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Crown Ethers as New Catalysts in the Highly Regioselective Halogenative Cleavage of Epoxides with Elemental Halogen

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The regioselective ring opening halogenation of some epoxides using elemental iodine and bromine in the presence of a series of new synthetic macrocycle diamides and also dibenzo-18-crown -6, 18-crown-6, and aza-18-crown-6 has been studied. The epoxides were subject to cleavage by elemental halogen (I_2 and Br_2) in the presence of these catalysts under mild reaction conditions in various aprotic solvents. In this study, reagents and conditions have been discovered with which the individual halohydrins can be synthesized in high yield and with more than 95% regioselectivity. The results can be discussed in terms of a four-step mechanism: (1) formation of a charge-transfer complex between catalyst and halogen, (2) release of halogen nucleophile from the complex, (3) reaction of the active nucleophile at the less sterically-hindered site in the epoxide, and (4) regeneration of catalyst. The major advantages of this method are high regioselectivity, simple regeneration of catalyst and its reuse through several cycles without a decrease in activity, and ease of workup of the reaction.

Introduction

There is a continued interest in the regioselective ring opening of oxiranes to the corresponding vicinal halohydrins. Although a variety of new and mild procedures to effect this transformation have been reported, most of them have some limitations.[1] Methods based upon hydrogen halides are not considered appropriate because of the formation of some unwanted byproducts and low regioselectivity.[2] Ring opening of unsymmetrically substituted oxiranes with chlorosilanes,[3] haloborane reagents,[4,5] Br_2/PPh_3,[6] Me_3SiBr,[7] Py·HCl,[8] Lewis acid metal halides,[9,10] $X_2Ti(O\text{-}i\text{-}pr)$,[11] Li_2NBr_4[12] and $n\text{-}Bu_4N^+Br^-/Mg(NO_3)_2$[13] have been reported. However, these methods are not always fully satisfactory and suffer from disadvantages such as acidity, handling and in situ preparation of reagent, noncatalytic nature of the reagents, and relatively long reaction times.[4c,11,14−16] Recently, it has been found that epoxides can be converted into iodohydrins and bromohydrins by means of elemental iodine and bromine,[17] but this method has some limitations such as low yield and regioselectivity with long reaction times and formation of acetonide byproducts in addition to the expected iodoadduct in acetone solution. Furthermore, iodination does not occur in CH_2Cl_2, $CHCl_3$, C_6H_6, CH_3CN, and THF solvents.

In conjuction with ongoing work in our laboratory on the synthesis and complex formation of macrocyclic compounds with natural molecules such as iodine and bromine,[18−20] we found that these compounds efficiently catalyzed the addition of elemental iodine and bromine to epoxides. Seven new macrocyclic diamides as well as dibenzo-18-crown-6, 18-crown-6, and aza-18-crown-6 were selected as catalysts in these reactions.

Here we report the synthesis of these novel macrocyclic diamides and the results of the reactions of some epoxides with elemental iodine and bromine in the presence of catalytic amounts of these macrocyclic compounds.

Results

(A) Preparation of Catalyst. Although macrocyclic amides were originally regarded as intermediated to aza crowns, only a few procedures have been developed for their preparation. Among these, carboxylic acid deriva-

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(8) Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Synth. Commun.* **1981**, *11*, 287.
(9) (a) Eisch, J. J.; Liu, Z. R.; Ma, X.; Zheng, G. X. *J. Org. Chem.* **1992**, *57*, 5140. (b) Iranpoor, N.; Salehi, P. *Synth. Commun.* **1997**, in press. (c) Shimizu, M.; Yoshida, A.; Tamotsu, F. *Synlett* **1992**, 204.
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(11) Alvarez, E.; Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 3429.
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(13) Suh, Y. G.; Koo, B. A.; Ko, J. A.; Cho, Y. S. *Chem. Lett.* **1993**, 1907.
(14) (a) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*(26), 3021. (b) Bonini, C.; Giuliano, C.; Righi, G.; Rossi, L. *Synth. Commun.* **1992**, *22*(13), 1863.
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(17) Konaklieva, M. I.; Dahi, M. L.; Turos, E. *Tetrahedron Lett.* **1992**, *33*(47), 7093.
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(19) Gangali, M. R.; Eshghi, H.; Sharghi, H.; Shamsipour, M. J. *Electroanal. Chem.* **1996**, *405*, 177.
(20) Massah, A. R. Ph.D. Thesis, Shiraz University , Shiraz, Iran, 1997.

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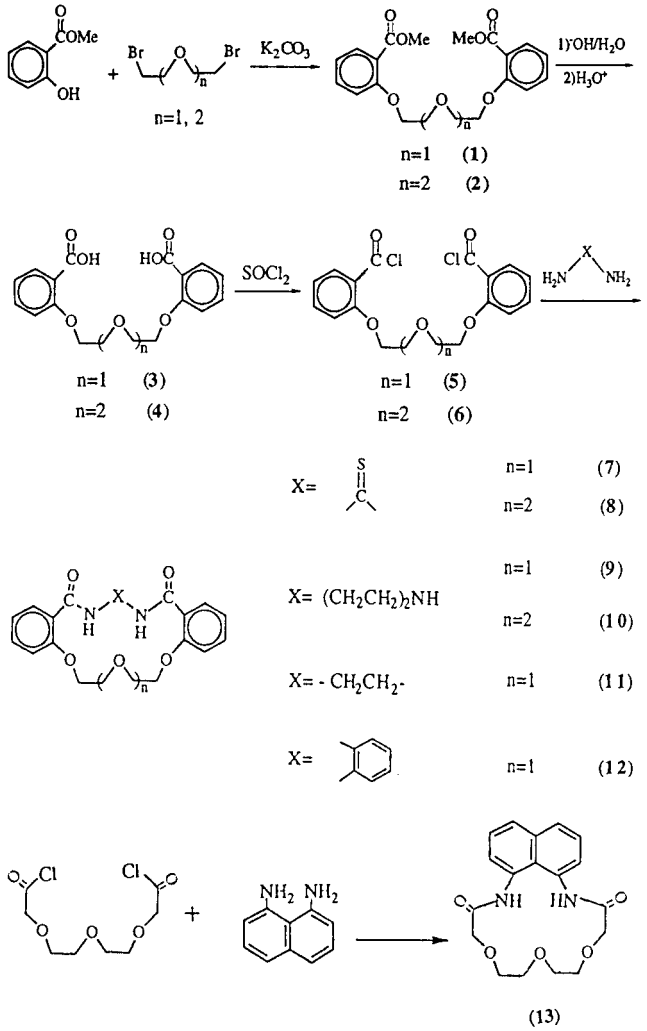
Scheme 1



