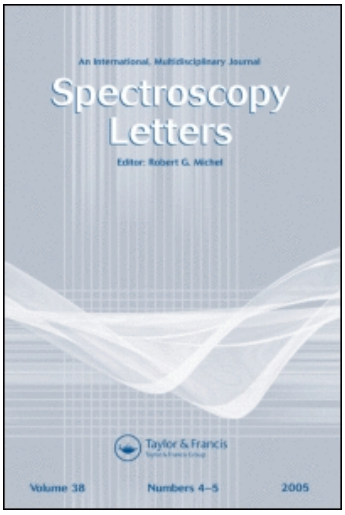

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^{1}H, ^{13}C and ^{19}F NMR Studies of the Diels-Alder Adduct of p-Fluoranil with Phencyclone. II. Hindered Phenyl Rotations and Anisotropic Effects in a Model Compound for Drugs

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^{1}H, ^{13}C and ^{19}F NMR STUDIES OF THE DIELS-ALDER ADDUCT OF p-FLUORANIL WITH PHENCYCLONE. II. HINDERED PHENYL ROTATIONS AND ANISOTROPIC EFFECTS IN A MODEL COMPOUND FOR DRUGS.

Key Words: One- and two-dimensional NMR, COSY, Tetrafluoro-1,4-benzoquinone, Stereochemistry, Conformations, Pharmaceuticals.

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ABSTRACT

The Diels-Alder adduct of phencyclone, compound 1, with p-fluoranil, compound 3, has been prepared in refluxing toluene. The adduct, compound 2, has been examined by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy at 300, 75 and 282 MHz, respectively. At ambient temperature, the unsubstituted bridgehead phenyl groups in adduct 2 are found to exhibit hindered rotation, resulting in slow exchange limit (SEL) ^{1}H NMR spectra. Full aryl proton assignments are made based on 1D and 2D (COSY45) NMR. The ^{19}F NMR (proton coupled) reveals one of the two ^{19}F signals to be a triplet. This resonance collapses to a singlet in the proton decoupled ^{19}F spectrum, implying an unexpected long range ^{1}H-^{19}F coupling. For the ^{13}C NMR spectrum, tentative assignments are presented. Data for compound 2 as a model compound for drugs are discussed in terms of the hindered aryl rotation and evidence of magnetic anisotropic effects.

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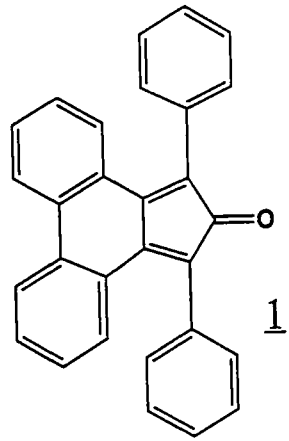
INTRODUCTION

As cited in the preceding accompanying article [1], hindered aryl rotations in drugs are of much importance. We have selected, as model compounds, a series of highly hindered adducts of phencyclone, compound 1, a potent Diels-Alder diene [2], for NMR studies of slow rotations about sp^2-sp^3 bonds to unsubstituted bridgehead phenyls and associated anisotropy effects (references cited in [1]). Initial ^1H and ^{13}C NMR studies have been extended to fluorine-19 [1,3] because of the growing importance of fluorine in medicinals [4]. We report here synthesis and NMR data for the adduct, compound 2, from 2,3,5,6-tetrafluoro-1,4-benzoquinone (p-fluoranil), compound 3, with compound 1.

