Enantioselective Anion Binding

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A Binol-Strapped Calix[4]pyrrole as a Model Chirogenic Receptor for the Enantioselective Recognition of Carboxylate Anions**

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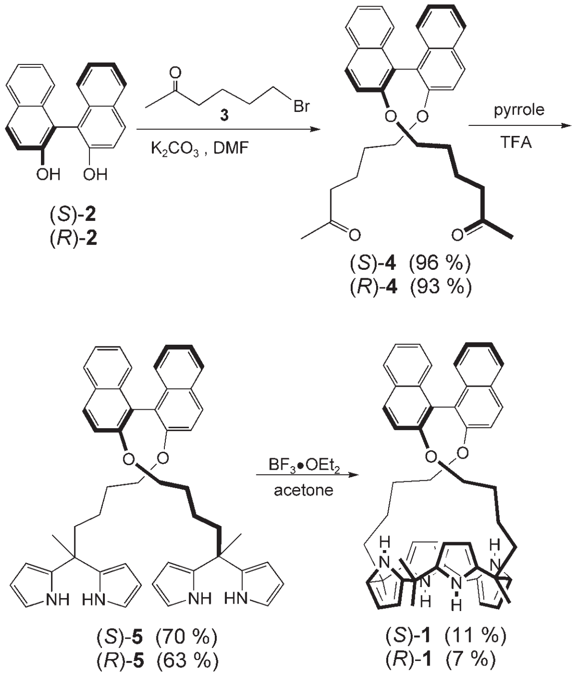
Receptors[1] with a strong selectivity for specific anionic substrates are interesting targets for the supramolecular chemical community.[2] Anions are ubiquitous in biology and in the environment, and it is thus expected that such species could play important roles in areas as diverse as drug development, environmental remediation, and catalysis. Among the various neutral anion-binding agents reported to date, the calix[4]pyrroles[3] have attracted particular attention because they are easy to prepare and because they bind certain anions (e.g., fluoride, chloride, dihydrogen phosphate, and carboxylates) strongly in aprotic solvents. While issues of ion-pairing and solvation are important,[3d] the selectivities for simple calix[4]pyrroles are often dominated by anion basicity effects (i.e., $F^- > Cl^- > Br^-$ in CH_2Cl_2).[3e] One way of producing more selective calix[4]pyrrole-type anion receptors would involve pre-organizing the host molecule. A pre-organized calix[4]pyrrole dimer for dicarboxylate recognition[4] and a urea-functionalized calix[4]pyrrole for pyrophosphate[5] recognition provide examples of this generalized approach. A different strategy, however, involves the use of so-called strapped calix[4]pyrroles.[6]

The introduction of a diametrical strap that bridges one face of the calix[4]pyrrole macrocycle provides a convenient means of introducing various functional groups with potentially controllable ancillary binding domains at or near the pyrrole NH-derived anion binding site. Several tunable strapped calix[4]pyrrole systems have been reported to date,[6] although more elaborate strapped systems containing built-in chiral-recognition moieties are still unknown. Such nonracemic calix[4]pyrroles would be potentially useful in that they might be expected to exhibit different affinities towards pairs of stereoisomers. Ultimately, such systems might allow for the separation of various enantiomeric guests, including amino acids, as has proved possible with a limited number of supramolecular hosts.[7]

Herein, we report the synthesis of the nonracemic calix[4]pyrrole **1** (*R*(+) or *S*(−)), which contains an optically active binol group (binol = 2,2′-dihydroxy-1,1′-binaphthyl) as the asymmetry-defining element, as well as the results of binding studies involving chiral carboxylate anions. This chirogenic calix[4]pyrrole appears to be an effective receptor for such anions.

The enantiomeric binol-strapped calix[4]pyrroles (*R*)-**1** and (*S*)-**1** were synthesized in three steps, as shown in Scheme 1. First, 6-bromo-2-hexanone (**3**)[8] was treated with (*R*)-(+)-1,1′-bi(2-naphthol) ((*R*)-**2**) or (*S*)-(−)-1,1′-bi(2-naphthol) ((*S*)-**2**) to afford the diketones (*R*)-**4** and (*S*)-**4** in 93% and 96% yield, respectively. Compounds (*R*)-**4** and (*S*)-**4** were



Scheme 1. Synthesis of the binol-strapped calix[4]pyrroles (*S*)- and (*R*)-**1**. TFA = trifluoroacetic acid. Note that only the (*S*)-enantiomers of **1**, **2**, **4**, and **5** are shown.

