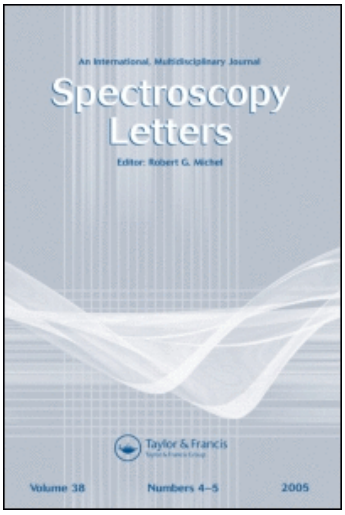

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STUDIES OF HINDERED ROTATION AND MAGNETIC ANISOTROPY BY ^{1}H, ^{19}F AND ^{13}C NMR IN MODELS FOR DRUGS. I. THE DIELS-ALDER ADDUCT OF PHENCYCLONE WITH N-2,2,2-TRIFLUOROETHYLMALEIMIDE, AND PRECURSORS.

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

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ABSTRACT

To gain understanding of hindered rotations and magnetic anisotropy in drugs, compounds of much intrinsic importance, we have investigated as a model compound the Diels-Alder adduct of phenycyclone with N-2,2,2-trifluoroethylmaleimide for study by ^{1}H, ^{19}F and ^{13}C NMR. The N-2,2,2-trifluoroethylmaleamic acid and maleimide precursors were examined by ^{1}H and ^{19}F NMR. The phencyclone adduct is shown by ^{1}H and ^{13}C NMR (at 300 and 75 MHz, respectively) to exhibit slow exchange limit spectra at ambient temperatures, arising from hindered rotation of the bridgehead unsubstituted phenyl groups.

INTRODUCTION

Hindered aryl group rotations in drugs can lead to enantiomerism due to axial chirality as in methaqualone [1] and a metabolite [2]; the skeletal muscle relaxant afloqualone [3]; a potential anti-psoriatic agent, Sch40120 [4]; and the sedative/hypnotic, mecloqualone [5]. Some NMR studies with

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lanthanide shift reagents (LSR) have been reported for chiral (famprofazone) [6] and achiral (antipyrine) [7] pharmaceuticals with potentially hindered N-phenyl rotations, and both ^{1}H and ^{13}C NMR have been discussed in relation to N-phenyl conformations in a series of antipyrine analogs [8]. Hindered aryl rotations are therefore of much significance.

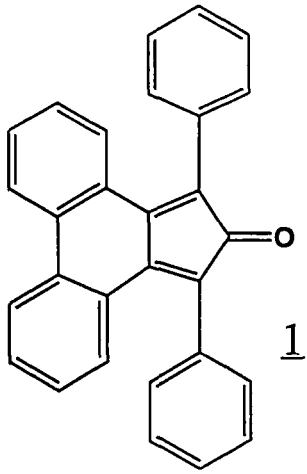
The potent Diels-Alder diene component, phencyclone, 1 [9], has been found to produce novel adducts by reaction with suitable dienophiles. The unsubstituted bridgehead phenyl groups in these adducts are severely hindered. Slow exchange limit (SEL) spectra are observed for both ^{1}H and ^{13}C of the phenyls (at ambient temperature) [10]. Most recently, we had extended the proton and carbon-13 NMR studies of these phencyclone adduct systems to fluorine-19, and reported the hindered rotation of both the bridgehead phenyls as well as the N-C_6F_5 group in the adduct of 1 with N-pentafluorophenylmaleimide [11].

In this present report, we extend the studies in fluorine-containing systems. 2,2,2-Trifluoroethylamine is converted to N-2,2,2-trifluoroethylmaleamic acid, 2, by reaction with maleic anhydride, and the maleamic acid is cyclodehydrated in hot acetic anhydride to give the N-2,2,2-trifluoroethylmaleimide, 3. The ^{1}H and ^{19}F data for 2 and 3 are reported. Reaction of 3 with 1 provides the adduct 4, which was studied by ^{1}H, ^{13}C and ^{19}F NMR.

EXPERIMENTAL

General NMR and other techniques have been described [10-13]. For ^{1}H NMR, chemical shifts are referenced to tetramethylsilane (TMS) as internal standard at 0 ppm; for ^{13}C NMR the central peak of the $CDCl_3$ signal was assigned a shift of 77.0 ppm; for ^{19}F NMR, $CFCl_3$ was used as internal standard at 0 ppm.