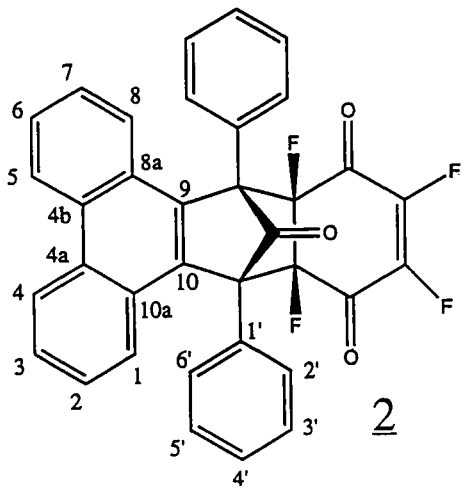
EXPERIMENTAL

General experimental procedures followed those described earlier [1,3], with NMR spectra obtained on a Bruker ACF300 spectrometer (7.05T) at ca. 300 MHz (^1H), 75 MHz (^{13}C) or 282 MHz (^{19}F) using a QNP "quad" probe and Aspect 3000 data system. ^{13}C and proton-decoupled ^{19}F spectra were obtained with composite pulse decoupling using a WALTZ16 sequence. Fluoranil and solvents were obtained from Aldrich Chemical (Milwaukee WI); phencyclone was obtained from Lancaster Synthesis (Windham NH). ^1H spectra were referenced to internal TMS (0.0 ppm); ^{13}C spectra were referenced to the central line of the $CDCl_3$ triplet (77.0 ppm); ^{19}F spectra were referenced to internal $CFCl_3$ (0.0 ppm). IR spectral data were obtained with a Perkin Elmer 1640 FTIR with DTGS detector using 3M disposable polyethylene IR cards (type 61). Reported melting points are uncorrected.

Preparation of Adduct, compound 2, from Phencyclone and p-Fluoranil: Fluoranil (300.2 mg, 1.67 mmol), and phencyclone (575.9 mg, 1.51 mmol) were refluxed in 25 ml toluene with a condenser topped by a drying tube of anh. $CaCl_2$, using magnetic stirring and Al foil to protect the sample from light. The intense green-black color of compound 1 was discharged after 2 days reflux to give a pale gold solution. Solvent was removed (rotary evaporator) and 4 x 45 ml



Structure of compound 1.



Structure of compound 2.

portions of CH_2Cl_2 were successively added and evaporated to dryness (rotary evaporator) to remove any traces of toluene. The crude residual solid contained appreciable 9,10-dibenzoylphenanthrene (DBP, based on ^1H NMR spectrum in $CDCl_3$; doublet at 8.81 ppm). Recrystallization of this crude product from abs. ethanol/hexane gave 403.3 mg of adduct 2 (in two crops, 47.5% based on phencyclone) which was recrystallized again from ethanol/hexane to give material that appeared free of DBP but which still contained small amounts of impurities based on aryl region ^1H NMR. (Alternatively, a second recrystallization using CH_2Cl_2 still left DBP contaminant.) Material that was doubly recrystallized from ethanol/hexane was used for subsequent characterization. The yellow-orange solid had mp. 218-222 (dec., became dark green-black, suggesting formation of compound 1). IR(cm^{-1}): 1809.1 (strained bridging ketone), 1712.6, 1667.9, 1448.7, 1357.8, 966.7, 752.3, 725.1, 697.1. See Tables and Results and Discussion for NMR data.

RESULTS AND DISCUSSION

Adduct 2 exhibited the aryl region ^1H NMR spectrum shown in Figure 1. Aside from the minor impurity peaks indicated, the distinct appearance of four equal intensity (2H) doublets is essentially consistent with an SEL spectrum in which the bridgehead unsubstituted phenyl groups are rotating slowly on the NMR timescale. With slow phenyl rotation, the ortho positions 2′ and 6′ and the meta positions 3′ and 5′ are rendered nonequivalent. The SEL regime predicts up to four doublets (H-1,8 and H-4,5 of the phenanthrenoid moiety; H-2′ and H-6′ of the phenyls) and five triplets (H-2,7, H-3,6, H-3′, 4′, 5′) in the absence of accidental overlaps. In contrast, a fast exchange limit (FEL) system would render both phenyl ortho positions equivalent; the meta positions would also be rendered equivalent. The FEL regime would yield a maximum of three doublets (including one double intensity [4H] signal for the phenyl ortho protons) and four triplets (including one double intensity [4H] signal for the meta protons). This is clearly ruled out for compound 2. If

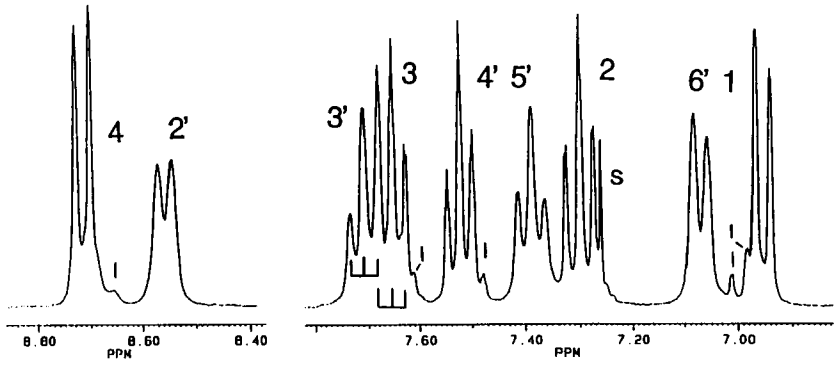


Figure 1. The 300 MHz ^{1}H NMR spectrum for the phencyclone-fluoranil adduct ($CDCl_3$, ambient temperature). Trace aryl region impurities are labeled I and the $CHCl_3$ solvent impurity is labeled S. Brackets denote triplets in the absorption region of H-3 and H-3′. The horizontal (chemical shift) and vertical (intensity) scales are uniform in both spectral regions.

