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Calix[4]arene-based ditopic receptor for dicarboxylates

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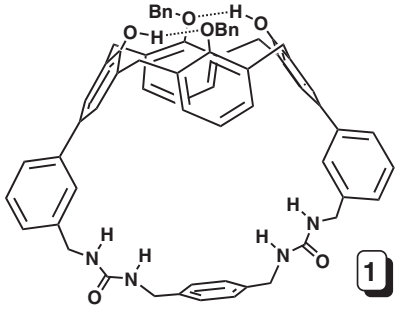
Abstract—Shape-selective recognition for the dicarboxylates in DMSO can be attained by a new calix[4]arene-based receptor **1** having two urea groups. Biologically active chorismate selectively bound in **1** over its dehydrated derivative. Molecular mechanics calculations gave a plausible explanation for the selective binding.

Carboxylates are involved in many biological recognition events, and some of them play a key role in the regulation of biological process. The selective recognition of carboxylates by synthetic receptors becomes a topic of current interest in supramolecular chemistry. Carboxylate recognition has been widely investigated with many artificial receptors,[1] including several calix[4]arene-based ones employing fluoro alcohol,[2] amide[3] and (thio)urea[4] on their upper rim. These calix[4]arene-based receptors can bind to mono- and dicarboxylates; however, the shape-selective recognition for dicarboxylates is limited so far. This is probably due to the limited binding environment in the pinched cone conformation of the O-alkylated calix[4]arenes.[3d,e,5] We envisioned to construct the pre-organized guest-binding space on the calix[4]arene upper rim in which dicarboxylates can accommodate selectively. During the last decade, our group has investigated the upper rim functionalized calixarene hosts for neutral guests.[6] In this paper we report the shape-selective recognition of dicarboxylates with calix[4]arene-based synthetic receptor **1** in DMSO.

Placing hydrogen-bonding groups on the calix[4]arene platform should be an effective strategy for a receptor of carboxylates. Two urea groups are attached with the aromatic linkages on the upper rim. The *para*-xylylene spacer and the lower rim intramolecular hydrogen bonding of phenolic hydroxyl groups keep the urea groups away from each other. This provides the large guest-binding space in which the urea groups will act simultaneously in grasping a proper bifunctional anion with hydrogen bonds.



The synthesis of **1** started from dibromocalix[4]arene **2**[7] according to Scheme 1. Compound **2** was subjected to react with sodiumhydride. The resulted diphenolate was treated with methoxymethylchloride to give dibromocalix[4]arene **3** only in the cone conformation. Palladium catalyzed coupling between **3** and organozinc reagent **4** proceeded smoothly, and subsequent treatment of TBAF gave diol **5**. Mitsunobu reaction of **5** with phthalimide, triphenyl phosphine, and DEAD in THF, followed by treatment with hydrazine gave diaminocalix[4]arene **6**.

The cyclization reaction of **6** with isocyanate equivalent **7** smoothly proceeded to give the diurea derivative,

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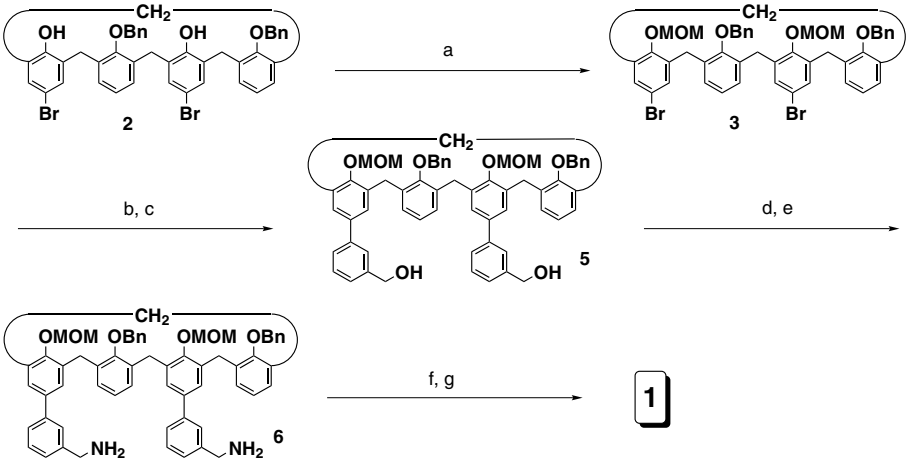


