Intramolecular Nucleophilic Catalysis by the Neighboring Hydroxyl Group in Acid- and Base-Catalyzed Hydrolysis of Aromatic Sulfonamides and Sultones. Mechanism of Intramolecular Nucleophilic Substitution at Sulfonyl Sulfur[1]

Anno Wagenaar and Jan B. F. N. Engberts*

Department of Organic Chemistry, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands

Received August 17, 1987

This paper reports kinetic data illustrating the effectiveness of the Thorpe–Ingold *gem*-dialkyl effect in speeding the intramolecular nucleophilic catalyzed conversion of *o*-(1-hydroxyalkyl)-*N*,*N*-dimethylbenzenesulfonamides **1** into the corresponding sultones **2** in acidic media. Huge rate accelerations are observed which increase with steric bulk of the alkyl substituents. It is proposed that relief of initial-state strain during the activation process is the dominating factor which governs the intramolecular catalysis. The mechanism of intramolecular nucleophilic displacement at sulfonyl sulfur, involving either a concerted ($S_N2(S)$) or a stepwise process, was investigated by using the conjugate base of the *o*-(1-methyl-1-hydroxyethyl)-substituted aromatic sultone **3**. Using ^1H and ^{13}C NMR spectroscopy, it was found that this alkoxide undergoes a rapid degenerate rearrangement ($\Delta^{\ddagger}G^{\ominus}$ = 53.5 kJ·mol^{-1} at 25 °C) rather than forming a symmetrical pentavalent sulfur intermediate of pseudotrigonal bipyramidal geometry. However, the high rate of the symmetrization reaction further illustrates the large rate enhancements induced by the *gem*-dialkyl substituents. The synthesis of the pivotal sultone **3** is outlined. As a spinoff of this work, a convenient synthesis of *o*-alkenylbenzenesulfonamides is briefly described.

In previous papers we have shown that sulfonamide hydrolysis can be accelerated by large factors if a neighboring carboxyl[2] or hydroxyalkyl group[1b] is present in the substrate. These reactions occur via efficient intramolecular nucleophilic displacement reactions involving either intramolecular or intermolecular acid catalysis. Base-catalyzed hydrolysis of sulfonamides can also been speeded enormously by intramolecular catalysis.[1a]

Herein we report further data illustrating the effectiveness of the Thorpe–Ingold *gem*-dialkyl effect[3] in accelerating intramolecular nucleophilic catalysis by a neighboring hydroxyl group in external acid-catalyzed sulfonamide hydrolysis. Furthermore we describe a series of experiments aimed at answering the question whether these rapid intramolecular nucleophilic substitutions at the sulfonyl moiety proceed via a concerted ($S_N2(S)$) pathway or via a stepwise route, involving a pentavalent sulfur intermediate. In the past we have presented experimental and theoretical evidence[2a,b] that intramolecular carboxyl-catalyzed hydrolysis of sulfonamides follows a stepwise mechanism involving a high-energy intermediate of trigonal bipyramidal geometry. Extensive and elegant work by Martin and his associates[4–6] has shown that properly substituted pentavalent sulfur species of this type are indeed accessible. By contrast, particularly Williams[7] has provided evidence that intermolecular nucleophilic substitution at sulfur in ordinary sulfonyl compounds occurs via a concerted pathway.

In an approach akin to that used by Martin,[6] we have concentrated our attempts on obtaining direct spectroscopic evidence for a pentavalent sulfur intermediate employing an aromatic sultone which, upon intramolecular nucleophilic attack, is transformed into either a highly symmetric intermediate or the corresponding transition state.

Scheme I

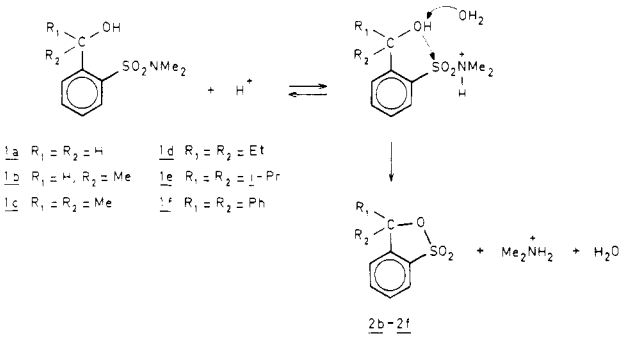


Table I. Pseudo-First-Order Rate Constants for the Acid-Catalyzed Hydrolysis of 1a–f in 1:1 (v/v) EtOH–H_2O in the Presence of 1.350 M HCl at 25 °C

compd	$10^5 k_{obsd}$, s^{-1}	k_{rel}
1a	*a*	
1b	0.41	44 × 10^{-3}
1c	92	1
1d	182	2.0
1e	1080	11.7
1f	9.22	0.10

[a] No reaction detectable after 7 months in 3:1 (v/v) CD_3CD_2OD–D_2O containing 1.26 M HCl at 25.50 °C.

Results and Discussion

The *gem*-Dialkyl Effect. Previously,[1b] we have shown that *o*-(1-hydroxyalkyl)-*N*,*N*-dimethylbenzenesulfonamides of type **1** in the presence of mineral acid undergo irreversible cyclization to the corresponding sultones **2**, pro-

(1) Part 10 in the series on intramolecular-catalyzed hydrolysis of sulfonamides. (a) Part 9: Drijfhout, J. W.; Wagenaar, A.; Engberts, J. B. F. N. *Tetrahedron Lett.* **1986**, *27*, 2423. (b) Part 8: Wagenaar, A.; Kirby, A. J.; Engberts, J. B. F. N. *J. Org. Chem.* **1984**, *49*, 3445.

