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Macrocyclic Polyethers as Enolate Activators in Homogeneous and Heterogeneous Systems

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The ability of macrocyclic polyethers to activate enolates has been studied in the alkylation of deoxybenzoin (**1**) with butyl derivatives *n*BuY (Y = Br, I, OMes) catalyzed by crown ether PHDB18C6 (**7**) or cryptand [2.2.2,C_{10}] (**8**) under phase-transfer catalysis (PTC) and homogeneous (chlorobenzene) conditions. The enolate reactivity is mainly determined by the ligand (cryptand>crown ether) and solvent (increasing with the polarity, in the order: toluene<chlorobenzene<1,2dichlorobenzene). Regioselectivity of the reaction is also remarkably affected by ligand and alkylating agent.

Keywords: Activation of enolates, lipophilic macrocyclic polyethers, phase-transfer catalysis (PTC), regioselectivity in alkylation reactions, solvent effects in PTC reactions, UV-vis determinations of enolates

Lipophilic crown ethers and cryptands are known to form stable inclusion complexes with alkali and alkaline-earth metal salts even in low polarity media to give very reactive "solvent separated" ion pairs.[1] In such complexes the anion is markedly activated due to the scarce stabilization by the complexed cation ($M^{n+} \subset Lig$) and the solvent. These polyethers are hence particularly attractive for measuring the reactivity of carbanionic species, especially in poor solvating media where the latter are present as ion pairs or ion pair aggregates.[2]

The present communication concerns the activation of enolates in the alkylation of deoxybenzoin (**1**) with several butyl derivatives (**2–4**) catalyzed by crown ether PHDB18C16 (**7**) or cryptand [2.2.2,C_{10}] (**8**) under liquid-liquid (LL) and solid-liquid (SL) phase-transfer catalysis (PTC) conditions with strong bases (NaOH, KOH). Comparison with the reactivity of tetrahexylammonium enolate $hexyl_4N^+E^-$ is also included (react. 1).[3]

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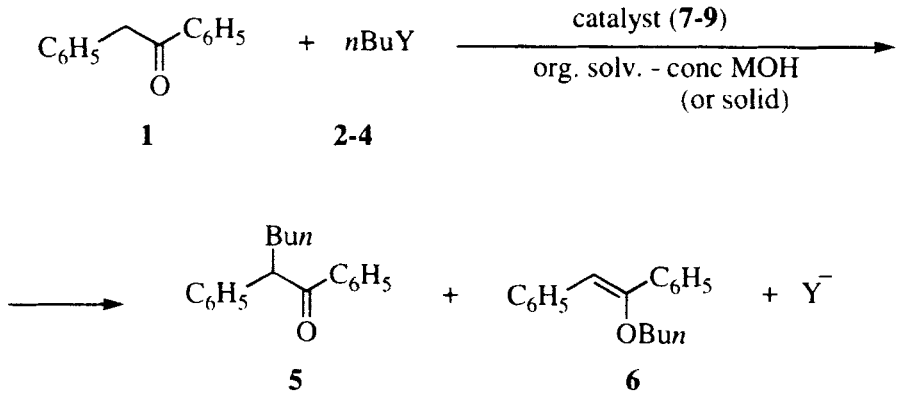


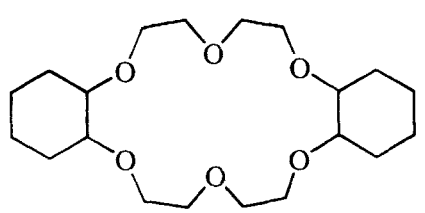
(1)

*n*BuY = *n*BuBr (**2**), *n*BuI (**3**), *n*BuOMes (**4**)

catalyst = PHDB18C6 **7**, [2.2.2, C_{10}] **8**, hexyl$_4$N$^+$Cl$^-$ **9**

solv. = toluene, chlorobenzene, 1,2- dichlorobenzene

MOH = NaOH, KOH



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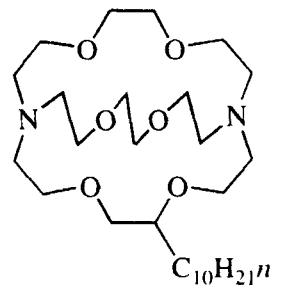

