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REACTIVITY OF NUCLEOPHILES TOWARDS X-3-(*p*-TOLYLSULFONYL)-1,2,3-BENZOXATHIAZOLE 2,2-DIOXIDES: KINETICS, ACTIVATION VOLUMES AND MECHANISM†

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The kinetics of the reaction of four X-3-(*p*-tolylsulfonyl)-1,2,3-benzoxathiazole 2,2-dioxides (X = 5-Cl, 5-Br, 5-NO_2 and 6-NO_2) with hydroxide ion and imidazole in aqueous acetonitrile and aqueous ethanol solutions were investigated at various pressures. The volumes of activation were all found to be negative and consistent with a bimolecular reaction involving considerable solvent electrostriction. No significant dependence on the solvent composition was found. © 1997 by John Wiley & Sons, Ltd.

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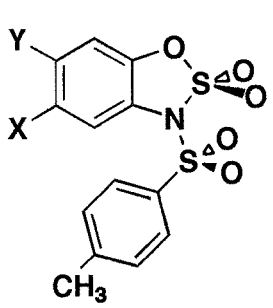
INTRODUCTION

The large difference in kinetic lability of cyclic sulfur-containing compounds compared with their acyclic analogues was noted and investigated by Kaiser[1] and others.[2–4] This type of reactivity difference was studied in some detail recently, and a review of the pertinent literature was provided.[5] The latter investigation reported the reactions of various nucleophiles with a series of newly synthesized compounds, 3-(*p*-toluenesulfonyl)-5-X-6-Y-1,2,3-benzoxothiazole 2,2-dioxides (hereafter referred to as cyclic sulfamates), where X and Y were a range of electron-withdrawing or electron-donating substituents, i.e. **1a**–**h**.

Most experiments were conducted using the hydroxide ion as the nucleophile, in an acetonitrile–water mixture. Based on analysis of a Hammett plot of the kinetic parameters, derived activation parameters, product identification (UV–visible spectra) and stoichiometric considerations, it was concluded that ring opening was virtually the exclusive reaction path and that the attack on the endocyclic sulfur resulted in the subsequent cleavage of the S–N bond to give **2**. Studies with other nucleophiles were less comprehensive, but it became clear that some nucleophiles attacked the tosyl or exocyclic sulfonyl sulfur atom rather than the ring or endocyclic sulfonyl sulfur atom to give **3** and **4**.

In order to illuminate further the properties and reactivity of these compounds, and also to examine in detail the products of reaction as a means of defining the mechanistic route of reaction with various nucleophiles, further extensive studies were conducted.[6] The synthetic aspects and product characterizations have been reported.[6] A further important finding was the degree to which the cyclic system and the benzene ring substituent influenced the acidity of the detosylated compounds, **3**.[6] From a Hammett plot of the pK_a values of sulfamates **3**, a rho value of 2·74 was obtained. This value and the increased acidity compared with those for an acyclic analogue were discussed. In addition, *ab initio* calculations were carried out to assess the



1	X	Y
a	H	H
b	Me	H
c	Cl	H
d	*t*-Bu	H
e	MeCO	H
f	Br	H
g	NO_2	H
h	H	NO_2

Scheme 1

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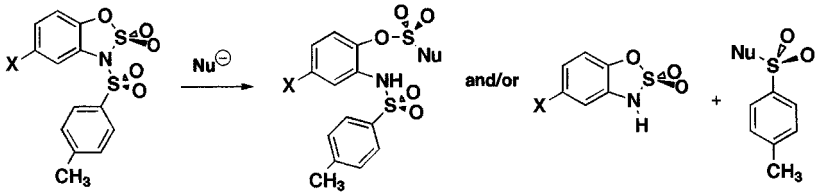


Scheme 2

effect of changes in geometry on pK_a.

