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EFFICIENT INTRAMOLECULAR NUCLEOPHILIC CATALYSIS IN THE BASE-CATALYZED HYDROLYSIS OF o-(1-HYDROXYALKYL)-N,N-DIMETHYLBENZENESULFONAMIDES[1]

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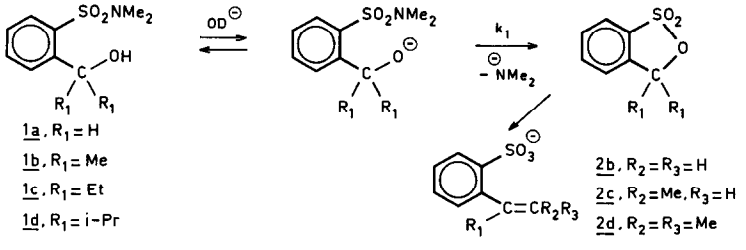
Summary: The title reaction, which proceeds via rate-determining formation of a sultone intermediate, is speeded enormously as a result of the gem-dialkyl effect of o-substituents $-C(R_1)_2OH$ with R_1 = Me, Et and i-Pr.

Both acid- and base-catalyzed hydrolysis of sulfonamides are generally slow reactions requiring drastic conditions.[2] In alkaline media, sulfonamides are even more stable than in the presence of acid and sometimes survive fusion with 80% NaOH at 250°C.[3] Shielding by the sulfonyl oxygen atoms for nucleophilic attack and the low leaving ability of the amine or amine anion are major reasons for this lack of reactivity.

In previous papers we have shown that large rate enhancements of the acid-catalyzed process can be achieved in the presence of a neighboring carboxyl[4,5] or hydroxyl group.[1] Herein we report a kinetic study of intramolecular base-catalyzed hydrolysis of N,N-dimethylbenzenesulfonamides carrying different o-(1-hydroxyalkyl) substituents ($-C(R_1)_2OH$; **1a**, R_1 = H; **1b**, R_1 = Me; **1c**, R_1 = Et; **1d**, R_1 = i-Pr).[6] We find that hydrolysis of **1a** in 1:1 (v/v) CD_3CD_2OD-D_2O containing 1.06 M NaOD is extremely slow, no reaction being detected after 14 weeks at 75°C (half-life, $t_{\frac{1}{2}}$ > 9 years).[8] Interestingly, the hydrolysis of **1b** - **1d** is speeded enormously by the presence of the gem-dialkyl group in the ortho-substituent and react under the same conditions with half-lives of less than 1 hour. The observed hydrolytic process and a likely reaction mechanism are shown in Scheme I. Reaction products are



Scheme I

dimethylamine and the olefins **2b** - **2d** (E/Z mixture in the case of **2c**, ratio dependent on temperature). Rates are first order in sulfonamide and OD^- and no deuterium is incorporated in **2b**- **2d**. The sulton intermediate[7] derived from **1b** was synthesized independently and upon treatment under the same reaction conditions reacted irreversibly to **2b** at least 100 times faster than the overall hydrolysis of the sulfonamide.[9] Therefore, the rate determining step will be nucleophilic attack by alkoxide oxygen on sulfonyl sulfur.[10] In view of the poor leaving ability of the amine anion, this step may proceed via a high-energy pentavalent sulfur intermediate.[11]

Pseudo-first-order rate constants and activation parameters for the base-catalyzed hydrolyses[12] are listed in Table I. The huge difference in reactivity between **1a** and **1b** - **1d**

Table I. Pseudo-first-order Rate Constants and Activation Parameters[a] for Base-Catalyzed Hydrolysis[b] of **1b** - **1d**

Compd	k_{obsd} x 10^5 (s^{-1}, 75°C)	$t_{\frac{1}{2}}$ (75°C)	$\Delta^{\#}G^{\theta}$ kJ.mol^{-1}	$\Delta^{\#}H^{\theta}$ kJ.mol^{-1}	$\Delta^{\#}S^{\theta}$ J.mol^{-1}.K^{-1}
1a		>9 years			
1b	20.6	56 min	102.4±0.1	56±1	-157±3
1c	27.5	42 min	105.2±0.1	80±3	-85±3
1d	38.5	30 min	102.5±0.1	67±1	-120±4