(2) (a) Graafland, T.; Wagenaar, A.; Kirby, A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1979**, *101*, 6981. (b) Graafland, T.; Nieuwpoort, W. C.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1981**, *103*, 4490. (c) Jager, J.; Graafland, T.; Schenk, H.; Kirby, A. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1984**, *106*, 139.

(3) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Ingold, C. K. *J. Chem. Soc.* **1921**, *119*, 305.

(4) Some of the papers most relevant for the present study include: (a) Martin, J. C.; Perozzi, E. F. *J. Am. Chem. Soc.* **1972**, *94*, 5519. (b) Lau, P. H. W.; Martin, J. C. *J. Am. Chem. Soc.* **1978**, *100*, 7077. (c) Lam, W. Y.; Martin, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 120. (d) Lam, W. Y.; Duesler, E. N.; Martin, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 127. (e) Lam, W. Y.; Martin, J. C. *J. Org. Chem.* **1981**, *46*, 4462.

(5) Perkins, C. W.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 1377.

(6) Perkins, C. W.; Wilson, S. R.; Martin, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 3209.

(7) D'Rozario, P.; Smyth, R. L.; Williams, A. *J. Am. Chem. Soc.* **1984**, *106*, 5027. See also: Kice, J. C. *Adv. Phys. Org. Chem.* **1980**, *17*, 158.

0022-3263/88/1953-0768$01.50/0

Table II. Synthesis of Sultones 2c–f

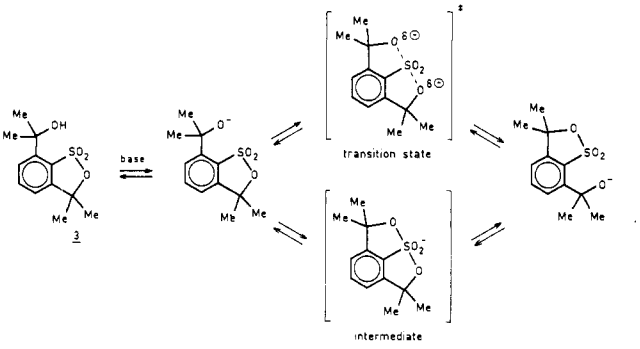
compd	x, g[a]	mmol	y, mL[a]	stirring time, min	yield, %	recryst solv	mp, °C
2c	0.50	2.52	5	60	88	EtOH	106–107 (lit.[19] 106)
2d	0.20	0.74	2	60	55	EtOH–H_2O (8:2)	91 (lit.[19] 91)
2e	0.20	0.67	2	15	99	EtOH	122–123
2f	0.50	1.36	10	900	96	EtOH	161–162 (lit.[21] 161–162)

[a] See Experimental Section.

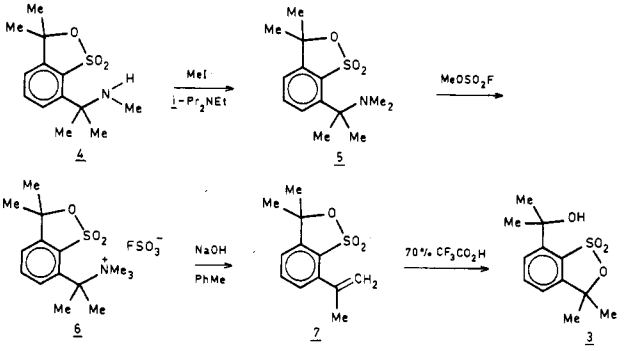
vided that at least one of the substituents R_1 and R_2 is alkyl instead of hydrogen (Scheme I). Pseudo-first-order rate constants and relative rate constants for an extended series of substrates **1b–f** are presented in Table I. The data illustrate the huge rate enhancements induced by *gem*-dialkyl substitution.[8] Whereas **1a** ($R_1 = R_2 = H$) shows no sign of cyclization after prolonged reaction times (Table I), the introduction of a single methyl group (**1b**) already speeds the reaction to a large extent. The second methyl (**1c**) leads to a further rate enhancement by a factor of ca. 225. Variation of the *gem*-dialkyl groups (**1c–f**) exerts moderate effects on the rates. As anticipated, the highest reactivity is observed for the substrate containing the most bulky alkyl group (**1d**, $R_1 = R_2 = i$-Pr). Since localized (field and/or inductive) and delocalized (resonance) electrical effects of alkyl groups are constant,[9] the substituent effects within the series **1a–e** will be largely steric in origin. Polarizability effects may also play a role but are most likely identical or nearly so in the initial state and transition state. Interestingly, the log k_{obsd} values for **1c–e** show a linear correlation with the Taft E_s parameter[10] (slope 0.46). Although this linearity may well be a coincidence, the trend may be taken as further evidence that the substituent effects are dominated by the steric bulk of R_1 and R_2. In accord with detailed studies of the *gem*-dialkyl effect operating on lactonization of hydroxy acids[11] and on intramolecular carboxyl-catalyzed hydrolysis of sulfonamides,[2c] we assume that the most important parameter governing the relative rate constants in the series **1a–f** is (partial) relief of initial state strain during the activation process.[12] However, these effects may be modulated by steric effects on the solvation of the initial and transition state and by, most likely small, effects of R_1 and R_2 on the initial protonation step.

