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A RE-EVALUATION OF THE ROLE OF TRIPHENYLPHOSPHINE IN DEMETHYLATION OF QUATERNARY HETEROCYCLIC SALTS

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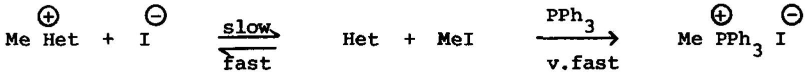
The dealkylation of quaternized heterocyclic compounds by reaction with triphenylphosphine in an aprotic solvent has been shown to be a particularly effective method. The reaction, in both the synthetic[1] and kinetic[2] studies, was presumed to be an S_N2 displacement of the quaternizing group by the PPh_3. In fact, dequaternization is preferentially brought about by a nucleophilic counterion (usually iodide) and the function of the PPh_3 is to mop up the alkyl halide, thus preventing the reverse quaternization from occurring. It has been shown[2] that pyridine does not react with the methyltriphenylphosphonium salt.



$$\overset{\oplus}{\text{Me Het}} + \overset{\ominus}{\text{I}} \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} \text{Het} + \text{MeI} \xrightarrow[\text{v.fast}]{\text{PPh}_3} \text{Me}\ \overset{\oplus}{\text{PPh}_3}\ \overset{\ominus}{\text{I}}$$

The results of some kinetic experiments on 1-methylquinolinium salts, upon which this conclusion is based, are listed in the Table. The disappearance of the $\overset{\oplus}{N}$-Me signal (δ=4.66ppm) was followed by nmr with dibenzyl ether (δ=4.51ppm) being used as internal standard. Good first order kinetic plots were obtained.

We originally noted (runs 1,2) that the iodide salt reacted much faster than did the perchlorate. For the more reactive 1,8-dimethylquinolinium salts a rate ratio $I^-/ClO_4^- \simeq 70$ was obtained. Thus, while PPh_3 will bring about dequaternization of the perchlorate salt, when account is taken of the approximately ten fold greater concentration of PPh_3 than of iodide, then iodide is almost a factor of 10^3 better than PPh_3 as a dequaternizing reagent. Bromide was then shown to be 1.5 times as efficient as iodide (3,4). In the original synthetic paper[1], it was noted that benzyl groups (all bromides) were displaced more readily than were methyl groups (all iodides), but the difference may largely be due to the different counterion rather than to the alkyl group.

Table. Demethylation of 1-methylquinolinium (Q^+) salts (0.15M) in sulfolane at 150°.

Run	PPh_3 (M)	Q^+ (salt)	Other (M)	10^3k_ψ (min^{-1})
1	1.41	I^-		7.82
2	1.38	ClO_4^-		v.slow
3	1.40	ClO_4^-	0.15 $Bu_4N^+I^-$	5.06
4	1.41	ClO_4^-	0.15 Et_4N^+ Br^-	7.59
5	1.42	I^-	0.14 $MePPh_3^+$ $MeSO_4^-$	4.97
6	1.41	I^-	0.15 Bu_4N^+ I^-	10.2
7	0.72	I^-		4.60
8	0.71	I^-	0.71 Ph_3CH	7.32
9	0.26	I^-	in 2:1(v/v)PhCl-sulfolane	28.6

A reaction between oppositely charged ions is retarded by an increase in ion concentration or in solvent polarity.[3] Runs 1 and 3 show the effect of the first factor but when reactions were carried out at constant ion concentration, the rate showed the expected dependence on iodide concentration (3,5,6). First order kinetics are observed since the iodide concentration remains constant during a reaction.

The reaction rate appeared (1,7) to also depend on the PPh_3 concentration but this was a medium effect; much the same rate increase was noted when triphenylmethane was substituted for the extra PPh_3(8). The significant effect on the rate of a decrease in solvent polarity is illustrated by the result of run 9.

Much less PPh_3 was also used in run 9. We investigated the relative reactivities of pyridine and PPh_3 toward methyl iodide in dimethylsulfoxide-$\underline{d}_6$ at room temperature by a competition method[4] and obtained $k_{PPh_3}/k_{C_5H_5N}=10$. For this reason, and also because PPh_3 does not appear in the rate equation, it became clear that a large excess of PPh_3 was not necessary to facilitate the reaction.

The results then are consistent with the proposal that iodide is the active demethylating reagent. This reaction is indeed the exact reverse of the quaternization reaction and the way is now open for a detailed study of the S_N2 transition state for the N-alkylation — N-dealkylation reaction.

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