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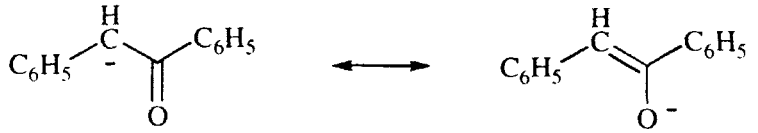

1a **1b**

TABLE I Influence of catalyst and base on the rate of the alkylation of deoxybenzoin (1) with *n*BuBr (2) under PTC and homogeneus conditions, at 25 ± 0.1 °C (react 1).[a]

Catalyst		*PTC conditions*				*Homogeneous conditions*[b]
		C_6H_5Cl – *aq base*		C_6H_5Cl – *solid base*		C_6H_5Cl
		Aq base	$10^3k\ M^{-1}\ s^{-1}$)	*Solid base*	$10^3k\ (M^{-1}\ s^{-1})$	$10^3k\ (M^{-1}\ s^{-1})$ $10^3k\ (M^{-1}\ s^{-1})$
PHDB18C6	7	NaOH 19 M	5.0	NaOH	3.4	2.7
PHDB18C6	7	KOH 13 M	9.3	KOH	13.5	
[2.2.2, C_{10}]	8	NaOH 19 M	126	NaOH	136	126
[2.2.2, C_{10}]	8	KOH 13 M	88			
hexyl$_4$N$^+$Cl$^-$	9			KOH	49.3	

[a]See ref. 3.
[b]Comparable amounts of preformed ($M^+ \subset$ Lig)E^- complex and *n*BuBr in anhydrous chlorobenzene.

TABLE II Influence of alkylating agent *n*BuY and ligand on the regioselectivity (O/C ratio) of reaction 1

nBuY	*Ligand*		*base*		*O/C ratio*
*n*BuI	crown ether	7	NaOH	19 M	0.0
*n*BuBr	crown ether	7	NaOH	19 M	0.002
	cryptand	8	NaOH	19 M	0.35
*n*BuOMes	crown ether	7	KOH	13 M	2.3
	cryptand	8	KOH	13 M	3.0
	cryptand	8	KOH	solid	3.8

Kinetic data reveal the major role that the ligand plays in determining both the reactivity of the enolate anion E^- (**1a,b**) (Table I) and the distribution of the alkylation products **5** and **6** (Table II). As reported in Table I, the rate constant k($M^{-1}s^{-1}$) increases in the order: crown ether < quaternary salt < cryptand. The enhancement of reactivity, up to 40 times, found on changing from crown ether **7** to cryptand **8** can be explained on the basis of the different ability of these ligands to activate the anion due to their topology. Whereas in the crown ether complexes there is still interaction between the anion and cation, in cryptates, where the metal cation is fully sequestered inside the tridimensional cavity of the ligand, such interaction is minimized, hence the anion is highly activated.[1c,e,f] Such behavior is confirmed by UV-vis spectroscopic determinations of these Q^+E^- species [Q^+= ($M^+ \subset$ Lig) or hexyl$_4$N$^+$] in chlorobenzene showing the highest absorption maximum wavelength (λ_{max}) values just with cryptand [2.2.2,C_{10}] (Table III). Since bathocromic shifts indicate a more efficient separation within the ion pair the data provide additional evidence for the better anion activation realized by this ligand.

Comparison with the homogeneous conditions shows that the PTC reaction rates can be reproduced by reacting the preformed ($M^+ \subset$ Lig)E^- complex with the alkylating agent in anhydrous chlorobenzene (Table I). The results clearly prove that the alkylation reaction (1) takes place in the organic phase and is the rate-limiting step of the overall process, the E^- extraction and the release of Y^- being fast processes. Consequently, in our system the enolate reactivity depends on the activation induced by the bulky cation Q^+, following the order: crown ether<quaternary cation<cryptand.

