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Synthesis and transport studies of a new class of cage-annulated chiral macrocycles

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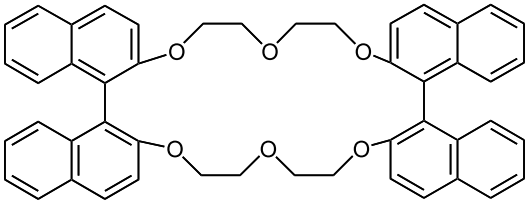
Abstract—The synthesis of a new class of chiral pentacycloundecane cage annulated macrocycles is reported. The ability of the chiral hosts to transport racemic phenylglycine methyl ester enantioselectively through a chloroform membrane in a U-tube was compared to that of related pyridine macrocycles. The cage annulated macrocycles showed weak to moderate enantioselectivity and very high rates of transport compared to previous systems reported using the same counter ion (PF_6^-). The rate of transport was slowed by changing to a relatively harder counter ion (Cl^-). © 2003 Elsevier Science Ltd. All rights reserved.

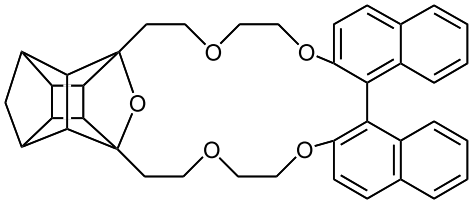
1. Introduction

Optically active crown ethers have been used successfully in transport studies of chiral ammonium ions[1–3] and in related studies.[4] Chiral host–guest studies are of interest to workers in areas such as catalysis,[5,6] enzyme mimics,[7,8] and enantiomeric separation of racemic mixtures.[9,10] Cram's bis-binol-derived crown ether, **1**, transports α-methylbenzylammonium ion with good enantioselectivity (ca. 78% *ee*) and at a moderate transport rate (0.6% h^{-1} with PF_6^- as counter-ion). A closely related, cage annulated crown ether **2** shows a very high rate of transport (approx. 3% h^{-1} with PF_6^- as the counter ion) and exhibits good enantioselectivity (ca. 79% *ee*) with the same guest and counter ion.[3]

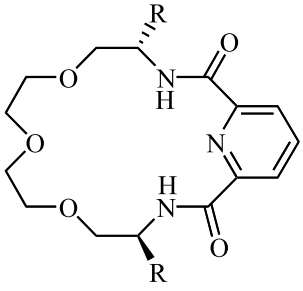
Bradshaw[4b] synthesized a series of host–guest systems that display moderate to good chiral recognition. However, due to their low lipophilicity, it is unlikely that these systems would function effectively as transport



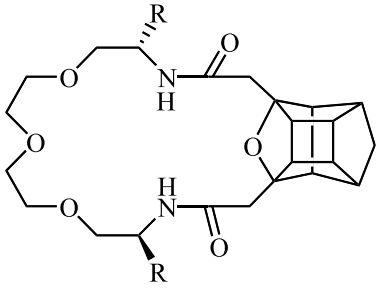
1



2



3. R=Ph
4. R=$CH(CH_3)_2$



5. R=Ph
6. R=$CH(CH_3)_2$

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agents. It has been reported both with chiral guests[3] as well as with metal ion transport experiments[9,10] that the cage annulation enhances the lipophilicity and consequent transport ability of host systems. The purpose of this study was to combine cage-annulation with Bradshaw's macrocycle, **3**,[11] in order to investigate enantioselectivity and transport ability of the resulting host system. We therefore decided to use a similar route to that described by Bradshaw[11] in order to synthesize macrocycle **3** and the novel macrocycles **4**, **5** and **6**.

2. Results and discussion

The reaction of pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione **7** with excess allylmagnesium bromide afforded the corresponding *endo*-8-*endo*-11-diol **8** (91% yield).[12] Subsequent dehydration of the diol **8** produced the corresponding hexacyclic ether, **9**.[12]

