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[10]Paracyclophanediamides and their octadehydro derivatives: novel exotopic receptors with hydrogen-bonding sites on the bridge

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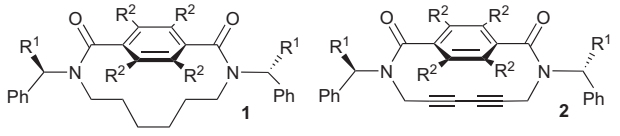
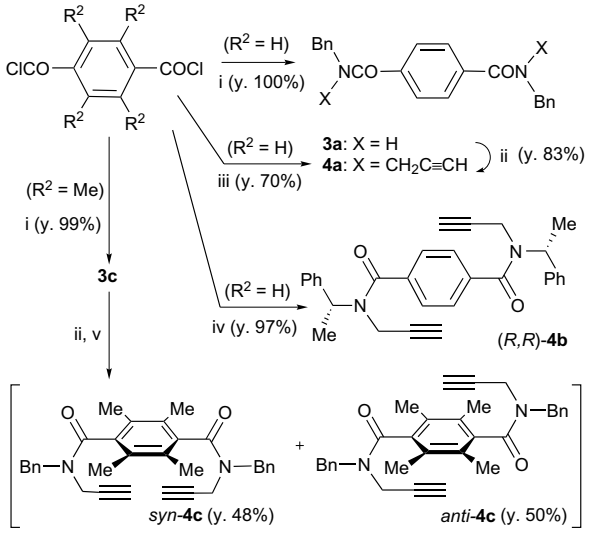
Abstract—2,9-Diaza-1,10-dioxo[10]paracyclophanes were prepared in short steps from the terephthaloyl chlorides via the corresponding 4,6-diyne derivatives, and the amide groups on the bridge endow the skeleton with the guest-binding properties as demonstrated by complexation with adrenaline by hydrogen bonds. The chiral auxiliaries on the bridge induce diastereomeric preference in terms of the planar chirality for the octadehydro derivative with a rigid diyne unit in crystal.

Cyclophanes belong to the special class of compounds[1] that have been attracting significant attentions of many chemists from the viewpoints of transannular interaction,[2] highly strained structures,[3] and the special properties derived thereof.[4] During the course of our studies on the novel exotopic receptors based on hydrogen bonds,[5] we have found the facile and practical route to obtain [10]paracyclophane derivatives **1** and **2** with amide functionalities on the bridge. Here we report the preparation and properties of the title receptors as the first member of [*n*]paracyclophanes with the guest-binding sites on the bridge.



[**a**: $R^1 = R^2 = H$; (*R*,*R*)-**b**: $R^1 = Me$, $R^2 = H$; **c**: $R^1 = H$, $R^2 = Me$]

Reaction of terephthaloyl chloride with benzylamine in CH_2Cl_2 gave *N*,*N*′-dibenzylterephthalamide **3a**[6] in quantitative yield, which was then treated with propargyl bromide/NaH to give *N*,*N*′-dibenzyl-*N*,*N*′-dipropargylterephthalamide **4a**,[6] the precursor of [10]paracyclophanediyne **2a**, in 83% yield (Scheme 1). This diamide was also obtained by treating terephthaloyl chloride with *N*-benzyl-*N*-propargylamine **5a**[7] in 70% yield. Similar reaction by using *N*-((*R*)-1-phenylethyl)-*N*-propargylamine **5b**[8] gave the chiral diamide



Scheme 1. Reagents and conditions: (i) $BnNH_2$, Et_3N–CH_2Cl_2; (ii) NaH, $BrCH_2C{\equiv}CH$, DMF; (iii) Bn–NH–$CH_2C{\equiv}CH$ **5a**, Et_3N–CH_2Cl_2; (iv) (*R*)-PhCHMe–NH–$CH_2C{\equiv}CH$ **5b**, Et_3N–CH_2Cl_2; (v) separation.

