Macrocyclic Polyethers as Enolate Activators in Base-Catalyzed Phase-Transfer Reactions

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A kinetic study of the alkylation reaction of deoxybenzoin (**1**) with alkylating agents **2**−**4**, catalyzed by PHDB18C6 **7** or [2.2.2,C_{10}]cryptand **8**, has been performed in chlorobenzene−aqueous (or solid) base (NaOH, KOH) two-phase systems, under liquid−liquid (LL) and solid−liquid (SL) phase-transfer catalysis (PTC) conditions. The results obtained seem to indicate a multistep mechanism where the ligand transfers the enolate from the interface to the bulk organic phase and the alkylation reaction is rate determining for all the process. The enolate reactivity strongly depends on the ligand and, to a lesser extent, on the base. The highest rate constant values are obtained under SL-PTC conditions and with [2.2.2,C_{10}]cryptand **8**, which realizes the best cation−anion separation and hence anion activation. In line with these data, UV−vis spectroscopic determinations of the complexed enolate $(M^+\subset Lig)R^-$ exhibit bathochromic shifts of the absorption maximum wavelength (λ_{max}) on changing from crown ether to cryptand. The distribution of the reaction products (O/C alkylation ratio) is also related to the different ability of the ligand to separate cation from anion in the ion pair.

Introduction

The reactions of anions generated by deprotonation of acidic or moderately acidic organic compounds represent a widely exploited part of phase-transfer catalysis (PTC) applications.[1] Such organic anions include enolates, alkoxides, anions from activated N−H and methylene substrates (benzylic and allylic ketones, imines, sulfones, nitriles), and even activated hydrocarbons. They are obtained in liquid−liquid (LL) or solid−liquid (SL) two-phase systems using concentrated alkaline solutions (usually 50% aqueous sodium hydroxide) or solid bases (NaOH, KOH, K_2CO_3) instead of expensive, and sometimes dangereous, hydrides, amides and organic alkoxides in strictly dry media. Alkylation reactions are among the most useful in organic synthesis, particularly C-alkylation that allows the formation of new carbon−carbon bonds.[1]

Two major mechanistic models, Starks "extraction" and Makosza "interfacial" mechanism,[1] were proposed in order to explain the carbanion formation and its reaction with the alkylating agent under PTC/OH conditions. Whereas the first mechanism requires the extraction of the hydroxide anion, paired with the quaternary cation Q^+, from the aqueous to the bulk organic phase, in the second one the deprotonation of the organic acid takes place at the aqueous−organic interface without the assistance of Q^+.[2] Both mechanisms invoke the phase-transfer cation−carbanion pair Q^+R^- as reacting species in the subsequent alkylation step.

Carbanion reactivity strictly depends on the Q^+ structure.[1b,c,3] Small, hydrophilic quaternary cations, like TEBA[4] or tetraethylammonium,[1b,c,3] were found to be the catalysts of choice in interfacial reactions. The preferential activity of these quaternary salts was explained in terms of the "accessibility" of their charged nitrogen center for pairing with carbanion, so favoring anion transport from interface to organic phase.[1b,c,3]

Whereas much work has been done in this field with quaternary salts,[1,3,4] few data concern the catalytic activity of macrocyclic polyethers,[5] despite their much higher stability to strong bases. In fact, the particular tendency of crown ethers and cryptands to effectively bind alkali and alkaline−earth metal salts, even in low polarity solvents, to produce very reactive "solvent separated" ion pairs is well documented.[6−9] The cation complexing properties of these ligands make them particularly attractive in determining the reactivities of carbanionic species, especially in poor solvating media where the latter are present as ion pairs or ion pair aggregates.[10]

To evaluate their ability to activate carbanions, we undertook a systematic study of the alkylation reaction of deoxybenzoin (**1**) with butylderivatives **2**−**4**, catalyzed by perhydrodibenzo-18-crown-6 (**7**) or [2.2.2,C_{10}] cryptand

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[1] (a) Dehmlow, E. V.; Dehmlow, S. S. In *Phase Transfer Catalysis*; VCH: Weinheim, 1993. (b) Starks, C. M.; Liotta, C. L.; Halpern M. In *Phase Transfer Catalysis−Fundamentals, Application and Industrial Perspectives*; Chapman and Hall: New York, 1994. (c) Halpern, M. C. In *Phase Transfer Catalysis−Mechanisms and Syntheses*; Halpern, M. C., Ed.; ACS Symposium Ser 659; American Chemical Society: Washington, DC, 1996.

[2] A new version of the interfacial mechanism that involves the quaternary cation in the deprotonation step has been recently proposed by Liotta and defined as "modified interfacial mechanism".[1b,c]

[3] (a) Halpern, M.; Sasson, Y.; Willner, I.; Rabinovitz, M. *Tetrahedron Lett.* **1981**, *22*, 1719. (b) Halpern, M.; Sasson, Y.; Rabinovitz, M. *Tetrahedron* **1982**, *38*, 3183. (c) Rabinovitz, M.; Cohen, Y.; Halpern, M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 960. (d) Mason, D.; Magdassi, S.; Sasson, Y. *J. Org. Chem.* **1990**, *55*, 2714.