Intramolecular Nucleophilic Substitution at Sulfonyl Sulfur. Although there is little doubt that the rate-determining step in the formation of the sultones **2** will be nucleophilic attack at sulfonyl sulfur,[1b] the question whether or not this reaction occurs via a pentavalent sulfur intermediate of trigonal bipyramidal geometry remains open. In an approach similar to that used by Martin et al.[4–6] we have synthesized a sultone **3**,[13] which, upon intramolecular nucleophilic attack at sulfonyl sulfur, could

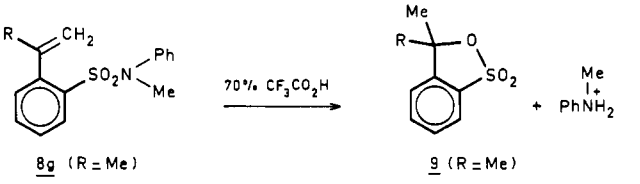
Scheme II



Scheme III



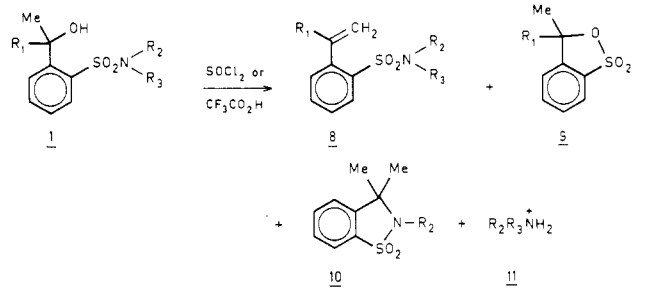
Scheme IV



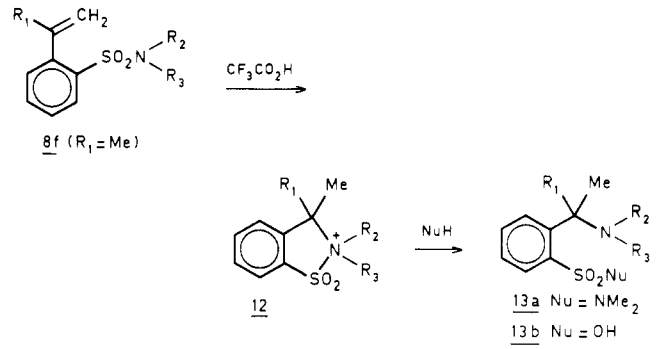
be transformed into a symmetric intermediate, readily identifiable by using ^1H and ^{13}C NMR spectroscopy (Scheme II). The synthesis of the pivotal sultone is outlined in Scheme III. The crucial precursor in this synthesis is the alkenyl sultone **7**, obtained via an E1 elimination from the ammonium salt **6**. The conversion of **7** into **3** was found to occur in a yield of only 30% and strong evidence for an equilibrium process was obtained. Thus, carrying out the reaction in 70% (v/v) CF_3CO_2D–D_2O led to extensive deuterium incorporation in *all* methyl groups and the methylene moiety of **7**. In addition, the same equilibrium mixture was obtained starting from either **7** or **3**. The participation of the ortho substituent in the equilibration is indicated by the observation that, under the same reaction conditions, sultone **2c** remains unchanged (no alkene formation and no incorporation of deuterium) in 70% (v/v) CF_3CO_2D–D_2O for several days. At 65 °C in the same medium, sulfonamide **8g** is transformed into the corresponding sultone **9** with a half-life of ca. 600 min (Scheme IV). Therefore we suggest that the reactions **7** → **3** and **8** → **9** proceed via acid-catalyzed hydration of the double bond, followed by intramolecular

(8) Compare also: Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.
(9) (a) Charton, M. *J. Org. Chem.* **1976**, *41*, 903. (b) Charton, M. *J. Am. Chem. Soc.* **1977**, *99*, 5687. (c) Charton, M. *Prog. Phys. Org. Chem.* **1981**, *13*, 119.
(10) (a) Taft, R. W. In *Steric Effects in Organic Chemistry*; Newman, M. S.; Ed.; Wiley: New York, 1956; Chapter 13. (b) Unger, W. H.; Hansch, C. *Prog. Phys. Org. Chem.* **1976**, *12*, 91.
(11) (a) Milstein, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158. (b) Winans, R. E.; Wilcox, C. F., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 4281. (c) Caswell, M.; Schmir, G. L. *J. Am. Chem. Soc.* **1980**, *102*, 4815.
(12) For a recent theoretical analysis of the origin of proximity effects on reactivity, see: Dorigo, A. E.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 3698.
(13) It is well-known that particularly five-ring sultones are very sensitive to alkaline hydrolysis: (a) Zaborsky, O. R.; Kaiser, E. T. *J. Am. Chem. Soc.* **1970**, *92*, 860. (b) Smith, J. H.; Inoue, T.; Kaiser, E. T. *J. Am. Chem. Soc.* **1972**, *94*, 3098.
(14) No rapid acid-catalyzed symmetrization reaction of **3** was observed either in pure CF_3CO_2H or CF_3CO_2D.
(15) Hesse, M.; Meier, H.; Leeh, B. In *Spektroskopische Methoden in der Organischen Chemie*; Thieme Verlag: Stuttgart, 1979; p 138.