The reason for chemoselectivity (exocyclic versus endocyclic nucleophilic attack) in cyclic sulfamates **1a**–**g** is still far from understood. Therefore, to investigate these systems further, kinetic studies of the reaction of hydroxide ion with cyclic sulfamates **1c** (5-chloro), **1f** (5-bromo), **1g** (5-nitro) and **1h** (6-nitro) have been carried out at atmospheric and elevated pressures and, in some cases, in different solvent compositions. The results are described and analyzed. This represents a more thorough and comprehensive study than that in which some preliminary findings were reported.[5]

In addition, the kinetics of reaction of imidazole with the 5-nitro (**1g**) and the 6-nitro compounds (**1h**), again at both atmospheric and elevated pressures, have been investigated and are reported. The rate laws were obtained and are simple, allowing a mechanistic interpretation of the derived activation volumes, ΔV^*. The value of this parameter as a diagnostic indicator of mechanism in both inorganic and organic reactions has been realized.[7,8]

EXPERIMENTAL

Materials. The cyclic sulfamates were those used in previous studies, or were new samples having identical characteristics and properties as described earlier.[5] Solutions of sodium hydroxide were made from standard high-concentration vials (Merck, Titrisol) of NaOH and Milli-Q water. Imidazole was obtained from Sigma. Acetonitrile and ethanol were of analytical reagent grade. Concentrations of mixed aqueous solvents used in the kinetic studies, prepared with Milli-Q water and the appropriate solvent, are expressed in volume percent before mixing.

Methods. The UV–visible spectra of products of the reactions were obtained using a Shimadzu Model 250 spectrophotometer. The reactions are too rapid at room temperature for conventional time range instruments, and were studied kinetically using a laboratory-built stopped-flow spectrophotometer or a Dionex D-110 spectrophotometer, at the wavelengths characterizing the product(s) absorption given in the tables. Temperature control was maintained to within ±0·1 °C by a thermostated circulating fluid. Data were acquired using an Apple IIe computer and processed by using kinetics software. All reactions were first order (for at least three half-lives), under the conditions of the experiments in which the hydroxide ion or imidazole concentrations were in large excess over the cyclic sulfamate concentrations. High-pressure kinetic measurements were made using a laboratory-built high-pressure stopped-flow spectrophotometer.[9] For reactions in moderate concentrations of organic solvent, Kel-F drive syringes could be used, but these were substituted by glass syringes at the highest concentration of acetonitrile. The temperature was controlled and the primary data were acquired and processed by methods identical with those for the atmospheric pressure kinetics. Plots of the logarithm of the rate constants (k_{obs}) versus pressure were obtained, and ΔV^* was calculated using a standard method. The plots, an example of which is shown in Figure 1, showed no evidence of curvature and therefore the values of ΔV^* cited refer to a pressure of 0·10 MPa.

RESULTS

The order of reaction for hydroxide ion reacting with cyclic sulfamates has previously been established as second overall,[5] first order in each of the cyclic sulfamate and hydroxide ion concentrations. The choice of solvent composition was dictated by solubility considerations. Cyclic sulfamates are virtually insoluble in water, as is the sodium hydroxide, at the concentrations used, in solvent mixtures containing a high percentage of acetonitrile. Earlier work has demonstrated the viability of application of the high-pressure kinetic technique to this type of reaction. Rate constants for reaction of hydroxide with **1g** and **1h** at different pressures in different solvent mixtures are listed in Table 1. The reactivity of hydroxide ion toward the halogen derivatives **1c** and **1f** was also examined at different pressures in a 50% acetonitrile–water mixture (Table 2). A typical example of a plot of ln k_{obs} versus pressure used to calculate the activation volumes is presented in Figure 1.

In a solution of excess imidazole, **1g** and **1h** undergo rapid reactions requiring the stopped-flow method for kinetic measurements. A compilation of rate constants obtained at atmospheric pressure is given in Table 3.

On plotting k_{obs} versus the imidazole concentration, a straight line, which passes through the origin within experimental error, is obtained for both nitro isomers (Figure 2), indicating that the reaction is first order in both imidazole concentration and cyclic sulfamate concentration. Since there is no intercept, a reverse reaction or a parallel solvolysis reaction are non-existent or negligible.

