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NUCLEOPHILIC SUBSTITUTION AT SULFONYL SULFUR ATOM : AMINOLYSIS OF 1-TOSYL-3-METHYL IMIDAZOLIUM CHLORIDE IN AQUEOUS MEDIUM.

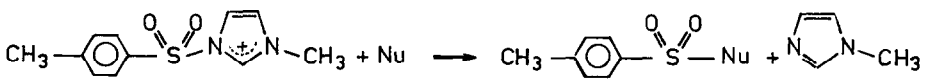
Pierre Monjoint[a,b] and Marie-Françoise Ruasse[a]

a) † Institut de Topologie et de Dynamique des Systèmes de l'Université Paris VII, associé au C.N.R.S., 1, rue Guy de la Brosse, 75005 PARIS - France.

b) Laboratoire de Chimie Organique Biologique de l'Université Paris XI, 91405 ORSAY - France.

Abstract. Kinetics of the reaction of 1-tosyl-3-methyl-imidazolium chloride with various amines were measured to examine the nature of sulfonyl transfer in enzymatic reactions. The activation parameters and the value of the Brønsted exponent, $\beta = 0.48$, are consistent with a small degree of bonding between the entering amine and the sulfur atom in the transition state. Similarities in the nucleophilic behavior of sulfonyl and carbonyl groups are detected.

Sulfonyl transfer is an important chemical modification of enzymes[1]. The strong inductive electrophilic effect of the sulfonyl group[2] has recently suggested that, for further complexation of aminoacids, a tosyl group could be a more suitable protector of N-peptide atoms than an acetyl or benzoyl group[3]. Despite this interest, conclusive data on the nucleophilic reactivity of the sulfonyl group are scarce[4]. This lack is all the more astonishing because there has been much work on various substrates such as carbonyl[5], sulfonate[6], and phosphate[7] groups. A first example of nucleophilic substitution at the sulfonyl sulfur atom where both the entering and leaving groups are amines, is reported here ; the use of the imidazolium leaving group, partly suggested by the recognized catalytic role of the imidazol residue in major biochemical reactions, could serve as a chemical model for biological processes.



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1-tosyl-3-methyl-imidazolium chloride is an appropriate substrate since substitutions at the sulfur atom occur readily[8], at rates which can be followed by standard stopped-flow methods. The chosen solvent is a 41/59 (0.488 mole fraction of water) ethanol-water mixture in which the sulfonamides formed are soluble. Kinetic experiments[9] are carried out under pseudo-first order conditions. The pseudo-first order rate constant, k_{obs}, is linearly related to the free amine concentration obtained from pH and pK_a measurements[10]. The

second-order rate constant, k_n, is obtained from the slope of k_{obs} vs amine concentration plots. The linear relationship between k_{obs} and the amine concentration rules out catalysis by a second molecule of amine. In all cases, the uncatalyzed hydrolysis was negligible.

TABLE : Experimental Results for the Aminolysis of 1 in EtOH-H_2O (0.488 mole fraction of water)

	Nucleophile	pK_a^{*} [a]	k_n [b,d]	$\Delta H^{\neq}$ [c]	$-\Delta S^{\neq}$ [c]
2	trifluoroethylamine	5.25	1.35	3.6	46
3	glycine ethyl ester	6.84	12.2	11.9	14
4	morpholine	8.48	484	7.5	21
5	ethanolamine	9.58	157	6.2	28
6	glycine	9.95	325	8.7	18
7	n-butylamine	10.24	400	5.2	29
8	di-iso-propylamine	10.86	2.5	12.7	14
9	piperidine	10.90	2196	7.9	17
10	iso-propylamine	10.92	26.5	13.1	8
11	tert-butylamine	11.56	5.9	7.9	29

a) Ionic strength held constant at 0.16 M with potassium chloride (Ref.10) ; b) Ref. 11 ; c) Activation enthalpies in Kcal/mole obtained from kinetic measurements at four temperatures between 278 and 323 K. ; activation entropies are in cal/mole.K ; d) in $M^{-1}.s^{-1}$; at 25°C.

Steric effects and enthalpy-entropy compensation.- Aminolysis of 1 is highly sensitive to steric effects in the entering group : unstrained amines react ca 10^2 times faster than strained amines. The corresponding activation parameters display a trend to enthalpy-entropy compensation. However, $\Delta H^{\neq}$ vs $\Delta S^{\neq}$ gives two straight lines (Fig.1) markedly separating amines with bulky substituents from those without. For similar activation enthalpies, activation entropies of bulky amines are ca 10 entropy units higher than those for smaller amines. If the activation enthalpies are corrected by the dissolution enthalpies of the amines[12], the two lines reduce to a single straight line. Consequently, the steric effects on the reaction of 1 can be attributed partly to a desolvation of the amines in the ground state and partly to a steric inhibition to solvation of the transition state.