Keywords: Cyclophane; [10]Paracyclophane; Hydrogen bond; Diyne; Receptor; Complexation; Adrenaline; Planar chirality; Dynamic cyclophane.
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(*R*,*R*)-**4b**[6] in 97% yield. When tetramethylterephthaloyl chloride[9] was used as a starting material, diamide **4c**[6] was obtained in 97% yield through the former two-step protocol via *N*,*N*′-dibenzyltetramethylterephthalamide **3c**.[6]

According to the X-ray analysis[10] of **4a**, the benzene core and the amide plane are twisted with a large dihedral angle [52.0(3)°] as has been commonly observed for *N*,*N*-dialkylbenzenecarboxamides.[11] In crystal, the molecule of **4a** is located on a crystallographic center of symmetry and adopts an *anti*-geometry with two carbonyl groups directed to the opposite sides in respect to the *p*-phenylene unit. By considering that the *syn*-form is also a stable conformer with the similar energy to *anti*-**4a**,[12] both forms may exist and interconvert freely in solution.[13] Due to the larger rotational barrier around C_{Ar}–C_{CO} bonds by additional four methyl groups, *syn*-**4c** and *anti*-**4c** are conformationally so stable that they could be isolated by chromatography nearly in the same yield, only the former of which can be applicable for the next intramolecular cyclization.

By using $Cu(OAc)_2$ in pyridine–MeCN[15] under the pseudo high-dilution conditions, the intramolecular oxidative coupling of the terminal acetylene units of **4a** proceeded smoothly[16] to give the desired cyclophanediyne **2a**,[6] which was then hydrogenated in the presence of Crabtree's catalyst (5 mol%) in CH_2Cl_2 to furnish [10]paracyclophane **1a**[6] in 18% yield over two steps. Similarly, tetramethylated derivative **1c**[6] was prepared from *syn*-**4c** via diyne **2c**[6] in 32% yield. In this way, we could demonstrate the applicability of the oxidative acetylene coupling to construct the cyclophane skeleton[17,18] even when the bridge contains heteroatomic functional groups such as amides. Relatively low yields of the two-step preparation of **1a**,**c** from **4a**,**c** may be due to the instability of diyne **2a**,**c** that decomposed easily upon concentration.[19] In contrast, (*R*,*R*)-**2b**[6] with the chiral substituent on the amide nitrogens could be isolated as stable crystals in 49% yield, which was hydrogenated to (*R*,*R*)-**1b**[6] in 99% yield.

According to the low-temperature X-ray analysis,[10] (*R*,*R*)-**2b** suffers from the severe angle strain at sp carbons [deviations from the linearity: 7.7 (6), 12.7 (6), 13.0 (6), 13.1 (6)°],[20,21] thus inducing the significant bending of the diyne bridge (Fig. 1). The *p*-phenylene and the diyne units are forced to arrange in a proximity with the closest transannular C···C contact of 2.85 Å,[21] suggesting the π–π interaction between the two chromophores. In the ^{1}H NMR spectrum of (*R*,*R*)-**2b**, *p*-phenylene protons resonate at δ 7.66 in $CDCl_3$, which are shifted to the downfield compared with that for (*R*,*R*)-**1b** (7.54) with the saturated carbon bridge or (*R*,*R*)-**4b** (7.59) without the cyclophane skeleton, showing the shielding effect by the diyne unit.[22] In the UV spectrum of (*R*,*R*)-**2b** in MeCN was observed a new band around 260 nm (Fig. 2), which is absent in (*R*,*R*)-**1b** or (*R*,*R*)-**4b** without the diyne unit. In the parent paracyclophane-4,6-diyne **6**[17] was previously observed the similar band, which was assigned to the intramolecular charge-transfer band from *p*-phenylene unit to the diyne. These results indicate that the present cyclophanediynes **2** inherit the intriguing features of **6**, and the functionalities on the bridge endow **2** with the additional properties.