the approximate "quintet" ca. 7.6-7.75 ppm in the ^{1}H NMR spectrum of compound 2 is recognized as the accidental partial overlap of two triplets, all four doublets and five triplets predicted for the SEL system are directly recognizable. Figure 2 shows the COSY45 spectrum for compound 2, using "high resolution" to distinguish, e.g., the 2x2 crosspeak for ^{5}J of H-1/4 or for ^{4}J of H-2′/6′ from the 3x3 crosspeak for ^{3}J of H-3′/4′ or H-2/3, etc. In addition to reducing signal intensity along the diagonal (compared to COSY90), the COSY45 also suggests changes in signs of coupling constants based on "tilting" in the off-diagonal crosspeaks [5]. This is clearly seen in crosspeaks for, e.g., 2′/4′, 3′/5′, 4′/6′, 2/4, etc., denoting negative values for these ^{4}J "W" couplings relative to the positive ^{3}J vicinal couplings. For the phenanthrenoid $(CH)_4$ spin system, with the sharp doublet at lowest field assigned to H-4,5, the three associated crosspeaks directly map out the coupled nuclei. The ^{3}J H-3/4 and ^{4}J H-2/4 couplings are both quite

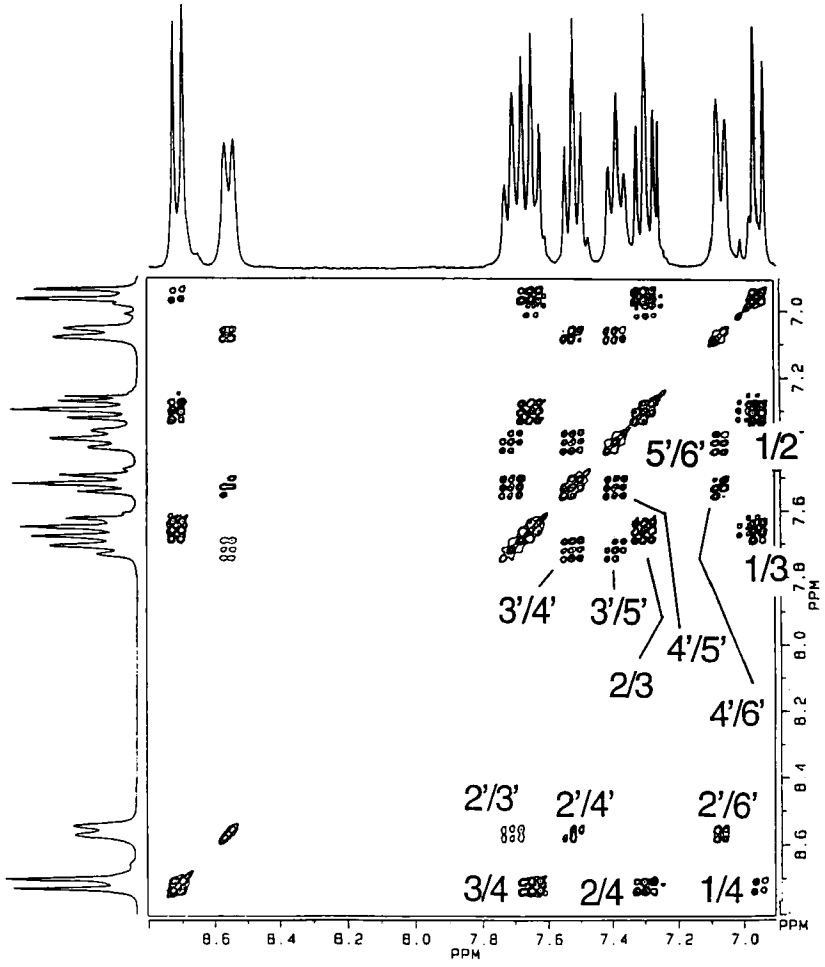


Figure 2. "High resolution" COSY45 spectrum of the phencyclone-fluoranil adduct. The spectral width in F2 was 571 Hz (6.90-8.80 ppm). The magnitude mode spectrum was acquired with 2 dummy scans and 16 acquisitions for each of 256 t_1 increments, zero-filling once in F1 and F2 for a final data matrix of 512 x 1024, to give a digital resolution of 1.1 Hz/point. Data were processed with unshifted sine-bell apodization in both dimensions and symmetrized. Crosspeaks are identified.

