Intramolecular General Base Catalysis in Aprotic Solvents

Lucio Senatore,* Ennio Ciuffarin,* Mauro Isola, and Mario Vichi

Contribution from the Istituto di Chimica Generale, Via Risorgimento 35, 56100 Pisa, Italy.
Received October 20, 1975.

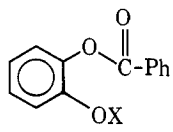
Abstract: The reaction of *o*-hydroxyphenyl benzoate (I) and *o*-methoxyphenyl benzoate (II) with *n*-butylamine or benzamidine has been studied in acetonitrile or in toluene. While so far general base catalysis was always found to account for relatively small rate accelerations, the rate data presented in this paper indicate that in aprotic solvents intramolecular general base catalysis may increase the rate of aminolysis reactions by a factor of 16 000 or more. Some data are against the concept of bifunctional reactivity of benzamidine.

Intramolecular catalysis has long been studied as a model reaction of enzymatic processes, since proximity effects are considered an important factor of enzymatic activity.[1] More recently it was also suggested that aprotic solvents are better models for enzymatic catalysis than aqueous solvents because the active centers are buried in lyophobic parts of the enzymes.[2] In this context, intramolcular catalysis by hydroxyl groups in ester aminolysis has already been studied by Menger.[3] It was found that in acetonitrile phenyl salicylate reacts with *n*-butylamine 130 times faster than the corresponding ortho methoxy ester. The rate acceleration was justified by suggesting acid catalysis either of the formation of the addition intermediate or the expulsion of the leaving group. There are only two other reported data related to the problem of intramolecular catalysis by ortho hydroxyl groups in aprotic solvents known to us. Vartak et al. found no rate acceleration when reacting the same pair of substrates studied by Menger[3] with aniline in nitrobenzene;[4] Snell cited in a footnote an experiment[5] never later elaborated or commented upon, which showed that the reaction of *o*-hydroxyphenyl acetate with *n*-butylamine in dioxane is first order in the nucleophile.

We are herewith reporting the first example of intramolecular general base catalysis in aprotic solvents by a hydroxyl group and the largest rate increase due to intramolecular general base catalysis found so far in any system.

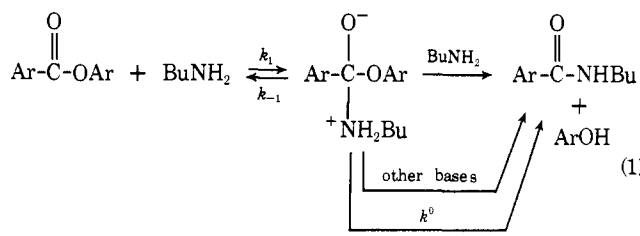
Results and Discussion

The reaction of *n*-butylamine with *o*-hydroxyphenyl benzoate (I) in toluene is first order in substrate and nucleophile and readily measurable at 25 °C (Table I). On the contrary, the *n*-butylaminolysis of *o*-methoxyphenyl benzoate (II) is

