Kinetics of Reaction of *p*-Nitrophenyl Methyl Carbonate with Nucleophiles in Aqueous Solution, and the Relative Ease of Acetyl and Methoxycarbonyl Transfer Reactions

By **Patricia M. Bond** and **Roy B. Moodie,*** Department of Chemistry, The University of Exeter, Exeter EX4 4QD

The rate constants for reaction of eight nitrogen and four oxygen bases with *p*-nitrophenyl methyl carbonate in water at 25 °C have been measured, and are closely similar to published values for *p*-nitrophenyl acetate. General acid catalysis is not observed in the methoxyaminolysis of the carbonate, unlike the acetate. Specific salt effects are shown to preclude conclusions regarding the extent of general base catalysis in these reactions. The rate constant for reactions of propylamine with the 1-methoxycarbonyl-4-methylpyridinium ion has also been measured, and is compared with the published value for the 1-acetyl compound.

WE have recently reported on the aminolysis[1] and pyridinolysis[2] of methyl chloroformate in aqueous solution, and shown that the results are best interpreted in terms of a mechanism proceeding through a zwitterionic tetrahedral intermediate which is only just stable enough to exist, formation or breakdown of which can be rate limiting depending on the basicity of the nucleophile. This is in agreement with recent conclusions regarding the mechanism of reaction with nucleophiles of esters with good leaving groups.[3] To check further the relevance of studies of methoxycarbonyl transfer reactions to acyl transfer reactions in general, we have now studied the reaction of *p*-nitrophenyl methyl carbonate for comparison with *p*-nitrophenyl acetate.[4] The effects of replacement of methyl by methoxy at the acyl carbon atom are reconciled with the proposed mechanism of ester aminolysis.[3]

RESULTS

Second-order rate constants k_n for reactions of nucleophiles with *p*-nitrophenyl methyl carbonate, determined as described (Experimental section), are in Table 1 and are compared in the last column with reported values for *p*-nitrophenyl acetate. *R* Is the value of k_n for the acetate [2,4-6] divided by that for the methyl carbonate. In the cases of methoxyamine and propylamine, a careful search was made for general catalysis. Both general acid and general base catalysis have been reported in the reaction of methoxyamine with *p*-nitrophenyl acetate,[6] and general base catalysis of the nucleophilic attack of ethylamine on the latter (by a second molecule of the amine) has also been claimed.[7] We chose propylamine rather than ethylamine because it is less volatile and we wished to extend the study to high concentrations of the free base.

Methoxyamine.—These results are in Table 2. An ionic strength of 0.5 mol dm^{-3}, rather than 0.2 mol dm^{-3} as used in most other cases (Table 1) gave more scope for the observation of general catalysis. No detectable general acid catalysis was found, but some general base catalysis may be present. Unavoidable uncertainties about specific salt effects, discussed further below, preclude firm conclusions. Least squares analysis showed that the results fitted equation (1) (in which the first term is for the water

$$10^4k/\text{s}^{-1} = 0.0113 + 14.85(\pm 0.20)[\text{B}] + 4.2(\pm 1.5)[\text{B}]^2 \quad (1)$$

reaction). In equation (1) [B] is the concentration of free base methoxyamine in mol dm^{-3}. Rate constants calculated from this equation are compared with observed values in Table 2.

Propylamine.—A small increase, outside experimental error, of the value of k_n with increasing propylamine concentration was noted using tris(hydroxymethyl)methylamine buffers at both pH 8.2 and 9.0 (see Table 1). Stopped-flow investigation at pH 11.5 and very much higher concentrations of propylamine revealed no further increase in k_n (Table 1). There is therefore either some general base catalysis which is limited in extent (because of a change in rate-determining step [3]) or the increase in k_n at constant pH is attributable to specific salt effects. (Sodium perchlorate was used to maintain the ionic strength at pH 8.2, and potassium chloride at pH 9.0.) The latter explanation is preferred because there was no smooth variation of k_n with the concentration of free base propylamine when different pH values were considered, but at each pH when the salt concentration was largely due to

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[1] E. A. Castro and R. B. Moodie, *J.C.S. Perkin II*, 1974, 658.