Scheme 1. Reagents and conditions: (a) MOMCl, NaH/DMF 70%; (b) $Pd(PPh_3)_4$, ZnCl/OTBS **4**/THF; (c) TBAF/THF 72%; (d) phthalimide, DEAD, PPh_3/THF 83%; (e) H_2NNH_2/EtOH 93%; (f) **7**/DMF 29%; (g) 6 N HCl/EtOH 97%.

which was treated with acidic ethanol. The desired receptor was given in reasonable yield.

Receptor **1** showed good solubility in DMSO, known as a highly competitive solvent to hydrogen bonding. The ditopic binding sites of **1** are solvated in DMSO and hence, multipoint hydrogen bonds between **1** and a guest are required for the effective complexation. Dicarboxylates **8**–**15** are selected as guests because of the complementary multipoint hydrogen bonds to the urea group[8] (Fig. 1).

^{1}H NMR spectrum of **1** in DMSO-d_6 gave the sharp N–H resonances. When bis(tetrabutylammonium)-4-*tert*-butylisopthalate **8** was added to the solution of **1**, the N–H resonances shifted down field. This indicative shifts provide the evidence for the formation of the hydrogen-bonded complex even in DMSO (Fig. 2).

The stoichiometry of the host–guest complex was studied by Job's plot. The amount of the host–guest complex reached a peak at the mole fraction of 0.5. This confirms 1:1 complex formation between the host and the guest. A nonlinear least square curve-fitting analysis[9] gave an association constant, $1100 \pm 200\ M^{-1}$.

The binding abilities of guests **9**–**16** toward **1** were evaluated in DMSO. In all cases, the characteristic down-field shift of the urea N–H resonance was observed. From the titration experiment, the association constants were estimated (Table 1).

All the ditopic guests **8**–**15** bind more strongly than benzoate **16**. Previously reported bisureido calix[4]arene selectively bound monocarboxylates over dicarboxylates.[4f] The different binding manners suggest that the *p*-xylylene spacer plays a crucial role in the dicarboxylate recognition. However, the *p*-xylylenebisurea unit itself hosts dicarboxylates.[10] The binding behavior of *N*,*N*″-(*p*-xylylene)bis(*N*′-benzylurea) **17**[11] was evaluated for the carboxylates (**9**: $K_a = 130 \pm 10\ M^{-1}$, **16**: $K_a = 43 \pm 3\ M^{-1}$). Dicarboxylate **9** complexes with **1** ca. four times as strongly as with **17** while monocarboxylate **16** does not shows any selective binding. This clearly indicated that

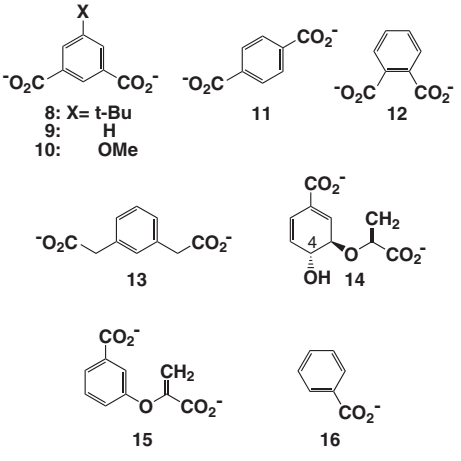


Figure 1. The carboxylates for the binding studies of **1**.

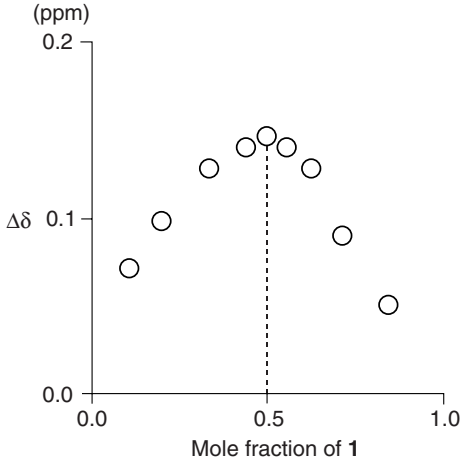


Figure 2. Jobs plot for guest **8** with **1**.

