Potentially Bifunctional Reactants. The Kinetics of Aromatic Nucleophilic Substitution by Benzamidine and n-Butylamine

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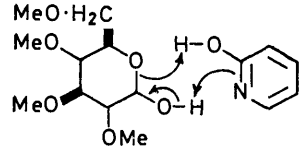
Halogen substitution of 1-chloro-2,4-dinitrobenzene in chlorobenzene by n-butylamine proceeds more rapidly than substitution by benzamidine, neither reactions requiring a catalyst. Halogen substitution of 4-fluoro-1,6-dinitronaphthalene in chlorobenzene is of the second order in n-butylamine and of the first order in benzamidine. This indicates that the amidine may react bifunctionally when catalysis is required, as no enhanced rate for the reaction of the amidine, with respect to the corresponding reaction of an amine of similar basicity, results when no catalysis is required. In the case of 1-fluoro-2,4-dinitrobenzene an intramolecularly catalysed pathway is available to reactions with either benzamidine or n-butylamine, so that the former is not particularly favoured with respect to the latter. The relevance of these results to the studies of model reactions for enzyme action is discussed.

SWAIN and BROWN's polyfunctional mode of catalysis [1] is of considerable interest both as a potentially general model for enzyme action [1,2] and as an accepted mode of catalysis in a variety of common reactions.[3] The primary need is that the two functionalities in the catalyst are in a suitable relative position so that the catalyst can fit concertedly to a cyclic transition state.

In the case of tautomeric molecules, such as 2-pyridone, bifunctional catalysis of, *e.g.*, the mutarotation of tetramethylglucose [1] (Scheme 1) has been properly termed 'tautomeric' catalysis.[3] These concepts have been extended to attack on atoms other than hydrogen. This is the case in the amidinolysis of esters by, for example, benzamidine (Scheme 2). This reaction has been kinetically studied in chlorobenzene as a model for enzyme action, with the idea that active sites of



SCHEME 1

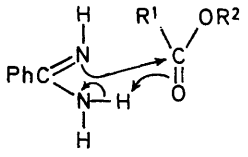
enzymes are hydrophobic regions.[2a] The observation that *p*-nitrophenyl acetate in chlorobenzene acetylates

[1] C. G. Swain and J. F. Brown, jun., *J. Amer. Chem. Soc.*, 1952, **74**, 2538.

[2] (*a*) F. M. Menger, *J. Amer. Chem. Soc.*, 1966, **88**, 3081; (*b*) D. R. Robinson and W. P. Jenks, *ibid.*, 1967, **89**, 7096; D. W. Tanner and T. C. Bruice, *ibid.*, p. 6954; G. C. Overberger, T. St. Pierre, C. Yaroslavsky, and S. Yaroslavsky, *ibid.*, 1966, **88**, 1184; J. C. Sheehan, G. B. Bennett, and J. A. Schneider, *ibid.*, p. 3455.

[3] R. P. Rony, *J. Amer. Chem. Soc.*, 1969, **91**, 6090.

benzamidine, with second order overall kinetics, *ca.* 15,000 times faster than an amine of comparable basicity, such as n-butylamine (where third order overall kinetics



SCHEME 2

and lack of catalysis by *N*-methylpiperidine were observed) was interpreted by Menger in terms of bifunctional reactivity of benzamidine (Scheme 2) and of participation by n-butylamine in a cyclic transition state involving two molecules of amine.[2a]

These conclusions were largely accepted,[3,4] * but they have been questioned by Anderson *et al.*[6] on the grounds that an amidine such as 1,4,5,6-tetrahydropyrimidine (for which they could not conceive a bifunctional adaptation in the transition state on the basis of the examination of molecular models) is acetylated by *p*-nitrophenyl acetate in chlorobenzene, with second-order kinetics, even faster than benzamidine, and the corresponding reaction of n-butylamine is catalysed by added triethylenediamine. Rather, they suggested that ' high electron density on the imine nitrogen and stabilisation of the transition state by dispersal of the positive charge over three atoms ' is responsible for the fast acetylation of amidines.[6]

We have recently presented data [7] which throw much doubt on these conclusions and give indirect support to Menger's mechanism.[2a] Our approach to the problem has been different from that of Anderson *et al.*[6] Instead of examining the acetylation of an amidine which, like 1,4,5,6-tetrahydropyrimidine, supposedly is unable to adapt itself bifunctionally in the transition state, we have examined the substitution of the halogen atom of 1-chloro-2,4-dinitrobenzene (CDNB) by benzamidine in chlorobenzene. In this case loss of both a proton and the leaving group is expected [8] to occur in a fast, uncatalysed step.[7] This is the first reported example of nucleophilic aromatic substitution by an amidine.