tives, such as malonic and α,ω-dicarboxylic acid esters,[21] labile diacid dichlorides,[22,23] and bis(α-chloroamide) compounds,[24−26] were allowed to react with various diamines under high dilution or for long reaction periods. In previous studies,[18] we reported a new efficient synthesis of macrocyclic diamides. No high dilution technique was required in this method. We applied this approach to the synthesis of dilactams **7**−**13** (Scheme 1).

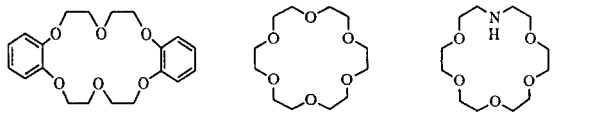
Methyl salicylate was reacted with diethyleneglycol dibromide or triethyleneglycol dibromide in acetone in the presence of potassium carbonate to give diesters **1** and **2** in 90 and 92% yields, respectively. Dicarboxylic acids **3** and **4** were obtained in quantitative yield by saponification of the corresponding diester followed by acid treatment. Treatment of **3** and **4** with thionyl chloride gave 90−95% yield of dicarboxylic acid dichlorides **5** and **6**. Cyclization was carried out with fast addition of diamine in CH_2Cl_2 (or a mixture of DMF/CH_2Cl_2) into a solution of dicarboxylic acid dichloride in CH_2Cl_2 over 5 s with vigorous stirring. Then, the mixture was stirred at room temperature for 20 min to give macrocyclic diamides in 69−80% yields.

Table 1. Halogenative Cleavage of Styrene Oxide in the Presence of Various Macrocyclic Compounds in CH_2Cl_2 at 25 °C

		time (h)		yield[a] (%)	
entry	catalyst (0.1 mol)	bromination	iodination	bromination	iodination
1	**7**	immed	immed	>95	>95
2	**8**	immed	immed	>95	>95
3	**9**	0.25	24 (20)[b]	90	50
4	**10**	0.3	18 (13)[b]	88	65
5	**11**	0.5	24	92	50
6	**12**	0.5	24	90	90
7	**13**	0.25	3.5	>95	90
8	**14**	0.25	2	>95	90
9	**15**	0.4	24	85	80
10	**16**	0.7	24	80	50
11		1	several days[c]	31[d]	0[d]

[a] GC yield. [b] Under reflux. [c] In the presence of excess of iodine. [d] Data taken from ref 17.

Other crown ethers that were used as catalysts in halogenation of epoxides are shown:



dibenzo-18-crown-6 (**14**) 18-crown-6 (**15**) aza-18-crown-6 (**16**)

(B) Halogenation of Epoxides. Epoxides of convenient volatility to allow GC analysis were chosen for study. As catalysts, some macrocyclic diamides that were synthesized according to Scheme 1 were used. Also, dibenzo-18-crown-6 (**14**), 18-crown-6 (**15**), and aza-18-crown-6 (**16**) were selected to represent some common crown ether catalysts. The results of the reactions of styrene oxide with elemental iodine and bromine in the presence of the above catalysts are summarized in Table 1. In each case, cleavage of the epoxide ring occurs and, upon thiosulfate workup, the corresponding iodohydrin and bromohydrin were obtained. The catalysts were easily recovered and could be reused several times. In comparison, the cleavage behavior of styrene oxide with elemental iodine and bromine in the absence of catalyst is given in entry 11.

As is shown in Table 1, yields of both iodination and bromination with this new methodology are quite good. Catalysts **7** and **8** are the most effective, and reactions occur instantaneously in the presence of these catalysts (Table 1, entries 1 and 2). In the presence of other catalysts, the reaction times for bromination and iodination at room temperature are in the range 0.25−0.7 and 3.5−24 h, respectively. However, iodination of styrene oxide with an excess of elemental iodine in the absence of catalyst did not occur even under reflux and extension of reaction time to several days, and unreacted styrene oxide was completely recovered. In addition, the yield of bromination reactions is very low in the absence of catalysts.

The results obtained with some representative epoxides in the presence of macrocycles **7** and **14** as catalyst

(21) (a) Tabushi, I.; Taniguchi, Y.; Kato, H. *Tetrahedron Lett.* **1977**, 1049. (b) Tabushi, I.; Okino, H.; Kuroda, Y. *Ibid.* **1976**, 4339.
(22) (a) Petranek, J.; Ryba, O. *Collect. Czech. Chem. Commun.* **1980**, *45*, 1567. (b) Petranek, J.; Ryba, O. *Ibid.* **1983**, *48*, 1945.
(23) (a) Pellisard, D.; Louis, R. *Tetrahedron Lett.* **1972**, *45*, 4589. (b) Dietrich, B.; Lehn, J. M.; Sauvage, J. P.; Blanzat, J. *Tetrahedron* **1973**, *29*, 1629.
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are summarized in Table 2 and are compared with the corresponding results obtained in the reaction of the same epoxides in the absence of catalyst (entries 4, 5, 9, 16, 20, and 27). On the other hand, for comparison, some other methods for conversion of epoxides to the corresponding halohydrins are given in Table 2, entries 6, 10−13, and 32. When epoxides were allowed to react in the presence of catalyst, increases in yield and regioselectivity were observed in all of the reactions studied. The increase appeared to be largely dependent on the type (Table 1) and amount of catalyst. Generally, the optimum amounts of the catalysts were found to be 0.1 mol for 1 mol of epoxide and halogen. However, in the case of styrene oxide and phenoxypropylene oxide reactions occurred in the presence of even 0.05 mol of catalyst **7** (Table 3 and Table 2, entries 2 and 18).