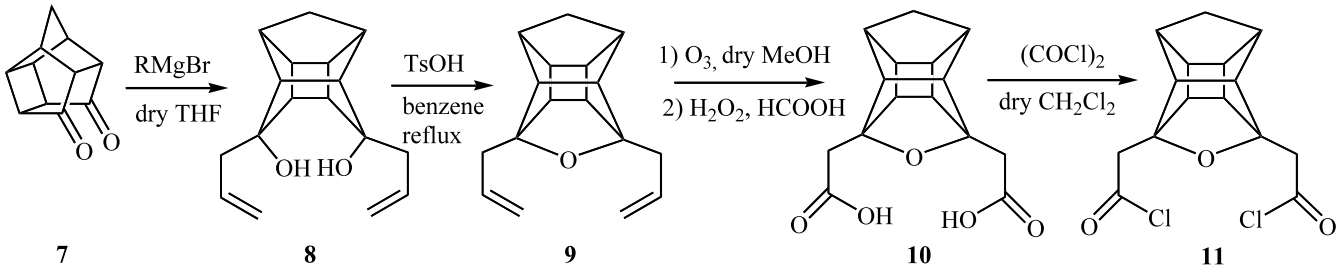
Ozonolysis of **9** followed by oxidative work-up afforded the corresponding diacid, **10** (76% yield). Subsequent reaction of **10** with oxalyl chloride produced the corresponding diacyl chloride, **11**, which then was coupled to the appropriate diamine to form macrocycles **5** and **6**, respectively (see Scheme 1).

Macrocycles **3** and **4** were synthesized in similar fashion, although thionyl chloride[11] was used to form the pyridine diacyl chloride **12**. Diamines **13** and **14** were synthesized by using established procedures.[11,13] The coupling reactions were performed at relatively high dilution (2 mmol diamine per dm^3 of solvent) and produced the desired products in yields of 25–43% (see Scheme 2).

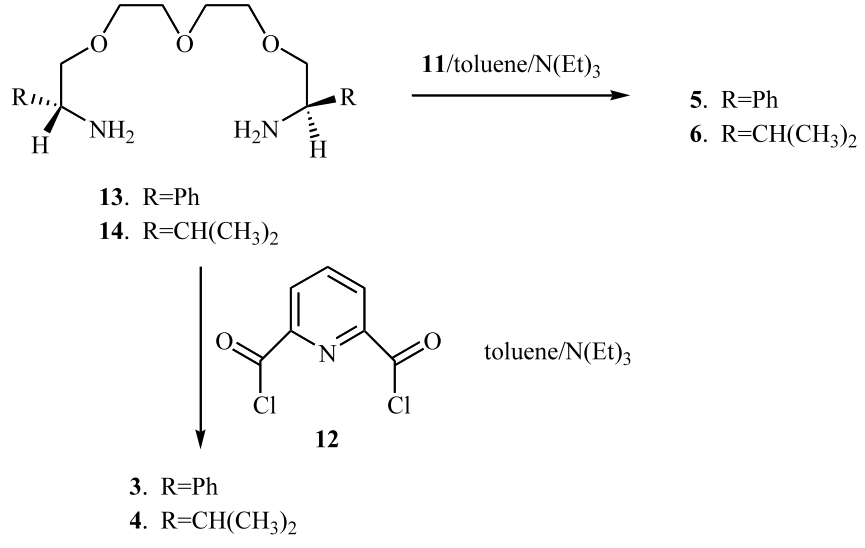
2.1. Transport studies

U-tube transport studies using observed optical rotation[2] is a rapid, time-dependent method that can be used to determine the enantioselectivity of a host–guest system. When promising enantioselectivity is observed, it then would be appropriate to pursue more accurate methods, e.g. W-tube experiments,[2] to determine a more accurate % *ee*. In order to permit direct comparison of the complexation properties of the new macrocycles with those already published, phenylglycine methyl ester hydrochloride was employed as the guest molecule. Complexation and transport of α-methylbenzylamine hydrochloride was also studied; however, this hydrochloride salt proved to be readily soluble in chloroform. In a control run, as much as 30% dissolved into the organic phase within 4 h.

Table 1 shows the results for the transport studies of macrocycles **5** and **6** with (±)-α-methyl-phenylglycinate



Scheme 1. Synthesis of **11**.



Scheme 2. Synthesis of macrocycles **3**–**6**.

Table 1. Differential transport of enantiomers of (±)-α-methyl-phenylglycinate hydrochloride by 0.027 M hosts **5** and **6** in $CHCl_5$ and PF_6^- as counter ion

Run no.	Time (h)	Host	% Transported	Dominant enantiomer	% *ee*
1	24	None	3±0.5		
4	1.5	**5**	18	*R*	27
5	2	**5**	24	*R*	20
6	4	**6**	24.5	*R*	25
7	8	**6**	29.7	*R*	22

hydrochloride with $LiPF_6$ in the source phase (α-arm). Hexafluorophosphate was used by Cram to promote salting-out of the guest into the organic phase.[2] The receiving phase (β-arm) was analyzed every 30 min until maximum optical rotation had been attained. Cage macrocycle **5** shows a very high rate of transport (12% h^{-1}) and poor preference for the *R*-enantiomer. Macrocycle **6** has a lower rate of transport and only weak selectivity for the *R*-enanantiomer.

