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Hydrolysis rates of alkyl and aryl sulfinamides: evidence of general acid catalysis

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Abstract—Sulfinamides are important in enantioselective synthesis, as rare post-translational modifications of proteins and as isosteres of the amide bond. Little is known about the rates of hydrolysis for aliphatic sulfinamides or the mechanism of hydrolysis. In this Letter, we show that sulfinamides hydrolyse by predominantly a non-specific acid/base catalysis with phosphate buffer but by varying the buffer concentration, it was possible to determine the hydrolysis rates of a range of sulfinamides with water through non-linear least squares regression.

Sulfinamides are unique isosteres of the amide bond,[1] closely mimicking the transition state of both the hydrolysis and cis–trans isomerism reactions of peptides, and therefore show potential as both protease[2–4] and PPIase[5] inhibitors. In fact they have been described both as substrates for proteases[6] and nanomolar inhibitors of proteases.[7] Sulfinamides have also recently found utility in enantioselective synthesis as chiral auxillaries[8,9] and highly stereoselective organocatalysts.[10] Sulfinamides have also been shown to form naturally in proteins between the ε-amino group of lysine and the sulfur of methionine and these adducts have been studied by mass spectrometry.[11] However, despite their chemical and biological importance and potential as drug motifs, few experimental studies have been performed on the hydrolysis of sulfinamides.[12–14] In addition, theoretical calculations[15,16] of the relative energies of potential reaction intermediates have proven inconclusive. Consequently, the exact mechanism by which sulfinamides undergo hydrolysis, and the rate-limiting step of the reaction, are still unclear. More importantly, in the design of enzyme inhibitors, the structural features affecting the rate of hydrolysis are unknown.

In order to understand the mechanism of sulfinamide hydrolysis more fully, and thereby design more stable sulfinamide-containing drugs or probes, we have for the first time, investigated the hydrolysis rates of simple aliphatic sulfinamides that incorporate different electronic and steric parameters. A small set of simple sulfinamides was synthesised from the corresponding sulfinyl chloride and two equivalents of amine at −78 °C in anhydrous dichloromethane (Supplementary data). It was essential to react the amines and sulfinyl chlorides at low temperature as they react violently at room temperature. The resulting amine hydrochloride was filtered off and the crude sulfinamide was washed with water and dried. This yielded pure sulfinamides in ∼70% yields.

The acid-catalysed hydrolysis of sulfinamides results in cleavage of the S–N bond and loss of an amine residue as the leaving group. The formation of this amine species causes an increase in the pH of the reaction mixture as the hydrolysis reaction proceeds (Supplementary Fig. S1). In order to simplify calculations, it is often convenient to use a buffer solution to maintain a constant pH, and subsequently determine the pseudo-first-order rate constants for the hydrolysis reactions. For this study, a phosphate buffer system ($H_3PO_4/H_2PO_4^-$ pH 3.0) was employed to maintain a constant pH throughout the hydrolysis reactions. Initially, it was found that the rate of hydrolysis was linearly dependent on the hydrogen ion concentration (Fig. 1). Unexpectedly, the rates of hydrolysis of the seven aliphatic sulfinamides

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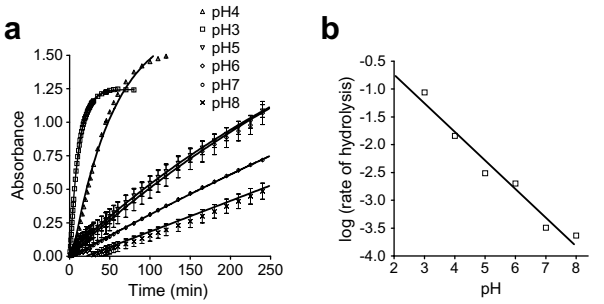


Figure 1. Rates of hydrolysis in 50 mM phosphate buffer from pH 3–8 for *N*-(methanesulfinyl)pyrrolidine **5**, fitted to a one-phase exponential associate (a). A log/log plot of reaction rate versus pH (b) shows a linear relationship, indicating that the observed reaction is acid catalysed and first order.

studied were also strongly dependent on the concentration of phosphate buffer used (Fig. 2). This suggests that general (non-specific) acid/base species can catalyse the hydrolysis of sulfinamides (Fig. 3).