However, other factors can exert a controlling influence, such as (1) steric hindrance of epoxides, (2) the rate of admixing the reagents, (3) the order in which the reagents are combined, and (4) the nature of solvent. Each can have a pronounced effect on the observed ratio of halohydrin isomers and overall yield.

A comparison of the reaction of epoxides with elemental bromine or iodine in the presence of a macrocyclic catalyst indicates that an increase in steric hindrance at the epoxide ring results in a general decrease in the rate of halohydrin formation (for example, compare Table 2, entry 1 with entry 29).

The order and rate in which the reagents are combined were found to exert a subtle influence on yield and regioselectivity in both bromohydrin and iodohydrin formation. For example, if bromine is added to epoxide before catalyst is added, two bromohydrin isomers are produced, but if the epoxide is added to catalyst and then bromine is added dropwise over a period of time, only one isomer is formed. Furthermore, fast addition of bromine reduced regioselectivity, too (Table 2, entry 21).

The reactions are completely anti-sterioselective as shown for cyclohexene oxide (Table 2, entries 29 and 31), in which only the trans isomers were detected. A contra-Markovnikov-type[27] regioselectivity is generally observed in these reactions. Interestingly, in many cases, this type of regioselectivity appears to be the opposite of that observed in ring opening of the same epoxides with hydrohalogenic acids, under classic acidic conditions[14a] (Table 2, entries 12 and 13).

The results of ring opening of styrene oxide in the presence of macrocycle **7** in various aprotic solvents are summarized in Table 3. The iodination and bromination reactions proceed most cleanly in CH_2Cl_2, $CHCl_3$, CH_3CN, and benzene solution, while those done in THF and acetone lead to a lower yield of halohydrins.

Discussion

The regiochemical mode of epoxide cleavage by elemental iodine or bromine in the presence of macrocycle catalyst can be viewed as occurring via nucleophilic attack by halide ion on the less sterically hindered epoxide carbon. This mechanism closely resembles the S_N2 model for aliphatic nucleophilic displacement. On the basis of our previous study on macrocycle diamides **17**−**19** and other works on the complexation of crown ethers with elemental halogens,[28,29] halogenative cleavage of epoxides occurs according to the following four-step mechanism:

The first step involves the formation of a 1:2 or 1:1 molecular complex between macrocycle and elemental halogen, in which halogen ion (X_3^-) exists as a contact ion pair:

$$\text{macrocycle} + 2X_2 \rightleftharpoons (\text{macrocycle}\cdots X^+)\, X_3^-$$

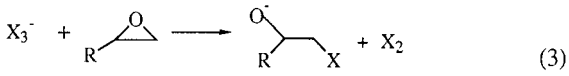
or

$$2\ \text{macrocycle} + 2X_2 \rightleftharpoons (2\ \text{macrocycle}\cdots X^+)\, X_3^- \quad (1)$$

In the second step this complex is further decomposed to release X_3^- ion into solution as

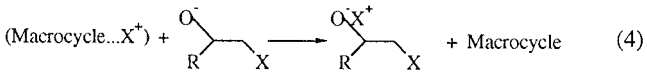
$$(\text{macrocycle}\cdots X^+)\, X_3^- \rightarrow (\text{macrocycle}\cdots X^+)\, X_3^- \quad (2)$$

Therefore, in this way, molecular iodine or bromine is converted to a nucleophilic halogen species in the presence of a suitable macrocycle and, in the third step, this ion participates in the ring opening reaction of epoxides:



(3)

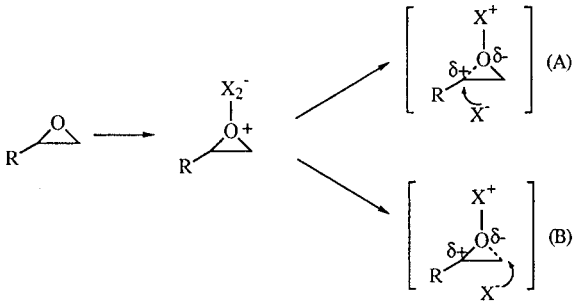
Finally, the catalyst is regenerated in step 4.



(4)

These steps occur continuously until all of the epoxides and halogen are consumed, and after workup, the catalyst can be recovered easily.

On the other hand, when catalyst is not present, cleavage of epoxides can occur via two limiting mechanistic pathways, either electrophilic attack by molecular halogen, behaving as Lewis acid, giving the more stable carbonium ion-like transition state (A), or via nucleophilic attack by halide ion on the epoxide or epoxide−halogen complex, giving the more stable transition state (B):



Most Lewis acidic compounds, such as titanium halides, foster electophilic opening of the epoxide ring to yield transition state A. When weaker Lewis acids are employed, namely bromine or iodine, nucleophilic attack, by the halide ions generated should be fostered and transition state B may be expected to be lower in energy. In

(27) Dela More, P. B. D.; Bolton, R. *Electrophilic Addition to Unsaturated Systems*; Elsevier Scientific: New York, 1966.

(28) Lowry, T. H.; Richardson , K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; pp 327−423.

(29) Semnani, A.; Shamsipur, M. *J. Chem. Soc., Dalton Trans.* **1996**, 2215.