Table 1. Kinetic data for reaction of OH^- with cyclic sulfamates **1g** nd **1h** in aqueous media at 25·0 °C and different pressures[a]

Compound	Medium (%, v/v)	Average k_{obs} (s^{-1})	*P* (MPa)
1g[b]	32% CH_3CN	1·54±0·02	5·0
		1·76±0·04	25
		1·99±0·03	50
		2·21±0·05	75
		2·49±0·10	100
1g[c]	80% CH_3CN	0·147±0·008	5·0
		0·166±0·010	25
		0·206±0·018	50
		0·206±0·011	75
		0·259±0·015	100
1h[c]	32% CH_3CN	2·32±0·04	5·0
		2·70±0·06	25
		2·97±0·05	50
		3·22±0·08	75
		3·67±0·09	100
1h[c]	80% CH_3CN	0·474±0·049	5·0
		0·627±0·061	25
		0·930±0·024	60
		0·747±0·058	100
		1·04±0·014	120
1h[c]	50% C_2H_5OH	9·50±0·38	5·0
		10·6±0·4	25
		11·9±0·6	50
		12·9±0·8	75
		15·2±1·0	100

[a] $[OH^-]=0·050$ M.
[b] $[\mathbf{1g}]=5·5\times10^{-5}$ M, $\lambda=400$ nm.
[c] $[\mathbf{1h}]=1·1\times10^{-4}$ M, $\lambda=400$ nm.

Table 2. Kinetic data for reaction of OH^- with cyclic sulfamates **1f** and **1c** in 50% (v/v) $CH_3CN–H_2O$ at 25·0 °C and various pressures[a]

Compound	Average k_{obs} (s^{-1})	*P* (MPa)
1f[b]	0·199±0·004	0·1
	0·235±0·003	5
	0·268±0·003	25
	0·321±0·006	50
	0·386±0·016	75
	0·433±0·002	100
	0·479±0·006	125
1c[c]	0·210±0·009	0·1
	0·220±0·004	5
	0·260±0·004	25
	0·298±0·006	50
	0·347±0·008	75
	0·416±0·008	100
	0·447±0·006	125

[a] $[OH^-]=0·050$ M.
[b] $[\mathbf{1f}]=2·24\times10^{-4}$ M; $\lambda=310$ nm.
[c] $[\mathbf{1c}]=4·9\times10^{-4}$ M; $\lambda=320$ nm.

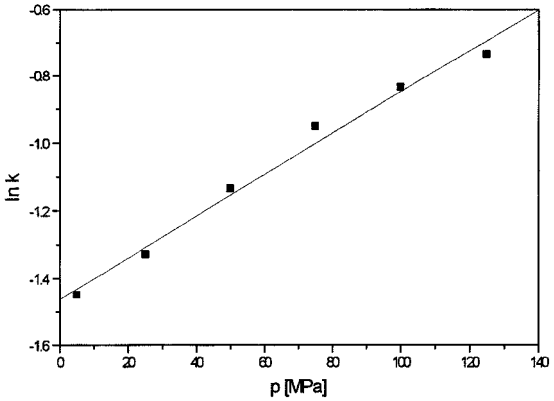


Figure 1. Plot of ln k_{obs} versus pressure for the reaction of **1f** with hydroxide ion in 50% (v/v) aqueous acetonitrile at 25·0 °C. $[\mathbf{1f}]=2·24\times10^{-4}$ M, $[OH^-]=0·05$ M

The pK_a of imidazole in water, 6·99,[10] is such that the concentration of hydroxide ion in the solution, produced by hydrolysis, contributes insignificantly to the observed reaction rate for the imidazole concentrations used. The kinetic results from comparable experiments for imidazole reacting with the isomeric 6-nitro isomer **1h** (Table 3) demonstrate that the rate law has the same form for the two isomers. However, as in the case of reaction with hydroxide ion, **1h** is more reactive than **1g**.

The reactivities of the two nucleophiles towards cyclic sulfamates cannot be considered in a directly comparative way, since the sites of attack of hydroxide and imidazole are different. It was established in earlier work,[5] and confirmed

Table 3. Kinetic data for reaction of imidazole with cyclic sulfamates **1g** and **1h** in 50% (v/v) $CH_3CN–H_2O$ at 25·0 °C

Compound	[Im] (M)	Average k_{obs} (s^{-1})
1g[a, b, c]	0·0265	0·0227±0·0002
	0·0265	0·0218±0·0005
	0·038	0·0400±0·0002
	0·0398	0·0331±0·0001
	0·050	0·0529±0·0007
	0·0530	0·0517±0·0006
	0·075	0·0792±0·0014
	0·088	0·0945±0·0004
	0·100	0·107±0·005
1h[d, e]	0·0150	0·0428±0·0002
	0·0300	0·0713±0·0043
	0·0400	0·0867±0·0013
	0·0500	0·122±0·012
	0·100	0·266±0·006

