The Synthesis of Rigid Polycyclic Structures for the Study of Diatropic or Steric Effects of a Phenyl Ring on CF Bond

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Supporting Information

**Abstract:** Polycyclic compounds 1a–c were synthesized to study the diatropic effects of a flanking phenyl ring on nearby CH and CF bonds. $^{19}$F NMR spectra of 1b and 1c were strongly deshielded compared with those of the ring-opened compounds 3b, 7b, and 7c. DMOl3 calculations on 1a–c provided quantitative bond lengths and torsional angles to support the conclusion that the downfield shifts in the $^{19}$F NMR spectra are mainly due to steric interactions between the CF bonds and the π clouds of the phenyl ring(s).

**Inter- and intramolecular CH–π and CF–π interactions play important roles in host–guest chemistry, molecular assembly, and the folding of proteins and polynucleotides.** The CH–π interaction is a weak force (0.5–2.5 kcal/mol) that is usually difficult to measure directly using molecules with flexible conformations. Therefore, the measurement of this weak interaction in molecules with intramolecular folding and unfolding has intrigued chemists for decades. Recently, Tsuzuki reported an excellent review that summarizes the need to study CF compounds are getting more popular in medicinal chemistry, and CF compounds are getting more popular in medicinal chemistry, molecular design in which the CF bond is pointing toward CH molecules has markedly increased. In order to study such conformationally rigid π molecular design, one needs to have a special through-space and/or through-bond assistance, and the repulsive interactions from overlap of lone-pair electrons on fluorine with the π electrons on the olefin. Furthermore, they reported that the fluorine was little perturbed by anisotropic effects from the π electrons of the alkene, and only a slight upfield shift relative to theoretical values of fluorine chemical shifts was observed. We report here the synthesis of the rigid polycyclic compounds 1a–c and subsequent NMR spectral studies and theoretical calculations to measure the diatropic effect of a phenyl ring on sterically close aryl CH (1a) and CF bonds (1b and 1c).

Tandem Diels–Alder reactions followed by sequential photocyclization reactions were the two key steps in our synthesis of the rigid polycyclic structures 1a–c. One of us and Winkler have provided excellent reviews of tandem Diels–Alder reactions demonstrating that they are exceptionally powerful methods in the synthesis of intricate polycarbo-cycles. Iodine-induced photocyclization of stilbene to phenanthrene has also been well-studied. The CH and CF bonds in the series of polycyclic frameworks 1a–c can be arranged in a very close proximity to the aromatic ring, and hence, $^{1}$H and/or $^{19}$F NMR spectroscopy can be used to estimate the strength of the interactions between them and the π-cloud of the phenyl ring. Moreover, theoretical calculations were carried out on the polycyclic frameworks 1a–c to obtain optimized geometries, bond distances, and torsional angles.

**Synthesis of 1a.** Compound 1a was obtained through a two-step sequence that started by refluxing tetraphenylcyclopenta-diene (2a) with 1,5-cyclooctadiene to afford compound 3a in 71% yield (Scheme 1). Iodine-catalyzed photocyclization

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of 3a in toluene afforded the target polycyclic compound 1a in 58% yield. Because the target compounds 1a and 3a have similar polarities ($R_f = 0.5$ in hexane eluent), it was difficult for us to obtain pure 1a even after repeated column chromatography. The $^1$H NMR spectrum of the purified sample of 1a still showed about 10% of the starting material 3a; however, their signals can be easily discerned through chemical shift analysis. In particular, a new doublet signal around 8.5 ppm appeared, which is regarded as one of the characteristic protons of the phenanthrene ring in 1a. Moreover, the signals of the aromatic protons of 1a showed a significant downfield shift compared with those of 3a (Figure S18 in the Supporting Information). Furthermore, the formation of 1a could be easily recognized by GC–MS analysis, which showed a new peak with retention time ($t_r$) of 50.9 min (with $m/z$ 462.5) as opposed to the peak for the starting material 3a at $t_r = 33.6$ min (with $m/z$ 464.6) (see Figure S20 in the SI). Finally, we were lucky to obtain a single crystal of 1a by crystallization from a mixed solvent of dichloromethane and ethanol (2.8 v/v). The single-crystal X-ray structure of 1a (shown in Scheme 1) proved that it has a rigid polycyclic structure.