Synthesis of N-2,2,2-Trifluoroethylmaleamic acid, 2 : A mixture of maleic anhydride (2980 mg, 30.39 mmol), 2,2,2-trifluoroethylamine hydrochloride (3000 mg, 22.14 mmol), anhydrous sodium acetate (2490 mg, 30.35 mmol) and 12 ml CH_2Cl_2 was vigorously stirred for ca. 1 h. The resulting white solid was filtered, washed with 2 ml CH_2Cl_2 and 2 ml H_2O, and dried, to yield the crude maleamic acid, 2 (3350 mg, nominal 16.99 mmol, 76.8% yield) with mp 95-100°. This was used directly for the next step. IR (KBr, cm^{-1}): 3246.7, 3084.0, 1714.0, 1575.8 (br), 1399.1, 1295.1, 1259.3, 1225.1, 1153.2, 991.6, 859.8, 838.4, 802.3, 764.6, 661.7, 635.6, 608.3, 550.5, 465.9. NMR (CD_3COCD_3): ^{19}F (ppm): -71.225 (triplet, ^{3}J[HCCF] = 9.41 Hz). ^{1}H:



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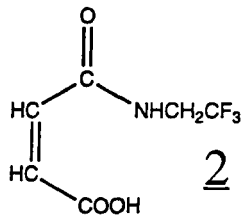

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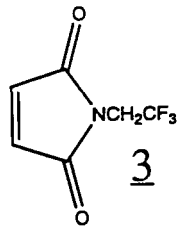

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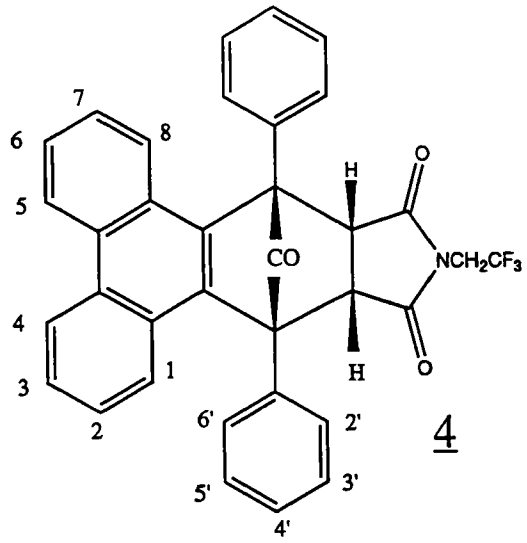
6.653 (2H,d) and 6.371(2H,d) AB quartet, ^{3}J[HC=CH]= 12.83 Hz; 4.189 (2H, q, ^{3}J [HCCF] = 9.39 Hz). Synthesis of N-2,2,2-trifluoroethylmaleimide, 3: A mixture of the crude maleamic acid, 2 (2000 mg, nominal 10.15 mmol), anhydrous sodium acetate (320 mg, 3.90 mmol) and acetic anhydride (3500 mg, 34.28 mmol) was heated for 30 min in a hot water bath, producing a dark brown solution. Upon cooling, crystals were deposited, which were separated by



filtration and washed/extracted with 20 ml petroleum ether (bp range 30-60°) followed by 5 ml CH_2Cl_2. The combined filtrate/washings were slowly evaporated to give brown crystals that were collected and washed with 5 ml petroleum ether and 2 ml CH_2Cl_2 to yield a yellow-tan solid crude maleimide, 3 (579 mg, nominal 3.23 mmol, 31.8%) with mp 50°, satisfactory for subsequent reaction with phencyclone. IR (KBr, cm^{-1}): 3112.5, 1720.4 (CO, v. strong), 1403.7, 1340.4, 1270.2, 1213.0, 1165.2, 1115.5, 1028.5, 840.2, 696.3, 670.3, 625.9, 535.7. NMR ($CDCl_3$): ^{19}F: -71.497 (triplet, ^3J[HCCF] = 8.55 Hz). ^1H: 6.842 (2H, s, HC=C); 4.141 (2H, q, ^3J[HCCF] = 8.59 Hz). Synthesis of Phencyclone Adduct, 4, from N-2,2,2-trifluoroethylmaleimide: To a vigorously stirred mixture of the crude maleimide, 3 (prepared as above) (450 mg, nominal 2.51 mmol) in 15 ml CH_2Cl_2, phencyclone was added in portions. Each increment of 1 initially produced the intense green-black phencyclone color which was allowed to discharge before the next addition. After a total of 700 mg (1.83 mmol) of 1 was added, decolorization of the mixture took about 10 min. At this point, solids in the mixture were separated by filtration and washed/extracted with 3 ml CH_2Cl_2. The combined filtrate and washings were concentrated (rotary evaporator) and deposited yellow crystals upon cooling. These crystals were collected and washed

