

# Effect of Cation-Complexing Agents on the Ba(II)-Assisted Basic Ethanolysis of Phenyl Acetate: From Cation Deactivation to Cation Activation

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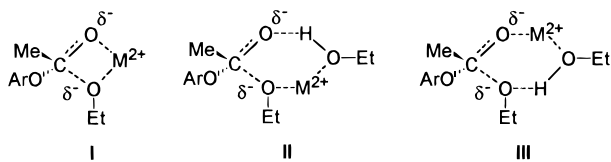
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A thorough investigation of the effect of adding cation complexing agents on the barium-assisted basic ethanolysis of phenyl acetate shows that any catalytic activity disappears upon sequestration of the metal ion by cryptand 222, but addition of the crown ethers 18C6, 15C5, and 12C4 yields ternary complexes of 1:1:1 (crown ether)–(metal ion)–ethoxide composition, in which instead of the expected cation deactivation a definite cation activation takes place. Clear-cut evidence was obtained that the quaternary complex  $[\text{EtOBa}(15\text{C}5)_2]^+$ , albeit substantially less reactive than the uncomplexed barium-bound ethoxide, is still more reactive than free ethoxide.

## Introduction

It has been widely recognized that anion properties (nucleophilicity and basicity) are deeply influenced by metal counterions<sup>1</sup> and, consequently, that addition of cation complexing agents can significantly alter rates and equilibria of reactions involving anionic species.<sup>2</sup>

The concept of anion activation upon addition of crown ethers and cryptands is well established.<sup>3,4</sup> It strictly applies to cases where free anions are more reactive than ion pairs and higher aggregates. Less common, yet well documented, are examples of cation-assisted reactions, where the cation-paired anion is more reactive than the free ion. Here cation capture by host ligands is believed to cause rate decrease through inhibition of cation participation.<sup>3,5</sup> A widely accepted mechanistic criterion is based on the idea that a rate decrease upon addition of cation complexing agents provides compelling evidence for a mechanism in which the metal cation plays a role as electrophilic catalyst.<sup>5,6</sup> Clear-cut examples of reactions where the metal counterion plays an unequivocal role as Lewis acid catalyst are provided by our studies of the influence of alkali and alkaline-earth metal ions on rates of basic methanolysis and ethanolysis of esters.<sup>7</sup> Our studies have revealed that in these reactions metal-bound alkoxide species are more reactive than free alkoxides, most likely on account of transition state stabilization via chelate structures having the form of a four-membered contact ion pair **I** or of the kinetically equivalent six-membered solvent shared ion pairs **II** and **III**.



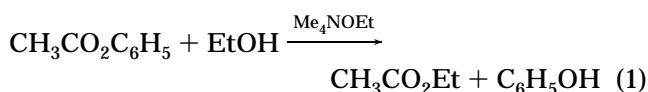
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We have now discovered a reaction system, namely, the reaction of barium ethoxide with phenyl acetate in ethanol, in which addition of the metal ion complexing agents 18-crown-6 (18C6), 15-crown-5 (15C5), and 12-crown-4 (12C4) does not result in the expected inhibition of cation participation. The results of this investigation are reported here and compared with the contrasting behavior observed with the 222 cryptate of barium ion.

## Results and Discussion

The  $\text{Me}_4\text{NOEt}$ -catalyzed ethanolysis of phenyl acetate (eq 1) is strictly first order in ester substrate and first order in  $\text{Me}_4\text{NOEt}$ . The previously determined<sup>8</sup> second-



order rate constant  $k_0 = 1.44 \pm 0.03 \text{ M}^{-1} \text{ s}^{-1}$  at 25.0 °C was reproduced with good precision by control experiments in the present work. Rate measurements carried out in the presence of excess 1.00 and 5.06 mM  $\text{Me}_4\text{NOEt}$  gave rate constant values of 1.41 and 1.43  $\text{M}^{-1} \text{ s}^{-1}$ , respectively. Solutions for rate measurements in the presence of barium ion were prepared by mixing equimolar amounts of  $\text{Ba}(\text{SCN})_2$  and  $\text{Me}_4\text{NOEt}$  immediately before use.<sup>9,10</sup> These solutions showed enhanced rates of ethanolysis of phenyl acetate relative to solutions containing  $\text{Me}_4\text{NOEt}$  alone. As shown in previous stud-

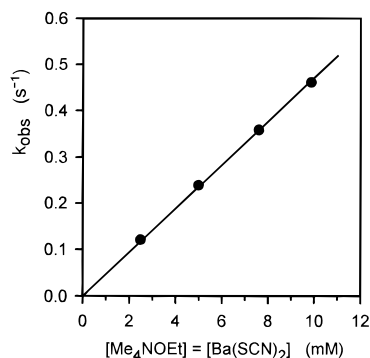
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(9) The thiocyanate salt was given preference over the bromide as a source of barium because mixtures of the former with  $\text{Me}_4\text{NOEt}$  showed a reduced tendency to yield a crystalline material on standing (see ref 10).