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then condensed with pyrrole in the presence of a catalytic amount of trifluoroacetic acid to give dipyrromethanes (*R*)-**5** and (*S*)-**5** in 63 % and 70 % yield, respectively. Condensation of the resulting products with neat acetone in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ afforded the desired chiral receptors (*R*)-**1** and (*S*)-**1** in 7 % and 11 % yield, respectively. Compounds (*R*)-**1** and (*S*)-**1** were fully characterized by ^{1}H NMR, ^{13}C NMR, and circular dichroism (CD) spectroscopy as well as by mass spectrometry.

The CD spectra of the two enantiomeric binol-strapped calix[4]pyrroles (*R*)-**1** and (*S*)-**1** were found to be essentially mirror images of each another (Figure 1).

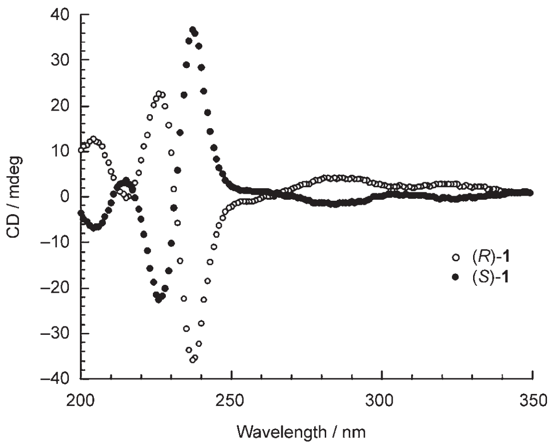


Figure 1. CD spectra of (*R*)-**1** and (*S*)-**1** in acetonitrile (1×10^{-5} M at 25 °C).

Preliminary studies designed to probe the enantioselective recognition characteristics of (*R*)-**1**[9] and (*S*)-**1** were carried out by ^{1}H NMR spectroscopy. Specifically, (*S*)-**1** was studied in the presence of the chiral anionic guests (*R*)-2-phenylbutyrate ((*R*)-PB) or (*S*)-2-phenylbutyrate ((*S*)-PB) (as the tetrabutylammonium salt) in deuterated chloroform at 298 K (see the Supporting Information).

Careful analysis of the ^{1}H NMR spectra obtained from a 1:1 mixture of host and guest [(*S*)-**1**/(*R*)-PB and (*S*)-**1**/(*S*)-PB] showed that receptor (*S*)-**1** binds (*S*)-PB more strongly than (*R*)-PB. This conclusion is based on the observation that the characteristic peak changes associated with anion binding (e.g., decreased NH peak intensity, transformation of the four sets of β-pyrrolic proton triplets into doublets, and the splitting of the CH_2 signal on the strap into a triplet) occur after the addition of only one equivalent of (*S*)-PB as guest. A slight upfield shift of the aromatic peaks of (*S*)-PB is also seen (see the Supporting Information). In contrast, the addition of three equivalents of guest is required in the case of (*R*)-PB. Once the carboxylate anion is bound, both complexes become conformationally rather rigid.

In an effort to determine the association constant (K_a) for the binding of (*S*)-**1** with (*S*)-PB, ^{1}H NMR spectroscopic titrations were performed with dilute samples ([(*S*)-**1**] $=1\times10^{-3}$ M in [D$_3$]acetonitrile). However, even under these conditions the association of receptor (*S*)-**1** with (*S*)-PB proved too strong to quantify, which means that $K_a(S)$ is greater than $10000\,\text{M}^{-1}$.[10] The association constants for the interaction of (*S*)-**1** with this pair of enantiomeric guests ((*R*)- and (*S*)-PB) were therefore determined in anhydrous acetonitrile by isothermal titration calorimetry (ITC; Figure 2).[11]