with CH_2Cl_2 to yield, after drying, 750 mg (1.34 mmol, 73% yield based on 1) of near white solid adduct, 4, used without further purification for NMR studies. Mp 254-257° (dec., gas evolution and darkening). IR (KBr, cm^{-1}): 3059.4, 1792.8 (strained ketone CO), 1724.0 (CO), 1499.4, 1448.6, 1393.0, 1347.5, 1268.0, 1137.8, 1047.5, 838.2, 777.9, 752.9, 724.2, 699.5, 605.9, 555.4, 508.3. NMR ($CDCl_3$): ^{19}F: -72.091 (triplet, ^3J[HCCF]=8.51 Hz). See Table for ^1H and ^{13}C NMR data.

RESULTS AND DISCUSSION

The spectra of Diels-Alder adduct 4 are fully consistent with hindered rotation of the bridgehead unsubstituted phenyls, resulting in slow exchange limit (SEL) ^1H and ^{13}C NMR spectra at ambient temperatures. The one-dimensional (1D) ^1H spectrum is shown in Figure 1. Aryl proton assignments follow from the 2D COSY45 spectra of Figure 2. The "high resolution" aryl region spectrum of Fig. 2a shows crosspeaks for long-range (^4J, ^5J) and vicinal couplings and reveals crosspeak fine structure. Starting with the assumption that the lowest field aryl proton signal at 8.655 ppm can be assigned to H-4,5 on the phenanthrenoid portion, three crosspeaks to this signal immediately define the four-spin $(CH)_4$ system of this moiety. The ^5J coupling of H-1/4 is recognizable by the 2x2 pattern in the crosspeak confirming coupling between these gross doublets. Note that the doublet at 8.291 ppm shows crosspeaks to four other resonances, defining the five-spin system of the bridgehead phenyls with five nonequivalent and anisochronous phenyl proton signals due to the slow C_6H_5 rotations. The 8.29 ppm signal, labelled H-2', shows a 2x2 crosspeak pattern to identify the ^4J coupling H-2'/6' between the termini of the phenyl $(CH)_5$ spin system. The presence of five distinct phenyl proton shifts must result from SEL rotation. The overall spectral simplicity is consistent with the mirror plane of symmetry in 4. The COSY spectrum (Fig. 2b) represents an aryl proton region expansion from a COSY acquired over a wide spectral width (ca. 8.8 to -0.1 ppm) and crosspeaks are seen exclusively for vicinal ^3J couplings. The full proton assignments for 4 are summarized in Table 1. The sp^3 bridgehead methine signal at 4.521 ppm is similar to observed shift values seen for other phencyclone adducts reported earlier; we tentatively assign the same endo stereochemistry to the Diels-Alder adduct, 4. The methylene quartet, resulting from vicinal coupling of the CH_2CF_3 group, is

Table 1. ^{1}H and ^{13}C NMR spectral data for adduct 4 (and selected reference compounds) with chemical shifts in ppm. Estimated observed couplings of 4 (in Hz) are given where available. (See Experimental and Results and Discussion.)

Compound 4, PROTON DATA (note 1)

Nucleus	δ, ppm	(Est'd J, Hz)	Phenanthrene (note 2)
1,8	7.11	7.54,0.82	7.86
2,7	7.20*	6.2	7.57
3,6	7.53	7.61	7.63
4,5	8.66	8.39	8.65
2′	8.29	7.82	
3′	7.72	7.61,1.02	
4′	7.53	7.61	
5′	7.43	7.59,1.21	
6′	7.21*	8.1	
CH(sp^3)	4.52		Maleimide, 3
CH_2	3.46	8.50(q)	4.14

4, CARBON DATA (PPM) (note 3)

Shifts	Relative Heights	Tentative Assignment
196.05	0.6	ketone CO
172.94	1.9	imide CO
133.45	2.6	Q
132.95	1.4	Q
131.55	1.8	Q
130.91	4.7	CH
129.41	4.8	CH
128.83	5.2	CH
128.71	5.2	CH
128.54	5.5	CH
127.13	5.1	CH
126.51	4.8	CH
125.95	1.8	Q
125.61	4.8	CH
123.04	5.3	CH
123.52	0.4	CF_3
119.81	0.4	
63.32	1.9	C_6H_5C
44.87	5.2	CH(sp^3)
39.61	.6	CH_2
39.13	.6	