Scheme V



Scheme VI



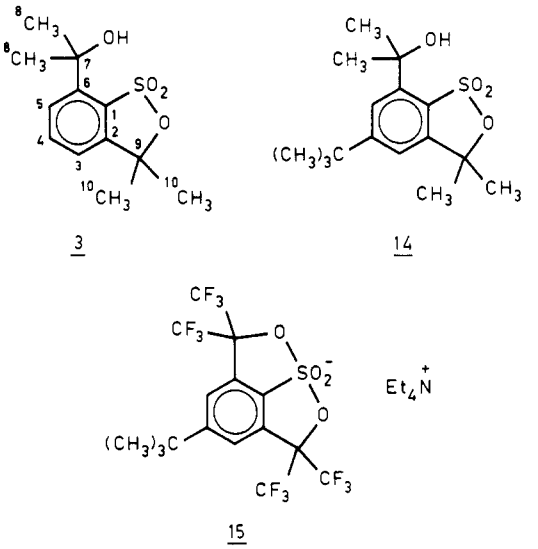
attack of the so-formed OH on the sulfonyl group. However, under suitable conditions dehydration of the intermediate *o*-(hydroxyalkyl)benzenesulfonamide can compete with sultone formation. In fact, this reaction constitutes a useful synthesis of *o*-alkenylbenzenesulfonamides of type **8** from *o*-(1-hydroxyalkyl)benzenesulfonamides[16] **1**. The reaction is illustrated for $R_1 = R_2 = Me$ and $R_3 = H$ in Scheme V. With a slight excess of $SOCl_2$, the product composition depends on temperature and the amount of $SOCl_2$ used. The initial products are **8**, **9**, and **11**; subsequently **8** is transformed into **10**. The same reaction takes place by using anhydrous CF_3CO_2H instead of $SOCl_2$, but in this medium **8** reacts faster to form **10**. Good yields of the *o*-alkenylbenzenesulfonamides can be obtained, however, by using a large excess of $SOCl_2$ in chloroform as the solvent (Table II). In some cases triethylamine was added to suppress rapid acid-catalyzed nucleophilic attack of the neighboring OH function to form the sultone.

The *o*-alkenylbenzenesulfonamides **8** are rather sensitive to acid-catalyzed hydrolysis. In anhydrous CF_3CO_2H, an ammonium salt **12** is formed from **8f** as an intermediate. The evidence includes the observation of magnetically equivalent methyl groups in the ^1H and ^{13}C NMR spectrum. As anticipated, deuterium is incorporated in the methyl groups if the reaction is conducted in CF_3CO_2D. In the presence of nucleophiles (NuH), rapid nucleophilic attack on the sulfonyl group leads to the final products **13** (Scheme VI). If one of the substituents R_2 or R_3 is hydrogen, the intermediate **12** is rapidly deprotonated and the cyclic sulfonamide[2a] is isolated in high yield.

Returning to the question of the mechanism of intramolecular nucleophilic attack at sulfonyl sulfur, sultone **3** was treated with Et_4NOH in CD_3OD as the solvent at room temperature. The ^1H NMR spectrum of the reaction product showed only one methyl signal, whereas the ^{13}C NMR spectrum revealed the presence of only two magnetically different aliphatic carbon atoms. These results are consistent with either the presence of a pentavalent sulfur species or with a dynamic equilibrium, rapid on the ^1H and ^{13}C NMR time scale, between two identical sultones (cf. Scheme II).[14] Similar ^1H and ^{13}C NMR data were obtained by using the potassium salt of **3** in CD_3OD.

^1H and ^{13}C NMR experiments at lowered temperatures provided unequivocal evidence for a dynamic equilibrium. In the ^1H NMR spectrum the methyl signals coalesce at −25 °C and analysis of the line broadening process[15] provides $\Delta^{\ddagger}G^{\ominus} = 53.5$ kJ·mol^{-1} (25 °C), $\Delta^{\ddagger}H^{\ominus} = 40$ kJ·mol^{-1}, and $\Delta^{\ddagger}S^{\ominus} = -45$ J·mol^{-1}·K^{-1}. Coalescence of the carbon signals in the ^{13}C NMR spectrum occurs at temperatures depending on the chemical shift difference ($\Delta\delta$, Hz); C-8/C-10 (−10 °C, $\Delta\delta$ 55), C-7/C-9 (15 °C, $\Delta\delta$ 400), C-2/C-6 (−20 °C, $\Delta\delta$ 45), C-3/C-5 (0 °C, $\Delta\delta$ 130). From these results we calculate[16] $\Delta^{\ddagger}G^{\ominus} = 55.6$ kJ·mol^{-1} (25 °C), $\Delta^{\ddagger}H^{\ominus} = 37$ kJ·mol^{-1}, and $\Delta^{\ddagger}S^{\ominus} = -62$ J·mol^{-1}·K^{-1}. The same dynamic equilibrium is observed for the potassium salt of **3** in the aprotic solvent acetonitrile (^1H NMR: coalescence of the methyl signals at ca. −25 °C).

In a previous study, Martin et al.[4b] described the preparation of the sultone **14** (by oxidation of the corresponding sultene), which differs from **3** only by the presence of an additional *tert*-butyl substituent. Although the NMR spectrum obtained from **14** with KH in ether showed a singlet for the aromatic protons, rapid equilibration between unsymmetrical anions was not ruled out. By contrast, Martin et al.[5] obtained compelling evidence for the sulfuranide dioxide **15** both in solution and in the solid state. The anion **15**, of pseudotrigonal bipyramidal geometry, was also prepared from the corresponding sultone which differs from **3** solely by the presence of four trifluoromethyl moieties instead of four methyl groups and, most likely more irrelevantly, by the presence of an additional *tert*-butyl substituent in the aromatic ring. Therefore it appears that, apart from the Thorpe–Ingold *gem*-dialkyl effect, anionic pentavalent sulfur species like **15** need further stabilization of the apical substituents by electronegative groups like CF_3. The conjugate acid of **15** does not show hypervalent bonding in the ground state but rather undergoes a rapid symmetrization reaction as evidenced by ^1H and ^{19}F NMR spectral data.[4b] The reported $\Delta^{\ddagger}G^{\ominus}$ for this process (58.5 kJ·mol^{-1})[4b] is very similar to the corresponding $\Delta^{\ddagger}G^{\ominus}$ for symmetrization of the anion formed from **3**. We emphasize, however, that these low $\Delta^{\ddagger}G^{\ominus}$ values for the degenerate sultone rearrangements nicely demonstrate how favorable orientation of reacting functional groups coupled with considerable strain energy in the initial state can lead to enormous rate enhance-



(16) These activation parameters are only approximate values since the coalescence temperatures have only limited accuracies.

