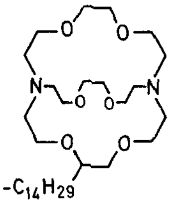
Phase-Transfer Catalysts: Synthesis and Catalytic Activity of a Tricyclohexyl[2.2.2]cryptand (Perhydrotribenzohexaoxadiaza[8.8.8]eicosane)

Dario Landini, Fernando Montanari, Franco Rolla*

Centro C.N.R. e Istituto di Chimica Industriale dell'Universita', Via C. Golgi 19, I-20133 Milano, Italy

Activation of anions through separation of ion-pairs in organic solvents of low polarity can be best realized by inclusion of salts in azamacrobicyclic polyethers (cryptands), in which the cation is completely surrounded by the ligand inside a tridimensional cavity having about a 1.0 nm diameter[1,2]. Cryptands, e.g. **1**, bearing long alkyl chains which afford a sufficiently high lipophilic character, are very efficient phase-transfer catalysts[3,4,5].

It was important to know if a larger separation between cation and anion in these systems is accompanied by an increase of their catalytic activity. For this reason we have prepared the tricyclohexyl[2.2.2]cryptand (**2**), in which three symmetrically disposed cyclohexane rings increase the size of the ligand.



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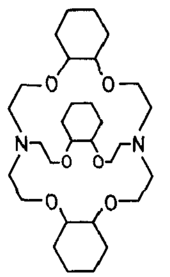

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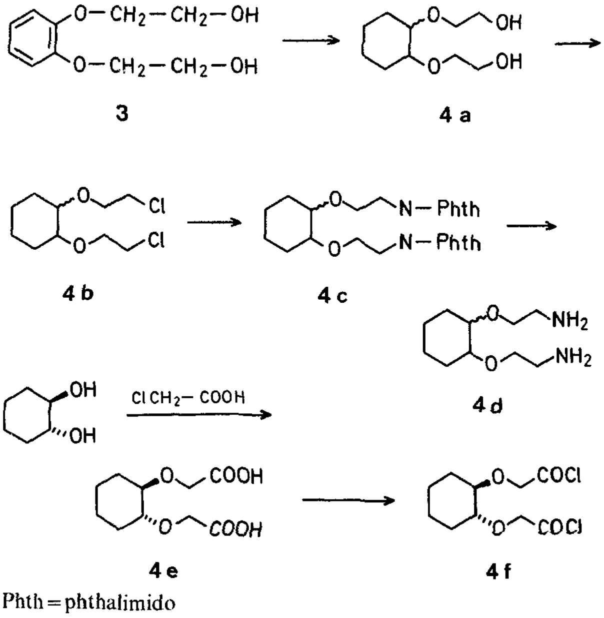
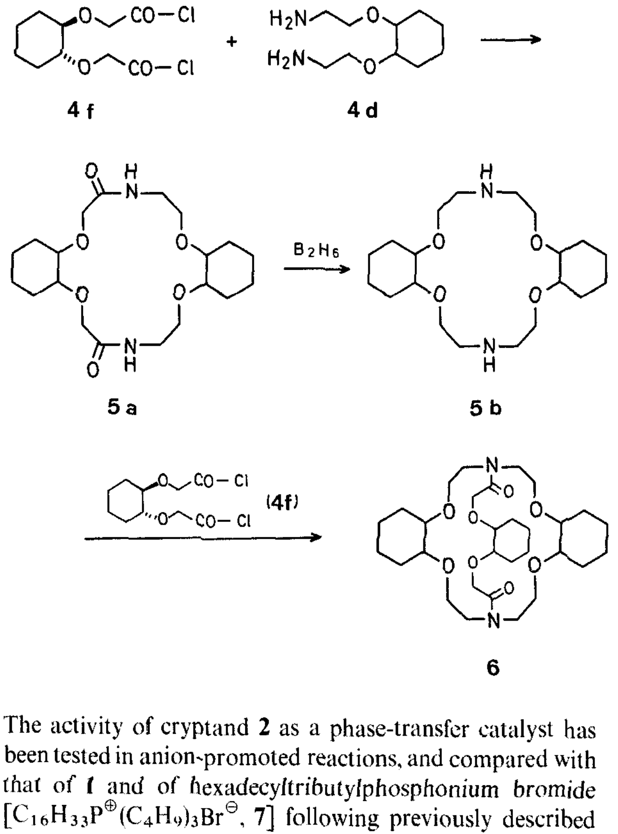
Alkaline condensation of pyrocatechol with 2-chloroethanol afforded the 1,2-bis[2-hydroxyethoxy]benzene (**3**) which, by catalytic hydrogenation in the presence of ruthenium on alumina, gave the corresponding cyclohexane derivative (**4a**), as a mixture of the two possible diastereoisomers. Through chloride (**4b**) and subsequent Gabriel synthesis, **4a** was converted into diamine (**4d**). By reaction of *trans*-1,2-cyclohexanediol with monochloroacetic acid, dicarboxylic acid (**4e**) was obtained, and from this the dichloride (**4f**).