Notes: (1) For proton data of 4, asterisks denote overlapping signals and estimated shifts for a complex multiplet from H-2,7 and H-6′. Other aryl proton signals of 4 appeared as gross doublets (H-1,2′,4) or gross triplets (H-3′,5′ and [isochronous] H-3, 4′). Since long range couplings in the aryl protons of 4 could not always be fully resolved, the reported observed splittings should be considered approximate. The CH_2 resonance of 4 is a quartet due to ^{3}J(HCCF). (2) These ^{1}H shift values for phenanthrene were determined for a solution (30.6 mg in 830 mg $CDCl_3$) at 21° based on 300 MHz 1D and 2D COSY45 NMR, as reported in Ref. [11]. (3) For carbon data of 4, nonprotonated quaternary aryl carbon signals of the phenanthrenoid and phenyl groups are labeled Q. Aryl methine signals, ca. 123-131 ppm, are labeled CH. For the CF_3, only the two stronger central peaks of the quartet (due to ^{1}J(CF) = 280.4 Hz] are tabulated. For the CH_2, the two central peaks of the quartet [due to ^{2}J(FCC) = 36.7 Hz] are indicated.

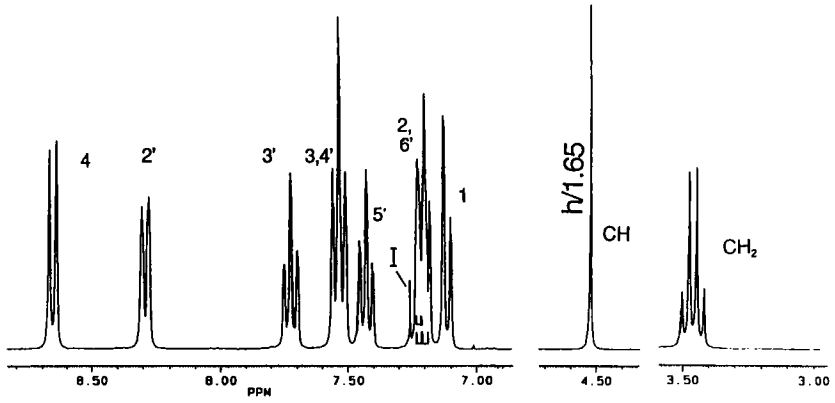


Figure 1. Expanded regions of the 300 MHz ^{1}H NMR spectrum of 4 (ambient temperature, $CDCl_3$). The $CHCl_3$ solvent impurity is marked I. Note that chemical shift and peak intensity scales may differ in each region.

centered at 3.459 ppm. Thus, this NCH_2 proton signal appears appreciably shielded compared to the corresponding resonance in the maleamic acid, 2 (at 4.189 ppm, in CD_3COCD_3) and in the maleimide, 3 (4.141 ppm, in $CDCl_3$). In particular, the NCH_2 ^{1}H resonance of 4 appears 0.682 ppm at higher field than in 3, consistent with anisotropic shielding in 4 by the phenanthrenoid ring system for endo stereochemistry. In the ^{19}F spectra, the CF_3 triplet for maleamic acid 2 appears at -71.225 ppm (in CD_3COCD_3) and -71.497 ppm (in $CDCl_3$) for maleimide 3. But adduct 4 shows the CF_3 signal at -72.091 ppm, which corresponds to a shielding of 0.594 ppm versus 3, and which may be attributable to phenanthrene ring shielding anisochrony. For previously reported N-alkylmaleimide adducts of 1, as for n-propyl or n-butyl analogs, the greatest indication of anisotropic shielding in the N-alkyl group of the adducts (with respect to the maleimides) appeared to be for protons beta to N, i.e., NCH_2CH_2. In the case of 4, this position is fluorinated rather than protonated, but evidence for ^{19}F shielding seems apparent.