ments. The rate constant for symmetrization of anionic **3** (k_{obsd} = 2640 s^{-1}, 25 °C) is about 10^7 times greater than k_{obsd} for intramolecular nucleophilic attack of the alkoxide moiety in the anion derived from **1c**. This respectable rate enhancement also demonstrates the different features affecting intra- and intermolecular reactions, since the intramolecular process is particularly fast for a neopentyl-like nucleophilic center, which is notoriously inreactive in intermolecular substitution reactions.[17]

Experimental Section

General. Melting points were determined on a Kofler hot-stage and are uncorrected. ^1H NMR spectra were measured at 60 MHz by using a Hitachi-Perkin-Elmer R24B spectrometer with solutions in $CDCl_3$ (unless otherwise stated) and TMS as an internal standard. The sultone equilibration reactions were followed with a Nicolet 1180 (200 MHz) spectrometer. ^{13}C NMR spectra were obtained with a Varian XL 100/15 spectrometer (solutions in $CDCl_3$). Microanalyses were performed in the analytical section of the department by Mrs. H. Draayer, J. Ebels, J. Hommes, and J. E. Vos.

Generally, oils were purified by Kugelrohr distillation. Rate constants (Table I) were measured by monitoring the reactions spectrophotometrically as described previously.[16] The pseudo-first-order rate constants (k_{obsd}) were reproducible to within 3%.

Materials. The syntheses of **1a–e**[1a] and **1f**[18] have been described previously. Sulfonamide **16** was prepared as a precursor for the synthesis of **8b**.

***o*-(1-Methyl-1-hydroxyethyl)-*N*-benzyl-*N*-methylbenzenesulfonamide (16).** A solution of *o*-(1-methyl-1-hydroxyethyl)-*N*-methylbenzenesulfonamide (2.29 g, 10 mmol) and NaOH (440 mg, 11 mmol) in 30 mL or ethanol (96%) was stirred for 1 h, and benzyl bromide (2.06 g, 12 mmol) was added. Stirring was continued for 4 h, and sodium bromide precipitated from the solution. After removing the solvent in vacuo, ether (50 mL) and water (20 mL) were added, and the ethereal layer was separated and dried over $MgSO_4$. Evaporation of the ether gave an oil, which was purified by flash chromatography:[19] yield of **16**, 2.9 g (91%). ^1H NMR δ 1.77 (s, 6 H), 2.77 (s, 3 H), 4.37 (s, 2 H), 5.27 (s, 1 H), 7.10–7.87 (m, 9 H); ^{13}C NMR δ 32.6, 34.2, 54.0, 72.6 (q), 127.0, 127.7, 128.0, 128.5, 129.5, 132.3, 135.3 (q), 137.7 (q), 149.3 (q). Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39; S, 10.04. Found: C, 63.64; H, 6.64; N, 4.39; S, 10.12.

Sultones 2c–f. General Procedure (Table II). The corresponding *o*-(hydroxyalkyl)benzenesulfonamide (**1c–f**, *x* g) was dissolved in *y* mL of 70% CF_3CO_2H and stirred for 15–60 min. The solution was poured into water, and the precipitate was filtered off and dried. Recrystallization gave the pure sultones **2c–f**.

3,3-Diisopropyl-3*H*-2,1-benzoxathiole 1,1-Dioxide (2e). ^1H NMR δ 0.94 (d, 6 H, *J* = 7 Hz), 0.98 (d, 6 H, *J* = 7 Hz), 2.48 (hextet, 2 H), 7.07–7.87 (m, 4 H); ^{13}C NMR δ 16.6, 17.3, 34.3, 122.0, 122.8, 130.0, 133.3, 139.8, 139.8 (q). Anal. Calcd for $C_{13}H_{18}SO_3$: C, 61.39; H, 7.13; S, 12.61. Found: C, 61.34; H, 7.15; S, 12.56.

Synthesis of Sultone 3 (Scheme III). 7-[1-Methyl-1-(dimethylamino)ethyl]-3,3-dimethyl-3*H*-2,1-benzoxathiole 1,1-Dioxide (5). Methyl iodide (1.56 mL, 25 mmol) was added to a solution of sultone **4**[1b] (4.5 g, 16.7 mmol) in 80 mL of absolute ethanol. After addition of ethyldiisopropylamine (3.5 mL, 20 mmol), the mixture was refluxed for 5 h. After evaporation of the solvent, the residue was stirred with 50 mL of anhydrous ether. The precipitated salt was filtered off. The filtrate was separated, and then the solvent was removed in vacuo. Sometimes it is recommended to wash the ether layer with a solution of $Na_2S_2O_3$ to remove small amounts of iodine. The sultone **5** was obtained in a yield of 81%. ^1H NMR δ 1.45 (s, 6 H), 1.75 (s, 6 H), 2.21 (s, 6 H), 7.00–7.67 (m, 3 H); ^{13}C NMR δ 23.7, 28.3, 38.6, 59.9 (q), 84.5 (q), 120.4, 125.4, 130.4, 133.4, 147.4 (q), 150.6 (q). Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.34; H, 7.47; N, 4.94; S, 11.31. Found: C, 59.29; H, 7.47; N, 4.84; S, 11.35.