[a] $[\mathbf{1g}]=2·08\times10^{-4}$ M.
[b] Duplicate kinetic runs with new solutions to establish reproducibility.
[c] $k_2=1·16\pm0·04$ M^{-1} s^{-1}.
[d] $[\mathbf{1h}]=1·1\times10^{-4}$ M.
[e] $k_2=2·67\pm0·16$ M^{-1} s^{-1}.

recently,[6] that the hydroxide ion attacks the endocyclic sulfur of **1g** with subsequent ring opening and loss of sulfate ion, leading to *N*-tosyl-2-amino 5-nitrophenol. A small fraction of detosylated sulfamate **3g** (X = nitro) is found (6%), indicating a minor pathway involving attack at the exocyclic sulfur.

By contrast, again using the 5-nitro sulfamate **1g**, imidazole attacks only the exocyclic sulfur atom, in a 2:1 imidazole:sulfamate stoichiometry, producing *p*-toluenesulfonylimidazole (**6**) while a second equivalent of imidazole forms the imidazolium salt **5**. This salt, on treatment with concentrated HCl, yields **3g**. Thus, imidazole leaves the cyclic system intact.

Amines such as *tert*-butylamine and benzylamine attack the exocyclic sulfur of **1g**. In each case a tosylated amine, analogous to **6**, and an ammonium salt comprised of the protonated amine and the detosylated sulfamate, analogous to **5**, are formed.

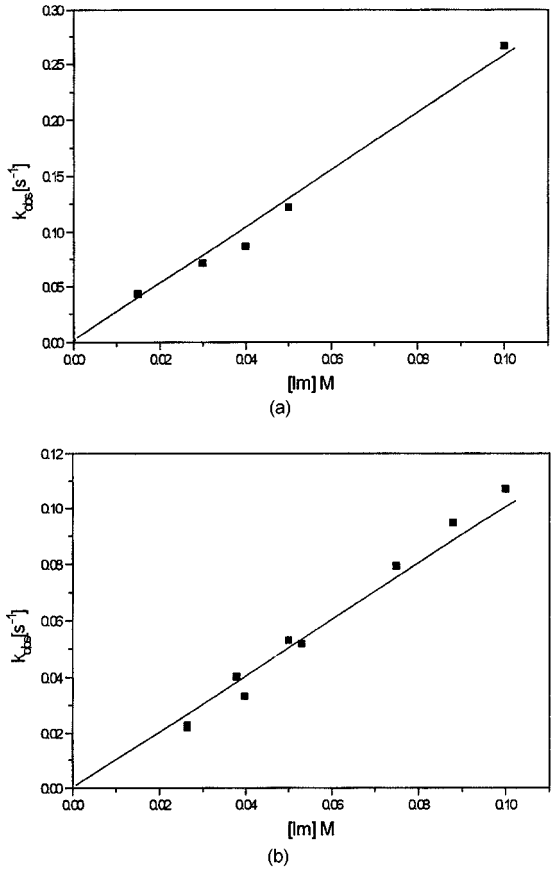


Figure 2. (a) Plot of k_{obs} versus imidazole concentration for reaction of **1h** with imidazole in 50% (v/v) aqueous acetonitrile at 25·0 °C. [**1h**] = $1{\cdot}1\times10^{-4}$ M. (b) Plot of k_{obs} versus imidazole concentration for reaction of **1g** with imidazole in 50% (v/v) aqueous acetonitrile at 25·0 °C. [**1g**] = $2{\cdot}08\times10^{-4}$ M

Product analyses were carried out at higher concentrations than can be used realistically in kinetic experiments. In discussing kinetic and activation parameters, it will be assumed that the same sites of nucleophilic attack as indicated by product analyses are applicable. The reactions of imidazole with nitro sulfamates **1g** and **1h** are accelerated by pressure; the kinetic data are given in Table 4.

