JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 2, 377–382 (1989)

ALKYLATING PROPERTIES OF PHOSPHATE ESTERS. 4. MEDIUM EFFECTS ON METHYLATION OF PYRIDINES BY TRIMETHYL PHOSPHATE

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ABSTRACT

The rates of *N*-methylation of pyridine and its ring-substituted derivatives by trimethyl phosphate were measured in D_2O and in $CDCl_3$. Relative rates, together with the solvent activity coefficients of substrates for the transfer from chloroform to water, were used for determining the solvent activity coefficients of the activated complexes for this S_N2 reaction. The results indicate early activated complexes for all pyridines, with the most nucleophilic substrate showing the most reactant-like activated complex.

Studies of solvent effects on the rates of quaternization of tertiary amines are almost a century old,[1] and the Menschutkin reaction, equation (1), proved to be a well tested and convenient model for studies of medium effects on the reactivity of organic systems.[2]

$$R_3N + R'X \longrightarrow R_3NR'^{+} + X^{-} \qquad (1)$$

The suitability of reaction (1) to mechanistic studies stems from the fact that it offers structural variations in both the nucleophilic and the electrophilic reagents, as well as that its rate can be measured in a great variety of solvents. It is generally accepted that the Menschutkin reaction can be described as a classical S_N2 reaction[3] with a rather early activated complex (AC), occurring not further than at *ca.* 0.2–0.3 of the way along the reaction coordinate.[4] Scrutiny of the available data revealed that studies of S_N2 reactions between non-ionic reactants seldom involved aqueous media, and that for reactions involving ions only in one isolated case the dialkylphosphate group was chosen as a leaving group (demethylation of trimethyl phosphate by azide ions).[5] Because of our interest[6] in the alkylating properties of organic phosphates, and because of the importance of the nucleophilic *O*-demethylation step in the 'triester' method of oligonucleotides synthesis,[7] we decided to investigate the effect of solvents on the reaction of methylation of the nitrogen atom in pyridine by trimethyl phosphate (TMP), equation (2).

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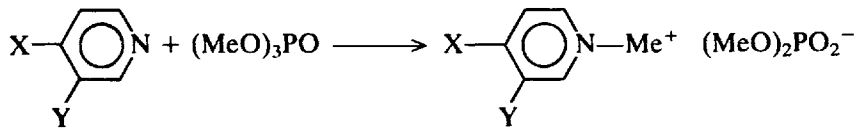
0894–3230/89/050377–06$05.00

Received 9 May 1988
Revised 8 July 1988



(2)

1a–e **2a-e**

a, X = Y = H
b, X = Me, Y = H
c, X = Et, Y = H
d, X = Y = Me
e, X = Me_2N, Y = H

Since we have recently observed[8] significant rate acceleration for the methyl group transfer from phosphate oxygen to nitrogen in water relative to other, even highly polar solvents, reaction (2) was studied in water and chloroform was selected as a weakly polar, aprotic solvent of reference.

RESULTS AND DISCUSSION

The methylation reaction (2) could be followed easily by ^{1}H-NMR spectroscopy because of the appearance of the signal of the N^+CH_3 group (s, δ *ca.* 4·4), the reduction in the intensity of the TMP signal (d, δ *ca.* 3·8), the appearance of the signal of the dimethylphosphate ion (d, δ *ca.* 3·6), and the appearance of the new set of signals in the range δ 7·0–9·0, due to the aromatic protons of the pyridinium ion. We have found, in agreement with the earlier report,[9] that (**1e**) undergoes methylation exclusively at the pyridine nitrogen atom. The results of the kinetic measurements obtained for (**1a**)–(**1e**) in D_2O and in $CDCl_3$ are listed in Table 1.

