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A Conformationally Reliable Spacer for Molecular Tweezers

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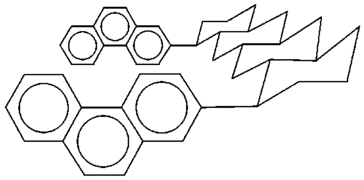
ABSTRACT



A reliable and rigid spacer, *trans,trans,trans*-perhydronaphthacene, for molecular tweezers was designed. A synthesis and molecular recognition study of its 1,14-disubstituted derivatives was carried out.

Most of the significant studies on molecular recognition using “tweezers”, typically constructed with two arms and one spacer, have been reported in recent years.[1] However, it seems to be difficult to carry out precise analyses, mainly because of intermolecular unanticipated nonbonded interactions. Additionally, the conformational flexibility of the host molecules increases the intricacy. Therefore, in recent works conformational flexibility has been minimized by using aromatic rings[1d] and/or fused polycyclic rings involving bridge heads.[1k] However, the analysis of steric repulsion against $\pi-\pi$ conjugations as well as the analysis of the constrained bond should be carried out more discreetly than that of typical normal bonds should be.

We report the design and synthesis of 1,10-diequatorial-substituted all-*trans*-fused perhydronaphthacene derivatives (Figure 1). We chose them for the following reasons. (1) The cyclohexane ring without large axial substituents is one of the most unstrained molecules. (2) When cyclohexane rings are *trans*-fused, the whole conformation becomes rigid enough. (3) In many of the available programs for conformational analysis, the conformation of cyclohexane derivatives can be optimized with high reliability and reproducibility. (4) The van der Waals distance between the two aromatic rings is appropriate for sandwiching a benzene derivative between them. (5) Lipophilic and/or $\pi-\pi$ interactions could turn out to be quite marked, since hydrogen bond and ionic interactions are completely absent.

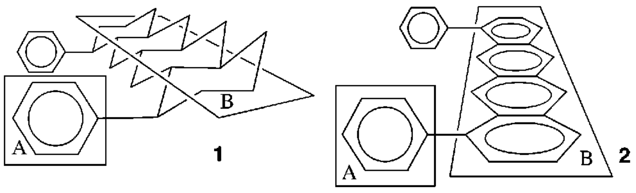


Figure 1.

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(1) (a) Haino, T.; Yanase, M.; Fukazawa, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 997. (b) Inouye, M.; Fujimoto, K.; Furusho, M.; Nakazumi, H. *J. Am. Chem. Soc.* **1999**, *121*, 1452. (c) Chen, C.-W.; Whitelock, H. W., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4921. (d) Zimmerman, S. C.; Zeng, Z.; Wu, W.; Reichert, D. E. *J. Am. Chem. Soc.* **1991**, *113*, 183. (e) Magnus, P.; Morris, J. C.; Lynch, V. *Synthesis* **1997**, 506. (f) D’Souda, L. J.; Maitra, U. *J. Org. Chem.* **1996**, *61*, 9494. (g) Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1990**, *112*, 7269. (h) van Doorn, A. R.; Bos, M.; Harkema, S.; van Eerden, J.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1991**, *56*, 2371. (i) Mink, D.; Deslongchamps, G. *Tetrahedron Lett.* **1996**, *37*, 7035. (j) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245. (k) Harmata, M.; Barnes, C. L.; Karra, S. R.; Elahmad, S. *J. Am. Chem. Soc.* **1994**, *116*, 8392.

(2) Muhammad, F.; Richards, N. G. J.; Guide, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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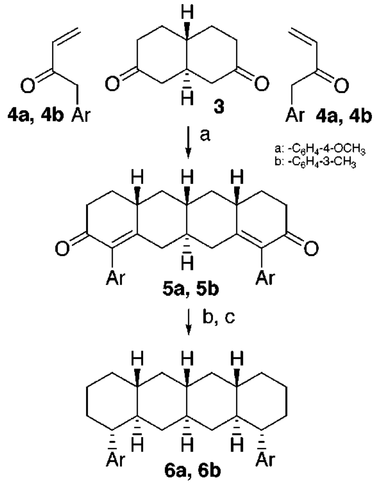
As a contrasting example to the compound **1**, we first carried out the conformational analysis of the compound **2**. We chose MacroModel version 6.02[2] for this preliminary examination.

Conformations of **2** were optimized using five calculation options (MM2″, MM3″, OPLS″, MMFF, and AMBER″). The resulting angles of the A/B planes are 60, 70, 70, 89, and 74°, respectively. The wide dispersion in these results can be explained by the independent parameters used for the estimation of the π-conjugation stabilization against steric repulsion. In contrast, our designed **1** has no π-orbital in the rigid spacer. In fact, plane angles A/B of **1** were briefly 90° in all the five calculation options.

Synthesis of bis(*p*-methoxyphenyl)perhydronaphthacene (**6a**) and bis(*m*-methylphenyl)perhydronaphthacene (**6b**) was carried out as shown in Scheme 1. The crude bis(enamine), prepared by condensation of *trans*-octaline-2,7-dione (**3**)[3] with pyrrolidine, was treated with the enone **4a**[4] followed by acidic aldol condensation of the resulting bis(1,4-diketone) to give the bis(enone) **5a** in 43% overall yield from **3**. The bis(enone) **5b** was also obtained from **3** with the enone **4b**[4] in 50% overall yield using reaction conditions similar to those for **5a**.

