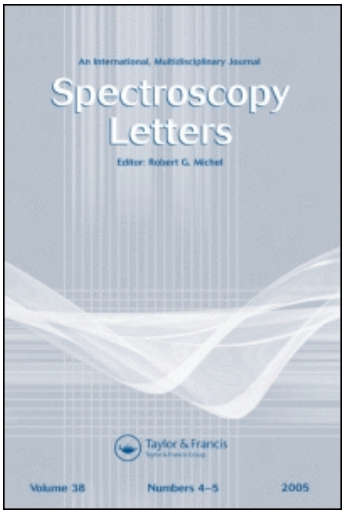


Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

Studies of Hindered Rotation and Magnetic Anisotropy by ^{1}H, ^{13}C and ^{19}F NMR. The Diels-Alder Adduct of N- Pentafluorophenylmaleimide and Phencyclone: A Model for Drugs.

Mohsena F. Amin[a]; Kevin Bynum[a]; Ronald Callahan[b]; Ron Prip[a]; Robert Rothchild[ac]
[a] Science Department, The City University of New York, John Jay College of Criminal Justice, New York, NY [b] Chemistry Department, New York University, Washington Place, New York, NY [c] The Doctoral Faculty, Graduate School and University Center, New York

To cite this Article Amin, Mohsena F. , Bynum, Kevin , Callahan, Ronald , Prip, Ron and Rothchild, Robert(1998) 'Studies of Hindered Rotation and Magnetic Anisotropy by ^{1}H, ^{13}C and ^{19}F NMR. The Diels-Alder Adduct of N-Pentafluorophenylmaleimide and Phencyclone: A Model for Drugs.', Spectroscopy Letters, 31: 3, 673 — 692
To link to this Article: DOI: 10.1080/00387019808002760
URL: http://dx.doi.org/10.1080/00387019808002760

SPECTROSCOPY LETTERS, 31(3), 673-692 (1998)

STUDIES OF HINDERED ROTATION AND MAGNETIC ANISOTROPY BY ^{1}H, ^{13}C AND ^{19}F NMR. THE DIELS-ALDER ADDUCT OF N-PENTAFLUOROPHENYLMALEIMIDE AND PHENCYCLONE: A MODEL FOR DRUGS.

Key Words: Dynamic NMR, One- and two-dimensional NMR, Restricted rotation, COSY, Stereochemistry, Pharmaceuticals, Analysis.

Mohsena F. Amin[a], Kevin Bynum[a], Ronald Callahan[b], Ron Prip[a], Robert Rothchild[a,c]*

(a) The City University of New York, John Jay College of Criminal Justice, Science Department, 445 West 59th Street, New York NY 10019-1128, (b) New York University, Chemistry Department, Washington Place, New York NY 10003, (c) The Doctoral Faculty, Graduate School and University Center, City University of New York

ABSTRACT

The potent Diels-Alder diene, phencyclone, 1, reacts with N-pentafluorophenylmaleimide, 2, to form an adduct, 3, characterized by ^{1}H, ^{13}C, and ^{19}F NMR at 300, 75 and 282 MHz, respectively. The one-dimensional (1D) and two-dimensional (2D) ^{1}H and ^{13}C NMR spectra of 3 at ambient temperatures imply a slow exchange limit (SEL) regime with respect to rotation of the unsubstituted bridgehead phenyl groups about severely hindered $C(sp^2)-C(sp^3)$ bonds. Major non-bonded interactions are expected between the ortho protons of the C_6H_5 groups and H-1,8 of the phenanthrenoid moiety of 3. ^{19}F 1D and 2D (COSY) NMR spectra show that the SEL regime also obtains for rotation about the N-C_6F_5 bond of 3, with five separate

* To whom correspondence should be sent at John Jay College

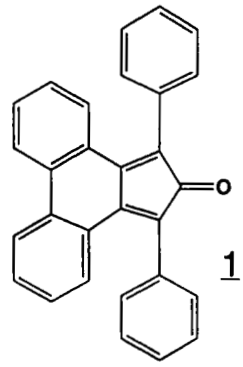
fluorine signals seen, consistent with a preferred conformation in which the C_6F_5 may lie roughly perpendicular to the plane of the pyrrolidinedione moiety, and may be in the mirror symmetry plane of 3. The results are considered relevant to hindered aryl rotations in numerous pharmaceuticals. Selected spectral data for 2 and precursors are also presented.

INTRODUCTION

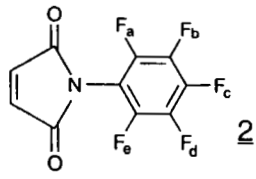
Numerous pharmaceuticals have been found to exhibit hindered rotations of unsubstituted C_6H_5 groups or substituted aryl groups. In the former case, hindered rotations and preferred conformations may have implications in the appearance of ^1H and ^{13}C NMR signals with respect to line broadening, numbers of signals, or chemical shifts (1-4). With suitably substituted aryl groups, hindered rotation may result in the existence of enantiomeric atropisomers which may even differ in pharmacological activity (5-9). We have been especially interested in examining hindered aryl rotations in a series of adducts of the potent Diels-Alder diene, phencyclone, 1 (10-18). We report here the results of one- and two-dimensional (1D, 2D) ^1H, ^{13}C and ^{19}F NMR studies on N-pentafluorophenylmaleimide, 2, and its precursor, and the Diels-Alder adduct, 3, of 1 with 2.