Table 1. Rate constants (M^{-1} s^{-1})[a] of methylation of pyridines by trimethyl phosphate at 40·0 °C

Substrate	$k_2(D_2O)$ × 10^5	k_{rel}	$k_2(CDCl_3)$ × 10^7	k_{rel}	$k_2(D_2O)/k_2(CDCl_3)$
1a	3·11	1·00	2·78	1·00	112
1b	5·11	1·64	6·94	2·50	74
1c	4·02	1·29	4·75	1·71	85
1d	7·34	2·36	10·0	3·60	73
1e	9·72	3·12	68·6	24·7	14

[a]Average of at least two runs; ± < 5%

It is interesting to note that the relative rates of methylation observed for substrates (**1a**), (**1b**) and (**1e**) in $CDCl_3$ are practically identical to those reported[10] for the same substrates in ethylation by iodoethane in dichloromethane at 25 °C (k_{rel} = 2·7 and 23·9, respectively). The same authors[10] found that in methanol the substituents had almost no effect on k_2 (k(**1e**)/k(**1a**) = 1·3) and attributed this to the hydrogen bonding of pyridine substrates by the solvent. Since in the aqueous medium, i.e. under conditions of an even stronger involvement of the pyridine

nitrogen in hydrogen bonding,[11] we observe significant substituent effects on the rate (k(**1e**)/k(**1a**) = 3·12), it seems that hydrogen bonding effects are not sufficiently strong to cancel the rate-accelerating effects of the ring substitutents.

Solvent effects on reaction rates can be dissected into substrates and activated complex contributions by means of introducing solvent activity coefficients, ${}^{O}\Gamma^{S}_{i}$,[2a] proportional to the change in the standard chemical potential of a species, i, on transfer from a reference solvent, O, to another solvent, S. For reaction (2) the relative rates of methylation, k_{rel}, can be expressed by equation (3).[2a]

$$\lg k_{rel} = \lg(k_S/k_O) = \lg {}^{O}\Gamma^{S}_{N} + \lg {}^{O}\Gamma^{S}_{TMP} - \lg {}^{O}\Gamma^{S}_{AC} \quad (3)$$

where S and O refer to D_2O and $CDCl_3$, respectively, as reaction media, and N, TMP and AC are related to the pyridine substrate, to trimethyl phosphate, and to the activated complex of reaction (2), respectively. Solvent activity coefficients of substrates (**1a**)–(**1e**) and of TMP were determined by measuring their distribution coefficients between water and chloroform,[12] and are included, together with the desired activity coefficients of the activated complex, calculated from equation (3), in Table 2. The last column of Table 2 gives solvent activity coefficients (also determined by distribution measurements) for the reaction products: *N*-methylpyridinium dimethylphosphates, (**2**).

Table 2. Solvent activity coefficents of species involved in reaction (2) at 40·0 °C. S = D_2O; O = $CDCl_3$

Nucleophile	$\lg {}^{O}\Gamma^{S}_{N}$	$\lg {}^{O}\Gamma^{S}_{TMP}$	$\lg {}^{O}\Gamma^{S}_{AC}$	$\lg {}^{O}\Gamma^{S}_{P}$
1a	1·20	0·57	−0·28	−4·17
1b	1·80	0·57	0·51	−4·43
1c	2·29	0·57	0·93	−3·58
1d	2·12	0·57	0·83	−3·98
1e	1·52	0·57	0·94	−4·50

Table 2 shows that all nucleophilic substrates are strongly destabilized, and TMP is moderately destabilized, upon transfer from chloroform to water. The reaction products, on the other hand, are very strongly stabilized in aqueous medium, so significant rate acceleration should be expected when reaction (2) is transferred from chloroform to water. The values of $\lg {}^{O}\Gamma^{S}_{AC}$ show that in the case of pyridine the activated complex is weakly stabilized, and in four other examples moderately destabilized, upon transfer from $CDCl_3$ to D_2O. The results indicate that in all cases the activated complexes occur rather early on the reaction coordinate, but are still far from the ionic products (**2**). Nevertheless, the oxygen to nitrogen methyl transfer seems to be more advanced in the AC of reaction (2) than is the ethyl transfer from iodoethane to triethylamine, where the destabilization of the activated complex upon transfer from chloroform to water is almost as big as is the total destabilization of both substrates.[13] Data included in Table 2 show that the position of the AC, although 'early', is not constant within this reaction series. Considering the average between the sum of the $\lg {}^{O}\Gamma^{S}_{i}$ values for substrates (i = N, TMP) and the $\lg {}^{O}\Gamma^{S}_{P}$ value as a value expected for the ideally symmetrical AC, it follows that the advancement of the methyl transfer decreases from 35 to 30, 28, 27 and 17% for (**1a**), (**1c**), (**1d**), (**1b**) and (**1e**), respectively. This variation in the position of the AC is

