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INTRAMOLECULAR CATALYSIS OF SULFONAMIDE HYDROLYSIS.

II. cis-2-CARBOXY-N-METHYL-N-PHENYLETHENESULFONAMIDE

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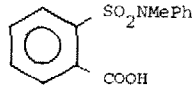
Our understanding of the factors responsible for the high efficiency of enzymic catalysis is based in large part on studies of intramolecular general acid-base catalysis. Much of the early work comprised the hydrolysis of groups involved in important biological processes, particularly carboxylic esters and amides.[1-4] More recently, the limits of efficiency of intramolecular catalysis have become of much interest,[5] and results from a wider range of reactions are relevant in this context.

Some time ago, we initiated studies on the hydrolysis of sulfonamides, a reaction which is normally exceedingly slow.[6] We showed[7] that the hydrolysis of the benzenesulfonamide 1 is 10^5-10^6 times faster than that of the p-carboxy compound, and ascribed this rate enhancement to catalysis by the neighbouring COOH group.



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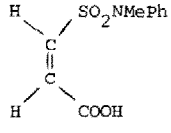

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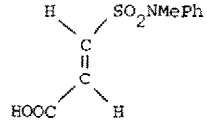

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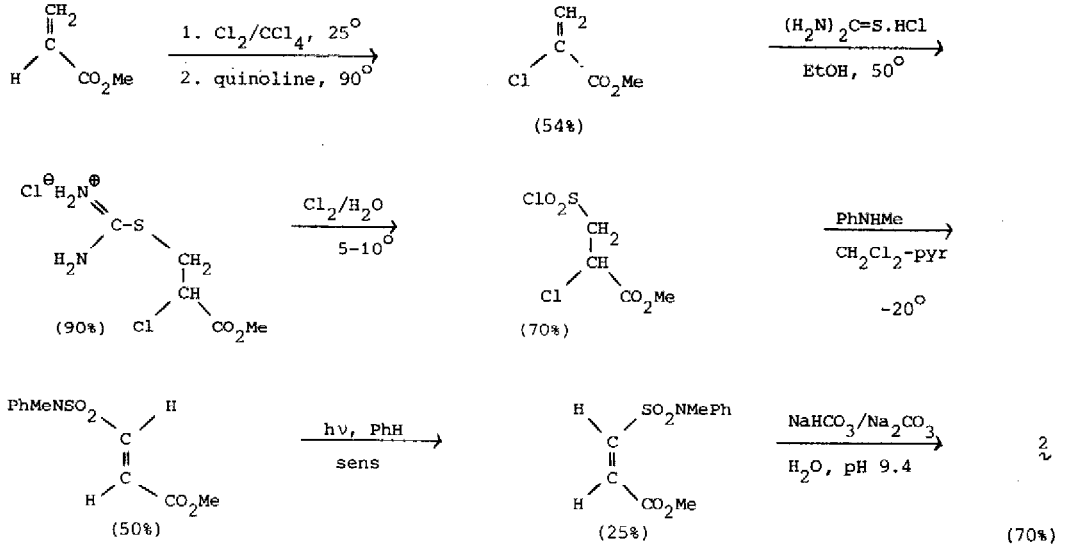
We have now prepared cis-2-carboxy-N-methyl-N-phenylethenesulfonamide (2) by the route shown (Scheme 1), and have compared its rate of hydrolysis[8] with that of the trans isomer 3.



Scheme 1

At 40 ± 0.1°, the rate of hydrolysis[9] of 2 is independent of pH up to pH 1.2, then falls at higher pH as the carboxyl group ionises. The pH-rate profile (Figure 1) is quantitatively accounted for by a "plateau" rate k_o = 1.75.10^{-3} sec^{-1} and pK_A = 2.01.

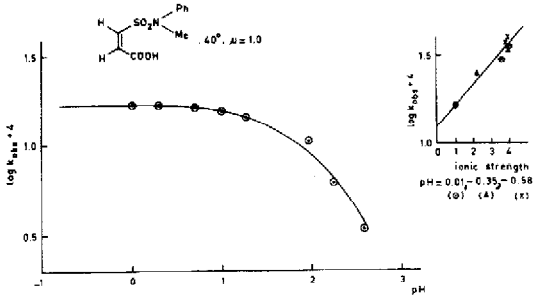
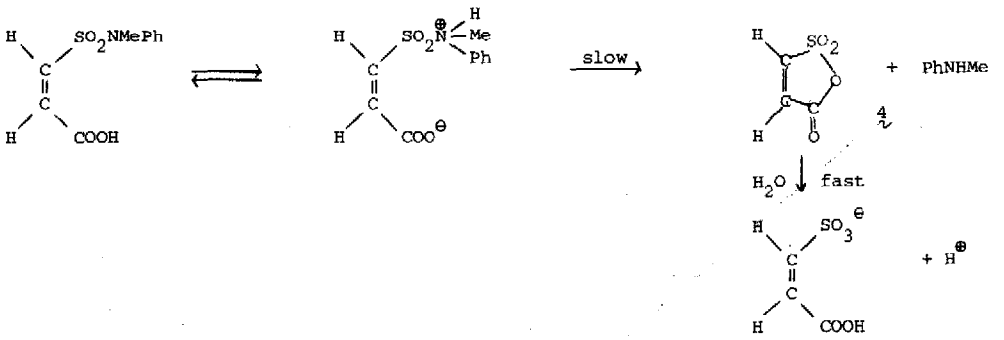


Figure 1. pH-Rate profile for the hydrolysis of 2 in water at 40° and ionic strength 1.0. Inset: the dependence of log k_{obsd} upon μ (HCl-NaCl) at various pH's.

