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Evidence for Hypervalent Intermediates in Acid Hydrolysis of Sulfinamide. ^{18}O Exchange and a Break in pH–Rate Profile

Tadashi Okuyama,* Jong Pal Lee,[1] and Kazunobu Ohnishi

Faculty of Engineering Science, Osaka University
Toyonaka, Osaka 560, Japan

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We report downward breaks in the pH–rate profiles for hydrolysis of simple sulfinamides and ^{18}O exchange from substrate to water during the course of this reaction. These data provide the first definitive evidence that nucleophilic substitution at sulfinyl sulfur may proceed by a two-step mechanism, through a hypervalent sulfurane reaction intermediate.

Nucleophilic substitution reactions of sulfinic acid derivatives usually occur with predominant inversion of configuration at sulfur.[2] These results are most often interpreted within the framework of a two-step addition–elimination mechanism with a trigonal-bipyramidal reaction intermediate (sulfurane).[2] However, they are also consistent with a concerted S_N2 displacement reaction that avoids formation of such an intermediate.[2] The isolation of stabilized bicyclic sulfuranes suggests that these species may form as intermediates of nucleophilic substitution reactions of sulfinic acid derivatives.[3] However, despite continuing efforts there are still no definitive experiments to demonstrate the formation of these species as reaction intermediates.

The observation of ^{18}O isotope exchange during hydrolysis of esters of carboxylic acids is accepted as definitive evidence for the formation of tetrahedral intermediates,[4] and by analogy ^{18}O exchange during the hydrolysis of sulfinic acid derivatives would provide strong evidence for the formation of a sulfurane reaction intermediate (Scheme 1). Previous attempts to detect this exchange reaction during alkaline hydrolysis of sulfinic esters[5] and sulfinamides[6] were unsuccessful. The observation of only a very small amount of ^{18}O exchange during acid-catalyzed hydrolysis of a sulfinic ester has been argued against the addition–elimination mechanism.[7]

We report here pH–rate profiles and ^{18}O-exchange data for hydrolysis reactions of *N*-arylbenzenesulfinamides **1**, which have been prepared according to a literature procedure.[8] The ^{18}O-labeled substrates were prepared by the same procedure, but starting with an ^{18}O-labeled benzenesulfinate salt that was prepared by alkaline hydrolysis of ethyl benzenesulfinate in $H_2{}^{18}O$.[9]

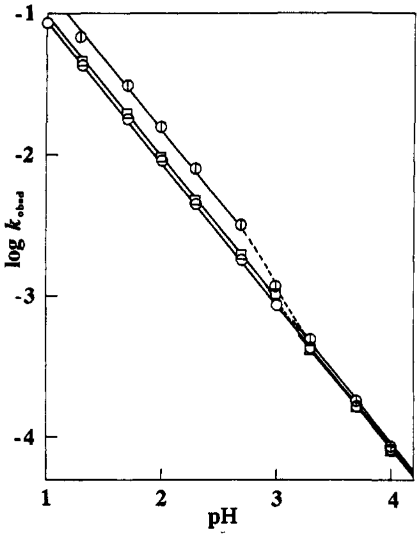
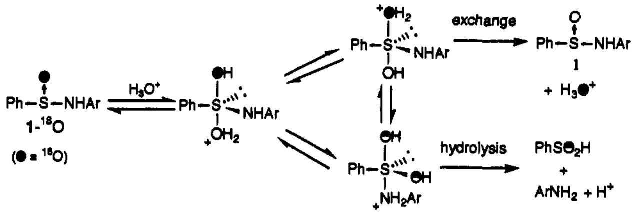
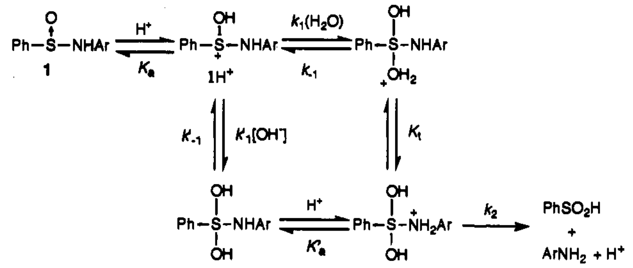


Figure 1. pH–rate profiles for hydrolysis of sulfinamides at 25 °C and the ionic strength of 0.10 ($NaClO_4$): ○, **1a**; □, **1b**; ⊖, **1c**.

Scheme 1



Scheme 2



The UV spectrum of **1** in dilute solution of aqueous perchloric acid changes smoothly, with sharp isosbestic points, to the spectrum of the reaction product of hydrolysis. These absorbance changes follow pseudo-first-order kinetics. Pseudo-first-order rate constants for hydrolysis of **1** were measured at 25 °C in aqueous solutions that contain measured amounts of perchloric acid (I = 0.10, $NaClO_4$). Figure 1 shows logarithmic plots of the observed rate constants (k_{obsd}) against the reaction pH. A linear plot with a slope of −1.0 is obtained for the reaction of unsubstituted *N*-phenylbenzenesulfinamide (**1a**), while the plots for the reactions of *N*-(*p*-methylphenyl)- (**1b**) and *N*-(*p*-methoxyphenyl)benzenesulfinamide (**1c**) show a break around pH 3. This break was not observed in the pH–rate profile for reaction of the *p*-chloro derivative (data not shown).

