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INTRAMOLECULAR CATALYSIS OF SULFONAMIDE HYDROLYSIS BY A NEIGHBOURING CARBOXYL GROUP

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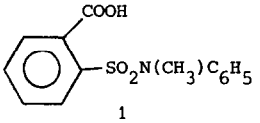
The acid-catalyzed hydrolysis of sulfonamides[1] normally proceeds only with extraordinary difficulty. Standard conditions include heating with concentrated hydrochloric acid in a sealed tube at 150-170° and treatment with 40% sulfuric acid in acetic acid at 50° for seven hours.[2] A detailed study of the reaction mechanism has not been made but the hydrolysis is undoubtedly initiated by (reversible) protonation at nitrogen.[3-5] A major reason for the lack of reactivity will then be the low basicity of sulfonamides[6] which prevents the formation of significant amounts of the conjugate acids (pK_a's ca. -6, based on the H_o scale) other than in highly acidic media.

In view of the mild conditions under which carboxamide hydrolysis can be carried out when intramolecular catalysis is provided by a neighbouring carboxyl group[7], we decided to investigate the feasibility of sulfonamide hydrolysis using the same strategy. In this communication we are pleased to report the first example of intramolecular catalysis of sulfonamide hydrolysis.

Solvolysis of 1[8] (pK_a 3.75)[9] in 50% (v/v) ethanol-water at 75 ± 0.1° for seven days



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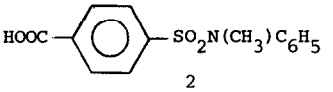

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gave N-methylaniline (93%), o-sulfobenzoic acid (3, 30%)[10], and ethyl o-sulfobenzoate (4, 30%). In contrast, the sulfonamide function of 2 (pK_a 4.08)[9] was completely unchanged after 73 days under similar reaction conditions (Table I). Partial esterification (ca. 25%) of the carboxyl group was the only change observed. The greatly enhanced reactivity of 1 is especially striking since o-substituents usually stabilize benzenesulfonamides towards acid-catalyzed hydrolysis.[1]

Table I. Hydrolysis of 2 in 50% (v/v) EtOH-H_2O at 75 ± 0.1° as a Function of Medium Acidity

HCl mol.l^{-1}	Reaction time	Yield of N-methylaniline (%)	Recovery of 2 (%)
- [a]	73 days	0	100[b]
0.11	75 days	0	100[b]
1.10	30 days	-[c]	ca. 94
	75 days	-[c]	ca. 50[b]
6.0	28 hours	81[d]	0

[a] 0.02 M solution of 2 with no acid added. Initial pH ca. 2.9 at 20°.
[b] Ca. 25% as the (carboxylic) ethyl ester; i.e. the COOH group has equilibrated with the solvent, which contains 24 mole % of EtOH.
[c] Presence of N-methylaniline detected by IR and GLC.
[d] Also isolated were 9% of p-sulfobenzoic acid and 70% of ethyl p-sulfobenzoate.

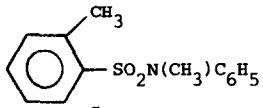
Approximate first order rate constants (k_{obsd})[11] for the hydrolysis of 1 are given in Table II. The modest increase of k_{obsd} in the concentration range 0.1-1.1 M HCl probably originates from a medium effect, and cannot be reconciled with a specific acid catalyzed process. The data are rather consistent with a reaction which is independent of pH in this region. The reaction evidently involves the undissociated (COOH) form of 1, since k_{obsd} falls under conditions where the carboxyl group is partly ionised (Table II), and at pH 9.7, where only the ionised form is present, 1 was unchanged after two months at 75°.

Table II. Pseudo First Order Rate Constants for the Hydrolysis of 1 in 50% (v/v) EtOH-H_2O at 75 ± 0.1° as a Function of Hydrochloric Acid Concentration at Constant Ionic Strength[a] (NaCl).

HCl mol.l^{-1}	NaCl mol.l^{-1}	$k_{obsd}.10^7$ sec^{-1}.
- [b,c]	1.102	59
0.112	0.990	146
0.366	0.736	165
1.102[d]	-	179

[a] μ = 1.102 mol.l^{-1}.
[b] pH ca. 2.4 at 20°. At initial pH ca. 5, k_{obsd} is ca. 8.10^{-7} sec^{-1}.
[c] In 50% (v/v) EtOD-D_2O: k_{obsd} also is 59.10^{-7} sec^{-1}.
[d] In the presence of 6.0 N HCl, k_{obsd} is ca. 500.10^{-7} sec^{-1}.

