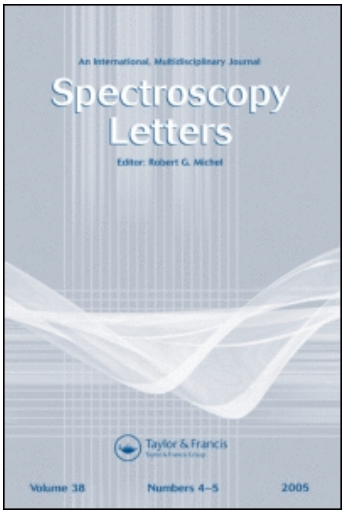

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NMR Studies of Hindered Rotation and Magnetic Anisotropy: The Diels–Alder Adducts of Phencyclone with *N*-Phenylmaleimide and *N*-(2-Trifluoromethylphenyl)maleimide. Ab Initio Calculations for Optimized Structures

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ABSTRACT

N-Phenylmaleimide, **2**, and *N*-(2-trifluoromethylphenyl)maleimide, **3**, were separately added to phencyclone, **1**, to yield the corresponding phen-

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cyclone Diels–Alder adducts, **4** and **5**. The resulting adducts (and some precursors) have been characterized by one- and two-dimensional ^{1}H and ^{13}C NMR at 300 and 75 MHz, and by ^{19}F NMR at 282 MHz, at ambient temperatures. The NMR data are consistent, for both adducts, with: (a) hindered rotation of the bridgehead unsubstituted phenyl groups about the $C(sp^2)–C(sp^3)$ bonds, based on slow exchange limit (SEL) spectra and (b) endo adduct configuration based on magnetic anisotropic effects in the ^{1}H NMR. The NMR spectra of the phencyclone adduct, **4**, of *N*-phenylmaleimide, indicate free rotation on the NMR timescales (fast exchange limit, FEL spectra) about the *N*-phenyl bond. The spectra for the adduct, **5**, of *N*-(2-trifluoromethylphenyl)maleimide are interpreted as consistent with SEL regimes, for the *N*-aryl rotations, with a single rotamer present in which the trifluoromethyl group is directed "out of" the adduct cavity, and away from the phenanthrenoid moiety. This conclusion is based, in part, on NMR data suggesting the apparent slow *N*-aryl bond rotation in a pair of atropisomers corresponding to the acetic acid addition products from the *N*-(2-trifluoromethylphenyl)maleimide. Evidence of magnetic anisotropic effects due to the phenanthrenoid moiety and proximal carbonyls is discussed. ^{1}H, ^{13}C, and ^{19}F assignments are presented and interpreted. Molecular modeling calculations at the Hartree–Fock level, 6-31G* basis set, were performed to provide geometry optimizations for energy-minimized structures of selected compounds.

Key Words: Dynamic NMR; One- and two-dimensional NMR; Homonuclear and heteronuclear chemical shift correlation NMR; HETCOR; COSY; Restricted rotation; ^{1}H, ^{13}C, and ^{19}F NMR; Hartree–Fock geometry optimizations; Stereochemistry; Maleimides.

INTRODUCTION

Phencyclone, **1**, serves as a potent Diels–Alder diene.[1] Previous studies of a number of adducts of phencyclone (and analogs) have confirmed a remarkable degree of steric hindrance.[2–7] Simple inspection of phencyclone adduct models [8] indicates that the bridgehead phenyl ortho protons, H-2′ and 6′, have a potential closest approach distance of as little as 0.1–0.2 Å with the phenanthrenoid moiety protons, H-1 and 8. Our NMR results have suggested that this steric congestion leads to the observed slow exchange limit (SEL) spectra for the unsubstituted bridgehead phenyls at ambient temperatures with medium field spectrometers, e.g., 200 or 300 MHz for ^{1}H and 50 or 75 MHz for ^{13}C. The bridgehead phenyls may thus be forced into a conformation which reduces repulsions with proximal groups. The adducts

previously studied have exhibited some striking magnetic anisotropic effects consistent with this proposed structure. We report here the preparation and NMR spectral data for the adducts, **4** and **5**, respectively, of phencyclone with *N*-phenylmaleimide, **2**, and with *N*-(2-trifluoromethylphenyl)maleimide, **3**. (See Fig. 1 for structures.) Potential hindered rotations for the $C-C_6H_5$ and the *N*-aryl bond rotations are evaluated based on the SEL or fast exchange limit (FEL) spectra, magnetic anisotropic effects, and ab initio molecular modeling calculations. These studies have broad basic significance concerning

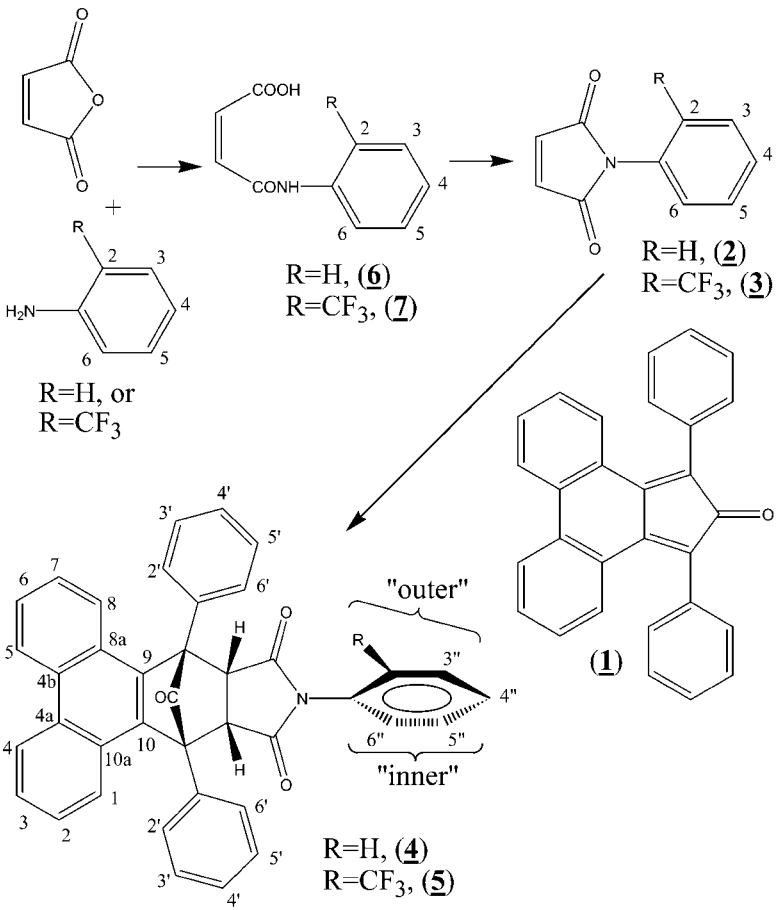

Figure 1. Structures of key compounds (with atom numbering) and summary of synthetic pathways.

hindered molecular motions, crowded molecules, and spatial aspects of magnetic anisotropy.