A small Brønsted exponent. The Brønsted plot for the data in the Table is shown in Fig. 2. A linear relationship is obtained with a β of 0.48 for compounds 2, 3, 5, 6 and 7. Positive deviations for piperidine and morpholine probably stem from abnormally low pK_a values[13] since both amines behave "normally" in the enthalpy-entropy plot. The negative deviations, observed for branched amines only, can reasonably be attributed to a reactivity decrease resulting from an enhanced sensitivity to steric effects when the electrophile is changed from protonated water to tosylate 1. Since the β-value for a complete transfer of a tosyl group is unknown, the magnitude of the obtained Brønsted exponent cannot be interpreted straightforwardly. However, considering the value of 1.24 for a complete sulfonate transfer[6], it is likely that the extent of bond formation and charge development on the attacking amine is not large. The

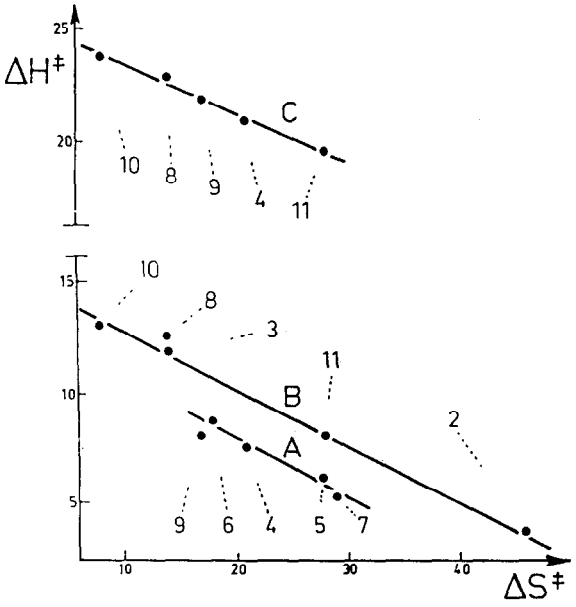

Figure 1. Enthalpy-entropy plots : A : small amines ; B : bulky amines ; C : activation enthalpies corrected by dissolution enthalpies.

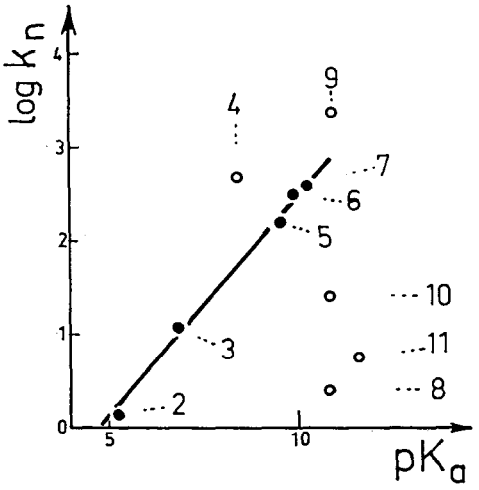

Figure 2. Effect of basicity on the second-order rate constants for the reaction of amines with 1-tosyl-3-methyl imidazolium chloride.

small degree of bonding between the entering nucleophile and the sulfur atom is confirmed by the absence of any deviation for the glycinate anion (6) : interactions between the charged nucleophile and the sulfonyl group are negligible. The value of 0.48 is near that of 0.44 for the reaction of anilines with benzenesulfonyl chloride[14], but significantly different from that of 1.0 for the aminolysis of p-nitrophenyl tosylate[13]; in this latter case, the general acid-base catalysis detected would suggest a stepwise mechanism. In this respect, it is noteworthy that no break in the Brønsted plot is observed at the pK_a of the imidazol group (7.13). By analogy with sulfate or phosphate transfer[6,7], this could also exclude a stepwise mechanism in the aminolysis of 1.

Similarities between sulfonyl and carbonyl transfers. The log-log correlation for the rate constants of the reaction of 1 with nucleophiles, with the corresponding rate constants for their reaction with 1-acetyl-imidazolium ion[15] is linear with a slope of 1.4 and an intercept of -8. Substituent effects are of same nature in both reactions. Kinetic data for 1-acetyl-imidazolium aminolysis have been interpreted by a symmetrical transition state with extensive bond formation ; this can occur either in a concerted mechanism or in a stepwise mechanism with almost identical transition states for formation and breakdown of the intermediate[15].

This result cannot be reliably transferred to the reactions of tosyl imidazolium ion since the demands of the sulfonyl and carbonyl centers on the entering and leaving groups could differ largely, even if they respond similarly to the amine substituent effects. The analogy between the nucleophilic behavior of the sulfonyl and that of the carbonyl group is confirmed by the linear correlation with almost unit slope between the reaction of 1 and that of 1-acetoxy-4-methoxy-pyridinium ion[16] with the same amines.

In addition to similarities between the nucleophilic reactivities of the sulfonyl and carbonyl centers, our results imply a rate-limiting transition state involving no extensive bond formation between the sulfur atom and the entering amino groups. As in the case of 1-acetyl-imidazolium ion reactions[5], the occurence of a pentacoordinate intermediate in sulfonyl transfers cannot, at present, be deduced from our results. It should be noted that the difficulties in attributing a specific mechanism[4] could arise from borderline situation for these reactions[17]. In this respect, rational changes in the reactant concentrations, in the medium and in the leaving group whose effects can be readily measured owing to the choice of 1 as substrate, could induce small but instructive shifts in the mechanism. Work to determine where sulfonyl transfer reactions fit into the general mechanism spectrum suggested by Jencks for nucleophilic substitutions[18], is in progress.

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