Synthesis of 1b. Encouraged by the successful synthesis of the polycyclic compound 1a, we then applied this methodology to construct the fluoride analogue 1b. The synthesis of fluorinated substrates 2b and 3b is shown in Scheme 2. The fluorinated substrate 2b was obtained through a three-step synthesis. First, the benzo condensation of 2-fluorobenzene was conducted using catalytic amount of sodium cyanide in ethanol to give the desired product, 2,2'-difluorobenzoin (5),$^{11}$ in 72% yield. Benzon 5 was then oxidized by copper(II) acetate in 80% acetic acid to afford 2,2'-difluorobenzil (6)$^{11}$ in 72% yield. Subsequent aldol condensation of 6 with dibenzyl ketone under alkaline conditions gave the difluorinated substrate 2b in 35% yield. After tandem Diels–Alder reactions of 2b with 1,5-cyclooctadiene, we obtained precursor 3b in 68% yield. The photocyclization of 3b with a catalytic amount of iodine was conducted by irradiation in a Rayonet photoreactor ($\lambda_{max} = 250$ nm) at room temperature (Scheme 3). The photocyclization reaction of compound 3b was completed within 6 h of irradiation at 254 nm.

Similar to the trouble we met in purifying the products of the photocyclization of 3a, we also had difficulty in purifying the products of the photocyclization of 3b because products 1a−c have similar polarities. Even after separation by column chromatography and recrystallization, the reaction mixture analyzed by HPLC still showed three major peaks at $t_r = 23.9, 24.8$, and 25.9 min with an area ratio of 8:85:5 (Figure S21 in the Supporting Information). After irradiation at 250 nm for 10 min, new signals around 8.5–9 ppm emerged, while signals of the aromatic protons of the starting compound 3b gradually decreased. The photocyclization reaction of compound 3b was completed within 6 h of irradiation at 254 nm.

Reagents and conditions: (a) cat. NaCN, EtOH, reflux, 4 days, 71%; (b) Cu(OAc)$_2$, 80% AcOH, reflux, 2 h, 72%; (c) KOH, dibenzyl ketone, EtOH, reflux, 1 h, 35%; (d) 1,5-cyclooctadiene, reflux, 24 h, 68%.

Scheme 1. Synthesis$^a$ and X-ray Crystal Structure of 1a

Scheme 2. Synthesis of 2b and 3b$^a$

Scheme 3. Products of the Photocyclization of 3b
CH bonds in 3b-III. Among the three major conformations of 3b, the conformation 3b-III became the most stable one and therefore led to the formation of compound 1c as the major product (85% in HPLC ratio).

All attempts to separate the product mixtures failed, and we could only collect a small amount of 1c by analytical HPLC separation. After obtaining the fluorinated polycyclic compound 1c and the mixture of 1b and 1c, we then took the intended measurement on CF−π interaction using 19F NMR spectroscopy. The 19F NMR spectra of 1b, 1c, and 3b showed the fluoride peaks at −91.0, −92.6, and −111.3 ppm, respectively, using hexafluorobenzene (δF = −162.2 ppm) as an external standard. To our big surprise, the 19F NMR peaks of 1b and 1c were downfield-shifted by 20.3 and 18.7 ppm, respectively, compared with that of 3b (Figure S15 in the Supporting Information); however, they were downfield-shifted by 30.2 and 29.8 ppm compared with those of 1,8-difluorophenanthrene 7b (δF = −121.2 ppm)13c and 1-fluorophenanthrene 7c (δF = −122.4 ppm)6i, respectively. Furthermore, compound 3b is downfield-shifted by 3.8 ppm compared with 8 (δF = −115.1 ppm). Since the C−F bonds of 1b and 1c are located very close to their phenyl rings, one would have expected to see a significant upfield shift in their 19F NMR resonances due to the diatropic shielding effect of the phenyl rings. To our surprise, the fluoride chemical shifts of 1b and 1c did not show any shielding effect of the phenyl ring but instead showed strong deshielding (vide supra)! Thus, the diatropic shielding effect of phenyl rings did not seem to play any role in determining the fluoride chemical shift of the C−F bond, and other factors must have played more important roles leading to the significant downfield shift of the 19F NMR peaks of 1b and 1c.

It has been reported that the ring-current effect is relatively less important in 19F NMR than in 1H NMR,14a,b whereas steric effects have a stronger influence on the chemical shift in 19F NMR. Even though the strong deshielding of the 19F NMR peaks of 1b and 1c were opposite to what we originally expected, the results are fully explainable by steric effects in fluorine NMR.14i The fluorine chemical shifts of para- and meta-substituted fluorobenzenes showed a reasonable correlation with the resonance and inductive effects of the substituents;14i−k however, because of the intramolecular steric effect between these substituents and the adjacent fluorine atom, the fluorine chemical shifts of ortho-substituted fluorobenzenes exhibit a poor correlation.14i−k Dolbier and others13,14 reported that all sterically congested or hindered organofluoride compounds are downfield-shifted in 19F NMR compared with those that are sterically unhindered (see Table 1). For example, the 19F NMR peaks of cis-9−11 were downfield-shifted by 3−6 ppm compared to those of trans-9−11;14a−c furthermore, the peaks of cis-13−15 were downfield-shifted by 1−8 ppm compared with those of trans-13−15.14d−f The deshielding effect of a bulkier substituent on the 19F NMR spectrum is even more obvious in compounds 12a−d, where the 19F NMR peak of 12d shows the largest downfield-shift effect when its 8-substituent changed from H to i-Bu (Δδ = 27.5 ppm).14a,b

