Kinetics and Mechanism of the Acid-catalysed Hydrolysis of *N*-Methyl-*N*-phenylsulphamate

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The catalytic effects of hydrochloric, perchloric, and sulphuric acids on the hydrolysis of *N*-methyl-*N*-phenylsulphamate salts have been examined and the data have been treated by the Bunnett and Bunnett–Olsen methods. Solvent isotope, salt, organic solvent, and temperature effects have also been probed. The mechanism of the acid-catalysed hydrolysis is postulated as involving two steps: a rapid protonation and a rate-determining *A*-2 nucleophilic attack by water.

THE solvolytic cleavage of the nitrogen–sulphur(VI) bond in sulphamates and related systems has been the subject of considerable study in recent times. Thus the hydrolysis of various sulphamyl chlorides,[1] of the medicinally important sulphamyl azides,[2] of heparin, a naturally occurring sulphamate,[3] and of the artificial sweeteners, the cyclamates,[4] have been studied. A number of biochemically important sulphate esters have been prepared by alcoholyses of various sulphamic acids.[5]

Because of our interest in both the mechanism of hydrolysis of sulphamates and of their metabolic breakdown and the possible involvement of water in both, we

[1] E. C. F. Ko and R. E. Robertson, *J. Amer. Chem. Soc.*, 1972, **94**, 573; *Canad. J. Chem.*, 1972, **50**, 946; O. Rogne, *J. Chem. Soc.*, 1969, 663.
[2] W. L. Matier, W. T. Comer, and D. Deitchman, *J. Medicin. Chem.*, 1972, **15**, 538.
[3] Y. Inoue and K. Nagasawa, *Carbohydrate Res.*, 1973, **31**, 359.
[4] J. M. Talmage, L. Chafetz, and M. Elefant, *J. Pharm. Sci.*, 1968, **57**, 1073; D. E. Johnson, H. B. Nunn, and S. Bruckenstein, *Analyt. Chem.*, 1968, **40**, 368.
[5] K. Nagasawa and H. Yoshidome, *Chem. and Pharm. Bull. (Japan)*, 1970, **18**, 2023.

have for some time been studying the kinetics of hydrolysis of various sulphamates [6] and sulphamides.[7] We present here our results on the 'mixed' aryl–alkyl derivative, *N*-methyl-*N*-phenylsulphamate.

EXPERIMENTAL

Materials.—Details of many of these have been given previously.[6a] Pyridine and *N*-methylaniline were distilled before use. *p*-Dioxan (B.D.H., AnalaR) was used as obtained. The synthesis of potassium and sodium *N*-methyl-*N*-phenylsulphamates were carried out by the method described for *N*-ethyl-*N*-phenylsulphamate.[8] Both salts were recrystallized three times from 97% ethyl alcohol and dried over phosphorus pentaoxide overnight *in vacuo*. Elemental analysis for C, H, N, and S on these materials and on their *S*-benzylthiouronium derivatives, m.p. 130°, were satisfactory.

Kinetic Measurements.—The method and instruments have been described previously.[6a] The temperature within the u.v. cells was accurate to ±0.5° and it was checked with a Pye Scalamp thermocouple galvanometer. Cells were preheated for 5 min at the reaction temperature prior to the addition of the substrate. The spectrum of the solution when hydrolysis was complete was identical to that of *N*-methylaniline in the same medium. Readings were generally taken at λ 266 nm but, in some cases, absorbances were measured at different wavelengths in the same medium and the rate constants calculated from these readings were the same, implying that only one species was involved. Good first-order rate constants were obtained either from the slopes of plots of $\log(D_t - D_\infty)$ against time or by the method of Guggenheim. All rate constants were determined in duplicate with an accuracy of ±5%.

RESULTS AND DISCUSSION

Effect of Acids and Basicity Constant.—The observed first-order rate constants for the catalytic effect of hydrochloric, perchloric, and sulphuric acid are given in Table 1. In order to emphasise the differences in the catalytic efficiencies of the different acids and to illustrate that the rate–acid profiles go through maxima, these data have been plotted in the Figure using H_0 as a measure of acid strength. We have previously observed, and commented on, similar maxima in the hydrolysis of sodium *N*-1-naphthylsulphamate.[6a] An expected and interesting feature of the maxima in the hydrolysis of *N*-methyl-*N*-phenylsulphamate is that their positions occur at lower acidities (H_0 *ca.* −1.3) than in the rate–acid profiles for *N*-1-naphthyl- (H_0 *ca.* −3.3) [6a] and phenyl-sulphamates (H_0 *ca.* −2.8).[6b] This shift of the maximum to lower acidities is consistent with the greater basic strength of *N*-methylaniline, compared with aniline or 1-naphthylamine. The catalytic order of acids is HCl > H_2SO_4 > $HClO_4$. It has been shown that carboxylates,[9a] which are hydrolysed by an *A*-2 mechanism, follow the order HCl ~ H_2SO_4 > $HClO_4$, whereas esters hydrolysing by an *A*-1 mechanism follow the order $HClO_4$ > H_2SO_4 > HCl. Thus Bunton *et al.*[9a] have