EXPERIMENTAL

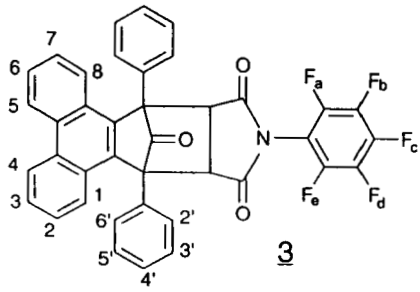
General NMR and other techniques were similar to those described earlier (13-18). Spectra were obtained on a Bruker ACF300 NMR spectrometer at 300 MHZ for ^1H, 75 MHz for ^{13}C and 282 MHz for ^{19}F using a QNP quad nuclear probe, B-VT 2000 variable temperature controller and Aspect A3000 computer. Standard Bruker microprograms were ordinarily used. Reported melting points are uncorrected. IR data were obtained on a Perkin-Elmer 1640 FTIR with DTGS detector at $2cm^{-1}$ resolution, using 3M disposable type 61 polyethylene IR cards; only selected peaks are reported. Reagents and solvents were obtained from Aldrich Chemical (Milwaukee WI),



1



2



3

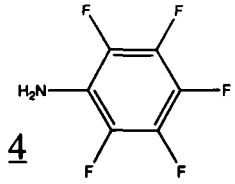
Cambridge Isotope (Andover, MA) or Lancaster Synthesis (Windham NH) and were used as supplied. For ^{19}F NMR, $CFCl_3$ was used as internal standard (at 0.00 ppm) and spectra were first acquired with wide spectral window to accurately define ^{19}F shifts for the samples relative to $CFCl_3$. The ^{19}F spectra were then reacquired with a narrower spectral width

encompassing only the solute ^{19}F signals (not $CFCl_3$) to achieve fine digital resolutions (ca. 0.5 Hz) in order to observe multiplet fine structure.

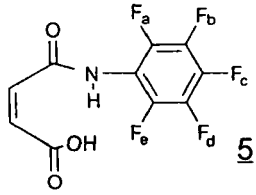
Synthesis of N-Pentafluorophenylmaleamic acid, 5: To a solution of maleic anhydride (freshly crushed briquettes, 0.559 g, 5.70 mmol) in 6 ml CH_2Cl_2, was added $C_6F_5NH_2$ (1.054 g, 5.76 mmol). The stirred mixture was gradually warmed and more CH_2Cl_2 was added to a final volume of ca. 55 ml. After the mixture was boiled for 5 min, solvent was removed (rotary evaporator, aspirator pressure, 52° bath temperature) to yield a yellow oil that crystallized to an off-white solid of crude 5 (1.549 g, 97.7) which was used directly for the next step. Mp (dec) 95-100°. IR: 1712.6, 1525.7, 1506.0, 1004.0, 965.6, 853.2. See Discussion and Tables for NMR data.

Preparation of N-Pentafluorophenylmaleimide,2: A mixture of the crude maleamic acid, 5 (1.374g, 4.89 mmol), anhydrous sodium acetate (0.180g, 2.19 mmol) and acetic anhydride (2.01g, 19.7 mmol), in a flask with reflux condenser topped by a drying tube (anh. $CaCl_2$), was heated for 25 min in a boiling water bath, giving a dark red solution that became semisolid on cooling to room temperature. After 1 week, the mixture was treated with 25 ml 1.5% aq. HCl. This was extracted with Et_2O, and the ether layer was washed with dilute HCl, satd aq $NaHCO_3$, and H_2O (2x), then dried (anh. Na_2SO_4) and solvent was removed (rotary evaporator, aspirator pressure, 43° bath temperature). The resulting slightly tan crude solid, 2 (1.079 g, nominal 4.10 mmol, 83%) had mp 79-85° and was used without further purification. IR: 1734.2, 1525.3, 1374.1 (shldr), 1361.7, 1297.7, 1143.4, 1070.2, 1049.9, 985.8, 822.0, 726.8, 694.8, 641.9. NMR data appear in Tables and Discussion.

Preparation of Diels-Alder adduct from phencyclone and N-pentafluorophenylmaleimide: To 451 mg crude 2 (nominal 1.71 mmol) in 15 ml CH_2Cl_2 was added 158 mg 1 (0.413 mmol). After 2 hr stirring, the intense green-black phencyclone color was largely discharged to give a clear yellow solution. (Note that a substantial excess of the crude maleimide [nominal



4



5

4.15-fold excess] can be used to assure quick decolorization and consumption of 1, since the unreacted maleimide is quite soluble and can readily be separated from the less soluble adduct, 3.) The mixture was allowed to stand ca. 3.5 weeks. Partial solvent removal (rotary evaporator) and addition of hexane gave tan solid, collected by vacuum filtration and air-dried, 257 mg (0.398 mmol, 96.4% based on phencyclone) of crude 3 which was adequate for subsequent spectral studies. Mp 214-216°. IR 1794.4 (bridging ketone CO), 1736.0 (shldr), 1732.6 (NCO), 1524.0 and 1519.5 (doublet), 1448.4, 1359.9, 1301.8, 1178.7, 993.7, 772.9, 754.6, 724.5, 698.0, 634.1. NMR data appear in Tables and Discussion.

RESULTS AND DISCUSSION

Condensation of pentafluoroaniline, 4, with maleic anhydride gives N-pentafluorophenylmaleamic acid, 5, which undergoes cyclodehydration with sodium acetate in acetic anhydride to give N-pentafluorophenylmaleimide, 2. Diels-Alder addition of 2 to phencyclone, 1, produced the adduct 3 for NMR studies. If the bridgehead phenyl rotation in 3 is slow on the NMR timescale (19), resulting in SEL spectra,

nine equal (2H) intensity aryl proton signals should be observed (barring accidental isochrony), comprising four gross doublets and five gross triplets. The multiplicity, assuming near-first-order spectra, would reflect the number of vicinal proton neighbors. Thus, the protons at the termini of the $(CH)_4$ spin system for the phenanthrenoid moiety [H-1,8 and H-4,5] would be doublets, as would the ortho protons, H-2',6', of the phenyls. [The latter protons are at the termini of the $(CH)_5$ spin system for each C_6H_5.] The five remaining aryl proton triplet signals would result from "non-terminal" methines within the $(CH)_4$ and $(CH)_5$ spin systems. Aryl ^{13}C spectra should show nine methine and four unprotonated signals for 3 at SEL, assuming no accidental overlaps, for the phenanthrenoid and C_6H_5 groups.