Phth = phthalimido

Condensation of **4f** with **4d** under high dilution conditions afforded the cyclic diamide **5a**, which was reduced with diborane to the corresponding diamine **5b**. The latter was condensed again with **4f** in high dilution conditions to give the bicyclic diamide **6**, which was then reduced with diborane to the diazamacrobicyclic polyether **2**, as a mixture of diastereoisomers[6]. Attempts of preparing **5b** by reduction of the corresponding aromatic diamide, obtained from pyrocatechol according to a scheme similar to that followed for **5a**, failed.



The activity of cryptand **2** as a phase-transfer catalyst has been tested in anion-promoted reactions, and compared with that of **1** and of hexadecyltributylphosphonium bromide [$C_{16}H_{33}P^{\oplus}(C_4H_9)_3Br^{\ominus}$, **7**] following previously described procedures (see Table)[7].

In Br/J and Br/CN substitutions in octyl bromide, the catalytic activity of cryptand **2** is 1.5–2 fold higher than that of **1**, which, as already known[3,4], is more efficient than quaternary salt **7**. In contrast **1** is more active than **2** in the reduction of 2-octanone to 2-octanol with boranate ion, and in the butylation of benzyl methyl ketone in alkaline medium, **2** is more efficient than **7**.

Variations of relative reactivities of **1** and **2** could depend on different stability constants of cryptates and on different partition and selectivity coefficients of anions. However, it has been found[8] that in the Br/J exchange reaction catalyzed by **1**, the latter remains entirely in the organic phase as cryptate $[K^{\oplus} \subset 1]J^{\ominus}$[9]. Therefore it seems reasonable to assume that, at least in this case, the higher catalytic activity of **2** is to be attributed to an enhanced nucleophilicity of $J^{\ominus}$, due to its increased distance from the cationic center.

1,2-Bis[2-hydroxyethoxy]benzene (3):

To a solution of pyrocatechol (55 g, 0.5 mol) and sodium hydroxide (50.5 g, 1.2 mol) in ethanol (500 ml) 2-chloroethanol (96 g, 1.2 mol) is added in 15 min, and the mixture is refluxed for 20 h under nitrogen. The solvent is removed, the resultant oil is dissolved in chloroform (1.5 l), and is washed with aqueous sodium hydroxide and water. Evaporation of the solvent affords **3**; yield: 64 g (75%); m.p. 78–80° (from benzene/petroleum ether).

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$C_{10}H_{14}O_4$ calc. C 60.60 H 7.12
(198.2) found 60.66 7.16

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.75$–4.20 (m, 10H); 6.90 ppm (s, 4H).