The rate of specific acid-catalysed hydrolysis for each sulfinamide was determined by varying the concentration of phosphate buffer (pH 3.0) between 1 and 200 mM, following the hydrolysis reaction with UV

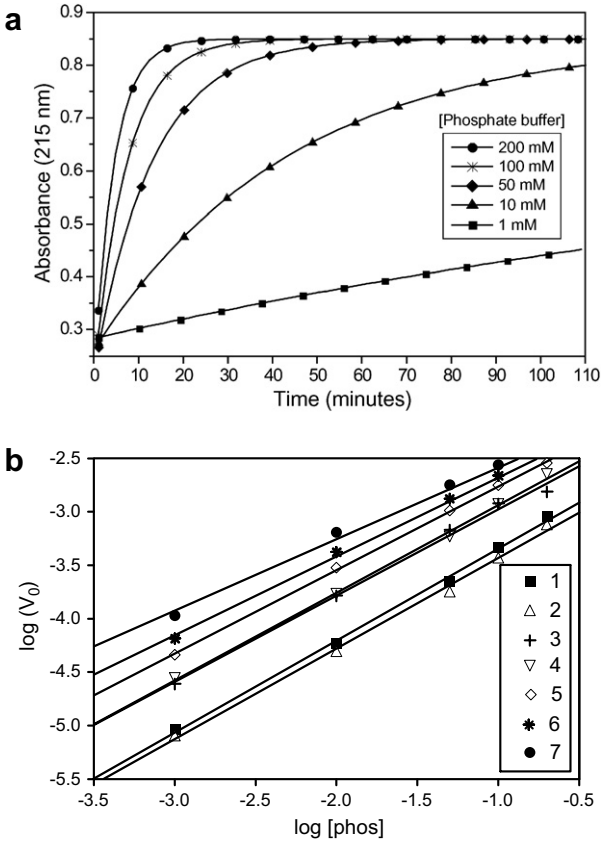


Figure 2. Effect of varying phosphate buffer concentration on the hydrolysis rate of alkyl sulfinamides. (a) Progress curves in 1–200 mM phosphate buffer (pH 3) of *N*-(methanesulfinyl)piperidine **6** and (b) log/log plots of initial velocities (v_0) versus phosphate concentration.

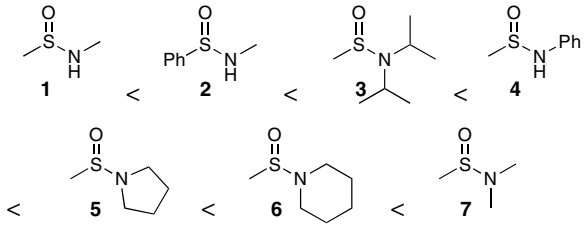


Figure 3. Order of pseudo-first-order rate constants for the specific H_3O^+-catalysed hydrolysis of seven aliphatic sulfinamides at 25 °C.