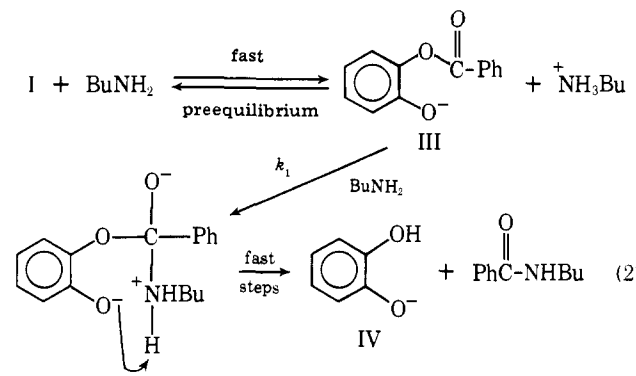


I, X = H
II, X = CH_3

much slower at that temperature and data have been obtained at 60 and 120 °C (Table I). At 120 °C the order in nucleophile is unity and the kinetic runs are linear in semilogarithmic plots (log *c* vs. time). At 60 °C and high amine concentration (0.5 M) the kinetics follows the usual first-order plot (Figure 1A) within experimental error, but at lower concentration (0.213 M) the reaction is complex (Figure 1B). If we recall that the experimental procedure (see Experimental Section) measures the concentration of the product, *o*-methoxyphenol, we can reasonably suggest that curve B is the first part of a plot representing the rate of *product* formation of a two-stage mechanism where the concentration of the intermediate is significant, so that the steady-state approximation does not apply. This interesting system could not be investigated further because of the extreme slowness of the reaction. The limited amount of data collected in this solvent, toluene, suggests that the butylaminolysis of *o*-methoxyphenyl benzoate (II) follows the general addition–elimination mechanism usually proposed for this type of reaction (eq 1).[6,7] In this hypothesis, the reaction can be first order in the nucleophile, second order in the nucleophile, or may present complex kinetics according to the relative rates of the various steps involved, which are modified by temperature or amine concentration changes.



(1)



III

(2)

Extrapolation of the rate data measured at 60 and 120 °C (at 0.5 M amine concentration where the reaction follows first-order kinetics at both temperatures) allows us to roughly estimate that at 25 °C I reacts 800 times faster than II. The fairly large reactivity of I with respect to II suggests for the butylaminolysis of I an *intramolecular* general base catalysis mechanism (eq 2). Since the reaction is first order in the nucleophile we must also assume that the dissociation preequilibrium is fast and completely displaced to the right.

While intramolecular nucleophilic catalysis can be excluded because of substrate's symmetry, intramolecular general acid catalysis of the undissociated *o*-OH group might also be suggested, but this is in contrast with data in acetonitrile (see below) and by Menger,[3] who found that acid catalysis of the butylaminolysis of phenyl salicylate accelerates the reaction 130 times but does not change the reaction order in the nucleophile, which is *two* for the butylaminolysis of both the

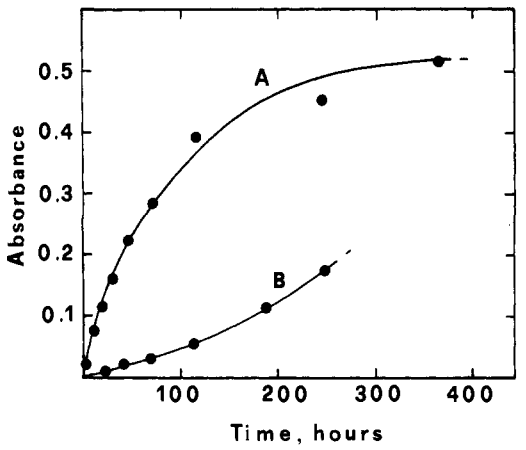


Figure 1. Reaction of *o*-methoxyphenyl benzoate (II) with *n*-butylamine at 60 °C in toluene. A, [*n*-butylamine] = 0.5 M; B, [*n*-butylamine] = 0.21 M.

Table I. Rate Data for the Reaction of *o*-Hydroxyphenyl (I) and *o*-Methoxyphenyl (II) Benzoates with *n*-Butylamine in Toluene

Ester	T, °C	$BuNH_2$, M	k_{obsd}, s^{-1}
I[a]	25	0.050	1.27×10^{-4}
		0.100	2.40×10^{-4}
		0.144	3.21×10^{-4}
		0.196	4.13×10^{-4}
II[b]	25	0.5	1.4×10^{-6},[c]
	60	0.21	*d*
		0.50	2.9×10^{-6}
	120	0.10	1.40×10^{-6}
		0.50	7.13×10^{-6}

[a] Concentration = 1.0×10^{-3} M. [b] Concentration = 1.5×10^{-4} M. [c] Extrapolated from higher temperatures. [d] See Figure 1B.

phenyl *o*-methoxybenzoate and the phenyl *o*-hydroxybenzoate.