The ^{13}C spectrum for 4, acquired with ^{1}H composite pulse decoupling (WALTZ-16) and relaxation delay of 3 sec., provides NOE signal enhancement for protonated carbons (but not for the CF_3

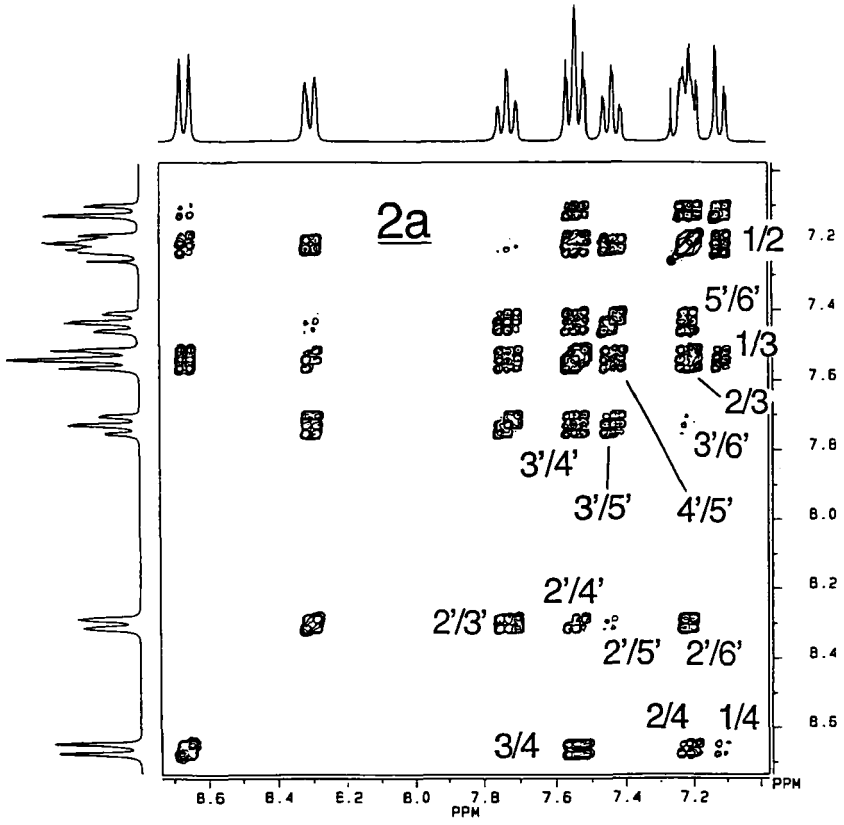


Figure 2. (a) "High resolution" COSY45 spectrum of adduct 4. The spectral width in F2 was 530 Hz (6.97 - 8.73 ppm). For each of 128 increments in t_1, 2 dummy scans and 8 acquisitions were used. Data were zero-filled once only in the F1 dimension for a final data matrix size of 256 x 512, for a digital resolution of 2.1 Hz/point. Data were processed with unshifted sine-bell apodization in both dimensions. The magnitude mode spectrum has been symmetrized. (b) "Low resolution" COSY45 spectrum of 4; expansion of aryl region is shown. F2 spectral width was 2674 Hz (-0.1 to 8.8 ppm). For each of 256 t_1 increments, 2 dummy scans and 16 acquisitions were used. Data were zero-filled once in each dimension for a final data matrix size of 512 x 1024, for a digital resolution of 5.2 Hz/point. Data were processed with unshifted sine-bell apodization in both dimensions. The magnitude mode spectrum has been symmetrized.