The undissociated form of 1 is thus hydrolysed in dilute acid many times faster than 2. In the absence of more detailed measurements we cannot make an exact calculation of the factor by which reactivity is enhanced, but it appears to be at least 10^5-10^6 in the region of the pK of the COOH group. In contrast, the sulfonanilide 5[8], with an ortho-methyl group, is hydrolysed[11] 65 times more slowly than 1 in 50% (v/v) EtOH-H_2O containing 1.102 M HCl.



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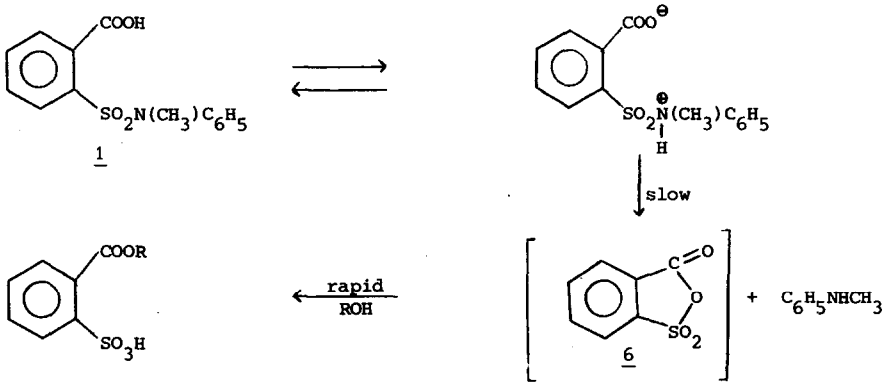
We conclude that the hydrolysis of the sulfonamide group of 1 is catalyzed by the neighbouring COOH group. First indications, particularly the lack of a significant solvent deuterium isotope effect (Table II), suggest that the likely mechanism is intramolecular nucleophilic catalysis[7] (Scheme I). We have prepared the anhydride 6 which is an intermediate in this mechanism, and have shown that under the reaction conditions it is rapidly solvolysed to a mixture of 3 and 4.[12]



3, R = H

4, R = C_2H_5

Scheme I

In 6 M HCl k_{obsd} for 2 has increased by a large factor, and is now of the same order of magnitude as that for the hydrolysis of 1. From the size of the increase it is clear that acid catalysis depends on H_o rather than on the concentration of the hydronium ion. In this respect, at least, the acid catalyzed hydrolysis of the sulfonanilide 2 resembles the same reaction of diphenylphosphinanilides, recently studied by Haake et al.[13], which appears to have distinct A-1 character.

Further work in progress is designed to produce sulfonamides which are subject to even more efficient intramolecular catalysis.

References

1. For a review, see: S. Searles and S. Nukina, Chem. Rev., 59, 1077 (1959).
2. P.D. Carpenter and M. Lennon, J.C.S. Chem. Comm., 664 (1973).
3. D. Klamann and G. Hofbauer, Monatsh. Chem., 84, 62 (1953).
4. D. Klamann and G. Hofbauer, Justus Liebigs Ann. Chem., 581, 182 (1953).
5. F.M. Menger and L. Mandell, J. Amer. Chem. Soc., 89, 4424 (1967).
6. a. R.G. Laughlin, J. Amer. Chem. Soc., 89, 4268 (1967).
   b. Phenol OH stretching frequency shifts, obtained in CCl_4 as the solvent, indicate that sulfonamides are weak hydrogen-bond acceptors ($\Delta\nu_{OH}$ ca. 150 cm^{-1}) and that the sulfonyl oxygen atoms are most likely the acceptors sites under these conditions, see: K. Hovius, G. Zuidema and J.B.F.N. Engberts, Rec. Trav. Chim., 90, 633 (1971).
7. For a review, see: A.J. Kirby and A.R. Fersht in "Progress in Bio-organic Chemistry", E.T. Kaiser and F.J. Kezdy, Ed., Wiley-Interscience, New York, N.Y., p. 1 (1971).
8. The preparation of the substrates will be described in the full paper.
9. pK_a's at 20° in 50% (v/v) EtOH-H_2O.
10. Isolated as its dimethyl ester formed upon treatment with diazomethane. Quantitative isolation of 3 and 4 is hampered by their water solubility.
11. Obtained by monitoring one or two peaks in the aromatic proton region of the NMR spectrum as a function of time. Satisfactory first order plots were obtained for at least more than three half-lives; k_{obsd} values (estimated error: ± 5%) were independent of the initial concentration of 1 in the concentration range studied (0.10-0.25 M).
12. After 24 hrs at 75° a 1:1 mixture of 3 and 4 was obtained. Under similar conditions 3 was converted into 4 in 40% yield.
13. D.A. Tyssee, L.P. Bausher, and P. Haake, J. Amer. Chem. Soc., 95, 8066 (1973).