1b, 1c, 1e, 2a–d, 3a–c, 4a,** and **6;** δ 0.19 for **1a** and **1d;** δ 0.22 for **5a** and **5c;** δ 0.23 for **4b;** and δ 0.25 for **5b.**

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Topologically Spherical Molecules. An Efficient Synthesis of C_{16}-Hexaquinacene and Its Lack of Neutral Homoaromatic Character

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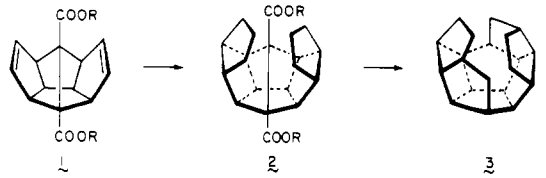
Abstract: The feasibility of gaining access to C_{16}-hexaquinacene in eight steps from the domino Diels–Alder adduct **5** was explored. With lithium hydride and methyllithium, this diacid was transformed to the diacetyl derivative **6** whose methyl groups were σ bonded by formation of the dienolate at low temperature and oxidative coupling with Cu(II). Selenium dioxide oxidation of the resulting 1,4-cyclohexanedione ring in **9** gave the pivotal trienedione **10.** When irradiated, **10** underwent efficient $\pi^2s + \pi^2s$ closure to the caged diketone **12,** a molecule ideally constructed stereoelectronically for ready cleavage of both of its 1,4-dicarbonyl systems. This transformation, which was achieved with zinc in hot acetic acid, produced **14** which was in turn converted to the title compound in three conventional steps. The electronic and structural properties of **4** are summarized, and a brief outline of preliminary reactions is given.

An efficient synthesis of the pentagonal dodecahedrane molecule requires development of a workable combination of regiocontrolled cyclopentane annulation, stereocontrolled incorporation of *all* 20 carbon atoms, and minimization of steric congestion during construction of the last of the requisite carbon–carbon bonds (total of 30). In two preceding papers,[2,3] we have described an attack on this problem beginning with **1**[4,5] and proceeding via appropriate annulation at its olefinic centers (→ **2**), more advanced ring closure, and cleavage of the



1 2 3

central σ bond to produce an octaquinane system of type **3.** Although many of the intermediates generated in that program hold considerable promise for continued progress toward the target polyhedron, our ability to elaborate additional useful carbon frameworks would have the virtue of expanding the number of synthetic prerogatives at the critical late stages of sphere construction. Herein we detail alternative synthetic strategy which again utilizes **1** as starting material, but otherwise differs intrinsically from the earlier approach. As before, heavy reliance has been placed upon maintenance of at least C_s or C_2 symmetry throughout, partly for aesthetic reasons and partly for brevity in synthetic manipulation. By such means, the triene **4,** known as C_{16}-hexaquinacene, has been

4

prepared in eight steps. The hydrocarbon is characterized by three mirror planes intersecting a threefold rotation axis. Additionally, its highly convex topology orients the double bonds in a most unique geometry and spatial relationship. The physical and chemical consequences of this arrangement, as known to the present time, also are discussed.

Synthesis

As alluded to above, the starting point was the readily available diacid **5** which, although already hexacyclic, does not have its five-membered rings properly arrayed relative to those in **4.** Therefore, some degree of structural reorganization was required. Furthermore, since **5** contains only 14 carbon atoms, it was imperative to incorporate two additional methine groups, or precursors to such functionality. This was achieved directly at the outset by sequential treatment of **5** with 2 equiv of lithium hydride and a comparable quantity of methyllithium, followed by dropwise addition to cold dilute hydrochloric acid. Diketone **6** was isolated in 94% yield. Alternative methodology exists for the conversion of hindered carboxylic acids to methyl ketones; the condensation of acid chlorides with lithium di-

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