(10) Kraft, D.; Cacciapaglia, R.; Böhmer, V.; Abu El-Fadl, A.; Harkema, S.; Mandolini, L.; Reinhoudt, D. N.; Verboom, W.; Vogt, W. *J. Org. Chem.* **1992**, *57*, 826.



**Figure 1.** Kinetic data for the reaction of phenyl acetate with equimolar mixtures of  $\text{Me}_4\text{NOEt}$  and  $\text{Ba}(\text{SCN})_2$  in ethanol at  $25.0\text{ }^\circ\text{C}$  (data from Table 1, entries 1–4). From the slope of the regression line  $k_{\text{EtOBa}} = 48\text{ M}^{-1}\text{ s}^{-1}$ .

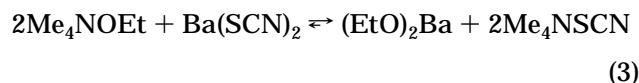
**Table 1. Pseudo-First-Order Rate Constants for the Reaction of Phenyl Acetate with Mixtures of  $\text{Me}_4\text{NOEt}$  and  $\text{Ba}(\text{SCN})_2$  in Ethanol at  $25.0\text{ }^\circ\text{C}$**

entry	$[\text{Me}_4\text{NOEt}]$ (mM)	$[\text{Ba}(\text{SCN})_2]$ (mM)	$k_{\text{obs}}$ ( $\text{s}^{-1}$ )
1	2.48	2.48	0.121
2	4.98	4.98	0.239
3	7.60	7.60	0.359
4	9.86	9.86	0.461
5	5.07	15.1	0.251
6	5.05	2.51	0.192
7	10.1	5.02	0.385

ies,<sup>8,10</sup> a barium-bound ethoxide species is quantitatively formed upon mixing (eq 2). This species, whose concen-



tration is stoichiometrically determined by that of the added reactants, behaves kinetically as a single species. This is clearly confirmed by the strict linearity of the plot of  $k_{\text{obs}}$  vs reactant concentration (Table 1, entries 1–4, and Figure 1), from which a second-order rate constant  $k_{\text{EtOBa}} = 48\text{ M}^{-1}\text{ s}^{-1}$  is obtained. This value is somewhat smaller than the value of  $65\text{ M}^{-1}\text{ s}^{-1}$  obtained for the ethanolysis of phenyl acetate catalyzed by a barium-bound ethoxide species prepared using  $\text{BaBr}_2$  as the source of barium, but under otherwise identical conditions.<sup>8</sup> It seems likely therefore, that the metal–ethoxide complex is significantly paired to the anion, either bromide or thiocyanate, contained in the added salt. Also consistent with the formulation of eq 2 is the finding that the reaction is insensitive to the amount of  $\text{Ba}(\text{SCN})_2$  exceeding the molar concentration of ethoxide (Table 1, entry 5 vs 2). On the other hand, cleavage of phenyl acetate in solutions in which the ethoxide/barium ratio is 2:1 (Table 1, entries 6 and 7) takes place with first-order specific rates, which are significantly higher than the values calculated for equimolar mixtures of  $\text{EtOBaSCN}$  and  $\text{Me}_4\text{NOEt}$ . It is apparent that 1 equiv of barium ion activates 2 equiv of ethoxide, which strongly suggests that extensive formation of the ion triplet  $(\text{EtO})_2\text{Ba}$  takes place (eq 3). If one assumes that ion

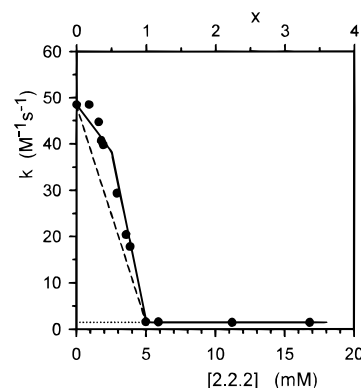


triplet formation is quantitative, the  $k_{\text{obs}}$  values listed in Table 1, entries 6 and 7, translate into a statistically corrected second-order rate constant  $k_{(\text{EtO})_2\text{Ba}} = 38\text{ M}^{-1}\text{ s}^{-1}$  for reaction of phenyl acetate with the ethoxide ion