EXPERIMENTAL

General NMR and other techniques were described earlier.[2,3] Spectra were obtained on a Bruker ACF300 NMR spectrometer (7.05 T) at 300 MHz for ^{1}H, 75 MHz for ^{13}C, and 282 MHz for fluorine, equipped with quad nuclear probe (QNP) and Aspect 3000 data system, at ambient temperatures in $CDCl_3$ unless otherwise noted. Proton shifts were referenced to internal tetramethylsilane (TMS) at 0.0 ppm. For ^{13}C spectra, shifts were referenced to the center line of the $CDCl_3$ triplet at 77.0 ppm; in d_6-acetone, shifts were referenced to the center line of the d_6-acetone septet at 29.8 ppm. Fluorine spectra were referenced to internal $CFCl_3$ at 0.0 ppm. Where proton decoupling was applied for ^{13}C or ^{19}F spectra, WALTZ16 was used for composite pulse decoupling. Standard Bruker microprograms were routinely employed for proton–proton and proton–carbon two-dimensional (2D) chemical shift correlation spectra. Typical "high-resolution" COSY45 spectra for aryl proton regions covered a sweep width of ca. 2.5–4.5 ppm with 128 or 256 increments in t_1 and 8 or 16 transients for each increment; crosspeaks corresponding to ^{3}J, ^{4}J, and ^{5}J for H–H couplings were usually seen. ^{13}C spectra were complicated by couplings to fluorine, and relaxation delays of 3 or 60 sec were used. Where some NMR spectral assignments were uncertain (e.g., because of unfavorable signal-to-noise ratios, etc.), we have shown them as tentative ("tent"). For the heteronuclear chemical shift correlation spectra (HETCOR, XHCORR), typically 128 increments in t_1 were used with 1024 transients for each increment. Reported melting points are uncorrected. IR data were obtained as KBr pellets on a Nicolet Impact 1600 or a Midac M2000 spectrometer. Reagents and solvents were obtained from Aldrich Chemical (Milwaukee, WI) or Lancaster Synthesis (Windham, NH) and were used without further purification. Geometry optimization calculations were largely performed using TITAN, version 1.0.5 (Wavefunction, Inc., 1999) on a Dell Pentium 4 PC with 1.4 GHz processor speed and 256 MB RAM. Most recently, we have used Spartan '02 ESSENTIAL (v. 1.0.2) or Spartan '02 for Windows (v. 1.0.2) on Dell Pentium 4 platforms with 1.4 (or 2.4) GHz processor speeds and 512 (or 1024) MB memory. Calculation parameters included the disabling of symmetry, turning convergence ON, and (for TITAN) specifying highest accuracy cutoffs for the SCF (IACC = 1), as suggested by Wavefunction, Inc. All software was obtained from Wavefunction, Inc. (Irvine, CA).

Synthesis of 4, the Phencyclone Adduct of *N*-Phenylmaleimide

Maleic anhydride (4.096 g, 41.77 mmol) was partially dissolved in ca. 50 mL of methylene chloride. Aniline (3.793 g, 40.73 mmol) was dissolved in ca. 20 mL methylene chloride and added dropwise to the magnetically stirred maleic anhydride mixture. A light yellow precipitate formed upon the addition. The mixture was then stirred without heat for several minutes. The resulting precipitate was collected by vacuum filtration and dried to give the crude product *N*-phenylmaleamic acid, **6**, (7.569 g, 97.2%). Proton NMR (d_6-acetone, ppm): 10.38 (br s, tent. NH); 7.72 (2H, d, H_{ortho}); 7.42 (2H, approx. t, H_{meta}); 7.23 (1H, approx. t, H_{para}); 6.71 (1H, d, $^3J = 12.90$, half of AB q, *cis* HC═CH); 6.37 (1H, d, $^3J = 12.80$, half of AB q, *cis* HC═CH, overlapped with s at 6.39 ppm [tent. impurity]).

N-Phenylmaleimide, **2**, was then synthesized by stirring *N*-phenylmaleamic acid (6.386 g, 33.42 mmol) with 1.215 g anh. sodium acetate and about 11 mL acetic anhydride in a boiling water bath for 30 min. The solution immediately turned yellow, then gradually became a transparent orange color. After cooling to room temperature, the product was washed with brine and saturated sodium bicarbonate solutions and extracted with methylene chloride. The combined organic extracts were then dried, and solvent removed under vacuum, giving crude product *N*-phenylmaleimide (4.547 g, 78.6%, mp 72–76°C). Proton NMR ($CDCl_3$, ppm): 7.51–7.42 (2H, m, approx. d, H_{ortho}); 7.41–7.28 (3H, complex m, $H_{meta,para}$); 6.85 (2H, s, HC═CH). See Discussion regarding impurity peaks. (Note that *N*-phenylmaleimide is commercially available from Aldrich, and its proton and ^{13}C NMR spectra have been published.[9])

N-Phenylmaleimide (371.4 mg, 2.145 mmol), phencyclone (769.2 mg, 2.011 mmol) and a few milligram of 2,6-di-*t*-butyl-4-methylphenol (BHT, see Discussion) were combined as a slurry in methylene chloride in a tightly capped screw cap (Teflon®-lined cap) vial (ca. 20 mL capacity) at room temperature. (Solvent was added to bring the mixture level to within 5 mm of the vial brim, in order to minimize headspace. See Discussion.) The mixture was then magnetically stirred overnight. After the dark green color of the reaction mixture was discharged (indicating consumption of **1**), 526.9 mg (44.2%, mp 300–302°C) of the product, **4**, phencyclone adduct of *N*-phenylmaleimide, was filtered from the solution. The material was dried and used for NMR studies. IR (KBr, cm^{-1}): 1792.4 s (strained bridging ketone C═O), 1774.3 w, 1707.9 s (imide C═O), 1498.5 s, 1448.1 w, 1381.6 s, 1214.6 w, 1196.4 s, 1164.3 w, 821.9 w, 781.6 w, 789.5 m, 749.5 m, 729.3 m, 701.1 m, 644.7 w, 616.5 w. NMR data appear in Tables 1 and 2.

Table 1. Proton chemical shifts for the phencyclone adducts.

Nucleus	δ (ppm)
Phencyclone adduct of N-(C_6H_5)maleimide	
H-1,8	7.17
H-2,7	7.19
H-3,6	7.53
H-4,5	8.67
H-2′	8.37
H-3′	7.72
H-4′	7.54
H-5′	7.45
H-6′	7.28
H-2″,6″	5.89
H-3″,5″	6.95
H-4″	7.04
CH	4.61
Phencyclone adduct of N-(2-$CF_3C_6H_4$)maleimide	
H-1,8	7.19
H-2,7	7.25
H-3,6	7.57
H-4,5	8.75
H-2′	8.32
H-3′	7.71
H-4′	7.53
H-5′	7.44
H-6′	7.27
H-3″	7.53
H-4″	7.19
H-5″	6.83
H-6″	4.42
CH	4.69

Note: Chemical shift data are relative to TMS for samples in $CDCl_3$. Note that gross signal multiplicities of aryl protons (d or t) were consistent with the numbers of vicinal proton neighbors (one or two, respectively).

Table 2. Carbon chemical shifts of the phencyclone adducts.

Nucleus	Shift (ppm)
Phencyclone adduct of N-phenylmaleimide	
C-1,8	125.84
C-2,7	126.84
C-3,6	127.20
C-4,5	123.03
C-2′	129.12
C-3′	129.38
C-4′	128.49
C-5′	128.67
C-6′	130.92
C═O (ketone)	196.91
$C(sp^3)C_6H_5$	63.58
C-2″,6″	125.62
C-3″,5″	128.73
C-4″	128.49
CH sp^3	44.76
C═O (imide)	173.38
Q	126.31
Q	128.42
Q	131.23
Q	133.41
Q	133.71
Phencyclone adduct of N-2-trifluoromethylphenylmaleimide	
C-1,8	126.06
C-2,7	126.95
C-3,6	127.39
C-4,5	122.90
C-2′	129.12
C-3′	129.42
C-4′	128.52
C-5′	128.64
C-6′	130.85
C═O (ketone)	196.71
$C(sp^3)C_6H_5$	63.51
C-3″	126.95
C-4″	126.64
C-5″	126.85
C-6″	126.12
CH sp^3	45.21

(*continued*)

Table 2. Continued.

