Nucleophilic Substitution at Sulphur. Reaction of *p*-Nitrophenyl Triphenylmethanesulphenate with n-Butylamine and Benzamidine

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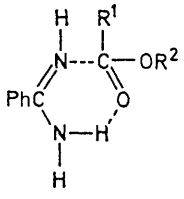
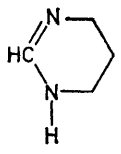
The reaction of n-butylamine with *p*-nitrophenyl triphenylmethanesulphenate is of the second order in nucleophile, but the reaction of benzamidine with the same substrate in the same solvent is of the first order in nucleophile. The same pattern is found when n-butylamine and benzamidine react with carboxylic esters and aromatic derivatives. It is suggested that this pattern has a common origin and that the first-order behaviour of benzamidine can be explained without resorting to bifunctional catalysis.

BIFUNCTIONAL catalysis by benzamidine has recently aroused interest as a possible model for enzyme action.[1,2] The structure of benzamidine is such that concerted cyclic transition states are likely and this can be responsible for the enhanced reactivity of benzamidine when the reaction requires both nucleophilic attack and proton transfer. A cyclic transition state (I) has been



(I)



(II)

suggested by Menger for the reaction of benzamidine with *p*-nitrophenyl acetate in chlorobenzene.[1] This conclusion has been generally accepted, but Anderson *et al.* have suggested that bifunctional catalysis cannot be the sole mechanism of amidinolysis in chlorobenzene, other non-concerted polar mechanisms being possible.[3] This suggestion was largely based on the fact that 1,4,5,6-tetrahydropyrimidine (II), an imidine whose structure makes bifunctional catalysis unlikely, reacts with *p*-nitrophenyl acetate 46 times more rapidly than benzamidine itself. This, however, was not considered sufficient proof to exclude bifunctional catalysis by benzamidine in other systems.[2]

Owing to the lack of general agreement about the role of benzamidine in nucleophilic substitutions, we considered it worth while to measure the reactivity of benzamidine with sulphur substrates. This seemed particularly interesting in connection with the problem of transition-state geometry for nucleophilic substitution at sulphur.[4]

We chose to investigate the behaviour of *p*-nitrophenyl triphenylmethanesulphenate since previous work had shown that the reaction of sulphenyl derivatives with amines in aprotic solvents of low dielectric constant such as benzene proceeds *via* the formation of an intermediate and has a rate-limiting proton-transfer step.[5,6] Chlorobenzene was chosen as solvent by analogy with similar work.[1,2]

RESULTS AND DISCUSSION

The reaction rates of *p*-nitrophenyl triphenylmethanesulphenate with n-butylamine and benzamidine were measured in chlorobenzene at 25 °C under pseudo-first-order conditions. The kinetics were simple up to 90% completion. The reaction with n-butylamine was of the second order in nucleophile (third order overall) and that with benzamidine was of the first order in nucleophile (second order overall). The data are in the Table.

Velocity constants for the nucleophilic substitution reaction of *p*-nitrophenyl triphenylmethanesulphenate with n-butylamine and benzamidine [a]

Nucleophile	10^2Concn./M	k'/l mol^{-1} s^{-1} [b]	k/l^2 mol^{-2} s^{-1} [c]
$BuNH_2$	2·00	1·64 × 10^{-2}	0·82
$BuNH_2$	3·00	2·58 × 10^{-2}	0·86
$BuNH_2$	4·00	3·24 × 10^{-2}	0·81
$BuNH_2$	5·00	4·31 × 10^{-2}	0·86
Benzamidine	0·665	88·2	
Benzamidine	1·33	92·5	
Benzamidine	1·33	86·5	
Benzamidine	2·00	92·0	
Benzamidine	2·66	89·9	

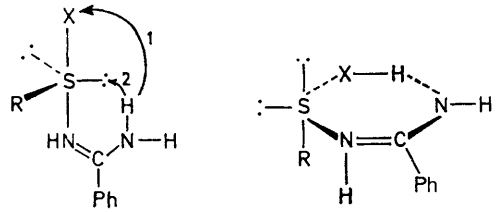
[a] Substrate concn., *ca.* 10^{-4}M; temp. 25 °C; solvent, chlorobenzene. [b] k' = Rate/[NPTS][Nucleophile]. [c] k = Rate/[NPTS][$BuNH_2$]^2.

The behaviour of *p*-nitrophenyl triphenylmethanesulphenate is therefore identical to that found for 4-fluoro-1,6-dinitronaphthalene [2] and *p*-nitrophenyl acetate [1] in the same solvent and with the same pair of nucleophiles, n-butylamine and benzamidine. In the last two systems the different behaviour of benzamidine relative to n-butylamine was explained by suggesting bifunctional catalysis.