**Table 2. Effect of Adding Cryptand 222 and 18C6, 15C5, and 12C4 Ethers to the Reaction of Phenyl Acetate with a 5.0 mM Equimolar Mixture of  $\text{Me}_4\text{NOEt}$  and  $\text{Ba}(\text{SCN})_2$  in Ethanol at  $25.0\text{ }^\circ\text{C}$ <sup>a</sup>**

[ligand] (mM)	$k$ ( $\text{M}^{-1}\text{ s}^{-1}$ )	[ligand] (mM)	$k$ ( $\text{M}^{-1}\text{ s}^{-1}$ )	[ligand] (mM)	$k$ ( $\text{M}^{-1}\text{ s}^{-1}$ )
222					
0.89	48.5	2.90	29.4	5.88	1.55
1.57	44.7	3.55	20.4	11.2	1.45
1.77	40.7	3.84	17.8	16.8	1.43
1.92	39.8	4.97	1.60		
18C6					
1.23	49.8	4.98	81.1	14.9	85.0
2.49	53.0	6.14	85.1	20.5	85.2
3.78	66.9	10.2	87.4		
15C5					
2.47	49.5	9.87	9.65	30.7	4.63
4.93	42.1	15.0	5.03	39.9	4.25
7.50	26.1	20.0	4.88	49.9	4.04
12C4					
2.54	59.0	12.2	50.1	49.7	13.3
4.97	62.4	20.3	34.8		
7.51	60.3	29.4	24.1		

<sup>a</sup> In the absence of additives  $k_{\text{EtOBa}} = 48\text{ M}^{-1}\text{ s}^{-1}$ .



**Figure 2.** Influence of added cryptand 222 (data from Table 2). The dashed line is based on eq 4 and the piece-wise full line is based on eqs 9–11. The horizontal dotted line represents the reactivity of free ethoxide.

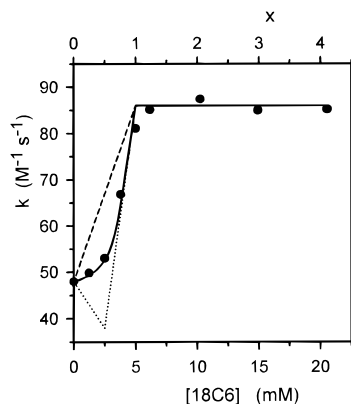
in the 2:1 complex. Comparison of this value with the values of 48 and  $65\text{ M}^{-1}\text{ s}^{-1}$  obtained for the species  $\text{EtOBaSCN}$  and  $\text{EtOBaBr}$ , respectively, shows that the reactivity of an  $\text{EtOBaX}$  species is influenced by the nature of X, but not to a dramatic extent.

**Influence of Cation-Complexing Agents.** Addition of a series of cation complexing agents including cryptand 222 and the crown ethers 18C6, 15C5, and 12C4<sup>11,12</sup> caused remarkable and largely unpredictable effects on rates of ethanolysis of phenyl acetate, as shown by the data listed in Table 2 and plotted in Figures 2–5. In all these experiments initial concentrations were as follows:  $[\text{PhOAc}] = 0.17\text{ mM}$ ;  $[\text{Me}_4\text{NOEt}] = [\text{Ba}(\text{SCN})_2] = 5.0\text{ mM}$ .

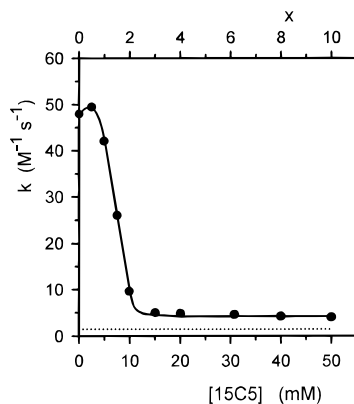
The only ligand showing the expected cation deactivation is cryptand 222 (Figure 2). Here, the reactivity drops upon addition of the ligand until the stoichiometric amount is added and eventually reaches a plateau value

(11) No binding data to barium ion in EtOH are available for these ligands in the extensive compilation published by Izatt and co-workers (ref 12), where the following  $\log K$  values in MeOH at  $25\text{ }^\circ\text{C}$  are reported: 2.2.2, 12.9; 18C6, 7.3; 15C5, 4.1 (1) and 2.6 (2); 12C4, 2.6 (1) and 2.4 (2). (1) and (2) refer to 1:1 and 2:1 ligand–metal complexes, respectively. It is assumed that the known data in MeOH can be taken as useful approximations for the unknown data in EtOH.