Nucleus	Shift (ppm)
C═O (imide)	173.00
Q	126.31
Q	131.09
Q	133.49
Q	133.66

Note: All chemical shift data above are relative to TMS for samples dissolved in $CDCl_3$. "Q" denotes signals due to unassigned non-protonated carbons. (Three more "Q" signals are expected for the phencyclone adduct of *N*-2-trifluoromethylphenylmaleimide. These signals were not observed. It is likely that they were not distinguishable from background noise due to low intensity caused by not being bonded to a hydrogen atom and to splitting by fluorine).

Synthesis of 5, the Phencyclone Adduct of *N*-(2-Trifluoromethylphenyl)maleimide

Maleic anhydride (2.054 g, 20.946 mmol) was partially dissolved in methylene chloride. 2-Trifluoromethylaniline (3.496 g, 21.70 mmol) in methylene chloride was added dropwise to the magnetically stirred maleic anhydride to give an opaque yellow mixture upon the addition. The mixture was then stirred without heat for 5 min. The resulting precipitate was collected (vacuum filtration) and dried, giving crude product *N*-(2-trifluoromethylphenyl)maleamic acid, **7** (4.282 g, 78.9%, mp 52–54°C). Proton NMR (d_6-acetone, ppm): 10.10 (1H, br s, NH); 7.74–7.83 (3H, m, aryl H); 7.57 (1H, t, $^3J = 7.36$, aryl H); 6.83 (1H, br d, $^3J = 12.74$, half of AB q, *cis* HC═CH); 6.44 (1H, sharp d, $^3J = 13.73$, half of AB q, *cis* HC═CH). ^{13}C NMR (d_6-acetone, ppm) (proton correlation, ppm, refers to chemical shifts of correlated protons from HETCOR results). Only major peaks are listed from spectrum acquired with 60 sec relaxation delay. See Discussion: 166.49 (C═O); 165.30 (C═O); 137.69 (tent. Q); 134.80 (6.44); 134.35 (tent. Q); 133.93 (ca. 7.75); 133.09 (6.83); 131.80 (tent. Q); 130.16 (ca. 7.82); 128.52 (7.57); 127.30 (narrow q, *J* ca. 5.16) (ca. 7.82). The CF_3 quartet was centered at 124.48 (peaks at 129.90, 126.28, 122.67, 119.06, $^1J = 272.5$). Fluorine NMR (d_6-acetone, ppm): −60.23, essentially no fine structure with proton decoupler on or off.

N-(2-Trifluoromethylphenyl)maleimide, **3**, was prepared by heating a mixture of the maleamic acid, **7** (0.908 g, 3.50 mmol), acetic anhydride

(2.625 g, 25.7 mmol), and 0.065 g (0.792 mmol) anh. sodium acetate (boiling water bath, ca. 30 min). Extraction of the product with CH_2Cl_2 and solvent removal yielded 696.2 mg *N*-(2-trifluoromethylphenyl)maleimide, **3** (74.8%, mp 80–96°C). Proton NMR ($CDCl_3$, ppm, see Discussion): 7.82 (1H, d, H-3); 7.69 (1H, t, H-5); 7.61 (1H, t, H-4); 7.29 (1H, d, H-6); 6.89 (2H, s, HC═CH). Carbon NMR ($CDCl_3$, ppm, see Discussion): 169.13 (C═O); 134.71 (HC═CH); 133.14 (C-5); 131.68 (C-6); 130.09 (C-4); 129.65 (q, CCF_3, $^2J = 31.04$); 129.14 (NC_{ipso}); 127.56 (narrow q, C-3, $^3J = 4.85$). The CF_3 quartet was centered at 122.84 (peaks at 128.28, 124.66, 121.03, 117.41, $^1J = 273.5$). Fluorine NMR ($CDCl_3$, ppm): −62.00, narrow s with ^1H decoupler on (peak width at half-height less than 0.6 Hz). With ^1H decoupler off, peak width at half-height ca. 2.3 Hz, possible br triplet but no distinct valleys.

The phencyclone adduct, **5**, was prepared by magnetically stirring phencyclone (0.394 g, 1.030 mmol) and *N*-(2-trifluoromethylphenyl)maleimide (0.313 g, 1.298 mmol) with a trace of BHT, using CH_2Cl_2 solvent in a capped screw cap vial (ca. 20 mL) overnight, as above. After solvent removal, the product was dried to give **5**, the phencyclone adduct of *N*-(2-trifluoromethylphenyl)maleimide (0.5446 g, 84.8%, mp 290–294°C), for NMR characterization. IR (KBr, cm^{-1}): 1787.8 s (strained bridging ketone C═O), 1722.8 s (imide C═O), 1608.4 w, 1498.0 m, 1454.6 m, 1377.8 s, 1318.7 s, 1277.3 w, 1218.2 w, 1182.7 s, 1165.0 s, 1155.2, 1127.5 s, 1060.5 m, 1034.9 m, 824.0 w, 778.7 w, 761.0 w, 747.1 m, 727.4 s, 719.5 m, 695.9 s, 644.6 w, 615.1 w. See Tables 1 and 2 for NMR data.

RESULTS AND DISCUSSION

Preparation of the desired *N*-aryl maleimides, **2** and **3**, by cyclodehydration of the respective maleamic acids, **6** and **7**, is fairly straightforward (See Fig. 1). *N*-Substituted maleimides, including both *N*-phenylmaleimide and *N*-(2-trifluoromethylphenyl)maleimide, serve as effective electron deficient Diels–Alder dienophiles with phencyclone. For small scale reactions with **1**, we have found it convenient to run the reactions in screw-cap vials, leaving minimal headspace to reduce the amount of oxygen that might lead to undesired side-reactions, such as air oxidation of **1** to 9,10-dibenzoylphenanthrene by oxidative decarbonylation. Small amounts of the free-radical trap, BHT, are added to the reaction mixture in an effort to suppress this oxidation and the possible free radical additions or polymerizations of maleimides.[2,3]

The ^{13}C NMR spectrum of *N*-(2-trifluoromethylphenyl)maleamic acid was puzzling in some respects, with many peaks appearing distinctly broad compared to other sharp peaks, with ca. 10 other weaker peaks in the aryl

carbon region that have not been listed above. The proton and ^{19}F spectra were rather free of extra minor peaks, indicating that the sample did not seem to contain substantial impurities. The fluorine spectra, with or without proton decoupling, showed no fine structure and was quite narrow, with peak widths at half-height of only 1.5 Hz (proton decoupled) or 2.6 Hz (proton coupled). We might speculate that some interconverting conformations of the maleamic acid might be occurring on the SEL side of an intermediate, peak-broadened regime, for some carbons in the ^{13}C spectrum, which might cause extra peaks or peak broadening, but such phenomena are not apparent from the proton or fluorine spectra. The key assignments for the carbon spectrum of this compound reflect observable crosspeaks in the HETCOR spectrum, and we have indicated the proton shifts correlated with these six carbons above. In the proton spectra, one half of the AB q is distinctly broadened, which might be attributed to long range coupling with the proximal amide NH.

