Tetrahedron Letters, Vol.32, No.44, pp 6277-6280, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Optically Active Mono and Bis(1,1'-Binaphthyl)-Cyclophanes: Large Differences in the Complexation of Naproxen Derivatives in Aqueous Solution

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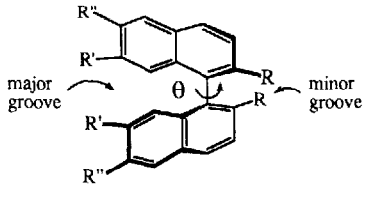
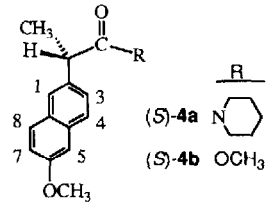
ABSTRACT *Four new optically active cyclophanes with apolar cavities shaped by the major grooves of the 2,2',6,6'- and 2,2',7,7'-tetraoxa-1,1'-binaphthyl units were prepared for the inclusion complexation of naproxen derivatives in aqueous solution. Macrocycles formed by one diphenylmethane and one binaphthyl spacer give stronger binding and, unexpectedly, a higher degree of chiral recognition than cyclophanes formed by two bridged binaphthyl derivatives.*

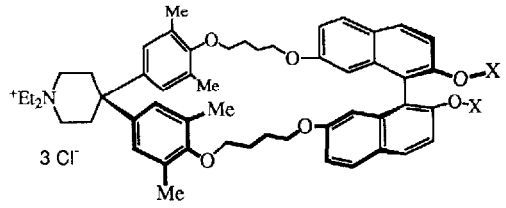
In 1989, we reported the synthesis of the (*R*)- and (*S*)-enantiomers of cyclophane **3** starting from the readily available optically pure 2,2',7,7'-tetraoxa-1,1'-binaphthyl spacer **1**.[1,2] These macrocycles form diastereomeric inclusion complexes of differential stability[3] with chiral naproxen [2-(6-methoxy-2-naphthyl)propionic acid] derivatives in D_2O/CD_3OD (60:40, v/v, 293 K). The largest difference in stability [$\Delta(\Delta G^o) = 0.33$ kcal mol^{-1}] was measured for the diastereomeric complexes of the bulky naproxen derivative **4a**, and this was explained in terms of differential steric interactions.[1] We reasoned that an even higher degree of chiral recognition would be observed for complexation occurring at recognition sites formed by *two* 1,1'-binaphthyl units. Therefore, starting from the enantiomerically pure spacers **1** and **2**, we prepared the optically active bis(binaphthyl)-cyclophanes **5** - **7** together with derivative **8**. Here, we give a preliminary account on the synthesis of these macrocycles and the unexpected results obtained in chiral recognition studies using naproxen derivatives.



