Transannular Interactions in Fluorine-substituted [3.3]Metacyclophanes

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Effects of fluorine substituents on transannular interaction in [3.3]metacyclophanes were examined on the basis of chemical and spectral properties of five [3.3]metacyclophanes possessing one or two fluorine atoms at the inner and/or outer positions.

It is well known that fluorine-containing aromatic compounds show unique properties as compared to the corresponding derivatives with other halogen atoms.[1] In particular, the strong electronegative fluorine causes polarization of π-systems through lone pair-π repulsion (I_π) as well as inductive effect. When a fluorine atom is introduced in one of the benzene rings of a cyclophane system, the polarization caused by the fluorine atom would be transmitted between the stacked benzene rings through-space via dipole-induced dipole interactions. Though several fluorine-containing cyclophanes have already been reported,[2] no systematic investigation on transannular interactions involving fluorine substituents has so far been made. Here we report chemical and spectral evidence suggesting strong transannular interactions between the benzene rings of fluorinated [3.3]metacyclophanes.[3]

Fluorinated [3.3]metacyclophanes **4a-e** were synthesized in two steps as outlined in Scheme 1. Reaction between bis(bromomethyl)benzene derivatives **1** and either TosMIC for symmetrically substituted cyclophanes or bis-TosMIC adduct **2** for asymmetrically substituted ones under phase-transfer conditions[4] provided [3.3]metacyclophanediones **3a-e**[5], which adopt an *anti* conformation as indicated by ^{1}H NMR spectroscopic analysis.

The Wolff-Kishner reduction of the diones **3a-e** to the corresponding hydrocarbons **4a-e**[5], which were shown to be in a *syn* conformation, was uneventful, except for the case of **4e**, where the reaction temperature had to be lowered from 200 °C to 160 °C, otherwise 9-fluoro-15-hydroxy[3.3]metacyclophane **4f**[5] was obtained in 83% yield as a sole product. This facile aromatic nucleophilic substitution is unusual in view of the fact that the S_NAr reactions of fluorobenzene derivatives only occur when they are substituted with strong electron-withdrawing groups. In contrast, similar S_NAr reactions were only marginally detectable for **4a** and **4c** with the outer fluorine atom. The inner fluorine substituents in **4b**, **4d**, and **4e** were intact under these conditions. Since appearance of **4e** precedes the formation of **4f** as monitored by TLC,[6] this ready S_NAr reaction is assumed to be assisted by the inner F substituent in the transannular ring via through-space stabilization of the intermediate anion as depicted in Figure 1.

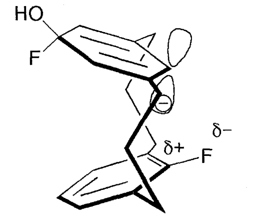
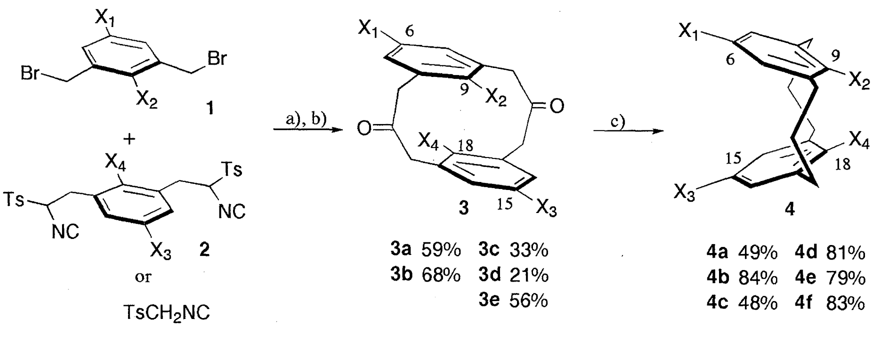


Figure 1. Stabilization by transannular interactions in the S_NAr reaction.

The through-space interactions in these cyclophanes can also be seen in their spectroscopic properties. The ^{1}H NMR spectra of **4b** and **4e** in a *syn* conformation showed a through-space ^{1}H-^{19}F coupling of 4.4 Hz for both compounds. No such couplings were observed for **3b** and **3e** in an *anti* conformation in which F and H are far apart. The ^{13}C NMR spectrum of **4d** showed, in addition to the characteristic large *ipso* ^{13}C-^{19}F coupling (253 Hz), a coupling of 10 Hz for the C-9 signal, which is assigned to a through-space coupling between C-9 and F at C-18.

It has been established that the p-orbital compression shifts of a ^{13}C signal is a good measure of electron repulsion in closely spaced π-systems.[7] In the present [3.3]metacyclophane system, the repulsion between inner carbons C-9 and C-18 are large enough to induce downfield shifts of 4-5 ppm. However, when the strong electron-withdrawing F is placed at C-9 and/or C-18, the electron density at the *ipso* position(s) decreased and almost no p-orbital compression shift was observed (Table 1). This reduced electron repulsion is considered to lend support for the stabilization in the transition state of the S_NAr reaction as depicted in Figure 1.