For the *N*-(2-trifluoromethylphenyl)maleimide, proton assignments for the termini of the aryl $(CH)_4$ spin system are based on chemical shift arguments, with H-3, ortho to the strongly electron-withdrawing CF_3 group, expected to be most deshielded. A standard "low resolution" COSY45 spectrum with 128 t_1 increments over a ca. 7 ppm sweep width was completely ambiguous in defining the aryl proton region, but a high resolution COSY45 using 128 t_1 increments over a 1 ppm sweep width exhibited "tilting" of the ^4J crosspeaks to distinguish them from the symmetrical ^3J (vicinal) crosspeaks. Further confirmation was provided by selective homodecoupling of the high field doublet at 7.29 ppm (H-6) which collapsed the low field triplet to a doublet, establishing the 7.69 ppm triplet as H-5. The carbon spectrum was fairly straightforward, with assignments for proton-bearing carbons obtained from the HETCOR spectrum. In the ^{19}F NMR with proton decoupler off, some suggestion of splitting of the fluorine signal was seen, but without any sharp multiplet structure.

The ^1H and ^{13}C NMR spectra of the adducts were obtained in $CDCl_3$ (the proton spectra are shown in Fig. 2). Although there was significant overlap in the aryl region of the ^1H spectra for both compounds, a signal for each of the protons and the multiplicity of each of the signals could be discerned using the high resolution proton–proton chemical shift correlation spectrum (COSY45) crosspeaks. The COSY45 spectrum was also used to assign proton chemical shifts (see Table 1). ^{13}C chemical shift assignments were made, to the extent possible, using both the ^{13}C spectra and proton–carbon correlation (HETCOR) spectra (see Table 2). We have not attempted to assign non-protonated quaternary aryl carbons. For the adduct **5**, some of these non-protonated carbons could not definitively be observed, which we attribute, in part, to splitting by ^{19}F (as for the CF_3CCN moiety), since the resulting

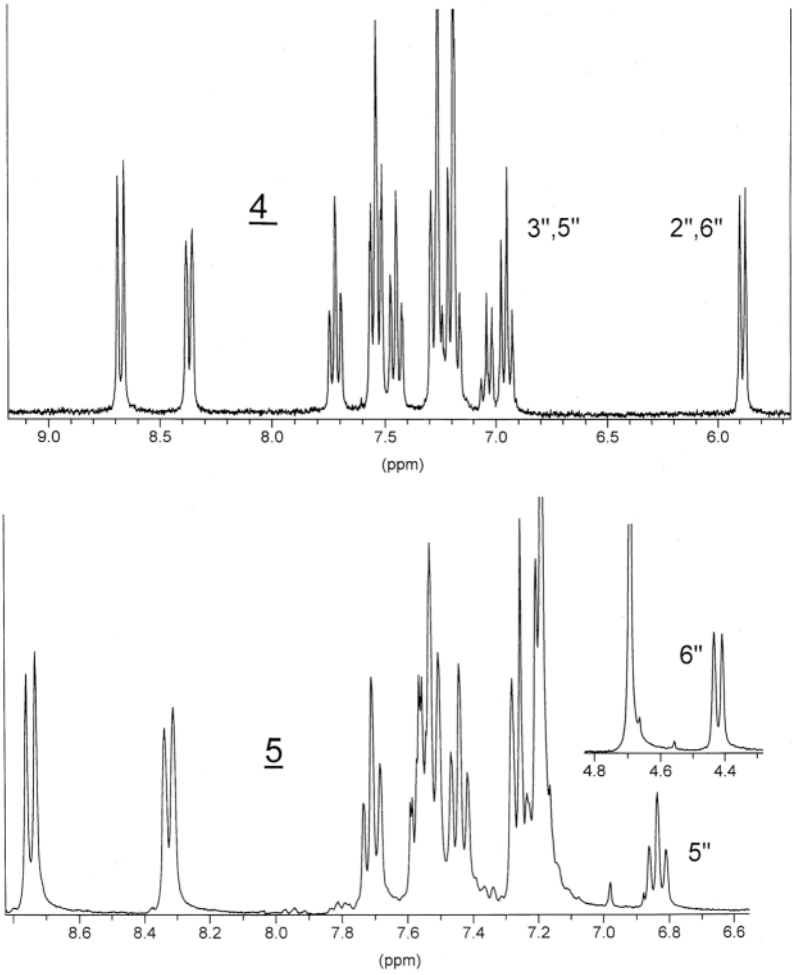

Figure 2. The 300 MHz proton NMR spectra for the phencyclone adducts **4** and **5**. The upper spectrum shows the aryl protons of adduct **4**; the singlet for the bridgehead methines is omitted. The lower spectra show the aryl protons of adduct **5**, ca. 6.7–8.8 ppm (left) and ca. 4.3–4.8 ppm (right).

multiplicity reduces the signal-to-noise ratio of the component peaks. Our spectrometer hardware does not allow fluorine decoupling to remove these splittings. We note that Sasaki and co-workers had reported the preparation of **4** in 1976, but the limited spectral dispersion from their low field NMR spectrometer (60 MHz) would have produced severe aryl proton

signal overlaps, preventing clear assignments needed for recognition of bridgehead phenyl hindered rotations.

In our hands, the isolated adducts seemed to be predominantly or exclusively single stereoisomers, presumably normal endo addition products expected from the Diels–Alder reaction.[1,10–13] Infrared spectra (KBr) for each adduct showed a strong band near 1790 cm^{-1}, consistent with the strained bridging ketone carbonyl of the adducts, implying that loss of this carbonyl had not occurred during adduct preparation or workup. Thermal decarbonylation, retro-Diels–Alder or other decomposition reactions of the phencyclone adducts are possibilities at elevated temperatures. The endo adduct stereochemistry would be consistent with the large magnetic anisotropic effects reported here for the *N*-aryl protons. The aryl region of the proton spectrum for each of the two adducts showed four correlated signals (two 2H triplets and two 2H doublets) from the $(CH)_4$ spin system of the rigid phenanthrenoid portion of the molecules. The aryl regions for each of the adducts also contained five correlated signals (two doublets and three triplets, each 2H intensity) from the $(CH)_5$ spin system of the bridgehead phenyl groups, unambiguously demonstrating slow $C-C_6H_5$ rotation about the $C(sp^3)-C(sp^2)$ bonds on the NMR timescales, resulting in the SEL proton and ^{13}C spectra. The proton spectrum for each of the two phencyclone adducts also contained a singlet corresponding to the bridgehead $C(sp^3)-H$, at 4.61 ppm for **4**, and 4.69 for **5**. For adduct **4**, additional signals were seen: 2H doublet at 5.89 ppm (H-2″,6″), 2H triplet at 6.95 ppm (H-3″,5″) and a 1H triplet at 7.04 ppm (H-4″). The latter three signals are assigned to the protons on the *N*-phenyl ring. Both the symmetry of this ring and the observation of three proton signals corresponding to this ring imply that the rotation about the *N*-phenyl bond yields a FEL spectrum at room temperature. Since rotation of the *N*-phenyl is a degenerate two-site exchange, each of the ortho protons, H-2″ and H-6″, must spend exactly 50% of its time in the two alternative environments. With the normal endo stereochemistry for preferred (kinetically favored) Diels–Alder adduct formation, these protons may either be directed "into" the adduct cavity, toward the phenanthrenoid moiety, or directed "out of" the cavity, away from the phenanthrenoid group. For the proton directed into the cavity, magnetic anisotropic shielding from the phenanthrenoid ring currents is expected. The chemical shift for the ortho protons, at 5.89 ppm, reflects this shielding on a "half-time" basis. If a normal aryl proton is considered to resonate at ca. 7.2 ppm in the absence of special anisotropic effects, then the observed upfield shift of ca. 1.3 ppm is the result of each of these protons spending half their time in the shielded environment.