Table 1. Binding constants (M^{-1}) of **1** with various carboxylates **8**–**16** in DMSO-d_6 at 298 K

Guest	K_a	Guest	K_a
8	1100 ± 200	**13**	650 ± 100
9	490 ± 30	**14**	600 ± 50
10	170 ± 10	**15**	150 ± 30
11	180 ± 10	**16**	43 ± 2
12	370 ± 30		

the combination of the calix[4]arene and the *p*-xylylenebisurea produced the selective recognition toward the dicarboxylates.

As expected, the shape selectivity of **1** toward the guests **9**, **11**, and **12** is very substantial, reflecting the directional interaction of the hydrogen bonding. It is known that in the case of hydrogen-bonding interaction between carboxylate anion and urea group, two linear hydrogen-bond pair is more stable than two bent pair (Fig. 3).[12]

Comparison of the binding constants for guests **8**–**10** suggested the importance of the electronic effect on the hydrogen-bonding interaction. A simple model building consideration suggested that the host is not large enough to accommodate the guests thoroughly within its cavity when two-bent hydrogen bonds between the carboxylate and urea groups were applied twice. Actually, the molecular mechanics calculation by MacroModel V.6.5 using MMFF force field[13] gave the most stable structure (Fig. 4a) in which the benzene ring of the guest stays outside from the host cavity. This implies that the nondirectional forces (van der Waals, CH/π, π–π stacking etc.) between the guest and the host cavity do not play an important role in the complex formation. Hence, Hammett plot of the binding strengths ΔG versus substituents constants σ_m (–*t*-Bu: −0.1, –OCH_3: 0.12)[14] gave a good correlation ($R^2 = 0.99$), suggesting that the basicity of the dicarboxylate regulates the guest selectivity.

In a series of flexible guests **13**–**15**, a sizable difference of the binding constant was observed. Although the number of the rotable bond in **14** and **15** is identical to each other, the binding constant of **14** is much larger than that of **15**. Compound **13** is the most flexible among the three, but its binding constant is rather similar to that of **14**.

Two types of hydrogen bonding are seen in the most stable structure of these complexes (Fig. 4). Favorable

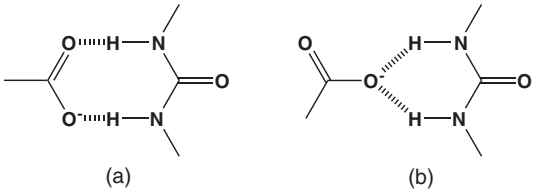


Figure 3. Two different types of the hydrogen-bonding interactions (a) linear, and (b) bent hydrogen bonding between carboxylate and urea groups.