In addition, Lectka and co-workers7 synthesized compounds 16a and 16b to investigate the intramolecular CF−π interactions. The C−F bond of 16b is very close to a double bond, causing a 16.0 ppm downfield shift of its 19F NMR resonance compared with that of 16a. The 19F NMR peak of 4-fluoro[2.2]paracyclophane (17)14g which has its CF bond parallel to a nearby phenylcyclophane, was downfield-shifted by only 2.3 ppm compared with that of fluorobenzene (18).14h It is important to note that our molecules 1b and 1c exhibited downfield shifts of 30.2 and 29.8 ppm in their 19F NMR spectra compared with those of 7b and 7c, respectively, which are by far the largest downfield shift effects ever reported. Thus, a nearby π cloud mainly exerts a steric effect on the 19F NMR peak of a CF bond instead of the traditional diatropic effect and therefore leads to strong downfield shifts of molecules 1b and 1c.

The fluorine chemical shifts of compounds 1b and 1c were also calculated by means of a published method,17 namely, gauge including atomic orbitals (GIAO) combined with B3LYP DFT using the cc-pVTZ basis set. The calculated fluorine chemical shifts of compounds 1b (δF = −101.9 ppm) and 1c (δF = −101.0 ppm) are upfield-shifted by 10.9 and 8.4 ppm compared with the observed values (Table S10 in the Supporting Information).

Dmol3 Calculations of the Conformations of 1a−c. In order to rationalize the conformations of 1a−c, we also calculated their geometry-optimized structures by the Dmol3 molecular modeling method15a,b and simulated in a CHCl3 environment, in which the B3LYP functional with the double-numeric-quality with polarization functions (DNP) basis set was used. The size of the DNP basis set is comparable to that of the Gaussian 6-31G++ basis set, but DNP is more accurate than a Gaussian basis set of the same size.15c The optimized geometries of 1a−c are displayed and related data of these calculations are summarized in Tables S1−S6 in the Supporting Information. In the optimized geometries of 1a−c, the distances between the tips of the C−H and C−F bonds to the center of a phenyl ring were measured to be 2.737, 3.367, and 3.393 Å, respectively. For most literature reports on CH−π interaction using 19F NMR, it is very close to a double bond, causing a 16.0 ppm downfield shift of its 19F NMR resonance compared with that of 16a. The 19F NMR peak of 4-fluoro[2.2]paracyclophane (17)14g which has its CF bond parallel to a nearby phenylcyclophane, was downfield-shifted by only 2.3 ppm compared with that of fluorobenzene (18).14h It is important to note that our molecules 1b and 1c exhibited downfield shifts of 30.2 and 29.8 ppm in their 19F NMR spectra compared with those of 7b and 7c, respectively, which are by far the largest downfield shift effects ever reported. Thus, a nearby π cloud mainly exerts a steric effect on the 19F NMR peak of a CF bond instead of the traditional diatropic effect and therefore leads to strong downfield shifts of molecules 1b and 1c.

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![Table 1. 19F NMR Data for Organofluoride Compounds 1b, 1c, 3b, and 7−18](Image)
as one would expect from the overlap of the \( \pi \) system with the fluoride or hydrogen atoms. As a result of the steric hindrance between phenanthrene and the flanking phenyl rings in the crystal structure of 1a, the conformations of phenanthrene and the cyclic skeleton (C1–C33–C32–C22–C29–C36) in 1a are nonplanar and a twisted boat, respectively. The distance between the tip of the CH bond and the center of a phenyl ring was determined to be 2.567 Å, and the torsional angle \( \Phi \) of 1a was shown to be 18.0°, so the Dmol3-calculated results for 1a were very close to those of the crystal structure of 1a. We infer that steric hindrance plays a pivotal role in the interactions between the CF bond(s) and the phenyl ring(s) in 1b and 1c, leading to their strong deshielding in the \( ^{19}F \) NMR spectra compared with those without such a sterically hindered environment.