The proton spectrum for **5**, the phencyclone adduct of *N*-(2-trifluoromethylphenyl)maleimide, exhibits [in addition to the (9 × 2H) phenanthre-

noid and bridgehead phenyl signals described above] two 1H doublets (7.53 and 4.42 ppm) and two 1H triplets (7.19 and 6.83 ppm). These four correlated signals are assigned to the protons of the $(CH)_4$ spin system of the trifluoromethylphenyl group. COSY results were confirmed by selective $^1H-^1H$ homodecoupling experiments. For example: (a) irradiation of the 4.42 ppm doublet collapsed the 6.83 ppm triplet to a doublet; (b) irradiation at 6.83 ppm collapsed the doublet at 4.42 ppm to a singlet; (c) irradiation at 7.19 ppm collapsed the 6.83 ppm triplet to a doublet. The 4.42 ppm doublet signal is at remarkably high field for an aryl proton, and must correspond to the proton H-6″, spending 100% of its time in the anisotropically shielded cavity of the endo adduct, appearing ca. 2.8 ppm at higher field than a "normal" aryl proton. (This is strikingly consistent with the estimated half-time shielding seen for the ortho protons of adduct **4**). The implication has to be that the predominant conformation of **5** must have the CF_3 directed "out" of the cavity if H-6″ is directed "in" (to experience its dramatic shielding). It might be argued that the appearance of four separate proton signals for the $CF_3C_6H_4$ cannot by itself indicate that we are seeing an SEL spectrum resulting from slow rotation about the nitrogen–aryl bond, since the 2-trifluoromethylphenyl group should give four proton signals even under FEL fast bond rotation conditions. In this latter case, each of the four protons, H-3″, 4″, 5″, 6″, would produce a time-averaged signal reflecting the sharply averaged signals from their respective "inside" and "outside" positions. If true fast rotation was accessible for the *N*-aryl of **5**, an equilibrium constant strongly favoring the conformation with the CF_3 out would result in H-6″ spending nearly all the time in the shielded inside position. That this FEL interpretation is, in fact, not the case, is addressed in detail below. We note at this point, however, that our results for proton NMR were fully consistent with results for the 1D carbon NMR and for the 2D HETCOR spectra. Thus, 12 HETCOR crosspeaks are seen for the aryl CH of **4**. For adduct **5**, 13 aryl CH crosspeaks are predicted from theory; only 12 were readily detected (of which two are partly merged) with the expected thirteenth very weak, which we attribute to one of the crosspeaks being diminished due to F-19 vicinal coupling to the relevant *C*H, assigned to C-3″.

We note the presence of ca. 6% (by proton NMR integration) of some impurities in our crude *N*-(2-trifluoromethylphenyl)maleimide sample, based on the following signals (ppm, *J* in Hz): 5.74 (dd, $^3J = 5.15$, 8.60, H_X); 5.465 (dd, $^3J = 4.82$, 9.17, $H_{X'}$); 3.30–3.42 (m, eight equal-intensity lines, $H_{M,M'}$); 2.84–2.96 (apparent pair of triplets, $H_{A,A'}$); 2.22 and 2.20 (s). Correct interpretation, and extraction of observed coupling constants for the higher field multiplets, i.e., 3.30–3.42 and 2.84–2.96 ppm, requires the recognition that each of these regions results from overlapping (rather than adjacent) double doublet (dd) patterns. Thus, even the apparent pair of triplets

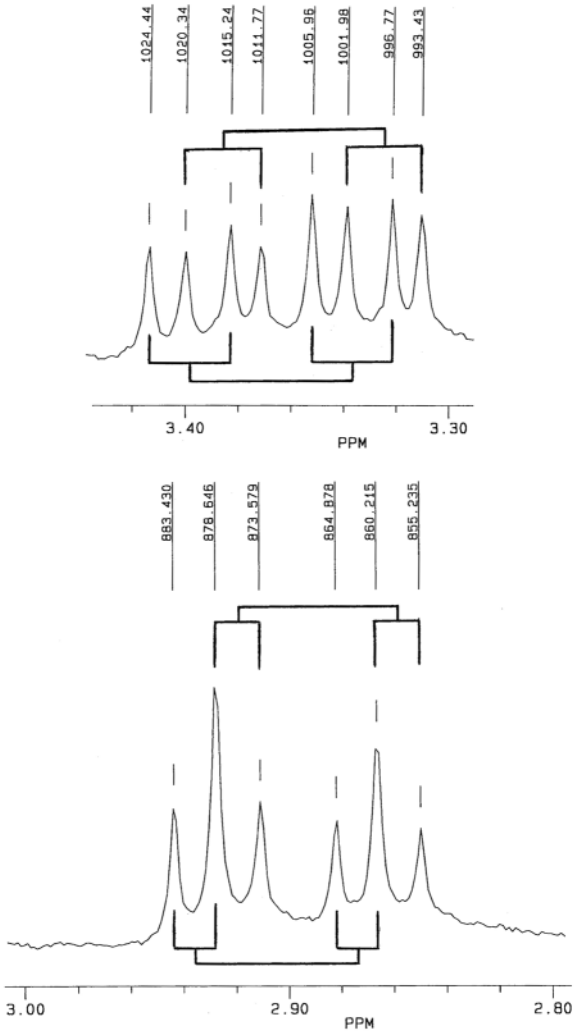

Figure 3. Expansions of ^{1}H NMR spectrum for mixture of syn and anti atropisomers of acetoxy derivatives of **3**. The region from ca. 3.30–3.42 ppm corresponds to the signals H_M and $H_{M'}$ and the region from ca. 2.84 to 2.96 ppm to the signals from H_A and $H_{A'}$ in our notation. The chemical shift scales and signal intensity scales are identical for each region. (The lower field pair of double doublet [dd] signals from the H_X and $H_{X'}$ protons is not shown.) The indicated brackets show how each multiplet is analyzed as an overlapping pair of dd signals, with the larger observed coupling corresponding approximately to the two bond geminal coupling, $^2J(H_A–H_M)$ and $^2J(H_{A'}–H_{M'})$, and the smaller observed coupling to the vicinal couplings to H_X or $H_{X'}$, respectively.

from 2.84 to 2.96 ppm is, in fact, the result of dd overlaps (see Fig. 3). This analysis allows us to assign the double doublet (dd) patterns as follows: 3.367 (dd, $^2J = 18.47$, $^3J = 9.19$); 3.355 (dd, $^2J = 18.36$, $^3J = 8.56$); 2.905 (dd, $^2J = 18.49$, $^3J = 4.72$); 2.888 (dd, $^2J = 18.38$, $^3J = 5.03$). Our earlier work in which simple *N*-substituted maleimides are prepared by sodium acetate-promoted cyclodehydrations of the corresponding maleamic acids in acetic anhydride has often resulted in crude product containing an impurity which displays three dd patterns in the proton NMR. These impurities are evidently the acetic acid addition products of the maleimides, i.e., the acetoxy pyrrolidinediones. This has been discussed by Wang.[14] The three protons on the acetoxy pyrrolidinedione ring produce the three dd patterns in the NMR as part of an approximate AMX pattern, with the deshielded proton (H–C–$OCOCH_3$) on the carbon bearing the acetoxy group, and the diastereotopic methylene pair appearing at higher field. The two protons of the CH_2 differ in being cis or trans with respect to the acetoxy group. Singlets ca. 2.2 ppm appear from the acetoxy signal. In the present system, from the (trifluoromethylphenyl)maleimide, there are two sets of three dd patterns, each set present in roughly equal amount, which we attribute to a pair of atropisomers resulting from hindered rotation about the *N*-aryl bond. The CF_3 group in the isomers may be syn or anti relative to the acetoxy group on the pyrrolidinedione ring (see Fig. 4). The fact that this interpretation and these assignments are correct is strongly supported

