A modular molecular tweezer designed using CAVEAT†

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A pair of water-soluble molecular tweezers designed using the computer program CAVEAT were prepared and their binding to an *N*-ethylquinolinium cation was demonstrated by ^{1}H NMR spectroscopy.

Receptors for aromatic groups are of interest for a variety of reasons including biological and biomimetic applications, and as components of chemosensors.[1–5] Several types of macrocyclic receptors that encapsulate aromatics and other guests have been studied including the natural cyclodextrins[6] and the designed calixarenes[7] and cyclophanes.[8] Molecular tweezers and clips have been developed that bear a pair of parallel or near-parallel aromatic binding groups connected by a spacer or linker between which an aromatic guest molecule can insert.[9–16] These non-macrocyclic receptors may be less limited in the size of the guest molecule that can be bound and have the potential to be more modular for convenient introduction of different aromatic binding groups for complementarity to different guests. Ideally the distance between binding groups should be about 7.0 Å or slightly less, as aromatic groups stack at an interplanar distance of $\leqslant$3.5 Å. A pioneering tweezer design by Whitlock and coworkers had a pair of caffeine molecules connected by a very flexible linker.[9] More recent efforts have been directed at tweezers or clips having the binding groups preorganized for guest binding. A recent design by Lehn has a cavity that is preorganized by metal ion binding to the linker.[10] An example of a type of more rigidly organized structure is the design from the group of Klärner having norbornane-linked aromatic groups, represented by **1** (Fig. 1).[11] The receptor surfaces in the Klärner systems are substantially non-parallel, but these receptor designs have given impressive binding results. The binding groups and linker are not fully distinct and binding may occur to the faces and edge of the guest molecule. In recent efforts, structures of this type have been made water-soluble and have been extended to cation receptors for lysine and arginine.[12] The tweezer system that best represents the ideal of linked parallel aromatic faces is that extensively developed by the Zimmerman group and represented by **2** in Fig. 1.[13–16] The original design has a pair of aromatic groups attached *via* single bonds to a dibenzacridine spacer. Several aromatic binding groups have been incorporated and numerous minor modifications of the linker have been made, including the incorporation of hydrogen bonding groups directed toward the central binding cavity. The linkage points are at a distance of about 7.24 Å, just above the approximately 7.0 Å ideal. As part of an ongoing project in the use of the computer program CAVEAT in molecular design, we undertook the application of CAVEAT to the design of a simple tweezer structure that might have features complementary to those of the Zimmerman system and related structures.[17–20]

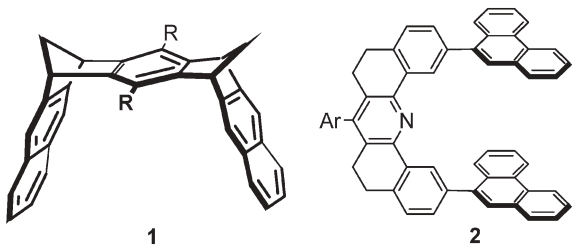

Fig. 1 Molecular tweezers of Klärner and Zimmerman.