Scheme 1[a]

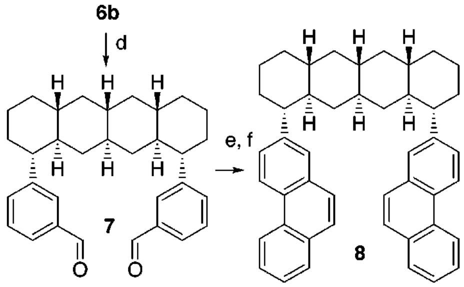


[a] Legend: (a) **3** + pyrrolidine/benzene, room temperature, 21 h, then **4** (1.2 equiv)/benzene, room temperature, 3 h, and then *p*-toluenesulfonic acid (TsOH) (cat.)/benzene, 5−24 h; (b) Li/ammonia/THF, −78 °C, 30 min; (c) 1,2-ethanedithiol/$BF_3 \cdot OEt_2$/CH_2Cl_2, room temperature, 2−14 h, and then Raney Ni/ethanol, reflux, 24 h.

Treatment of **5a** with lithium/ammonia[5] gave the corresponding diketone in 40% yield, which was converted to **6a** via the dithioketal in 57% overall yield. Transformation of **5b** to **6b** was also carried out under conditions similar to those for **6a** in 30% overall yield.

The binding ability of **6a** and **6b** with regard to a variety of benzene derivatives was evaluated by a ^{1}H NMR titration technique in $CDCl_3$. However, no significant change of chemical shift of the peaks was observed. Therefore, to increase the interactive π-surface, the phenanthrene derivative **8** was synthesized from **6b** as follows (Scheme 2). Bisbromination of the *m*-methyl group of **6b**, followed by hydrolysis with calcium carbonate[6] and then oxidation with pyridinium chlorochromate, gave the dialdehyde **7** in 61% overall yield. The reaction of **7** with diethyl benzylphosphonate gave the *trans*-stilbene derivative, which was converted to the phenanthryl derivative **8** with ultraviolet irradiation in the presence of iodine,[7,1e] and 1-butene oxide. The yield was 45% after purification by column chromatography.

Scheme 2[a]



[a] Legend: (d) *N*-bromosuccinimide/CCl_4, room temperature, 10 min, then $CaCO_3$/1,4-dioxane/water, room temperature, 19 h, and then pyridinium chlorochromate/CH_2Cl_2, room temperature, 2 h; (e) $C_6H_5CH_2PO(OEt)_2$/NaH/DME, room temperature, 40 h; (f) UV/1-butene oxide/iodine/benzene, 10 h.

The ability of **8** to bind to 1-cyano-3,5-dinitrobenzene (**9**) was determined by a ^{1}H NMR titration technique in $CDCl_3$. Significant changes in peaks ascribable to **8** and **9** were

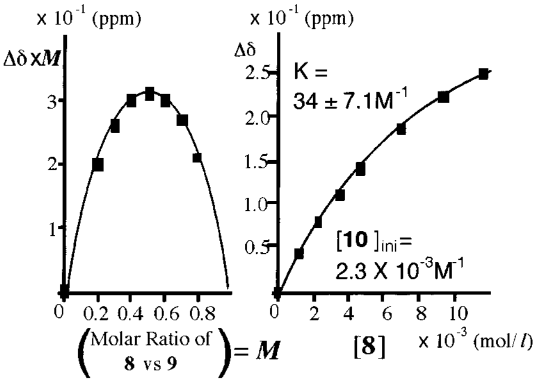


Figure 2. Job's plot and curve-fitting analysis of **8** with **9** using the Δδ value of H-6 of phenanthryl groups at 25 °C.

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(3) Jones, J. B.; Dodds, D. R. *Can. J. Chem.* **1987**, *65*, 2397.

(4) The enones **4a** and **4b** were prepared from the corresponding amides with vinylmagnesium bromide given in the following paper: Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(5) Although we have used many hydrogenation conditions for **5a**, the *cis,trans,cis*-fused ring was always obtained exclusively.

observed. A Job's plot analysis (Figure 2) confirmed the 1:1 stoichiometry of the complex. The association constant of the complex, which was determined by a nonlinear curve-fitting analysis using the Gauss−Newton algorithm,[8] was 34 ± 7.1 M^{-1} at 25 °C. Although similar titration experiments were carried out for phenanthrene and **9** for comparison, no significant changes were observed. Thus, the presence of the perhydronaphthacene moiety as a spacer is essential for the recognition of **9**.

In conclusion, we have synthesized tweezers bearing a very rigid and reliable residue, the all-*trans*-fused perhydronaphthacenyl moiety. The bis(phenanthryl) derivative recognizes 1-cyano-3,5-dinitrobenzene. We believe that feedback from our experimental results will help delineate the relationship between unanticipated nonbonded interactions and the various parameters used by the theoretical methods. We are now synthesizing other derivatives of perhydronaphthacene for further study of molecular recognition.

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Supporting Information Available: Experimental procedures and characterization data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Smith, J. G.; Dibble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762.

(7) Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769.

(8) (a) Conners, K. A. *Binding Constants;* Wiley: New York, 1987**.** (b) Leggett, D. J. *Computational Methods for the Determination of Formation Constants*; Modern Inorganic Chemistry Series; Plenum Press: New York, London, 1985.