[4] Makosza, M. *Pure Appl. Chem.* **1975**, *43*, 439.

[5] (a) Dehmlow, E. V.; Schrader, S. *Z. Naturforsch.* **1990**, *45b*, 409. (b) Dehmlow, E. V.; Richter, R. *Chem. Ber.* **1993**, *126*, 2765. (c) Dehmlow, E. V.; Klanck, R. *J. Chem. Res., Synop.* **1994**, 448.

[6] Lehn, J. M. *Pure Appl. Chem.* **1980**, *52*, 2303 and references therein.

[7] Cox, B. G.; Schneider, H. *Pure Appl. Chem.* **1990**, *62*, 2259.

[8] Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721.

[9] Landini, D.; Maia, A.; Penso, M. *Comprehensive Supramolecular Chemistry*; Lehn, J. M., Ed.; Pergamon Press: Oxford, 1996; Vol. 1, Chapter 11.

[10] (a) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737. (b) Hogen-Esch, T. E. *Adv. Phys. Org. Chem.* **1977**, *15*, 153.

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Table 1. Effect of Catalyst and Base on the Second-Order Rate Constants of the Alkylation Reaction of Deoxybenzoin (1) with *n*-BuBr (2) under LL- and SL-PTC Conditions, at 25 ± 0.1 °C[a]

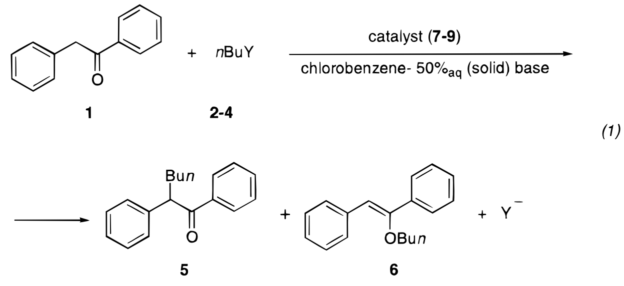
	LL-PTC (chlorobenzene−aq base)			SL-PTC (chlorobenzene−solid base)		
catalyst	aq base[b]	10^3k^c (M^{-1} s^{-1})	hydration state *n* of $(M^+\subset Lig)R^-\cdot nH_2O^c$	solid base	10^3k^c (M^{-1} s^{-1})	hydration state *n* of $(M^+\subset Lig)R^-\cdot nH_2O^c$
PHDB18C6 **7**	19 M NaOH	5.0	0.3	NaOH	3.4^d $(2.7)^{e,f}$	<0.2
PHDB18C6 **7**	13 M KOH	9.3	0.6	KOH	13.5^g	0.3
[2.2.2,C_{10}] **8**	19 M NaOH	126	<0.2	NaOH	136 $(126)^{e,f}$	
[2.2.2,C_{10}] **8**	13 M KOH	88	0.3			
hexyl$_4N^+Cl^-$ **9**				KOH	49.3	

[a] A chlorobenzene solution (15 mL) of deoxybenzoin (**1**) (0.2 M), *n*-BuBr (**2**) (0.3 M), and catalyst (0.0015−0.02 M) and a water solution (8 mL) of base or solid (40−50 molar equiv) base. [b] Same H_function value for NaOH and KOH.[20] [c] Average of at least two determinations. The error in these values is estimated to be 5 −10%. [d] $k = 54.5 \times 10^{-3}$ (M^{-1} s^{-1}) in the case of *n*-BuI (**3**). [e] *k* value under homogeneous conditions. [f] A chlorobenzene solution (15 mL) of $(M^+\subset Lig)R^-$ complex (0.022−0.066 M) and *n*-BuBr (**2**) (0.015−0.06 M). [g] $k = 6.0 \times 10^{-3}$ (M^{-1} s^{-1}) in the case of *n*-BuOMes (**4**).

8 under LL- and SL-PTC conditions. Results have been compared with those obtained, under homogeneous conditions, in anhydrous chlorobenzene. A comparison of catalytic activity of crown ether **7**, cryptand **8**, and tetrahexylammonium chloride **9** is also included.

Results

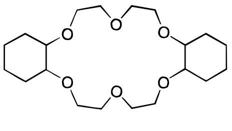
Kinetics were performed under a nitrogen atmosphere by stirring, at 1300 ± 50 rpm, a chlorobenzene solution (15 mL) of deoxybenzoin (**1**) (0.2 M), alkylating agent **2**−**4** (0.3 M), and catalyst **7**−**9** (0.0015−0.02 M) with an aqueous solution (8 mL) of base (NaOH 19 M, KOH 13 M) or solid base (40−50 molar equiv), at 25 ± 0.1 °C (reaction 1).