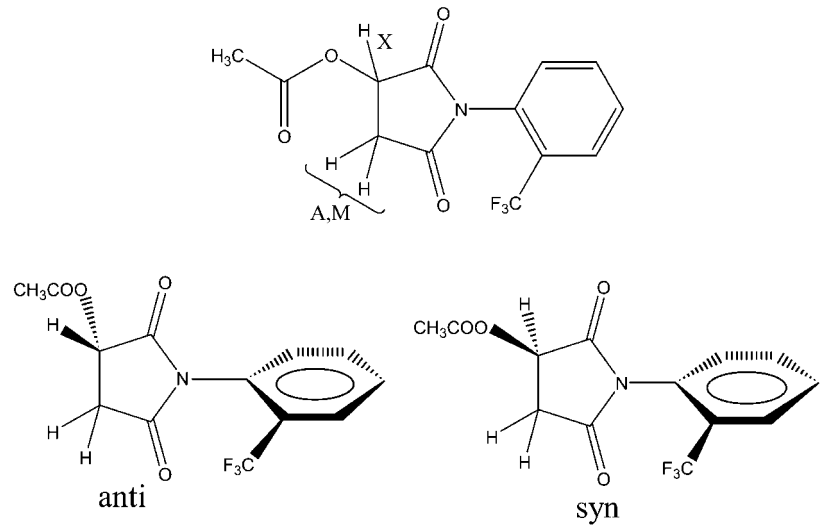

Figure 4. Representations of the syn and anti atropisomers of acetoxy derivatives of **3**.

by the presence in the spectrum of our crude *N*-phenylmaleimide of three double doublets: 5.57 ppm (dd, $^3J = 4.98$, 8.93, *H*C–OCOCH$_3$); 3.33 (dd, $^2J = 18.46$, $^3J = 8.92$); 2.87 (dd, $^2J = 18.43$, $^3J = 5.05$), and the singlet at 2.20 ppm for the acetoxy group. Our spectral data for the (trifluoromethylphenyl)maleimide impurity is perfectly consistent with this explanation only if *N*-aryl rotation in the acetoxy pyrrolidinediones is slow on the NMR timescale. If the *N*-aryl ring in these acetoxy compounds rotated fast on the NMR timescale, only three (rather than six) dd resonances could be seen. If there is demonstrably slow *N*-aryl rotation in these acetoxy pyrrolidinediones, in which the pyrrolidinedione rings have some flexibility, then there should certainly be slow *N*-aryl rotation in the phencyclone adducts, since the rigidity of the imide rings in adducts **4** and **5** would reduce the likelihood for the *N*-aryl rotation. Our conclusions are supported by the computational results discussed below.

Additional important examples of magnetic anisotropic effects are also seen for both adducts in the proton NMR resonances for the bridgehead phenyls, with these protons H-2′, 3′, 4′, 5′, 6′ covering a chemical shift range from ca. 8.3 to 7.3 ppm, surprising for phenyl rings bearing no substituents or conjugated groups, and connected only to the sp^3 bridgehead carbon. Significant anisotropic contributions must result from the proximal ketone and imide carbonyls, as well as from the phenanthrenoid moiety. We have not attempted to establish whether H-2′ or H-6′ is directed towards the ketone carbonyl, but for labeling purposes in the computational results below, we refer to H-2′ as being proximal to this ketone.

Ab Initio Structure Calculations

Geometry optimization calculations were performed at the Hartree–Fock level with the 6-31G* basis set. This is considered to provide good accuracy for energies of optimized conformers, at reasonable cost in terms of calculation times.[15–17] Our earlier work with MacSpartan or PC Spartan for Windows could not be extended to the molecules in this present report because of limits on maximum numbers of atoms or basis functions. The newer software used here potentially allows up to 200 atoms or 2000 basis functions (for the TITAN Hartree–Fock module). Our present ab initio HF/6-31G* calculations appear to be the highest level that has been applied to these compounds. Many of the calculations were routinely run several times with different software packages to confirm reproducibility or to locate the lowest energy optimized structures. Data presented here reflect the lowest energy calculations, regardless of the software or platform used.

Geometry optimization results for **2** and **3**; for the phencyclone adducts, **4** and **5**; and for the acetoxy derivatives of the maleimides showed the effects of severe repulsions with the imide carbonyls. The *N*-aryl ring was almost perpendicular to the heterocyclic ring for each trifluoromethylphenyl analog, and significant twisting away from coplanarity with the imide ring was even seen for the *N*-phenyl of **2** and **4**. Relevant dihedral angles are summarized in Table 3. The average dihedral angle between the imide and *N*-$CF_3C_6H_4$ rings was between 86–94°, except for the severely hindered hypothetical syn adduct of **5**. (See Table 3 for selected dihedral angles and Table 4 for selected interatomic distances and distances from specified atoms to bonds in the phenanthrenoid group. Note that for compounds with the CF_3 group, the Tables refer to F_{distal} for the fluorine directed away from the imide carbonyls, and to $F_{a,b}$ for the pair of fluorines that are directed towards the carbonyls. For the adducts, dihedral angles of the bridgehead phenyl groups are defined with C-2′ arbitrarily designated as proximal to the bridging ketone carbonyl. For adduct **4**, H-6″ refers to the *N*-phenyl *ortho*-hydrogen directed into the cavity.) Some representative optimized structures are shown in Fig. 5. Note that the signs of the tabulated dihedral angles may reflect the sense of the axial chirality in selected portions of the structures, as optimized.

We note some difficulties in obtaining consistent convergence for the geometry optimizations of the phencyclone adducts, particularly using TITAN, with numerous calculations resulting in "stuck optimizations," but we ultimately obtained two fully completed runs for adduct **5** with the CF_3 group anti (directed out of the adduct cavity) as well as five completed runs with the CF_3 syn (directed into the adduct cavity. The acetoxy derivatives showed much less tendency for stuck optimizations, and three completed optimizations were obtained for each of these atropisomeric derivatives. Considering the lowest energy structures obtained, we found an energy difference of 0.005996 hartrees, or 3.76 kcal/mol for the *syn*- and *anti*-phencyclone adducts, **5**, with the anti lower in energy (1 hartree = 627.5 kcal/mol). For the acetoxy derivatives, the anti isomer was favored by a much smaller amount, only 0.0003559 hartrees or 0.22 kcal/mol. This is consistent with our observation of near-equal amounts of the acetoxy atropisomers and with only one isomer of adduct **5**.

Despite these difficulties, it was found that essentially all of the calculated structures for each compound were superficially quite similar, even when the stuck optimizations were examined. The better (lower) energy values from the stuck optimizations usually differed from the fully completed and converged values by only ca. 0.0002 au or less, which amounts to energy differences of less than ca. 0.12 kcal/mol. It is suggested that at least part of the convergence difficulties here are associated with rather flat energy surfaces over which slightly different rotational isomers are interconverted, making it difficult to locate true global energy minima. A few general observations

Table 3. Calculated geometric parameters: dihedral angles (degrees) and energies (au, hartrees).