TABLE 1

Observed first-order rate constants ($10^3k/s^{-1}$) for the hydrolysis of potassium *N*-methyl-*N*-phenylsulphamate at 40°

Acid strength (M)	HCl	$HClO_4$	H_2SO_4
0.1	0.16	0.18	0.18
0.1 [a]	0.59		
0.25	0.38		
0.5	0.63	0.84	0.55
1.0	1.12	0.99	0.95
1.0 [a]	2.36		
1.5		1.33	
2.0	1.53	1.53	1.74
2.5		1.51	
3.0	1.86	1.50	1.67
4.0	1.81	1.08	1.40
5.0	1.67	0.77	1.12
6.0	1.20		
6.0 [a]	1.13		
7.0	1.28		
8.0	1.10		
10.0			0.07

[a] DCl in D_2O.

suggested that the catalytic order of acids can serve as a diagnostic of mechanism. The same catalytic order of acids as observed in the hydrolysis of *N*-methyl-*N*-phenylsulphamate has also been observed in the acid-catalysed hydrolysis of benzamide,[9b] of carboxylic anhydrides,[9c,d] of acetylglycine; [9e] and of *N*-t-butylbenzaldoxime and 2-t-butyl-3-phenyloxaziridine,[9f] all of which involve bimolecular attack of water in the transition state. This criterion has also been used to support a unimolecular *A*-1 mechanism in the hydrolysis of certain sydnones.[9g] The profiles in the Figure therefore support the involvement of an *A*-2 mechanism. Bunnett *w* and *w** [10] and Bunnett and Olsen [11] plots were carried out on the data in Table 1. The following values of pK_{BH^+} (based on H_0 with *m*, acid used, and method employed, respectively, in parentheses) were used in the calculations: −0.92 (1.09, HCl, u.v.), −0.99 (1.17, HCl, n.m.r.), −0.83 (0.94, $HClO_4$, n.m.r.), and −0.93 (0.86,

[6] (*a*) W. J. Spillane, N. Regan, and F. L. Scott, *J.C.S. Perkin II*, 1974, 445; (*b*) W. J. Spillane, C. B. Goggin, N. Regan, and F. L. Scott, *Internat. J. Sulfur Chem.*, in the press; (*c*) W. J. Spillane, F. L. Scott, and C. B. Goggin, *ibid.*, 1971, **1**, 223; (*d*) W. J. Spillane, C. B. Goggin, N. Regan, and F. L. Scott, *ibid.*, 1973, **8**, 281; (*e*) W. J. Spillane, *J. Pharm. Sci.*, 1973, **62**, 1394.

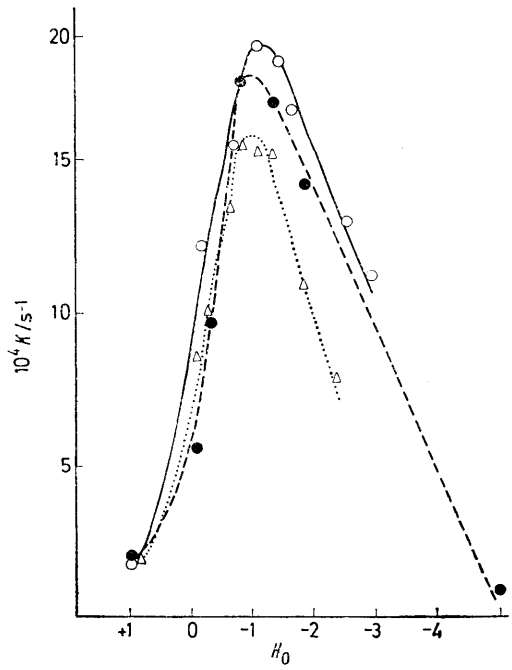
[7] W. J. Spillane, J. A. Barry, and F. L. Scott, *J.C.S. Perkin II*, 1973, 481.