Y = Br (**2**), I (**3**), OSO_2Me (**4**)
base = NaOH, KOH
catalyst = PHDB18C6 **7**, [2.2.2, C_{10}] **8**, hexyl$_4N^+Cl^-$ **9**

Rates were measured by GLC analysis of the organic phase, following the disappearance of the substrate **1** and the appearance of the alkylation products **5** and **6** with respect to tetradecane as internal standard. Reaction rates increased with increasing stirring speed, remaining constant beyond 1200−1250 rpm (Figure 1). As a consequence, measurements were performed at 1300 ± 50 rpm, in the “plateau” region.

A study of the partition coefficients showed that the PTC catalysts **7**−**9** are entirely in the organic phase.[11]



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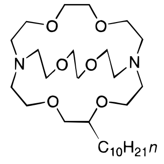

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Titrimetric and UV−vis determinations of the organic phase showed that under reaction conditions: the following occurred. (i) In the absence of ligand no appreciable amounts of alkaline enolate R^-M^+ are detected whereas, in the presence of catalyst, a concentration of enolate R^- equal to that of the PTC agent is formed after a few minutes ($\Delta t \leq 5$). The concentration of Q^+R^- ($Q^+ = (M^+\subset Lig)$ or hexyl$_4N^+$) remains constant for a long time (120 min or more) and is unchanged after addition of a molar excess (30−50 molar equiv) of NaBr or KBr. (ii) The maximum absorption wavelength (λ_{max}) of the enolate strongly depends on both the ligand (cryptand > crown ether) and base (solid base > aqueous base) (Table 2). In addition, the hydrogen−deuterium exchange reaction on α,α′-dideuteriodeoxybenzoin (**1c**) was complete in 2−3 min when catalyzed by PHDB18C6 **7**, after more than 4 h without ligand (see Experimental Section).

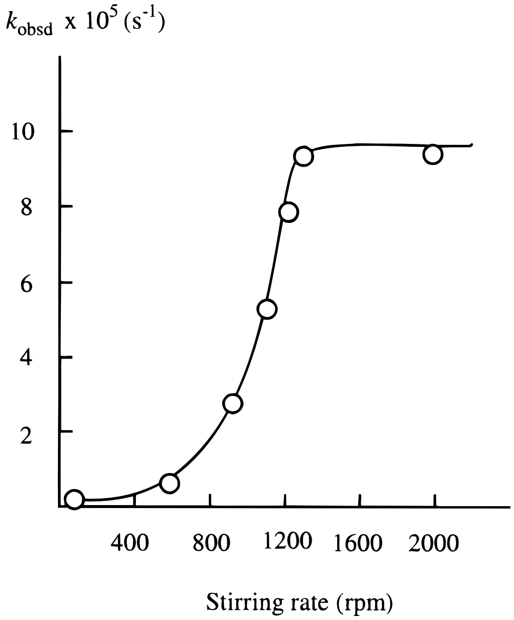
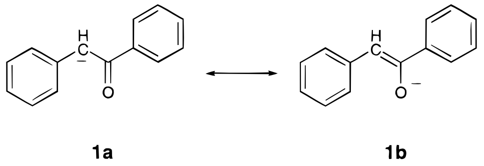


Figure 1. Effect of the stirring rate (rpm) on the observed rate constant k_{obsd} (s^{-1}) of the reaction of deoxybenzoin (**1**) with *n*-BuBr (**2**) catalyzed by PHDB18C6 **7** in the 18.9 M PhCl−NaOH two-phase system, at 25 °C.



Karl Fischer determinations of the organic phase revealed a hydration state of the enolate, up to 0.6 mol

Table 2. UV−Vis Spectral Data (λ_{max}, nm) for Q^+R^- Complexes in Chlorobenzene from PhCl−Aqueous Base and PhCl−Solid Base Two-Phase Systems, at 25 °C[a,b]

	(λ_{max}, nm)			
	NaOH		KOH	
Q^+	19 M	solid	13 M	solid
($Na^+\subset$PHDB18C6)	384	384		
($K^+\subset$PHDB18C6)			385	390
hexyl$_4N^+$				395
($Na^+\subset$[2.2.2,C_{10}])	391	407		
($K^+\subset$[2.2.2,C_{10}])			389	402

[a] $[Q^+R^-] = 2-2.5 \times 10^{-4}$ M. [b] Average of at least two determinations.