	Energy (au)	Dihedral angles (°)		
			O=*C*–N–C–C(2)	O=*C*–N–C–C(6)
2, Phenylmaleimide	−586.9501329		51.47, −128.57	51.45, −128.51
3, $CF_3C_6H_4$maleimide	−922.5672956		91.94, −91.85	88.18, −88.03
		O=*C*–C–C_{ipso}–C(2′)	O=*C*–N–C–C(2″)	O=*C*–N–C–C(6″)
Adduct, **4**	−1770.5285508	52.19, −52.94	119.39, −62.46	117.45, −60.69
Adduct **5** (anti, out)	−2106.1470656	51.70, −51.75	92.62, −92.61	87.40, −87.37
Adduct **5** (syn, in)	−2106.1410692	52.07, −52.34	95.91, −94.59	85.47, −84.03
		O=C–C–*O*–Ac	O=*C*–N–C–C(2)	O=*C*–N–C–C(6)
Acetoxy derivative (anti)	−1150.4024799	43.25	93.91, −94.03	86.08, −85.99
Acetoxy derivative (syn)	−1150.4021524	46.89	89.62, −93.17	86.83, −90.38
	N–C–C(2)–*C*F_3	C_{ipso}–C(2)–C–F_{distal}	C_{ipso}–C(2)–C–*F*(a,b)	
3, $CF_3C_6H_4$maleimide	−0.07	−179.99	60.01, −60.02	
	N–C–C(2″)–*C*F_3	C_{ipso}–C(2″)–C–F_{distal}	C_{ipso}–C(2″)–C–*F*(a,b)	
Adduct **5** (anti, out)	−0.01	179.98	59.89, −59.92	
Adduct **5** (syn, in)	0.13	−179.60	60.58, −59.75	
	N–C–C(2)–*C*F_3	C_{ipso}–C(2)–C–F_{distal}	*H*(X)–C–C–*H*(A,M)	
Acetoxy derivative (anti)	0.00	−178.99	18.72, 141.45	
Acetoxy derivative (syn)	0.24	−179.28	22.76, 146.01	

Table 4. Calculated geometric parameters: distances (angstroms) between atoms and from atoms to bonds.

		H(2,6) to N–C=*O*		
2, Phenylmaleimide		2.756, 4.440		
		2.756, 4.440		
	F(a,b) to N–C=*O*	H(6) to N–C=*O*		
3, $CF_3C_6H_4$maleimide	3.170, 4.436	3.608, 3.611		
	3.171, 4.434			
	H(2″,6″) to N–C=*O*	H(2′) to ketone C=*O*	H(6′) to imide C=*O*	H(6″) to bond **4a–4b**
Adduct **4**	2.930, 4.223	2.723, 2.744	2.556, 2.563	3.552
	2.934, 4.227			
	F(a,b) to N–C=*O*			
Adduct **5** (anti, out)	3.152, 4.419	2.716, 2.718	2.557, 2.558	3.554
	3.152, 4.420			
				F(a,b) to bond **4a–4b**
Adduct **5** (syn, in)	3.195, 4.417	2.718, 2.724	2.524, 2.535	3.337, 3.365
	3.159, 4.465			
Acetoxy derivative (anti)	3.282, 4.534			
	3.177, 4.415			
Acetoxy derivative (syn)	3.145, 4.442			
	3.155, 4.399			
	H(6″) to **4a–10a**; **4b–8a**	H(6″) to **4–4a**; **4b–5**	H(6″) to **10–10a**; **8a–9**	H(6″) to **9–10**
Adduct **4**	3.409, 3.976	3.522, 3.601	3.422, 4.122	3.787
Adduct **5** (anti, out)	3.598, 3.599	3.467, 3.467	3.708, 3.710	3.831
	F(a,b) to **4a–10a**; **4b–8a**	F(a,b) to **4–4a**; **4b–5**	F(a,b) to **10–10a**; **8a–9**	F(a.b) to **9–10**
Adduct **5** (syn, in)	3.188, 3.199	3.290, 3.348	3.203, 3.207	3.580, 3.587

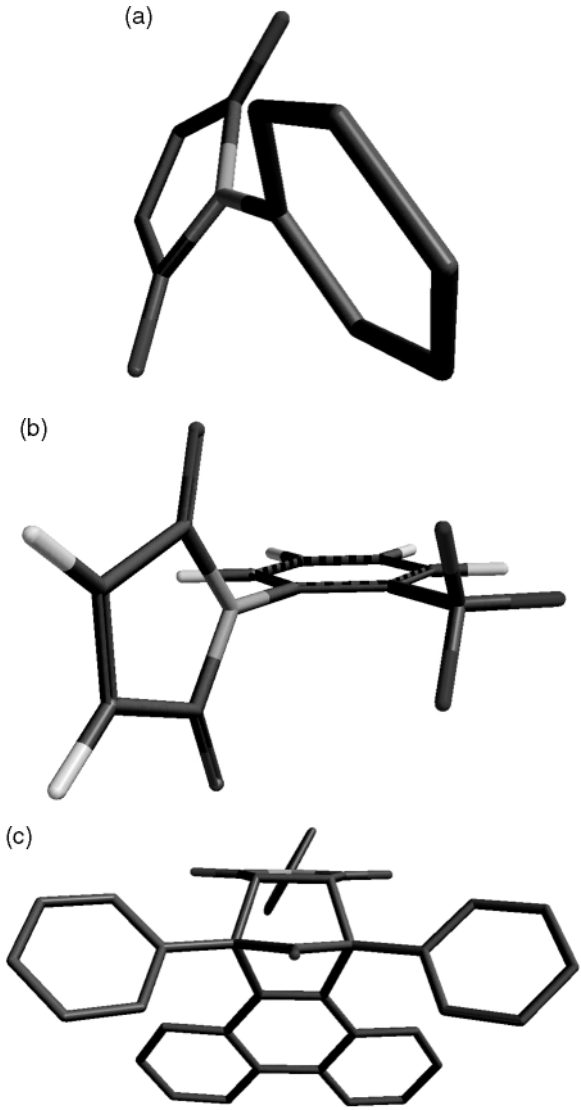

Figure 5. Selected HF/6-31G* optimized structures for compounds. Hydrogens are hidden for clarity in most of the representations. (a) *N*-phenylmaleimide, **2**; (b) *N*-(2-trifluoromethylphenyl)maleimide, **3**; (c) adduct **4**, from phencyclone and **2**; (d) isolated adduct *anti*-**5**, from phencyclone and **3**; (e) hypothetical adduct *syn*-**5**, from phencyclone and **3**; (f) *anti*-acetoxy derivative from **3**; (g) *syn*-acetoxy derivative from **3**. (*View this art in color at www.dekker.com.*)

(continued)