These pH–rate profiles can be accommodated by a two-step mechanism through sulfurane reaction intermediates (Scheme 2) and a change in rate-determining step at pH ca. 3 for the reactions of **1b** and **1c**, but not for **1a**. Sulfuranes can exist in a variety of configurations and states of protonation. For simplicity, Scheme 2 represents only the different states of protonation and ignores the mixtures of configurations of the individual species. The pool of intermediates shown in Scheme 2 partition between return to substrate by loss of water from the O-protonated and neutral species (k_{-1} and k'_{-1}, respectively) and formation of product by expulsion of aniline from the N-protonated species (k_2). The rate-determining step for hydrolysis will be determined by the relative rates of these steps, and this depends on the energy of the respective transition states. There

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[1] Visiting Scientist, 1993. Present address: Department of Chemistry, Dong-A University, Pusan 604-714, Korea.

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is net development of positive charge at the aniline nitrogen in the transition state for product formation (k_2). The positive charge will be stabilized by electron-donating substituents at the aniline ring, and this will make the second step faster and progressively less rate determining on moving from **1a** (unsubstituted aniline) to **1b** (*p*-methyl-substituted aniline) to **1c** (*p*-methoxy-substituted aniline). We suggest that the shapes of the pH–rate profiles in Figure 1 are consistent with rate-determining breakdown of the intermediate for reaction of **1a**, and rate-determining formation of the intermediate for the reactions of **1b** and **1c** at low pH. The barrier to conversion of the pool of reaction intermediates (Scheme 2) to products is expected to increase with increasing pH relative to the barrier to return of the intermediates to substrate. This would be due to an increase in the concentration of the neutral sulfurane intermediate, for which there exists a rapid pathway for return to substrate (k'_{-1}), but which should only react very slowly with expulsion of the anilide anion to form product. The accumulation of the neutral sulfurane at increasing reaction pH is reflected by breaks in the pH–rate profiles for the reactions of **1b** and **1c**, as the rate-determining step changes from formation (first step) to breakdown (second step) of the sulfurane intermediate. The constant slopes of −1 for the reaction of **1a** (Figure 1) and the *p*-chloro derivative (not shown) are consistent with rate-determining breakdown of the sulfurane across the entire pH range examined.

Equation 1 gives the relationship between k_{obsd} for reaction of **1** and the rate and equilibrium constants in Scheme 2. The limiting

$$k_{\mathrm{obsd}} = \left(\frac{[\mathrm{H}^+]}{K_a + [\mathrm{H}^+]}\right)\left(\frac{k_1 k_2 K_t [\mathrm{H}^+] + k'_1 k_2 K_t K_w}{k_{-1}[\mathrm{H}^+] + k_2 K_t [\mathrm{H}^+] + k'_{-1} K'_a K_t}\right) \tag{1}$$

catalytic constants at the low and high pH levels are k_1/K_a and $k_1k_2K_t/k_{-1}K_a$, respectively, and a break occurs at pH = −log($k'_{-1}K'_a/k_2$), if we can assume $K_a \gg [\mathrm{H}^+]$ and $k_2K_t \gg k_{-1}$.[10] Approximate parameters obtained for **1b** and **1c** are k_1/K_a = 0.96 and 1.46 $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$; $k_1k_2K_t/k_{-1}K_a$ = 0.83 and 0.92 $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$; −log($k'_{-1}K'_a/k_2$) = 3.2 and 3.0, respectively. The $k_1k_2K_t/k_{-1}K_a$ value for **1a** is 0.865 $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$.

Table 1. Oxygen Isotope Exchange during Acid Hydrolysis of the Labeled Sulfinamides[a]

substrate	[HClO$_4$]/M	vol % CH$_3$CN	reaction time[b]/min	excess % ^{18}O[c]
1a-^{18}O			0	37.5[d]
	0.01	<1	1.25	36.1
	0.001	<1	13	36.1
	0.001	20	26	34.9
	0.001	50	57	31.8
1b-^{18}O			0	34.6[d]
	0.001	<1	11	30.5
	0.001	<1	22[e]	26.2
	0.001	50	42	26.2

[a] Reactions were carried out in perchloric acid containing some acetonitrile at 25 °C. The ionic strength was kept at 0.10 (NaClO$_4$) when the acetonitrile content was <1%, while it was not adjusted in other acetonitrile solutions. [b] One half-life of the hydrolysis unless otherwise noted. [c] Accurate to <±0.5%. [d] The excess ^{18}O content before hydrolysis. [e] Two half-lives.

If the rate-determining step for hydrolysis of **1** is breakdown of the sulfurane intermediate, then this species should be formed in a preequilibrium step. This would lead to exchange of the ^{18}O label from substrate to solvent during the course of the hydrolysis reaction. This prediction was confirmed by the results of the following experiment. The ^{18}O-labeled substrates **1a**-^{18}O (37.5% excess ^{18}O) and **1b**-^{18}O (34.6% excess ^{18}O) were hydrolyzed in aqueous perchloric acid at 25 °C; the reaction was quenched at 1–2 half-times by neutralization; and, the unreacted substrate was extracted with dichloromethane. The concentrated extracts were analyzed by mass spectrometry[11] to determine excess ^{18}O above natural abundance. The results of these experiments, summarized in Table 1, show that there has been substantial loss of label from unreacted substrate during the hydrolysis reaction.[12] These results may best be accommodated by a mechanism involving a sulfurane reaction intermediate, which may undergo rearrangement by pseudorotation as illustrated in Scheme 1.

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(10) The relation $k_1K_t/k_{-1} = k'_1K_w/k'_{-1}K'_a$ was used to derive the equations.

(11) Mass spectra were recorded on a JMS DX303 spectrometer. We thank Mr. Kazuo Fukuda for the measurements.

(12) The labeled substrate **1b**-^{18}O was left standing in a 0.1 M NaClO$_4$ solution at 25 °C for 15 h without any detectable ^{18}O exchange.