intense 2x3 crosspeaks, but the H-2/4 crosspeak shows definite tilting when a higher contour level (less sensitive) is used for plotting. Although the ^5J H-1/4 crosspeak is clearly seen in the $(CH)_4$ system, the ^5J crosspeaks H-2′/5′ and H-3′/6′ are too weak to be seen for the phenyl $(CH)_5$ spin systems, but all other ^3J and ^4J crosspeaks are apparent. Crosspeak correlations to the apparent "quintet" ca. 7.6-7.75 ppm indicate that this signal results from two triplets, confirming the SEL interpretation. Labeling the 7.73 ppm doublet as the phenyl H-2′ signal, the phenyl signals H-2′,3′,5′,6′ appear to be broader (and shorter) than the other signals. We attribute this to some chemical exchange broadening, since the phenanthrenoid proton signals and that of the phenyl H-4′ (on the phenyl rotation axis) are sharper. On this NMR timescale, phenyl rotation may not be slow enough to achieve a fully SEL regime. Assignments are summarized in Table 1.

Compared to ^1H NMR shifts in phenanthrene, adduct 2 shows shielding of 0.91 and 0.27 ppm for H-1,8 and H-2,7, respectively. (See Table 1.) Anisotropic shielding of these nuclei could result from rotation of the bridgehead phenyls in compound 2 to reduce repulsions between the ortho phenyl protons and H-1,8 [6a]. Appreciable differences in aryl ^1H NMR shifts for compound 2 compared to other adducts of compound 1 must result from differences in the dienophile-derived portions. Different equilibrium conformations of adduct bridgehead phenyls could occur. Anisotropic contributions from the dienophile-derived moiety, e.g., enedione system of compound 2, could play some role [6b]; inductive effects should be less important.

The ^{19}F NMR data for adduct 2 and the precursor fluoranil, compound 3, are given in Table 1. Adduct 2 exhibits two equal-area signals, consistent with expected structure, at -129.60 and -161.72 ppm. Remarkably, the downfield signal appears in the proton-coupled spectrum as a triplet (J=1.77 Hz) due to splitting by protons, as shown by the collapse of the triplet to a singlet with broadband

Table 1. NMR spectral data for adduct 2 and selected reference compounds. See Notes.

PROTON DATA

Nucleus	Adduct 2 Chemical shift (ppm)	(Est'd J, Hz)	Phenanthrene (Note 1)
1	6.955	8.36	7.86
2	7.300	7.71	7.57
3	7.653	8.32	7.63
4	8.715	8.42	8.65
2′	8.558	7.73	
3′	7.709	7.96	
4′	7.523	7.39	
5′	7.389	7.33	
6′	7.071	7.77	

FLUORINE DATA

Adduct (ppm)	Fluoranil
-161.72 br s	-142.12
-129.60 t (J=1.77 Hz)	

CARBON DATA (ppm)

Adduct 2 Shifts	Tentative Assignments (Note 2.)
194.48	bridging ketone CO
149.92	sp^2 FC=CF (approx. dd, J=295, 7 Hz)
93.56	sp^3 FC bridgeheads (approx. dd, J=246.2, 21.5 Hz)
66.21	C_6H_5C (poss. t, J ca. 12.7 or 9.6 Hz)
Aryl Carbons	
128.79	sharp, intense, nonexchanging
128.71	aryl methines
127.81	C-1,8; 2,7; 3,6; 4,5; 4′
125.15	
123.87	
131.16	Broad, intense, exchanging
129.27	aryl methines
128.61	C-2′, 3′, 5′, 6′
(128.66)	uncertain
131.95	unprotonated, unsplit by ^{19}F
125.42	(possibly C-4a,4b; C-8a,10a)
Fluoranil, 3 (Note 3.)	
170.94	CO (approx. triplet of mults., ^2J ca. 30 Hz)
141.03	FC=CF (doublet of mults., ^1J ca. 289 Hz)