The search for intramolecular general base catalysis was continued in the more suitable solvent acetonitrile, where the reactions could be followed at room temperature for both substrates I and II.

The *n*-butylaminolysis of II in acetonitrile at 25 °C (Table II) is second order in the nucleophile ($k_2 = 1.33 \times 10^{-5}$ M^{-2} s^{-1}). Addition of tetra-*n*-butylammonium perchlorate (0.05 M) increases the rate 1.5 times, which is a reasonable salt effect. Addition of *n*-butylamine hydrochloride increases the rate and at the same time adds a term first order in *n*-butylamine to the rate equation.

$$k_{obsd}\ (s^{-1}) = (1.33 \times 10^{-5})[BuNH_2] + (3.84 \times 10^{-5})[BuNH_2]^2 \quad (3)$$

This term can be attributed to general base catalysis by chloride ion, a not unusual behavior in aminolysis reactions in aprotic solvents.[8]

These data indicate that the mechanism of the butylaminolysis of II in acetonitrile is again that shown by eq 1. This mechanism, in fact, predicts that when the concentration of the intermediate is negligible and the steady-state approximation can be applied, the reaction is second order in the nucleophile (when the uncatalyzed path is negligible) as is found in pure acetonitrile or of mixed order in the presence of catalysts.

The *n*-butylaminolysis of I in acetonitrile at 25 °C, on the other hand, presents unusual features. The reaction is first order in the nucleophile when its concentration is higher than

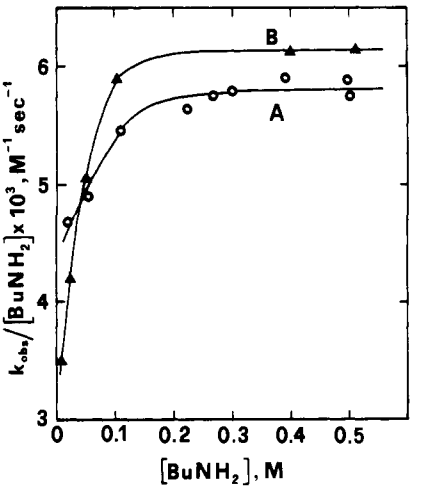


Figure 2. Reaction of *o*-hydroxyphenyl benzoate (I) with *n*-butylamine at 25 °C in acetonitrile. A, no additives; B, [*n*-$BuNH_3^+Cl^-$] = 0.057 M.

Table II. Rate Data for the *n*-Butylaminolysis of *o*-Methoxyphenyl Benzoate (II) in Acetonitrile at 25 °C[a]

$BuNH_2$, M	Additives	$k_{obsd} \times 10^5$, s^{-1}	$(k_{obsd}/[BuNH_2]) \times 10^5$, M^{-1} s^{-1}
0.507		0.337	0.666
0.754		0.7	0.933
0.950		1.20	1.27
1.00		1.33	1.33
0.535	$BuNH_3^+Cl^-$,	1.83	3.43
0.85	0.057 M	4.00	4.69
1.10		5.77	5.26
0.53	$Bu_4N^+ClO_4^-$,	0.448	0.85
0.808	0.0527 M	1.41	1.75
1.18		2.77	2.36

[a] Substrate concentration = 2×10^{-4} M.

0.2 M. At lower concentrations of nucleophile the rate decreases slightly, as shown in Figure 2A (Table III). This behavior is in accord with the mechanism of intramolecular general base catalysis shown by eq 2 by assuming that the dissociation equilibrium is completely displaced to the right only at amine concentration higher than 0.2 M. A fast preequilibrium is also suggested by a very fast reaction (faster than the mixing time, about 4 ms, of a "stopped-flow" spectrophotometer) which precedes the measured reaction. The rapid spectral change observed upon mixing the reactants is very small: an auxochromic shift of 3 nm and a 3% decrease in absorbance at 272 nm. The observed change in spectrum, albeit small, is outside experimental error and can be reasonably attributed to the dissociation or ion-pair formation of the substituted phenol I.[9] If this hypothesis is correct, one would expect that addition of a tertiary base such as triethylamine would displace the preequilibrium completely to the right and that the reaction would be first order in *n*-butylamine even at the lowest concentration of *n*-butylamine. This is in fact observed (Table III). However, the data at high *total* amine concentration have lower precision because of the higher sensitivity of the product catechol (IV) to oxidation.