This reaction has been compared with the halogen substitution by n-butylamine of the same substrate in chlorobenzene.[7] The kinetics (first order with respect to the nucleophile in both cases) were consistent with an uncatalysed process in both cases. Moreover, the reaction of benzamidine was markedly slower than that of n-butylamine, thus suggesting that bifunctional reactivity [2a] and not a general electronic factor [6] is responsible for the high rate of amidinolyses of esters.

* Rony [3] gives many examples of ' tautomeric ' catalysis. We have added to the list and have made some criticisms of ref. 56 of Rony's paper.[5]

[4] H. J. Gold, *J. Amer. Chem. Soc.*, 1968, **90**, 3402.
[5] (*a*) F. Pietra and D. Vitali, *Tetrahedron Letters*, 1966, 5701; (*b*) *J. Chem. Soc.* (*B*), 1968, 1318.

This conclusion is not absolutely convincing. However, it could be put on an unequivocal basis if bifunctional reactivity by amidines could be shown for those aromatic nucleophilic substitutions in which the loss of both a proton and a leaving group is expected [8] to occur in a rate-limiting, catalysed step. This would also be relevant to the problems of polyfunctional catalysis and to the exploitation of aromatic nucleophilic substitution reactions.

We report here the reactions in chlorobenzene of benzamidine with 1-fluoro-2,4-dinitrobenzene (FDNB) or 4-fluoro-1,6-dinitronaphthalene (FDNN) and the corresponding reactions of n-butylamine.

RESULTS

N-n-Butyl-4,7-dinitro-1-naphthylamine was prepared from 4-chloro-1,6-dinitronaphthalene (CDNN); [9] *N*-n-butyl-2,4-dinitroaniline was available from previous work.[10]

N-(2,4-Dinitrophenyl)benzamidine was prepared from FDNB and benzamidine hydrochloride in good yield in ethanol–water in the presence of sodium hydrogen carbonate (1 equiv.). This method failed with CDNN. Therefore, to achieve *N*-4,7-dinitronaphthylation of benzamidine we tried the usually [11] more reactive FDNN. FDNN in chlorobenzene with neat benzamidine gave *N*-4,7-dinitronaphthylbenzamidine in high yield.

Kinetic data for the reactions (Tables 1 and 2) were obtained by following the formation of the products by u.v. absorption spectroscopy. Formation of products was quantitative. The data for the reactions of n-butylamine with CDNB or FDNN in chlorobenzene are in Table 1; those for the reactions of benzamidine with CDNB, FDNB, or FDNN in chlorobenzene are in Table 2. Table 3 shows the activation parameters for all reactions except that of benzamidine with FDNB.

TABLE 1

Rates for the reactions of n-butylamine with A 1-chloro-2,4-dinitrobenzene; B 4-fluoro-1,6-dinitronaphthalene in chlorobenzene; k is the second-order rate coefficient, Rate/[Substrate][$BuNH_2$]; k' is the third-order rate coefficient, Rate/[Substrate] [$BuNH_2$]^2

A [a]

(Initial concn. 1·5—3·1 × 10^{-4}, temp. 84·5°, unless otherwise stated.)

10^2[$BuNH_2$]/mol l^{-1}	1·00	2·74	2·74 [b]
10^2k/l mol^{-1} s^{-1}	1·55	1·59	0·520

B

[Initial concn. 1·9—3·2 × 10^{-4}, temp. 84·2°, unless otherwise stated.)

10^3[$BuNH_2$]/mol l^{-1}	3·65	18·0	71·9	71·9 [c]
10^5k/l mol^{-1} s^{-1}	1·47	7·77	32·7	18·7
$10^2k'$/l^2 mol^{-2} s^{-1}	4·04	4·28	4·55	2·60

[a] Data from ref. 7. [b] Temp. 59·8°. [c] Temp. 61·4°.

[6] H. Anderson, C. Su, and J. W. Watson, *J. Amer. Chem. Soc.*, 1969, **91**, 482.
[7] G. Biggi, F. Del Cima, and F. Pietra, *Tetrahedron Letters*, 1971, 2811.
[8] F. Pietra, *Quart. Rev.*, 1969, **23**, 504.
[9] G. Biggi and F. Pietra, *J. Chem. Soc.* (*B*), 1971, 44.
[10] F. Pietra and D. Vitali, *J. Chem. Soc.* (*B*), 1968, 1200.
[11] F. Pietra, D. Vitali, and S. Frediani, *J. Chem. Soc.* (*B*), 1968, 1595.

