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Cyclophosphazenic Polypodands from Commercial Mixtures of Polyethylene Glycol Monoalkyl Ethers, "Brij": a Valid and Convenient Alternative to the Most Common Phase-Transfer Catalysts

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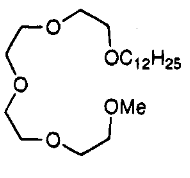
The catalytic activity of cyclophosphazenic polypodand **3b**, obtained as a crude mixture from the commercial Brij 30, was compared with that of the corresponding pure ligand in a number of solid−liquid (SL) and liquid−liquid (LL) phase-transfer reactions. The comparison was also extended to the commonly used catalysts **4**−**9** under the same conditions. The obtained results show that the crude mixture of **3b**, due to its excellent cation-binding properties, has a catalytic efficiency higher than that exhibited by the other ligands. Furthermore its catalytic activity is comparable to that of the much more expensive **3b**, in line with the very close complexation values found in both systems. For this reason the cheap and efficient crude mixture can be considered competitive with the most common phase-transfer catalysts, particularly under SL-PTC conditions.

Cyclophosphazenic polypodands **3a**−**c** have recently been synthesized from hexachlorophosphazene (**1**) and the appropriate polyethylene glycol monoalkyl ether **2a**−**c**, under solid−liquid phase-transfer catalysis (SL-PTC) conditions (Scheme 1).[1] This new class of "octopuslike" molecules is characterized by excellent cation-binding properties, even in solvents of low polarity. Stoichiometries of the complexes reach values of 12 and 17 moles of salt per mole of ligand for $NaOC_6H_5$ and LiI respectively.[1c−4] As expected, **3a**−**c** are found to be very efficient phase-transfer agents in a wide variety of PT reactions including nucleophilic substitution reactions, reductions, C- and O-alkylations, and oxidations. Their catalytic activity is much higher than that of open-chain analogues like the monopodand PEG **4** and also the SL-PT catalyst TRIDENT-1 (**6**).[1c,2]



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$PEG400Me_2$

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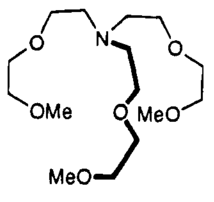

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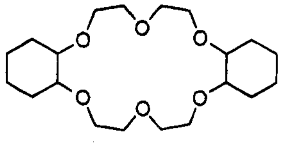

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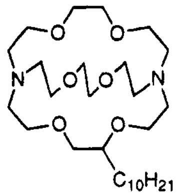

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Anion activation realized by these cyclophosphazenic polypodands, in particular by **3b** and **3c**, is comparable to that of perhydrodibenzo-18-crown-6 **7** (PHDB-18-crown-6).[3] Hence these ligands could be considered, in principle, a valid alternative to the more sophisticated cyclic systems.[3] Unfortunately, the use, on a large scale, of the catalysts **3a**−**c** is limited due to their high cost. As Table 1 shows, polypodand **3b** is in fact much more expensive than all the most common PT catalysts (quaternary onium salts, PEGs, crown ethers), its price being comparable to that of the lipophilic cryptand $[2.2.2,C_{10}]$ **8**.

In order to make these ligands more competitive we have realized the synthesis of **3b** (Scheme 1) starting from Brij 30, a commercially available mixture of the tetraethylene glycol monododecyl ether, much cheaper than **2b** (Table 1). The crude mixture of **3b** (hereinafter called **3b′**), obtained with yields ≥80%, has a cost much lower (about 400 folds) than that of the pure ligand, comparable with that of a typical quaternary ammonium salt like $Bu_4N^+Br^-$ (Table 1).

In this paper the complexing ability and catalytic activity of the crude mixture **3b′** have been compared with those of the pure polypodand **3b** in a number of typical SL and LL-PT reactions. The comparison was extended to the commonly used open-chain and cyclic catalysts **4**−**9** under the same conditions.