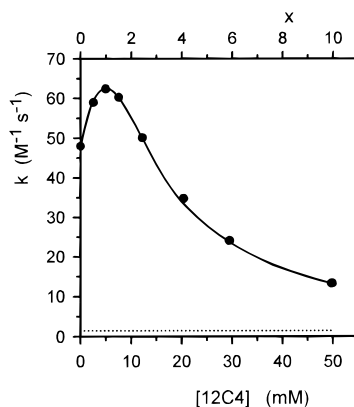
(12) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Breuning, R. L. *Chem. Rev.* **1991**, *91*, 1721.



**Figure 3.** Influence of added 18C6 (data from Table 2). The dashed line is based on eq 12, and the piece-wise dotted line is based on eqs 9 and 15.



**Figure 4.** Influence of added 15C5 (data from Table 2). The horizontal dotted line represents the reactivity of free ethoxide.



**Figure 5.** Influence of added 12C4 (data from Table 2). The horizontal dotted line represents the reactivity of free ethoxide.

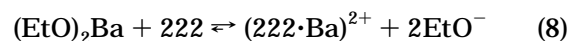
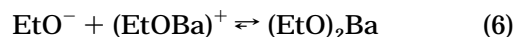
( $k_0 = 1.44 \text{ M}^{-1} \text{ s}^{-1}$ ) which is the same as that measured in the presence of  $\text{Me}_4\text{NOEt}$  alone. This value can be taken as a measure of the intrinsic reactivity of free ethoxide ion. It appears therefore that the barium cryptate behaves as a kinetically inert species,<sup>13</sup> which indicates that “through the window” interactions of the cryptated metal ion with the ethoxide reactant and with the anionic transition state are negligibly small. It is clear, however, that a situation in which the differential interaction of the cryptated barium ion with reactant and transition state happens to be exactly of the same

magnitude as that of the tetramethylammonium cation is a possibility that, albeit unlikely, cannot be ruled out.

It is worth noting that the reactivity drop upon ligand addition (Figure 2) does not follow the dashed line of eq 4 expected for a kinetic titration taking place according

$$k = k_{\text{EtOBa}} - (k_{\text{EtOBa}} - k_0)x \quad \text{if } 0 \leq x \leq 1 \quad (4)$$

to the simple process described by eq 5. In eq 4  $x$  is defined as the mole ratio of added ligand to barium. In the early part of the titration, the rate appears to be hardly sensitive to the addition of the cryptand. This is due to the fact that the ethoxide liberated during the first half-titration (eq 5) reacts with  $(\text{EtOBa})^+$  to give the ion triplet  $(\text{EtO})_2\text{Ba}$  (eq 6), whose statistically corrected reactivity is only slightly lower than that of  $(\text{EtOBa})^+$ .



The overall process is given in eq 7. Counterions of charged species are omitted henceforth for simplicity. In the second half-titration there is a steep reactivity drop because destruction of  $(\text{EtO})_2\text{Ba}$  takes place according to eq 8. On the basis of eqs 7 and 8, eqs 9–11 are easily derived. Figure 2 shows that data points fit the idealized rate profile given by the piecewise full line based on eqs 9–11 reasonably well.

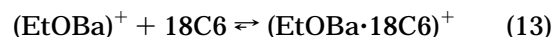
$$k = k_{\text{EtOBa}} - (k_{\text{EtOBa}} - k_{(\text{EtO})_2\text{Ba}})2x \quad \text{if } 0 \leq x \leq 0.5 \quad (9)$$

$$k = 2k_{(\text{EtO})_2\text{Ba}} - k_0 - (k_{(\text{EtO})_2\text{Ba}} - k_0)2x \quad \text{if } 0.5 \leq x \leq 1 \quad (10)$$

$$k = k_0 \quad \text{if } 1 \leq x \quad (11)$$

In the case of 18C6 (Figure 3) addition of the ligand causes a rate increase, until a plateau value ( $k_{\text{EtOBa}18\text{C6}} = 86 \text{ M}^{-1} \text{ s}^{-1}$ ) is reached when 18C6 is equimolar with respect to  $\text{EtOBaSCN}$ . This implies that the crown-complexed barium ion is still able to bind ethoxide to give the ternary complex  $(\text{EtOBa} \cdot 18\text{C6})^+$ , which is significantly more reactive than the uncomplexed ion pair  $(\text{EtOBa})^+$ . The rate increase in the region of  $x$  from 0 to 1 does not exhibit the linear dependence (eq 12) expected on the basis of a complete conversion of  $(\text{EtOBa})^+$  into  $(\text{EtOBa} \cdot 18\text{C6})^+$  (eq 13), shown as a dashed line in Figure 3.

