Preparation and Spectral Properties of Disubstituted [2.2]Metacyclophanes

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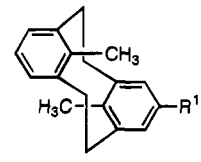
Cyclophane compounds provide intriguing models for investigation of intramolecular and transannular electronic effects in the forced proximity and particular orientation of two π-systems. Staab and co-workers have reported a large series of donor–acceptor paracyclophane systems including [2.2]paracyclophane–quinhydrones[3] and covered the relationship between donor–acceptor orientation and charge-transfer transition.[4] We have also shown the synthesis and the spectra of some [2.2]-quinhydronophanes.[5] On the other hand, we have also been very interested in a transannular interaction between two aromatic rings in [2.2]metacyclophane (MCP) systems because this interaction is obviously responsible for unusual reactivity of [2.2]MCPs. For the purpose of its quantitative estimation, we have prepared [2.2]MCPs with an azobenzene unit and discussed their spectral properties in terms of a transannular interaction.[6] In order to gain a deeper insight into this interaction, we decided to prepare [2.2]MCPs with a different kind of functional group on each ring because we were particularly interested in knowing how the π-electron state in the substituted [2.2]MCPs could be affected by the electron-donor or the electron-acceptor nature of the substituent through transannular interaction. In this paper, we report on the synthesis of substituted [2.2]-MCPs and the correlation between their spectra and Hammett substituent constants.

Electrophilic substitution of [2.2]MCPs (**1a**) is sometimes accompanied by side reactions such as transannular ring closure, resulting in difficulties in the separation of the substituted [2.2]MCPs. Thus, we first prepared the [2.2]MCP diazonium salt which is a potential intermediate for the synthesis of 5-substituted [2.2]MCPs.[7] Nitration of **1a** with fuming HNO_3 gave a nitro[2.2]MCP (**1b**) in 85% yield.[8] After reduction of **1b** with Pd–C/H_2, the resulting amino compound was treated with isopentyl nitrite in EtOH and THF to afford a diazonium salt (**1c**) in 87% yield. The details on synthetic applications of this salt will be described elsewhere. Pyrolysis of the salt **1c** at 100 °C under reduced pressure (1 Torr) for 4 h afforded fluoro[2.2]MCP (**1d**) in 98% yield. And methoxy[2.2]MCP (**1e**) was obtained by stirring salt **1c** in MeOH (78% yield). Furthermore, iodine was introduced by treating salt **1c** with I_2 to give iodo[2.2]MCP (**1f**) in 72% yield; however, when **1a** was reacted with I_2 in the presence of HIO_4 and H_2SO_4, separation from the diiodo compound was necessary, resulting in only 10% yield of **1f**.[9] Reduction of **1g**[10] with $LiAlH_4$ gave methyl[2.2]MCP (**1h**) in 31% yield accompanied by a hydroxymethyl derivative in 63% yield. Compound **2a** was easily prepared by nitration of **1f** according to a reported method.[7] However, in nitration of **1e** with $Cu(NO_3)_2$, a hydropyrenequinone compound, a ring closure product, was only identified instead of **2b**. Thus, **2a** was treated with sodium methoxide to afford the desired **2b** in 59% yield. Formylation of **1d** and **1h** with dichloromethyl methyl ether gave **2c** and **2d** in 76 and 81% yield, respectively.

Table 1. Absorption Maxima[a] for [2.2]MCPs 1a,b, 1d–h, and 2a–d

compound	λ_{max} (nm)	log ϵ
1a	298	1.94
1b	346	4.18
1d	303	2.08
1e	314	2.81
1f	302	2.51
1g	332	3.22
1h	302	2.49
2a	342	4.06
2b	367	4.94
2c	325	3.55
2d	331	3.58

[a] In $CHCl_3$ at 25 °C.



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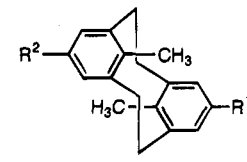

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1a; R^1=H **1e**; R^1=OCH_3 **2a**; R^1=I R^2=NO_2

1b; R^1=NO_2 **1f**; R^1=I **2b**; R^1=OCH_3 R^2=NO_2

1c; R^1=$N_2^+BF_4^-$ **1g**; R^1=CHO **2c**; R^1=F R^2=CHO

1d; R^1=F **1h**; R^1=CH_3 **2d**; R^1=CH_3 R^2=CHO

The electronic spectra of [2.2]MCPs provide information about the nature of transannular electronic interaction in their π-electron system. The absorption maxima of these substituted [2.2]MCPs are summarized in Table 1. The UV spectrum of [2.2]MCP (**1a**) is designated as the "cyclophane spectrum", which is indicated by the loss of fine structure of the benzenoid band and the bathochromic shift with a decrease in intensity as compared with open chain model compounds. The UV spectra of the monosubstituted [2.2]MCPs can be characterized by bathochromic shifts in comparison with those of [2.2]MCP **1a**. It corresponds to the shift of benzene on monosubstitution. Although, as it is well-known Hammett-type correlations with electronic spectral data are usually poor; the Hammett substituent constants[11] are widely used to express the electronic effects of substituent. Thus, λ_{max} values for the monosubstituted [2.2]MCPs are plotted against σ_p of the substituent as shown in Figure 1. A V-shaped line was obtained similarly, as in the case of monosubstituted benzene systems. We have paid a great deal of attention to the absorption properties of