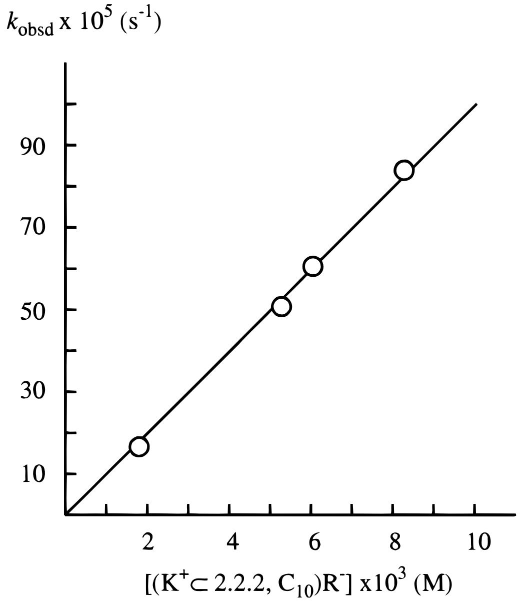


Figure 2. Dependence of the observed rate constant k_{obsd} (s^{-1}) on the catalyst concentration, $[(K^+\subset 2.2.2,C_{10})R^-] \times 10^3$ (M), for the reaction of deoxybenzoin (**1**) with *n*-BuBr (**2**) in the 13 M PhCl−KOH two-phase system, at 25 °C. For reaction conditions see Table 1, footnote *a*.

of H_2O per mole, depending on the ligand and the base (Table 1). Blank experiments showed that no appreciable reaction occurred in the absence of catalyst after 20 half-lives with respect to the slowest catalyzed reaction.

A kinetic order of 1.0 in the alkylating agent was determined for *n*-BuBr (**2**) in the range 0.15−0.6 M of alkyl bromide keeping a constant concentration of both deoxybenzoin (**1**) (0.2 M) and catalyst **7** (0.02 M). The reactions follow pseudo-first-order kinetics (eq 2) up to at least 2 half-lives.The observed rate constants (k_{obsd}, s^{-1}) are linearly dependent on the concentration of the complexed enolate $(M^+\subset Lig)R^-$ (eq 3) in the range examined (0.0015−0.02 M), as shown in Figure 2 for cryptand [2.2.2,C_{10}] **8**.

$$\text{rate} = k_{obsd}[n\text{-BuY}] \tag{2}$$

$$k_{obsd} = k[(M^+\subset \mathrm{Lig})R^-] \tag{3}$$

The second-order rate constants ($k_{obsd}/[(M^+\subset Lig)R^-]$, $M^{-1}\ s^{-1}$) are reported in Table 1, together with the *k* ($M^{-1}\ s^{-1}$) value obtained with hexyl$_4N^+Cl^-$ (**9**), for comparison purposes.

Table 3. Effect of Alkylating Agent and Ligand on the Distribution of the C- and O-Alkylation Products 5 and 6 in Reaction 1

alkylating agent	ligand	base	C-alk **5** (%)	O-alk **6** (%)
n-BuI (**2**)	PHDB18C6 **7**	NaOH 19 M	100	
n-BuBr (**3**)	PHDB18C6 **7**	NaOH 19 M	99.8	~0.2
	[2.2.2,C_{10}] **8**	NaOH 19 M	74	26
n-BuOMes (**4**)	PHDB18C6 **7**	KOH 13 M	30	70
	[2.2.2,C_{10}] **8**	KOH 13 M	25	75
	[2.2.2,C_{10}] **8**	KOH solid	21	79

Kinetic measurements were also performed in anhydrous chlorobenzene by reacting comparable amounts of the preformed complex $(M^+\subset Lig)R^-$ (0.02−0.06 M) and *n*-BuBr (**2**) (0.015−0.06 M) (reaction 4, Table 1). Rates were determined following the disappearance of **1** via GLC analysis of the organic phase. Reactions (4) follow a second-order kinetic (5).

$$(M^+\subset \mathrm{Lig})R^- + n\text{-BuBr} \xrightarrow{\mathrm{PhCl}} n\text{-BuR} + (M^+\subset \mathrm{Lig})Br^- \tag{4}$$

$$\text{rate} = k[(M^+\subset \mathrm{Lig})R^-][n\text{-BuBr}] \tag{5}$$

The distribution of the reaction products, **5** and **6** (eq 1), determined by GLC analysis of the reaction mixture at 100% conversion, depends on both ligand and alkylating agent. Whereas with crown ether **7** and *n*-BuBr (**2**) or *n*-BuI (**3**) reaction 1 is highly regioselective and the C-alkylated **5** is the only product, with cryptand **8** up to 26% of **6** is obtained. The O-alkylated **6** is always the main product with *n*-BuOMes (**4**), whatever the ligand may be (Table 3).

Discussion

Reaction Mechanism. Experimental results suggest the following mechanism (eqs 6−8) for reaction 1:

$$(R-H)_{org} + (M^+OH^-)_{aq} \rightleftharpoons (R^-M^+)_{int} + H_2O \tag{6}$$

$$(R^-M^+)_{int} + (\mathrm{Lig})_{org} \rightleftharpoons [(M^+\subset \mathrm{Lig})R^-]_{org} \tag{7}$$

$$[(M^+\subset \mathrm{Lig})R^-]_{org} + (R'-Y)_{org} \rightarrow (R-R')_{org} + [(M^+\subset \mathrm{Lig})Y^-]_{org} \tag{8}$$

The first step (eq 6) involves the reaction of hydroxide ion with deoxybenzoin R−H to form the corresponding enolate R^- wich remains at the interfacial region of the system.[1,16] In the second step (eq 7) the enolate is transferred by the ligand, as $(M^+\subset Lig)R^-$ complex, from the interfacial region to the bulk organic phase. Titrimetric determinations have confirmed that R^-M^+ is present in the organic phase exclusively as the $(M^+\subset Lig)R^-$ complex.