In contrast, rapidly rotating bridgehead phenyls in 3 would result in fast exchange limit (FEL) spectra due to rapid exchange of the two ortho positions, 2' and 6', in the phenyl groups, and the two meta positions, 3' and 5'. This could give rise to seven aryl proton signals, including one 4H and two 2H doublet signals, in addition to one 4H and three 2H triplet signals. An FEL system for 3 should show four unprotonated aryl carbon signals and only seven CH aryl carbon signals for phenanthrenoid and phenyl groups, with two of the seven aryl CH signals being double intensity, i.e., C_6H_5 ortho and meta. (Note that extensive complex splitting of ^{13}C by ^{19}F in the C_6F_5 group effectively results in the non-appearance of the carbon signals: they are lost in the noise because of low peak heights within the ^{13}C multiplet signals.)

In fact, the ^1H NMR spectrum for 3 in $CDCl_3$ (ambient temperature) shows, in addition to a 2H singlet at 4.73 ppm for the two methine bridgeheads, an aryl ^1H region which superficially shows five 2H and two 4H multiplets, suggesting the FEL system. (See Figure 1.) More careful inspection reveals the presence of three 2H doublets, centered at 8.69 ppm, 8.28 ppm (slightly broad) and 7.13 ppm (strong leaning). An FEL system can not account for three 2H intensity

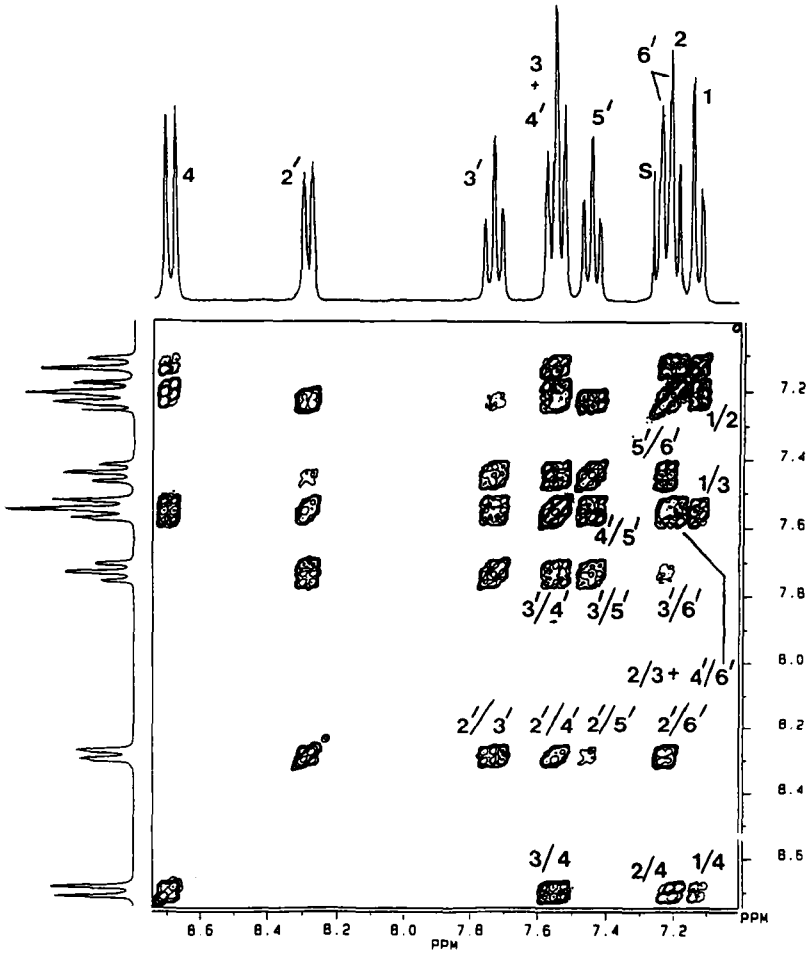


Figure 1. The 300 MHz aryl region ^1H spectrum for adduct 3 in $CDCl_3$ at ambient temperature, shown as the projection spectrum for the COSY45 spectrum. (The singlet at 4.73 ppm for the two bridgehead methines is omitted. The $CHCl_3$ solvent impurity is marked S.) For the COSY45, the F2 spectral width was 528 Hz. The spectrum is in the magnitude mode, with 2 dummy scans and 16 acquisitions for each of 128 increments in t_1, zero-filled once only in the F1 dimension for a final data matrix size of 256 x 512, to give a digital resolution of 2 Hz/point in each dimension. Data were processed with unshifted sine-bell apodization in both dimensions and symmetrized.

doublets, implying that this is an SEL system with coincidental overlaps. The two-dimensional (2D) chemical shift correlation spectra clarified the assignments. COSY90 (not shown) effectively revealed the presence of $(CH)_4$ and $(CH)_5$ spin systems. Starting from the assumption that the lowest field doublet could be assigned to H-4,5 of the phenanthrenoid moiety (based on our earlier work in this series), the 8.69 ppm doublet showed crosspeak correlations to the 2H triplet at 7.55 ppm, the 4H approximate triplet at 7.20 ppm and the strongly leaning doublet at 7.125 ppm (weak correlation). These would define the phenanthrenoid $(CH)_4$ system. The slightly broad doublet at 8.28 ppm reveals correlations to four other signals: 2H triplet at 7.73 ppm, 4H triplet at 7.55 ppm, 2H triplet at 7.44 ppm (weak crosspeak) and the distorted 4H triplet ca. 7.20 ppm. This maps out the $(CH)_5$ spin system of the slowly rotating bridgehead C_6H_5 rings. The less-sensitive COSY45 experiment (Figure 1) provided the advantages of reduced intensity of peaks along the diagonal as well as crosspeak "tilting" to unambiguously distinguish vicinal ^3J couplings (positive signs) from ^4J W-couplings (negative signs) (20). Crosspeak intensity alone does not always permit distinguishing ^3J and ^4J crosspeaks in these adducts of 1. Use of fine digital resolution for COSY45 or COSY90 in the incremented t_1 dimension permits distinguishing, e.g., the "2x2" matrix of the ^4J crosspeak for H-2′/6′, from "2x3" or "3x3" crosspeaks. With suitably low contour level (more sensitive) for both COSY90 and COSY45, even small long-range couplings, e.g., H-1/4, H-2′/5′, H-3′/6′, could be detected (21). Crosspeaks correlating to the 4H multiplet ca. 7.2 ppm are slightly displaced from one another, confirming slight chemical shift differences between the gross triplet (assigned to H-2,7 at 7.20 ppm) and the gross doublet (assigned to H-6′ at 7.22 ppm). Assignments are summarized in Table 1.