Nucleophilic substitution at sulphur is believed to occur *via* backside displacement, closely similar to that which applies to S_N2 substitutions at saturated carbon.[4,7] The geometry of this transition state prevents bifunctional action of benzamidine providing the nucleophilic push at the reaction centre as well as the electrophilic pull of the leaving group (III, 1). On the other hand, in the hypothesis that the first-order behaviour of benzamidine

[1] F. M. Menger, *J. Amer. Chem. Soc.*, 1966, **88**, 3081.
[2] G. Biggi, F. Del Cima, and F. Pietra, *J.C.S. Perkin II*, 1972, 188.
[3] H. Anderson, C. Su, and J. W. Watson, *J. Amer. Chem. Soc.*, 1969, **91**, 482.
[4] E. Ciuffarin and A. Fava, *Progr. Phys. Org. Chem.*, 1968, **6**, 81.
[5] E. Ciuffarin and G. Guaraldi, *J. Amer. Chem. Soc.*, 1969, **91**, 1745.
[6] E. Ciuffarin and F. Griselli, *J. Amer. Chem. Soc.*, 1970, **92**, 6015.
[7] W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, 1970, **92**, 2731.

towards sulphenyl derivatives has to be accounted for by bifunctional catalysis, two transition-state geometries can be envisaged (charges being neglected), *viz.*, (III, 2) and (IV), both trigonal bipyramidal. The transition state represented by (IV) with entering and leaving groups both in the radial position, would be consistent with the fact that nucleophilic substitutions at sulphur ordinarily occur with inversion of configuration, but not



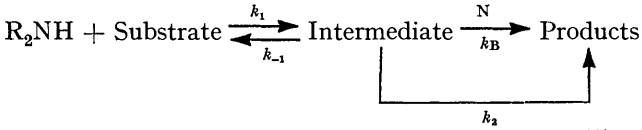
(III) (IV)

necessarily *via* a linear transition state.* However, a radial–radial nucleophilic substitution for sulphenyl substrates appears to be very unlikely insofar as it requires that one electron pair be situated in an apical position which would result in a large stereoelectronic strain with the attendant large increase of the transition-state energy.[9] Transition state (III, 2) would be consistent with the commonly accepted idea that nucleophilic substitution at sulphur occurs from the backside, with entering and leaving groups occupying the apical positions of the trigonal bipyramidal transition state.[4] In this case, proton transfer would not facilitate the reaction through the expulsion of the leaving group but would serve efficiently to decrease charge separation. This would be in accord with the suggested formation of sulphurans as reaction intermediates in reactions at sulphur.[10] The formation of sulphuran would then be followed by a fast and probably concerted electrocyclic elimination of HX.[10]

Although the latter interpretation may be appealing, there is no independent evidence that it may be correct. Rather, we suggest that the behaviour of benzamidine, as compared with n-butylamine, does not imply bifunctional catalysis for reaction at sulphenyl sulphur any more than at carbonyl or at aromatic carbon. The following discussion forms the basis of our contention.

The much greater reactivity of benzamidine than of n-butylamine was deduced by comparing the second-order rate constant measured with benzamidine (k_{Benz}) with the ' intercept ' ($k^{\circ}_{BuNH_2}$) at zero amine concentration (undetected but considered equal or smaller than the experimental error) obtained by plotting the second-order rate constant (k_{BuNH_2}) against the concentration of n-butylamine.[1,2] The justification given by Menger [1] was that ' a more meaningful comparison would be between the benzamidinolysis reaction and the reaction of a *single* n-butylamine molecule (the monomer) with the ester, for these two reactions are of the same order in nucleophile '. An amine dimer was considered responsible for the second order in n-butylamine and consequently it was assumed that there exists an undetectable (within experimental error) very slow reaction between *p*-nitrophenyl acetate and *single* n-butylamine molecules. Dimer formation was preferred to general base catalysis because addition of *N*-methylpiperidine caused only a small rate increase (30%) which was attributed to a medium effect. However, it was later shown [3] that the reaction *is* base-catalysed when steric factors are minimized. Therefore, dimer formation as the explanation for the second order in n-butylamine appears unlikely and along with it the assumption that the undetected intercept corresponds to the reaction with monomer.

Aromatic nucleophilic substitutions proceed *via* an addition–elimination mechanism. Thus, the intercept at zero n-butylamine concentration corresponds to a supposedly present uncatalysed reaction path (1) whose rate constant is composite, $k^{\circ}_{BuNH_2} = k_1k_2/k_{-1}$.[2] The assumption here is that benzamidine greatly assists the uncatalysed path. In fact, when $k_2 \gg k_B[N]$ [equation (1)] the reaction becomes first order in nucleophile.