DISCUSSION

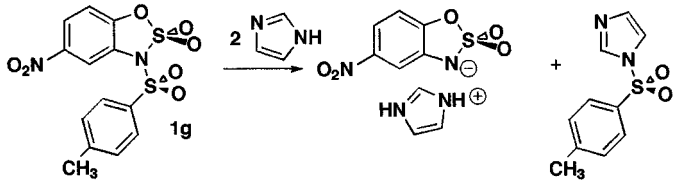
Kinetics at ambient pressure

The kinetics of the reaction of hydroxide ion with several cyclic sulfamates in acetonitrile–water mixtures have been reported previously,[5, 6] and only the esssential characteristics need to be reiterated here. The rate law indicates a second-order reaction, first order in each reactant; the Hammett rho value is +2·2, denoting an increase in electron density at the reaction locus in the transition state. For the nitro cyclic sulfamates **1g** and **1h**, the second-order rate constants increase with increasing water content of the binary solvent mixture, a result consistent with increasing ionic or polar character in the transition state as the solvent dielectric constant is increased. These findings pointed to the hydroxide ion having the ability to cause increased polarization within the sulfamate as the hydroxide ion attacks the heterocyclic ring.

The reaction of imidazole, selected because of its uncharged nature, with nitro compounds **1g** and **1h** is also characterized by a rate law which is second order, first order in the concentration of each reactant. At 25·0 °C the rate constants in 50% acetonitrile–water for **1g**[5] are $14{\cdot}8\,\text{M}^{-1}\,\text{s}^{-1}$ for reaction with hydroxide ion and $1{\cdot}16\,\text{M}^{-1}\,\text{s}^{-1}$ for reaction with imidazole (Table 3). The relative reactivity of **1h** and **1g** towards imidazole is 2·67/1·16 = 2·30, the same as found for hydroxide ion, i.e. 34·1/14·8 = 2·30.[5] The rate constants for reaction of hydroxide ion are about 13 times larger than those for reaction of imidazole, i.e. 14·8/1·16 = 12·8 for **1g** and 34·1/2·67 = 12·8 for **1h**. The 10-fold difference in rate constants manifests itself in a small difference in the free energies of activation for the two reactions. Perhaps it is fortuitous that the free energies of activation are not significantly different, since the comparison is between two dissimilar reactions, a charged nucleophile reacting with the endocyclic sulfur atom and a neutral nucleophile reacting with the exocyclic sulfur, yielding totally different products. If charged and uncharged nucleophiles were to attack a common site in the substrate, and the reactions were amenable to solution kinetics studies, perhaps more could be learned regarding the significance of the selectivity of nucleophiles. Currently we are investigating reagents which might fit this criterion.

Activation parameters

It had been shown earlier that the unsubstituted compound **1a** in its reaction with hydroxide ions was characterized by



Scheme 3

a ΔH^* of about 45 kJ mol^{-1} in either 50% ethanol–water or 80% acetonitrile–water. This indicated a modest enthalpy barrier to reaction for a process having a second-order rate constant of 0·44 M^{-1} s^{-1} at 25·0 °C in 50% acetonitrile–water, about 11 orders of magnitude slower than a diffusion-controlled rate constant, and that the reaction is not very sensitive in its activation to cosolvent. This suggests that changes in solvation between the initial state and the transition state, if any, are associated mostly with solvating water in the two 50:50 (v/v) mixtures. The faster reaction in the ethanol mixture is therefore a consequence of a rather general medium effect. The corresponding values of ΔS^* were about -85 J mol^{-1} K^{-1}; these are consistent with a bimolecular reaction, and where possibly additional solvent restriction occurs. However, entropies of activation are not, as here, quantifiably attributable to particular processes. A preliminary temperature dependence study[11] of the kinetics of the reaction of imidazole upon **1g** in 50% acetonitrile–water yielded a surprisingly small ΔH^* (27·2 kJ mol^{-1}) and a large negative ΔS^* (-156 J mol^{-1} K^{-1}). The latter suggests that there is a considerable increase in electrostriction on reaching the transition state, in addition to the intrinsic contribution from the ordering of species in a bimolecular reaction.