TABLE 2

Second-order rate coefficient (k = Rate/[Substrate][Benz]) for the reactions of benzamidine (Benz) with A 1-chloro-2,4-dinitrobenzene; B 4-fluoro-1,6-dinitronaphthalene; C 1-fluoro-2,4-dinitrobenzene in chlorobenzene

A [a]

(Initial concn. 1·1—3·1 × 10^{-4}, temp. 84·5°, unless otherwise stated.)

10^3[Benz]/mol l^{-1}	1·45	2·90	2·90	
10^3k/l mol^{-1} s^{-1}	2·31	2·37	0·486 [b]	

B

(Initial concn. 1·9—3·5 × 10^{-4}, temp. 84·2°, unless otherwise stated.)

10^3[Benz]/mol l^{-1}	1·45	3·36	21·2	21·2 [c]
10^2k/l mol^{-1} s^{-1}	1·27	1·41	1·60	0·440

C

(Initial concn. 1·2—3·2 × 10^{-5}, temp. 29·7°.)

10^4[Benz]/mol l^{-1}	2·57	6·45	32·2	49·5
$10k$/l mol^{-1} s^{-1}	2·51	2·91	3·04	3·09

[a] Data from ref. 7. [b] Temp. 59·8°. [c] Temp. 61·4°.

TABLE 3

Activation parameters for the reactions of n-butylamine or benzamidine with 1-chloro-2,4-dinitrobenzene (CDNB) or with 4-fluoro-1,6-dinitronaphthalene (FDNN) in chlorobenzene

Substrate	Nucleophile	$\Delta H^{\ddagger}$/kcal mol^{-1}	$-\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
CDNB	$BuNH_2$	10 [a]	39 [a]
	Benzamidine	15 [a]	28 [a]
FDNN	$BuNH_2$	5	52
	Benzamidine	11	37

[a] Data from ref. 7.

DISCUSSION

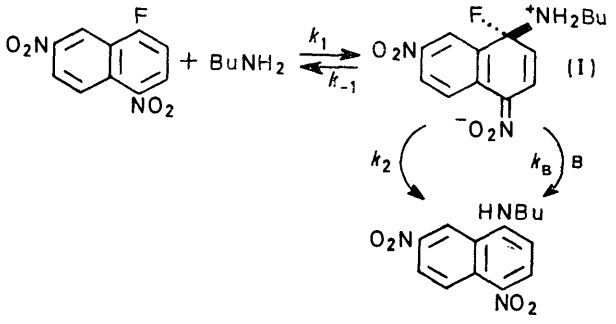
In the case of the reaction of n-butylamine with CDNB, simple second-order kinetics (first order in amine) have been obtained (Table 1A). No attempt has been made to explore this reaction for a broader range of amine concentration since similar results have been obtained for the reaction in benzene.[10] In the case of FDNN (Table 1B) kinetics which are nearly exactly third order (second order in amine) have been obtained instead.

These observations are in line with our previous experience with reactions of this type in non-polar, non-protic solvents [8] and can be rationalised by the addition–elimination mechanism shown in Scheme 3 for the case of FDNN (where B represents a base).

If the steady state treatment applies, equation (1) is obtained. In the case of the fluoro-compound,

$$k = (k_1k_2 + k_1k_B[B])/(k_{-1} + k_2 + k_B[B]) \quad (1)$$

owing to the high energy of the C–F bond in the intermediate (I)* and the large solvation requirements of the fluoride ion, one should expect that $k_{-1} \gg k_2 + k_B[B]$. Therefore, as the nucleophile is itself a base, second-order kinetics in n-butylamine are to be expected, as was actually found.



SCHEME 3

In the case of CDNB a mechanism of the type shown in Scheme 3 may be operative by analogy with FDNN and all other cases where there is evidence for an intermediate of type (I) along the reaction pathway.[8] However, decomposition of the intermediate into products must occur in a fast, uncatalysed step.

For CDNB the same kinetic order was obtained for benzamidine as for n-butylamine (Table 2A). The reactivity of benzamidine is *ca.* 10 times lower than that of n-butylamine (at 60°).