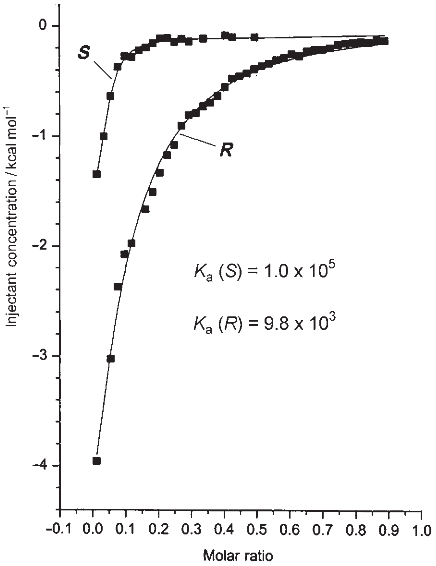
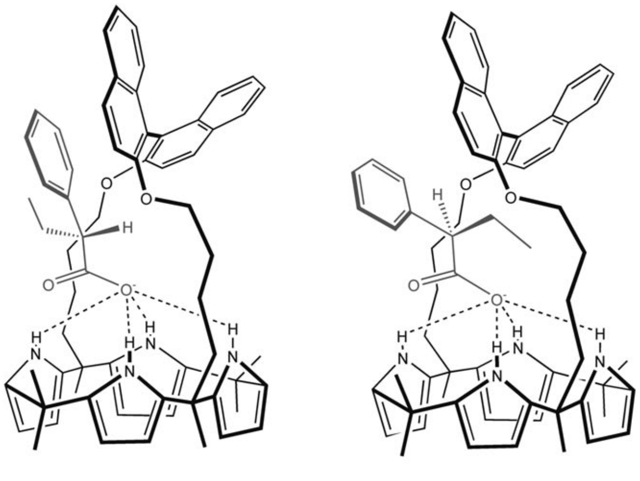


Figure 2. ITC curves corresponding to the interaction of binol-strapped calix[4]pyrrole (*S*)-**1** (5×10^{-4} M in anhydrous acetonitrile) with (*R*)- and (*S*)-PB; these substrates are labeled as (*R*) and (*S*), respectively.

The association constants for the binding of (*R*)- and (*S*)-PB to (*S*)-**1** ($K_a(R)=9.8\times10^3$ and $K_a(S)=1.0\times10^5\,\text{M}^{-1}$, respectively) were obtained with the curve-fitting program[12] supplied with the ITC instrument. As expected on the basis of the initial ^{1}H NMR spectroscopic studies, the association constant for the interaction of (*S*)-**1** with (*S*)-PB proved to be larger than that recorded for (*S*)-**1** with (*R*)-PB. In fact, $K_a(S)$ was found to be around 10-times larger than $K_a(R)$. This value corresponds to an energetic preference of 1.38 kcal mol^{-1} in favor of the (*S*)-enantiomer at room temperature. Thus, we can conclude that the binol-strapped calix[4]pyrrole (*S*)-**1** can distinguish between appropriately chosen sets of enantiomeric anionic guests.

The proposed binding modes for the complex formed between the binol-strapped calix[4]pyrrole (*S*)-**1** and both (*R*)- and (*S*)-PB are shown in Figure 3. These depictions serve to illustrate the intuitively appealing assumption that the lower association constant observed for the combination of (*S*)-**1** and (*R*)-PB reflects unfavorable steric interactions between the chiral, nonracemic receptor and the phenyl group of the guest. In contrast, the larger association constant observed for (*S*)-**1** and (*S*)-PB can be rationalized in terms of favorable π–π interactions between one of the receptor naphthyl groups and the phenyl group of the bound substrate.

Further support for the above conclusions came from density functional theory (DFT) calculations carried out for complexes (*S*)-**1**·(*R*)-PB and (*S*)-**1**·(*S*)-PB.[13] The results of these calculations are shown in Figure 4.[18] Both complexes are characterized by hydrogen-bond interactions between the



(*S*)-**1**•(*S*)-PB (*S*)-**1**•(*R*)-PB

Figure 3. Proposed binding modes for the diastereomeric complexes formed between receptor (*S*)-**1** and (*S*)- and (*R*)-PB showing the relevant intermolecular interactions (dashed lines indicate hydrogen bonds). Note the destabilizing steric interactions that are present in the latter structure.

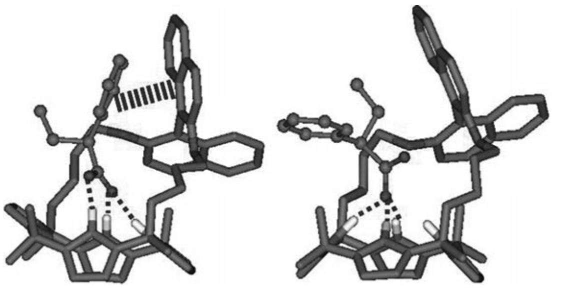


Figure 4. Optimized geometries at the B3LYP/6-31+G*//B3LYP/3-21G* level are shown for the complexes between (*S*)-**1** and (*S*)-PB (left) and (*R*)-PB (right). Note that only in the complex (*S*)-**1**·(*S*)-PB is a (presumably stabilizing) π–π interaction between one of the naphthyl groups and the substrate phenyl group favored. This interaction is shown with a thick dashed line, thin dashed lines denote NH···OC hydrogen bonds.

