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HYDROXIDE ION INITIATED REACTIONS UNDER PHASE TRANSFER CATALYSIS CONDITIONS—IV

EFFECT OF CATALYST STRUCTURE

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Abstract—The nature of the quat-anion interactions in a PTC/OH^- system was probed by examining the reactivity and selectivity of a CA/O-ambident anion towards an alkylating agent in the presence of various quats. It is suggested that the *accessibility* of the positive N center of the quat for association with the anion is the major factor in determining the behavior of PTC/OH^- reactions proceeding through the Makosza mechanism.

The critical component of "phase transfer catalysis" (PTC) reactions is the catalyst. The most popular catalysts are quaternary ammonium and phosphonium ions (quats). The role of the catalyst is to maintain the presence of the reacting anion in the reaction medium. For most of the anions studied, this is accomplished by the extraction of the anion from an aqueous phase reservoir into the organic phase.[1-5] In such systems the effectiveness of the PT catalyst was shown to depend mainly on the organophilicity of the quat, with other structural factors much less important.[4,5] In contrast, OH^- ion initiated reactions performed under phase transfer catalysis conditions, PTC/OH^- systems, attain maximum reactivity generally with quats of low organophilicity.[6-8] In addition, the low extractability of the OH^- ion into the organic phase for these low organophilic quats[9] cannot explain the observed reactivity of PTC/OH^- systems according to the extraction (Starks') mechanism.

In light of the outstanding preparative achievements[10a] and the apparent atypical behavior of PTC/OH^- systems, the investigation of the effect of quat structure in these systems is warranted. Such studies have hitherto dealt with the effect of quat structure on reactivity in an empirical manner, i.e. which catalyst affords the highest conversion per fixed time,[6-8] with little attempt being made in explaining the causes for the observed influence of quat structure. We wish to present data regarding the selectivity and reactivity of a PTC/OH^- system dependent on quat structure. We believe that it is possible to draw conclusions from these data relating to the nature of the interactions between quat and counteranion which may be used to explain the reactivity of this system and other systems believed to proceed through one of the generally accepted mechanisms of PTC/OH^- reactions.

RESULTS

We chose to investigate the alkylation of deoxybenzoin, **1**, by dimethyl sulfate (1,5 equivs) in the presence of 5 mol % quaternary ammonium and phosphonium bromides (Table 1), 50% aqueous NaOH and benzene at 34° (reaction 1).[11]

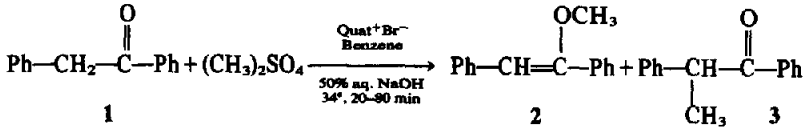
The parameter measured was r_1, the ratio of the O-alkylation product to the C-alkylation product. The ratio was determined by ^1H NMR (300 MHz) band areas. The results of the dependence of r_1 on quat structure are presented in Table 1.

The reaction with each catalyst was run at least three times, and the reproducibility of r_1 was between ±1% and ±3% of the values reported in Table 1 for most of the catalysts. The reproducibility of the TBA, TPA, TOA and TOdA salts was ±4% and for MTB ±8%. The reproducibility of the r_1 values was maintained when different conversions were obtained.

The general reactivity trends observed at different reaction times were confirmed by additional reactivity experiments. Each catalyst was run twice more (reproducibility ±3% or less for most of the catalysts; TEA, MTO, TPrA, TOA, THA and TDoA ±6%) for 30 min under identical conditions (Experimental). A control experiment containing no catalyst yielded 27% products (average of 3 runs) after 3 hr and 20 min and less than 5% after 30 min, with an average r_1 of 1.20. The results of the dependence of reactivity on quat structure are presented in Table 1.

In addition, no increase in the conversion at 30 min was observed as the concentration of the alkylating agent was increased from 1.0 equiv to 4.0 equivs (TBABr as catalyst).

The dependences of the r_1 values and the conversions at 30 min of the system on the length of the alkyl chain in



1 **2** **3**

Reaction 1.