Addition of salts such as tetra-*n*-butylammonium perchlorate does not appreciably affect the rate of reaction. The addition of *n*-butylamine hydrochloride (5.7×10^{-2} M) has a minor accelerating effect (≈5%) when the concentration of *n*-butylamine is higher than approximately 0.2 M. On the other

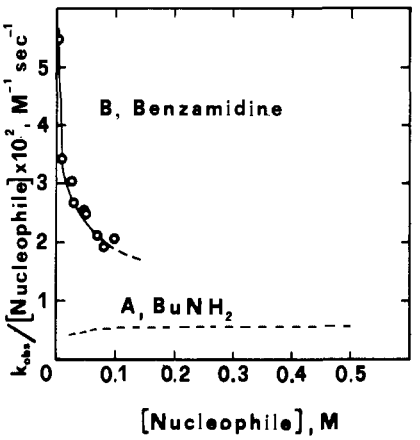


Figure 3. Reaction of *o*-hydroxyphenyl benzoate, (I) with *n*-butylamine, A (from Figure 2), and benzamidine, B, at 25 °C in acetonitrile.

Table III. Rate Data for the *n*-Butylaminolysis of *o*-Hydroxyphenyl Benzoate (I) in Acetonitrile at 25 °C[a]

$BuNH_2$, M	Additives	$k_{obsd} \times 10^3$, s^{-1}	$(k_{obsd}/[BuNH_2]) \times 10^3$, M^{-1} s^{-1}
0.0214		0.1	4.69
0.0535		0.262	4.91
0.225		1.26	5.65
0.267		1.54	5.76
0.3		1.75	5.81
0.39		2.31	5.92
0.49		2.89	5.89
0.501		2.88	5.76
0.01	$BuNH_3^+Cl^-$,	0.035	3.5
0.025	0.057 M	0.105	4.2
0.052		0.262	5.05
0.103		0.608	5.90
0.4		2.46	6.14
0.51		3.12	6.13
0.0245	Et_3N,	0.14	5.75
0.327	0.3 M	1.92	5.89
0.43		2.4	5.60
0.54		3.04	5.6
0.0534	$Bu_4N^+ClO_4^-$,	0.275	5.14
0.107	0.05 M	0.577	5.40
0.178		0.983	5.52
0.535		3.08	5.76

[a] Substrate concentration = 2×10^{-4} M.

hand, at lower concentrations of nucleophile the hydrochloride has a marked retarding effect on the reaction, as shown in Figure 2 (Table II). This is quite easily explained by the scheme of eq 2, since addition of $BuNH_3^+$ displaces the preequilibrium to the left and therefore decreases the rate of reaction.

The rate data indicate that I reacts 850 times faster than II at 0.5 M amine concentration. This value is similar to that estimated for the same reaction in toluene at the same concentration in amine. The much larger rate of reaction of the ionized form of I than that of II and comparison of the kinetic behavior of the two substrates indicate that the ionized *o*-hydroxyl group acts as a very efficient intramolecular general base. At lower amine concentration the rate ratio is larger, and one can calculate a value of about 16 000 at the lowest concentration of *n*-butylamine experimentally used.