7-[1-Methyl-1-(trimethylammonio)ethyl]-3,3-dimethyl-3*H*-2,1-benzoxathiole 1,1-Dioxide Fluorosulfonate (6). "Magic methyl" (CH_3OSO_2F; 2.715 g, 23.8 mmol; *caution!*) was added slowly to a solution of **5** (4.5 g, 15.9 mmol) in 45 mL of dichloromethane (free from water and ethanol). The mixture was refluxed for 6 h, and the precipitate was filtered off, washed with dichloromethane, and dried. The yield was 5.5 g (87%). ^1H NMR (D_2O) δ 2.17 (s, 6 H), 2.54 (s, 6 H), 3.38 (s, 9 H), 7.75–8.33 (m, 3 H); ^{13}C NMR (D_2O) δ 24.2, 28.0, 50.6, 76.7, 96.7, 126.5, 127.1, 131.8, 134.3, 135.4, 147.8. Anal. Calcd for $C_{15}H_{24}FNO_6S_2$: C, 45.32; H, 6.09; S, 16.13. Found: C, 45.32; H, 6.04; S, 16.39.

7-(2-Propenyl)-3,3-dimethyl-3*H*-2,1-benzoxathiole 1,1-Dioxide (7). Sultone **6** (6.96 g, 17.5 mmol) was suspended in a mixture of toluene (100 mL) and an aqueous mixture of NaOH (12.5 M). The mixture was refluxed for 6 h under nitrogen. The dimethylamine was trapped in an aqueous solution of HCl. Another 100 mL of toluene and 100 mL of water were added. The organic layer was separated, washed with dilute HCl, and dried over $MgSO_4$. Evaporation of the solvent provided almost pure **7** (3.43 g, 82%). Recrystallization gave the analytical sample, mp 108 °C. ^1H NMR δ 1.80 (s, 6 H), 2.22 (br s, 3 H), 5.40 (br s, 2 H), 7.07–7.70 (m, 3 H); ^{13}C NMR δ 23.5, 28.4, 89.1 (q), 119.0 (t), 128.8 129.3 (q), 133.6, 139.2 (q), 139.8 (q), 144.7 (q). Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.48; H, 5.92; S, 13.45. Found: C, 60.56; H, 5.99; S, 13.34.

7-(1-Methyl-1-hydroxyethyl)-3,3-dimethyl-3*H*-2,1-benzoxathiole 1,1-Dioxide (3). Sultone **7** (3.0 g, 12.6 mmol) was dissolved in 30 mL of 70% CF_3CO_2H and kept at 75 °C for 4 days. Then the solution was poured into 100 mL of dichloromethane. After neutralization with 300 mL of an ice-cold aqueous sodium carbonate solution, the organic layer was separated and dried over $MgSO_4$. Removal of the solvent in vacuo gave an oily product, which was chromatographed over silica (200–400 mesh) by using dichloromethane as the eluent. The first fraction contained the starting material; continued chromatography now with ether–dichloromethane (2:3) as the eluent provided pure sultone **3** (1.13 g, 35%, mp 140 °C). ^1H NMR δ 1.70 (s, 6 H), 1.77 (s, 6 H), 2.93 (br s, 1 H), 7.00–7.67 (m, 3 H); ^{13}C NMR δ 28.4, 31.2, 73.0, 87.8, 120.5, 126.5, 128.9, 133.8, 145.4 (q), 147.5 (q). Anal. Calcd for $C_{12}H_{16}SO_4$: C, 56.23; H, 6.29; S, 12.51. Found: C, 56.17; H, 6.33; S, 12.42. If the reaction was carried out under the same conditions in 70% CF_3CO_2D–D_2O, ^1H NMR analysis showed 41% deuterium incorporation in all methyl groups and the methylene moiety of **7**. The potassium salt of **3** was prepared according to the method of Martin et al.[4b] ^1H NMR (CD_3OD) δ 1.74 (s, 12 H), 7.5–7.8 (m, 3 H); ^{13}C NMR (CD_3OD) δ 30.2, 81.5 (q), 125.2, 130.1, 135.6, 148.7. ^{13}C NMR of **3** in CD_3OD in the presence of Et_4NOH (27 °C): δ 7.7, 30.2, 53.1, 53.2, 53.4, 81.5 (q), 125.2, 129.5, 135.7, 148.3.

Synthesis of *o*-Alkenylbenzenesulfonamides 8. General Procedure (Scheme V). A mixture of the *o*-(1-hydroxyalkyl)-*N*,*N*-dialkylbenzenesulfonamide **1** (10 mmol) and freshly distilled thionyl chloride (10 mL) in 20 mL of chloroform (free from ethanol) was refluxed for 4–8 h. Sometimes 1.5 equiv of triethylamine was added to avoid the formation of the sultone (Scheme V). The thionyl chloride was removed by distillation. The resulting residue was dissolved in chloroform and washed with an aqueous solution of sodium bicarbonate. After drying of the organic layer over $MgSO_4$, the solvent was evaporated. Pure sulfonamides of type **8** were obtained after recrystallization.

***o*-2-Propenyl-*N*-methylbenzenesulfonamide (8a)**: yield, 92%; mp 82–83 °C (from benzene–petroleum ether, 1:6). ^1H NMR δ 2.17 (s, 3 H), 2.53 (s, 3 H), 4.7 (br s, 1 H), 4.87 (br s, 1 H), 5.20 (br s, 1 H), 7.03–7.60 (m, 3 H), 7.95–8.10 (m, 1 H); ^{13}C NMR δ 25.3, 29.0, 114.9, 127.0, 129.5, 130.1, 132.4, 135.4 (q), 142.8 (q), 146.2 (q). Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63; S, 15.18. Found: C, 56.88; H, 6.14; N, 6.54; S, 15.21.