The ^{13}C spectra of 3 in both $CDCl_3$ and CD_3COCD_3 appeared consistent with the SEL regime for slow C_6H_5 rotation (Table 1, Figure 2). With standard undegassed samples, a 3 sec

Table 1. NMR spectral data for adduct 3 and related compounds, with chemical shifts in ppm. Estimated observed couplings (in Hz) are given where available.

Compound 3, PROTON DATA				3, CARBON DATA, δ		
Nucleus	δ,ppm	(Est'd J, Hz)	Phenanthrene (ref. 26) (See Note c.)	($CDCl_3$)	Tentative Assignment	(CD_3COCD_3)
H-1,8	7.13	(8.37,1.06)	8.12	195.64	ketone CO	196.47
H-2,7	7.20*	(8.28,0.71)	7.82	171.27	$N(CO)_2$	172.79
H-3,6	7.55	(ca. 7.67, 1.18)	7.88	133.31	Q	135.06
H-4,5	8.69	(8.41)	8.93	133.03	Q	134.48
				131.720 }	Q, split peak {	132.566
				131.703 }	(1.2 Hz sep'n) {	132.550
H-2'	8.28	(7.85)		130.96	CH	132.16
H-3'	7.73	(7.63,1.02)		129.44	CH	129.967
H-4'	7.55	(ca. 7.67, 1.18)		128.757	CH	129.883
H-5'	7.44	(7.58, 1.14)		128.733	CH	129.136
H-6'	7.22*	(8.28)		128.60	CH	129.096
				127.22	CH	127.87
CHCO	4.73	(0)		126.58	CH	127.18
				126.03	Q	126.96
				125.61	CH	126.68
				123.13	CH	124.14
				63.52	C_6H_5C	64.36
				45.67	2xCH	46.79

Notes: See Results and Discussion. (a) In carbon data, nonprotonated quaternary aryl carbons of the phenanthrenoid and C_6H_5 groups are labelled Q. Carbons of the C_6F_5 did not give observable signals due to extensive ^{19}F splitting. Shifts are reported to 0.001 ppm for near-isochronous signals. Aryl methines designated CH absorbed ca. 123-132 ppm. ^{13}C shifts in CD_3COCD_3 are reported relative to the central line of the CD_3 signal as 29.8 ppm; in $CDCl_3$, the central line of the solvent triplet was used as the reference at 77.0 ppm. Relaxation delays of 1 sec (for ^1H) or 3 sec (for ^{13}C) were used. (b) In proton data, asterisks denote overlapping signals and estimated shifts. (c) For this present work, we independently determined the ^1H shifts for phenanthrene (30.6 mg/830 mg $CDCl_3$, 21°) from 300 MHz 1D and 2D COSY45 NMR as follows: H-1,8 (7.86 ppm), H-2,7(7.57 ppm), H-3,6(7.63 ppm), H-4,5(8.65 ppm), H-9,10 (7.71 ppm). However, the older literature values are shown in the Table above.

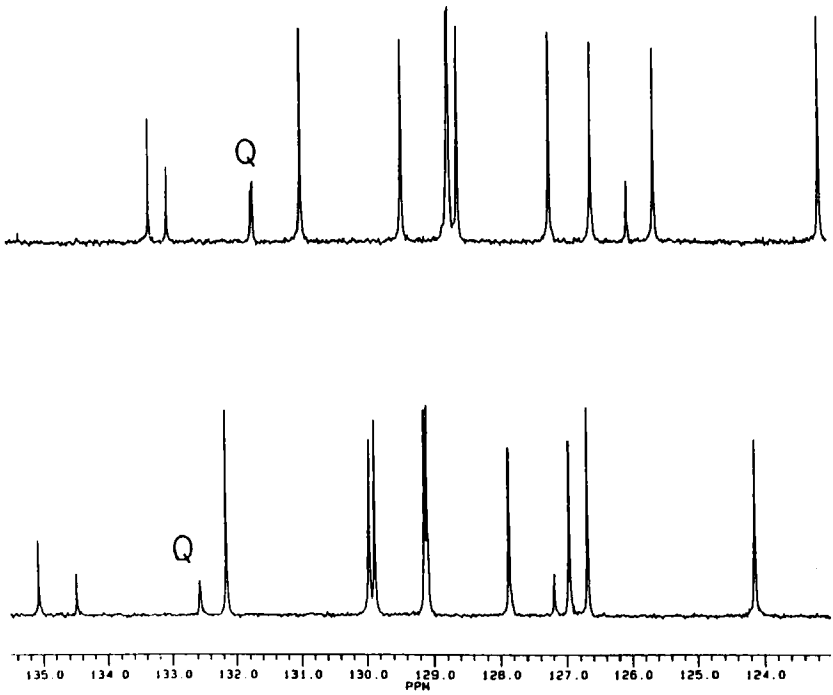


Figure 2. The aryl region ^{13}C NMR of 3 (75 MHz) in $CDCl_3$ (upper trace) and CD_3COCD_3 (lower trace), with composite pulse decoupling of protons, 3 sec relaxation delay, undegassed samples. Q denotes the split quaternary signal. (Carbons of the C_6F_5 are not seen due to extensive splitting by ^{19}F.) The four weaker signals are the non-protonated carbons.