Diastereomeric 1,2-Bis[2-hydroxyethoxy]cyclohexanes (4a):
Compound **3** (19.8 g, 0.1 mol) in ethanol (80 ml) is hydrogenated on 5% Ru/Al_2O_3 (1 g) at 80 atm and 100° for 5 h to give **4a** as an oily mixture of the two diastereoisomers; yield: 19.7 g (97%); $n_D^{23} = 1.4735$; that is used as such. A distilled sample has b.p. 144–146°/4 torr; $n_D^{22} = 1.4792$.

$C_{10}H_{20}O_4$ calc. C 58.80 H 9.87
(204.3) found 58.60 9.94

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.00$–2.10 (m, 8H), 3.40–3.85 ppm (m, 12H).

1,2-Bis[2-chloroethoxy]-cyclohexanes (4b):
To a solution of **4a** (20.4 g, 0.1 mol) in dry pyridine (15.8 g, 0.2 mol) thionyl chloride (31.7 g, 0.26 mol) is added under stirring at 0° in 30 min. The mixture is refluxed for 3 h, poured in to ice/water, extracted with ether, washed with 10% aqueous hydrochloric acid and water, and distilled. Pure **4b** is obtained; yield: 19.1 g (79%); b.p. 112–114°/3 torr; $n_D^{22} = 1.4822$.

$C_{10}H_{18}Cl_2O_2$ calc. C 49.80 H 7.52
(241.2) found 49.98 7.68

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.00$–2.10 (m, 8H); 3.38–3.95 ppm (m, 10H).

1,2-Bis[2-phthalimidoethoxy]cyclohexanes (4c):
A toluene solution (250 ml) of **4b** (24.1 g, 0.1 mol) and hexadecyltributylphosphonium bromide (5.08 g, 0.01 mol), and solid potassium phthalimide (64.9 g, 0.35 mol) are refluxed overnight and worked-up as previously reported[10] to give **4c**; yield: 41.6 g (90%); m.p. 86–90°; after crystallization from isopropanol it has m.p. 89–91°.

$C_{26}H_{26}N_2O_6$ calc. C 67.51 H 5.67 N 6.06
(462.5) found 67.60 5.58 6.04

^{1}H-N.M.R. ($CDCl_3$): $\delta = 1.00$–1.95 (m, 8H); 3.30–3.65 (m, 2H); 3.68–3.82 (t, 8H); 7.60–7.95 ppm (m, 8H).

1,2-Bis[2-aminoethoxy]cyclohexanes (4d):
A solution of **4c** (46.2 g, 0.1 mol) and hydrazine hydrate (12.0 g, 0.24 mol) in ethanol (1.25 l) is refluxed for 3 h, then cooled at 0°, and acidified (pH 1) with concentrated hydrochloric acid (50 ml). The mixture is refluxed again for 30 min, and the *N,N*-phthaloylhydrazine filtered off. The solvent is removed, the residue dissolved in water (500 ml), filtered, and the solution evaporated to dryness. The obtained oil is dissolved in methanol (400 ml) and basified (pH 14) with sodium methoxide. Distillation of solvent gives a syrup, which is extracted with boiling dichloromethane. Filtration and evaporation gives **4d** as an oil; yield: 12.0 g (60%).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.85$–2.12 (m, 8H); 1.48 (s, br, 4H); 2.70–2.95 (t, 4H); 3.28–3.70 ppm (m, 6H).

The mixture of the diastereomeric dipicrates has m.p. 150–170° (from ethanol).

$C_{22}H_{28}N_8O_6$ calc. C 40.00 H 4.27 N 16.97
(660.5) found 39.91 4.20 16.81

***trans*-1,2-Cyclohexanediyldioxydiacetic Acid (4e):**
trans-Cyclohexane-1,2-diol[11] (11.6 g, 0.1 mol), potassium *t*-butoxide (61.7 g, 0.55 mol), and dry *t*-butanol (350 ml) are refluxed with stirring for 30 min. A solution of chloroacetic acid (18.9 g, 0.2 mol) in *t*-butanol (150 ml) is added in 45 min and refluxing and stirring are continued overnight. The mixture is poured into ice/water, *t*-butanol removed in vacuo, and the resultant solution is extracted with chloroform. The aqueous phase, acidified with concentrated hydrochloric acid (pH 0) is evaporated. The solid is extracted with boiling chloroform and the solvent evaporated. Crystallization of the residue from ethyl acetate affords **4e**; yield: 5.5 g (24%); m.p. 115–117°.