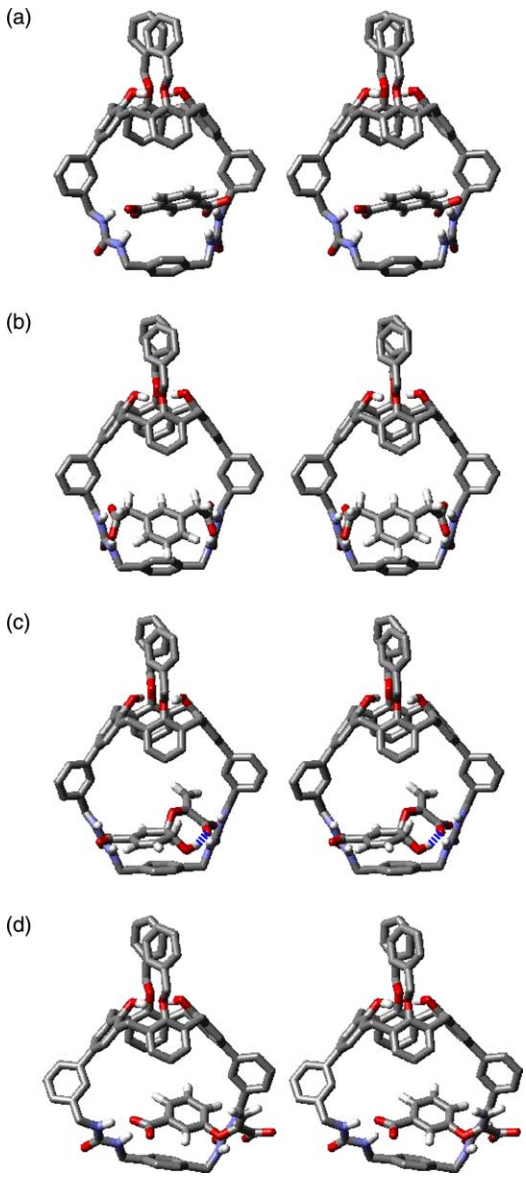


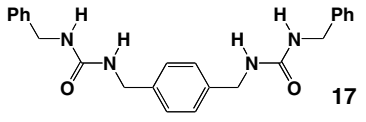
Figure 4. Stereo drawings of the complexes of **1** (a) with **9**, (b) with **13**, (c) with **14**, and (d) with **15**, obtained by MacroModel calculation.

double two linear hydrogen-bond pairs can explain the large binding constant of **13**, which can be attained due to the flexibility of the side chain of **13**. However, an entropic cost for adjusting to the favorable guest conformation prevented to have much larger binding constant. Because of the smaller number of the rotable bond in **14** and **15**, bent hydrogen-bond pair was seen in both complexes **1**·**14** and **1**·**15**. This is a reasonable explanation of the small binding constant of the latter. Extra stabilization of the former complex might be the further reduction of the flexibility of the guest. It deduces the entropic cost for the complex formation (Fig. 4c). The intramolecular hydrogen-bonding interaction between the C4 hydroxyl group and the side chain carboxylate is well known even in polar solvents[15] and it reduces the conformational flexibility of the guest. Nondirectional forces between the host cavity wall and the guest might be the favorable interaction in the complex formation in these cases.

In conclusion, we developed the upper rim functionalized calix[4]arene receptor having two urea groups, capable of binding selectively to the dicarboxylates over the monocarboxylate. The shape selective recognition among the dicarboxylates were achieved. Molecular mechanics calculation gave a helpful information for the rational explanation of the selectivity.