relaxation delay produced four clearly lower intensity signals for the nonprotonated aryl carbons and nine intense signals for the aryl methines (using composite pulse decoupling, CPD, of protons). In $CDCl_3$, two of the nine aryl methine signals were minimally separated (less than 2 Hz) at ca. 128.74 ppm. The DEPT spectrum, which confirmed the distinction between 4° and CH aryl carbons, showed no separation of the peaks near 128.7 ppm (not shown). In

CD_3COCD_3, there are two pairs of close aryl CH signals, near 129.9 ppm (6.4 Hz separation) and near 129.1 ppm (3.0 Hz separation) so that acetone-d_6 is marginally superior in resolving all 13 aryl carbon peaks for the SEL regime. The weak 4° carbon signal at 131.7 ppm ($CDCl_3$) and 132.6 ppm (CD_3COCD_3) consistently appeared split, in both solvents, with a separation ca. 1.2 Hz. This was seen in different batches of 3 and with different spectral acquisitions. The explanation escapes us. A very speculative explanation may involve ^{19}F - ^{13}C coupling, which would involve a seven-bond coupling at the minimum; perhaps a through space coupling mechanism is operative (22). We have not explored this further since it does not appear directly related to the hindered bridgehead phenyl rotations of 3. We note that maleimide 2 showed ^{13}C NMR signals ($CDCl_3$) at 135.32 ppm (HC=CH) and 166.76 ppm (C=O), and ^1H absorption at 6.99 ppm.

The ^{19}F NMR spectrum of 3 in $CDCl_3$ shows five distinct equal-intensity signals (Figure 3) as three gross triplets and two gross doublets. This is consistent with five fluorines of the $(CF)_5$ spin system in nonequivalent environments. The ^{19}F -^{19}F COSY spectrum is also shown in Figure 3. The results are fully explained if the C_6F_5 group is forced into a conformation roughly perpendicular to the average plane of the pyrrolidinedione ring, i.e., the C_6F_5 lies in the plane of mirror symmetry of 3. This could result from steric repulsions between the imide carbonyls and the "ortho" fluorines, F_a and F_e. For five fluorine resonances to be observed, the C_6F_5 ring must be in the SEL regime with respect to rotation about the N-C_6F_5 bond. The anisotropic shielding effects from the phenanthrenoid moiety of 3 (and perhaps from the ketone carbonyl and bridgehead phenyls, as well) could then render anisochronous the signals of the syn or anti "ortho" fluorines (and, likewise, the syn or anti "meta" fluorines). The homonuclear ^{19}F-^{19}F COSY45 spectrum unexpectedly reveals that the lower field ortho fluorine signal, F_a, correlates to the higher field meta fluorine, F_b. If the phenanthrenoid moiety of 3 exerts anisotropic

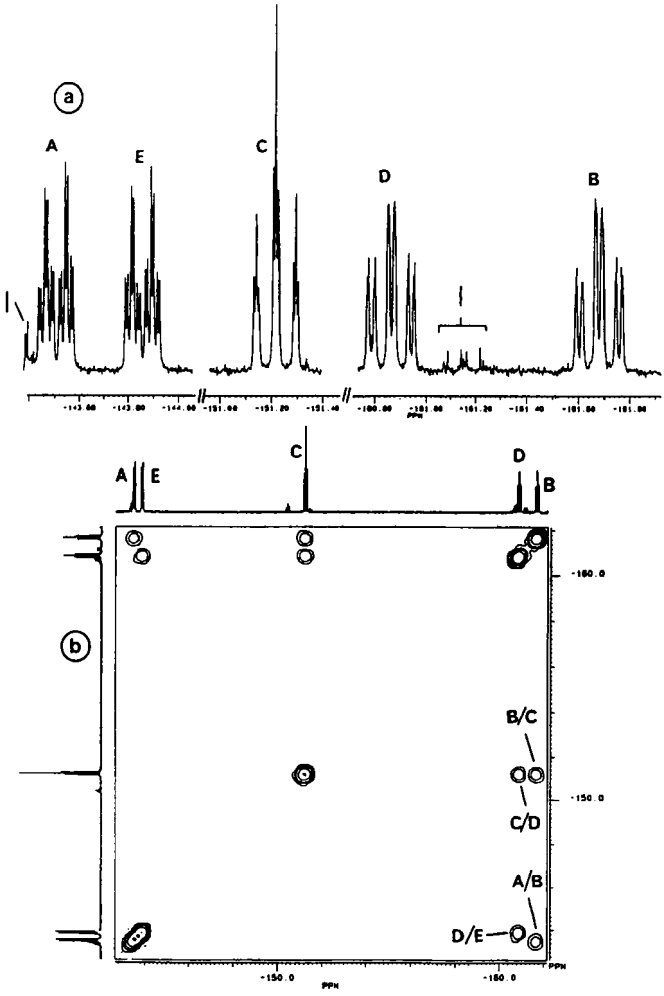


Figure 3. (a) High resolution ^{19}F spectrum of 3 ($CDCl_3$, ambient temperature) at 282 MHz. Some minor impurity signals are noted by I. [Note: Digital resolution is ca. 0.5 Hz/point. The vertical signal intensity and chemical shift axes are uniform for each expanded region.] (b) The $^{19}F-^{19}F$ COSY45 spectrum of 3 in $CDCl_3$, with a spectral width of 5556 Hz in F2. The magnitude mode spectrum was acquired with 64 increments in t_1, zero-filling once in both F1 and F2 to a final data matrix size of 128 x 256, using unshifted sine-bell apodization in both dimensions, and symmetrized.

shielding, it might have been expected that both of the fluorines syn to the phenanthrenoid portion (i.e., syn ortho and syn meta) would be at higher field than the respective anti fluorines, but this is clearly not the case. It is possible that required spatial positioning for the fluorines relative to the phenanthrenoid group is critical, or that the other anisotropic groups (such as the ketone or phenyls) exert opposing effects on the vicinal syn and vicinal anti fluorines at the ortho and meta positions of the C_6F_5. A last hypothesis is that proximity between the syn ortho fluorine and the phenanthrenoid system leads to crowding and deshielding of this fluorine. (This presumes endo stereochemistry in 3.)