Table 2. Reaction of Epoxides with Elemental Bromine and Iodine in the Presence of Representative Catalyst

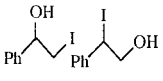
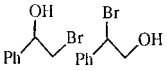
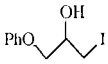
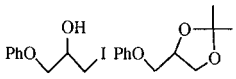
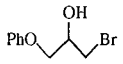
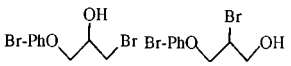
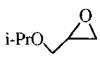
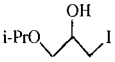
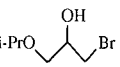
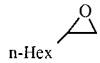
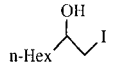
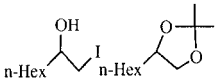
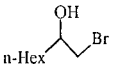
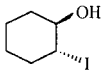
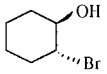
entry	epoxide	catalyst (0.1)	conditions	Product(s)	Reaction time (h)	yield%[a]	ref.
1		**7**	I_2,r.t,CH_2Cl_2		immed.	>95	
2[b]	"	"	"	"	0.15	>95	
3	"	**14**	I_2,r.t,CH_2Cl_2	"	2	90	
4	"	-	I_2(excess), CH_2Cl_2,reflux	N.R	-	-	17
5	"	-	I_2,r.t,acetone		2	83	17
6	"	-	LiI,AcOH, THF,r.t		1.3	87(1:2)	13a
7	"	**7**	Br_2,r.t,CH_2Cl_2		immed.	>95	
8	"	**14**	Br_2,r.t,CH_2Cl_2	"	0.25	>95	
9	"	-	Br_2,r.t,CH_2Cl_2		1	31	17
10	"	-	n-$Bu_4N^+Br^-$/ $Mg(NO_3)_2$,$CHCl_3$		5	78(5:1)	12
11	"	-	$(Me_2N)_2BBr/CH_2Cl_2$ N_2 atm.	"	12	75(1:4.5)	4c
12	"	-	HBr,$CHCl_3$		0.25	>99	14a
13	"	-	HI, $CHCl_3$		0.25	>99	14a
14		**7**	I_2, CH_2Cl_2 reflux		4	>95	
15	"	**14**	I_2, CH_2Cl_2 reflux	"	10	80	
16	"	-	I_2,r.t., acetone		-	94(1:1)	17
17	"	**7**	Br_2,r.t,CH_2Cl_2		immed.	>95	
18[b]	"	"	"	"	0.5	>95	
19	"	**14**	Br_2,r.t,CH_2Cl_2	"	0.5	92	
20	"	-	"		-	88(5:1)	17
21[c]	"	**7**	"	"	0.5	90(6:1)	
22		**7**	I_2, CH_2Cl_2 reflux		10	90	
23	"	**14**	I_2, CH_2Cl_2, reflux	"	14	80	
24	"	**7**	Br_2,r.t.,CH_2Cl_2		1	90	
25		**7**	I_2, CH_2Cl_2,reflux		16	90	
26	"	**14**	I_2, CH_2Cl_2, reflux	"	18	75	
27	"	-	I_2,acetone		-	79(1:4)	17

Table 2 (Continued)

entry	epoxide	catalyst (0.1)	conditions	Product(s)	Reaction time (h)	yield%[a]	ref.
28	"	**7**	Br_2,CH_2Cl_2		3	90	
29		**7**	I_2, CH_2Cl_2,reflux		20	87	
30	"	**14**	"	"	24	78	
31	"	**7**	Br_2,r.t.,CH_2Cl_2		3.5	90	
32	"	-	LiBr, AcOH, THF,r.t.	"	5	90	13a

[a] GC yield. [b] Reaction was carried out in the presence of 0.05 mol of catalyst. [c] Fast addition of bromine to mixture of catalyst and epoxide or catalyst and epoxide was added to bromine

Table 3. Halogenation Reaction of Styrene Oxide in the Presence of 0.05 Mol of Catalyst 7 in Various Solvents at 25 °C

		time (h)		yield[a] (%)	
entry	solvent	bromination	iodination	bromination	iodination
1	CH_2Cl_2	0.05	0.15	>95	>95
2	$CHCl_3$	0.1	0.3	>95	90
3	C_6H_6	0.1	0.15	>95	92
4	CH_3CN	0.1	0.2	90	90
5	CH_3COCH_3	0.5	2	85	75
6	THF	0.5	2	65	30

[a] GC yield.

this case, the cleavage leads to a mixture of secondary alcohol and primary alcohol products.[9a]

The variation in yield and rate of cleaving epoxides by elemental iodine or bromine in the presence of different catalyst (**7**−**16**) can be satisfactory rationalized in terms of the suggested mechanism. The macrocycles **7** and **8** are the most active catalysts in these reactions. According to the mechanism, in both macrocycles **7** and **8** complexation with I_2 and, hence, elaboration of I_3^- occurred much faster than with other catalysts. In support of this mechanism, reaction of catalysts with iodine was followed by UV spectroscopy (Figure 1). Figure 1 shows only the characteristic UV band for macrocycles **7** and **8** (and only slightly for **13**) at 364 nm, and other macrocycle−iodine systems studied do not show this characteristic band. This band is well known to be specific for the formation of triiodide ion, I_3^-, in the complex formation process between iodine and different electron-pair-donating ligands.[29−32] Especially in the case of catalysts **7** and **8** this band appeared immediately and clarified the much faster complexation of I_2 with macrocycles **7** and **8** and consequently formation of I_3^-. The most important factor, which probably contributed to the special behavior of **7** and **8**, is the presence of a C=S group in these two macrocyclic structures.