$C_{10}H_{16}O_6$ calc. C 51.32 H 6.89
(232.2) found 51.40 6.90

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.90$–2.50 (m, 8H); 3.02–3.55 (m, 2H); 4.12–4.30 (d, 4H); 8.54 ppm (s, br, 2H).

***trans*-1,2-Cyclohexanediyldioxydiacetyl Dichloride (4f):**
This is prepared in a quantitative yield via reaction of **4e** with oxalyl chloride according to a general procedure[12], and used as such.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.90$–2.33 (m, 8H); 3.17–3.52 (m, 2H); 4.52–4.66 ppm (d, 4H).

The corresponding diamide **4g**, has m.p. 130.5–131.5° (from dimethoxyethane).

$C_{10}H_{18}N_2O_4$ calc. C 52.16 H 7.88 N 12.17
(230.3) found 52.33 7.95 12.05

Macrocyclic Diamides (5a):
Compounds **4d** (39.4 g, 0.19 mol) in dry benzene (700 ml) and **4f** (26.9 g, 0.1 mol) in dry benzene (700 ml) are simultaneously, added to dry benzene (1.6 l) under high dilution conditions[12]. The crude product is purified by column chromatography (neutral alumina, chloroform as eluent) to give **5a**; yield: 26.0 g (66%); m.p. 93–96° (from benzene/petroleum ether).

$C_{20}H_{34}N_2O_6$ calc. C 60.28 H 8.60 N 7.03
(398.5) found 60.02 8.57 6.93

^{1}H-N.M.R. ($CDCl_3$) spectrum shows the presence of two diastereoisomers: $\delta = 0.82$–2.25 (m, 16H); 2.63–4.00 (m, 12H); 3.95–4.22 (four s, 4H); 7.50–8.29 ppm (m, 2H).

Macrocyclic Diamines (5b):
Product **5a** (3.98 g, 0.01 mol) in dry tetrahydrofuran (26 ml) at 0° is reduced with diborane gas according to the usual procedure[13]. After hydrolysis and removal of the solvent in vacuo, the residue is extracted with boiling chloroform and the solution dried over molecular sieves. Evaporation, stirring of the residue with 9 normal hydrochloric acid/tetrahydrofuran (1:1, 50 ml) for 1 h at room temperature, and evaporation in vacuo at 80° gibes **5b** hydrochloride. Methanol (50 ml) is added and the mixture is basified with sodium methoxide. Remotion of methanol and extraction with dichloromethane affords **5b** as an oil; yield: 3.11 g (85%).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 0.82$–1.93 (m, 16H); 2.33 (s, br, 2H); 2.57–3.00 (t, 8H); 3.00–3.30 (m, 4H); 3.40–3.78 ppm (t, 8H).

The mixture of the diastereomeric dipicrates has m.p. 180–183° (from ethanol).

$C_{32}H_{44}N_8O_{18}$ calc. C 46.37 H 5.35 N 13.52
(828.7) found 46.00 5.43 13.15

Table. Influence of the catalyst on nucleophilic reactions carried out under phase-transfer conditions

Substrate[a]	Reagent[b]	Catalyst[c]	Temperature	$t_{1/2}$[d] (min)
n-C_8H_{17}—Br	KJ[e]	2	60°	30
		1	60°	45
		7	60°	90
	KCN[e]	2	60°	22
		1	60°	45
		7	60°	70
n-C_6H_{13}—CO—CH_3	KBH_4[f]	2	20°	285
		1	20°	120
		7	20°	450
C_6H_5—CH_2—CO—CH_3	n-C_4H_9Br[g]/ NaOH[h]	2	20°	25
		1	20°	16
		7	20°	54