pyrrole NH protons and the oxygen atom of (*R*)-PB. However, these two complexes differ substantially in the relative orientation of the benzene ring of the guest. In the optimized structure of (*S*)-**1**·(*S*)-PB, the guest is recognized by what we presume to be stabilizing π–π interactions between the benzene ring of the guest and one of the naphthyl groups of the host (as well as by pyrrole NH–carboxylate anion hydrogen bonds). No such π–π interactions are seen in the case of (*S*)-**1**·(*R*)-PB and, in fact, this latter complex is characterized by unfavorable steric effects involving the phenyl ring of the substrate. (*S*)-**1**·(*S*)-PB is computed to be 5.5 kcal mol^{-1} more stable than (*S*)-**1**·(*R*)-PB. Although this calculated difference in energy (and hence in relative stability) is larger than that observed experimentally, it underlines the fact that the (*S*)-PB complex is energetically more favored than the corresponding (*S*)-**1**·(*R*)-PB pair. In other words, both the titration experiments and the computational studies support the key conclusion that the binol-strapped calix[4]pyrrole (*S*)-**1** selectively recognizes an appropriately chosen enantiomeric substrate ((*S*)-PB in the present case) over the corresponding enantiomer ((*R*)-PB).

In conclusion, we have synthesized a new set of chiral receptors, namely the binol-strapped calix[4]pyrroles (*R*)-**1** and (*S*)-**1**. The resulting association constants K_a were found to be around 10-times larger in the case of the *S*-configured guest (*S*)-PB than in the case of the *R* enantiomer. The present work thus supports the emerging notion that strapped calix[4]pyrroles represent a new, specialized class of "smart" molecular receptors whose binding properties can be fine-tuned for specific applications, including enantiomeric anion recognition.

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[1] a) *Supramolecular Chemistry of Anions* (Eds.: A. Bianchi, K. Bowman-James, E. García-España), Wiley, New York, **1997**; b) F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, *97*, 1609–1646; c) P. D. Beer, P. A. Gale, *Angew. Chem.* **2001**, *113*, 502–532; *Angew. Chem. Int. Ed.* **2001**, *40*, 486–516; anion sensors: d) A. W. Czanik, *Acc. Chem. Res.* **1994**, *27*, 302–308; e) A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515–1566; f) K. P. Xiao, P. Buhlmann, S. Nishizawa, S. Amemiya, Y. Umezawa, *Anal. Chem.* **1997**, *69*, 1038–1044; g) P. D. Beer, *Acc. Chem. Res.* **1998**, *31*, 71–80; h) C. Suksai, T. Tuntulani, *Chem. Soc. Rev.* **2003**, *32*, 192–202; i) R. Martínez-Máñez, F. Sancenón, *Chem. Rev.* **2003**, *103*, 4419–4476; j) R. J. Fitzmaurice, G. M. Kyne, D. Douheret, J. D. Kilburn, *J. Chem. Soc. Perkin Trans. 1* **2002**, 841–864.

[2] *Comprehensive Supramolecular Chemistry* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, K. S. Suslick), Pergamon, Oxford, **1996**.

[3] a) P. A. Gale, J. L. Sessler, V. Král, *Chem. Commun.* **1998**, 1–8; b) J. L. Sessler, P. Anzenbacher, Jr., K. Jursíková, H. Miyaji, J. W. Genge, N. A. Tvermoes, W. E. Allen, J. A. Shriver, P. A. Gale, V. Král, *Pure Appl. Chem.* **1998**, *70*, 2401–2408; c) J. L. Sessler, P. A. Gale in *The Porphyrin Handbook*, *Vol. 6* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), Academic Press, San Diego, **1999**, pp. 257–278; d) J. L. Sessler, D. E. Gross, W.-S. Cho, V. M. Lynch, F. P. Schmidtchen, G. W. Bates, M. E. Light, P. A. Gale, *J. Am. Chem. Soc.* **2006**, *128*, 12281–12288; e) J. L. Sessler, S. Camiolo, P. A. Gale, *Coord. Chem. Rev.* **2003**, *240*, 17–55.

[4] W. Sato, H. Miyaji, J. L. Sessler, *Tetrahedron Lett.* **2000**, *41*, 6731–6736.

[5] P. Anzenbacher, Jr., K. Jursikova, J. L. Sessler, *J. Am. Chem. Soc.* **2000**, *122*, 9350–9351.