The decrease in regioselectivity that results by merely reversing the order of mixing of epoxide and halogen, namely the slow addition of epoxide to bromine or fast addition of bromine to epoxide, before catalyst was added, can readily be understood from the model. When the initial epoxide was introduced (in the absence or presence of catalyst), it would encounter an excess amount of bromine; electrophilic attack by bromine can then occur, giving the transition state A, and bromine anions will attack the more substituted carbon. On the other hand, slow addition of bromine to the mixture of catalyst and epoxide fosters the four-step mechanism presented above in which all of the elemental bromine is converted to Br_3^- by the catalyst and it then attacks the less substituted carbon selectively.

In conclusion, we have found that suitable macrocyclic compounds can catalyze the regioselective ring opening of epoxides by elemental iodine and bromine under neutral conditions. Especially nothworthy are the ease of catalyst regeneration and reuse, the compatibility of these reaction conditions with a variety of sensitive functional groups, as well as the convenience of this procedure, which make this synthetic technique highly useful.

Experimental Section

Instrumentation, Analyses, and Starting Material. NMR spectra were recorded using either a Bruker Avance DPX-250 or a Varian EM 390 (90 MHz) spectrometer in pure deuterated solvents. IR spectra were obtained on an Impact 400 D Nickolet FTIR spectrometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument at 70 eV. UV spectra were recorded on a Philips PUB 700 spectrometer. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-10A instrument with a flame ionization detector using a column of 15% carbowax 20 M chromosorb W acid-washed 60−80 mesh. Elemental analyses were performed at the National Oil Co. of Iran at Tehran Research Center. Column chromatography was carried out on short columns of silica gel 60 (230−400 mesh) in glass columns (2−3 cm diameter) using 15−30 g of silica gel per 1 g of crude mixture. Melting points were determined in open capillary tubes in a Buchi-510 circulating oil melting point apparatus. Epoxides, crown ethers, and other chemical materials were purchased from Fluka, Aldrich, and Merck in high purity and were used without further purification. Compounds **1**, **3**, and **5** are known compounds, and their spectroscopic and physical data were compared with the literature data.[18]

(30) Andrews, L. J.; Keefer, R. M. *J. Org. Chem.* **1987**, *52*, 2690.
(31) (a) Nour, E. M.; Shahada, L. A. *Spectrochim. Acta. Part A* **1988**, *44*, 1277. (b) Nour, E. M. *Ibid.* **1991**, *47*, 743.
(32) (a) Mizuno, M.; Tanaka, J.; Harada, I. *J. Phys. Chem.* **1981**, *85*, 1789. (b) Andrews, L.; Prochaska, E. S.; Loewenschuss, A. *Inorg. Chem.* **1980**, *19*, 463.

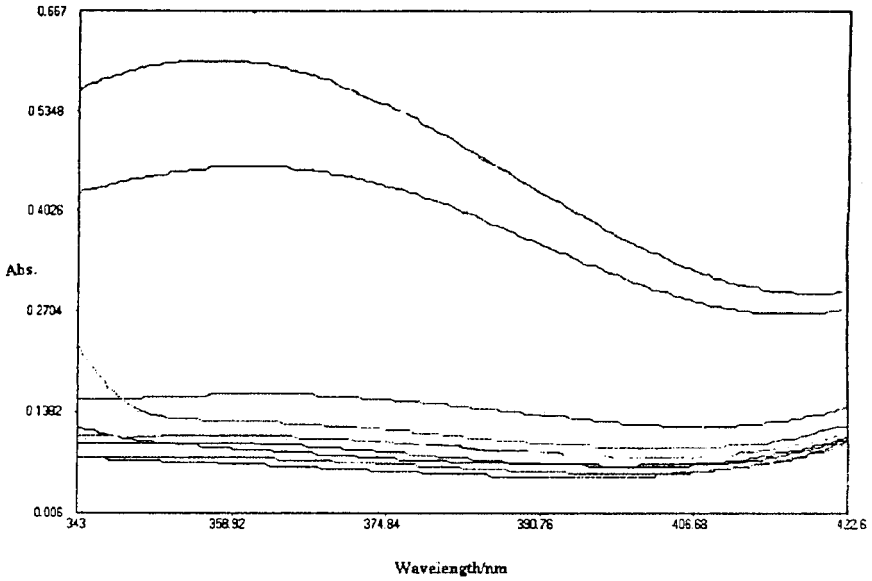


Figure 1. Absorption spectra of used macrocycle−iodine complexes. Spectra from bottom to top refer to macrocycles **12**, **16**, **10**, **9**, **15**, **14**, **13**, **8**, and **7**:iodine complexes.

1,10-Bis(2′-methyl benzoate)-1,4,7,10-tetraoxadecane (2). A mixture of triethylene glycol dibromide (27.6 g, 0.1 mol) and methyl salicylate (30.5 g, 0.2 mol) in acetone (500 mL) containing potassium carbonate (20 g) was refluxed for 7 days. The mixture was cooled, and the solid was filtered and solvent evaporated. Chloroform (400 mL) was added, and the organic layer was washed with cold 10% aqueous sodium hydroxide solution (2 × 100 mL) and then with water (2 × 100 mL) and was dried with anhydrous magnesium sulfate. The solvent was evaporated to give a yellow viscous oil of **2**: yield 38.5 g (92%); R_f 0.72 (CH_2Cl_2−CH_3OH/96−4); IR (neat) 785 (m), 1115 (s), 1225 (s), 1350 (s), 1602 (m), 1723 (m), 2978 (s), 3065 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 3.8 (s, 6H), 3.85 (s, 4H), 3.95 (t, 4H, J = 4.5 Hz) 4.15 (t, 4H, J = 4.5 Hz), 6.8−7.1 (m, 4H), 7.35 (dt, 2H, J_1 = 7.5 Hz, J_2 = 2.0 Hz), 7.7 (dd, 2H, J_1 = 8.0 Hz, J_2 = 2.0 Hz); MS m/z 419 (M^+ + 1, 0.4), 418 (M^+, 3.2), 372 (1.2), 240 (1.9), 210 (8.0), 179 (71.0), 166 (11.3), 165 (26.6), 152 (36.5), 135 (17.0), 121 (base peak), 92 (13.6), 77 (34.2). Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.13; H, 6.22. Found: C, 63.14; H, 6.20.