[2] P. Bond, E. A. Castro, and R. B. Moodie, *J.C.S. Perkin II*, 1976, 68.

[3] A. C. Satterthwaite and W. P. Jencks, *J. Amer. Chem. Soc.*, 1974, **96**, 7018.

[4] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.

[5] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.

[6] L. do Amaral, K. Koehler, D. Bartenbach, J. Pletcher, and E. H. Cordes, *J. Amer. Chem. Soc.*, 1967, **89**, 3537.

propylammonium chloride, similar values of k_n (6.8, 6.2, and 7.2 mol^{-1} dm^3 s^{-1}) were found. Furthermore, the value of k_n was found to increase from 5.5 to 6.8 mol^{-1} dm^3 s^{-1} when 0.17 mol dm^{-3} potassium chloride was replaced by the same concentration of tetramethylammonium chloride in the reaction in tris(hydroxymethyl)methylamine buffer at pH 9.0. Specific salt effects have been noted before in similar reactions,[9] and highlight the uncertainty which attaches to limited extents of general catalysis. Specific salt effects would entirely account for the very small enhancement of catalytic constant with increasing base concentration in the reaction of ethylamine with *p*-nitrophenyl acetate which has been reported and attributed [7] to general base catalysis. In this connection we investigated using stopped-flow spectrophotometry the reaction of *p*-nitrophenyl acetate with propylamine at very much higher concentrations of the free base (0.014—0.8 mol dm^{-3}) than previously used,[4] and obtained a second-order rate constant [16($\pm$1) mol^{-1} dm^3 s^{-1}, mean of 18 runs] in exact agreement with that previously reported.[4] Clearly no general base catalysis is detectable in this reaction.

TABLE 1

Second-order rate constants k_n for reactions of nucleophiles with *p*-nitrophenyl methyl carbonate in water at 25 °C and (unless otherwise noted) an ionic strength of 0.2 mol dm^{-3}

Nucleophile	pK_a [a]	pH	Additional buffer	$10^2[B]_t$ [b]	Number of runs	k_n [c]/mol^{-1} dm^3 s^{-1}	R [d]
Water	(−1.74)	4.7	0.02—0.04 mol dm^{-3} Acetate		6	2.04 (±0.04) × 10^{-8}	0.4
3-Chloropyridine	2.98	3.0		20—40	2	6.9 (±0.7) × 10^{-6}	2.4
Acetate [e]	4.61	4.7		2—4	6	4.8 (±1.3) × 10^{-6}	1.30
Methoxyamine [f]	4.74				15	1.48 (±0.02) × 10^{-3}	1.35
Pyridine [g]	5.32	7.9	0.05 mol dm^{-3} Tris [h]	5—20	4	2.22 (±0.04) × 10^{-3}	1.26
Imidazole	7.09	8.2	0.05 mol dm^{-3} Tris [h]	2—7.5	5	0.31 (±0.01)	1.87
Tris [h]	8.17	8.2		5—40	5	6.5 (±0.3) × 10^{-4}	1.78
Methoxyethylamine	9.45	10.3		2.4—120	16	1.43 (±0.1)	1.89
4-Dimethylaminopyridine [i]	9.52	9.2—9.7		0.08—0.2	4	43 (±2)	1.28
Phenolate	9.74	9.8		1—10	6	0.72 (±0.01)	1.35
Propylamine	10.72	8.2	0.05 mol dm^{-3} Tris [h]	5—15	4	5.9—6.8 [j]	
		9.0	0.12 mol dm^{-3} Tris [h]	2—18	5	5.4—6.2 [j]	
		11.5		50—100	10	7.2 (±0.2)	2.2
Hydroxide [i]	(15.74)	11—12		0.1—1	5	4.7 (±0.1)	2.0