***o*-2-Propenyl-*N*-benzyl-*N*-methylbenzenesulfonamide (8b)**: yield, 88%; bp 200 °C (0.1 mmHg, Kugelrohr distillation). ^1H NMR δ 2.10 (s, 3 H), 2.60 (s, 3 H), 4.23 (s, 2 H), 4.80 (br s, 1 H), 5.17 (br s, 1 H), 7.00–7.43 (m, 8 H), 7.70–7.93 (m, 1 H); ^{13}C NMR δ 25.3, 33.5, 53.5, 115.4, 126.9, 127.4, 127.9, 128.3, 129.0, 130.8, 132.1, 135.8 (q), 136.8 (q), 143.3 (q), 144.7 (q). Anal. Calcd for

(17) Alder, R. W.; Baker, R.; Brown, J. M. *Mechanism in Organic Chemistry*; Wiley-Interscience: London, 1971; p 204.
(18) Watanabe, H.; Schwartz, R. A.; Hauser, C. R. *J. Chem. Soc., Chem. Commun.* **1969**, 287.
(19) von Sachs, F.; von Wolff, F.; Ludwig, A. *Chem. Ber.* **1904**, *37*, 3252.
(20) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(21) Mustafa, A.; Hilmy, M. K. *J. Chem. Soc.* **1952**, 1339.

$C_{17}H_{19}NO_2S$: C, 67.74; H, 6.35; N, 4.65; S, 10.64. Found: C, 67.55; H, 6.43; N, 4.50; S, 10.55.

o-Ethenyl-*N*,*N*-dimethylbenzenesulfonamide (8c): yield, 47%. The compound rapidly polymerized upon heating. The oily, crude **8c** was purified by chromatography over silica (60–120 mesh), using first petroleum/ether (bp 40–60 °C) and then dichloromethane as the eluent. ^{1}H NMR δ 2.70 (s, 6 H), 5.33 (br s, 1 H), 5.58 (br s, 1 H), 7.13–7.97 (m, 5 H); ^{13}C NMR δ 36.9, 117.8, 127.3, 128.0, 129.5, 132.6, 133.9 (q), 134.2, 137.3 (q). No correct elemental analysis could be obrained because of polymerization.

o-3-Penten-2-yl-*N*-methylbenzenesulfonamide (8d,e, mixture of *E*/*Z* isomers; from 1d): yield, 98%. One isomer (**8d**) had mp 88–91 °C (from petroleum ether, bp 60–80 °C). ^{1}H NMR δ 1.04 (t, 3 H), 1.38 (dd, 3 H), 2.58 (d, 3 H), 4.36 (br t, 1 H), 5.65 (br t, 1 H), 7.05–8.10 (m, 4 H); ^{13}C NMR δ 12.5, 15.0, 29.5, 31.1, 121.2, 126.8, 129.7, 131.5, 132.3, 136.4 (q), 140.6 (q), 143.3 (q). Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85; S, 13.40. Found: C, 60.18; H, 7.20; N, 5.83; S, 13.29. The other isomer is a liquid and showed the following NMR data: ^{1}H NMR δ 0.94 (t, 3 H), 1.80 (d, 3 H), 2.4 (dq, 2 H), 2.49 (d, 3 H), 4.36 (br q, 1 H), 5.38 (br q, 1 H), 7.05–8.10 (m, 4 H). No definite assignment of the *E* and *Z* isomers could be made on the basis of the available data.

o-2-Propenyl-*N*,*N*-dimethylbenzenesulfonamide (8f): yield, 90%; mp 52–53 °C (from petroleum ether, bp 40–60 °C). ^{1}H NMR δ 2.12 (s, 3 H), 2.73 (s, 6 H), 4.77 (br s, 1 H), 5.17 (br s, 1 H), 7.00–7.50 (m, 3 H), 7.70–7.90 (m, 1 H); ^{13}C NMR δ 25.3, 36.9, 115.3, 126.9, 129.3, 130.9, 132.2, 135.6 (q), 143.7 (q), 144.9 (q). Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22; S, 14.23. Found: C, 58.80; H, 6.70; N, 6.22; S, 14.34.

Sulfonamide **8f** was also prepared from *o*-2-propenylbenzenesulfonyl chloride (**17**) and dimethylamine. Sulfonamide **8g** was obtained by a similar procedure.

o-2-Propenylbenzenesulfonyl Chloride (17). Sodium *o*-2-propenylbenzenesulfonate[1b] (2.0 g, 9.08 mmol) was suspended in thionyl chloride (3 mL), a few drops of DMF were added, and the mixture was kept at 70 °C for 2 h. Then the mixture was poured into water containing sufficient sodium bicarbonate to neutralize the acid. The aqueous mixture was extracted with ether (3 × 25 mL). Separation of the ethereal layer and evaporation of the solvent gave oily **17** (1.65 g, 84%), which was purified by Kugelrohr distillation [bp 100 °C (0.1 mmHg)]. ^{1}H NMR δ 2.15 (s, 3 H), 5.00 (s, 1 H), 5.32 (s, 1 H), 7.13–7.80 (m, 3 H), 8.00 (br m, 1 H); ^{13}C NMR δ 24.9, 117.4, 127.8, 128.7, 131.4, 134.9, 141.7 (q), 142.1 (q), 143.8 (q). Anal. Calcd for $C_9H_9O_2SCl$: C, 49.89; H, 4.19; S, 14.80; Cl, 16.36. Found: C, 49.72; H, 4.19; S, 14.90; Cl, 16.42.

o-2-Propenyl-*N*,*N*-dimethylbenzenesulfonamide (8f). A mixture of 2 mL of 40% dimethylamine (in water) and **17** (0.5 g, 2.31 mmol) in benzene (10 mL) was refluxed for 2 h. The mixture was poured into cold water, neutralized with a dilute solution of HCl, and extracted with benzene (3 × 25 mL). The benzene layer was dried over $MgSO_4$. Evaporation of benzene gave almost pure **8f** (0.43 g, 82%). Pure **8f** (vide supra) was obtained after one crystallization from petroleum ether (bp 40–60 °C).