NMR data for precursors to 3 were also obtained. The N-pentafluorophenylmaleimide, 2, showed an ^{19}F NMR spectrum in $CDCl_3$ (Figure 4) with the expected three resonances: a gross doublet, 2F intensity, at -143.35 ppm attributed to the two ortho fluorines; a simple triplet of triplets, 1F intensity, at -151.40 ppm attributed to the para fluorine (^3J = 21.46 Hz); and a gross triplet, 2F intensity, at -161.14 ppm for the two meta fluorines. With fine digital resolution of 0.5 Hz/point, considerable spectral complexity is apparent, as seen in Fig. 4. Because of the symmetry in 2, we can not readily distinguish conformational preferences, i.e., coplanar versus perpendicular, for the C_6F_5 and heterocyclic rings. An AA'BB'C system results in either case and only three fluorine resonances are expected, whether SEL or FEL conditions obtain for C_6F_5 rotation. Since steric repulsions between the ortho fluorines and the imide $N(CO)_2$ carbonyls should be similar in both 2 and 3, and since the presence of five ^{19}F resonances for 3 requires SEL perpendicular C_6F_5 and pyrrolidinedione rings, the same situation may be present for 2 as well.

With 3, the low field ortho fluorine is designated F_a and resonates at -143.51 ppm as a doublet of triplets of doublets, dtd, with observed couplings of ca. 22.3, 6.8 and 2.5 Hz. The vicinal meta fluorine F_b resonates at highest

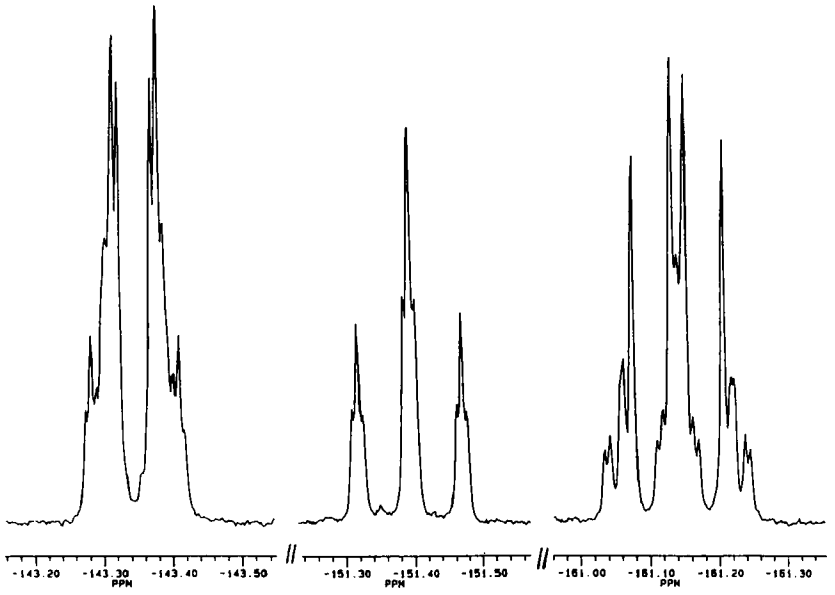


Figure 4. ^{19}F NMR spectrum of N-pentafluorophenylmaleimide, 2, in $CDCl_3$ at 282 MHz, showing expansions of (left to right): ortho fluorines (as approximate doublet); para and meta fluorines (as approximate triplets). (See Note for Fig. 3a.)

field, -161.68 ppm, as a triplet of double doublets (approximately), tdd, with couplings of about 21.9, 6.9 and 1.6 Hz. The para fluorine F_c absorbs at -151.22 ppm as a clean tt, observed couplings of 21.5 and 2.6 Hz. Meta fluorine F_d appears at -160.87 ppm as an approximate tdd, observed couplings 22.0, 6.7 and 1.6 Hz. The higher field ortho fluorine F_e appears at -143.86 ppm, dtd, observed couplings 22.5, 7.0 and 2.8 Hz. (Couplings are believed accurate to $\pm$ 0.2 Hz.) The large couplings of ca. 22 Hz are assigned as vicinal ^3J couplings. The simple tt pattern for the para fluorine permits rigorous assignment of the ^4J "W" couplings J_{ac} and J_{ce} as 2.6 Hz. For F_a and F_e to appear as

dtd multiplets, we must conclude accidental isogamy of $^4J_{ae}$ = $^5J_{ad}$ = 6.8 Hz for F_a, and similarly $^4J_{ae}$ = $^5J_{be}$ = ca. 7 Hz for F_e. Using these approximate coupling constants, for the meta fluorines F_b and F_d, the five-bond couplings $^5J_{be}$ and $^5J_{ad}$ are the larger values (ca. 7 Hz) and the four-bond coupling $^4J_{bd}$ must be the smaller value (ca. 1.5 Hz). The complexity of ^{19}F - ^{19}F couplings in fluoroaromatics is well known and leads to considerable variation in ^3J, ^4J and ^5J magnitudes, depending upon structure (23). For 2, ^{19}F spectral complexity did not permit us to confidently extract coupling constants except for the para fluorine, with ^3J = 21.46 Hz and ^4J = 2.08 Hz. Comparing ^{19}F chemical shifts for 2 and 3 shows that the para fluorine of 2 at -151.40 ppm appears only 0.18 ppm upfield of the analogous F_c at -151.22 ppm in adduct 3. However, the meta fluorines F_b and F_d in 3 are shifted in opposite directions relative to the -161.14 ppm meta fluorine signal in 2, with F_b resonating by 0.54 ppm to higher field (at -161.68 ppm) and F_d 0.27 ppm to lower field (at -160.87 ppm). Compared to the -143.35 ppm ortho fluorine signal in 2, 3 shows F_a 0.16 ppm upfield at -143.51 ppm, and F_e 0.51 ppm to higher field at -143.86 ppm. Clearcut evidence for anisotropic shielding by the phenanthrenoid group in 3 of fluorines is not apparent, especially if the shielding should manifest itself most strongly for the vicinal ortho/meta pair of fluorines syn to the phenanthrenoid, e.g., F_e/F_b. In 3, F_b and F_e show the larger upfield shifts relative to signals in 2, but F_b and F_e are on "opposite sides" of the C_6F_5 ring; they are not vicinal, based on ^{19}F-^{19}F COSY45 results.