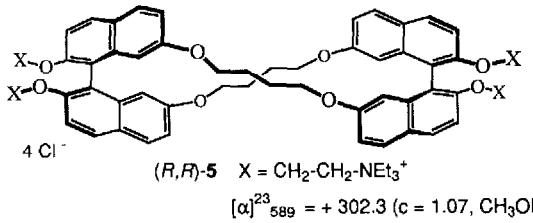
	R	R'	R''
1	OH	OCH_2Ph	H
2	OCH_2Ph	H	OH



	R
(*S*)-**4a**	N
(*S*)-**4b**	OCH_3

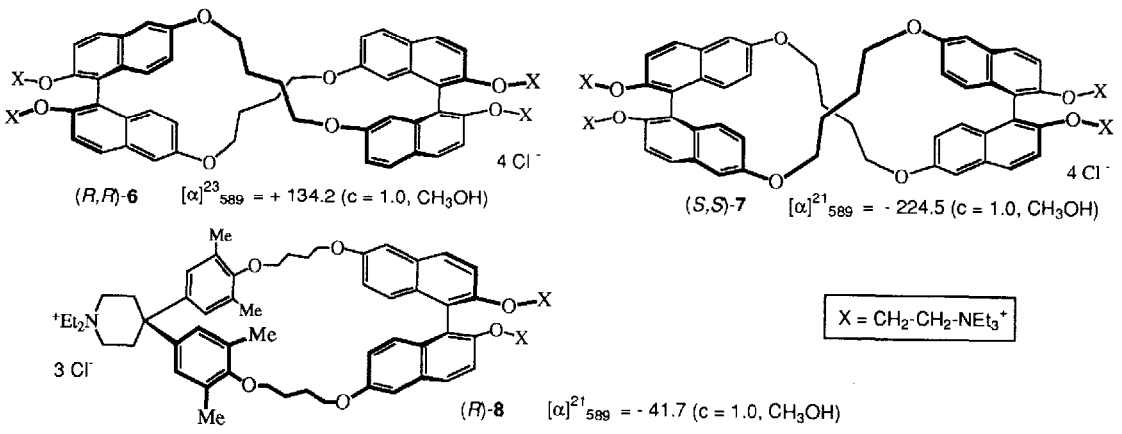


(*R*)-**3** X = CH_2-CH_2-NEt_3^+



(*R,R*)-**5** X = CH_2-CH_2-NEt_3^+

$[\alpha]^{23}_{589}$ = + 302.3 (c = 1.07, CH_3OH)



The synthesis of the new spacers (*R*)- and (*S*)-**2**, which starts from optically pure 2,2'-dihydroxy-1,1'-binaphthyl[4], is shown in Scheme 1.[5] The preparation of (*R,R*)-**6** is described in Scheme 2, and the construction of the three other new cyclophanes follows a similar protocol. The high optical purity (e.e. > 99%) of the target macrocycles was demonstrated (a) by chiral chromatography[6] and (b) by the ^{1}H NMR binding studies with optically active naproxen guests which showed only one diastereomeric complex in each titration.

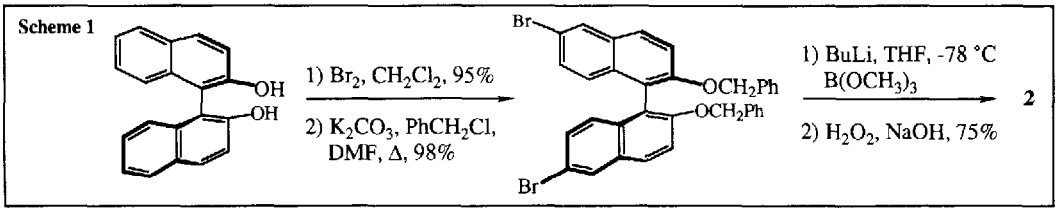
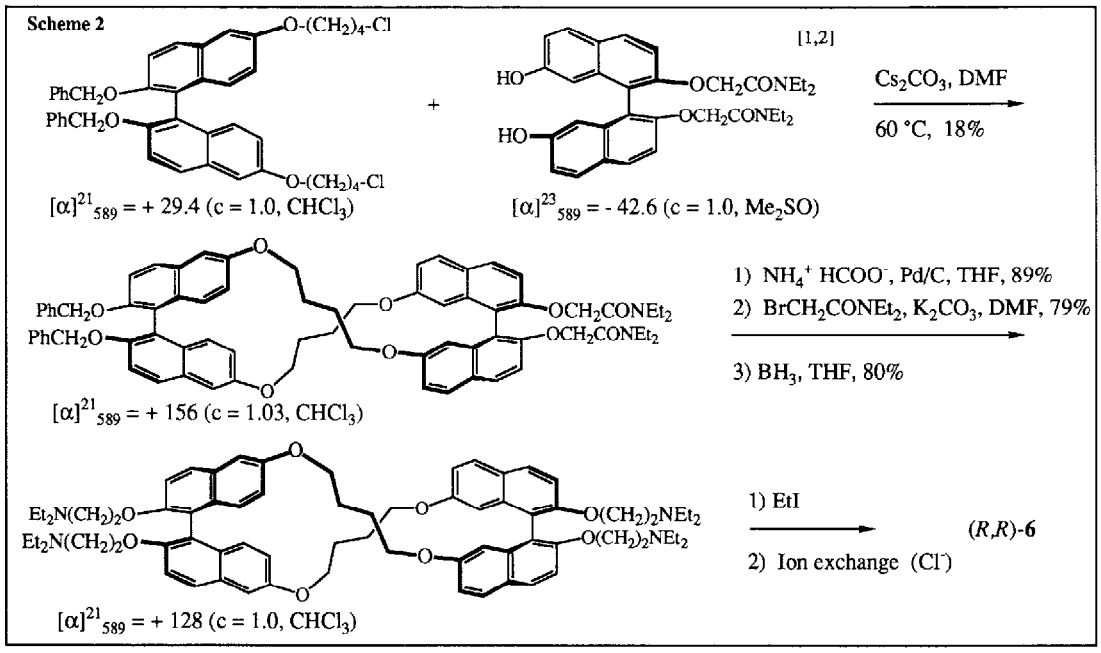