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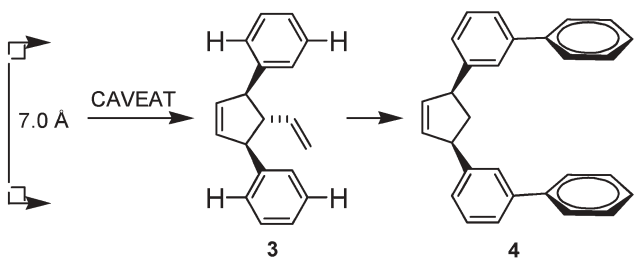
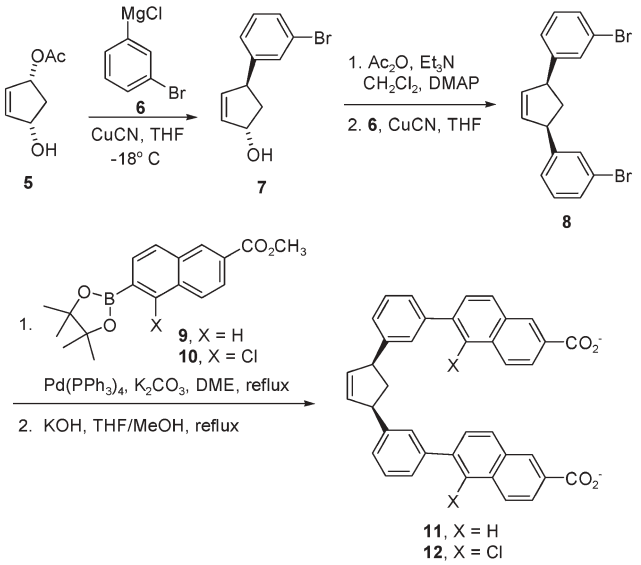
The design approach is illustrated in Scheme 1. A pair of parallel vectors at a distance of 7.0 Å was used to define a CAVEAT search of the TRISUB database of trisubstituted monocyclic hydrocarbons.[20] Fourteen unique potential linker structures were identified from this search, including structure **3**. In this structure both the bonds to the hydrogens *ortho* and *meta* to the point of attachment of the phenyl rings to the cyclopentene match the defined vector pair. The vinyl group is present simply because the database contains only trisubstituted structures and thus **3** is representative of a group of structures having different "extra" substituents at different positions of the cyclopentene. Deletion of the vinyl substituent and attachment of phenyl groups in place of the *meta* hydrogens of **3** gives the minimal tweezer structure **4**. Computational modeling of this structure indicated a 7.2 Å distance between points of attachment of the phenyl rings, with a dihedral angle about the phenyl–phenyl bonds of 62° needed for the faces of the outer phenyl rings to be parallel.

Based on this linker structure, the tweezer **11** was initially prepared as shown in Scheme 2. **11** incorporates naphthalene rings as binding groups with a carboxylate on each naphthalene to impart aqueous solubility. The racemic diol monoacetate **5** was prepared following literature methods by reaction of



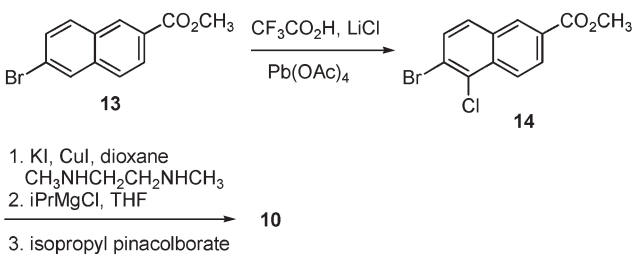
Scheme 1 Design of a molecular tweezer using CAVEAT.



Scheme 2 Synthesis of two molecular tweezers.

cyclopentadiene with singlet oxygen followed by reduction to the diol and acetylation.[21] Reaction of **5** with 3-bromophenyl magnesium chloride **6**, prepared by reaction of *meta*-bromoiodobenzene with isopropylmagnesium chloride, formed **7**.[22] These conditions have been shown to give inversion as shown.[23,24] The chloride counterion was critical for good S_N2 *vs.* S_N2' selectivity. Acetylation of the hydroxyl group of **7** followed by reaction again with the Grignard reagent **6** formed **8**. Attempts to form **8** in a single step from the diacetate of cyclopentenediol gave a large amount of S_N2' substitution product. Suzuki coupling of **8** with two equivalents of the boronic ester **9**, derived by Miyaura reaction of methyl 6-bromo-2-naphthoate, followed by ester hydrolysis gave **11**.[25,26]

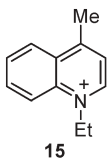
Also prepared was the corresponding tweezer **12** having chlorine substituents on each naphthalene ring. The chlorines were incorporated to influence the dihedral angle between the naphthyl and phenyl rings as described below. Synthesis of the necessary chlorinated boronic ester **10** began with chlorination of methyl 6-bromo-2-naphthoate **13**, with the desired 5-chloro product **14** purified from the mixture of isomeric products (Scheme 3). Attempts to directly convert **14** to the boronic ester **10** were unsuccessful. The transformation to **10** was achieved by initial reverse transhalogenation of the bromide to the iodide.[27] This reaction did not go to completion and separation of product from unreacted starting material was not successful. Isopropylmagnesium chloride reacted only with the iodide to form the aryl



Scheme 3 Additional steps in the synthesis of the chlorinated tweezer.