Because of low solubility in $CDCl_3$, the N-pentafluorophenylmaleamic acid, 5, had to be examined in more polar solvents, CD_3COCD_3 or CD_3SOCD_3, so chemical shifts can not be compared to results in $CDCl_3$ for the other compounds. The ambient temperature ^{19}F spectra of 5 in d_6-acetone or d_6-dimethyl sulfoxide were only moderately resolved with respect to fine structure. Variable temperature (V/T) ^{19}F NMR studies indicated some unusual temperature dependence. We plan to report these results separately. We note here

Table 2. ^{19}F NMR chemical shifts at 282 MHz (ppm).

Nucleus	3	2	5
F_a	-143.51	-143.35	-144.14
F_b	-161.68	-161.14	-162.94
F_c	-151.22	-151.40	-157.46
F_d	-160.87	-161.14	-162.94
F_e	-143.86	-143.35	-144.14

Notes to Table: Chemical Shifts are relative to $CFCl_3$ as internal standard at 0.00 ppm, in $CDCl_3$ for adduct 3 and maleimide 2, or in d_6-DMSO for maleamic acid 5, at ambient temperatures. Nucleus label designations are based on gross multiplicities (i.e. doublets for ortho [F_a, F_e], triplets for meta [F_b, F_d] and para [F_c], relative peak areas, and ^{19}F-^{19}F COSY45 data (for 3). See Results and Discussion.

only the d_6-DMSO results at 20°, which exhibited somewhat broad signals of a 2F intensity gross "doublet" (ortho) at -144.14 ppm, 1F intensity triplet (para, ^3J = 23.0 Hz) at -157.46 ppm, and 2F intensity gross "triplet" (meta) at -162.94 ppm. Note that the ^1H NMR of 5 (CD_3COCD_3, ambient temperature) showed the expected AB quartet for the olefinic protons at 6.74 and 6.46 ppm, with observed coupling 12.53 Hz, consistent with cis geometry for the HC=CH group. The broad amide NH signal was assigned at 10.17 ppm. NMR data for $C_6F_5NH_2$, 4, have been reported for both ^1H and ^{13}C (24) and ^{19}F (25). Table 2 summarizes the ^{19}F NMR shift data from this present work for the phencyclone adduct, 3, the maleimide 2, and the maleamic acid 5.

The ^1H NMR for 3 indicates chemical shifts and magnetic anisotropic effects within the bridgehead phenyls and the phenanthrenoid moiety similar to previously reported adducts of 1 with N-substituted maleimides (13-18). This suggests similarities with respect to equilibrium conformations of the C_6H_5 groups and probably also the stereochemistry of the

Diels-Alder addition, presumably endo. Table 1 includes ^1H NMR data to compare 3 with the parent, phenanthrene. The striking shift differences between corresponding protons in the phenanthrenoid moiety of 3 and the reference hydrocarbon were discussed by us earlier. They are consistent with strong shielding by the C_6H_5 rings, i.e., for H-1,8 of 3.

CONCLUSIONS

We have reported the preparation of N-pentafluorophenylmaleimide, 2, by cyclodehydration of the maleamic acid, 5, derived from reaction of pentafluoroaniline, 4, with maleic anhydride. Phencyclone, 1, undergoes Diels-Alder addition with 2 to form the adduct, 3. The 300 MHz ^1H and 75 MHz ^{13}C NMR spectra of 3 in $CDCl_3$ (or CD_3COCD_3) at ambient temperature are fully consistent with SEL systems with respect to sterically hindered rotations of the unsubstituted bridgehead phenyls about the $C(sp^2)$-$C(sp^3)$ bonds, suggesting nonbonded interactions between the phenyl ortho H-2',6' and the phenanthrenoid H-1,8, similar to previously prepared adducts in this series. ^{19}F NMR studies (282 MHz) were also carried out on 2, 3 and 5. While the presence of three fluorine resonances in 2 and 5 was expected, corresponding to ortho (2F), meta (2F), and para (1F) signals, 3 showed five equal intensity fluorine signals, as two gross doublets (ortho F_a, F_e), and three gross triplets (meta F_b, F_d and para F_c). This implies: (a) hindered rotation and an SEL regime for C_6F_5 rotation about the $C(sp^2)$-N bond in 3, and (b) a preferred conformation in which the C_6F_5 ring essentially lies in the mirror plane of 3, perpendicular to the pyrrolidinedione ring. Both ^1H and ^{19}F 2D NMR (COSY45 or COSY90) were employed to define correlations and permit assignments of the respective spin systems.

ACKNOWLEDGMENTS

Partial support has been provided by the U.S. Education Department Minority Science Improvement Program (grant nos. G008641165 and 1-132553815-A1), National Science Foundation

(grant nos. DUE9750675 and USE9152822), the Forty-Five Foundation, and the Professional Staff Congress - City University of New York Research Award Program (to R.R.).

LITERATURE REFERENCES

1. A. Elias, T.G. Roberts, K.S. Venkatasubban, R. Rothchild. NMR studies of drugs: antipyrine and analogs. Use of achiral and chiral lanthanide shift reagents to examine hindered rotation. Spectrosc. Lett. 1997; 30(8): in press.

2. K.S. Venkatasubban and R. Rothchild. NMR studies of drugs: antipyrine and analogs. ^{1}H and ^{13}C chemical shift dispersion as conformation indicator for the N-phenyl ring. Spectrosc. Lett. 1997; 30(8): in press.

3. L.A. LaPlanche, R. Rothchild. Unusual hindered rotation of an unsubstituted phenyl group. Variable temperature ^{1}H NMR studies and preliminary ^{13}C assignments in Ketazolam. Spectrosc. Lett. 1990; 23(8): 1041-1063.