[8] D. Z. Zavel'skii and L. A. Lishnevskaya, *Zhur. obshchei Khim.*, 1958, **28**, 1019.

[9] (*a*) C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 1258; (*b*) C. A. Bunton, S. J. Farber, A. J. G. Milbank, C. J. O'Connor, and T. A. Turney, *J.C.S. Perkin II*, 1972, 1869; (*c*) C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, 1965, **30**, 1365; (*d*) C. A. Bunton, N. A. Fuller, S. G. Perry, and J. Pitman, *J. Chem. Soc.*, 1962, 4478; (*e*) J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 685; (*f*) C. J. O'Connor, E J. Fendler, and J. H. Fendler, *ibid.*, p. 1744; (*g*) S. Aziz, A. J. Buglass, and J. G. Tillett, *J. Chem. Soc.* (*B*), 1971, 1912; (*h*) G. Calvaruso and F. P. Calvasino, *ibid.*, p. 483.

[10] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956, 4968, 4973, 4978.

[11] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1917.



Observed first-order hydrolysis rate constants for potassium *N*-methyl-*N*-phenylsulphamate at 40° as a function of acidity in HCl (○), H_2SO_4 (●), and $HClO_4$ (△)

H_2SO_4, n.m.r.).[12] The substrate was regarded as being moderately basic so the functions plotted were (1)—(3).

$$\log 10^4k - \log\{10^4h_0/(h_0 + K_{BH^+})\} \quad vs.\ \log a_w\ (w\ \text{plot}) \quad (1)$$

$$\log 10^4k - \log\{10^4H^+/(h_0 + K_{BH^+})\} \quad vs.\ \log a_w\ (w^*\ \text{plot}) \quad (2)$$

$$\log 10^4k - \log\{10^4\ BH^+/(BH^+ + B)\} \quad vs.\ \{H_0 + \log H^+\}\ (\Phi\ \text{plot}) \quad (3)$$

The Bunnett *w* plot showed marked scatter and the values of *w** and Φ obtained are given in Table 2. Bunnett has demonstrated that either *w* or *w** must be curved if a

TABLE 2

Bunnett and Bunnett and Olsen correlations of rate data at 40° for potassium *N*-methyl-*N*-phenylsulphamate

Acid	Concentration range (M)	Slope	Correlation coefficient	No. of points
HCl	0.5—8.0	−3.6 (*w**)	0.99	10
HCl	0.5—8.0	0.59 (*φ*)	0.99	8
$HClO_4$	0.1—5.0	−3.2 (*w**)	0.99	9
$HClO_4$	0.1—5.0	0.49 (*φ*)	0.99	7
H_2SO_4	0.5—10.0	−2.00 (*w**)	0.98	7

wide range of acid is included;[11] thus the failure of the *w* plot is not unexpected. Bunnett has found that *w** values < −2 are consistent with the involvement of water as a nucleophile in the transition state, and thus the three values of *w** in Table 2 indicate that water plays such a role in the transition state leading to hydrolysis products (Scheme). The Bunnett and Olsen *φ* para-

$$\underset{B}{Ar(Me)NSO_3^-} + H^+ \overset{\text{Fast}}{\rightleftharpoons} \underset{BH^+}{Ar(Me)\overset{+}{N}HSO_3^-} \xrightarrow{\text{Slow, } k_2} Ar(Me)\overset{+}{N}H_2\cdot HSO_4^-$$

SCHEME

meters support this conclusion since *φ* values in the approximate range +0.22 to +0.56 have been interpreted as implying that water is involved as a nucleophile in the rate-limiting step.

Salt Effects.—Table 3 shows the effect of added sodium chloride and perchlorate on the rate of hydrolysis of

TABLE 3

Salt effects on the hydrolysis of potassium *N*-methyl-*N*-phenylsulphamate in perchloric acid at 40°

Acid strength (M)	Added salt (M)	$10^3k/s^{-1}$
2.0		1.53
2.0	3.0 [a]	1.20
2.0	3.0 [b]	0.73
5.0		0.77
5.0	1.5 [a]	0.59
5.0	1.5 [b]	0.47
5.0	2.0 [a]	0.55
5.0	2.0 [b]	0.38

[a] Added NaCl. [b] Added $NaClO_4$.