[a] Of the conjugate acid of the nucleophile at the quoted ionic strength (the figures for water and hydroxide are conventional). [b] Total concentration of nucleophile (free base + conjugate acid). [c] Errors are standard errors with weights assigned as previously, unless otherwise noted. [d] The ratio of k_n for reaction of the nucleophile with *p*-nitrophenylacetate [2,4–6] (25 °C, ionic strength 1.0 mol dm^{-3}) to the value of k_n given in previous column. [e] Low buffer concentrations were used to give an accurate value for the rate constant for water; the acetate rate constant is therefore imprecise. [f] Ionic strength 0.5 mol dm^{-3}, full details in Table 2. [g] Rate constant calculated on the assumption that only the monomer is catalytically active, and using a dimerisation constant [8] of 0.5 mol^{-1} dm^3. [h] Tris(hydroxymethyl)methylamine. [i] Ionic strength 0.1 mol dm^{-3}. We thank M. D. Broderick and T. J. Young for these measurements. [j] A small increase in catalytic constant with increasing concentration of free base amine is attributed to a specific salt effect; see text.

TABLE 2

Rate constants for reaction of *p*-nitrophenyl methyl carbonate in aqueous methoxyamine buffers prepared from methoxyamine hydrochloride and sodium hydroxide, at 25 °C and ionic strength 0.5 mol dm^{-3} made up with sodium chloride

[B] [a]	[BH+] [a]	10^4k_{obs} [b]/s^{-1}	10^4k_{calc} [d]/s^{-1}
0.05	0.005	0.77	0.76
0.10	0.01	1.47	1.54
0.15	0.015	2.3	2.3
0.20	0.02	3.1	3.2
0.23	0.023	3.6	3.6
0.23	0.023	3.8	3.6
0.04	0.02	0.62	0.61
0.14	0.07	2.2	2.2
0.20	0.10	3.2	3.2
0.025	0.075	0.38	0.39
0.05	0.15	0.78	0.76
0.075	0.225	1.17	1.15
0.10	0.30	1.57	1.54
0.03	0.24	0.47	0.46
0.04	0.32	0.60	0.61

[a] Concentration of free base methoxyamine. [b] Concentration of the methoxyammonium ion. [c] Observed first-order rate constant. [d] Calculated value using equation (1).

Reaction of 1-*Methoxycarbonyl*-4-*methylpyridinium Ion with Propylamine*.—This was for comparison with the similar reaction of 1-acetyl-4-methylpyridinium ion.[8] 1-Methoxycarbonyl-4-methylpyridinium is formed as an intermediate in the hydrolysis of methyl chloroformate in 4-methylpyridine buffers;[2] its formation and disappearance can be observed spectrophotometrically at 270 nm and the rate constants for these processes have been measured.[2] In the present work, an aqueous solution of methyl chloroformate was mixed within 15 min of preparation (the half-life for hydrolysis of methyl chloroformate is 20 min [1]) with an aqueous 4-methylpyridine buffer containing propylammonium chloride (and potassium chloride to give an ionic strength of 0.2 mol dm^{-3}) in a stopped flow apparatus. Conditions were chosen such that the formation of the intermediate was rapid compared with its decomposition; the latter followed a first-order course with the rate constant (k_{obs}) given in Table 3. The value of k_{obs} for the background reaction in the absence of propylamine, 0.04 s^{-1}, is larger than that

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[7] D. Oakenfull, *J.C.S. Perkin II*, 1973, 1006.

[8] A. R. Fersht and W. P. Jencks, *J. Amer. Chem. Soc.*, 1970, **92**, 5432, 5442.

[9] J. M. Sayer and W. P. Jencks, *J. Amer. Chem. Soc.*, 1969, **91**, 6353; J. P. Fox and W. P. Jencks, *ibid.*, 1974, **96**, 1436.

reported for the hydrolysis of the 1-methoxycarbonyl-4-methylpyridinium ion,[2] no doubt because this process is general-base-catalysed by 4-methylpyridine as is the unsubstituted pyridine reaction.[2] A linear increase of k_{obs} with the concentration of free base propylamine was observed, yielding a rate constant for the reaction of the latter with the 1-methoxycarbonyl-4-methylpyridinium ion of 2.5×10^4 mol^{-1} dm^3 s^{-1}. The rate constant for the reaction of propylamine with the 1-acetyl-4-methylpyridinium ion [7] is 1.54×10^6 mol^{-1} dm^3 s^{-1}.