References and notes

1. For recent reports on synthetic receptors see: (a) Best, M. D.; Tobey, S. L.; Anslyn, E. V. *Coord. Chem. Rev.* **2003**, *240*, 3–15; (b) Fitzmaurice, R. J.; Lyne, G. M.; Douheret, D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841–864; (c) Chen, H.; Weiner, W. S.; Hamilton, A. D. *Curr. Opin. Chem. Bio.* **1997**, *1*, 458–466; (d) Beer, P. D.; Schmitt, P. *Curr. Opin. Chem. Bio.* **1997**, *1*, 475–482.
2. Pelizzi, N.; Casnati, A.; Ungaro, R. *Chem. Commun.* **1998**, 2607–2608.
3. (a) Casnati, A.; Massera, C.; Pelizzi, N.; Stibor, I.; Pinkassik, E.; Ugozzoli, F.; Ungaro, R. *Tetrahedron Lett.* **2002**, *43*, 7311–7314; (b) Sansone, F.; Baldini, L.; Casnati, A.; Lazzarotte, M.; Ugozzoli, F.; Ungaro, R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4842–4847; (c) Lazzarotto, M.; Sansone, F.; Baldini, L.; Casnati, A.; Cozzini, P.; Ungaro, R. *Eur. J. Org. Chem.* **2001**, 595–602; (d) Cameron, B. R.; Loeb, S. J. *Chem. Commun.* **1997**, 573–574; (e) Beer, P. D.; Drew, M. G. B.; Hesek, D.; Nam, K. C. *Chem. Commun.* **1997**, 107–108; (f) Casnati, A.; Fabbi, M.; Pelizzi, N.; Pochini, A.; Sansone, F.; Ungaro, R.; Modugno, E. D.; Tarzia, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2699–2704; (g) Beer, P. D.; Drew, M. G. B.; Hazlewood, C.; Hesek, D.; Hodacova, J.; Stokes, S. E. *Chem. Commun.* **1993**, 229–231.
4. (a) Tongraung, P.; Chantarasiri, N.; Tuntulani, T. *Tetrahedron Lett.* **2003**, *44*, 29–32; (b) Stastny, V.; Lhaták, P.; Michlová, V.; Stibor, I.; Sykora, J. *Tetrahedron* **2002**, *58*, 7207–7211; (c) Budka, J.; Lhaták, P.; Michlová, V.; Stibor, I. *Tetrahedron Lett.* **2001**, *42*, 1583–1586; (d) Arduini, A.; Secchi, A.; Pochini, A. *J. Org. Chem.* **2000**, *65*, 9085–9091; (e) Pelizzi, N.; Casnati, A.; Friggeri, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1307–1311; (f) Casnati, A.; Fochi, M.; Minari, P.; Pochini, A.; Reggiani, M.; Ungaro, R.; Reinhoudt, D. N. *Gazz. Chim. Ital.* **1996**, *126*, 99–106.
5. (a) Scheerder, J.; Vreekanmp, R. H.; Engbersen, J. F. J.; Verboon, W.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476–3481.
6. (a) Haino, T.; Nitta, K.; Fukazawa, Y. *Tetrahedron Lett.* **2000**, *41*, 4139–4142; (b) Haino, T.; Nitta, K.; Saijo, Y.; Matsumura, K.; Hirakata, M.; Fukazawa, Y. *Tetrahedron Lett.* **1999**, *40*, 6301–6304; (c) Haino, T.; Matsumura, K.; Harano, T.; Yamada, K.; Saijyo, Y.; Fukazawa, Y. *Tetrahedron* **1998**, *54*, 12185–12188; (d) Haino, T.; Katsutani, Y.; Akii, H.; Fukazawa, Y. *Tetrahedron Lett.* **1998**, *39*, 8133–8136; (e) Haino, T.; Akii, H.; Fukazawa, Y. *Synlett* **1998**, 1016–1018.
7. Shimizu, S.; Shirakawa, S.; Sasaki, Y.; Hirai, C. *Angew. Chem. Int. Ed.* **2000**, *39*, 1256–1259.
8. (a) Fitzmaurice, R. J.; Kyne, G. M.; Douheret, D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841–864; (b) Rossi, S.; Kyne, G. M.; Turner, D. L.; Wells, N. J.; Kilburn, J. D. *Angew. Chem. Int. Ed.* **2002**, *41*, 4233–4236; (c) Linton, B. R.; Goodman, M. S.; Fan, E.; Arman, S. A. v.; Hamilton, A. D. *J. Org. Chem.* **2001**, *66*, 7313–7319; (d) Benito, J. M.; Gómez-Garcia, M.; Blanco, J. L. J.; Mellet, C. O.; Fernandez, J. M. G. *J. Org. Chem.* **2001**, *66*, 1366–1372; (e) Schmuck, C.; Lex, J. *Org. Lett.* **1999**, *1*, 1779–1781; (f) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072–7080; (g) Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369–370.
9. (a) Connors, K. A. *Binding Constants*; John Wiley and Sons: New York, 1987; (b) Leggett, D. J. *Modern Inorganic Chemistry Series Computational Methods for the Determination of Formation Constants*; Plenum: New York and London, 1985.
10. Fan, E.; Van Arman, S. A.; Kincaid, S.; Hamilton, A. D. *J. Am. Chem. Soc.* **1993**, *115*, 369–370.
11. Leung, M.-K.; Lai, J.-L.; Lau, K.-H.; Yu, H.-h.; Hasiao, H.-J. *J. Org. Chem.* **1996**, *61*, 4175–4179,



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12. Theoretical calculations for the linear and bent hydrogen-bonding geometries on the complex between formate and urea were carried out by B3LYP/6-31G(d) using Spartan program. The results indicate that the linear hydrogen-bonding geometry is 4.0 kcal/mol more stable than the bent one.
13. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440–467.
14. (a) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195; (b) McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420–427.
15. (a) Wiest, O.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 11628–11639; (b) Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5008–5013.