1,10-Bis(2′-benzoic acid)-1,4,7,10-tetraoxadecane (4). A solution of 1,10-bis(2′-methyl benzoate)-1,4,7-tetraoxadecane (**2**, 41.8 g 0.1 mol) in 10% aqueous NaOH (500 mL) was refluxed for 24 h. The mixture was cooled, washed with chloroform (2 × 100 mL), acidified with 6 N HCl, and extracted with CH_2Cl_2 (5 × 150 mL). The solvent was evaporated and the resulting yellow solid was recrystallized from acetone to give white crystals of **3**: yield 39 g (100%); mp 111−113 °C; R_f 0.55 (CH_2Cl_2−CH_3OH/96−4); IR (KBr) 780 (m), 1100 (m), 1230 (s), 1350 (s), 1602 (m), 1716 (s), 2864 (s), 2980 (s), 3073 (w), 3280 (br s) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 3.8 (s, 4H), 3.85 (t, 4H, J = 4.5 Hz), 4.25 (t, 4H, J = 4.5 Hz), 6.8−7.1 (m, 4H), 7.35 (dt, 2H, J_1 = 8.0, J_2 = 2.0 Hz), 7.9 (dd, 2H, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 8.5 (b, 2H); MS m/z 373 (M^+ − OH, 10.0), 210 (2.6), 209 (17.5), 166 (4.0), 165 (34.9), 152 (4.9), 138 (15.6), 121 (base peak), 92 (10.9). Anal. Calcd for $C_{20}H_{22}O_8$: C, 61.54; H, 5.64. Found: C, 61.53; H, 5.67.

1,10-Bis(2′-benzoyl chloride)-1,4,7,10-tetraoxadecane (6). 1,10-Bis(2′-benzoic acid)-1,4,7-tetraoxadecane (**4**, 9.75 g, 0.025 mol) was heated in thionyl chloride (50 mL) for 4 h at 50−60 °C. The thionyl chloride was evaporated at low temperature to give **6** as a yellow solid in 95% yield: mp 47−49 °C; IR (KBr) 775 (m), 1153 (s), 1255 (s), 1598 (m), 1780(s), 2890 (s), 3055 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 3.8 (s, 4H), 3.85 (t, 4H, J = 4.5 Hz), 4.25 (t, 4H, J = 4.5 Hz), 6.8−7.1 (m, 4H), 7.35 (dt, 2H, J_1 = 8.0 Hz, J_2 = 2.0 Hz), 8.0 (dd, 2H, J_1 = 8.0 Hz, J_2 = 2.0 Hz); MS m/z 328 (M^+ − $COCl_2$, 10.1), 210 (4.5), 209 (10.9), 166 (4.1), 165 (36.2), 152 (4.2), 138 (19.9), 121 (base peak), 92 (41.1). Anal. Calcd for $C_{20}H_{20}O_6Cl_2$: C, 56.21; H, 4.68. Found: C, 56.24; H, 4.66.

General Procedure for the Synthesis of Catalysts. A solution of diamine (2 mmol) in CH_2Cl_2 (or a mixture of DMF/CH_2Cl_2) (50 mL) was added quickly to a vigorously stirring solution of diacid chloride (2 mmol) in CH_2Cl_2 (50 mL) at room temperature. The mixture was stirred for a further 20 min and then was washed with bicarbonate solution (2 × 50 mL). The organic layer was dried over magnesium sulfate, and the solvent was evaporated to give a solid (or oily) product. The crude product was purified by column chromatography using petroleum ether (bp = 60−80 °C)−ethyl acetate as eluent. Macrocycles **9**, **11**, and **12** were prepared according to ref 18, and their spectroscopic and physical data were compared with those in the literature data.

1,15-Diaza-3,4;12,13-dibenzo-16-(thiocarbonyl)-5,8,11-trioxacyclohexadecane-2,15-dione (7): yellow crystals; 75% yield; mp 160−162 °C; R_f 0.75 (CH_2Cl_2−CH_3OH/95−5); IR (KBr) 750 (m), 1246 (s), 1298 (s), 1508 (m), 1602 (m), 1669 (m), 1729 (m), 2925 (m), 3288 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.66 (t, 4H, J = 4.00 Hz), 4.23 (t, 4H, J = 4.00 Hz), 6.90 (dd, 2H, J_1 = 8.25 Hz, J_2 = 0.5 Hz), 7.07 (dt, 2H, J_1 = 7.25 Hz, J_2 = 1.00 Hz), 7.43 (dt, 2H, J_1 = 7.75 Hz, J_2 = 1.75 Hz), 7.76 (dd, 2H, J_1 = 7.75 Hz, J_2 = 1.75 Hz), 12.37 (b, 2H); MS m/z 387 (M^+ + 1, 0.5), 386 (M^+, 2.3), 267 (4.7), 253 (0.3), 213 (5.5), 196 (17.2), 179 (10.9), 165 (19.5), 121 (base peak), 120 (87.1), 105 (12.6), 92 (65.5); UV ($CHCl_3$) λ 260.8 (ϵ_{max} = 26 780) , 310 nm (ϵ = 19 200). Anal. Calcd for $C_{19}H_{18}N_2O_5S$: C, 59.07; H, 4.66; N, 7.25. Found: C, 59.11; H, 4.69; N, 7.23.