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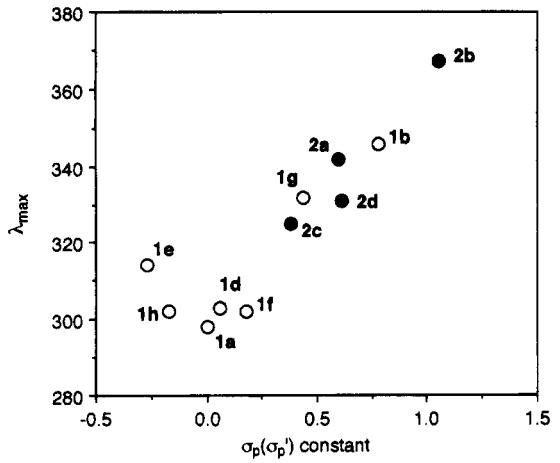

Figure 1. Correlation between λ_{max} and the $\sigma_p(\sigma_p')$ constant of the substituent in the [2.2]MCPs system.

disubstituted [2.2]MCPs from a viewpoint of an effect of the electronic properties of two kinds of substituents on the spectra. Here, the difference in the σ_p values of the functional groups is defined as the substituent constant for disubstituted [2.2]MCPs (**2a–d**), which is also shown in Figure 1. Interestingly, λ_{max} values for **2a–d** show a linear relationship against their defined σ_p values (σ_p'). For example, **2b** exhibits a great bathochromic shift which extends into the visible region. When the two substituents are of the same type such as in **2a** and **2c**, their spectra are similar to those of the monosubstituted [2.2]MCP **1b** and **1g** because each of the substituents decreases the conjugation of the other. In **2d**, both substituents do not possess strong electron-donating or electron-accepting properties, resulting in a smaller bathochromic shift as compared with that of **2b**. Compound **2b** is expected to possess some interesting properties because it has two aromatic rings with a strong electron-withdrawing group and a moderately strong electron-releasing group in close proximity. For example, **2b** exhibits an emission maximum at 562 nm, which is the first [2.2]MCP showing a strong fluorescence.[12] The estimated dipole moment of **2b** is 6.193 D[13] which is attributable to a push–pull effect of the substituents through a transannular interaction. Such a change in a π-electron state must influence the NMR spectra of these [2.2]MCPs. In fact, while the internal methyl protons of [2.2]MCP **1a** appear at δ 0.56 (the shielding effect of the opposite ring), the signals for two kinds of methyl protons of **2b** appear at δ 0.34 and 0.78, respectively. Such a significant difference in the chemical shifts results from extensive deviation of π-electron density between two aromatic rings due to a cooperative effect of the electron-donor and the electron-acceptor substituents.

From these results, it can be concluded that the [2.2]-MCP system is a nonplanar molecule with one conjugated system due to a strong transannular interaction between two aromatic rings.

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were recorded at 500 MHz in $CDCl_3$. Mass spectra were obtained at 75 eV using a direct-inlet system. Column chromatography was carried out on silica gel (Wako gel, C-300).

Pyrolysis of Diazonium Salt 1c. After **1c** (140 mg, 0.40 mmol) was pyrolyzed at 100 °C under reduced pressure (1 Torr), the crude product was chromatographed using CH_2Cl_2 as an eluent, giving 5-fluoro-8,16-dimethyl[2.2]metacyclophane **(1d)** (92 mg, 90%) as colorless prisms (MeOH): mp 212–213 °C; ^{1}H NMR δ 0.54 (3H, s), 0.74 (3H, s), 2.60–3.10 (8H, m), 6.60–7.20 (5H, m); MS *m/z* 254 (M^+). Anal. Calcd for $C_{18}H_{19}F$: C, 85.00; H, 7.53. Found: C, 85.20; H, 7.61.

Preparation of 5-Methoxy-8,16-dimethyl[2.2]metacyclophane (1e). The solution of diazonium salt **1c** (140 mg, 0.40 mmol) in MeOH (20 mL) was stirred at room temperature under a nitrogen atmosphere. After 42 h, the reaction mixture was evaporated *in vacuo* to leave the residue, which on chromatography using toluene as an eluent afforded **1e** (83 mg, 78%) as a colorless plate (MeOH): mp 135–137 °C; ^{1}H NMR δ 0.53 (3H, s), 0.74 (3H, s), 3.77 (3H, s), 2.60–3.10 (8H, m), 6.70–7.20 (3H, m), 6.71 (2H, s); MS *m/z* 266 (M^+). Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.53; H, 8.43.