Notes: (1) Phenanthrene ^1H data from ref. [3], 30.6 mg in 830 mg $CDCl_3$ at 21°. (2) The adduct 2 ^{13}C data is considered quite tentative. See Results and Discussion. (3) The fluoranil ^{13}C data reflect estimates for the ^{13}C-^{19}F coupling constants due to extensive fine structure in the complex multiplets, but the gross doublet ca. 141 ppm is unambiguously assignable to FC=CF based on the large direct coupling [12].

proton decoupling (WALTZ16), seen in Figure 3. Through-bond coupling here would require transmission through a minimum of five bonds, if the lowfield triplet is assigned to the bridgehead sp^3(CF) fluorine split by ortho protons H-2′ or H-6′. However, based on reported fluorine chemical shifts, the downfield signal of compound 2 at -129.6 ppm may more reasonably be assigned to the vinylic sp^2(CF) fluorines, since tertiary alkyl fluorines, such as bridgehead fluorines (as in 1H-perfluorobicyclo[2.2.2]oct-2-ene, compound 4) resonate at high fields, ca. -220 to -230 ppm [7]. Reported shifts for vinyl fluorines cover a very wide range, with the cis vinyl fluorines in compound 4 absorbing at -135.6 and -148.6 [7]; in compound 3 they resonate at -142.12. If the low field triplet signal in compound 2, at -129.6 ppm, is due to vinyl fluorines, we considered a possible direct through-space coupling [8a,9] to account for splitting. Using CS Chem3D software, and assuming normal endo stereochemistry in compound 2, two possible "boat-like" conformations seem possible for the six-membered enedione ring (Figure 4), in which the FC=CF moiety can be syn or anti to the phenanthrenoid system. The syn conformer places the FC=CF closer to the phenanthrenoid moiety. The calculated distance from the vinyl fluorines to the nearest phenanthrenoid protons, H-1,8, was 3.56 Å. The distance from the sp^3 bridgehead fluorines to H-1,8 was 4.42 Å. In the anti conformer, the distance from the vinyl fluorines to H-1,8 was 5.52 Å, and the distance from the bridgehead fluorine to H-1,8 remained 4.42 Å. All of these distances are greater than the sum of the van der Waals radii for H and F (about 2.55 Å). Through-space coupling may require smaller distances [9,10]. These are possible if coupling involved a phenyl proton with the phenyl in a favorable conformation proximal to the bridgehead fluorine, but not possible for the vinyl fluorines in either syn or anti isomer. Calculated closest approach of ortho proton to bridgehead fluorine was about 1.70 Å in either syn or anti, but closest approach to FC=CF was ca. 3.28 or 3.96 Å for syn and anti conformers,

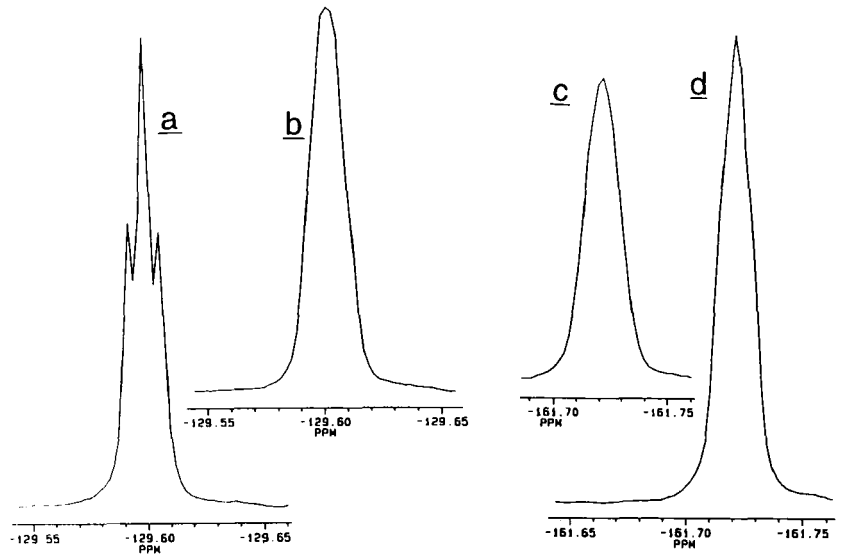


Figure 3. ^{19}F NMR spectrum at 282 MHz for the phencyclone-fluoranil adduct. Traces (a) and (c) are proton-coupled; (b) and (d) are proton-decoupled using composite pulse decoupling (WALTZ16). Horizontal (shift) axes, in Hz/cm, are uniform in all traces. Digital resolution was ca. 0.6 Hz/point. The triplet (J = 1.77 Hz) of trace (a) is collapsed to a singlet with proton decoupling: trace (b). The high field fluorine resonance of trace (c) exhibits little narrowing based on half-height peak width when proton decoupling is applied to give trace (d).

respectively. We note that steric compression may lead to deshielding via van der Waals effect [8b].