In the final step (eq 8) the complexed enolate reacts with the alkylating agent R′Y within the organic phase

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(11) Landini, D.; Maia, A., Montanari, F. *J. Am. Chem. Soc.* **1984**, *106*, 2917.

(12) (a) Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.* **1986**, *51*, 3187; (b) **1986**, *51*, 5475.

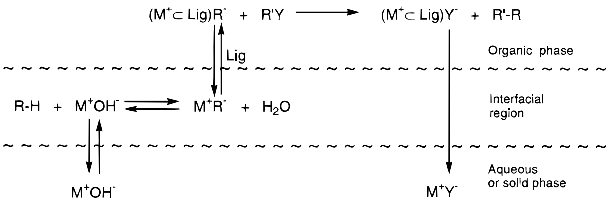
(13) Landini, D.; Maia, A. *Tetrahedron* **1991**, *47*, 1285.

(14) (a) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988. (b) March, J. *Advanced Organic Chemistry*; John Wiley and Sons: New York, 1992; Chapter 10.

(15) Landini, D.; Maia, A.; Montanari, F.; Rolla F. *J. Org. Chem.* **1983**, *48*, 3774.

(16) On the basis of our results we cannot exclude the involvement of the catalyst in the interfacial deprotonation.[2.]

to give product. The alkylation reaction is the rate-determining step of the overall process, the enolate formation and the release of the leaving group Y^- being relatively fast processes. This is supported, in particular, by the following experimental results: (i) The reaction rate does not depend on the stirring above 1200−1250 rpm (Figure 1). (ii) The reactions follow regular pseudo-first-order kinetics (eq 2) and the observed rate constants (k_{obsd}, s^{-1}) are linearly related to the concentration of the complexed enolate in the organic phase (eq 3, Figure 2). In addition, the reactivity sequence obtained with the alkylating agents **2**−**4** (I > Br > OMes) is that expected on the basis of the intrinsic nucleofugacity of the leaving group (Table 1).[14,15] (iii) Reaction rates can be reproduced under homogeneous conditions by reacting comparable amounts of preformed complex $(M^+{\subset}Lig)R^-$ and alkylating agent **2** (Table 1, eq 4). (iv) H/D exchange is orders of magnitude faster than the fastest PTC reaction. The overall mechanism of the reaction 1 can be illustrated by the following scheme:



Reactivity of the Enolate. Effect of the Ligand. Kinetic results highlight the fundamental role that the ligand plays in activating the enolate anion R^- **1a,b** of deoxybenzoin (**1**). As reported in Table 1, changing from crown ether **7** to cryptand **8**, the rate constant of reaction 1 increases up to 40-fold.

Such behavior is most likely due to the different ability of these macrocycles to activate the anion.[6,9,17] Cryptands form stable inclusion complexes in which the metal cation is fully sequestered inside the tridimensional cavity of the ligand, and its interaction with the anion is minimized. These "solvent separated" ion pairs are particularly reactive in low polarity media since the anion is scarcely stabilized by both the solvent and the bulky cation. By contrast, in the complexes of crown ethers, the metal ion can still interact with the counteranion from a direction perpendicular to the plane of the ring. As a consequence, anion activation is greatly determined by interaction with the cation, decreasing with increasing charge density. The effect is remarkable in weakly polar solvents, where the lower assistance by the medium makes the ion pair still more intimate and hence less reactive.[9,17]

Differences are also revealed by UV−vis spectroscopic determinations of these complexes in chlorobenzene. As Table 2 shows, the absorption maximum wavelength (λ_{max}) of complexed enolates $(M^+{\subset}Lig)\ R^-$ is always shifted to higher values on passing from crown ether **7** to cryptand **8** whatever the cation may be. Since bathochromic shifts correspond to more efficient interionic separation within the ion pair,[18,19] the higher λ_{max} values obtained with cryptates represent another independent proof of the better cation−anion separation realized by these ligands.