4. L.A. LaPlanche, R. Rothchild. Low-temperature two-dimensional heteronuclear shift correlation spectroscopy of a 1,4-benzodiazepine. Spectrosc. Lett. 1991; 24(1): 99-126.

5. A. Mannschreck, H. Koller, G. Stühler, M.A. Davies, J.Traber. The enantiomers of methaqualone and their unequal anticonvulsive activity. Eur. J. Med. Chem. - Chim. Ther. 1984; 19(4): 381-383.

6. M. Blumenstein, J. Ross, R. Rothchild. NMR studies of drugs. Methaqualone. Approaches to rigorous ^{1}H and ^{13}C assignments with applications of achiral and chiral shift reagents. Spectrosc. Lett. 1990; 23(2): 189-221 and references cited therein.

7. A. Poropatich, R. Rothchild. ^{1}H NMR spectral simplification with achiral and chiral lanthanide shift reagents. 2-Methyl-3-(2'-hydroxymethylphenyl)-4(3H)-quinazolinone. Spectrosc. Lett. 1990; 23(1): 29-43.

8. R. Rothchild, H. Wyss. NMR studies of drugs. Applications of lanthanide shift reagents to afloqualone, an axially chiral quinazolinone. Spectrosc. Lett. 1994; 27(2): 225-246.

9. R.J. Friary, M. Spangler, R. Osterman, L. Schulman, J.H. Schwerdt. Enantiomerization of an atropisomeric drug. Chirality 1996; 8: 364-371.

10. T. Sasaki, K. Kanematsu, K. Iizuka. Molecular design by cycloaddition reactions. XXV. High peri- and

regiospecificity of phencyclone. J. Org. Chem. 1976; 41 (7): 1105-1112.

11. L.A. LaPlanche, Y. Xu, R. Benshafrut, R. Rothchild, E.A. Harrison, Jr. NMR studies of hindered rotation of unsubstituted bridgehead phenyl rings in the phencyclone-norbornadiene adduct. Spectrosc. Lett. 1993; 26(1): 79-101.

12. Y. Xu, L.A. LaPlanche, R. Rothchild. Assignment of ^{13}C resonances in the phencyclone-norbornadiene adduct via 2D NMR. ^{13}C evidence for hindered rotation of unsubstituted bridgehead phenyl rings. Spectrosc. Lett. 1993; 26(1): 179-196.

13. R. Callahan, R. Rothchild, H. Wyss. NMR studies of hindered rotation. The Diels-Alder adduct of phencyclone with p-benzoquinone: restricted motion of bridgehead phenyls. Spectrosc. Lett. 1993; 26(9): 1681-1693.

14. R. Benshafrut, R. Callahan, R. Rothchild. NMR studies of hindered rotation. The Diels-Alder reaction of phencyclone with maleic anhydride: restricted motion of bridgehead phenyls. Spectrosc. Lett. 1993; 26(10): 1875-1888.

15. K. Bynum, R. Rothchild. NMR studies of hindered rotation. The Diels-Alder adduct of phencyclone with N-n-propylmaleimide: restricted motion of bridgehead phenyls. Spectrosc. Lett. 1996; 29 (8): 1599-1619.

16. K. Bynum, R. Rothchild. NMR studies of hindered rotation. The Diels-Alder adduct of N-n-butylmaleimide with phencyclone: restricted motion of bridgehead phenyls. Spectrosc. Lett. 1996; 29(8): 1621-1634.

17. K. Bynum, R. Rothchild. Analysis of hindered rotation and magnetic anisotropy by NMR. Models for drugs and agricultural compounds. The Diels-Alder adduct of phencyclone with N-carbamoylmaleimide. Spectrosc. Lett. 1997; 30(4): 727-749.

18. K. Bynum, R. Rothchild. NMR studies of hindered rotation. The Diels-Alder adduct of 4-methyl-1,2,4-triazoline-3,5-dione with phencyclone: Restricted rotation of unsubstituted bridgehead phenyls. Spectrosc. Lett. 1997; 30(8): in press.

19. J.K.M. Sanders, B.K. Hunter. Modern NMR Spectroscopy: A Guide for Chemists, 2nd ed. Oxford, New York, etc.: Oxford Univ., 1993; pp. 205-211, 216-222.

20. K. Nakanishi, ed. One-dimensional and Two-dimensional NMR Spectra by Modern Pulse Techniques. Tokyo:

Kodansha, 1990 (Mill Valley CA: University Science Books) pp. 100, 102, 106, 211, 212, and references cited therein.

21. J.K.M. Sanders, B.K. Hunter. Modern NMR Spectroscopy: A Guide for Chemists, 2nd ed. Oxford, New York, etc.: Oxford Univ., 1993; pp. 117, 142-143.

22. (a) H. Günther. NMR Spectroscopy - an Introduction. New York: John Wiley, 1980; pp. 120, 121, 352, 353. (b) E. Breitmaier, W. Voelter. Carbon-13 NMR Spectroscopy. High Resolution Methods and Applications in Organic Chemistry and Biochemistry. 3rd ed. New York: VCH, 1987 p. 270 and references cited therein.

23. E.F. Mooney. An Introduction to ^{19}F NMR Spectroscopy. New York and London: Heyden & Son, 1970. Chapt. 4, pp. 39-53, 84-89.

24. C.J. Pouchert, J. Behnke. The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra, edition I. Milwaukee WI: Aldrich Chemical, 1993; vol. 2, p. 535 C.

25. E.F. Mooney. An Introduction to ^{19}F NMR Spectroscopy. New York: Heyden and Son, 1970, pp. 39, 40, 84.

26. a) H. Günther. NMR Spectroscopy, 2nd ed. New York: John Wiley, 1992, p. 518; b) C.W. Haigh, R.B. Mallion. Proton magnetic resonance of planar condensed benzenoid hydrocarbons. I. Analysis of spectra. Mol. Phys. 1970; 18: 737-750.

Date Received: October 24, 1997
Date Accepted: December 11, 1997