Expansions of the (proton-decoupled) carbon NMR spectrum of compound 2 are shown in Figure 5. It was expected to be quite complex due to splitting by fluorine. Assignments (Table 1 and Fig. 5) are tentative. The weak signal at 194.5 ppm is assigned to the strained bridging ketone carbonyl, possibly slightly broadened due to vicinal coupling with the bridgehead fluorines. With expected normal endo Diels-Alder adduct stereochemistry, a small FCCC dihedral angle is

expected (to "exo" fluorine), leading to small couplings. We could not assign the enedione carbonyls; extensive geminal coupling to both sets of fluorines could cause high multiplicity, leading to the signal being lost in the noise. Weak approximate double doublet signals centered at 149.9 and 93.6 ppm are assigned to the vinyl FC=CF and bridgehead CF, respectively [7]; the large one-bond direct couplings indicate fluorine-bearing carbons. Very weak peaks ca. 66.2 ppm were assigned to the sp^3 C_6H_5-C, largely based on analogy to other adducts of compound 1; geminal coupling to bridgehead fluorines is expected. We reasoned that vicinal FCCC splitting by bridgehead fluorines might lead to unobservable signals for some nonprotonated aryl carbons (i.e., phenyl ipso C-1′ and phenanthrenoid C-9,10). The aryl region (ca. 122-133 ppm) shown in Fig. 5(a) and (b) was assigned as follows. Two weak sharp peaks at 125.42 and 131.95 ppm (labeled Q) may be the remaining nonprotonated phenanthrenoid carbons, C-4a,4b and C-8a,10a. The more intense signals would be protonated aryl carbons. An SEL regime could account for nine aryl methines. It is apparent that some of the stronger signals are especially narrow and tall; five of these signals are labeled CH. Three other signals, with roughly comparable area, are short and broadened (labeled br); two of these are well resolved and one is quite overlapped. A fourth broad peak may be present at 128.66 ppm, severely overlapped. If bridgehead phenyl rotation in compound 2 were not sufficiently slow on the NMR timescale to fully achieve the SEL regime (of nine sharp CH signals), some residual chemical exchange broadening might result. The system may be shifted away from the SEL slightly towards an intermediate exchange rate if the phenyls rotate at a modest rate. Four phenyl positions, the ortho 2′,6′, and the meta 3′,5′, could be exchange broadened. The para 4′ position lies on the phenyl rotation axis, so the 4′ signal should not be broadened by 180° phenyl rotation [11]. Thus, the five sharp CH signals are attributed to the