Comparison with the quaternary enolate $hexyl_4N^+R^-$ indicates that the reactivity of this "loose" ion pair falls between that of crown ether **7** and cryptand **8** complexes (Table 1). Quaternary ammonium salts have been extensively used as phase-transfer catalysts in the alkylation of deoxybenzoin (**1**) under PTC/OH^- conditions.[1,3] In these reactions, where the anion transport from the interface to the bulk phase is rate limiting, the enolate reactivity strongly depends on the ability of the quaternary cation to effectively bind the anion.[3] In this case small quats, like tetrahethylammonium bromides, were found to be catalysts of choice due to their optimum balance between hydrophobicity and "accessibility".[1,3] In addition, a linear correlation of catalytic activity with interfacial activity for a series of symmetrical quaternary ammonium bromides was obtained in PTC alkylation systems.[3d]

In our case, since the alkylation reaction (eq 8) is the rate-determining step, the major role of the quaternary cation is the enolate activation. For this purpose the bulky $hexyl_4N^+$ cation is particularly suitable.[1] The sequence of reactivity found (crown ether < quaternary salt < cryptand) reflects the increasing cation−anion separation of the ion pair Q^+R^- ($Q^+ = (M^+{\subset}Lig)$ or $hexyl_4N^+$) as confirmed also by the relative (λ_{max}) values increasing in the same order [$\lambda_{max}(K^+{\subset}crown)R^- < \lambda_{max}\ hexyl_4N^+R^- < \lambda_{max}\ (K^+{\subset}cryptand)R^-$] (Table 2).

Effect of the Base. The enolate reactivity also depends on the base used. When the catalyst is crown ether **7** the rate constant increases, about 2 times, changing from 19 M NaOH to 13 M KOH (with the same H_- basicity function).[20] Enhancement is even more pronounced (up to 4-fold) with the corresponding solid base (SL-PTC), due to increased anhydricity of the anion.[11]

Spectroscopic UV−vis determinations of these complexes in chlorobenzene are in excellent agreement with these results (Table 2). Indeed, for both systems the maximum absorption wavelength of the potassium complex $(K^+{\subset}PHDB18C6)R^-$ is always shifted to a λ_{max} value higher than that of the corresponding sodium complex. Since red shifts are usually found in contact ion pairs with increasing cation ionic radius,[18,19] our data confirm that cation−anion interaction is still present in crown ether complexes. This is probably the reason why the λ_{max} value of the complex $(Na^+{\subset}crown)R^-$ is not affected by the change from LL- to the more anhydrous SL-PTC conditions (Table 2). With this "harder" Lewis acid, removal of the hydration sphere must be balanced by a larger interaction with the anion.[21] The result is a slight increase,[21] or even a decrease, in enolate reactivity, as found in our case (Table 1).

Unlike PHDB18C6 **7** with cryptand **8** the rate constant decreases slightly on going from NaOH to KOH (Table 1). Presumably, such behavior is due to a better fitting of the cryptand with Na^+, resulting in more efficient ion pair separation and hence higher activation of the anion. In line with these results it can be seen that the absorption spectra exhibit the highest λ_{max} value with the sodium complex $[Na^+{\subset}(2.2.2,C_{10})]R^-$ (Table 2).

Interestingly, our spectroscopic data provide additional evidence of the major role played by solvent molecules

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(17) Maia, A. *Pure Appl. Chem.* **1995**, *67*, 697.
(18) Hogen-Esch, T. E.; Smid, J. *J. Am. Chem. Soc.* **1966**, *88*, 307.
(19) Xie, L.; Streitwieser, A. *J. Org. Chem.* **1995**, *60*, 1339 and references therein.
(20) Yagil, G. *J. Phys. Chem.* **1967**, *71*, 1034.
(21) Landini, D.; Maia, A.; Montanari, F.; Pirisi, F. M. *J. Chem. Soc., Perkin Trans. 2* **1980**, 46.

in competing with the ligand for the metal ion, and thus in determining cation selectivity.[22,23] The trend we found in chlorobenzene ($Na^+ > K^+$) parallels that obtained by other authors for 18-crown-6 in THF[24] and the gas phase[25,26] ($Li^+ > Na^+ > K^+ > Rb^+ > Cs^+$). It reflects the intrinsic cation selectivity of these macrocycles and contrasts the well-known sequences ($K^+ > Na^+ \sim Rb^+ > Cs^+$) by Pedersen[27] and Izatt[8] in polar solvents (H_2O, methanol). In fact, in the latter the reversed order is mainly due to the specific solvation of the cation by the medium that increases with increasing charge density.[23]

Distribution of the Alkylation Products. As Table 3 shows, the distribution of the alkylation products, C-alkylated **5** and O-alkylated **6**, is also related, in the low polar chlorobenzene, to the ability of the ligand to separate cation from anion in the ion pair. With crown ether **7** the preferential association of the complexed cation with the center of the ambident O/C enolate anion with the maximum electron density, the oxygen, hinders reaction at this site. As a result, alkylation of the less electronegative center, the carbon, is favored and only the C-alkylation product **5** is obtained.