in agreement with the Reactivity–Selectivity Principle,[14] and with the earlier observation[15] that in the quaternization of substituted pyridines by iodomethane the most nucleophilic substrates showed the most reactant-like activated complexes.

EXPERIMENTAL

NMR spectra were recorded on a superconducting FT Bruker AC300 spectrometer with TMS or sodium 3-(trimethylsilyl) propanesulfonate as internal standards. UV spectra were recorded on a Beckman Acta MIV spectrophotometer. Pyridine (M&B) was distilled from potassium hydroxide pellets and stored over molecular sieves. 4-Methyl- (BDH), 4-ethyl- (Aldrich) and 3,4-dimethylpyridine (K&K) were distilled immediately before use. 4-Dimethylaminopyridine (Aldrich) was recrystallized from ethyl acetate; mp 112–113 °C. Chloroform (Merck, Uvasol grade), chloroform-d_1 (Aldrich, Gold Label), deuterium oxide (Merck, Uvasol grade) were used as supplied. Trimethyl phosphate (BDH) was distilled immediately before use; bp 37 °C (0.6 mm).

N-Methylpyridinium dimethyl phosphates, **2a–2e** were prepared as follows. Equimolar (0·01 mole) amounts of (**1**) and TMP were placed in sealed tubes and heated at 105 °C for 53 h.The crude products were washed several times with dry ether, dried over P_4O_{10}, dissolved in chloroform and passed through a silica gel column using methanol/chloroform (2:1) as eluting solvent. All salts (**2**) were highly hygroscopic solids and no good elemental analysis results could be obtained for anhydrous products. Satisfactory results could be however, obtained for hydrated salts.

(**2a**). ^{1}H-NMR (D_2O): δ 3·58 (6H, d, J_{HP} = 10·75 Hz, 2 × OCH_3), 4·40 (3H, s, NCH_3^+), 8·05 (2H, t, J_{HH} = 5·4 Hz, 3-H, 5-H), 8·54 (1H, t, J_{HH} = 5·4 Hz, 4-H), 8·80 (2H, d, J_{HH} = 5·4 Hz, 2-H, 6-H). Found: C, 36·82; H, 7·23; N, 5·56. Calc. for $C_8H_{14}NO_4P{\cdot}3H_2O$: C, 35·17; H, 7·38; N, 5·13%.

(**2b**). ^{1}H-NMR (D_2O): δ 2·65 (3H, s, 4-CH_3), 3·59 (6H, d, J_{HP} = 10·8 Hz, 2 × OCH_3), 4·32 (3H, s, NCH_3^+), 7·86 (2H, d, J_{HH} = 6·5 Hz, 3-H, 5-H), 8·59 (2H, d, J_{HH} = 6·5 Hz). Found: C, 36·16; H, 8·06; N, 4·95. Calc. for $C_9H_{16}NO_4P{\cdot}4H_2O$: C, 35·41; H, 7.92; N, 4.59%.

(**2c**). ^{1}H-NMR (D_2O): δ 1·32 (3H, t, J_{HH} = 8·5 Hz, CH_3), 2·95 (2H , q, J_{HH} = 8·5 Hz, CH_2), 3·58 (6H, d, J_{HP} = 12·0 Hz, 2 × OCH_3), 4·32 (3H, s, NCH_3^+), 7·88 (2H, d, J_{HH} = 7·2 Hz, 3-H, 5-H), 8·55 (2H, d, J_{HH} = 7·2 Hz, 2-H, 6-H). Found: C, 41·20; H, 7·79; N, 5·05. Calc for $C_{10}H_{18}NO_4P{\cdot}2H_2O$: C, 42·20; H, 7·83; N, 4·95%.