In conclusion, we have designed and synthesized a series of rigid polycyclic structures 1a–c where the key steps of the synthesis involves (1) tandem Diels–Alder reactions and (2) the photocyclization followed by extrusion of F\(_2\), H\(_2\), and HF synthesis involves (1) tandem Diels (hexane, R\(_n\) nonplanar and a twisted boat, respectively. The distance from the di

### EXPERIMENTAL SECTION

**General Methods.** Column chromatography was performed on 70–230 or 230–400 mesh silica gel, thin-layer chromatography (TLC) was performed on aluminum plates coated with silica gel 60 F\(_{254}\). Melting points were determined with a melting-point apparatus and are uncorrected. \(^1H\) NMR spectra were measured with a 300 MHz spectrometer with the residual solvent peak (usually CHCl\(_3\) or DMSO-\(d_6\)) as the internal standard. Natural-abundance \(^13C\) NMR spectra were recorded using pulse Fourier transform techniques with a 300 MHz spectrometer operating at 75.4 MHz. \(^19F\) NMR spectra were measured on a 470 MHz spectrometer with the solvent peak (CDCl\(_3\)) as an external standard (\( \delta_F = -162.2 \) ppm).

**Photocyclization of 3a to 1a.** A mixture of compound 3a (0.10 g, 0.215 mmol) and a catalytic amount of iodine (0.547 mg, 0.0022 mmol) in THF (250 mL) was stirred at room temperature and irradiated in a Rayonet photoreactor at 300 nm for 8 h. The solvent was removed under reduced pressure. The residue was dissolved in CH\(_2\)Cl\(_2\) washed with a 10% aqueous solution of Na\(_2\)SO\(_4\) followed by a saturated aqueous solution of Na\(_2\)CO\(_3\) and dried over anhydrous MgSO\(_4\) and then the solvent was evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (hexane, \( R_f = 0.5 \)) to afford a mixture of 3a and 1a in which 1a was obtained in 58% yield based on \(^1H\) NMR peak ratios. Single crystals of 1a were obtained from crystallization of the mixture of 3a and 1a using a mixed solvent of dichloromethane and ethanol (2:8 v/v). \(^1H\) NMR (300 MHz, CDCl\(_3\)):

**Synthesis of 2b.** To a solution of 6 (0.49 g, 1.99 mmol) and KOH (0.06 g, 1.07 mmol) in EtOH (15 mL) was added 1,3-diphenylacetone (0.42 g, 1.99 mmol), and the mixture was refluxed for 30 min and then cooled to room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between H\(_2\)O (30 mL) and CH\(_2\)Cl\(_2\) (50 × 3 mL). The combined organic layers were dried over anhydrous MgSO\(_4\) and evaporated. The residue was recrystallized from EtOH to afford the product 2b as a dark-red solid in 35% yield. Mp 160–161 °C. \(^1H\) NMR (CDCl\(_3\), 300 MHz):

**Synthesis of 3a.** Compound 2a (2.50 g, 6.51 mmol) in 1,5-cyclooctadiene (10 mL) was heated at reflux for 4 days. After cooling to room temperature, the suspension was filtered to afford the product 3a as a white solid (2.14 g, 71%). Mp 305–306 °C. \(^1H\) NMR (300 MHz, CDCl\(_3\)):

**Synthesis of 3b.** A solution of compound 2b (0.10 g, 0.238 mmol) in 1,5-cyclooctadiene (0.37 mL) was heated at reflux for 12 h. After cooling to room temperature, the suspension was filtered to afford the product 3b as a white solid (8.30 mg, 68%). Mp 275–276 °C. \(^1H\) NMR (300 MHz, CDCl\(_3\)):

**Photocyclization of 3b to 1a–c.** A mixture of compound 3b (0.1 g, 0.199 mmol) and a catalytic amount of iodine (5.0 mg, 0.0197 mmol) in THF (100 mL) was stirred at room temperature and irradiated at 250 nm in a Rayonet photoreactor for 8 h. The solvent was removed under reduced pressure. The residue was dissolved in CH\(_2\)Cl\(_2\) washed with a 10% aqueous solution of Na\(_2\)SO\(_4\) followed by a saturated aqueous solution of Na\(_2\)CO\(_3\) and dried over anhydrous MgSO\(_4\) and then the solvent was evaporated under reduced pressure. The resulting residue was purified by column chromatography (hexane, \( R_f = 0.5 \)) and recrystallization. However, the reaction mixture analyzed by HPLC still showed three major peaks at \( t_r = 23.9, 24.8, 25.0 \).
and 25.9 min with an area ratio of 8:85:5. The mixture of compounds 1a–c was also confirmed by EI-MS and HRMS. For 1a: m/z 463 ([M + H]+); HRMS (EI) calc'd for C36H29F 480.2253, found 480.2253. For 1b: m/z 481 ([M + H]+); HRMS (EI) calc'd for C36H29F, 480.2253, found 480.2250. For 1b: m/z 498 (M—); HRMS (EI) calc'd for C36H29F, 498.2159, found 498.2163. The 1b: 1c: 1a peak-area ratio was determined to be 8:85:5 by HPLC analysis.

**REFERENCES**