By contrast, the regioselectivity of reaction 1 noticeably drops with the more efficient complexing agent [2.2.2,C_{10}] **8**. In this case, owing to the better cation−anion separation realized by this ligand, the nucleophilicity of the enolate O-center increases, as does the quantity of O-alkylated product (Table 3). Also with *n*-BuOMes (**4**) the quantity of **6** increases slightly on going from crown ether to cryptand. However, as was expected,[28] with this "harder" alkylating agent, the O-alkylated product, derived from the "harder" O-terminus of the ambident anion, was the main product in all cases.[29]

Experimental Section

General Methods. Potentiometric titrations were performed with a Metrohm 670 Titroprocessor by using a combined glass electrode isolated with a potassium chloride bridge. Karl Fischer analyses were carried out with a Metrohm 684 KF coulometer. ^1H NMR spectra were recorded on a Bruker AC 300 spectrometer, using C_6D_6 and tetramethylsilane as external and internal standards, respectively. GLC data were obtained with a Perkin-Elmer 8310 equipped with a 50 × $^1/_8$ in. OV-101-5% on Chromosorb WHP 100/120 mesh column. UV−vis spectra were recorded on a Perkin-Elmer LAMBDA 6 spectrophotometer.

Melting points (Pyrex capillary) were determined on a Büchi melting point apparatus and have been corrected.

Materials and Solvents. Inorganic bases (KOH, NaOH) were Analar grade commercial products used as such. Catalysts **7**−**9** were commercially available products, used without further purification. Chlorobenzene was Analar dry commercial product, stored over molecular sieves, under nitrogen. Karl Fischer titrations showed a water content ≤20 ppm. Deoxybenzoin (**1**), alkylating agents **2**−**4**, benzylphenyl ether, and tetradecane were utilized as purchased.

α,α′-Dideuteriodeoxybenzoin (**1c**) was prepared by adding, in a 50 mL flask, solid MeONa (0.15 g, 2.78 mmol) to a solution of deoxybenzoin (**1**) (1.0 g, 5.10 mmol) in monodeuteriomethanol (10 mL) under a nitrogen atmosphere at room temperature. After 90 min of stirring, D_2O (5 mL) was added and the mixture was extracted with ethyl ether (3 × 10 mL). The organic phase was washed with D_2O (2 × 10 mL), then dried over Na_2SO_4, and evaporated under reduced pressure. The α,α′-dideuteriodeoxybenzoin (**1c**) was obtained as a white solid (0.79 g, 78%): mp 53−54 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22−8.10 (m, 10H).

Determination of the Enolate 1a,b Formation. A standardized chlorobenzene solution (10 mL) of α,α′-dideuteriodeoxybenzoin (**1c**) (0.1 M), PHDB18C6 **7** (0.05 M), and benzyl phenyl ether (0.1 M) as internal standard was magnetically stirred under a nitrogen atmosphere with an aqueous solution of 13 M KOH (7 mL) in a flask thermostated at 25 ± 0.1 °C. Samples (1 mL) were withdrawn at various times, by stopping the stirrer for 20−40 s to allow adequate separation, and analyzed by ^1H NMR (chlorobenzene, C_6D_6 as external reference). The H/D exchange percentage was evaluated by following the appearance of the singlet at δ 3.82 ($-COCH_2$-Ph) and using the singlet of phenyl benzyl ether at δ 4.80 (OCH_2Ph) as standard. An analogous experiment was performed in parallel without ligand.

A standardized chlorobenzene solution (15 mL) of deoxybenzoin (**1**) (0.2 M) and catalyst **7**−**9** (0.01−0.04 M) was magnetically stirred under nitrogen with the appropriate aqueous or solid base (40−50 molar equiv) in a flask thermostated at 25 ± 0.1 °C. At various times, aliquots of the organic phase (2−3 mL) were withdrawn, after stopping the stirring for 20−40 s, quenched in ice-cold MeOH (50 mL) and potentiometrically titrated with 0.01 N HCl.

In a flask thermostated at 25 ± 0.1 °C a standardized chlorobenzene solution (15 mL) of deoxybenzoin (**1**) (2×10^{-4} M) and catalyst **7**−**9** ($4-6 \times 10^{-4}$ M) was magnetically stirred under nitrogen with the appropriate base. At various times, samples of the organic phase (3 mL) were withdrawn, after phase separation, placed in a 1 cm cuvette, previously purged with argon, and analyzed by UV−vis spectroscopy (Table 2).

Kinetic Measurements. In a typical LL-PTC procedure, the reaction flask thermostated at 25 ± 0.1 °C was charged with an aqueous solution (8 mL) of 19 M NaOH or 13 M KOH and a standardized chlorobenzene solution (15 mL) of deoxybenzoin **1** (0.2 M), catalyst **7**−**9** (0.0015−0.02 M), alkylating agent **2**−**4** (0.3 M), and tetradecane (0.1 M) as internal standard. The heterogeneous mixture was mechanically stirred at 1300 ± 50 rpm under nitrogen. Samples of the organic phase (0.5 mL) were withdrawn at various times, stopping the stirrer for 40−60 s, and quenched with an acidic and saturated aqueous solution of KBr (1 mL). The organic phase was separated after centrifugation and analyzed by GLC (see General Methods).