1,18-Diaza-3,4;15,16-dibenzo-19-(thiocarbonyl)-5,8,11,14-tetraoxacyclononadecane-2,18-dione (8): yellow crystals; 70% yield; mp 150−152 °C; R_f = 0.7 (CH_2Cl_2−CH_3OH/95−5); IR (KBr) 752 (m), 1245 (s), 1300 (s), 1517 (m), 1600 (m), 1669 (w), 1730 (m) 2925 (m), 3325 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.52 (s, 4H), 3.76 (t, 4H, J = 5.00 Hz), 4.33 (t, 4H, J = 5.00 Hz), 6.97 (dd, 2H, J_1 = 8.25 Hz, J_2 = 0.50 Hz), 7.06 (dt, 2H, J_1 = 7.25 Hz, J_2 = 1.00 Hz), 7.48 (dt, 2H, J_1 = 7.75 Hz, J_2 = 1.75 Hz), 7.79 (dd, 2H, J_1 = 8.00 Hz, J_2 = 1.75 Hz), 12.35 (d, 2H); MS m/z 431 (M^+ + 1, 0.5), 430 (M^+, 1.5), 223 (1.3), 196 (17.1), 165 (20.5), 147 (10.6), 121 (base peak), 120 (50.3), 62 (45.3), 43(41); UV ($CHCl_3$) λ 260.2 (ϵ_{max} = 25 800), 308 nm (ϵ = 18 500). Anal. Calcd for $C_{21}H_{22}N_2O_6S$: C, 58.60; H, 5.12; N, 6.51. Found: C, 58.63; H, 5.09; N, 6.47.

1,18,21-Triaza-3,4;15,16-dibenzo-5,8,11,14-tetraoxacyclotetraeicosane-2,17-dione (10): white solid; 80% yield; mp 59−61 °C; R_f = 0.14 (CH_2Cl_2−CH_3OH/96−4); IR (KBr) 760 (s), 1105 (s), 1228 (s), 1300 (s), 1600 (m), 1650 (s), 2925 (m), 3380 (br s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.45 (t, 1H, J

= 4.25 Hz), 3.00 (dt, 4H, J_1 = 4.50 Hz, J_2 = 2.00 Hz), 3.7 (t, 4H, J = 4.50 Hz), 3.80 (s, 4H), 3.90 (dt, 4H, J_1 = 4.50 Hz, J_2 = 2.00 Hz), 4.10 (t, 4H, J = 4.50 Hz), 6.80 (dd, 2H, J_1 = 8.00 Hz, J_2 = 1.75 Hz), 7.00 (dt, 2H, J_1 = 7.00 Hz, J_2 = 0.75 Hz), 7.20 (dt, 2H, J_1 = 8.00 Hz, J_2 = 2.00 Hz), 8.00 (dd, 2H, J_1 = 8.00 Hz, J_2 = 2.00 Hz), 8.50 (b, 2H); MS *m*/*z* 457 (M^+, 0.5), 428 (8.6), 415 (3.8), 372 (11.7), 209 (16.3), 165 (42.1), 121 (base peak), 105 (5.4), 73 (13.8), 64 (10.4); UV ($CHCl_3$) λ 228.8 (ϵ_{max} = 21 500), 283.2 nm (ϵ = 7500). Anal. Calcd for $C_{24}H_{31}N_3O_6$: C, 63.02; H, 6.78; N, 9.19. Found: C,63.04; H, 6.75; N, 9.21.

1,15-Diaza-2,3,4-naphthyl-8,11,14-trioxacyclohexadecane-6,16-dione (13): white crystals; 69% yield; mp 47−48 °C; R_f = 0.35 (CH_2Cl_2−CH_3OH/96−4); IR (KBr) 757 (s), 810 (s), 987 (w), 1140 (s), 1205 (m), 1272 (m), 1327 (m), 1425 (m), 1590 (w), 1653 (s), 2840 (m), 2925 (m), 3045 (w), 3235 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.83 (s, 8H), 4.33 (s, 4H), 7.51 (dt, 2H, J_1 = 8.25 Hz, J_2 = 2.25 Hz), 7.78 (d, 2H, J = 7.25 Hz), 7.88 (d, 2H, J = 7.00 Hz), 9.25 (s, 2H); MS *m*/*z* 346 (M^+ + 2, 0.3), 345 (M^+ + 1, 2.1), 344 (M^+, 10.1), 225 (4.5), 197 (6.9), 185 (10), 184 (25.5), 182 (4.5), 169 (11.4), 155 (3.8), 97 10.1), 83 (13.6), 69 (26), 43 (base peak), 41 (52.4); UV ($CHCl_3$) λ 246.2 (ϵ_{max} = 1040), 307.8 nm (ϵ = 760). Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.79; H, 5.81; N, 8.14. Found: C, 62.83; H, 5.79; N, 8.16.

General Procedure for Halogenative Cleavage of Epoxides. Epoxide (1 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of catalyst (0.1 mmol) in CH_2Cl_2 (5 mL) at room temperature. Next, a solution of elemental halogen (1 mmol) in CH_2Cl_2 (5 mL) was added dropwise during 15 min to the above mixture. The progress of reaction was monitored by TLC and GLC. After complete disappearance of the starting material, the reaction mixture was washed with 10% aqueous $Na_2S_2O_3$ (2 × 10 mL) and water (2 × 10 mL). The aqueous layer was further extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to give crude alcohol−catalyst. The crude products were purified by crystallization in diethyl ether. After cooling, the catalyst was filtered off and washed with cold ether. The filtrate was evaporated and pure halohydrin obtained. The halohydrins obtained throughout this procedure were identified by comparision, where possible, with authentic samples prepared in accordance with literature procedures.[9b,14a,13,33]

1-Bromo-2-octanol: ^1H NMR ($CDCl_3$, 250 MHz) δ 0.89 (t, 3H, J = 6.5 Hz), 1.25−1.63 (m, 8H), 1.86 (q, 2H, J = 7.1 Hz), 2.22 (s, 1H), 3.42 (t, 2H, J = 7.1 Hz), 3.75−3.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 14.01, 22.52, 29.14, 31.68, 35.05, 40.73, 71.02; IR (neat) 720 (m), 830 (m), 1050 (s), 1075 (s), 1125 (m), 1225 (m), 1265 (m), 1385 (m), 1425 (m), 1470 (s), 2860 (vs), 2935 (vs), 2970 (vs), 3380 (br s) cm^{-1}.