TABLE 3

Rate constant for catalysis by propylamine of the disappearance of the 1-methoxycarbonyl-4-methylpyridinium ion, formed *in situ* from methyl chloroformate in an aqueous 4-methylpyridine buffer at 25 °C (total concentration of 4-methylpyridine 0.044 mol dm^{-3}, pH adjusted with HCl and ionic strength to 0.2 mol dm^{-3} with KCl)

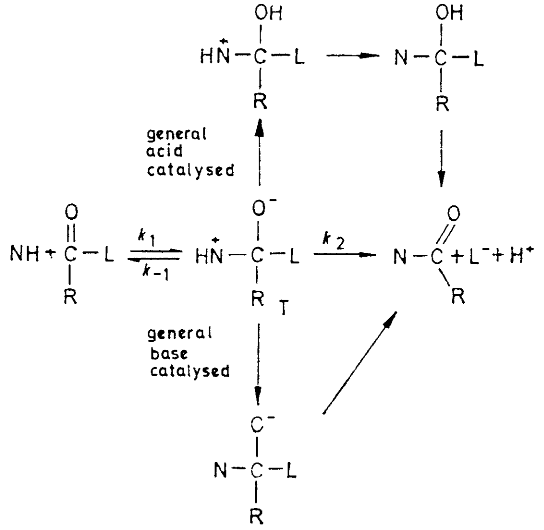
$10^5[B]$ [a]	pH	k_{obs} [b]/s^{-1}	$10^{-4}k_n$ [c]/mol^{-1} dm^3 s^{-1}
0	7.22	0.04	
1.18	7.19	0.31	2.63
2.37	7.18	0.59	2.49
4.53	7.17	1.12	2.47

[a] Concentration of propylamine free base. [b] Calculated from the disappearance of the rapidly formed peak at 270 nm, observed by stopped flow spectrophotometry. [c] Second-order rate constant for reaction of propylamine with the 1-methoxycarbonyl-4-methylpyridinium ion, calculated as $(k_{obs} - 0.04\ \text{s}^{-1})/[B]$.

DISCUSSION

Comparison of the Reactivities of p-*Nitrophenyl Acetate and* p-*Nitrophenyl Methyl Carbonate*.—There is a remarkable qualitative and quantitative similarity for a wide range of nucleophiles as is evident from Table 1. This is strong evidence for a similarity of mechanism in acetyl and methoxycarbonyl transfer. The most significant difference is the absence of general acid catalysis (by the methoxyammonium ion) of the reaction of methoxyamine with the methyl carbonate (Table 2), whereas such an effect is quite marked with the acetate.[6] This is consistent with the mechanism which has been proposed,[3] in which the term for general acid catalysis is attributed to rate-limiting protonation of the negatively charged oxygen of the initially formed zwitterionic tetrahedral intermediate (T in the Scheme in which NH is the nucleophile and L is the leaving group). The replacement of R = Me by R = MeO would be expected for polar reasons to disfavour such a process. For the same reason general base catalysis should be *favoured* by the same replacement. This cannot be verified because of uncertainties about specific salt effects, however the fact that of all the nucleophiles studied water is the only one which reacts faster with the methyl carbonate than with the acetate (Table 1) may be because in this case the rate-limiting step is proton removal from T by a second molecule of water.