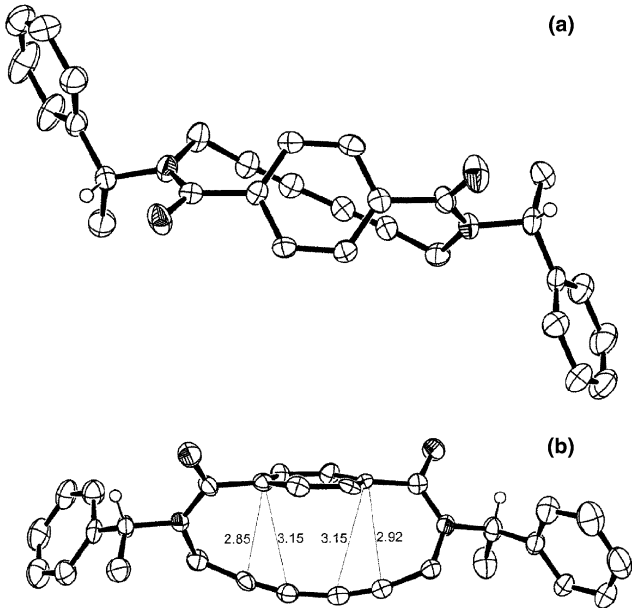


Figure 1. Molecular structure of cyclophanediyne (*R*,*R*)-**2b** determined by X-ray analysis at −120 °C. Hydrogen atoms except those on the asymmetric centers are omitted for clarity: (a) top view, (b) side view.

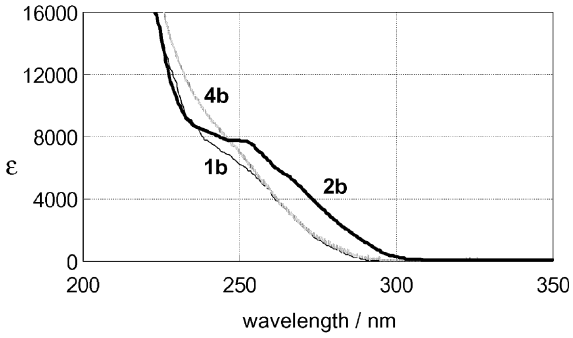
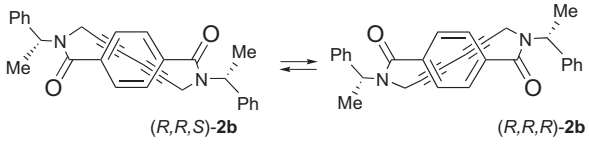


Figure 2. UV spectra of (*R*,*R*)-**1b** (thin solid line), (*R*,*R*)-**2b** (thick solid line), and (*R*,*R*)-**4b** (broken line) measured in MeCN.

It is noteworthy that all of the molecules in the crystal of (*R*,*R*)-**2b** adopt one of the two diastereomeric conformations (Scheme 2). Thus, the planar chirality of the cyclophane skeleton[23] is fixed to *S* in crystal under the control of the asymmetric centers on the bridge. On the other hand, another conformer may also be present in solution. These two conformers may coexist at rapid equilibrium since only one set of signals were observed in the



Scheme 2.

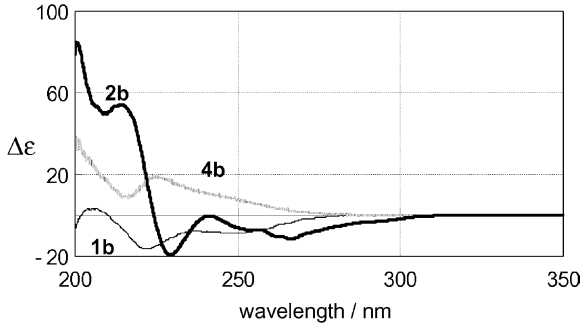
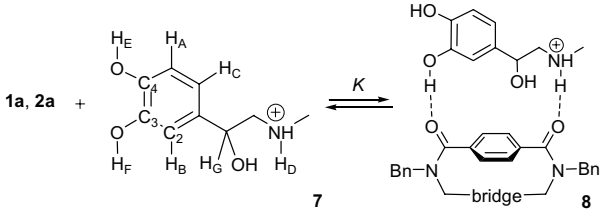


Figure 3. CD spectra of (*R*,*R*)-**1b** (thin solid line), (*R*,*R*)-**2b** (thick solid line), and (*R*,*R*)-**4b** (broken line) measured in MeCN.

^{1}H NMR spectrum at room temperature, which did not exhibit significant changes upon cooling to −70 °C. Yet, the strong intensity of the CD signal shown in Figure 3 suggests that (*R*,*R*)-**2b** still exhibits diastereomeric preference[24] in solution, which might be a favorable characteristics for its use as a chiral receptor.