(1)

However, another possibility exists, which was not previously discussed or excluded,[2] of comparing homogeneous rate constants, such as the comparison between the rate with benzamidine and the maximum rate measurable with n-butylamine. At high concentration of n-butylamine the second step of the intermediate complex mechanism (1) is fast, $(k_B[N] + k_2) \gg k_{-1}$, so that the experimental constant becomes $k_{exp} = k_1$. The first-order behaviour of benzamidine can be explained without resorting to an at any rate undetectable ' uncatalysed path ' in the reaction with n-butylamine. When $k_B[N]/k_{-1}$ is much smaller than unity the intermediate reverts largely to reactants and the order in nucleophile is two, but when it is much larger than unity the rate is governed solely by k_1 (formation of the intermediate). This changes the order in nucleophile from two to one. The change of order depends only on $k_B[N]/k_{-1}$ and is independent of k_1. Therefore we need consider only the factors that might influence $k_B[N]/k_{-1}$ and can neglect those which might affect the value of k_1. [However, it is likely that the rate of formation of the intermediate and the reactivities of n-butylamine and benzamidine are comparable since electronic stabilization puts basicity and consequently nucleophilicity of benzamidine in a range comparable with that of n-butylamine; see

* A geometry of this type has been suggested for certain substitutions of sulphinyl derivatives.[8]

[8] J. D. Day and D. J. Cram, *J. Amer. Chem. Soc.*, 1965, **87**, 4398.

[9] F. H. Westheimer, *Accounts Chem. Res.*, 1968, **1**, 70.

[10] (*a*) B. M. Trost, R. La Rochelle, and R. C. Atkins, *J. Amer. Chem. Soc.*, 1969, **91**, 2175; (*b*) B. M. Trost, W. L. Scinski, and I. B. Mants, *ibid.*, p. 4320.

later.] A higher proportion of return to reactants is favoured for n-butylamine because the amine function is a very good leaving group (formal positive charge on nitrogen) while at the same time proton abstraction from the amine–substrate complex by a second molecule of amine is subject to steric hindrance (the more so the bulkier the substrate). Only at very high concentration of n-butylamine (usually experimentally inaccessible) would the formation of the intermediate be rate-limiting. In some cases there is an indication that the mechanism changes with increasing amine concentration ($k_B[N] \simeq k_{-1}$), as for example for the reaction of 1-fluoro-2,4-dinitrobenzene with n-butylamine in benzene.[11] On the contrary, the intermediate which is formed with benzamidine presents an electronic delocalization which decreases the charge on the *imide* nitrogen with consequent little tendency to revert to reactants. At the same time the proton is abstracted from the *amide* nitrogen which is far from the reaction centre and therefore easily accessible to a second molecule of base (the nucleophile itself) in a fast step. That is. while with n-butylamine the formation of the intermediate is rate-limiting only at very high concentration of amine, with benzamidine such a situation may be reached at very low concentration.

We have so far neglected the possibility of an uncatalysed path. Sometimes, however, there is an uncatalysed path. This is the case with aromatic substrates possessing *o*-nitro-groups which function as internal bases for proton abstraction.[11] In these cases the reaction *via* the n-butylamine-catalysed path proceeds at a rate similar to that of the uncatalysed path and ' catalysis ' by benzamidine is very small.[2] When the *o*-nitro-group is entirely responsible for the proton abstraction in a fast step (k_1 rate-limiting),[11] benzamidine does not catalyse the reaction at all.[12] These observations are in our opinion a further demonstration that bifunctional catalysis is not the explanation for the first-order behaviour of benzamidine, because the supposed formation of a ring and the presumed good fit of the two benzamidine functions are unable substantially to decrease the transition state energy relative to that of the reaction with n-butylamine which does not possess a built-in fit for bifunctional catalysis.

Therefore not only has bifunctional catalysis by benzamidine not yet been proved but it is also unlikely for nucleophilic substitution of carboxylic esters, aromatic substrates, and, *a fortiori*, bivalent sulphur compounds.

Since it has been demonstrated beyond reasonable doubt that nucleophilic substitution at aromatic carbon [13] and at sulphur [6] proceeds *via* an intermediate, we are inclined to think that the reaction of amines with *p*-nitrophenyl acetate in chlorobenzene follows a similar intermediate complex mechanism. Some of the data by Menger [1] and by Anderson *et al.*[3] seem to suggest this conclusion. The rate constant for the reaction of benzamidine with carboxylic esters decreases at very low nucleophile concentration suggesting a change in mechanism, *i.e.*, in terms of equation (1) this would occur when the value of $k_B[N]$ has decreased so much to become comparable with k_{-1}.