Table 1. Dependence of selectivity and reactivity on quat structure[a]

No. of carbons	Quat	Name	Chains[b]	r_1[c]	Conversion[d]
4	$(CH_3)_4N^+$	TMA[e]	1 1 1 1	0.82	21%
8	$(C_2H_5)_4N^+$	TEA[e]	2 2 2 2	1.68	85%
10	$(C_4H_9)N^+(C_2H_5)_3$	BTE	2 2 2 4	1.79	100%
12	$(C_3H_7)_4N^+$	TPrA[e]	3 3 3 3	1.95	77%
13	$CH_3N^+(C_4H_9)_3$	MTB[e]	1 4 4 4	1.35	95%
14	$(C_2H_5)N^+(C_4H_9)_3$	ETB	2 4 4 4	1.82	79%
14	$(C_8H_{17})N^+(C_2H_5)_3$	OTE	2 2 2 8	1.72	98%
16	$(C_4H_9)_4N^+$	TBA[e]	4 4 4 4	1.88	54%
19	$(C_{16}H_{33})N^+(CH_3)_3$	CTM[e]	1 1 1 16	0.99	f
20	$(C_5H_{11})_4N^+$	TPA[e]	5 5 5 5	1.70	45%
20	$(C_8H_{17})N^+(C_4H_9)_3$	OTB	4 4 4 8	1.79	42%
24	$(C_6H_{13})_4N^+$	THA[e]	6 6 6 6	1.63	40%
25	$CH_3N^+(C_8H_{17})_3$	MTO[e]	1 8 8 8	1.29	67%
26	$(C_2H_5)N^+(C_8H_{17})_3$	ETO	2 8 8 8	1.63	47%
28	$(C_4H_9)N^+(C_8H_{17})_3$	BTO	4 8 8 8	1.59	36%
32	$(C_8H_{17})_4N^+$	TOA[e]	8 8 8 8	1.53	29%
48	$(C_{12}H_{25})_4N^+$	TDoA[e]	12 12 12 12	1.40	26%
72	$(C_{18}H_{37})_4N^+$	TOdA[e]	18 18 18 18	1.16	16%
16	$(C_4H_9)_4P^+$	TBP[e]	4 4 4 4	1.77	f

[a]See reaction 1, [b]numbers represent the number of carbons on each normal alkyl chain, [c]average of no less than three runs, [d] at 30 min; average of two runs; [e] commercially available. [f]not determined.

symmetrical tetraalkyl ammonium (TLA) bromides are shown in Figs. 1(a) and (c) respectively. The dependences of the r_1 values and the conversions at 30 min of the system on quat structure of non-symmetrical C_LH_{2L-1} $(C_KH_{2K-1})_3N^+Br^-$ ammonium (LTK) bromides are shown in Figs. 1(b) and (d) respectively.

DISCUSSION

Two major mechanisms have been presented to explain the behavior of PTC systems, the Starks mechanism[1] (Scheme 1; adapted to an alkylation reaction) and the Makosza mechanism[12] (Scheme 2).

It can be seen in Fig. 1(c) that as the organophilicity of the quat increases from TEA to TOA reactivity decreases, not in accord with the Starks mechanism. Moreover, the extraction of the OH^- ion by symmetrical tetraalkyl ammonium ions increases as the alkyl chain length increases (THA > TPA > TBA)[9]. It is therefore concluded that the Starks mechanism is not applicable in this alkylation reaction.