Results and Discussion

Complexation Extent of 3b, 3b′, 4−7 under SL-PTC Conditions. The complexing ability of the above

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0022-3263/94/1959-5059$04.50/0

Scheme 1. Synthesis of Cyclophosphazenic Polypodands 3a–c

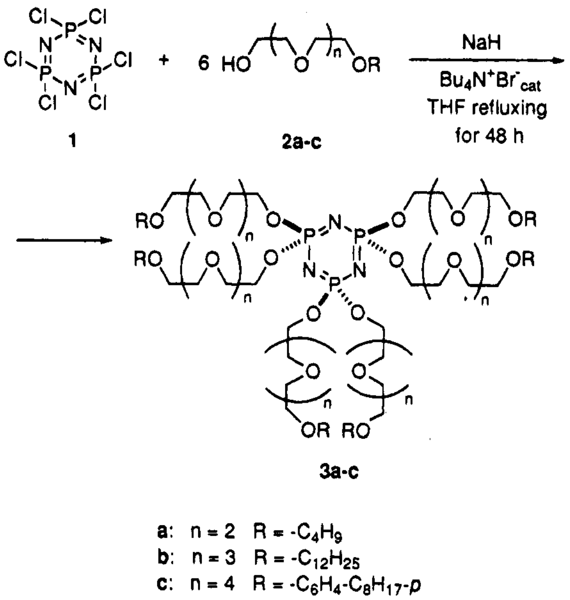

Table 1. Comparison of Cost (per unit of weight) for Polypodand 3b and Its Crude Mixture with Some Common Phase-Transfer Catalysts[a]

catalyst	cost[b]
Brij 30	0.57
$Bu_4N^+Br^-$	1
3b′	3[c]
TRIDENT-1 (**6**)	6
$PEG400Me_2$ (**5**)	13
PHDB-18-crown-6 (**7**)	73
2b	366
3b	1128[c]
[2.2.2,C_{10}] (**8**)	1770

[a] From Fluka and Aldrich catalogues. [b] Referred to $Bu_4N^+Br^-$. [c] These values have been obtained taking into account the commercial costs of the reagents and the relative yields, 60 and 80% for **3b** and **3b′** respectively.

Table 2. Complexation Extent[a,b] **under SL-PTC Conditions, at 60 °C**[c]

	ligand					
NaY	4	5	6	7	3b′	3b
NaI	0.2	0.6	0.95	0.95	3.3	4.0
NaBr	*d*	*d*	*d*	0.12	0.15	0.17
NaSCN	0.32	0.36	1.0	1.0	5.4	5.6
$NaOC_6H_5$	1.4	3.0	1.0	2.0	11	12

[a] Defined as complexed NaY mol/ligand mol. [b] Average of at least four determinations. The error in these values is estimated to be <10%. [c] A chlorobenzene solution (25 mL) of ligand (0.5–4 × 10^{-2} M) and 100 mol equiv of NaY, as solid phase. [d] Undetectable quantity.

catalysts was evaluated for a number of sodium salts NaY (Y = I, Br, SCN, OC_6H_5) by stirring a chlorobenzene solution of ligand with a molar excess (100 mol equiv) of salt, as solid phase, at 60 °C (Table 2).

The complexation extent, expressed as moles of complexed NaY per mole of ligand, was determined by potentiometric titration of the anion Y^- in the organic phase. As shown in Table 2 the values obtained increase markedly, changing from the simple monopodand PEG **4** up to polypodand **3b** in the order **4** ≈ **5** ≤ **6** ≤ **7** ≪ **3b′** ≤ **3b**.[6]

In particular it is worth noting that, for all the salts examined (Table 2), the data found for **3b** and **3b′** are comparable, with small differences in favor of the pure ligand, in the range 4–20%.

Table 3. Activity of Catalysts under SL-PTC Conditions in Reaction 1[a]

			reaction time[b] (h)				
X	Y^-	T (°C)	**3b**	**3b′**	**4**	**5**	**6**
OSO_2Me	I^-	60	0.7[c]	0.9	4	2.5	2.3[c]
Cl	I^-	80	20	25	200	150	–
Br	SCN^-	100	1.3[c]	1.3	10	3	2.5[c]

[a] A chlorobenzene solution (5 mL) of substrate (5 mmol), catalyst (0.25 mmol), and internal standard (2.5 mmol), with 25 mmol of NaY as solid phase. [b] Conversion ≥95%, by GLC analysis. [c] Reference 1c.

