Influence of Counter Ion Structure on the Direction of the Phase Transfer Catalytic Methylation of an Enol [1]

Eckehard V. Dehmlow* and
Sabine Schrader
Fakultät für Chemie, Universität Bielefeld,
Universitätsstraße 25, D-4800 Bielefeld 1

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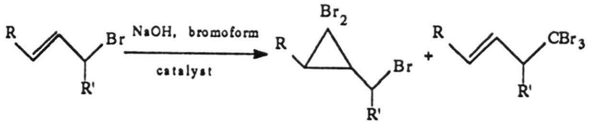
Phase transfer catalytic (PTC) methylations of deoxybenzoin by dimethyl sulfate can be steered towards enol ether formation by large, sterically shielded ammonium ions or – more strongly – by large highly delocalized phospho-iminium (and presumably other large) cations. The C-alkylation direction is favoured by small, hard ammonium ions of the type $RNMe_3^+$ and by crown ethers, particularly benzo-crowns. O/C ratios can be varied between 0,75 and 63, the largest effects so far reported for ambident anions. These results should give guide-lines for alkylations of other ambident ions.

Influences of catalyst structures on regioselectivities of phase transfer catalysis reactions have been observed occasionally (survey [2]), but systematic studies of this aspect are rare. Recently we investigated (a) catalyst steering of halide exchange in mixed dihalocarbenes $HCBr_2Cl \rightarrow$ CBrCl (expected carbene) + CCl_2 + CBr_2 [3] and (b) the carbene addition/substitution competition



[1, 4]. In both cases, the multitude of tested catalysts could be devided into 3 classes:

A. "Hard" and sterically accessible cations. These favour fast carbene generation so that little or no halide exchange (reaction a) and almost no substitution (reaction b) occur. Quaternary ammonium ions with 3 or 4 methyl groups and benzo-crown ethers belong into this class.

B. "Soft", sterically shielded and large, highly delocalized cations, such as tetraphenylarsonium or bis(triphenylphosphin)-iminium cations. These stabilize anions CX_3^- and thereby promote extensive halide exchange (reaction a) or substitution (reaction b).

C. The majority of "typical" phase transfer catalysts, quaternary phosphonium and ammonium salts, exhibit intermediate behaviour.

The observed effects can be rather large. Thus, cinnamyl bromide can give under standardized conditions carbene addition / substitution ratios between 92:1 (catalyst: hexadecyltrimethylammonium bromide) and 1:91 (catalyst: tetraphenylarsonium chloride) [1].

It seemed important to investigate if similar catalyst structure effects are present in other types of reactions. Rabinovitz, Sasson, and coworkers [5, 6] studied O- *vs.* C-alkylation of the deoxybenzoin anion under PTC using a limited but revealing range of catalysts. A maximal variation in the O-/C-ratios between 0.82 (NMe_4^+) and 1.77 (PBu_4^+) was observed.

$$\begin{aligned}&\mathrm{Ph{-}CH_2{-}CO{-}Ph} \rightarrow\\&\mathrm{Ph{-}CH{=}C(OCH_3){-}Ph} +\\&\mathrm{Ph{-}CH(CH_3){-}CO{-}Ph}\end{aligned}$$

It was shown that the sterically available catalyst cations influence a relatively higher degree of C-alkylation. This is due presumably to preferred association of the small cation (plus a few coextracted water molecules) with the most negative position of the anion, the oxygen. Thereby the C-position is left relatively more free for alkylation. We felt it worthwhile to expand these experiments into several directions:

a) study crown ethers, especially benzo-crowns as catalysts,
b) use large, sterically shielded and highly delocalized cations of group B (see above), and
c) see if there is an effect of the counter ion brought in with the catalyst at the start of the reaction.

Not unexpectedly, methyl iodide conversions with deoxybenzoin give only C-alkylation, no matter what is the catalyst. Using dimethyl sulfate under conditions somewhat similar to the ones of the Israeli workers [6] we obtain the results of Table I. Where a comparison is possible the data of our study agree well with the results from the Israeli re-

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* Reprint requests to Prof. Dr. E. V. Dehmlow.

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Table 1. O- *vs.* C-Alkylation of deoxybenzoin under standardized conditions (20 mmol deoxybenzoin, 1 mmol catalyst, 22 mmol Me_2SO_4, 20 ml toluene, 20 ml 50% NaOH, 6 h, 60 °C).