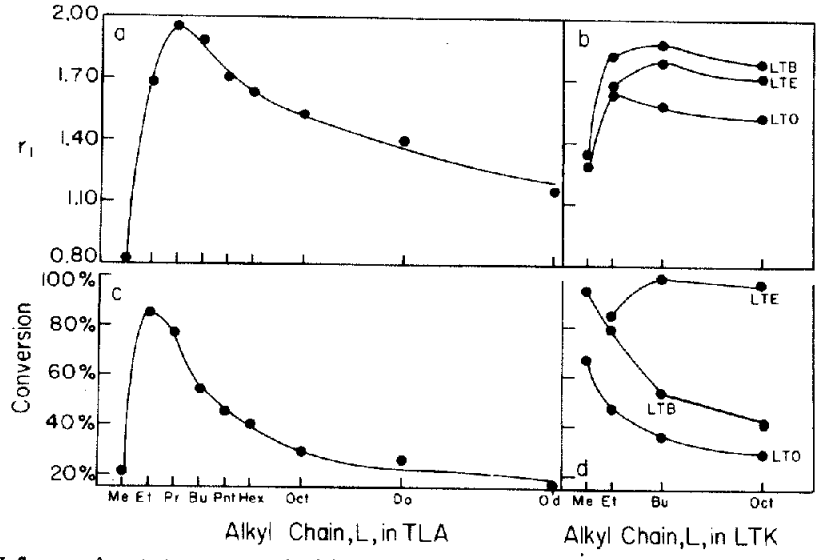


Fig. 1. Influence of quat structure on selectivity and reactivity; (a) r_1 values of symmetrical quats, TLA, (b) r_1 values of nonsymmetrical quats, LTK, (c) conversions at 30 min for symmetrical quats, TLA, (d) conversions at 30 min for nonsymmetrical quats, LTK.

Step 1: $[Q^+Br^-]org/aq + OH^- aq \rightleftharpoons [Q^+OH^-]org + Br^- aq$
Step 2: $[Q^+OH^-]org + R\text{-}H\ org \rightleftharpoons [Q^+R^-]org + H_2O$
Step 3: $[Q^+R^-]org + R'X\ org \rightarrow R\text{-}R'org + [Q^+X^-]\ org$

Scheme 1. Starks' mechanism.

Step 1. $Na^+ aq + OH^- aq + R\text{-}H\ org \rightleftharpoons [Na^+R^-]\ int + H_2O$
Step 2: $[Na^+R^-]\ int + [Q^+Br^-]\ org \rightleftharpoons [Q^+R^-]\ org + Na^+ aq + Br^- aq$
Step 3: $[Q^+R^-]\ org + R'\text{-}X \rightarrow R\text{-}R' + [Q^+X^-]\ org$

Scheme 2. Makosza's mechanism.

On the other hand, there is evidence that the Makosza mechanism is valid for alkylation reactions. It has been shown that the deprotonation of phenylacetonitrile occurs at the interface prior to the alkylation by ethyl bromide.[13] Makosza has demonstrated the importance of phase boundary reactions in the absence of catalyst.[14] According to the Makosza mechanism the organic anion, R^-, is anchored at the interface until a quat cation removes it from the interface into the bulk organic phase. Dehmlow has confirmed the presence of such ion pairs, Q^+R^-, containing organic anions derived from such weakly acidic compounds as fluorene, in benzene.[10b] In the ethylation of phenylacetonitrile[13] the alkylation reaction (Step 3) was shown not be the sole rate determining step. In our reaction, utilizing the highly reactive alkylating agent, dimethyl sulfate, step 3 is likewise not the rate determining step, as no increase in conversion was observed as the alkylating agent concentration was increased. Other reactions believed to proceed via the Makosza mechanism exhibit a maximum reactivity with alkyltriethyl ammonium ions, whereas with the more lipophilic or less lipophilic homologous quats lower yields were obtained.[6,8] Similar reactivity trends are observed in our reaction (Figs. 1(c) and (d)).

We propose that our results may be explained in terms of the Makosza mechanism and that the governing factor in systems where the Makosza mechanism is valid is the *accessibility* of the positively charged N site of the quat towards the association site of the anion, providing that the quat is not extremely hydrophilic. A quat is considered increasingly accessible as the length of the alkyl chains becomes shorter, with particular significance given to the shortest alkyl chain. We shall show how accessibility affects the qualitative trends of reactivity and selectivity observed in our system.

Reactivity. In order to discuss the effect of quat structure on reactivity, we must first determine the rate limiting step. As shown above, the rate limiting step must occur prior to the alkylation reaction (Step 3, Scheme 2). If step 1 were rate determining we would not expect the observed dependence of reactivity on quat structure. Therefore, the efficiency of catalysis will depend upon the ability of the quat to compete with the Na^+ ion for association with the organic anion, R^-, and to remove it from its anchored position at the interface and transfer it into the bulk organic phase where the anion is freer for reaction.