The reaction of FDNN with benzamidine, however, is nearly exactly of the second order overall (first order with respect to benzamidine). Clearly, the overall rates for this reaction and the corresponding one of n-butylamine, where second-order kinetics in amine were obtained, must be governed by different rate equations. The kinetics of the reaction of n-butylamine are given by equation (2). Therefore, the second-order rate coefficient for the reaction of FDNN with benzamidine

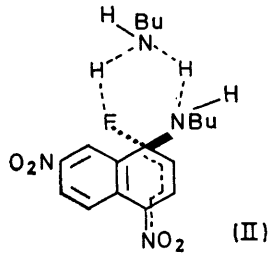
$$k = \text{Rate}/[\text{FDNN}][BuNH_2] = k_0 + k_{BuNH_2}[BuNH_2] \quad (2)$$

is determined by the value of the k_0 term of equation (2) (*cf.* the corresponding treatment of the reaction of n-butylamine).† As the value of k_0 [equation (2)] is *ca.* zero, benzamidine is much more reactive, in a mechanistically meaningful sense, than n-butylamine. In other words, the two reactions differ in an important mechanistic detail, *i.e.* different transition states are formed. The transition state for the reaction of n-butylamine is approximated by structure (II), where a cyclic transition state is drawn to avoid charge separation (which is rare in non-polar, non-protic solvents).[2a,5]

The illustrated transition state for the benzamidine reaction [structure (III)] takes the bifunctional reactivity of benzamidine into account. The cyclic

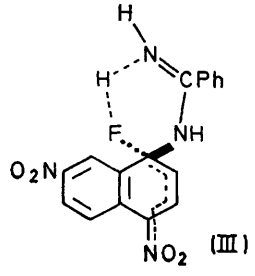
* Here, for simplicity, the negative charge is shown on only one nitro-group. In any case, the structure shown in Scheme 1 is an oversimplification, as in non-polar, non-protic solvents there is little tendency for charge creation [2a,5b] (see later). Whether the intermediate (I) or its conjugate base better represents the actual intermediate [8] is not relevant to the main conclusions of the present work.

† This situation is formally similar to that already encountered in discussing leaving group mobilities, where the same treatment was applied (F. Pietra and F. Del Cima, *Tetrahedron Letters*, 1967, 4573).



(II)

transition state is permissible both from the steric and from the electronic point of view.



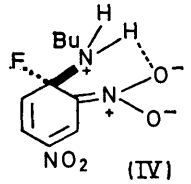
(III)

The activation parameters for the two types of reaction (Table 3) cannot be meaningfully compared, as they refer to overall rates. The activation parameters for the k_0 term of equation (2) would be required for the n-butylamine reaction, and it is not accessible for the reasons already given.

The kinetics of the reaction of FDNB with benzamidine (Table 2) are nearly exactly second order overall (first order with respect to benzamidine). Kinetic data for the reaction of FDNB with n-butylamine are available for benzene solutions,[10] where a less than linear increase of the second-order rate coefficient (k = Rate/[FDNB][$BuNH_2$]) with [$BuNH_2$] was observed. This was taken as evidence for a change in the rate-limiting step, from the rate-limiting decomposition of an addition intermediate of the type shown in Scheme 3 into products, at low amine concentrations, to the rate-determining formation of that intermediate, at high amine concentrations.[10] However, even at low amine concentrations, where, in a small range of amine concentration, the linear form of equation (3) is approximately obeyed, the k_0 term has a sizable magnitude.

$$k = \text{Rate}/[\text{FDNB}][\text{BuNH}_2] = k_0 + k_{\text{BuHN}_2}[\text{BuNH}_2] \quad (3)$$

Such drastically different kinetic behaviour between FDNN (where, within the accuracy of the measurements, k_0 is *ca.* 0) and FDNB can be attributed to *ortho*-nitro-group assistance [structure (IV)]. Therefore, greater reactivity for benzamidine than for n-butylamine (in the mechanistically meaningful sense expressed above) shows up to a much lesser extent here than in the case of FDNN.



(IV)

In conclusion, we believe we have provided an unequivocal example of bifunctional reactivity for an amidine (for FDNN). We have also proved that when no catalysis is required, as with CDNB, such a bifunctional reaction pathway does not intervene and benzamidine is actually less reactive (by a rather large factor if the rates are extrapolated to room temperature at which amidinolyses of esters have been studied [2a,6]) than n-butylamine, which has similar base strength (in water). We have further shown that intramolecularly catalysed pathways may be available to both amidine and amine reactions (as in the case of FDNB), and thus the amidine does not show any particularly enhanced reactivity. Besides their relevance to the problem of polyfunctional catalysis and the mechanism of aromatic nucleophilic substitution, the results support the bifunctional mechanism of the reactions of benzamidine with esters suggested by Menger.[2a]

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. The u.v. spectra were taken with Unicam SP 800 or Beckman DU spectrophotometers. ^{1}H N.m.r. spectra were taken with a JEOL C-604L spectrometer at 30° with tetramethylsilane as reference.