The most interesting property of the newly prepared cyclophanes is the guest binding ability thanks to the hydrogen-bonding sites on the bridge. Preliminary complexation study was carried out for achiral receptors **1a** and **2a**. Racemic adrenaline **7** was chosen as a guest and the complexation was investigated by ^{1}H NMR spectroscopy in $CDCl_3$ containing 2% CD_3CN. The guest binding to the cyclophane receptor **1a** was evident by the significant down-field shift of the NH (H_D) and OH protons (H_F at C3) of guest **7** although another OH proton (H_E at C4) did not show similar behavior (Scheme 3). Notable feature is that only one (H_B at C2) of the three aromatic protons of **7** exhibits considerable up-field shift



Scheme 3.

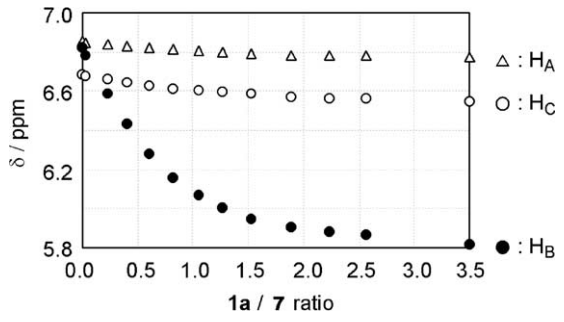


Figure 4. NMR titration curves for **7** (2.07×10^{-3} mol dm^{-3}) with **1a** showing the changes of aromatic protons in **7** ($CDCl_3$ containing 2% CD_3CN at 25 °C).

from δ 6.82 to 5.82 (Fig. 4), suggesting that this proton is shielded by the benzene core of **1a**. The benzyl proton (H_G) showed similar up-field shift from δ 4.83 to 4.26. Based on these spectral changes, one can imagine the supramolecularly doubly bridged cyclophane structure **8** for the complex with the guest NH and OH being hydrogen-bonded to the amide carbonyls of the receptor. Quite similar spectral changes were observed upon admixing **2a** and **7**. By analyzing the titration curves with assuming 1:1 stoichiometry, the association constants (K) of 4500 and 600 mol^{-1} dm^3 were obtained for **1a**·**7** and **2a**·**7**, respectively, thus demonstrating the guest binding property of the newly prepared [10]paracyclophane receptors. Smaller value of K in the latter may be related to less flexibility of the bridge in **2a**.

It is also interesting to study the structural perturbation on the cyclophane geometry upon complexation. When the guest binding at the bridge causes the dynamic geometrical changes resulting in the significant modification of the transannular interaction, drastic changes in UV, fluorescence, or CD spectra are expected.[25] Studies on such novel sensory systems named as 'dynamic-cyclophane receptors' are now under way by designing other exotopic receptors with hydrogen-bonding sites on the bridge.

Acknowledgements

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Supplementary data

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 247059 [(*R*,*R*)-**2b**] and 239588 (**4a**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. ORTEP drawing of **4a** (Fig. S1) was submitted as electronic supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.115.

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13. The rotational barrier for C_{Ar}–C_{CO} seems much lower than that for C_{CO}–N, the latter of which was determined to be 15.3 kcal mol^{-1} on the basis of VT-NMR (T_c = 323 K and $\delta\Delta$ = 135 Hz for the CH_2 unit of propargyl groups). The comparable values (14–17 kcal mol^{-1}) for the structurally related systems were reported in Ref. 14.
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22. Comparisons of the NMR chemical shifts in **2a** (δ 7.66), **1a** (7.53), and **4a** (7.60) also support this explanation.

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24. Monte Carlo conformational searches using MacroModel 6.5 (MMFF, GB/SA solvation model for $CHCl_3$) showed that the (*R*,*R*,*S*)-conformer with the similar geometry to the X-ray structure has the lowest energy, and the most stable (*R*,*R*,*R*)-conformer is located at the energy level of 1.06 kcal mol^{-1} higher than that. This calculation suggests that the planar chirality of *S* is predominant also in solution although the CD signal is difficult to comprehend due to the overlap of many couplets based on the multiple exciton couplings.
25. Upon addition of adrenaline to a dilute solution of diynes **2a** (10^{-5} mol dm^{-3}) were observed only minor changes in UV and fluorescence spectra, probably due to the inefficient complexation under such diluted conditions suitable for optical spectroscopy.