For all the other nucleophiles, the reaction is thought to involve the steps with rate constants k_1, k_{-1}, and k_2 only. In most cases the step with rate constant k_2 is rate limiting,[3] but this cannot be true for hydroxide and phenolate. These must be worse leaving groups than *p*-nitrophenolate, making k_1 rate limiting, but the comparison extends to them (Table 1). In either case the replacement of methyl by methoxy at acyl carbon produces only a small deactivation, presumably because the ground state stabilisation by mesomeric interaction between the methoxy and the carbonyl oxygens is largely offset by inductive stabilisation when R = MeO (Scheme) of the tetrahedral intermediate-like transition state, whether this be in the k_1 or k_2 step.



SCHEME

Comparison with the Relative Ease of Acetyl and Methoxycarbonyl Transfer in Other Reactions.—The ratio of rate constants for the reaction of nucleophiles with the acetate and the methyl carbonate of *p*-nitrophenol is seen (Table 1) to vary within the narrow limits of 1.3 and 2.4, apart from the water reaction for which the ratio is 0.4. Much higher ratios are observed for the reaction of water with the 1-acetyl- or 1-methoxycarbonyl-imidazolium,[10,11] pyridinium,[2,7] and 4-methylpyridinium [2,7] ions, for which the ratios (25 °C in water) are 270, 250, and 190 respectively. Similarly, acetyl chloride [12] is hydrolysed at 0 °C very much more rapidly than methyl chloroformate. These higher ratios are not restricted to reactions with water because for the reaction of propylamine with the 1-acetyl- or 1-methoxycarbonyl-4-methylpyridinium ion it is 62. High ratios with more reactive acyl compounds are not in accord with the Hammond postulate,[13] and suggest a change in mechanism. It is not likely that any form of general catalysis is involved because this tends to be significant with the less reactive compounds.[6] A working hypothesis is that for the more reactive compounds the tetrahedral intermediate is too unstable to exist, and that

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[10] D. G. Oakenfull and W. P. Jencks, *J. Amer. Chem. Soc.*, 1971, **93**, 178.

[11] R. B. Moodie and R. Towill, *J.C.S. Perkin II*, 1972, 184.

[12] V. Gold and J. Hilton, *J. Chem. Soc.*, 1955, 838.

[13] G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

high ratios are characteristic of one step displacement reactions. We plan further work to probe this point.

EXPERIMENTAL

Materials.—*p*-Nitrophenyl methyl carbonate was prepared by the slow addition of methyl chloroformate to a cold alkaline solution of *p*-nitrophenol. After extraction with ether and recrystallisation from petroleum ether it had m.p. 114—116 °C (lit.,[14] 114—115 °C). Propylamine, methoxyethylamine, pyridine, 3-chloropyridine, and 4-methylpyridine were purified by distillation, and 4-dimethylaminopyridine (light petroleum), methoxyamine hydroxide (ethanol–ether), and imidazole (benzene) by recrystallisation from the indicated solvents. Water was freed from CO_2, and for the reactions in acetate buffer doubly rather than singly distilled.

Kinetic Methods.—An appropriate portion of an acetonitrile solution of *p*-nitrophenyl methyl carbonate was added by syringe at zero time to the buffer solution in a thermostatted cell in a Unicam SP 500 or SP 1800 spectrophotometer. Wavelengths used were either 400 (pH >7) or 330 nm (pH <5). For the stopped-flow experiments the two limbs of the Nortech 'Canterbury' stopped-flow apparatus were loaded respectively with the buffer solution at twice the required concentration and an aqueous solution of *p*-nitrophenyl methyl carbonate or methyl chloroformate. In the latter case a wavelength of 270 nm was used.

Reactions were followed for 2—3 half-lives and first-order rate constants k determined in the usual way.

Second-order rate constants k_n were calculated from the equation $k_n = (k - k_0)/[B]$, in which [B] is the concentration of the free base form of the nucleophile, and k_0 is the value of k at the same pH and concentration of additional buffer (if any), when $[B] = 0$.

Determination of pH was by means of a Radiometer 26A pH meter.

We thank the Royal Society for a loan towards the purchase of the stopped-flow spectrophotometer.

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[14] P. Brown and C. Djerassi, *J. Amer. Chem. Soc.*, 1967, **89**, 2711.