Grignard that was reacted with isopropyl pinacolatoborate to form **10**, from which unreacted **14** was readily separated.[28] Suzuki coupling of **10** with the functionalized linker **8** followed by ester hydrolysis formed **12** (Scheme 2).

The 1-ethyl-4-methylquinolinium cation **15** was chosen as a convenient water-soluble guest. Complex formation was studied by NMR titration in D_2O. ^1H NMR spectra were acquired upon addition of increasing amounts of **11** to a solution of the iodide salt of **15** (see ESI† for spectra). An upfield shift of all the aromatic protons of **15** was observed. The proton at C-2 and the protons of the N-CH_2 group of **15** gave distinct signals for which the change in chemical shift was easily quantified. Changes of $\geqslant 1$ ppm were observed, while changes due to dilution were less than 0.1 ppm. Data fitting gave an association constant of 950 M^{-1}. Binding of **15** to the chlorinated tweezer **12** was also studied by NMR titration. Similar chemical shift changes were observed, but greater line-broadening was observed such that peak positions could not be accurately discerned beyond the first three injections. The line-broadening may be attributed to reversible association on the NMR time-scale. The association constant estimated from the first three injections was 330 M^{-1}.



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The binding could be diminished by self-association of the receptor and by the lack of complete preorganization of the somewhat flexible tweezer. While individual resonances for **11** and **12** could not be discerned, the protons of the naphthalene rings are also shifted significantly upfield upon binding of **15**. This suggests an absence of π-stacking in the receptor solution alone and thus minimal self association. A conformational search of **11** (PM3) gave a mixture of conformers due to rotation about the cyclopentenyl–phenyl and phenyl–naphthyl single bonds. The lowest energy conformer exhibits an edge to face interaction between the two naphthyl groups, though these calculations do not include solvent effects.

The binding constants for **11** and **12** are within the range observed in binding of aromatic guests to other receptors,[29–31] though some examples of about 10-fold stronger binding of aromatic guests have been observed.[12,32] Thus while the tweezers **11** and **12** do not exhibit as high affinity as the best related receptors, they do exhibit fairly similar affinity within a much more modular and open structure that should be amenable to binding of a range of sizes and shapes of guests.

In our system as well as in the Zimmerman tweezers, the relative position of the pair of aromatic surfaces of the tweezer is influenced by the dihedral angle between the receptor face rings and the aromatic rings of the linker. The barrier to rotation is expected to be too small to observe atropisomers.[33] In our system the ideal dihedral angle for aligned parallel surfaces is about 62°, while the Zimmerman tweezers are based on a 90° dihedral angle. Deviation from the dihedral angle by rotating both aromatic surfaces in the same direction from the ideal brings the faces closer together and results in a horizontal displacement of one surface relative to the other.[16] A somewhat horizontally displaced

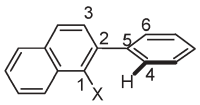

Table 1 Dihedral angles for 1-substituted-2-phenylnaphthalenes[a]

	Dihedral angle/°		
X	C1–C2–C5–C4	C3–C2–C5–C6	$E_{opt} - E_{62°}$ /kJ mol^{-1}
H	45.2	45.2	−1.89
Cl	68.8	65.8	−1.21

[a] Calculated at the HF/6-31G* level.