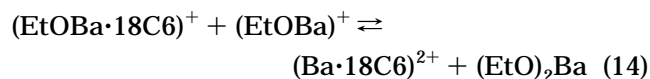
$$k = k_{\text{EtOBa}} + (k_{\text{EtOBa}18\text{C6}} - k_{\text{EtOBa}})x \quad \text{if } 0 \leq x \leq 1 \quad (12)$$



In the first half-titration  $k$  appears to be rather insensitive to the concentration of added ligand, but in the second half-titration a steep rate increase is observed. Since it seems very likely that binding of 18C6 to barium ion is complete under the reaction conditions,<sup>11</sup> the nonlinear shape of the titration plot provides unequivocal indication that the composition of the system in the titration experiment is not one in which the fraction of the crown-complexed metal-bound ethoxide species increases in proportion to the amount of added crown ether.

(13) Interestingly, the 222 cryptate of potassium ion has been reported to act as a catalyst in the reaction of ethoxide ion with *p*-nitrophenyl methanesulfonate in ethanol: Pregel, M. J.; Buncel, E. *J. Am. Chem. Soc.* **1993**, *115*, 10.

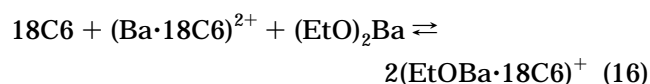
As a reasonable explanation of the observed results, we suggest that a certain amount of the  $(\text{EtOBa}\cdot 18\text{C6})^+$  species is transformed into  $(\text{EtO})_2\text{Ba}$  as shown by eq 14,



where two metal species compete for the common  $\text{EtO}^-$  ligand. That the equilibrium of eq 14 is not completely shifted to the right is clearly shown by the fact that the titration profile does not follow the piecewise dotted line of eq 9 in the first half-titration and eq 15 in the second half-titration (Figure 3). The actual shape of the titration

$$k = 2k_{(\text{EtO})_2\text{Ba}} - k_{\text{EtOBa}\cdot 18\text{C6}} + (k_{\text{EtOBa}\cdot 18\text{C6}} - k_{(\text{EtO})_2\text{Ba}})2x \quad \text{if } 0.5 \leq x \leq 1 \quad (15)$$

plot suggests a more balanced situation. In other words, addition of 18C6 up to 0.5 molar equiv transforms a reactive  $(\text{EtO})_2\text{Ba}$  species into a mixture of comparable amounts of more reactive  $(\text{EtOBa}\cdot 18\text{C6})^+$  and less reactive  $(\text{EtO})_2\text{Ba}$ , with the net result that modest changes of the overall reactivity are observed. But in the second half-titration a gradual transformation of the least reactive  $(\text{EtO})_2\text{Ba}$  into the most reactive  $(\text{EtOBa}\cdot 18\text{C6})^+$  takes place (eq 16), and consequently, a steep reactivity in-



crease is observed. The shape of the titration plot indicates that transformation of the initial  $(\text{EtO})_2\text{Ba}$  species into the ternary complex  $(\text{EtOBa}\cdot 18\text{C6})^+$  is virtually complete upon addition of 1 molar equiv of 18C6 ( $x = 1$ ).

A markedly different behavior is experienced by 15C5 (Figure 4). The rate profile shows an apparent insensitivity to addition of small amounts of ligand, but further addition causes a marked reactivity drop. The plateau value of  $4.1 \text{ M}^{-1} \text{ s}^{-1}$  reached when  $x > 2$  is substantially higher, however, than the second-order rate constant of  $1.44 \text{ M}^{-1} \text{ s}^{-1}$  for reaction of free ethoxide. Interpretation of these observations involves the formation of the ternary complex  $(\text{EtOBa}\cdot 15\text{C5})^+$ , which is presumably more reactive than  $(\text{EtO})_2\text{Ba}$  but involved in a ligand-exchange process analogous to that described in eq 14. The two factors appear to be closely balanced, with the net result of a substantial insensitivity to the addition of the crown ether in the initial portion of the profile. The steep reactivity drop caused by further addition of the ligand is due to the formation of the quaternary complex  $[\text{EtOBa}(15\text{C5})_2]^+$ , which is much less reactive than  $(\text{EtOBa}\cdot 15\text{C5})^+$  but still more reactive than free ethoxide. This interpretation is supported by the well-documented tendency of 15C5, not experienced by 18C6, to give stable 2:1 complexes with metal ions.<sup>11</sup> A striking feature emerging from the data is that the metal ion is still capable of assisting the attack of ethoxide ion on the ester carbonyl, in spite of its being sandwiched between two crown ether molecules. It is remarkable that the transition state of the latter reaction is a complex formed by no less than five species, namely, substrate ester, ethoxide nucleophile, metal ion, and two ligand molecules.