Table 1 summarizes the results of the 500 MHz ^{1}H NMR binding studies that were performed at 293 K with (*R*)- or (*S*)-**4a** as the guests in D_2O/CD_3OD (60:40, v/v). Titrations with the methyl ester of naproxen (**4b**) gave similar results. The K_a and $-\Delta G^o$ values in Table 1 are averages of the data obtained by evaluating the complexation-induced shifts of all individual aromatic naproxen resonances in ^{1}H NMR titrations with constant guest concentration. The following conclusions can be drawn from the complexation studies.

(1) Cyclophane **3**, in which a 2,2',7,7'-tetraoxa-1,1'-binaphthyl (7,7'-BN) unit is bridged by a diphenylmethane (DPM) unit, forms by far the most stable complexes with (*R,S*)-**4a** and other naproxen derivatives.[1] This is in sharp contrast to the fact that no significant binding was observed with **5** which incorporates two 7,7'-BN units. Preliminary modeling studies[7] suggest that the lack of binding is due to the conformation of the binaphthyl units. In the lowest energy conformations of **5**, the binaphthyl units prefer to adopt a small dihedral angle ($\theta \approx 70 - 75°$)[8] about their chirality axis which narrows the cavity width which is crucial for binding.[9] The O···O distances at the major grooves of the spacers are reduced to ≈ 5.5 - 6.0 Å which leads to the closing of any potential binding site. In contrast, bridging the chiral spacer in **3** with the wide open DPM unit (O···O distance ≈ 8.5 - 9.0 Å)[8] enforces a larger dihedral angle in the binaphthyl unit ($\theta = 81°$, O···O distance at the major groove = 6.4 Å in the current lowest energy conformation of **3**), and a more preorganized binding site is obtained.



(2) Cyclophanes **6** - **8**, which incorporate one or two 2,2',6,6'-tetraoxa-1,1'-binaphthyl (6,6'-BN) units, respectively, all show good binding in the binary solvent mixture. The O···O distance at the major groove of the 6,6'-BN unit (10.0 Å at θ = 90°) is significantly larger than in the 7,7'-BN unit (7.1 Å at θ = 90°). This leads to a more open binding site in the 6,6'-BN-cyclophanes, even at dihedral angles θ much smaller than 90°. However, the comparison between the mono(binaphthyl)-hosts **3** and **8** (Table 1) clearly shows that an open 7,7'-BN major groove is geometrically a more suitable chiral spacer for a flat aromatic binding site than the 6,6'-BN major groove. The formation of inclusion complexes by the three 6,6'-BN-macrocycles is supported by large complexation-induced upfield shifts of the ^{1}H NMR resonances of the guest and the differential up and downfield shift pattern of the host protons which is characteristic for many cyclophane-arene complexes.[10] According to the ^{1}H NMR data, the 7,7'-BN-cyclophane **3** forms tighter, more structured complexes than the 6,6'-BN-macrorings **6** - **8**.