Catalytic Activity of 3b′ in Nucleophilic Substitution Reactions under SL-PTC Conditions. Comparison with 3b and Other Ligands 4–6. Catalytic activity of **3b′** was evaluated in typical nucleophilic substitution reactions (1) and compared with that exhibited, under the same conditions, by **3b** and other open-chain ligands **4–6** (Table 3).

$$n\text{-}C_8H_{17}X + NaY_{solid} \xrightarrow[C_6H_5Cl]{Lig_{(cat)}} n\text{-}C_8H_{17}Y + NaX_{solid} \quad (1)$$

X = OSO_2Me, Br, Cl
Y^- = I^-, SCN^-
Lig = **3b**, **3b′**, **4-6**

Reactions were all performed in a chlorobenzene–solid NaY (Y^- = I^-, SCN^-) two-phase system by using catalytic amounts (0.05 mol equiv) of ligand and a molar excess of inorganic salt with respect to the substrate. The reaction progress (up to 95–98% of conversion) was followed via GLC analysis of the organic phase by using an appropriate internal standard.

As shown in Table 3, **3b′** always has a catalytic activity comparable with that of the much more expensive **3b**. In fact the reaction times are of the same order in all cases. The data are in agreement with the very close values of complexation found (Table 2).

These high values also explain the better catalytic efficiency of such polypodands with respect to the other ligands **4–6** (Tables 2 and 3).

Catalytic Activity of 3b′ in Alkylation Reactions under LL-PTC Conditions. Comparison with Ligands 3b, 4–7. The C-alkylation of benzyl methyl ketone with *n*-butyl bromide was performed in the chlorobenzene–50% aqueous NaOH two-phase system at room temperature in the presence of catalytic amounts (0.05 mol equiv) of ligand (**3b**, **3b′**, or **4–7**) and with a 1:1.5 molar ratio ketone/alkyl bromide (reaction 2). The reaction progress, for conversion ≥95%, was monitored

$$C_6H_5CH_2COCH_3 + n\text{-}C_4H_9Br \xrightarrow[C_6H_5Cl\text{-}\ 50\%_{aq}\ NaOH,\ r.t.]{Lig_{(cat)}} C_6H_5CH(C_4H_9)COCH_3 + NaBr \quad (2)$$

Lig = **3b**, **3b′**, **4-7**

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(6) The only exception is represented by the sodium phenoxide for which the sequence becomes: **6** < **4** < **7** < **5** ≪ **3b′** ≤ **3b**.

Table 4. Catalytic Activity in the Alkylation Reaction 2 under LL-PTC Conditions at Room Temperature[a]

	catalyst					
	3b	**3b′**	**4**	**5**	**6**	**7**
reaction time[b] (h)	4.5	5.5	73	10	8	1.2

[a] A chlorobenzene solution (1 mL) of benzyl methyl ketone (1 mmol), *n*-butyl bromide (1.5 mmol), catalyst (0.05 mmol), dodecane (0.5 mmol), and 50% aqueous NaOH (1 mL), at rt. [b] Conversions ≥98%, by GLC analysis.

Table 5. Catalytic Efficiency and Anion Activation in the S_N2 Reaction (1) $MeSO_3^-/I^-$ under SL-PTC Conditions at 60 °C[a]

catalyst	$10^2[I^-]$ in the organic phase (M)	10^5k_{obsd}[b] (s^{-1})	k_{rel}	10^3k[c] ($M^{-1}\ s^{-1}$)	k_{rel}
3b	8.0	86[d]	13	10.7	1.3
3b′	6.6	71	11	10.7	1.3
PHDB-18-C-6 (**7**)	1.9	42	6.5	22[e]	2.6
[2.2.2, C_{10}] (**8**)	2.0	26.5	4	14.6[f]	1.7
$(C_6H_{13})_4N^+I^-$ (**9**)	2.0	17	2.6	8.5	1
PEG **4**	0.32	6.4[d]	1	20	2.3

[a] A chlorobenzene solution (10 mL) of substrate (0.2 M), catalyst (0.02 M), and internal standard (0.1 M) with 20 mmol of NaI. [b] Average of at least two determinations. The error in these values is estimated to be 5%. [c] Defined as $k_{obsd}/[I^-]$. [d] Data from ref 1c. [e] In the case of KI, $k = 10.7 \times 10^{-3}$ ($M^{-1}\ s^{-1}$) (from ref 3). [f] $k = 14.5 \times 10^{-3}$ ($M^{-1}\ s^{-1}$) in the case of KI.

by GLC analysis of the organic phase with respect to dodecane as an internal standard (Table 4).

Also in this case catalytic efficiency of the crude mixture is comparable to that of the pure ligand, as indicated in Table 4 by the corresponding reaction times (5.5 and 4.5 h, respectively).