[a] At 25°C. [b] In 1:1 (v/v) CD_3CD_2OD-D_2O containing 1.06 M NaOD.

is another manifestation of the "gem-dialkyl effect" which often provides large rate enhancements in the formation of small ring systems.[1,13-15] The effect cannot be explained in terms of electronic effects, but is most likely the result of initial-state strain which is partly relieved in the transition state for the formation of the sultone intermediate (Scheme I). From the half-lives of the hydrolysis of **1b** - **1d** we estimate a lower limit of 10^9 M for the effective molarity (EM)[16] of the alkoxide nucleophile formed from **1b** - **1d** (pK_a ca. 18)[17] in the alkaline medium. This EM reveals the very high efficiency of the intramolecular nucleophilic catalysis in the rate-determining step.

Assuming that **1b** - **1d** react via the same mechanism, the relative reactivities within the series **1b** - **1d** deserve some comment. First, we note that the size of the alkyl groups R_1 has only a modest effect on the relative rates of hydrolysis for **1b** - **1d**. Second, the large differences in $\Delta^{\#}H^{\theta}$ and $\Delta^{\#}S^{\theta}$ in the series **1b** - **1d** (Table I) suggest that the rates are influenced by a combination of structural and solvation effects. These effects have their

own temperature dependencies and, therefore, the relative rates are strongly dependent on temperature: at 20°C **1c** < **1d** < **1b** but at 75°C **1b** < **1c** < **1d**. The present results do not allow a dissection of all factors determining the relative rates within the series **1a** - **1d**. These factors include entropic advantages (partly affected by the rotational barrier of the o-$C(R_1)_2OH$ substituent), steric desolvation, partial overcoming of repulsion between reacting groups in the initial state and, of course, the pK_a of the OH function.[19]

In summary we note that the present findings provide a further striking demonstration of the notion that highly efficient intramolecular catalysis can be achieved in simple molecules by appropriate positioning of the catalytic moiety and the group undergoing the chemical transformation.

References and Footnotes

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6. The sulfonamides **1a** - **1d**, the sultone derived from **1b**,[7] and the olefin **2b** (sole reaction product after hydrolysis of **1b**) were characterized by satisfactory elemental analyses and by spectral data consistent with the proposed structures. The structures of **2c** and **2d** were fully supported by ^1H- and ^{13}C-NMR spectral data.
7. The sulfonamide **1b** cyclizes to the sultone under acidic conditions. The structure was proven by independent synthesis (ref. 1).
8. Under the same reaction conditions, the same lack of reactivity was observed for N,N-dimethylbenzenesulfonamide and o-methyl-N,N-dimethylbenzenesulfonamide.
9. Rate constant for hydrolysis of this sultone to **2b** in 0.4770 M NaOH (μ = 1.000 M, NaCl) at 25.5°C (pH 13.68) is $k_{obs} = 1.98 \times 10^{-4}\ s^{-1}$.
10. During the hydrolysis of **1b** - **1d** no sultone intermediate could be detected using NMR spectroscopy.
11. This type of intermediate has been proposed in the intramolecular carboxyl-catalyzed hydrolysis of sulfonamides, see ref. 5a. For a general discussion, see D'Rozario, P., Smyth, R.L. and Williams, A., J. Am. Chem. Soc. (1984) **106**, 5027.
12. Rate constants (± 4%) were determined using the NMR technique described previously.[5a] Thermodynamic activation parameters were calculated from at least three rate constants over the temperature range 55-75°C. Satisfactory Eyring plots were obtained.

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19. The pK_a of **1a** is expected to be smaller than those of **1b** - **1d**, since there is less steric hindrance to solvation of the conjugate base. Thus, the lack of reactivity of **1a** cannot be atrributed to the presence of a lower concentration of the conjugate base of **1a**.

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