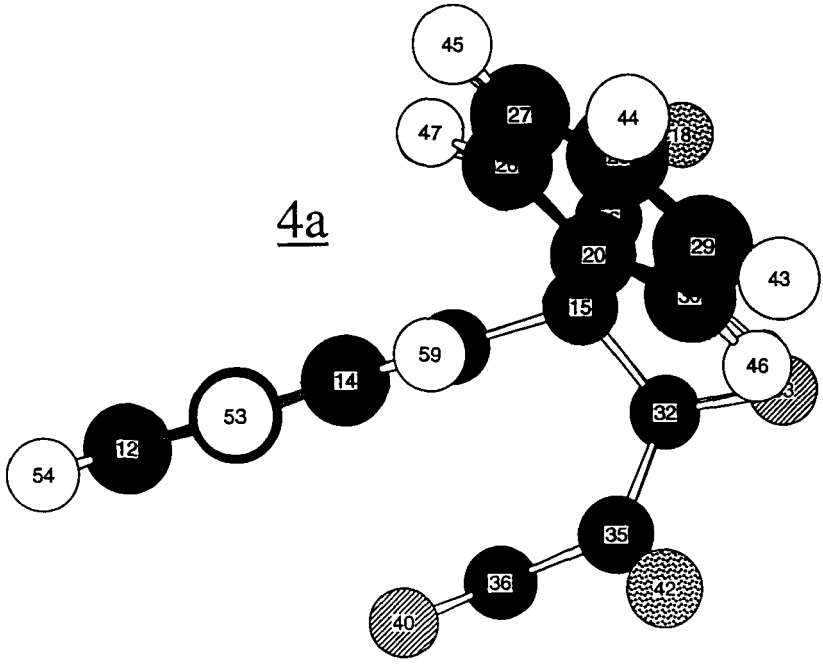


Figure 4. CS Chem3D representations of adduct 2, showing the expected endo stereochemistry for a Diels-Alder kinetic product. Two different hypothetical "boat-like" conformations are shown for the six-membered enedione ring. Structure (a) shows the syn conformer, with the FC=CF moiety flipped close to the phenanthrenoid moiety. Structure (b) shows the anti conformer, in which the FC=CF is flipped to a distal position relative to the phenanthrenoid group. See Results and Discussion for calculated interatomic distances. Note that the conformations shown for the bridgehead phenyls are arbitrary and have not been energy-minimized; we have emphasized this by showing different phenyl conformations for the syn and anti structures. In both cases, the sigma (mirror) plane of the adduct is the plane of the paper and the phenanthrene ring is seen edge-on. Atom 40 denotes the vinylic fluorine close to the observer and atom 59 would correspond to H-1. Atom 33 is the bridgehead sp^3(CF).

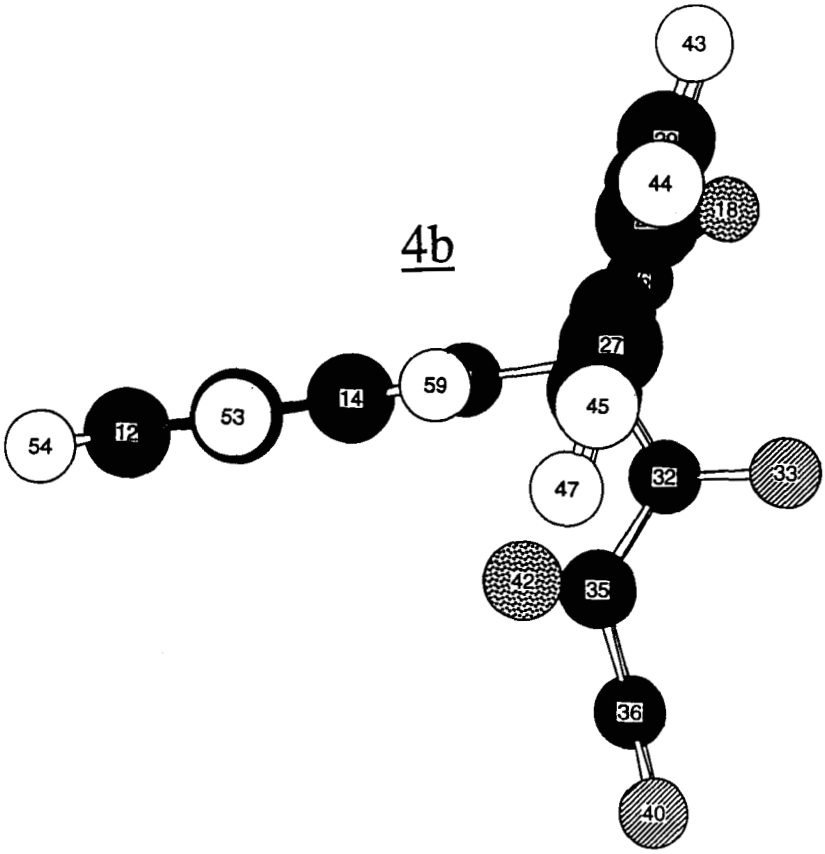


Figure 4. . Continued

phenanthrenoid and para phenyl methines. We reiterate that this analysis is quite tentative. (A mixed solvent system of $CD_3COCD_3/CDCl_3$ was tested to achieve better signal dispersion, but poor acetone-solubility of compound 3 resulted in unacceptable signal-to-noise ratio even after 30,000 acquisitions.)