Very recently general base catalysis was discussed as very inefficient as compared to nucleophilic catalysis.[11] Our data show that certain substrates in particular experimental conditions display rate accelerations due to general base catalysis comparable to those of nucleophilic catalysis. The following considerations may help to clarify the relatively low efficiency of general base catalysis. The rate of reaction in a general base catalyzed mechanism is given by eq 4, derived from eq 1.

$$\frac{k_{obsd}}{[BuNH_2]} = \frac{k_1(k^0 + k_{BuNH_2}[BuNH_2] + k_B[B])}{k_{-1} + k^0 + k_{BuNH_2}[BuNH_2] + k_B[B]} \quad (4)$$

In aqueous solvents, k^0 (the uncatalyzed path, which includes the solvent-catalyzed path) is high enough, compared to k_{-1}, to make the effect of other bases present in solution of minor importance. The upper limit in reaction rate is $k_{obsd}/[BuNH_2] = k_1$, i.e., the rate constant for the formation of the intermediate, no matter how strong the general base present in solution can be. In nonaqueous solvents the value of k_{-1}, return of the addition intermediate to reactions, on the contrary is generally quite high, and k^0 is usually nil. Thus, large rate accelerations can only be observed when addition of very efficient bases; such as intramolecular bases, changes the slow step from breakdown of the intermediate to products to formation of the intermediate.

The evidence of Kirby[11] suggesting that intramolecular general base catalysis is intrinsically a relatively inefficient form of catalysis must be referred to aqueous solvents only. In aprotic solvents the effect of intramolecular general base catalysis may be quite large and this may have a bearing on the possible role of general base catalysis in enzymatic reactions if we accept the suggestion that the microscopic solvent characteristics of the active centers of enzymes are better mimicked by nonaqueous solvents.[2]

For a better understanding of the mechanism of intramolecular general base catalysis we have studied the reactivity of I with benzamidine (Table IV), which has also been shown to induce large rate accelerations.[12-14] Figure 3 shows that the behavior of benzamidine (solid line) is opposite to that of *n*-butylamine (dashed line). However, the two plots can be referred to the same mechanism, i.e., dissociation preequilibrium of I, followed by the rate-determining nucleophilic attack.

Because of increasingly disturbing oxidation of the product catechol in the reactions with benzamidine, these could not be performed with the required precision at concentrations of benzamidine larger than 0.1 M. It appears, however, that $k_{obsd}/[benzamidine]$ tends to a minimum, constant, value. Since the basicity of benzamidine is similar to that of *n*-butylamine,[12] it seems safe to assume that I also dissociates in the presence of benzamidine. From our knowledge of the behavior of benzamidine in aprotic solvents,[12-14] we can suggest that the reaction with benzamidine does not need the assistance of a general base and that the nucleophilic attack is the rate-

Table IV. Rate Data for the Reaction of *o*-Hydroxyphenyl Benzoate (I) with Benzamidine in Acetonitrile at 25 °C[a]

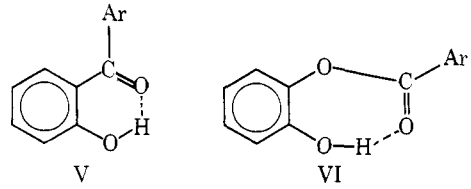
Benzamidine, M	$k_{obsd} \times 10^3$, s^{-1}	$(k_{obsd}/[benzamidine]) \times 10^2$, M^{-1} s^{-1}
0.0049	0.268	5.47
0.0067	0.231	3.43
0.027	0.825	3.06
0.027	0.722	2.67
0.0455	1.155	2.54
0.049	1.22	2.48
0.0685	1.44	2.11
0.08	1.54	1.93
0.098	2.01	2.05

[a] Substrate concentration = 1×10^{-4} M.

determining step. Thus, the experimental fact that I is more reactive than the dissociated form (III) can be a combination of two possible effects: general acid catalysis by the undissociated *o*-OH group or electronic effects (the undissociated phenol is a better leaving group). The same accelerating effects are probably present also in the *n*-butylaminolysis of I, but are completely obscured by the much larger rate effects due to general base catalysis.