The reactivity profile for the 12C4 case (Figure 5) shares many features with the profile reported in Figure 4 for the 15C5 case. This is not surprising, as 12C4 is also known to form 2:1 complexes with metal ions,<sup>11</sup> albeit

of significantly lower stability than those formed by 15C5. Upon addition of 12C4 the rate increases until an  $x$  value of 1 is reached. This clearly indicates the formation of a more reactive ternary complex  $(\text{EtOBa}\cdot 12\text{C4})^+$ . Further addition of 12C4 causes the gradual conversion of the ternary complex into the less reactive quaternary complex  $[\text{EtOBa}(12\text{C4})_2]^+$ . No plateau is reached in the high 12C4 concentration region, on account of its being a much weaker binder than 15C5.

## Conclusions

The results reported in this work show that the barium ion-catalyzed ethanolysis of phenyl acetate exhibits the expected cation deactivation upon complexation when the barium is either sequestered by cryptand 222 or sandwiched between two crown ether ligands. However, rate enhancements are obtained upon formation of 1:1 complexes with 18C6, 12C4, and possibly, also with 15C5.<sup>14</sup> This does not necessarily imply that a crown-complexed barium ion binds to the transition state resembling the tetrahedral intermediate more strongly than uncomplexed barium. It simply means that the differential energy between transition state and reactant is (slightly) in favor of the reaction carried out in the presence of 1 mol equiv of crown ether. Our data do not allow a dissection of catalysis into reactant state and transition-state effects, but since it seems very likely that ion pairing is weakened by cation binding to a crown ether, the enhanced catalysis upon addition of 1 mol equiv of crown ether is essentially an initial state effect. In other words, cation binding to a crown ether destabilizes the barium ethoxide pair more strongly than the barium–(transition state) pair, with the net result that the activation free energy is decreased. The finding that a barium ion can be incorporated into a crown ether complex of defined geometry and still be catalytically active will be useful in the design and construction of supramolecular transacylation catalysts in which the catalytic site is provided by an alkaline-earth metal ion bound to a crown ether moiety.

## Experimental Section

**Materials.** Phenyl acetate was distilled under vacuum. Reagent-grade commercial samples of  $\text{Ba}(\text{SCN})_2 \cdot 3\text{H}_2\text{O}$ , cryptand 222, and crown ethers were used as received. Other materials, apparatus, and techniques were as reported previously.<sup>10</sup>

**Kinetics.** Reaction progress was monitored by following absorbance changes due to the release of phenoxide ion at  $\lambda = 300 \text{ nm}$ . All reactions were carried out under pseudo-first-order conditions with the base concentration *ca.* 30 times greater than substrate concentration. Absorbance readings spanning 8–15 half-lives were fitted to the integrated first-order eq (17) by means of a nonlinear least-squares procedure

$$(A_t - A_0) = (A_\infty - A_0)[1 - \exp(-k_{\text{obs}}t)] \quad (17)$$

in which  $A_\infty$  and  $k_{\text{obs}}$  were treated as adjustable parameters. Nonlinear least-squares calculations were carried out with the program SigmaPlot for Windows, 1.02 (Jandel Scientific). The error in  $k_{\text{obs}}$  is estimated to be not greater than  $\pm 3\%$ .

**Acknowledgment.** Financial contributions from MURST and from CNR, Progetto Strategico Tecnologie Chimiche Innovative are greatly acknowledged.

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(14) We have deliberately avoided the use of the expression "ligand-accelerated catalysis" (LAC), because the concept of LAC, as defined and thoroughly discussed by Sharpless and co-workers (ref 15) in the context of asymmetric reactions catalyzed by transition metals, is not strictly applicable to our system.

(15) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.