A quat in which the positive N center is relatively accessible for interaction and one that can approach the anion site closely may compete with the Na ion more successfully for anion association. Such a quat may also assist more effectively leaving group removal if properly oriented. Increased accessibility may, therefore, explain the kinetic behavior of the decreasing rates in the following ammonium series: alkyltriethyl > alkyltributyl > alkyltrioctyl; MTO > ETO > BTO > TOA; MTB > ETB > TBA > OTB; TEA > TBA > THA > TOA; MTB >MTO.

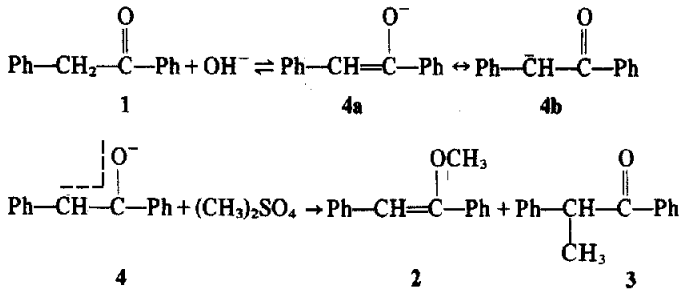
Many of the small quats are also accessible quats and their kinetic behavior may be influenced by two additional factors: hydrophilicity or an alternative mechanism. Our model reaction was run in the presence of 50% NaOH aq and the salting out effect is a major factor allowing catalysis for the relatively non-organophilic quats. Even so, TMA was the only quat not detectable at all in the organic phase by the 300 MHz ^1H NMR spectrometer. TEA was detected to an extent of less than 10% based on the quantity of catalyst introduced into the system. Thus, very low organophilicity may influence the behavior of extreme cases and may explain the low reactivity of TEA relative to BTE (the only deviation in Fig. 1(d)). The second possibility is a different mechanism as may be the case with CTM where micellar catalysis is probable.

It is worthwhile to note that Makosza's catalyst, triethylbenzylammonium (TEBA) lies in the structural range between BTE and OTE, and has proven itself as a near optimal catalyst in many PTC/OH^- reactions. We believe that these catalysts achieve the optimal degree of the combination of accessibility and non-hydrophilicity to remove organic anions from the interface into the bulk organic phase and leave them sufficiently free for reaction, in reactions that proceed through the Makosza mechanism,†

Selectivity. The product determining step involves the attack of an ambident O-/C-enolate anion on an alkylating reagent (Scheme 3). The factors determining the O-/C-alkylation ratio, r_1, of O-/C-ambident ions are discussed in depth in the literature and cover a wide range of variable reaction conditions.[10d] The choice of deoxybenzoin and dimethyl sulfate provided a system sensitive to kinetic factors and yielding intermediate r_1 values (corresponding to 45–66% O-alkylation). The major relevant factors determining r_1 in our system are constant (nature of the enolate, alkylating agent, temperature, solvent and concentration) except for the catalyst.

The single most influential factor on the properties of an enolate anion is the uneven charge distribution. The O-site possesses a higher electron density than the C-site, especially in the enolate derived from deoxybenzoin due to the resonance structure **4a** in which the whole π-system is conjugated. Positively charged or polar species, such as the quat or water molecules, will therefore compete for association with the O-site. In an earlier report[15] we applied Kornblum's concept[16] of "selective solvation" of the O-site of an enolate anion to the water molecules extracted into the organic phase in this PTC/OH^- reaction. In a two phase system containing 50% NaOH aq few water molecules are available for such association and we conluded that significant association between the quat and the O-site of the enolate occurs. The extent of attack of the highly reactive alkylating agent at the O- or C-site should be greatly influenced by the association envelope preferably sur-

†It has been suggested[10c] that TEBA's special reactivity is due to "specific anion-cation interactions in the ion pairs $[NR_3^+PhCHCN]$" of Makosza's reactions, but such interactions have not been speculated upon until this report.