Table 4. Kinetic data for the reaction of imidazole with cyclic sulfamates **1g** and **1h** in 50% (v/v) CH_3CN–H_2O at 25·0 °C

Compound	Average k_{obs} (s^{-1})	P (MPa)
1g[a]	0·0469±0·0010	10
	0·0538±0·0005	25
	0·0616±0·0008	50
	0·0769±0·0020	75
	0·0902±0·0010	100
1g[a]	0·0490±0·0011	5
	0·0602±0·0008	40
	0·0832±0·0015	80
	0·0904±0·0015	100
	0·102±0·002	120
1h[b]	0·172±0·002	5
	0·217±0·004	25·5
	0·246±0·003	50
	0·274±0·003	75
	0·290±0·008	101·5

[a] [**1g**] = 4·8 × 10^{-4} M; [Im] = 4·0 × 10^{-2} M; λ = 400 nm.
[b] [**1h**] = 1·1 × 10^{-4} M; [Im] = 5·0 × 10^{-2} M; λ = 400 nm.

The activation volume, ΔV^*, which frequently can be measured with greater precision than ΔS^*, is often a better indicator of mechanism than is the latter parameter. If the volume change is wholly intrinsic, i.e. no charge changes occur so that there is no solvational contribution to ΔV^*, the measured volume change can be ascribed semi-quantitatively to particular mechanistic features. A summary of the results for the reactions of both hydroxide ion and imidazole is given in Table 5.

The results for the kinetics, at various pressures, of hydroxide attack upon the two nitro sulfamates **1g** and **1h** in 50% acetonitrile–water were reported earlier.[5] The value of ΔV^* was -15 cm^3 mol^{-1} in each case. An associatively activated reaction, as this one is, would typically yield an intrinsic volume change of about -10 cm^3 mol^{-1}, although this can only be regarded as a guideline value. Therefore, it would be very speculative to attribute quantitatively the difference between the observed value and this estimate as the solvational component. It may be argued that if upon reaction the highly solvated hydroxide loses its solvation sphere to the bulk solvent and this is not compensated for by an increase in electrostriction in another part of the substrate, induced by the incoming hydroxide, then this could lead to a positive solvational contribution to ΔV^*. The fact that ΔV^* is even more negative than the guideline value for association of two species indicates that the solvational component is zero or even negative, albeit of modest

Table 5. Activation volumes for reaction of hydroxide ion and imidazole with cyclic sulfamates in aqueous solvent mixtures at 25·0 °C

Nucleophile	Compound	Medium (%, v/v)	ΔV^* (cm^3 mol^{-1})
OH^-	**1g**	32% CH_3CN	−12·3±0·6
		50% CH_3CN	−15·1±0·3
		80% CH_3CN	−13·9±2·0
OH^-	**1h**	32% CH_3CN	−11·2±0·9
		50% CH_3CN	−15·7±0·5
		80% CH_3CN	−13±5
		50% C_2H_5OH	−12·1±0·9
	1f	50% CH_3CN	−15·1±0·9
	1c	50% CH_3CN	−14·9±0·8
Im	**1g**	50% CH_3CN	−17·9±0·7
Im	**1g**	50% CH_3CN	−16·2±0·8
Im	**1h**	50% CH_3CN	−15·9±2·7

magnitude (about $-5\ cm^3\ mol^{-1}$). Therefore, it appears that the hydroxide ion retains much of its solvation sheath, the transition state is 'early' and the solvation component arises from induction of additional polar character by the hydroxide ion in the transition state.

Investigations of reactions with **1c** and **1f** in 50% acetonitrile–water and with **1g** and **1h** in other solvent mixtures were carried out in order to determine whether this situation was restricted to the nitro analogues or was a function of the solvent composition. Although the second-order rate constants are considerably less for the 5-halo compounds **1c** and **1f** than for the nitro analogues, the dependence of the rate constant on pressure is virtually identical for all four cyclic sulfmates in a 50% acetonitrile–water mixture. This indicates that the electron-withdrawing power of the substituent causes solvation differences at the reaction site that are not sufficiently significant to affect the solvation component of the activation volume. However, it is conceivable that the intrinsic and solvational components both vary so as to yield coincidentally about $-15\ cm^3\ mol^{-1}$ in all cases. With high percentages of acetonitrile, e.g. 80%, the values of ΔV^* could not be obtained with sufficient precision to claim that they are statistically different from the values obtained in 50% acetonitrile. When the water content is higher (32% acetonitrile), ΔV^* is 3–4 $cm^3\ mol^{-1}$ less negative, outside the experimental error for the two nitro compounds **1g** and **1h**, possibly indicating a slight shift along the reaction coordinate for the transition state, i.e. a somewhat less early transition state, consistent with more desolvation of the incoming hydroxide ion into the water rich mixture. The reaction is faster in mixtures of higher water content. Therefore, this argument is not supported by the accepted correlation between rate constant and volume of activation.