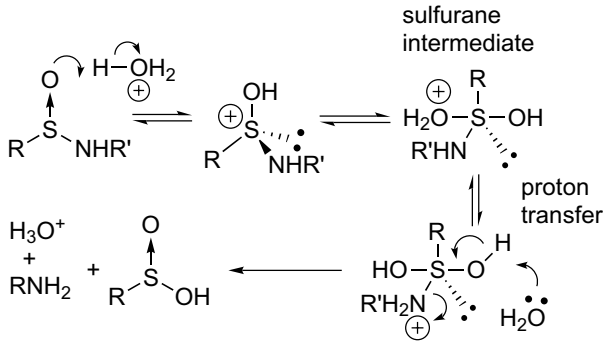
spectroscopy (Fig. 2a). The initial rates were plotted against the phosphate concentration to reveal that the reaction was pseudo-first order with respect to phosphate concentration (Fig. 2b), and subsequently using the Dynafit[17] package to calculate the pseudo-first-order rate constant for the specifically H_3O^+-catalysed and phosphate catalysed reaction (Supplementary Figs. S3-10). The Dynafit package uses a non-linear least-squares regression algorithm to fit data to a set of arbitrary reaction mechanisms. This allowed the rates of specific and general acid catalysis to be separated, and the pseudo-first-order rate constants determined individually. The pseudo-first-order rate constants for the H_3O^+-catalysed hydrolysis of the six sulfinamides studied are given in Table 1.

The phenomenon of general acid catalysis has been described previously in other species such as imines,[18,19] but has not been previously described in sulfinamides. The existence of general acid catalysis in sulfinamides has important implications for hydrolysis studies that employ buffer systems to maintain a constant pH throughout the reaction. However, as alluded to by Cordes and Jencks,[18] the kinetic difference between general acid catalysis and specific acid/general base catalysis is ambiguous. Therefore, it is possible that the hydrolysis of sulfinamides is catalysed by the general acid H_3PO_4, which assists in protonation of the sulfinamide, or by the general bases $H_2PO_4^-$ and HPO_4^{2-}, which assist in abstraction of a proton at some stage in the reaction. Clearly, a more detailed examination of the mechanism of sulfinamide hydrolysis, including the initial site of protonation and the rate limiting step of the reaction, is required to assist in distinguishing between these two possibilities.

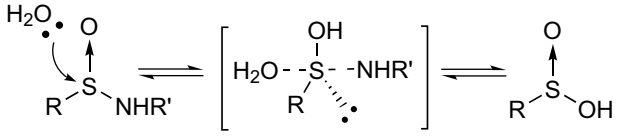
The majority of nucleophilic displacement reactions at a chiral sulfinyl sulfur atom occur with inversion of stereochemistry.[20] This inversion can be accommodated by either a two-step addition–elimination mechanism (Scheme 1), involving a hypervalent trigonal bipyramidal sulfurane intermediate, or by a concerted S_N2 displacement mechanism (Scheme 2), involving a transition state and no sulfurane intermediate. Okuyama, et al.[21,22] found evidence of ^{18}O exchange from $^{18}O{=}S$ to $H_3{}^{18}O^+$ during the acid catalysed hydrolysis of sulfinamides, which can only occur through a sulfurane intermediate, thus supporting a two-step addition–elimination mechanism. The two-step mechanism also explains nucleophilic substitution reactions that do not proceed with 100% inversion. In these cases, pseudo-

Table 1. Rates of specific acid (k_{cat}) and non-specific acid (k_{phos}) catalysis of seven alkyl sulfinamides determined in phosphate buffer

Compound		MW	μM	Response	k_{phos}	k_{cat} ($\times 10^{-6}$)
$CH_3SONHCH_3$	**1**	93.15	532	0.00194	0.01355	5.49 ± 0.08
$PhSONHCH_3$	**2**	155.22	202	−0.00486	0.00837	6.55 ± 0.1
$CH_3SON(CH(CH_3)_2)_2$	**3**	163.28	397	0.00128	0.01439	10.5 ± 0.3
$CH_3SONHPh$	**4**	155.22	107	−0.00748	0.03286	18.4 ± 0.1
$CH_3SONPyrrolidine$	**5**	133.21	157	0.00409	0.01170	19.7 ± 0.3
$CH_3SONPiperidine$	**6**	147.24	408	0.00168	0.01272	32.9 ± 0.5
$CH_3SON(CH_3)_2$	**7**	107.18	604	0.001733	0.01547	55.7 ± 0.6



Scheme 1. Two-step addition–elimination mechanism of sulfinamide hydrolysis.