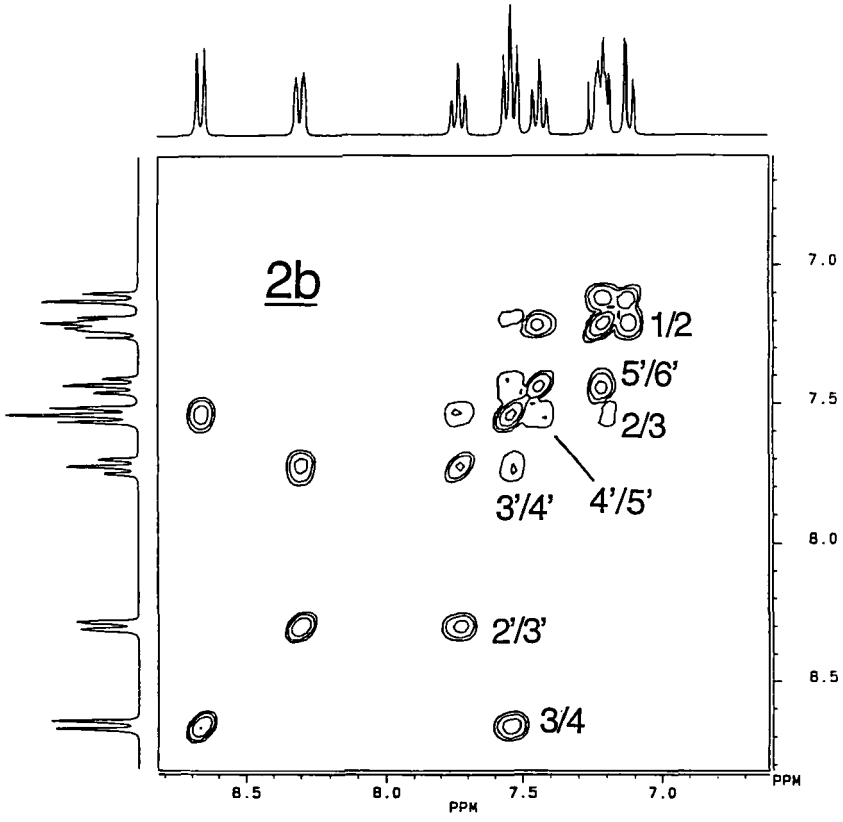


Figure 2. Continued

signal) and allows an easy distinction between the aryl methine signals and the much weaker unprotonated carbons. However, even with 10,000 acquisitions, the expected quartet signals for the CF_3 (^1J = 280.48 Hz) at 121.67 ppm, and for the CH_2 (^2J [FCC] = ca. 36.7 Hz) at 39.37 ppm, are rather weak. Only three of the four peaks of each quartet were significantly observable above noise. Uniformity of spacing between the three observed peaks of each quartet provided confidence in these assignments and allowed us to distinguish the CF_3 absorption from the nearby aryl carbon peaks.

Our reported values appear consistent with earlier values for NMR ^{13}C data of the CF_3 in CF_3CO_2H, at 115 ppm (^1J = 283.8 Hz) [14]. With the parameters used by us, even the two big central peaks of the CF_3 quartet for the carbon NMR spectrum of 4 were less than one-tenth the height of the weakest aryl methine signal (and less than 5% on an area basis). The four unprotonated aryl carbon signals of 4 were each ca. 35-55% of the peak heights of the aryl methine signals (ca. 13-29% on an area basis). Thus, we readily assigned four unprotonated aryl carbon and nine protonated aryl methine signals for 4, precisely as predicted for the SEL phenyl rotation in the adduct.

As we have reported for other N-alkylmaleimide Diels-Alder adducts of 1, substantial anisotropic effects seem apparent in the ^1H NMR spectrum of adduct 4, if comparisons are drawn between the phenanthrenoid moiety of 4 and the parent hydrocarbon, phenanthrene. Table 1 summarizes ^1H and ^{13}C NMR data for 4 and includes recent ^1H data for phenanthrene [11]. Note that shifts for H-3,6 and H-4,5 in 4 (phenanthrene numbering) are essentially unchanged from the values of phenanthrene, but H-2,7 of 4 is relatively shielded by 0.37 ppm, and H-1,8 of 4 is strongly shielded by 0.75 ppm, compared to the phenanthrene values. This is consistent with a preferred conformation for the bridgehead phenyls of 4 roughly perpendicular to the phenanthrenoid plane. Such a conformation would reduce severe nonbonded interactions between phenanthrenoid moiety H-1,8 in 4 with the phenyl ortho protons H-2',6', and would place H-1,8 (and, to a lesser extent, H-2,7) in the anisotropic shielding cones of the bridgehead phenyls. The wide range of chemical shifts for the phenyl protons in 4, 1.08 ppm, implies that substantial anisotropic effects are operating here as well [15]. These may result from the strained bridging ketone carbonyl as well as the imide carbonyls, and from the phenanthrenoid portion.

CONCLUSIONS

We report the preparation of N-2,2,2-trifluoroethylmaleamic acid, 2, and its conversion to the corresponding maleimide, 3. The Diels-Alder adduct of 3 with phencyclone, 1, was obtained and characterized by ^1H, ^{19}F and ^{13}C NMR. The ^1H and ^{13}C NMR spectra (at 300 and 75 MHz, respectively) of this adduct 4 are consistent with an SEL regime due to hindered bridgehead phenyl rotations at ambient temperatures in $CDCl_3$. The ^1H and 282 MHz ^{19}F NMR spectra

are reported for 2 and 3. Shielding for the fluorine signal in 4 relative to 3 is suggested as being consistent with endo stereochemistry in adduct 4, in which the CF_3 group could be anisotropically shielded by the phenanthrenoid moiety. Additional examples of anisotropic shielding in the ^1H spectrum of 4 reflect possible phenyl conformations to reduce nonbonding repulsions. 2D COSY45 spectra were used to define assignments and correlations in 4.

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