As expected on the basis of the different catalyst topology, catalytic activity of the other ligands **4**–**7** spans a wide range of values.[7] Whereas the crown ether PHDB-18-C-6 **7** results in complete conversion after only 1.2 h, more than three days are necessary in the presence of the simple monopodand **4** (Table 4).

Kinetics of Nucleophilic Substitution Reactions under SL-PTC Conditions. The rates of displacement of the methanesulfonic group in *n*-octyl methanesulfonate by NaI (reaction 1) were measured in the presence of the catalysts **3b′** and **7**–**9** as previously described[1c] for ligands **3b** and **4** (see Experimental Section). In all cases the reactions obey a pseudo-first-order kinetic eq 3 up to at least two half-life times. The observed (k_{obsd}, s^{-1}) and

$$\text{rate} = k_{obsd}[\text{substrate}] \qquad (3)$$

the second-order ($k = k_{obsd}/[I^-]$, $M^{-1}\ s^{-1}$) rate constants are reported in Table 5.

The observed rate constants (k_{obsd}) follow the order: polypodands > crown ether > cryptand > quaternary salt > monopodand. This anomalous trend is largely determined by the catalyst complexing ability, particularly high in the case of polypodands **3b** and **3b′** (Table 2). These "many-armed" ligands have a catalytic activity 11–13 times higher than that exhibited by the corresponding monopodand PEG **4**, clear evidence of a cooperative effect of the six polyethereal chains in the complexation process.

However, by comparing the second-order rate constants that take into account the actual concentration of nucleophile (I^-) in the organic phase,[9] we observe that the highest values are obtained with ligands **4**, **7**, and **8**, in the order: crown ether ≈ PEG > cryptand. As expected on the basis of their relative ability of cation–anion separation, cryptates (that realize the best model of solvent-separated ion pair) should on the contrary be the most reactive.[3,8a,c,10,11] This apparent discrepancy can most likely be explained by assuming for crown ether **7** and PEG **4** a possible involvement of the cation ("electrophilic catalysis") in the activation process of reaction 1. In fact, in the complexes of **4** and **7** the metal cation can still interact with the substrate, thus favoring the departure of the leaving group. This is less likely, on the contrary, with cryptates of **8**, where the metal cation is fully sequestered in the cavity of the ligand. Two experimental facts support this hypothesis: (1) the decrease in rate constant changing from Na^+ to K^+ observed in the case of crown ether **7** (Table 5, footnote e); (2) the independence of the nature of the metal cation found with cryptand **8** (Table 5, footnote f).[12]

Conclusions

The cyclophosphazenic polypodand **3b′** obtained, in high yields, as a crude mixture from the commercially available Brij 30 has a complexing ability and catalytic activity comparable with those of the much more expensive pure **3b**. The low cost, similar to that of a common quaternary onium salt, combined with an excellent catalytic efficiency, make the ligand **3b′** competitive with the most traditional phase-transfer agents, especially under SL-PTC conditions.

Experimental Section

General Methods. Potentiometric titrations were carried out with a Metrohm 670 Titroprocessor by using silver or glass and calomel electrodes, this last isolated with a potassium sulfate bridge. ^1H NMR spectra were performed on a Bruker AC 300 spectrometer by using tetramethylsilane as internal standard. ^{31}P NMR spectra were recorded on a Varian XL 200 spectrometer using 85% H_3PO_4 as an external reference. GC data were obtained with an Alltech RSL-150 column (10 m × 0.35 mm polydimethylsiloxane, 0.25 μm thickness) or Superox II column (10 m × 0.35 mm polyethylene glycol, 0.25 μm thickness).

Materials and Solvents. Inorganic salts were Analar grade commercial products, used without further purification and kept in a dessicator; C_6H_5ONa was prepared according to the literature.[13] *n*-Butyl bromide, *n*-octyl bromide, *n*-octyl chloride, hexachlorophosphazene (**1**), and benzyl methyl ketone were commercially available compounds used as purchased; *n*-octyl methanesulfonate, bp 112–114 °C (2 mm) n^{20}_D 1.4398, was prepared according to the literature [lit.[14] bp 110–114 °C

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[7] These results are mainly determined by two factors: (i) the quantity of carbanion present in the organic phase; (ii) the anion activation induced by the catalyst. As it is well known[8] they are maximized at the same time by cyclic ligands like PHDB-18-C-6 **7**.