arrangement of π-stacking surfaces is preferred, and thus this displacement of receptor surfaces may not be of great significance if a fairly optimal displaced arrangement of the guest relative to both receptor surfaces can be achieved. The current computing power permits this issue to be addressed computationally at a higher level than the molecular mechanics calculations reported for the Zimmerman system. Table 1 shows the calculated dihedral angles for 2-phenylnaphthalene and 1-chloro-2-phenylnaphthalene as models for tweezers **11** and **12**, respectively. Without the chlorine, the dihedral angle is about 17° smaller than the ideal while with the chlorine, it is about 5° greater than the ideal. This indication that the chlorine substituent should provide a more ideal dihedral angle provided the justification for its introduction. The energetic cost of distorting the dihedral angle to the ideal is moderately greater for the system without the chlorine, though the difference in distortion energy is small relative to the difference in angle of distortion. The cost of distorting both dihedral angles of the receptor to the ideal would be double these values, and could impede binding about three- and five-fold for **11** and **12**, respectively. While some distortion from the most stable dihedral angle may occur, it seems unlikely that full distortion to the ideal occurs but rather that binding occurs to a less ideal structure of the tweezer. This seems likely to also be the case with the Zimmerman tweezers. Our observation that the tweezer without chlorine binds its guest about three-fold more strongly suggests that this issue is not so important. The diminished binding of the chloro-substituted tweezer may be attributed to the inductive effect of chlorine, which results in weaker binding to an electron-deficient guest.

The molecular tweezer system described here is easily synthesized and modular, such that various aromatic surfaces for guest binding should be readily introduced. The comparison of the receptors with and without chlorine suggest that precise tuning of the dihedral angle between linker and binding groups is not critical, which further simplifies the design and synthesis of receptors based on this structure. The linker moiety may be complementary to the conceptually similar Zimmerman system, especially in regard to possible positions for introduction of other functional groups to bind additional functionality of targeted guest molecules. The general design may be widely applicable to receptors for other aromatic compounds.