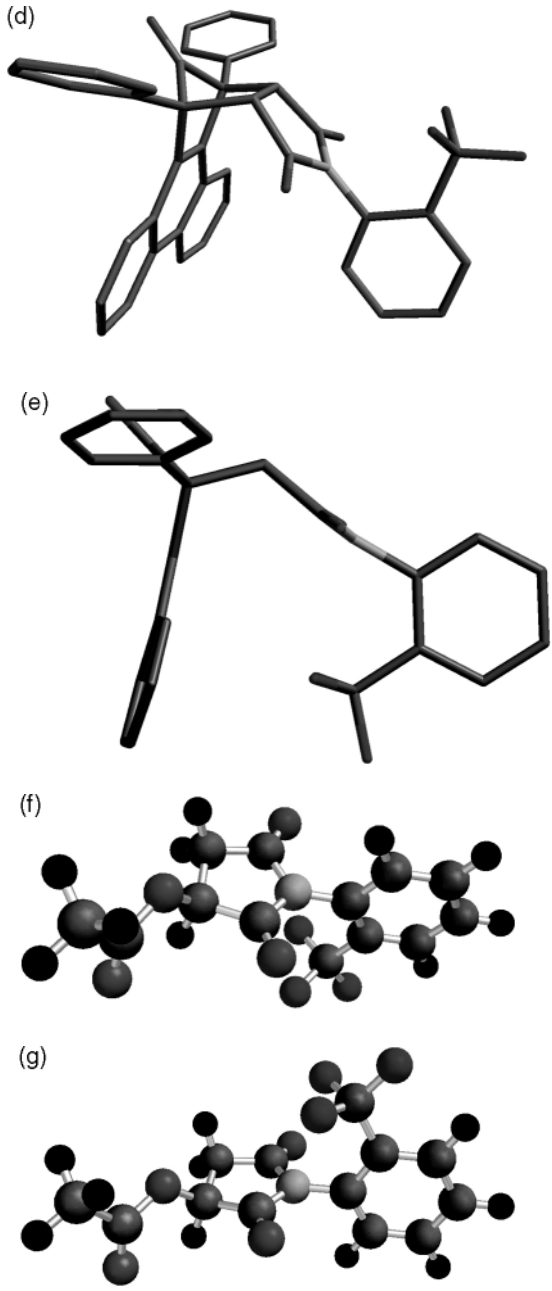

Figure 5. Continued.

that we made include the following. (a) Some non-planarity of the phenanthrenoid moiety is seen in the optimized adduct structures; if this three-ring aromatic portion is regarded as having a "butterfly-like" structure, then the outer rings ("wings") are slightly folded toward the *N*-aryl ring. (b) Some pyramidalization at the nitrogen is seen, with the *N*-aryl portion folding away from the phenanthrenoid moiety in the hindered syn adduct of **5** (with the CF_3 directed into the cavity). In this conformer, the nitrogen is displaced 0.070 Å from the plane defined by its three directly bonded neighbors. Surprisingly, for the anti adduct of **5**, the *N*-aryl portion is actually tipped slightly into the cavity, towards the phenanthrenoid moiety, with the nitrogen displaced 0.035 Å from the plane of its neighbors. For adduct **4**, the *N*-phenyl is also tipped slightly towards the phenanthrenoid portion, by a small amount; the nitrogen was 0.012 Å from the plane of its neighbors. (c) The conformations of the bridgehead phenyls relative to the ketone carbonyl are very consistent in both of the adducts **4** and **5**, ca. 52° for the O=*C*–C–C(ipso)–*C*(2′) dihedral angle magnitudes. For the acetoxy pyrrolidinediones, the calculated dihedral angles for H_X–C–C–H_M and for H_X–C–C–H_A appear to be in modest agreement with the observed vicinal couplings, based on the Karplus relationship.[18]

CONCLUSIONS

The NMR spectra for the phencyclone adducts of *N*-phenylmaleimide and of *N*-(2-trifluoromethylphenyl)maleimide have been acquired. Full ^{1}H assignments, and extensive ^{13}C assignments have been made. Both compounds show SEL ^{1}H and ^{13}C spectra for the bridgehead phenyl group rotation. The *N*-phenylmaleimide adduct exhibits FEL ^{1}H and ^{13}C spectra for rotation about the *N*-phenyl bond. The *N*-(2-trifluoromethylphenyl)maleimide adduct is considered to have SEL spectra for the *N*-aryl bond rotation, with a single adduct conformer present in which the bulky *ortho*-trifluoromethyl group is directed away from the interior of the molecule.

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REFERENCES

1. Sasaki, T.; Kanematsu, K.; Iizuka, K. Molecular design by cycloaddition reactions. XXV. High peri- and regiospecificity of phencyclone. J. Org. Chem. **1976**, *41* (7), 1105–1112.
2. Callahan, R.; Bynum, K.; Prip, R.; Rothchild, R. Synthesis of Diels–Alder adducts of phencyclone and NMR studies of hindered rotations of unsubstituted bridgehead phenyls: microscale experiments in organic chemistry. Chem. Educator **1998**, *3* (2), S1430–4171 ((98) 02192-4 Avail. URL: http://journals.springer-ny-com/ched).
3. Callahan, R.; Marshall, K.; Rothchild, R.; Rosmarion, K. Syntheses of phencyclone analogs. Applications for NMR studies of hindered rotations and magnetic anisotropy in crowded Diels–Alder adducts. The Chemical Educator [online] **2001**, *6*, 227234 DOI 10.1007/s00897010488a.
4. Bynum, K.; Rothchild, R. 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.
5. Bynum, K.; Rothchild, R. 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.
6. Bynum, K.; Rothchild, R. 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.
7. Amin, M.; Bynum, K.; Callahan, R.; Prip, R.; Rothchild, R. Studies of hindered rotation and magnetic anisotropy by ^{1}H, ^{13}C and ^{19}F NMR. The Diels–Alder adduct of *N*-pentafluorophenyl maleimide and phencyclone: a model for drugs. Spectrosc. Lett. **1998**, *31* (3), 673–692.
8. Büchi/Brinkmann stereomodels, Brinkmann Instruments, Inc., Westbury NY 11590.
9. Pouchert, C.J.; Behnke, J. The Aldrich library of ^{13}C and ^{1}H FT NMR spectra. Aldrich Chemical **1993**, *1* (2), 1453C (Milwaukee, WI).
10. Eto, M.; Setoguchi, K.; Harada, A.; Sugiyama, E.; Harano, K. Phencyclone Diels–Alder adducts as a new crystalline host. Role of C–H$\cdots\pi$ and C–H$\cdots$O interactions. Tetrahedron Lett. **1998**, *39* (52), 9751–9754.
11. Yoshitake, Y.; Misaka, J.; Setoguchi, K.; Abe, M.; Kawaji, T.; Eto, M.; Harano, K. Non-hydroxylic clathrate hosts of $[4+2]\pi$ cycloadducts of phencyclone and *N*-arylmaleimides: recognition of aromatic guests. J. Chem. Soc. Perkin Trans. 2 **2002** (9), 1611–1619.
12. Yoshitake, Y.; Misaka, J.; Abe, M.; Yamasaki, M.; Eto, M.; Harano, K. Carboxylic acid clathrate hosts of Diels–Alder adducts of phencyclone and 2-alkenoic acids. Role of bidentate C–H$\cdots$O hydrogen bonds

between the phenanthrene and carbonyl groups in host–host networks. Org. Biomol. Chem. **2003**, *1* (7), 1240–1249.
13. Tan, R.Y.S.; Russell, R.A.; Warrener, R.A. The application of ^{13}C-N.M.R. spectroscopy to the determination of the stereochemistry of Diels–Alder adducts. Tetrahedron Lett. **1979**, *20* (52), 5031–5034.
14. Wang, Z.Y. Syntheses of some *N*-alkylmaleimides. Synth. Commun. **1990**, *20* (11), 1607–1610.
15. Jensen, F. *Introduction to Computational Chemistry*; John Wiley: New York, 1999.
16. *TITAN Tutorial and User's Guide*; Wavefunction, Inc.: Irvine, CA, and Schrödinger, Inc. 1999, (Portland, OR).
17. Hehre, W.J.; Shusterman, A.J.; Nelson, J.E. *The Molecular Modeling Workbook for Organic Chemistry*; Wavefunction, Inc.: Irvine, CA, 1998.
18. Günther, H. *NMR Spectroscopy: Basic Principles, Concepts, and Applications in Chemistry*, 2nd Ed.; John Wiley: New York, 1995.

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