Scheme 3.

rounding the O-site. The accessibility of TMA, for example, is large and consequently the electrostatic attraction between the quat N-site and the enolate O-site should be strong. The tightly bound TMA quat hinders attack at the oxygen thereby inducing a relatively large extent of C-alkylation. An increase in chain length should bring about a rapid decrease in the accessibility of the N of the quat and hence the extent of O-alkylation increases as the O-site is less tightly bound, as can be seen in Fig. 1(a) in the trend of increasing r_1 TMA < TEA < TPrA.

In the alkyltributyl and the alkyltrioctyl ammonium series, the Me derivatives (MTB and MTO respectively) afford the most C-alkylation, as the possibility of close association due to the short Me group is realized. Increase to the Et derivatives (ETB and ETO respectively) affords larger extents of O-alkylation due to reduced accessibility.

The dependence of the r_1 values on quat structure, as seen in Figs. 1(a) and (b), indicate that more than one factor affects the outcome of the product determining step. The behavior of quats of enhanced accessibility (those with Me, or less so, Et groups) is governed by their accessibility, a property determining the extent of an electrostatic interaction. As the length of the alkyl chains increase in symmetrical tetraalkyl ammonium ions, the accessibility decreases and quats such as TBA or larger, are of negligible accessibility. On the other hand, larger quats possess increasing bulkiness. Although the quat-enolate ion-pair becomes looser as chain length increases, quat-enolate association still exists, especially in the nonpolar benzene. Assuming this association to hold for even large quats (e.g. TDoA), increasing chain length may result in decreasing O-alkylation due to increasing bulkiness, a steric factor, thereby hindering approach of the alkylating agent to the O-association site. Bulkiness is the dominating factor for large quats, the accessibility being low. A maximum r_1 value at TPrA may result from an N-site which is not sufficiently accessible to tightly bind the association site of the anion but also not bulky enough to considerably hinder attack at this site. It can also be seen that the accessibility (electrostatic) effect of Me is larger than the bulkiness (steric) effect of octyl.

In the alkyltrioctyl series the bulkiness induced by the three bulky octyl chains is the dominating factor, and as long as no special accessibility effect exists (as for MTO), bulkiness governs and hence the decrease in r_1 from ETO to BTO to TOA. In the alkyltributyl series the three Bu groups do not lend large effects towards either accessibility or bulkiness and the results of MTB, and less so ETB, are influenced mainly by accessibility as the bulkiness cannot be very large. In the alkyltriethyl series the fair accessibility of the three small Et groups determines the general nature of the quat and the trend observed is similar to that of the alkyltributyl series, just understandably displaced in favor of C-alkylation. Even by replacing one Me of TMA by a cetyl chain, the extent of accessibility is reduced.† Comparison of the phosphonium salt, TBP, with the analogous ammonium salt, TBA, demonstrates the increased bulkiness of TBP relative to TBA, accessibility being low in both cases.

The importance of accessibility in determining reactivity in reactions proceeding through the Makosza mechanism is seen in Fig. 2 where the conversion is plotted opposite r_1 (the reciprocal of selectivity). Two classes of quats may be distinguished in the Fig, those with high conversions and low conversions at corresponding r_1 values. The catalysts which conform to the high conversion behavior (at corresponding selectivities) are mainly those with Me or Et groups. Those with Me groups (MTB and MTO) combine particularly high reactivity (in their homologous series) with a high degree of C-alkylation. This is strong evidence for the proposed influence of accessibility on reactivity (ability to associate with and remove R^- from the interface into the bulk organic phase) and selectivity (strong O-site association).

EXPERIMENTAL

Most of the materials were commercially available (Table 1) and were used with no further purification and were stored in the

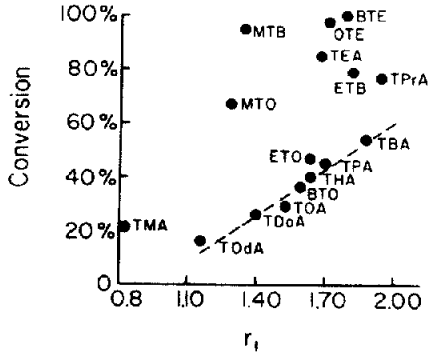


Fig. 2. Conversion—r_1 Relationship. Note deviations of particularly accessible quats (OTB not included, see Table 1).