Scheme 2. Concerted (S_N2) mechanism of sulfinamide hydrolysis.

rotation of the trigonal bipyramidal sulfurane intermediate results in partial retention of stereochemistry.[23,24]

While available evidence[25] supports a two-step addition–elimination mechanism for sulfinamide hydrolysis, the initial site of protonation and the rate limiting step of the reaction are still unclear, and are the subject of conflicting arguments. Ab initio calculations by Bagno et al.[26] have shown the oxygen protonated form of CH_3SONH_2 to be 10.6 kcal mol^{-1} more stable than the nitrogen protonated form. The oxygen protonation model is also supported by ^{14}N NMR studies of several sulfinamides,[26] which show no evidence of ^{14}N line narrowing that is characteristic of nitrogen protonation. However, studies of the infrared spectra of sulfinamides by Bujnicki et al.[27] showed the S=O and N–CH_2 IR peaks to shift to higher wavenumbers on protonation. The authors concluded that this must be the result of nitrogen protonation as this is the only case in which the strength of S=O and N–C bonds increase. It was also found that ^{15}N NMR signals of sulfinamides shift upfield upon protonation, indicative of the nitrogen atom becoming more positive, as would occur on protonation.[19]

Our results suggest that while initial protonation of the oxygen is more likely than protonation of the nitrogen, it is not the rate limiting step in the hydrolysis reaction. Comparison of compounds **1** and **2** shows that replacement of a methyl group on the sulfur side with a more electron-donating aromatic ring only slightly increases the rate of hydrolysis. The presence of the aromatic ring on the sulfur side should result in an increase in electron density on the sulfinyl oxygen atom, thus facilitating protonation. A far larger increase in hydrolysis rate would be expected if initial protonation of the oxygen were the rate limiting step. Conversely, comparison of compounds **1** and **4** shows that replacement of a methyl group on the nitrogen side with an electron-withdrawing aromatic ring actually increases the rate of hydrolysis threefold. The presence of the aromatic ring on the nitrogen side should withdraw electrons away from the nitrogen, making protonation less favourable, and subsequently decreasing the rate of hydrolysis. Clearly, if nitrogen protonation does occur, it is not the rate-limiting step of the hydrolysis reaction.

The most surprising results of the current work are that the tertiary sulfinamides (**5**–**7**) had the fastest rates of hydrolysis. For example, adding another methyl to the nitrogen side of *N*-methylmethanesulfinamide **1** resulted in over an order of magnitude increase in hydrolysis rate. However, the cyclic tertiary sulfinamides were more stable but still not as stable as any of the secondary sulfinamides. This may be accounted for in the relative rigidity of the 5- and 6-membered rings compared to dimethyl **7** derivative and supports the hypothesis that the rate limiting step is proton transfer from the oxygen to the nitrogen, which would require more reorganisation from the cyclic sulfinamides. The rates of hydrolysis for this small set of compounds could not be correlated to any single factor such as pK_a of the leaving group, MW, volume etc. The slower rates of hydrolysis of the sulfinamides containing a secondary nitrogen atom may, however, be the result of stabilisation by intermolecular hydrogen bonding. The large dipole moment of the S–O group is conducive to the formation of particularly strong hydrogen bonds, which would stabilise the molecules and result in slower rates of hydrolysis.

In conclusion, we have found that aliphatic secondary sulfinamides are relatively stable at basic pH but can be readily hydrolysed at pH 3 and that tertiary sulfinamides are considerably more reactive than secondary sulfinamides. The rate of hydrolysis has been shown to be strongly dependent on the buffer concentration and that phosphate was a most effective buffer for promoting hydrolysis suggesting a non-specific acid/base catalysis. These results are important in the design of sulfinamide-based enzyme inhibitors and peptide isosteres.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.081.

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