1-Iodo-2-octanol: ^1H NMR ($CDCl_3$, 250 MHz) δ 0.89 (t, 3H, J = 7.0 Hz), 1.26−1.58 (m, 10H), 2.24 (s, 1H), 3.24−3.55 (m, 3H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 14.09, 16.45, 22.62, 25.56, 29.12, 31.70, 36.89, 70.91; IR (neat) 725 (m), 1015 (br s), 1105 (m), 1130 (m), 1185 (s), 1385 (s), 1425 (s), 1465 (s), 1475 (s), 2870 (vs), 2940 (vs), 2970 (s), 3400 (br s) cm^{-1}.

2-Bromocyclohexanol: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.26−1.42 (m, 3H), 1.78−1.98 (m, 3H), 2.18−2.32 (m, 1H), 2.32−2.38 (m, 1H), 2.68 (s, 1H), 3.58−3.64 (m, 1H), 3.82−3.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 19.79, 24.48, 27.02, 33.95, 36.59, 62.13, 75.66; IR (neat) 690 (s), 793 (w), 865 (m), 960 (s), 1038 (m), 1075 (br s), 1123 (m), 1189 (s), 1372 (m), 1460 (s), 2882 (s), 2960 (br s), 3425 (br s) cm^{-1}.

2-Iodocyclohexanol: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.26−1.44 (m, 3H), 1.75−1.95 (m, 3H), 2.15−2.3 (m, 1H), 2.3−2.35 (m, 1H), 2.72 (s, 1H), 3.58−3.62 (m, 1H), 3.9−4.0 (m, 1H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 19.79, 24.51, 26.56, 32.75, 35.40, 59.84, 71.59; IR (neat) 690 (s), 790 (w), 870 (m), 948 (s), 1038 (w), 1082 (br s), 1123 (m), 1189 (s), 1372 (m), 1462 (s), 2882 (s), 2960 (br s), 3425 (br s) cm^{-1}.

1-Phenoxy-3-bromo-2-propanol: ^1H NMR ($CDCl_3$, 250 MHz) δ 2.75 (s, 1H), 3.61 (d, 2H, J = 5.0 Hz), 4.03 (q, 1H, J = 2.0 Hz), 4.11 (d, 2H, J = 7.0 Hz), 6.78 (d, 1H, J = 5.0 Hz), 6.94 (d, 2H, J = 8.0 Hz), 7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 69.58, 69.77, 69.93, 115.01, 116.82, 121.86, 129.99, 132.79; IR (neat) 641 (w), 688 (m), 756 (m), 823 (m), 1038 (s), 1112 (w), 1239 (s), 1375 (m), 1494 (s), 1588 (s), 2878 (m), 2925 (s), 3059 (m), 3415 (br s) cm^{-1}.

1-Phenoxy-3-iodo-2-propanol: ^1H NMR ($CDCl_3$, 250 MHz) δ 3.1 (s, 1H), 3.48 (d, 2H, J = 5.0 Hz), 4.06 (q, 1H, J = 2.0 Hz), 4.13 (d, 2H, J = 7.0 Hz), 6.78−6.9 (m, 3H), 7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 67.18, 69.67, 70.01, 114.98, 116.87, 121.79, 129.89, 132.86; IR (neat) 650 (w), 678 (w), 760 (m), 823 (m), 1038 (s), 1113 (w), 1240 (s), 1375 (m), 1494 (s), 1588 (s), 2877 (m), 2927 (s), 3050 (m), 3418 (br s) cm^{-1}.

1-(Isopropyloxy)-3-bromo-2-propanol: ^1H NMR ($CDCl_3$, 250 MHz) gd 1.16 (d, 6H, J = 4.0 Hz), 2.78 (s, 1H), 3.42−3.65 (m, 5H), 3.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 22.34, 35.40, 69.59, 70.40, 72.70; IR (neat) 675 (m), 798 (w), 923 (m), 1051 (s), 1085 (s), 1125 (s), 1375 (m), 1467 (m), 2871 (m), 2925 (m), 2972 (s), 3435 (br s) cm^{-1}.

1-(Isopropyloxy)-3-iodo-2-propanol: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.15 (d, 6H, J = 4 Hz), 2.92 (s, 1H), 3.38−3.59 (m, 5H), 3.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 22.78, 36.2, 67.3, 69.8, 72.5; IR (neat) 743 (w), 923 (m), 1050 (s), 1085 (s), 1128 (s), 1375 (m), 1467 (m), 2870 (m), 2926 (m), 2975 (s), 3472 (br s) cm^{-1}.

2-Bromo-1-phenylethanol: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.98 (s, 1H), 4.01 (m, 2H), 4.98 (t, 1H, J = 5.0 Hz), 7.19−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 57.39, 67.97, 128.32, 129.30, 129.37, 138.98; IR (neat) 689 (m), 766 (m), 823 (m), 1036 (s), 1115 (w), 1233 (s), 1375 (m), 1494 (m), 1600 (s), 2875 (m), 2935 (s), 3064 (m), 3405 (br s) cm^{-1}.

2-Iodo-1-phenylethanol: ^1H NMR ($CDCl_3$, 250 MHz) δ 2.02 (s, 1H), 3.76 (d, 2H), 4.78 (t, 1H, J = 5.0 Hz), 7.17−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 54.69, 66.90, 128.22, 129.10, 129.21, 138.17; IR (neat) 748 (m), 915 (m), 1032 (s), 1121 (w), 1243 (s), 1365 (m), 1492 (m), 1602 (s), 2885 (m), 2930 (s), 3061 (m), 3398 (br s) cm^{-1}.

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