[a] Benzene was used as solvent in the borohydride reductions otherwise no solvent was used for the substrate.
[b] Saturated aqueous solution.
[c] 0.01 mol-equiv.
[d] By G.L.C. analysis.
[e] 5 mol-equiv.
[f] 1.5 mol-equiv.
[g] 1.1 mol-equiv.
[h] 3 mol-equiv as 50% aqueous solution.

Macrobicyclic Diamides (6):

Products **5b** (3.70 g, 0.01 mol) in dry benzene (450 ml) and **4e** (3.90 g, 0.0145 mol) in dry benzene (450 ml) are simultaneously added to a solution of triethylamine (2.63 g, 0.026 mol) in dry benzene (900 ml) in 8 h at room temperature according to a general described procedure[12]. The crude product is chromatographed (neutral alumina, chloroform as eluent) to give **6** as a mixture of diastereoisomers; yield: 3.20 g (56%); m.p. 98–108° (from petroleum ether).

$C_{30}H_{50}N_2O_8$	calc.	C 63.58	H 8.89	N 4.94
(566.7)	found	63.28	8.78	4.84

^{1}H-N.M.R. ($CDCl_3$): δ=0.78–2.50 (m, 24H); 2.67–3.38 (m, 22H); 3.97–4.70 ppm (m, 4H).

Perhydrotribenzohexaoxadiaza[8.8.8]eicosanes (2):

Product **6** (1.13 g, 0.002 mol) in dry tetrahydrofuran (11 ml) is reduced with diborane gas to give **2** as an oil; yield: 1.02 g (95%).

$C_{30}H_{54}N_2O_6$	calc.	C 66.88	H 10.10	N 5.20
(538.8)	found	66.90	10.33	4.98

^{1}H-N.M.R. ($CDCl_3$): δ=0.68–2.23 (m, 24H); 2.42–3.06 (m, 12H); 2.97–3.33 (m, 6H); 3.33–4.09 ppm (m, 12H).

M.S.: m/e=538 (M^+).

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[1] J. M. Lehn, *Structure and Bonding* Vol. 16, Springer Verlag, *Berlin, 1973, p. 1 ff.*

[2] J. J. Christensen, D. J. Eatough, R. M. Izatt, *Chem. Rev.* **74**, 351 (1974).

[3] M. Cinquini, F. Montanari, P. Tundo, *J. Chem. Soc. Chem. Commun.* **1975**, 393.

[4] M. Cinquini, F. Montanari, P. Tundo, *Gazz. Chim. Ital.* **107**, 11 (1977).

[5] D. Clement, F. Damm, J. M. Lehn, *Heterocycles* **5**, 3903 (1977).

[6] They are; *trans, trans, trans* (in phase); *trans, trans, trans* (out of phase); *trans, trans, cis* (in phase); *trans, trans, cis* (out of phase).

[7] D. Landini, A. M. Maia, F. Montanari, F. M. Pirisi, *Gazz. Chim. Ital.* **105**, 863 (1975).

[8] Unpublished data from this laboratory.

[9] The mathematical sign of inclusion $K^{\oplus} \subset \mathbf{1}$ (**1** includes $K^{\oplus}$) is used to designate inclusion complexes[1].

[10] D. Landini, F. Rolla, *Synthesis* **1976**, 389.

[11] A. Roebuck, H. Adkins, *Org. Synth. Coll. Vol.* 3, 217 (1955).

[12] B. Dietrich, J. M. Lehn, J. P. Sauvage, J. Blousat, *Tetrahedron* **29**, 1029 (1973).

[13] G. Zweifel, H. C. Brown, *Org. React.* **13**, 24 (1963).

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