It is experimentally impossible to measure the rate of reaction of I (completely undissociated) with *n*-butylamine, but we may assume that its reactivity is similar to that of II, given the similarity of the two substrates. Thus, we can calculate a rate ratio of 20 000 or higher for the reaction of I with benzamidine and *n*-butylamine. One would be tempted to suggest that the high reactivity of benzamidine with I is due to bifunctional behavior. On the other hand, benzamidine reacts with III only 3–4 times faster than *n*-butylamine. It would appear that benzamidine is a bifunctional reactant with I and not with III. However, we must recall that the rate determining step for the reaction of III with *n*-butylamine and benzamidine is the nucleophilic attack, which in both cases is followed by fast steps. Since bifunctional reactivity should be important especially in the nucleophilic attack (by minimizing charge separation), we would have expected to find that benzamidine reacts much faster than *n*-butylamine not only with I, but with III, too. This expectation being unfulfilled, we prefer to believe that benzamidine does not behave as a bifunctional reactant and that its high reactivity can be explained in the framework of an addition–elimination mechanism as previously suggested,[14,15] but with the additional feature of a substrate present in two forms of different reactivity.

It remains to be explained why the phenyl *o*-hydroxybenzoate has a very small dissociation constant,[3] while in the same experimental conditions the *o*-hydroxyphenyl benzoate dissociates quite easily. One can only suggest a stronger hydrogen bond between the hydroxyl proton and the carbonyl oxygen in the six-member ring V than in the seven-member ring VI.



Experimental Section

Materials. Benzamidine was prepared as described.[12] Toluene, acetonitrile, *n*-butylamine, and triethylamine were dried and purified by conventional methods. Tetrabutylammonium perchlorate was recrystallized from water and dried over P_2O_5 at 80 °C under vacuum. *n*-Butylammine hydrochloride was recrystallized from dry acetonitrile.

N-Benzoylbenzamidine[17] was twice recrystallized from petroleum ether (100–150 °C); mp 102–103 °C (lit. 98–99 °C).

o-Hydroxyphenyl benzoate[18,19] was recrystallized from boiling water; mp 135 °C (lit. 128 °C).

o-Methoxyphenyl benzoate[20] was recrystallized twice from ethanol and once from light petroleum ether; mp 59–60 °C (lit. 57–58 °C).

N-*n*-Butylbenzamide,[21] prepared with a variety of methods, could not be crystallized (lit. mp 40.5[21a], 42 °C[21b]). It was distilled and obtained as a clear oil (bp 141 °C (0.6 mmHg)). Ir, NMR, elemental analysis, and thin layer chromatography all indicated a pure product.

o-Hydroxyphenol (catechol) was recrystallized twice from benzene after decoloration with charcoal; mp 105–106 °C.

Kinetics. The reaction of *o*-methoxyphenyl benzoate in toluene was followed by sealing equal amounts of the reacting solutions in glass vials which were thermostatted at the appropriate temperature and withdrawn at time intervals. The content of the cooled vials was extracted with a known volume of 0.1 M NaOH. The aqueous solution was then analyzed by uv spectroscopy. This procedure determined the concentration of the product *o*-methoxyphenol.

The reaction of *o*-hydroxyphenyl benzoate in toluene and all reaction in acetonitrile were followed at 25 °C in the thermostatted cell compartment of a uv spectrophotometer (Beckmann DU, Unicam SP 800). The reactions with *n*-butylamine were followed at 270–280 nm; the reactions with benzamidine were followed at 300–320 nm.

All reactions gave good linear first-order plots. However, in some cases (at relatively high amine concentration) the instability of the infinity value due to oxidation of the products made it necessary to use a calculated value from the concentration and extinction coefficient of the products. These runs have been given a lower precision in the treatment and discussion of the data. Also, when the oxidation of products was noticeable in the first part of the reaction (up to 50%), as determined by a change in the form of the spectrum, the run was discarded.

In all cases where the infinity value was constant, the experimental and mock infinity agreed within experimental error.

Acknowledgment. This work was supported by CNR, Rome.

References and Notes

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