An analogous procedure was followed under SL-PTC conditions using ground solid NaOH or KOH (40−50 molar equiv) instead of the aqueous bases. Reaction rates were determined following the disappearance of the substrate **1** and/or the appearance of the alkylation products (**5** and **6**). The pseudo-first-order rate constants (k_{obsd}) were computer generated by plotting log [substrate] vs time and determining the slope of the straight lines. The second-order rate constants k (M^{-1} s^{-1}) were evaluated by dividing k_{obsd} by the complexed enolate concentration.

In the kinetic measurements under homogeneous conditions, a standardized chlorobenzene solution (5 mL) of alkylating agent **2** (0.045−0.18 M) and tetradecane (0.03−0.09 M) was added, in a flask thermostated at 25 ± 0.1 °C under nitrogen, to a standardized chlorobenzene solution (10 mL) of deoxybenzoin (**1**) (0.03−0.09 M) and catalyst **7** or **8** (0.033−0.099 M), previously stirred with ground solid NaOH for 10−15 m, to generate the enolate complex $(M^+ \subset Lig)R^-$. Timing

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[22] Takeda, Y.; Ohyagi, Y.; Akabori, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3381.

[23] Solov'ev, V. P.; Strakhova, N. N.; Raevsky, O. A.; Rüdiger, V.; Schneider, H. J. *J. Org. Chem.* **1996**, *61*, 5221.

[24] Smid, J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 112.

[25] Glendening, E. D.; Feller, D.; Thompson, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 10657.

[26] Lee, S.; Wyttenbach, Von Helden, G.; Bowers, M. T. *J. Am. Chem. Soc.* **1995**, *117*, 10159.

[27] (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017. (b) Pedersen, C. J.; Frensdorff, H. K. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 16.

[28] Ho, T. *Chem. Rev.* **1975**, *75*, 1.

[29] An analogous rationale was previously given by Kornblum et al. to explain the different O/C ratio found in the alkylation of phenoxides and β-naphthoxides with alkyl halides on changing solvent polarity. These authors attributed the effect of the medium on orientation to the different specific solvation, and hence activation, of the atom with higher charge density.[30]

was started. At various times aliquots of the organic phase (0.5 mL) were withdrawn, quenched, and analyzed as described above for PTC reactions.

The second-order rate constants were evaluated using a least-squares computer program from the eq $1/([B]_o-[A]_o)\ln([B][A]_o/[A][B]_o) = kt$, where A = alkylating agent and B = enolate or *vice versa*. All rates involved at least 10 samplings and gave correlation coefficients of 0.995 or better.

Reaction Products. 1,2-Diphenyl-1-hexanone (**5**) was prepared by adding a solution of deoxybenzoin (**1**) (2.0 g, 10 mmol), PHDB18C6 **7** (0.22 g, 0.59 mmol), and *n*-BuBr (**2**) (1.4 g, 10 mmol) in benzene (10 mL) with 19 M NaOH (10 mL). The mixture was stirred for 17 h at room temperature under a nitrogen atmosphere, added with water (20 mL) and extracted with ethyl ether (3 × 20 mL). The organic phase, washed with 10% aqueous HCl (20 mL) and then with water (20 mL), was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (230−400 mesh) with a 97:3 mixture of light petroleum (bp 40−60 °C)−ethyl ether as eluent affording 1,2-diphenyl-1-hexanone (**5**) (2.15 g, 85%) as a solid: mp 63−64 °C [lit.[31] mp 64 °C]; ^1H NMR (300 MHz, $CDCl_3$) δ 7.0−8.1 (m, 10H, Ar), 4.50 (t, 1H), 0.70−2.40 (m, 9H).

1-Butoxy-1,2-diphenylethene (**6**) was obtained by adding a solution of deoxybenzoin (**1**) (3.92 g, 20 mmol), PHDB18C6 **7** (0.404 g, 1.10 mmol), and *n*-butyl methanesulfonate (**4**) (3.04 g, 20 mmol) in benzene (20 mL) with 13 M KOH (15 mL). The mixture was stirred for 20 h at room temperature, under nitrogen, diluted with water (20 mL), and extracted with Et_2O (2 × 20 mL). The organic phase, washed with 10% aqueous $NaHCO_3$ (20 mL) and then with water (20 mL), was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (230−400 mesh) with a 99:1 mixture of light petroleum (bp 40−60 °C)−ethyl ether as eluent affording 1-butoxy-1,2-diphenylethene (**6**) (3.72 g, 74%) as a viscous oil: bp 96−98 °C (0.1 mm), $n^{20}_D = 1.6024$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10−8.0 (m, 10H, Ar), 6.1 (s, 1H), 3.71 (t, 2H), 1.30−2.0 (m, 4H), 0.95 (t, 3H). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67, H, 7.99. Found: C, 85.71, H, 7.95.

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(30) Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* **1963**, *85*, 1148.

(31) Billard, F. *Bull. Soc. Chim.* **192**, *29*, 429.