CONCLUSIONS

The Diels-Alder adduct 2, obtained by reaction of phencyclone, compound 1, and p-fluoranil, compound 3, has

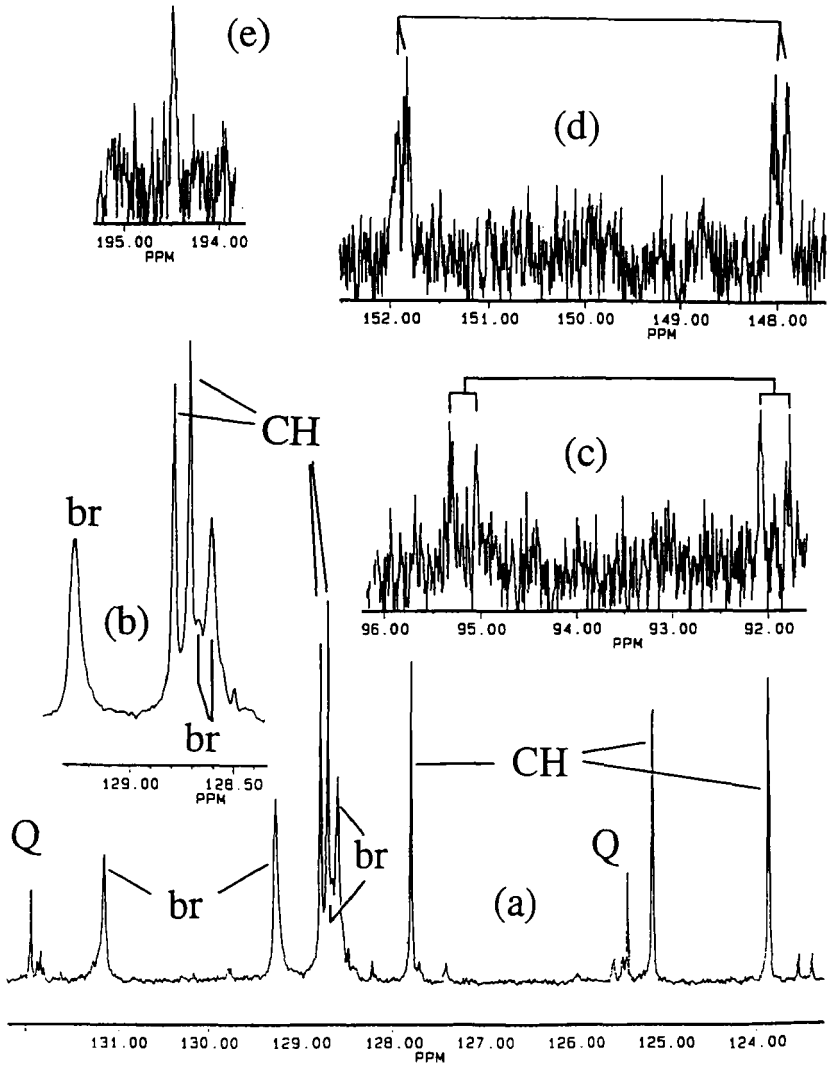


Figure 5. The 75 MHz ^{13}C NMR spectrum of adduct 2 in $CDCl_3$ at ambient temperature. The bottom trace, (a), shows the "aryl region" with two weak signals, Q, for unprotonated carbons; five intense sharp signals, CH, for nonexchanging methines; four strong broad signals, br, for exchanging methines. Trace (b) expands the region ca. 128.5-129.5 ppm. Traces (c) and (d) show the approximate double doublets for the bridgehead sp^3(CF) and vinyl FC=CF signals, respectively. Trace (e) shows the strained bridging ketone absorption. Note that identical vertical and horizontal scales are used for the latter three traces. A total of 10,186 acquisitions were used, with a relaxation delay of 3s and a pulse width of 6.7 μs.

been examined by 300 MHz ^{1}H and 282 MHz ^{19}F NMR in $CDCl_3$ at ambient temperatures. The proton 1D and 2D (COSY45) spectra allow full assignments and clearly demonstrate the slow hindered rotations of the unsubstituted bridgehead phenyls of compound 2, with nine anisochronous equal area aryl methine signals. Nonbonded repulsions are believed to involve the phenyl ortho protons with phenanthrenoid H-1,8, with the bridging ketone and enedione carbonyls, and the bridgehead sp^3(CF) fluorines. Substantial anisotropic effects seem evident. The ^{19}F spectrum of compound 2 without ^{1}H decoupling indicated that the lower field fluorine signal is a triplet; with ^{1}H decoupling, the ^{19}F signal collapses to a singlet. Possible explanations for a long range ^{1}H-^{19}F coupling based on a through-space effect are presented. Seemingly unusual ^{19}F shifts are considered with respect to possible anisotropic or van der Waal's effects. Preliminary ^{13}C NMR data (75 MHz) are given, with tentative assignments.

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