Uncatalysed paths have been found also for nucleophilic substitutions of *p*-nitrophenylacetate with diamines.[3] In this case intramolecular (but not bifunctional) catalysis seems to be a convincing explanation. 1,3-Diaminopropane can easily form a six-membered ring, providing an intramolecular path for proton removal.

Anderson *et al.* suggested that electronic stabilization might be responsible for the ' enhanced reactivity ' of benzamidine towards carboxylic esters.[3] Biggi *et al.* excluded this explanation for nucleophilic aromatic substitution on the ground that, when the formation of the intermediate is rate-limiting, benzamidine reacts more slowly than n-butylamine as, for instance, with 1-chloro-2,4-dinitrobenzene.[2] Their contention was that, were electronic stabilization responsible for the enhanced reactivity of benzamidine, it should show up in every case and not only when proton abstraction is rate-limiting. On the other hand electronic stabilization must be present. In fact, without such stabilization one cannot suggest that benzamidine reacts with its imide nitrogen which should be less basic than its amide nitrogen. Moreover, the fact that the basicity of benzamidine is, albeit slightly, higher than that of n-butylamine indicates that electronic stabilization is important at least as far as basicity is concerned. Without electronic stabilization the basicity of benzamidine would be of the same order of magnitude as that of benzamides which are neither basic nor nucleophilic. To state that benzamidine, an amine of the same basicity as n-butylamine, does not present electronic stabilization because it reacts almost at the same rate as n-butylamine, as is the case with 1-chloro-2,4-dinitrobenzene,[2] is wrong in principle. The correct conclusion is that benzamidine presents towards 1-chloro-2,4-dinitrobenzene an electronic stabilization similar to that towards the proton. Thus, electronic stabilization *is* present as suggested by Anderson *et al.*,[3] even though it is *not* responsible for the enhanced reactivity of benzamidine (when it is found).

EXPERIMENTAL

Materials.—*p*-Nitrophenyl triphenylmethanesulphenate[14] and benzamidine [1] were prepared as described. n-Butylamine was a commercial product which was distilled once from NaOH pellets and once from sodium. Chlorobenzene was refluxed for 12 h over P_2O_5, distilled, refluxed for 12 h over anhydrous potassium carbonate, and fractionated. *N*-n-Butyltriphenylmethanesulphenamide was characterized previously.[5]

N-(*Triphenylmethylthio*)*benzamidine.*—This was prepared either by mixing stoicheiometric amounts of benzamidine

[11] F. Pietra and D. Vitali, *J. Chem. Soc.* (*B*), 1968, 1200.
[12] G. Biggi, F. Del Cima, and F. Pietra, *Tetrahedron Letters*, 1971, 2811.
[13] F. Pietra, *Quart. Rev.*, 1969, **23**, 504.
[14] L. Senatore, E. Ciuffarin, and A. Fava, *J. Amer. Chem. Soc.*, 1970, **92**, 3035.

and *p*-nitrophenyl triphenylmethanesulphenate (or triphenylmethanesulphenyl chloride) in chlorobenzene (or benzene) or by stirring a solution of *p*-nitrophenyl triphenylmethanesulphenate (or triphenylmethanesulphenyl chloride) in chlorobenzene (or benzene) for 24 h with an aqueous equimolar solution of benzamidine hydrochloride containing a 50% excess of sodium hydrogen carbonate. Evaporation of the organic layer yielded the *product* in good yield (80—90%), m.p. 160—168 °C. It is difficult to obtain a pure product since in solution slow decomposition occurs. Crystallization was tried from light petroleum (b.p. 100—160 °C), ethyl alcohol, isopropyl alcohol, chloroform–light petroleum (b.p. 30—50 °C), and benzene–light petroleum (b.p. 30—50 °C). In each case only the first fraction was similar or slightly better than the product before crystallization. The best sample, obtained after repeated recrystallization in very low yield, had m.p. 171—174 °C (Found: C, 78·6; H, 5·8; N, 6·85; S, 8·35. $C_{26}H_{22}N_2S$ requires C, 79·15; H, 5·6; N, 7·1; S, 8·1%). The n.m.r. spectrum is compatible with the suggested structure and did not show any impurity.

Kinetics.—All solutions were prepared in a dry-box. The reactions with n-butylamine were followed at 340 nm with a Unicam SP 800 recording spectrophotometer equipped with a thermostatted cell compartment. Reactions with benzamidine were followed at 340 nm with a Durrum stopped-flow spectrophotometer.[15] In all cases investigated, the experimental infinity spectra were identical within experimental error to those calculated from the absorbances of the expected products.

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[2/1742 *Received, 25th July,* 1972]

[15] For a description of the apparatus and the treatment of the kinetic data see G. Tomalin, M. Trifunac, and E. T. Kaiser, *J. Amer. Chem. Soc.*, 1969, **91**, 722.