Very rapid transport by macrocycles **5** and **6** makes it difficult to determine when the observed optical rotation reaches a maximum, since at some stage the concentration gradient will work against enantioselectivity,[2] after which time the % *ee* will begin to decrease. Thus, rapid transport of the guest by the macrocyclic host renders determination of the observed optical rotation difficult and increases the error in measurement of optical rotation. This was not a complication in previous reports,[2,3] wherein the rate of transport was considerably slower. To overcome this problem when macrocycles **5** and **6** were employed as hosts, the rate of transport was slowed by replacing PF_6^- as the counter ion with Cl^-.

Table 2 shows the results obtained for the same host–guest systems by using HCl in the source phase. The receiving phase was analyzed every 60 min until maximum enantiomeric excess had been attained. Comparison of the enantioselectivities in Tables 1 and 2 confirms that a more accurate measurement of the enantioselectivity is possible with slower rates of transport as reported in Table 2. Macrocycle **6** shows moderate enantioselectivity for the (*R*)-methyl phenylglycinate (68% *ee*). Host **5** still shows weak preference for the (*R*)-enantiomer (29% *ee*).

The pyridine macrocycles **3** and **4** display poor transport ability with both counter ions. The presence of host could be detected in both the source and receiving phases after 24 h, thereby disqualifying hosts **3** and **4** as candidates for transport studies. This observation indicates that they are capable of forming a relatively strong host–guest complex, but they are unable to transport the guest into the organic phase due to their low lipophilicity.

3. Conclusion

A new class of chiral macrocycles has been synthesized. They exhibit the highest rate of transport (12% h^{-1} with PF_6^- as counter ion) reported to date, but with moderate to poor enantioselectivity. It is clear that incorporation of the cage into macrocycles increases the lipophilicity and transport ability of the host system. Although transport rate is secondary in importance to enantioselectivity in transport experiments, it nevertheless would be advantageous to develop a system that exhibits both high enantioselectivity as well as a high rate of guest transport. At present, efforts are underway in our laboratory to develop a computational model that will enable us to predict and to improve the enantioselectivity of our macrocycles.

4. Experimental

Melting points are uncorrected. All UV readings were recorded by using a Varian Carey 1E UV–vis spectrophotometer. Optical rotations were taken on an Optical Activity polarimeter. All mass spectrometric analyses were carried out on a VG70-70E mass spectrometer. FAB mass spectra were obtained by bombardment of samples with xenon atoms (1 mA at 8 keV). *m*-Nitrobenzyl alcohol was used as matrix. NMR spectra were recorded on a Varian Unity Inova-300 MHz spectrometer. Elemental microanalyses were obtained at the University of Natal. Spectroscopic grade $CHCl_3$ was filtered through alumina before use to remove any traces of ethanol. All amino acids were bought from Novabiochem.

Table 2. Differential transport of enantiomers of (±)-methyl phenylglycinate hydrochloride by 0.027 M hosts **5** and **6** in $CHCl_5$ and Cl^- as counter ion

Run no.	Time (h)	Host	% Transported	Dominant enantiomer	% *ee*
1	24	None	1±0.5		
2	12	**5**	16	*R*	29
3	19	**5**	22	*R*	22
4	12	**6**	6.8	*R*	48
5	18	**6**	13.2	*R*	68

4.1. 5,5-Dicarboxymethyl-4-oxahexacyclo[5.4.1.0^{2,6}.0^{5,10}.0^{5,9}.0^{8,11}]dodecane 10