Preparation of 5-Iodo-8,16-dimethyl[2.2]metacyclophane (1f). To a suspension of I_2 (110 mg, 1.6 mmol), 18-crown-6 (30 mg, 0.1 mmol), and potassium acetate (90 mg, 0.9 mmol) in $CHCl_3$ (10 mL) was added diazonium salt **1c** (140 mg, 0.4 mmol). After the reaction mixture was stirred at room temperature for 3 h, it was poured into 10% aqueous sodium hydrogen sulfite. The organic layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo* to leave the residue, which was chromatographed with toluene as an eluent to give **1f** (105 mg, 73%) as colorless prisms (hexane): mp 190–192 °C (lit.[9] mp 190–192 °C).

Reduction of 1g. To a suspension of $LiAlH_4$ (270 mg, 7.2 mmol) and $AlCl_3$ (990 mg, 7.2 mmol) in THF (20 mL) was added the solution of **1g** (150 mg, 0.51 mmol) in THF (6 mL). After the reaction mixture was refluxed for 10 h, it was poured into a large amount of ice–water and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, concentrated, and chromatographed, using toluene as an eluent, giving 5,8,-16-trimethyl[2.2]metacyclophane **(1h)** (40 mg, 31%) as colorless prisms (cyclohexane): mp 162–165 °C; ^{1}H NMR δ 0.56 (3H, s), 0.63 (3H, s), 2.24 (3H, s), 2.60–3.05 (8H, m), 6.70–7.20 (3H, m), 6.92 (2H, s); MS *m/z* 250 (M^+). Anal. Calcd for $C_{19}H_{22}$: C, 91.14; H, 8.86. Found: C, 91.06; H, 8.65.

Preparation of 5-Methoxy-13-nitro-8,16-dimethyl[2.2]-metacyclophane (2b). To a solution of sodium (230 mg, 9.8 mmol) in MeOH (10 mL) were added a solution of **2a** (200 mg, 0.49 mmol) in DMF (40 mL) and copper iodide (190 mg, 1.0 mmol). The reaction mixture was refluxed at 100 °C under an argon atmosphere. After 4 h, the mixture was poured into a large amount of ice–water and extracted with toluene. The extract was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The resulting residue was chromatographed using CH_2Cl_2 as an eluent to afford crude **2b**. Recrystallization from toluene gave **2b** (90 mg, 59%) as pale yellow prisms: mp 310–313 °C; ^{1}H NMR δ 0.34 (3H, s), 0.78 (3H, s), 2.00–2.90 (8H, m), 3.70 (3H, s), 6.52 (2H, s), 7.80 (2H, s); MS *m/z* 311 (M^+). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.57; H, 6.55; N, 4.68.

Formylation of 1d. To a solution of **1d** (50 mg, 0.20 mmol) and dichloromethyl methyl ether (1.0 g, 8.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise $TiCl_4$ (1.7 g, 9.0 mmol) at 0 °C. After the reaction mixture was stirred for 10 min, it was poured into a large amount of ice–water. The organic layer was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*, and the residue was chromatographed using toluene as an eluent. The product obtained from the eluate was recrystallized from hexane to give 5-fluoro-13-formyl-8,16-dimethyl[2.2]metacyclophane **(2c)** (43 mg, 79%) as colorless prisms: mp 229–230 °C; ^{1}H NMR δ 0.48 (3H, s), 0.81 (3H, s), 2.60–3.00 (8H, m), 6.87 (2H, d, J = 9.16 Hz), 7.25 (2H, s), 9.85 (1H, s); MS *m/z* 282 (M^+). Anal. Calcd for $C_{19}H_{19}OF$: C, 80.82; H, 6.78. Found: C, 81.06; H, 6.74.

Formylation of 1h. Compound **1h** (20 mg, 0.08 mmol) was formylated as described in the preparation of **2c**, giving 5-formyl-8,13,16-trimethyl[2.2]metacyclophane **(2d)** (18 mg, 0.065 mmol) as colorless prisms (hexane): mp 196–199 °C; ^{1}H NMR δ 0.48 (3H, s), 0.69 (3H, s), 2.26 (3H, s), 2.60–3.10 (8H, m), 6.93 (2H, s), 7.63 (2H, s), 9.83 (1H, s); MS *m/z* 278 (M^+). Anal. Calcd for $C_{20}H_{22}O$: C, 86.29; H, 7.97. Found: C, 86.27; H, 7.99.

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