o-2-Propenyl-*N*-methyl-*N*-phenylbenzenesulfonamide (8g). A mixture of *N*-methylaniline (0.75 g, 7 mmol) and **17** (1.08 g, 5 mmol) in pyridine (10 mL) was heated overnight at 80 °C. Workup was carried out as described for **8f**. The yield was 67%. Kugelrohr distillation gave pure **8g**, mp 55 °C. ^{1}H NMR δ 2.03 (s, 3 H), 3.20 (s, 3 H), 4.75 (s, 1 H), 5.05 (s, 1 H), 7.0–7.7 (m, 9 H); ^{13}C NMR δ 25.5, 38.3, 115.2 (t), 126.1, 126.7, 126.8, 128.8, 129.6, 130.9, 132.3, 136.1 (q), 141.3 (q), 143.9 (q), 144.8 (q). Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87; S, 11.16. Found: C, 66.91; H, 5.97; N, 4.86; S, 11.12.

Synthesis of 13a,b (Scheme VI). o-[1-Methyl-1-(dimethylamino)ethyl]-*N*,*N*-dimethylbenzenesulfonamide (13a). A solution of **8f** (0.5 g, 2.22 mmol) in 100% CF_3CO_2H (5 mL) was stirred at 25 °C for 4 days. The solvent was distilled off, and the residue was poured into 10 mL of a 40% aqueous solution of dimethylamine. The solid sulfonamide was filtered off, dried, and crystallized from ether–*n*-hexane. The yield of **13a** was 0.4 g (70%), mp 102–103 °C. ^{1}H NMR δ 1.47 (s, 6 H), 2.12 (s, 6 H), 2.75 (s, 6 H), 7.00–7.67 (m, 4 H); ^{13}C NMR δ 23.9, 37.4, 38.3, 60.6, 126.2, 128.2, 128.3, 131.2, 139.4 (q), 151.9 (q). Anal. Calcd for $C_{13}H_{22}N_2O_2S$: C, 57.75; H, 8.20; N, 10.36; S, 11.86. Found: C, 57.67; H, 8.17; N, 10.35; S, 11.79.

o-[1-Methyl-1-(dimethylamino)ethyl]benzenesulfonic Acid (13b). If the reaction mixture (see **13a**) is poured into water and the solvent is removed, the sulfonic acid **13b** is formed. A pure sample (mp 257 °C dec) is obtained after crystallization from 96% ethanol (yield 82%). ^{1}H NMR (D_2O) δ 1.87 (s, 6 H), 2.75 (br s, 6 H), 7.5–7.8 (m, 3 H), 8.06–8.23 (m, 1 H); ^{13}C NMR (D_2O) δ 23.2, 38.0, 67.9 (q) 129.8, 130.7, 131.6, 132.9, 135.6 (q), 142.3 (q). Anal. Calcd for $C_{11}H_{17}NO_3S$: C, 54.30; H, 7.04; N, 5.76; S, 13.18. Found: C, 53.91; H, 6.97; N, 5.63; S, 13.31.

Registry No. **1a**, 91190-73-7; **1b**, 91190-75-9; **1c**, 91190-74-8; **1d**, 107106-09-2; **1e**, 107106-10-5; **1f**, 22185-04-2; **2c**, 81403-42-1; **2d**, 112320-43-1; **2e**, 112320-44-2; **2f**, 15448-98-3; **3**, 112320-50-0; **3**·K, 112320-59-9; **4**, 91190-82-8; **5**, 112320-46-4; **6**, 112320-48-6; **7**, 112320-49-7; **8a**, 112320-51-1; **8b**, 112320-52-2; **8c**, 51119-86-9; (*E*)-**8d**, 112320-53-3; (*Z*)-**8d**, 112320-54-4; **8f**, 112320-55-5; **8g**, 112320-56-6; **13a**, 112320-57-7; **13b**, 112320-58-8; **16**, 112320-45-3; **17**, 81403-44-3; *o*-$HOC(Me)_2C_6H_4SO_2NHMe$, 91190-80-6; $BrCH_2Ph$, 100-39-0; *o*-$H_2C{=}C(Me)C_6H_4SO_3H{\cdot}Na$, 79347-33-4; $HNMe_2$, 124-40-3; MeNHPh, 100-61-8.

Reduction of Benzophenone with Metal Hydrides. A Kinetic Isotope Effect and Substituent Effect Study

Hiroshi Yamataka* and Terukiyo Hanafusa

The Institute of Scientific and Industrial Research, Osaka University, Ibaraki, Osaka 567, Japan

Received July 31, 1987

Carbonyl carbon kinetic isotope effects (KIEs) have been determined for the reduction of benzophenone-7-^{14}C with various metal hydrides at 25 °C. The observed KIEs are as follows: BH_3/THF, $^{12}k/^{14}k$ = 1.035 ± 0.002; AlH_3/Et_2O, 1.021 ± 0.004; 9-BBN/THF, 1.027 ± 0.004; DIBAL/hexane, 1.000 ± 0.003; $LiAlH_4$/THF, 1.017 ± 0.007. The relative reactivities of ortho-, meta-, and para-substituted benzophenones with these reagents were also determined by the competition experiments. The absence of ^{14}C KIE, the small ρ value (0.5), and the absence of steric rate retardation due to ortho substituents in the reduction of the ketone with DIBAL suggest that the reaction goes through the rate-determining electron transfer from DIBAL to the ketone. The reactions of other reducing agents showed positive KIE as well as a variable extent of steric effect and are concluded to proceed via a polar mechanism. The difference in the nature of the transition state is discussed on the basis of these results.

The reduction of carbonyl compounds with metal hydrides is one of the elemental processes in organic syntheses, and recent achievement in developing stereoselective reductions of prochiral carbonyl compounds with

0022-3263/88/1953-0772$01.50/0