Catalyst Cation/Anion	% O-Alkylation HSO_4^-	Cl^-	Br^-	I^-	% C-Alkylation HSO_4^-	Cl^-	Br^-	I^-	O/C-Ratio HSO_4^-	Cl^-	Br^-	I^-	Conversion (%)
None	50				23				2.2				73
Benzo-15-crown-5	47				53				0.9				100
18-Crown-6	54				45				1.2				99
1,3-Dimesityl-benzo-15-crown-5	43				57				0.8				100
Dicyclohexano-18-crown-6	53				47				1.1				100
Naphtho(2.3)-15-crown-5	54				46				1.2				100
NMe_4^+	62				38				1.6				100
		55				41				1.3			96
			52				48				1.1		100
				48				52				0.9	100
NEt_4^+	86				14				6.1				100
		82				18				4.6			100
			79				21				3.8		100
				59				41				1.4	100
$NProp_4^+$	92				8				11.5				100
		93				7				13.3			100
			90				10				9.0		100
				71				29				2.4	100
NBu_4^+	90				10				9.0				100
		94				6				5.6			100
			79				21				3.8		100
				71				29				2.4	100
$NPen_4^+$	88				11				8.0				99
		93				7				13.3			100
			85				15				5.7		100
				75				25				3.0	100
$NHex_4^+$	91				7				12.1				98
		84				16				5.3			100
			71				25				2.8		96
				65				35				1.9	100
$NHep_4^+$	88				12				7.3				100
		85				15				5.7			100
			84				16				5.3		100
				76				24				3.2	100
$NOct_4^+$	82				13				6.3				95
		77				19				4.1			96
			71				29				2.4		100
				63				28				2.3	91
$NMeOct_3^+$		84				16				5.6			100
				63				37				1.7	100
$NPenBu_3^+$			91				8				11.3		99
$Me_2N(C_{12}H_{25})_2^+$		62				38				1.6			100
$Me_2N(C_{18}H_{37})_2^+$		70				30				2.3			100
$PhCH_2NEt_3^+$		65				35				1.9			100
			58				42				1.4		100
				56				44				1.3	100
$PhCH_2NMe_3^+$		73				27				2.7			100
$PhNMe_3^+$		55				45				1.2			100
$C_{16}H_{33}Me_3^+$		74				26				2.8			100
			65				34				1.9		99
$C_{16}H_{33}NEt_3^+$			68				32				2.1		100
$C_{16}H_{33}NBu_3^+$			89				9				9.9		98
$MeN(isoBu)_3^+$		96				4				24			100
			92				8				11.5		100
$(Me_2N)_3P{=}N{=}P(NMe_2)_3^+$		89				1.4				63			90
$P[-N{=}P(NMe_2)_3]_4^+$		88				3				29			91

search [6] although we aimed at quantitative conversions. Semikinetic runs ascertained that the O/C ratio did not change in the course of the reaction. Furthermore, there is a slower non-catalytic process (first entry of the table) that gives an O/C ratio of 2.2.

Close inspection of the table reveals

(1) The crown ethers (especially benzo-15-crown-5 and its dimesityl derivative) favour C-alkylation strongly, as do quaternary ammonium ions NMe_4^+, $PhNMe_3^+$, and $RNMe_3^+$. All these have small, sterically available head groups. It is instructive in this respect to follow O/C ratios in a series of chlorides: $C_6H_5N(CH_3)_3^+$ 1.2, $C_6H_5CH_2N(CH_3)_3^+$ 2.7, and $C_{16}H_{33}N(CH_3)_3^+$ 2.8. These show clearly how steric bulk of the cations increases O-alkylation. The last mentioned catalyst, cetyltrimethylammonium, is known to catalyze micellar reactions. It is open to question (*cf.* also [6]) whether a micellar conversion occurs under the present conditions. The close resemblance of the benzyltrimethylammonium and cetrimide values suggests that a "normal" PTC process is involved.

It is very likely that these "hard" cations associate preferentially with the oxygen site of the enolate anion, forming a rather tight ion pair. Thus attack by the alkylating agent is fostered at carbon.

(2) Quite surprisingly, the O/C ratios obtained with the onium salt catalysts are very dependent on what is the starting anion brought in with the catalyst. All of the data given in the table are average values of at least two runs, and the reproducibilities of the O- and C-alkylation values are generally ±5% making the small and large O/C ratios less secure and assertive. Nevertheless it is apparent that O/C ratios are highest and about equal for hydrogensulfate and chloride, lower for bromide, and lowest (favouring C-alkylation) for iodide. Off hands one might have suspected catalyst poisoning by lipophilic anions like iodide. But, first of all the deoxybenzoin enolate must be much more lipophilic than iodide, and secondly no large differences in rates are found. Thus, the observed effects must be of a more complex origin. Hydrogensulfate and chloride values can be considered standard as these counter ions are hydrophilic (HSO_4^- is transformed into hardly extractable SO_4^{2-}) and non-disturbing. Bromide and iodide give much higher C-alkyl proportions, and this must be due to the intervention of a competing alkylation by CH_3Br and CH_3I, formed in the process:

$$(CH_3O)_2SO_4 + Br^-(I^-) \rightarrow CH_3Br(I) + CH_3O-SO_3^-$$

We assume therefore that the alkylations in the presence of bromide and iodide progress in form of a complex scheme:

a) non-catalytic direct alkylation

b) alkylation by phase transfer catalysis with dimethyl sulfate

c) phase transfer catalytic generation of CH_3Br or CH_3I

d) phase transfer catalytic alkylation by the latter species

It is not astonishing then that small changes in the catalyst cation structure will bring about rather large additional effects as so many rate constants are involved. Still, it is noteworthy that a zig-zagging is observed in the results from the symmetrical cations: For instance O-alkylation yields of the NR_4Br (R = CH_3 through C_8H_{17}) are: 52, 79, 90, 79, 85, 71, 84, and 71% respectively. Here very intricate effects of cation size and cation-anion interaction must come into play.

Concentrating once more on the symmetrical cations, it is quite clear that the smallest, sterically least congested NMe_4^+ gives highest C-alkylation, but the opposite is not true: maximum O-alkylation is found (Cl^- or HSO_4^- counter ions) already with $N(C_3H_7)_4^+$ to $N(C_5H_{11})_4^+$, and there is a marked decline with the higher members. Again a number of opposing steering factors must be present.

(3) Much higher extents of O-alkylation are observed though with two types of cations: the sterically very demanding triisobutylmethylammonium and highly delocalized phospho-imonium salts [7]. Thus, the catalyst steering of the O- *vs.* C-reaction paths can vary O/C ratios between 0.75 (1,3-dimesitylbenzo-15-crown-5) and 63 (bis[tris-(dimethylaminophosphin)]iminium chloride) at the extremes.

It may be assumed that the soft cations form much looser ion pairs separated by solvent molecules. These species are O-methylated preferentially.

The intrinsic O- or C-directing effects of the various cations could be determined free of complicating anion influences if salts $[NR_4^+O^--CPh=CH-Ph]$ were available in substance. Unfortunately, all experiments in this direction were in vain, such substances could not be obtained.

Catalyst influences on the alkylation of deoxybenzoin found here are the largest ones so far reported in the literature for reactions of ambident anions. It must be stressed, however, that alkylations of ambident anions are influenced by many factors among which are structure of substrate and alkylating agent, leaving group, concentrations, solvent, temperature, and structure of the cation. It may not surprise therefore that the results detailed here cannot be adapted to other systems in a simple way. Preliminary experiments showed that substrates such as 10-methylanthrone, acridone, 4-pyridine, and dibenzoylmethane exhibit only small catalyst susceptibilities with a strong dependence on the alkylating agent employed.

Nevertheless the results of this study should give guidelines to make projections as to the catalyst influences in new PTC reactions of ambident anion.

Experimental

General method for the alkylations

20 mmol deoxybenzoin, 20 ml toluene, 1 mmol catalyst, 20 ml 50% aqueous sodium hydroxide, and 22 mmol dimethyl sulfate were stirred at 60 °C under nitrogen for 6 h. Thereafter the mixture was diluted by water. The organic layer was separated off, dried (Na_2SO_4), and concentrated in vacuo. The mixture was analyzed by gas chromatography (3% OV 17 80/100 mesh 3 column, 200 °C). Reference was taken to a calibrating curve prepared by use of known mixtures of the two products.

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[1] Applications of Phase Transfer Catalysis, Part 50. Part 49: E. V. Dehmlow and J. Wilkenloh, Liebigs Ann. Chem. **1990,** in press.

[2] E. V. Dehmlow and S. S. Dehmlow, "Phase Transfer Catalysis", 2nd ed., Verlag Chemie, Weinheim, Deerfield Beach, Basel (1983).

[3] E. V. Dehmlow and J. Stütten, Liebigs Ann. Chem. **1989,** 187.

[4] E. V. Dehmlow and J. Wilkenloh, Tetrahedron Lett. **28,** 5489 (1987), *cf.* also [1].

[5] M. Halpern, Y. Sasson, I. Willner, and M. Rabinovitz, Tetrahedron Lett. **22,** 1719 (1981).

[6] M. Halpern, Y. Sasson, and M. Rabinovitz, Tetrahedron **38,** 3183 (1982).

[7] We thank Dr. R. Schwesinger University of Freiburg, for the generous gift of $[(H_3C)_2N]_3P{=}N{=}P[N(CH_3)_2]_3Cl$ and $P[N{=}P(N(CH_3)_2)_3]_4Cl$; R. Schwesinger, and H. Schlemper, Angew. Chem. **99,** 1212 (1987); Angew. Chem., Int. Ed. Engl. **26,** 1167 (1987).

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