A solution of the diene **9**[12] (3.3 g) in dry methanol (100 mL) was cooled to −78°C via application of an external dry ice–acetone bath and then was purged with argon during 20 minutes. Ozone was bubbled into the mixture until a blue-purple color persisted, thereby indicating the presence of excess ozone and completion of reaction. Excess ozone was flushed from the reaction vessel with a stream of argon, and the reaction mixture was concentrated in vacuo. Hydrogen peroxide (30 mL, 30%) was added dropwise to a stirred, ice bath cooled mixture of the ozonide and formic acid (21 mL). The resulting mixture was stirred at ambient temperature during 1 h and then was refluxed gently during 12 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was concentrated in vacuo. Pure **10** (2.895 g, 76%) was thereby obtained as a colorless microcrystalline solid: mp 175–175.5°C; IR (KBr): ν_{max} 3180(s), 2980(s), 1720(vs) cm^{-1}; FAB+ MS (*m*-nitrobenzyl alcohol): *m*/*z* 408 [M+H]$^+$; ^{1}H NMR [DMSO, 300 MHz]: δ_H 1.45 (AB, J_{AB} = 10 Hz, 1H), 1.83 (AB, J_{AB} = 10 Hz, 1H), 2.36–2.80 (m, 12H), 12.15 (br s, 2H, D_2O exchangeable); ^{13}C NMR [DMSO, 50 MHz]: δ_C 37.94 (t), 41.27 (d), 42.81 (t), 44.04 (d), 47.91 (d), 58.55 (d), 92.56 (s) and 171.40 (s); anal. calcd for $C_{15}H_{16}O_4$ C, 65.21; H, 5.84: Found C, 65.39; H, 5.71.

4.2. General procedure for preparing macrocycles 3 and 4[11]

A suspension of the 2,6-dimethylpyridine dicarboxylic acid (4 mmol) was refluxed in freshly distilled thionyl chloride (10 mL) under argon overnight. The homogeneous mixture was concentrated in vacuo to afforded **12** as pale brown oil. Mixtures of diamine **13**/**14** (4 mmol) and NEt_3 (1.5 mL) in toluene (750 mL) and diacyl choride **12** (4 mmol) in toluene (750 mL) were added simultaneously, dropwise with stirring, to toluene (250 mL) during 10 h at 0°C under argon. The resulting mixture was stirred at ambient temperature during 1 day and then was concentrated in vacuo. The product was purified via column chromatography on silica gel by eluting varying ratios of EtOAc/$CHCl_3$ followed by fractional recrystallization of the eluate thereby obtained from toluene.

4.2.1. (4*S*,14*S*)-(−)-4,14-Diisopropyl-6,9,12-trioxa-5, 15,21 - triazabicyclo[15.5.1]henicosa - 1(20),17(21),18-triene-2,16-dione 4. Macrocycle **4** was prepared as described above. The crude product was purified by chromatography on silica gel using ethyl acetate/hexane as eluents to give a yellow oil from which the pure product **4** (26%) was recrystallized from toluene to give white crystals: mp 84–85°C; $[\alpha]_D^{22}$ −113.6 (*c* 0.02, $CHCl_3$); IR (KBr) 3320–3350(s), 1663(vs) cm^{-1}; FAB+ MS (*m*-nitrobenzyl alcohol): *m*/*z* 408 [M+H]$^+$; ^{1}H NMR [$CDCl_3$, 300 MHz]: δ_H 0.90 (m, 12H), 1.53 (AB, J_{AB} = 10.5 Hz, 1H), 1.87 (m, 3H), 2.40–2.75 (m, 10H), 2.79 (AB, J_{AB} = 15.5 Hz, 1H), 2.90 (AB, J_{AB} = 14.8 Hz, 1H), 3.45–3.85 (m, 12H), 6.97 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 8 Hz, 1H); ^{13}C NMR [$CDCl_3$, 75 MHz]: 19.86(q), 20.11(q), 29.73(d), 55.67(d), 70.30(t), 71.14(t), 72.13(t), 125.08(d), 138.67(d), 149.22(s), 163.38(s); calcd for $C_{21}H_{33}N_3O_5$: C, 61.9; H, 8.16; N, 10.31; Found: C, 62.0; H, 8.2; N, 10.5.

4.3. General procedure for preparing macrocycles 5 and 6

A solution of **10** (4 mmol) in oxalyl chloride (10 mL) was refluxed under argon during 12 h. The resulting homogeneous mixture was concentrated in vacuo to yield **11** as a pale brown oil. Mixtures of the diamine **13**/**14** (4 mmol) and NEt_3 (1.5 mL) in toluene (750 mL) and the diacyl choride **11** (4 mmol) in toluene (750 mL) were added simultaneously, dropwise with stirring, to toluene (250 mL) during 10 h at 0°C under argon. The resulting mixture was stirred at ambient temperature during 1 day and then was concentrated in vacuo. The product was purified via column chromatography on silica gel by eluting with ethyl acetate/dichoromethane followed by fractional recrystallization of the eluate thereby obtained from toluene.