†Assuming micellar catalysis to occur with CTM, even within a micelle an orientation of the quat-enolate ion pair must exist and the results indicate that a large extent of O-site association occurs.

dark or dry according to need. Those catalysts synthesized were prepared by refluxing the trialkylamine with a molar quantity of the appropriate alkyl bromide in acetonitrile for two days. The catalysts were recrystallized from ethanol or acetonitrile, were washed with diethyl ether and in certain cases were kept at −15° until crystallization or solidification, OTEBr, MTBBr and ETBBr are extremely hygroscopic. OTBBr and BTOBr were obtained as pastes. Catalyst purity of >95% was confirmed by microanalysis and NMR.

The ^{1}H NMR spectra were obtained on a Bruker WH-300 pulsed FT spectrometer operating at 300.133 MHz. The field/frequency regulations were maintained by locking to the solvent deuterium. The free induction decay signals were digitized and accumulated on an Aspect-2000 computer (32K). r_t values and conversions were determined by the ratios of the integration bands of the following peaks:

(1) − S 4.26 ppm, (2) − S 6.10 ppm, (3) qt 4.68 ppm.

The reaction vessel was a flat bottomed 21 mm diameter cylindrical glass flask which contained a rounded magnet (3 mm diam, 10 mm length). Fresh standard solns containing 100 mg Deoxybenzoin and 96 mg dimethyl sulfate per 2.00 ml soln (in benzene) were prepared within 10 min of every run. 2.00 ml of this soln were added to 5.0 mol % catalyst weighed to ±0.1 mg in the reaction vessel and stirred for 5 min. 400 μl 50% aq NaOH was then added, stirring commenced and run 20–80 min (corresponding to *ca* 90% conversion for each catalyst). Four reaction vessels were run simultaneously and were carefully centered on a Cenco magnetic stirring unit operating at 2700 rpm. The temp was maintained at 34 ± 1°. Workup consisted of diluting the mixture with 5 ml benzene, 5 ml H_2O followed by phase separation drying over $MgSO_4$ and evaporation at 50°. The resulting oil was dissolved in $CDCl_3$ and its spectrum run within 1½ hr. For the conversion determination, the reactions were run for 30 min after which the mixture was poured into a 10 mm test tube and allowed 10 min for phase separation. The upper clear organic layer was removed by means of a pippette and evaporated. The NMR spectra in $CDCl_3$ were run within an hour and a half.

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REFERENCES

[1]C. Starks, *J. Am. Chem. Soc.* **93**, 195 (1971).
[2]C. Starks and R. Owens, *Ibid.* **95**, 3613 (1973).
[3]A. Herriott and D. Picker, *Ibid.* **97**, 2345 (1975).
[4]D. Landini, A. Maia and F. Montanari, *Ibid.* **100**, 2796 (1978).
[5]D. Landini, A. Maia and F. Montanari, *J. Chem. Soc. Chem. Commun.* 112 (1977).
[6]M. Makosza and B. Serafinowa, *Rocz. Chem.* **39**, 1223 (1965).
[7]J. Dockx, *Synthesis* 441 (1973).
[8]E. Dehmlow and M. Lissel, *Tetrahedron Letters* 1783 (1976).
[9]E. Dehmlow, M. Slopianka and J. Heider, *Ibid.* 2361 (1977).
[10]E. Dehmlow and S. Dehmlow, *Phase Transfer Catalysis*. Verlag Chemie, Weinheim (1980), [a]pp. 84–169, [b]p. 33, [c]p. 39, [d]pp. 120–133 and refs cited.
[11]First performed by A. Merz and R. Tomahogh, *J. Chem. Res.* S273, M3070 (1977).
[12]M. Makosza, *Pure Appl. Chem.* **43**, 439 (1975).
[13]R. Salaro, S. D'Antone and E. Chiellini, *J. Org. Chem.* **45**, 4179 (1980).
[14]M. Makosza and E. Bialecka, *Tetrahedron Letters* 183 (1977).
[15]M. Halpern, Y. Sasson, I. Willner and M. Rabinovitz, *Ibid.* 1719 (1981).
[16]N. Kornblum, P. Berrigan and W. LeNoble, *J. Am. Chem. Soc.* **85**, 1141 (1963).