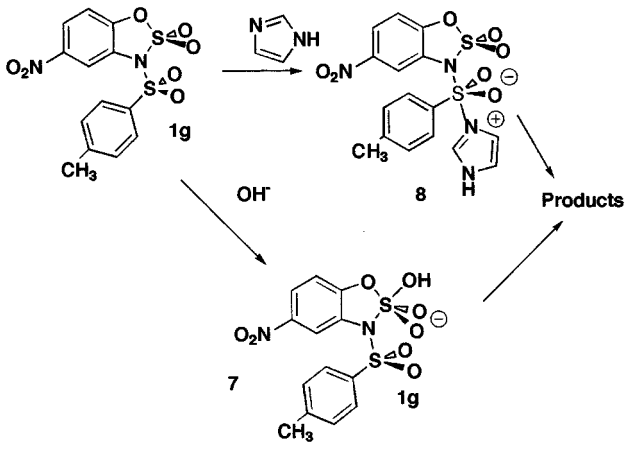
A slight decrease was noted in ΔV^* (from $-15{\cdot}7$ to $-12{\cdot}1\ cm^3\ mol^{-1}$) for **1h** by replacement of 50% acetonitrile with 50% ethanol, accompanied by an increase in rate constant. (See Table 1 and Ref. 5). The free energy barrier to reaction is reduced by the presence of the ethanol, but the alcohol makes only a marginal difference to the solvational component, comparable to that found in water-rich acetonitrile mixtures.

The rates for the exocyclic reaction of imidazole with sulfamates **1g** and **1h** are also accelerated by pressure, yielding ΔV^* values of -16 and $-18\ cm^3\ mol^{-1}$, respectively, for reaction in a 50% acetonitrile solution.

The stoichiometry of the reaction between imidazole and the cyclic sulfamates is two imidazole equivalents for each one of the latter, based on product characterization. The second imidazole is involved in a presumably very fast reaction with the protonated form of **6** to give **5**. This proton transfer takes place after the rate-determining step and thus has no effect on ΔV^*. A qualitative interpretation of the ΔV^* values for the reaction follows. The products of reaction subsequent to exocyclic sulfur attack are *N*-tosylated imidazole **6** and an imidazolium salt **5** in which the endocyclic sulfur containing ring is intact. In the transition state the incipient tosylated imidazole, i.e. *N*-protonated **6**, is not yet detached from the parent and there is both positive and negative charge development. There is species reduction, and consequently negative ΔV^* values are expected, and found. The magnitude of the negative value of ΔV^* implies increased electrostriction in addition to that caused by the associative nature of the reaction. The reactants are uncharged, so the increase in solvation is a result of increasing polar character of the transition state.

CONCLUSION

Nucleophilic substitution at sulfonyl sulfur may or may not proceed through an intermediate having five ligands arranged in a trigonal bipyramidal manner about the sulfur atom or it may be concerted, i.e. S_N2-like withut intermediate formation. Arguments for substitution taking place with or without an intermediate have been presented by other groups and are referenced.[5] Our results, which show



Scheme 4

that the transition state has a reduced volume compared to the reactants, can be interpreted to support either possibility. The negative ΔV^* is consistent with a concerted reaction in which structures **7** and **8** are not intermediates but transition states with partially formed bonds between each nucleophile (imidazole in **7** and hydroxide ion in **8**) and the sulfur atom and between the sulfur atom and the leaving group. On the other hand, if these reactions (one or both) take place with formation of a short lived intermediate, i.e. **7** or **8**, it appears that the rate-determining step occurs before intermediate formation. That is, the nucleophile to sulfur bond is being formed without the leaving group to sulfur bond being broken.

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