At concentrations of acid above 1M the pseudo-first order rate constant increases with the concentration of HCl, but since the same effect can be obtained by adding NaCl to the same ionic strength (Figure 1) it seems clear that this is a salt effect. In sharp contrast, the hydrolysis of the trans compound (3, pK_A = 2.97 at 40°) is too slow to be measured under these conditions. After treatment with 1M HCl in 60% (v/v) dioxane-water at 40° for 3 months at least 95% of 3 was recovered unchanged. These are the results expected if the hydrolysis of the sulfonamide group of 2 is subject

to highly efficient intramolecular catalysis by the neighbouring COOH group. The efficiency of catalysis, and the relatively low solvent deuterium isotope effect (k_{D_2O}/k_{H_2O} = 1.36 at 40° in 0.1 M HCl), are most readily reconciled with a mechanism involving intramolecular nucleophilic catalysis[10-12] (Scheme 2).



Scheme 2

The thermodynamic parameters of activation ($\Delta H^{\ddagger}$ = 18.6 ± 0.2 kcal.mole^{-1}, $\Delta S^{\ddagger}$ = -11 ± 1 e.u.) can also be accomodated by this mechanism.[13]

The most interesting result is the very high reactivity of 2. Its half-life in 0.1 M HCl at 40° is 6.5 min, which may be compared with the reaction time of the order of a day in 25% HCl at 100°, necessary for the hydrolysis of ordinary sulfonamides.[6] The overall rate enhancement for 2 must be at least 10^8-fold, one of the largest yet observed in a simple system free from strain or conformational restraints. It is further noteworthy that intramolecular catalysis is a great deal more efficient than in the same reaction of 1: the rate of hydrolysis of 2, extrapolated to 75° from our data, is 610 times faster than that of 1 at this temperature (in 50% aqueous ethanol).[14] This pattern is quite different from that found for the corresponding carboxylic amides, in that phthalanilic acid (k_{obsd} = 2.6 10^{-4} sec^{-1} at 25.8°)[15] is actually hydrolysed slightly faster than maleanilic acid (k_{obsd} = 3.10^{-4} sec^{-1} at 39°).[16,17] This difference in behaviour must reflect the greater sensitivity of the sulfonamide hydrolysis reaction to the change in geometry from the aromatic to the ethylenic system,[18] since the two systems are electronically rather similar. We are currently investigating the influence of structure on the catalytic efficiency in a series of related sulfonamides.

References and Notes

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5. For a review, see: M.I. Page, Chem. Soc. Rev., 295 (1973).
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8. Hydrolysis of 2 at 40° and pH 1 provided pure cis-2-carboxyethenesulfonic acid (90%) and N-methylaniline (95%) as the only products.
9. Rates could be easily measured by following the absorption at 235 nm as a function of time.
10. The cyclic anhydride 4 was prepared independently and was found to hydrolyse at least two orders of magnitude faster than 2 in 0.1 M HCl at 40°. Rate measurements in chloroacetic acid-sodium chloroacetate buffers indicated the absence of general acid catalysis by chloroacetic acid.
11. Unambiguous evidence for reversible protonation of sulfonamides at nitrogen was obtained by NMR: F.M. Menger and L. Mandell, J. Am. Chem. Soc., 89, 4424 (1967).
12. A similar isotope effect has been found for the hydrolysis of N-methylcitraconamic acid which also involves intramolecular nucleophilic catalysis: A.J. Kirby and P.W. Lancaster, J.C.S. Perkin Trans., 2, 1206 (1972).
13. The kinetically equivalent intramolecular general acid-base catalysis involving general base catalysis by the ionized carboxyl moiety will be associated with $\Delta S^{\ddagger}$ values of -20 e.u. or lower (in H_2O), cf. ref. 3.
14. In this solvent system $\Delta H^{\ddagger} = 18.2 \pm 0.3$ kcal.mole^{-1} and $\Delta S^{\ddagger} = 16 \pm 1$ e.u. for solvolysis of 2.
15. H. Morawetz and J. Schafer, J. Am. Chem. Soc., 84, 3783 (1962).
16. A.J. Kirby and P.W. Lancaster, unpublished results.
17. In this respect, the behaviour of diethyl phosphonate systems is similar to that of the carboxylic amides: cf. J.P.J. van der Holst, C. van Hooidonk, and H. Kienhuis, Rec. Trav. Chim., 93, 40 (1974).
18. Of course, the carboxylic amides and sulfonamides differ in their site of protonation (O vs N). We suggest that nucleophilic attack by the carboxylate anion on sulfonyl sulfur, as implicated in Scheme 2, occurs via an apical-apical pentaco-ordinate transition state. Investigation of molecular models reveals that on entering this transition state for 1, the ammonium group must be positioned in close proximity to the ring hydrogen atom in the ortho position to the SO_2 group. This steric effect is, of course, absent in the hydrolysis of 2 and might contribute to the difference in rate of hydrolysis between 1 and 2.