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HYDROXIDE ION INITIATED REACTIONS UNDER PHASE TRANSFER CATALYSIS CONDITIONS II. THE ROLES OF WATER AND QUAT[1]

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Abstract: The effects of water molecules and quat structure are shown to be significant in determining the behavior of alkylation reactions of weakly acidic carbon acids under PTC/OH$^-$ conditions.

The roles of water and quat structure in phase transfer catalysis have long been recognized as major factors influencing the progress and outcome of the reactions performed under PTC conditions (2-7). Quantitative studies relating to a number of nucleophiles have shown a dependence of reactivity upon the extent of hydration of the nucleophile in the organic phase (2,3). The effect of quat structure on the reactivity of single step S_N2 reactions has been quantitatively investigated (5), and an empirical study of the effect of quat structure on the yield of an alkylation reaction has been reported (7). Data regarding the influence of water on hydroxide ion initiated reactions of organic substrates of low acidity (pKa > 16) performed under PTC conditions is not readily available. Mechanism oriented investigations of the effect of quat structure on such PTC/OH$^-$ reactions have not yet been reported. This is presumably due to the difficulty of experimental measurement, probably resulting from the low extractability of the hydroxide ion into the organic phase and compounded by the non-simple kinetic expressions involved in the relevant series of successive reactions. We wish to present our results with the purpose of putting forth a hypothesis regarding the roles of water and quat in PTC/OH$^-$ reactions of weakly acidic organic substrates.

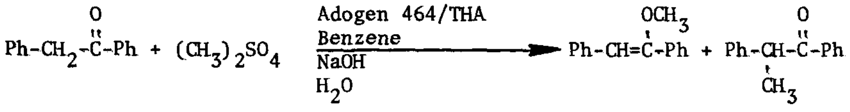
Our approach was to examine the influence of the quantity of water molecules available for organic phase hydration and the influence of quat structure on the selectivity of a given system. We chose as a model the alkylation reaction of the ambident C-/O-anion

TABLE: O-/C-ALKYLATION SELECTIVITY DEPENDENCE ON HYDROXIDE ION CONCENTRATION AND QUAT STRUCTURE

Quat	NaOH	$r_1 = \frac{\text{O-alk } (\underline{2})}{\text{C-alk } (\underline{3})}$ [a]	Conversion	Water molecules per ion in aqueous phase
Adogen[d]	solid	1.46	90-98%[b]	
Adogen[d]	50%	1.37[c]	90-98%[b]	1.1
Adogen[d]	40%	1.22	90-98%[b]	1.6
Adogen[d]	30%	1.15	90-98%[b]	2.6
Adogen[d]	25%	1.10	73%	3.3
Adogen[d]	20%	1.10	59%	4.4
THA[e]	solid	1.73	90-98%[b]	
THA[e]	50%	1.64	90-98%[b]	1.1
THA[e]	40%	1.53	90-98%[b]	1.6
THA[e]	30%	1.46	90-98%[b]	2.6

a) Average of 2-5 runs, extreme values differed by 5% or less;[f] b) Quantitative conversion (also followed by GC), is easily achieved but since it is difficult to quantitatively determine the dialkylated products, the reactions were stopped at 90-98% conversion for assaying; c) This value is valid at 33%, 65%, 73% and 95% conversion; d) Tricaprylmethylammonium; e) Tetrahexylammonium; f) Bruker WH-300 spectrometer, ^2H lock, deuterochloroform.

derived from deoxybenzoin (1) generated in PTC/OH$^-$ systems of differing hydroxide ion concentration and differing quat (Table).

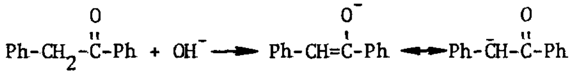


$$\mathrm{Ph{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}Ph} + \mathrm{(CH_3)_2SO_4} \xrightarrow[\text{NaOH}\ \ \mathrm{H_2O}]{\text{Adogen 464/THA}\ \ \text{Benzene}} \mathrm{Ph{-}CH{=}\overset{OCH_3}{C}{-}Ph} + \mathrm{Ph{-}\underset{CH_3}{CH}{-}\overset{O}{\overset{\|}{C}}{-}Ph}$$