N-methyl-*N*-phenylsulphamate. It is seen that both salts depress the rate of hydrolysis perchlorates doing so more than chlorides. Bunton *et al.*[9a] have shown that the salt effect of anions of low charge density such as perchlorates is slightly negative in *A*-2 acid-catalysed ester hydrolysis and anions of high charge density such as chloride hinder only slightly or assist the hydrolysis. For an *A*-1 type mechanism both chlorides and perchlorates assist the hydrolysis significantly. This criterion has also been applied to carboxylic anhydrides.[9h] Thus, the data in Table 3 suggest that the substrate is undergoing reaction by an *A*-2 pathway.

Solvent Isotope Effect.—From the data in Table 1 solvent isotope effects (k_{D_2O}/k_{H_2O}) of 3.71 (0.1M-HCl), 1.97 (1.0M-HCl), and 0.94 (6.0M-HCl) can be calculated. Deuterium oxide is a weaker base than water and therefore nucleophilic attack by D_2O in an *A*-2 mechanism will be less effective than H_2O. However, the substrate will be able to compete with the solvent for a deuteron in D_2O more effectively than for a proton in H_2O and thus the concentration of the protonated species will be greater in D_2O than in H_2O and consequently, the rate should be faster in the former. As in the case of amides, the effect will be to shift the maximum in the rate–acid profile to lower acidities.[13] The above solvent isotope effects are consistent with a reaction involving a rapid pre-equilibrium followed by bimolecular deuterium oxide or water attack. When protonation is substantially

[12] W. J. Spillane, unpublished work.
[13] C. J. O'Connor, *Quart. Rev.*, 1970, **24**, 553.

complete * k_{D_2O}/k_{H_2O} *ca.* 1. When the pre-equilibrium is significant, at lower acidities, $k_{D_2O}/k_{H_2O} > 1$. Thus, the magnitude of the solvent isotope effect at a given acid strength reflects the relative importance of the protonation or the hydrolytic nitrogen–sulphur bond cleavage steps at that acid strength. The solvent isotope effect in 0.1M-acid is rather large (3.7). This value is outside the range normally associated with either an *A*-1 or an *A*-2 mechanism. However, large values of k_{D_2O}/k_{H_2O} were found by Candlin and Wilkins for the hydrolysis of hydroxylamine *N*-monosulphonates (2.86) and other related sulphonates, which involve a pre-equilibrium protonation followed by nucleophilic attack by water.[14] Similar large isotope effects have been observed in acetal hydrolysis.[15]

Solvent Effects.—Kice has found that the rate constant for a typical *A*-1 hydrolysis reaction increases quite sharply with dioxan content of water–dioxan mixtures containing a fixed amount of acid, while the rate constant for hydrolysis by an *A*-2 mechanism is increased to a much lesser degree for the same change in dioxan content.[16] He has used this as a test of mechanism in the hydrolysis of aryl sulphates (*A*-1) [16a] and *S*-alkyl and *S*-aryl thiosulphates (*A*-1) [16b] by comparing the relative change in rates, $k/k_{40\%\ \text{dioxan}}$, for a change from 40 to 80% dioxan. Kice compares his data with that of Bunton and Hendy for the acid-catalysed hydrolysis of the methyl selenate system $MeOSeO_3^-$ (*A*-2).[17] We have found, however, that for *N*-phenylsulphamate the relative change in rate depends not only on the substrate, but also on the acid strength.[6b] Kice's comparison of his data, measured at a fixed acid level of 0.5M-$HClO_4$, with that of Bunton and Hendy, measured at a level of 0.1M-$HClO_4$, may not therefore be valid. Accordingly, in Table 4, the data, with one exception, relate to 0.5M-$HClO_4$. For the *N*-cyclohexylsulphamate system, data at 0.5M-$HClO_4$ were not available and we have used data at 0.72M. We feel that its inclusion is satisfactory because the difference between the rate constants for its hydrolysis measured at acid levels of 0.5 and 0.72M should not be more than a factor of 1.04.[6c] The aryl thiosulphates and aryl sulphates show the largest relative rate changes and the cyclohexylsulphamate displays the smallest change. We have previously,[6c] on the basis of this and other evidence, viewed the acid-catalysed hydrolysis of cyclohexylsulphamate as being *A*-2. The increase in relative rate for *N*-phenylsulphamate is hardly large enough to place it in the *A*-1 category, though it appears to be too large to place it in the *A*-2 category. We feel that in this instance this criterion is inconclusive.