The regioselectivity of the reaction (O/C ratio) is also affected by the ligand (Table II). It is worth noting that with crown ether the preferential association of the complexed cation with oxygen favors the alkylation of the less electronegative center, the carbon, and hence only the C-alkylation product is obtained. By contrast

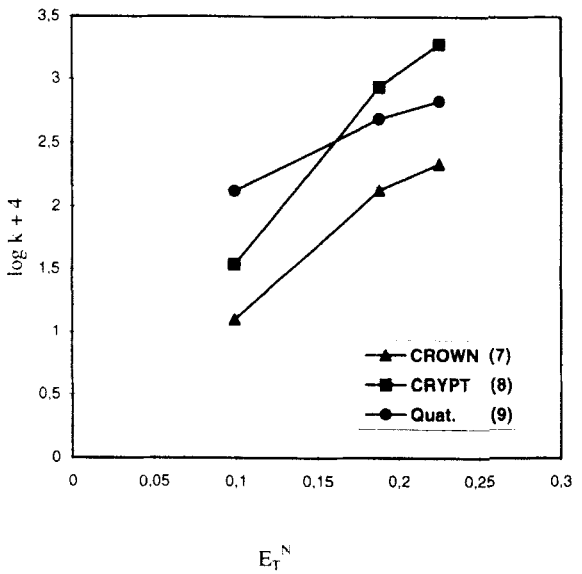

FIGURE Effect of the solvent polarity, log **k** *vs* E_T^N, in the reaction (1) with *n* BuBr catalyzed by **(7)-(9)**.[E_T^N = 0,099 (toluene), 0,188 (chlorobenzene), 0,225 (1,2 dichlorobenzene)]

cryptand, that realizes a much better cation-anion separation, leads to an increase in the nucleophilicity of the enolate O-center, resulting in greater quantity of O-alkylated product and, hence, lower regioselectivity.[4]

A further increase in reactivity occurs on changing the solvent polarity and the type of base. On passing from toluene to the more polar 1,2-dichlorobenzene an enhancement of 5, 17 and 55 times the rate constant is found for the quaternary salt, crown ether and cryptand, respectively (Figure). In good agreement with these results spectroscopic determinations in the three solvents show that the absorption maximum wavelength (λ_{max}) of the enolate Q^+E^- is always shifted to higher values with increasing the polarity of the medium regardless of the catalyst. Interestingly, cryptand **8**, the most efficient ligand, also exhibits the highest bathocromic shift ($\Delta\lambda$ =23 nm) (Table III).

The effect of the base is much less pronounced. The ligand and the H-function[6] being the same, the enolate reactivity increases, up to 2–4 fold, on passing from NaOH to KOH (lower cation-anion interaction) and from the aqueous to solid base (increased anidricity of the enolate) (Table I).

The data as a whole indicate that the rate of reaction (1) is maximized when catalyzed by cryptand **8** in the 1,2-dichlorobenzene-solid KOH two-phase system (Fig. 1). As shown in Figure 1, on changing from crown ether in toluene to cryptand in 1,2-dichlorobenzene enhancements of more that two powers of ten are obtained. For synthetic applications, however, the less efficient crown ether **7** is the catalyst of choice due to its much lower cost and higher tendency to promote regioselective reactions [*i.e.* 100% C-alk **5** with *n*BuBr (**3**) and 70% O-alk **6**, with *n*BuOMes (**4**) (Table II)].

TABLE III UV-vis spectral data (λ_{max}, nm) of QE enolates in toluene, chlorobenzene and 1,2-dichlorobenzene from org. solv.-solid KOH two-phase systems, at 25 ± 0.1 °C[a]

Q^+	(λ_{max}, nm)		
	toluene (E_T^N = 0.099) [b]	*chlorobenzene* (E_T^N = 0.188) [b]	*1,2- dichlorobenzene* (E_T^N = 0.225) [b]
($K^+ \subset$ PHDB18C6)	387	390[c]	397
$hexyl_4N^+$	392	395[c]	397
($K^+ \subset$ [2.2.2, C_{10}])	392	402[c]	415

[a][Q^+E^-] = 2–3x10^{-4} M.
[b]See ref 7.
[c]See ref 3.

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