1 2 3

100mg Deoxybenzoin (0.51 mmol), 5 mol % Adogen 464 (MW=458) or tetrahexylammonium (THA) bromide, 300 mol % dimethyl sulfate and benzene (total organic volume 2.00 ml) were magnetically stirred with solid or aqueous NaOH (containing 310 mg NaOH) at room temperature. Several reactions were stirred simultaneously under identical conditions. Workup consisted of dilution in benzene and water, separation and drying of the organic phase over $MgSO_4$ and evaporation under reduced pressure at 40°C. Within a short interval, never exceeding 1½ hours, the ^{1}H-NMR (300 MHz) spectrum of the crude reaction product mixture was run, taking special care to adjust the phase and integration bands for maximum reliability. The results are summarized in the Table, where "r_1" represents the ratio of O-alkylation products to mono-C-alkylation products.

Kornblum has shown that in the homogeneous alkylation of C-/O-ambident organic anions the fraction of C-alkylation increases as the ability of the solvent to promote hydrogen bonding increases thereby increasing the "selective solvation" of the oxygen site rendering it non-preferred for attack (8). The product determining step of our model reaction involves the attack of the monoanion 4 of deoxybenzoin on the highly reactive alkylating agent dimethyl sulfate. This kinetically controlled step should be greatly influenced by the orientation of all the relevant factors around the enolate anion during the attack. The oxygen site of 4 bears most of the negative charge density of the anion and there is competition between the quat and water molecules for association with the highly negative center. The number of water molecules available for hydration of the enolate in the organic phase (at the moment of attack of the alkylating agent) is an inverse function of the sodium hydroxide concentration in the aqueous phase. At low hydroxide ion concentrations more water molecules are available to accompany the enolate in the organic phase, and assuming "selective solvation" of the oxygen site by the water molecules to apply here, the extent of C-alkylation should be greater than that at high hydroxide ion concentration where the oxygen should be more accessible for attack due to the lack of a hydration envelope. It is seen in the Table that the trend of "r_1" values is consistent with this explanation, i.e. a decrease in the extent of C-alkylation as the sodium hydroxide concentration increases.



$$\mathrm{Ph{-}CH_2{-}\overset{O}{\overset{\|}{C}}{-}Ph} + \mathrm{OH^-} \longrightarrow \mathrm{Ph{-}CH{=}\overset{O^-}{\overset{|}{C}}{-}Ph} \longleftrightarrow \mathrm{Ph{-}\bar{C}H{-}\overset{O}{\overset{\|}{C}}{-}Ph}$$

1 4a 4b

Concentrated aqueous NaOH is considered to be an efficient dessicant of the nonpolar organic phase in two phse systems (9). It would seem from the results presented here that concentrated aqueous NaOH may serve as an effective but not absolute dessicant of the organic phase. The enolate anion in this system may therefore be only partially hydrated, thereby allowing the possibility of association between the oxygen site and the quat. Depending upon the extent of hydration of the oxygen atom, the quat-enolate system may be an intermediate state between "intimate" and "solvent separated" ion pair. The tightness of such an ion pair should be directly proportional to the accessibility of the positive charge located on the nitrogen atom in the quat. One may consider the positive charge on the nitrogen atom in the quat of THA quite "shielded" by four tetrahedrally placed hexyl groups and not very accessible for association. The positive charge on the nitrogen atom in the quat of Adogen, one face of which contains a methyl group, would be relatively much more accessible for association. Assuming this to be the case in the model reaction, it would be expected that the extent of O-alkylation of the enolate-Adogen ion pair should be smaller than that of the looser enolate-THA ion pair. The results in the Table are indeed consistent with this explanation.

Previous reports have demonstrated the hydration (2,3) and quat ion pairing (10) of anions actually transferred from the aqueous phase to the organic phase. Lipophilic substrates such as deoxybenzoin undergo deprotonation either at the interface (11) or in the bulk organic phase, in cases where the quat is capable of extracting the OH^- ion into the organic phase (12). On the basis of our results we conclude that significant association occurs between the enolate anion and water molecules and between the enolate anion and the quat. It therefore seems that the relevant factors governing the selectivity of the alkylation site of the C-/O-ambident anion are (1) the quantity of water molecules available for organic phase "selective solvation" of the enolate anion, determined by the aqueous NaOH concentration, and (2) the tightness of the quat-enolate ion pair determined by the accessibility of the central nitrogen atom of the quat.

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