Thomas and Leveson [18] have correlated the effects of changing the dioxan content of dioxan–water mixtures containing 0.1M-acid using Bunnett type plots of log $k + H_0$ against log a_w and have assigned the mechanism on the basis of the slopes of those plots. Neither Kice's, Bunton and Hendy's, nor our own data can be treated in this way because the data are too limited and/or acid strengths other than 0.1M were used.

TABLE 4

Effect of % dioxan in dioxan–water mixtures on the relative rates of hydrolysis of a number of substrates [a]

% Dioxan	$C_6H_5OSO_3^-$ [b]	$C_6H_5SSO_3^-$ [c]	cyclo-$C_6H_{11}NHSO_3^-$ [d]	$C_6H_5N(CH_3)SO_3^-$ [e]
40	(1.0)	(1.0)	(1.0)	(1.0)
60	5.0	6.0	3.1	7.4
70				16.0
80	67	110	8.4	28.5

[a] Sodium salts were used in each case. [b] See ref. 16*a*; data measured at 30.1° for 0.5M-$HClO_4$ solutions. [c] See ref. 16*b*; data measured at 70° for 0.5M-$HClO_4$ solution. [d] See ref. 6*c*; data measured at 95° for 0.72M-$HClO_4$ solutions. [e] Data at 25° for 0.5M-$HClO_4$ solutions; $k_{40\%\ \text{dioxan}} = 1.10 \times 10^{-3}\ s^{-1}$.

Temperature Effects.—The entropy data in Table 5 do not appear to be sufficiently negative for hydrolysis by an *A*-2 mechanism since entropy values in the range −30 to −90 J mol^{-1} K^{-1} are associated with bimolecular nucleophilic hydrolysis of trialkylamine–, pyridine–, and α-picoline–sulphur trioxide adducts.[19] It is unlikely that these entropy values, especially the value in 11.6M-HCl, are composites involving an entropy term for the protonation (which will be complete in 11M-acid) and hydrolysis steps. We have found similar low negative or even positive values for the entropy involved in the hydrolysis of most other sulphamates, *e.g.* *N*-aryl [6a,b]

TABLE 5

Effect of temperature and activation parameters for the hydrolysis of potassium *N*-methyl-*N*-phenylsulphamate in hydrochloric acid

T/K [a]	297	313	324.8	331	337.6
10^3k/s^{-1}	0.202	1.15	4.84	9.9	14.4
$\Delta H^\ddagger$/kJ mol^{-1} = 90.6	$\Delta S^\ddagger$/J mol^{-1} K^{-1} = −11.1				
T/K [b]	298.5	316	337		
10^3k/s^{-1}	0.0514	0.748	7.00		
$\Delta H^\ddagger$/kJ mol^{-1} = 92.8	$\Delta S^\ddagger$/J mol^{-1} K^{-1} = −15.7				

[a] Hydrolysis carried out in 6.0M–HCl. [b] Hydrolysis carried out in 11.6M-HCl.

* Using the equation $\log I = -mH_0 + pK_{BH^+}$ and the values of pK_{BH^+} and m given above, one can readily calculate that protonation should be virtually complete in HCl of strength *ca.* 7.5M (H_0 *ca.* −2.7). In DCl, protonation should be complete even at lower acidities.

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[15] R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, New Jersey, 1973, 2nd edn., p. 291.

[16] (*a*) J. L. Kice and J. M. Anderson, *J. Amer. Chem. Soc.*, 1966, **88**, 5242; (*b*) J. L. Kice, J. M. Anderson, and N. E. Pawloski, *ibid.*, p. 5245.

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[18] C. W. Thomas and L. L. Leveson, *J.C.S. Perkin II*, 1973, 20.

[19] I. G. Ryss, L. P. Bogdanova, S. L. Idel's, and T. N. Kotylar, *Russ. J. Inorg. Chem.*, 1969, **14**, 1577; *Kinetika i Kataliz*, 1970, **4**, 1057; E. J. Fendler and J. H. Fendler, *Chem. Comm.*, 1967, 1261.

and *N*-alkyl [6c,d] and we have suggested borderline or mixed mechanisms to account for these. This phenomenon seems to be general for the hydrolysis of monosubstituted sulphamates many of which, on the basis of independent mechanistic criteria do have water involved in their decomposition. We feel therefore that a more probable explanation for these entropy values lies in differences in solvation between the intermediate zwitterion and the transition state. There will be less concentration of charge in the transition state than in the zwitterion, and we would expect a progressive decrease in hydration along the reaction path leading to the transition state. This would imply that an increase in entropy would occur and thus the entropies in Table 5 could be consistent with an *A*-2 mechanism.

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