Table 1: Association constants K_a and free energies of formation $-\Delta G^o$ for the diastereomeric complexes between (*R*,*S*)-**4a** and binaphthyl-cyclophanes in D_2O/CD_3OD (60:40, v/v, T = 293 K).[a] The calculated differences in stability between diastereomeric complexes $\Delta(\Delta G^o)$ are also given.

	(*R*)-**4a**		(*S*)-**4a**		
host	K_a (L mol^{-1})	$-\Delta G^o$ (kcal mol^{-1})	K_a (L mol^{-1})	$-\Delta G^o$ (kcal mol^{-1})	$\Delta(\Delta G^o)$ (kcal mol^{-1})
(*R*)-**3**[b]	2490	4.55	1405	4.22	0.33
(*R*)-**8**	560	3.69	395	3.49	0.20
(*R*,*R*)-**6**	320	3.36	375	3.45	- 0.09
(*S*,*S*)-**7**	435	3.53	455	3.54	≈ 0
(*R*,*R*)-**5**	no significant complexation observed				

[a] Errors in K_a: ± 10 %. [b] Reference 1.

(3) The degree of chiral recognition in the complexes of hosts **3** and **8**, which are shaped by one chiral spacer and one achiral DPM unit, is surprisingly higher than in the complexes of the bis(binaphthyl)-cyclophanes **6** and **7**. Only the $\Delta(\Delta G^{o})$ values calculated for the diastereomeric complexes of **3** and **8** with (*R,S*)-**4a** represent significant differential stabilities outside the error of the binding assay. All three 6,6'-BN-cyclophanes **6** - **8** act as efficient chiral solvating agents, and differential complexation shifts of the resonances of both host and guest are observed in the diastereomeric inclusion complexes of **4a/b** and other naproxen derivatives. For the naphthalene resonances of the esters (*R*)-**4b** and (*S*)-**4b** bound to (*R,R*)-**6**, the following upfield complexation shifts at saturation binding, $\Delta\delta_{sat}$ (ppm, numbers in parentheses for resonances of the (*S*)-ester), were calculated from titrations in which 90% of saturation binding was observed: 1-H: 1.13 (1.19); 3-H: 0.81 (0.88); 4-H: 0.89 (1.07); 5-H: 0.68 (0.74); 7-H: 0.56 (0.58); 8-H: 0.85 (0.92).

(4) The unexpected binding obtained within a series of related chiral cyclophanes demonstrates that we are not yet able to predict and control in a satisfying way the conformational preferences of large flexible macrocycles with molecular weights around 1000 Daltons or their apolar inclusion complexes in protic environments. In our original design,[1,9] we had hoped to accomplish efficient chiral recognition between naproxen derivatives and binaphthyl-cyclophanes based on three differential host-guest interactions: (i) apolar surface interactions within the cavity, (ii) steric interactions between the cavity walls and the naproxen substituents, and (iii) π-π interactions between the naphthalene rings of the binaphthyls and the carboxyl residues of the substrates. From this study, we conclude that it will be difficult to achieve a high degree of enantioselectivity in complexation processes based solely on these interactions. Efficient chiral recognition requires the introduction of oriented bonding interactions, e.g. hydrogen bonding or strong dipolar or charge alignment, as an additional discriminating force in diastereomeric complexes.[1, 11] The results described above suggest that macrocycle **3**, by far the best binder (Table 1), should be the most suitable candidate among the binaphthyl-cyclophanes for further functionalization.

Acknowledgment: This work was supported by the National Institutes of Health (NIH). P.P.C. thanks the NIH for a MARC Predoctoral Fellowship. We thank Syntex Corporation for a generous gift of (*R*)-naproxen.

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(Received in USA 30 July 1991)