(8) For general reviews see *inter alia:* (a) Montanari, F.; Landini, D.; Rolla, F. *Top. Curr. Chem.* **1982**, *101*, 147. (b) Gokel, G. W. Crown Ethers and Cryptands. Monographs in *Supramolecular Chemistry*; Stoddart J. F., Ed.; University of Birmingham: U.K., 1991. (c) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; Verlag Chemie: Weinheim, New York, 1993.

(9) In all cases the observed rate constants (k_{obsd}) are linearly related to the concentration of the nucleophile in the organic phase, as previously found for **3b** and **7**.[3]

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(2 mm), $n^{20}{}_{D}$ 1.4392]. $(C_6H_{13})_4N^+I^-$ (**9**), PHDB-18-crown-6 (**7**), [2.2.2,C_{10}] (**8**), PEG400Me$_2$ (**5**), and tris(3,6-dioxaheptyl)amine, "TRIDENT-1" (**6**), are commercially available products.

Tetraethylene glycol methyl dodecyl ether, PEG **4**, was obtained as previously described.[1c] The synthesis of cyclophosphazenic polypodand **3b** was realized according to an already reported procedure:[1b] $n^{24}{}_{D}$ 1.4605; ^1H NMR ($CDCl_3$) δ 0.70–1.50 (m, 138 aliphatic H), 3.28–4.16 (m, 108 ethereal H); ^{31}P NMR ($CDCl_3$) δ 19.45 [s, P(OR)$_2$]. Anal. Calcd for $C_{120}H_{246}N_3O_{30}P_3$: C, 62.55; H, 10.76; N, 1.82. Found: C, 62.50; H, 10.80; N, 1.75.

Brij 30 used for the synthesis of cyclophosphazene **3b′** was a commercially available mixture utilized as such: $n^{22}{}_{D}$ = 1.4527; ^1H NMR ($CDCl_3$) δ 0.75–1.62 (m, aliphatic H), 3.3–3.75 (m, ethereal H). The ratio of the relative intensities of the peaks aliphatic H/ethereal H is 1.33 instead of 1.28 for $C_{12}H_{25}(OCH_2CH_2)_4OH$. For the sake of comparison, the physical and spectroscopic data of the commercially available pure tetraethylene glycol dodecyl ether (**2b**) are: $n^{22}{}_{D}$ = 1.4519; ^1H NMR ($CDCl_3$) δ 0.74–1.60 (m, 23 aliphatic H), 3.25–3.74 (m, 18 ethereal H).

Synthesis of Cyclophosphazene 3b′. To a stirred suspension of NaH (8 g, 0.33 mol) in anhyd THF (50 mL) was added a solution of the commercially available Brij 30 (main component tetraethylene glycol dodecyl ether (**2b**) 50.76 g, 0.14 mol) and $Bu_4N^+Br^-$ (1 g, 0.0031 mol) in THF (150 mL) dropwise and the mixture refluxed for 6 h. To this reaction mixture a THF solution (50 mL) of the hexachlorophosphazene (**1**) (4.9 gr, 0.014 mol) was added over 30 min and then refluxed for 2 days. The precipitated NaCl was filtered off and washed with CH_2Cl_2. The combined organic layers were evaporated under reduced pressure. The oily residue was purified by column chromatography (silica gel) at first using CH_2Cl_2 and CH_2Cl_2/MeOH (80:1) as eluants to remove the excess of Brij 30 and then CH_2Cl_2/MeOH (10:1) to afford 25.8 g of **3b′** as a pale yellow oil (80%): $n^{18}{}_{D}$ = 1.4663; ^1H NMR ($CDCl_3$) δ 0.75–1.75 (m, aliphatic H), 3.20–4.30 (m, ethereal H). The ratio of the relative intensities of the peaks aliphatic H/ethereal H is 1.16 instead of 1.28 for $C_{120}H_{246}N_3O_{30}P_3$: ^{31}P NMR ($CDCl_3$) δ 19.44 [s, P(OR)$_2$]. Anal. Calcd (see **3b** above). Found: C, 62.81; H, 11.26; N, 1.65.

Commercial chlorobenzene was used without further purification; for the kinetic determinations it was carefully purified and dried with standard methods.[15]

General Procedure for the Reactions under SL- and LL-PTC Conditions, the Kinetic Measurements, and the Complexation Extent. The apparatus and the procedures used were as described in previously reported papers.[1c,3]

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