[6] a) D. W. Yoon, H. Hwang, C. H. Lee, *Angew. Chem.* **2002**, *114*, 1835–1837; *Angew. Chem. Int. Ed.* **2002**, *41*, 1757–1759; b) C. H. Lee, H. K. Na, D. W. Yoon, D. H. Won, W. S. Cho, V. M. Lynch, S. V. Shevchuk, J. L. Sessler, *J. Am. Chem. Soc.* **2003**, *125*, 7301–7306; c) C. H. Lee, J. S. Lee, H. K. Na, D. W. Yoon, H. Miyaji, W. S. Cho, J. L. Sessler, *J. Org. Chem.* **2005**, *70*, 2067–2074; d) H. Miyaji, H.-K. Kim, E.-K. Sim, C.-K. Lee, W.-S.

Cho, J. L. Sessler, C.-H. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 12510 – 12512.

[7] For a recent review of chiral recognition of anions, see: a) I. Stibor, P. Zlatuskova, *Top. Curr. Chem.* **2005**, *255*, 31 – 63; for other selected papers, see: b) J. L. Sessler, A. Andrievsky, V. Král, V. Lynch, *J. Am. Chem. Soc.* **1997**, *119*, 9385 – 9392; c) A. Tejeda, A. I. Oliva, L. Simón, M. Grande, M. C. Caballero, J. R. Morán, *Tetrahedron Lett.* **2000**, *41*, 4563 – 4566; d) C. Schmuck, *Chem. Eur. J.* **2000**, *6*, 709 – 718; e) L. J. Lawless, A. G. Blackburn, A. J. Ayling, M. N. Pérez-Payán, A. P. Davis, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1329 – 1341; f) P. Laurent, H. Miyaji, S. R. Collinson, I. Prokes, C. J. Moody, J. H. R. Tucker, A. M. Z. Slawin, *Org. Lett.* **2002**, *4*, 4037 – 4040; g) H. Miyaji, G. Gasser, S. J. Green, Y. Molard, S. M. Strawbridge, J. H. R. Tucker, *Chem. Commun.* **2005**, 5355 – 5357; h) S. González, R. Peláez, F. Sanz, M. B. Jiménez, J. R. Morán, M. C. Caballero, *Org. Lett.* **2006**, *8*, 4679 – 4682.

[8] W. Zhang, C. Li, *J. Org. Chem.* **2000**, *65*, 5831 – 5833.

[9] The ^{1}H and ^{13}C NMR spectra of (*R*)-**1** are identical to those of (*S*)-**1**.

[10] The signals for the four pyrrole NH protons of calix[4]pyrrole (*S*)-**1** were found to disappear upon the addition of 1.0–1.2 equivalents of (*S*)-2-phenylbutyrate.

[11] a) F. P. Schmidtchen, *Org. Lett.* **2002**, *4*, 431 – 434; b) ITC measurements were performed as follows: Solutions of the chosen receptor in acetonitrile were made up so as to provide a receptor concentration range of 0.1–1 mM. These solutions were then individually titrated with the appropriate alkylammonium salts at (30 ± 0.01) °C. The original heat pulses were normalized using reference titrations carried out using the same salt solution but in pure acetonitrile.

[12] Non-linear curve-fittings were performed with Origin 7.0 (OriginLab Co.) using a 1:1 fitting program provided by the ITC manufacturer (MicroCal, Inc.).

[13] An initial conformational analysis of each molecular system was performed by molecular dynamics (MD) simulation using the SANDER module of AMBER employing the parm99 force field.[14] From the MD simulation trajectory for each molecular system, a total of 200 structures were collected which were then subjected to an optimization procedure using the AM1 semiempirical method[15] to find the energy minima that would be used as initial structures for the DFT calculations at the B3LYP/3-21G level[16] using the Gaussian 98 package.[17] Frequency calculations were performed to verify the identity of each stationary point as a minimum. To provide a more complete description of the interactions with anionic guests, single-point energy calculations were then carried out at the B3LYP/6-31G+G* level using the optimized geometries obtained from the B3LYP/3-21G* analyses.

[14] D. A. Case, D. A. Pearlman, J. W. Caldwell, et al. see Supporting Information, AMBER 7, University of California, San Francisco, **2002**.

[15] a) M. J. S. Dewar, W. Thiel, *J. Am. Chem. Soc.* **1977**, *99*, 4899 – 4907; b) M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, *J. Am. Chem. Soc.* **1985**, *107*, 3902 – 3909.

[16] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648 – 5652.

[17] M. J. Frisch et al. see Supporting Information, Gaussian 98, Revision A.7 Gaussian, Inc., Pittsburgh PA, **1998**.

[18] Subsequent to submission of this manuscript a single-crystal X-ray structure of a 3,3′-dibromonaphthyl derivative of (*S*)-**1** was obtained. This structure proved analogous to that calculated for receptor (*S*)-**1** in the absence of an added substrate.