Materials.—Chlorobenzene was fractionally distilled over P_2O_5. n-Butylamine, 1-chloro- and 1-fluoro-2,4-dinitrobenzene, and 4-fluoro-1,6-dinitronaphthalene were purified as described previously.[10,11] Benzamidine was purified as reported.[2a] *N*-n-butyl-2,4-dinitroaniline was available from previous work.[10]

N-(2,4-*Dinitrophenyl*)*benzamidine.*—Benzamidine hydrochloride hydrate (Aldrich) (1·9 g) and sodium hydrogen carbonate (2·5 g) were dissolved in water and added to 1-fluoro-2,4-dinitrobenzene (2·03 g, 10·9 mmol) in ethanol (2 ml). The solution was heated at reflux for 1 h, cooled to room temperature, neutralised, and then cooled to 4°. A yellow *precipitate* (2·8 g, 90%) was obtained which was repeatedly recrystallised from ethanol; m.p. 155—156° (Found: C, 54·7; H, 3·7; N, 19·8. $C_{13}H_{10}N_4O_4$ requires C, 54·6; H, 3·5; N, 19·6%), $\lambda_{max.}$ (chlorobenzene) 330 nm (log ε 4·09). The ^{1}H n.m.r. spectrum supports the assigned structure. A by-product was obtained as red crystals (0·15 g), m.p. 146—149°. Analytical figures are consistent with the product being *benzamidinium* 2,4-*dinitrophenolate* (Found: C, 50·9; H, 4·0; N, 18·1. $C_{13}H_{12}N_4O_5$ requires C, 48·4; H, 4·0; N, 18·4%). The structure was confirmed by the u.v. and ^{1}H n.m.r. spectra.

N(4,7-*Dinitronaphthyl*)*benzamidine.*— 4-Fluoro-1,6-dinitronaphthalene (0·07 g, 0·3 mmol) and benzamidine (0·43 g, 3·5 mmol) were dissolved in chlorobenzene (80 ml) and heated at 70° for 3 h. Evaporation of the solvent and preparative t.l.c. on silica gel of the residue [benzene–acetone (9 : 1, v/v)] yielded crystals (0·08 g, 75%). Repeated recrystallisation from benzene afforded yellow *crystals*, m.p. 204—205° (Found: C, 60·4; H, 3·3; N, 16·9. $C_{17}H_{12}N_4O_4$ requires C, 60·8; H, 3·6; N, 16·7%), $\lambda_{max.}$

(chlorobenzene) 390 nm (log ε 4·11). The ^{1}H n.m.r. spectrum confirmed the assigned structure.

N-*n-Butyl*-4,7-*dinitro*-1-*naphthylamine*.— 4-Chloro-1,6-dinitronaphthalene (0·1 g, 0·4 mmol) was dissolved in an excess of n-butylamine and heated at reflux for several h. The excess of n-butylamine was evaporated off and the residue was chromatographed on a thick layer of silica gel [benzene–acetone (96 : 4, v/v)], giving orange crystals (0·089 g, 75%). Crystallisation from ethanol–water gave orange *crystals*, m.p. 163—164° (Found: C, 57·9; H, 4·9; N, 14·3. $C_{14}H_{15}N_3O_4$ requires C, 58·2; H, 5·2; N, 14·5%), $\lambda_{max.}$ (chlorobenzene) 396 and 420 nm (log ε 4·19 and 4·15). The ^{1}H n.m.r. spectrum confirmed the assigned structure.

Kinetics.—The progress of all the reactions was followed by determining the u.v. absorption at the long-wave maximum of the nitroaromatic product. In all cases the Lambert–Beer law was obeyed and the values for complete reaction agreed within 2% with those for a solution prepared from authentic materials. The reaction of FDNB was directly followed in a cuvette placed in the thermostatted cell compartment of the spectrophotometer. All other reactions were carried out by the sealed ampoule method. In all cases an excess of amine or amidine over the aromatic substrate was used and excellent first-order plots were obtained up to 90% completion.

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