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Notes and references

1 R. Breslow and S. D. Dong, *Chem. Rev.*, 1998, **98**, 1997.
2 A. Gissot and J. Rebek, *J. Am. Chem. Soc.*, 2004, **126**, 7424.
3 K. Uekama, F. Hirayama and T. Irie, *Chem. Rev.*, 1998, **98**, 2045.
4 H.-h. Yu, A. E. Pullen, M. G. Büchel and T. M. Swager, *Angew. Chem., Int. Ed.*, 2004, **43**, 3700.
5 S. K. Kim, S. H. Lee, J. Y. Lee, J. Y. Lee, R. A. Bartsch and J. S. Kim, *J. Am. Chem. Soc.*, 2004, **126**, 16499.
6 K. A. Connors, *Chem. Rev.*, 1997, **97**, 1325; V. T. D'Souza and K. B. Lipkowitz, *Chem. Rev.*, 1998, **98**, 1741; W. S. Cai, Y. M. Yu and X. G. Shao, *J. Mol. Model.*, 2005, **11**, 186.
7 A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713; *Calixarenes – A Versatile Class of Macrocyclic Compounds*, ed. J. Vicens and V. Bohmer, Kluwer, Norwell, MA, 1991; *Calixarenes Revisited*, ed. C. D. Gutsche, Royal Society of Chemistry, Cambridge, UK, 1998; *Calixarenes 2001*, ed. Z. Asfari, V. Bohmer, J. Harrowfield and J. Vicens, Kluwer, Norwell, MA, 2001; *Calixarenes in Action*, ed. L. Mandolini and R. Ungaro, Imperial College Press, London, UK, 2000.
8 I. Tabushi and K. Yamamura, *Top. Curr. Chem.*, 1983, **113**, 145; F. N. Diederich, *Cyclophanes*, The Royal Society of Chemistry, Cambridge, 1991; F. Vögtle, *Cyclophane Chemistry*, John Wiley & Sons Ltd., Chichester, 1993; R. Gleiter and H. Hopf, *Modern Cyclophane Chemistry*; Wiley-VCH Verlag, Weinheim, 2004.
9 C.-W. Chen and H. W. Whitlock, *J. Am. Chem. Soc.*, 1978, **100**, 4921.
10 A. Petitjean, R. G. Khoury, N. Kyritsakas and J.-M. Lehn, *J. Am. Chem. Soc.*, 2004, **126**, 6637.
11 F.-G. Klärner and B. Kahlert, *Acc. Chem. Res.*, 2003, **36**, 919.
12 M. Fokkens, C. Jasper, T. Schrader, F. Koziol, C. Ochsenfeld, J. Polkowska, M. Lobert, B. Kahlert and F.-G. Klärner, *Chem.–Eur. J.*, 2005, **11**, 477.
13 S. C. Zimmerman and C. M. VanZyl, *J. Am. Chem. Soc.*, 1987, **109**, 7894; S. C. Zimmerman, K. W. Saionz and Z. Zeng, *Proc. Natl. Acad. Sci. U. S. A.*, 1993, **90**, 1190.
14 S. C. Zimmerman, Z. Zeng, W. Wu and D. E. Reichert, *J. Am. Chem. Soc.*, 1991, **113**, 183; S. C. Zimmerman, W. Wu and Z. Zeng, *J. Am. Chem. Soc.*, 1991, **113**, 196; S. C. Zimmerman and Z. Zeng, *J. Org. Chem.*, 1990, **55**, 4789; S. C. Zimmerman and W. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 8054.
15 S. C. Zimmerman, M. Mrksich and M. Baloga, *J. Am. Chem. Soc.*, 1989, **111**, 8528; S. C. Zimmerman, C. M. VanZyl and G. S. Hamilton, *J. Am. Chem. Soc.*, 1989, **111**, 1373.
16 S. C. Zimmerman, *Top. Curr. Chem.*, 1993, **165**, 71.
17 G. Lauri and P. A. Bartlett, *J. Comput. Aided Mol. Des.*, 1994, **8**, 51.
18 W. Yang, H. He and D. G. Drueckhammer, *Angew. Chem., Int. Ed.*, 2001, **40**, 1714.
19 H. Huang and D. G. Drueckhammer, *Chem. Commun.*, 2005, 5196; Y. Zhu and D. G. Drueckhammer, *J. Org. Chem.*, 2005, **70**, 7755.
20 Y. Yang, D. Nesterenko, R. P. Trump, K. Yamaguchi, P. A. Bartlett and D. G. Drueckhammer, *J. Chem. Inf. Model.*, 2005, **45**, 1820.
21 C. R. Johnson and T. D. Penning, *J. Am. Chem. Soc.*, 1988, **110**, 4726.
22 P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis and V. A. Vu, *Angew. Chem., Int. Ed.*, 2003, **42**, 4302.
23 Y. Kobayashi, M. Ito and J. Igarashi, *Tetrahedron Lett.*, 2002, **43**, 4829.
24 T. Ainai, M. Ito and Y. Kobayashi, *Tetrahedron Lett.*, 2003, **44**, 3983.
25 N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.
26 T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508.
27 A. Klapars and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 14844.
28 O. Baron and P. Knochel, *Angew. Chem., Int. Ed.*, 2005, **44**, 3133.
29 A. W. Schwabacher, S. Zhang and W. Davy, *J. Am. Chem. Soc.*, 1993, **115**, 6995.
30 D. B. Smithrud, T. B. Wyman and F. Diederich, *J. Am. Chem. Soc.*, 1991, **113**, 5420.
31 A. R. Bernardo, J. F. Stoddart and A. E. Kaifer, *J. Am. Chem. Soc.*, 1992, **114**, 10624; T. T. Goodnow, M. V. Reddington, J. F. Stoddart and A. E. Kaifer, *J. Am. Chem. Soc.*, 1991, **113**, 4335.
32 T. J. Shepodd, M. A. Peti and D. A. Dougherty, *J. Am. Chem. Soc.*, 1988, **110**, 1983.
33 F. Grein, *J. Phys. Chem. A*, 2002, **106**, 3823.