(**2d**). ^{1}H-NMR (D_2O): δ 2·43 (3H, s, 3-CH_3), 2·54 (3H, s, 4-CH_3), 3·58 (6H, d, J_{HP} = 12·0 Hz, 2 × OCH_3), 4·27 (3H, s, NCH_3^+), 7·77 (1H, d, J_{HH} = 7.2 Hz, 5-H), 8·40 (1H, d, J_{HH} = 7·2 Hz, 6-H), 8·47 (1H, s, 2-H). Found: C, 42·82; H, 7·80; N, 5·07. Calc. for $C_{10}H_{18}NO_4P{\cdot}2H_2O$: C, 42·40; H, 7·83; N, 4·95%.

(**2e**). ^{1}H-NMR (D_2O): δ 3·20 (6H, s, $N(CH_3)_2$), 3·60 (6H, d, J_{HP} = 10·76 Hz, 2 × OCH_3), 3·91 (3H, s, NCH_3^+), 6·87 (2H, d, J_{HH} 8·1 Hz, 3-H, 5-H), 7·96 (2H, d, J_{HH} = 8·1 Hz, 2-H, 6-H). Found: C, 39·01; H, 8·40; N, 8·98. Calc. for $C_{10}H_{19}N_2O_4P{\cdot}2H_2O$: C, 40·27; H, 7·77; N, 9·39%.

Rate measurement

The equimolar solutions of both substrates were equilibrated in a water bath at 40·0 °C and mixed in an NMR tube to give the initial concentration of (**1**) and TMP *ca.* 0·3 M. The tube was placed in a water bath at 40·0 °C and the NMR spectra of these solutions were recorded

periodically. The progress of reaction was monitored by recording the integration curves corresponding to the selected signals of substrates and products. For all runs good second-order kinetics were obtained and the runs were reproducible to $\pm<5\%$. The runs were followed to at least 60% completion, except for the reaction of pyridine with TMP in $CDCl_3$, where the reaction was so slow that it was followed to only 25% completion.

Distribution coefficients

0·1–0·2 mmol of (**1**) was distributed between two solvents by shaking it with a mixture of D_2O and $CDCl_3$ (10 ml each) at 40 °C; each solvent being previously saturated with the countersolvent. The concentrations of the solutes in the aqueous and organic phase were then determined by separating the two phases and recording their UV spectra. The following values of the molar extinction coefficients (at given absorption maxima) were used: (**1a**) 2700 (256 nm), D_2O; 2000 (258 nm), $CDCl_3$. (**1b**) 2400 (255 nm), D_2O; 2100 (256 nm), $CDCl_3$. (**1c**) 3500 (254 nm), D_2O; 2300 (254 nm), $CDCl_3$. (**1d**) 2700 (260 nm), D_2O; 2700 (265 nm), $CDCl_3$. (**1e**) 17300 (279 nm), D_2O; 16400 (260 nm), $CDCl_3$.

For products (**2**), because of their poor solubilities in chloroform, a large excess of chloroform was used for the distribution experiments, and in order to determine the concentration of a solute in the organic phase, the products were re-extracted from chloroform to a small volume of water. The following values of extinction coefficients were used: (**2a**) 2100 (258 nm); (**2b**) 1900 (255 nm); (**2c**) 3600 (255 nm), D_2O; (**2d**) 3600 (262 nm), D_2O; (**2e**) 18200 (276 nm).

The distribution coefficient of TMP was determined by measuring the relative concentrations of the solute in the aqueous and organic phase using ^{1}H-NMR spectroscopy. The relative concentrations were determined by comparing the intensity of the TMP signal (δ *ca.* 3·77, d) with the intensity of the standard (acetic acid, δ *ca.* 2·1, s) which was added in equal amounts to both phases after the separation.

All distribution experiments were made at least in triplicate and the distribution coefficients were reproducible to $\pm 5\%$.

ACKNOWLEDGEMENTS

Financial support from the University of Pretoria and the Council for Scientific and Industrial Research is gratefully acknowledged.

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