4.3.1. Macrocycle 5. Macrocycle **5** was prepared as described above. The crude product was purified by chromatography on silica gel by eluting with ethyl acetate/dichloromethane to give a clear oil from which the pure product **5** (37%) was recrystallized from toluene to give colorless crystals: mp 94–97°C; $[\alpha]_D^{22}$ +6.8 (*c* 0.01, CH_2Cl_2); IR (KBr): ν_{max} 3343(s), 3307(s), 2958(s), 2870(m), 1674(vs), 1517(s), and 1109(s) cm^{-1}; FAB+ MS (*m*-nitrobenzyl alcohol), *m*/*z* 585 [M+H]$^+$. ^{1}H NMR [$CDCl_3$, 300 MHz]: δ_H 1.49 (AB, J_{AB} = 10.5 Hz, 1H), 1.82 (AB, J_{AB} = 10.6 Hz, 1H), 2.15–2.80 (m, 10H), 2.89 (AB, J_{AB} = 15.5 Hz, 1H), 2.98 (AB, J_{AB} = 14.8 Hz, 1H), 3.45–3.95 (m, 12H), 5.09–5.30 (m, 2H), 7.12–7.53 (m, 10H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8 Hz, 1H); ^{13}C NMR [$CDCl_3$, 75 Hz]: δ_C 39.55 (t), 39.58 (t), 41.00 (d), 41.35 (d), 43.15 (t), 43.68 (d), 43.98 (d), 46.22 (d), 49.76 (d), 52.80 (d), 52.85 (d), 56.36 (d), 60.06 (d), 70.22 (t), 70.89 (t), 70.94 (t), 73.91 (t), 73.94 (t), 93.98 (s), 94.05 (s), 126.62 (d), 127.01 (d), 128.04 (d), 140.25 (s), 140.32 (s), 169.14 (s); calcd for $C_{35}H_{41}N_2O_6$: C, 71.9; H, 6.9; N, 4.79; Found: C, 71.1; H, 7.1; N, 4.9.

4.3.2. Macrocycle 6. Macrocycle **6** was prepared as described above. The crude product was purified by chromatography on silica gel by eluting with ethyl acetate/hexane as eluents to give a clear oil from which the pure product **6** (34%) was recrystallized from chloroform/hexane to give white crystals: mp 103–105°C; $[\alpha]_D^{22}$ −93.3 (*c* 0.0074, $CHCl_3$); IR (KBr): 3300–3350(s), 1670(vs), 1529(s) cm^{-1}; FAB+ MS (*m*-nitrobenzyl alcohol), *m*/*z* 518 [M+H]$^+$. ^{1}H NMR [$CDCl_3$, 300 MHz]: δ_H 0.96 (AB, J_{AB} = 10.5 Hz, 1H), 1.01 (AB, J_{AB} = 10.6 Hz, 1H), 2.14 (septet, 2H), 3.51–3.96 (m, 12H), 8.00 (t, 1H), 8.33 (d, 2H), 8.47 (d, 2H). ^{13}C NMR [$CDCl_3$, 50 MHz]: 19.8(q), 20.1(q), 29.8(d), 55.6(d), 70.3(t), 71.1(t), 72.2(t), 125.1(d), 138.6 (d), 149.2 (s), 163.3 (s); calcd for $C_{29}H_{44}N_2O_6$: C, 67.42; H, 8.58; N, 5.42; Found: C, 67.3; H, 8.4; N, 5.3.

4.4. U-tube transport experiments

Cation transport experiments were performed in a simple U-tube apparatus by using a previously published procedure.[2] Thus, a solution of optically active macrocycle (27 mmol dm^{-3}) in $CHCl_3$ (10 mL) was placed in a 14 mm i.d. U-tube at 30°C. Into the source phase of the U-tube was introduced 5.0 mL of a solution that contained the guest ammonium salt (i.e. racemic methyl ester, 1.0 mmol and $LiPF_6$ (0.8 mol dm^{-3}) in aqueous HCl (and 0.08 mol dm^{-3}). Into the receiving phase of the U-tube was placed 0.10 mol dm^{-3} aqueous HCl (5.0 mL, 0.50 mmol). A small magnetic stirring bar was used to mix the $CHCl_3$ and aqueous layers at a constant rate. The UV absorbance of the aqueous receiving was measured at $\lambda_{max} = 286$ nm. The optical rotation measured using a 20 cm polarimetry cell (3 mL).

The rate of transport was slowed by using 0.8 mol dm^{-3} HCl in the source phase.

Acknowledgements

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