The UV spectra of cyclophanes **4a-e** are shown in Figure 2. The sharp bands at ca. 270 nm are characteristic of the fluorobenzene units and their intensities correspond to the number of the units as expected. The most interesting feature is the appear-



	X1	X2	X3	X4
a	F	H	H	H
b	H	F	H	H
c	F	H	F	H
d	H	F	H	F
e	F	H	H	F
f	OH	H	H	F

Scheme 1. Synthesis of fluoro[3.3]metacyclophanes; a) NaOH, *n*-Bu_4NI, CH_2Cl_2-H_2O, high-dilution conditions; b) HCl; c) $H_2NNH_2{\cdot}H_2O$, KOH, $HO(CH_2CH_2O)_3H$, 200 °C (**4a-d**, **4f**) or 160 °C (**4e**), 3 h.

Table 1. Selected ^{13}C-NMR (100 Mz, CDCl$_3$) data and compression shifts $\Delta\delta^a$ of **3** and **4**

		3		4	
		C-9	C-18	C-9	C-18
a	δ	131.2	135.5	129.8	134.1
	J_{CF}	3	—	—	—
	$\Delta\delta$	(+5.6)	(+5.4)	(+4.2)	(+4.0)
b	δ	161.5	133.0	159.3	130.2
	J_{CF}	249	—	239	—
	$\Delta\delta$	(+1.6)	(+2.9)	(-0.6)	(+0.1)
c	δ	131.2	131.2	129.8	129.8
	J_{CF}	3	3	—	—
	$\Delta\delta$	(+5.6)	(+5.6)	(+4.2)	(+4.2)
d	δ	160.2	160.2	159.9	159.9
	J_{CF}	248	248	253, 10	253, 10
	$\Delta\delta$	(+0.3)	(+0.3)	(±0.0)	(±0.0)
e	δ	130.4	161.5	126.1	159.4
	J_{CF}	4	248	—	—
	$\Delta\delta$	(+4.8)	(+1.6)	(+0.5)	(-0.5)

[a] The values $\Delta\delta$ in parentheses denote compression shifts as compared to the corresponding fluoro-*m*-xylenes or *m*-xylene. The value J_{CF} is in Hz.

ance of a new band at ca. 310 nm for **4e**, which is absent in the spectra of isomeric **4c** and **4d**. The origin of this band is not clear but may be arising from charge-transfer interactions and associated with the high reactivity of **4e** in aromatic nucleophilic substitution.

The spectroscopic properties as well as the unusual reactivity clearly indicate the strong transannular π-π interactions in these fluorocyclophanes, the detailed structural analysis of which is in progress.

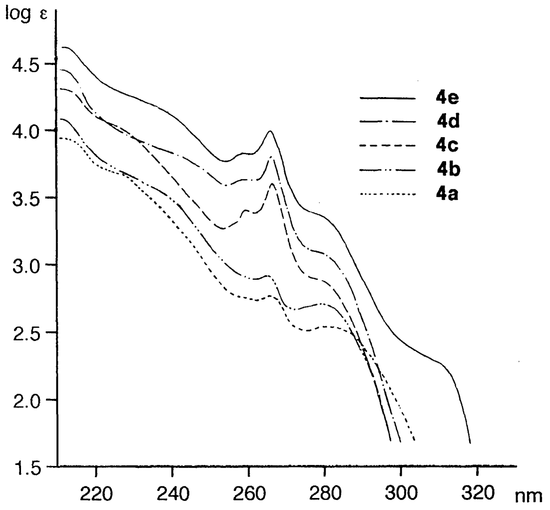


Figure 2 . Electronic spectra of **4a-e** in cyclohexane. Offset by +0.2 log ε unit from the below.

References and Notes

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5 Satisfactory analytical and spectroscopic data have been obtained for the new compounds; **3a**: colorless plates (benzene); mp 184-185 °C, **3b**: colorless plates (benzene); mp 205-206.5 °C, **3c**: colorless granules (benzene); mp 231-231.5 °C, **3d**: colorless needles (benzene); mp 229-230 °C, **3e**: colorless needles (benzene); mp 209-210 °C, **4a**: colorless plates (MeOH); mp 84.5-85 °C, **4b**: colorless needles (EtOH); mp 69-70 °C, **4c**: colorless needles (MeOH); mp 106-106.5 °C, **4d**: colorless needles (MeOH); mp 107.5-108 °C, **4e**: colorless plates (MeOH); mp 83-83.5 °C, **4f**: colorless needles (*n*-hexane); mp 134.5-135 °C.

6 In a separate experiment, we confirmed that the isolated **4e** underwent the conversion to **4f** by treatment with KOH at 200 °C in triethylene glycol containing hydrazine.

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