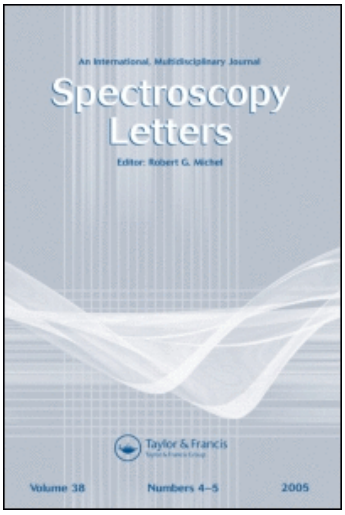

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NMR Studies of Crowded Diels–Alder Adducts of 3,6-Dibromophencyclone with *N*-(2,6-Dialkylphenyl)maleimides. Hindered Rotations and Magnetic Anisotropy. Ab Initio Calculations for Optimized Structures of the Precursor Maleimides and Their Adducts with Phencyclone and 3,6-Dibromophencyclone

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ABSTRACT

6,9-Dibromo-1,3-diphenyl-*2H*-cyclopenta[*l*]phenanthren-2-one (commonly known as 3,6-dibromophencyclone), **1b**, reacted with *N*-(2,6-dimethylphenyl)maleimide, **2a**; with *N*-(2,6-diethylphenyl)maleimide, **2b**; and with *N*-(2,6-diisopropylphenyl)maleimide, **2c**, respectively, to yield the corresponding Diels–Alder adducts, **4a–c**. The adducts were extensively characterized by NMR (7 T) at ambient temperatures using one- and two-dimensional (1D and 2D) proton and carbon-13 techniques for assignments. Slow exchange limit (SEL) spectra were observed, demonstrating slow rotations on the NMR timescales, for the unsubstituted bridgehead phenyl groups [$C(sp^3)$–C(aryl sp^2) bond rotations] and for the 2,6-dialkylphenyl groups [$N(sp^2)$–C(aryl sp^2) bond rotations]. Substantial magnetic anisotropic shifts were seen in the adducts. For example, in the *N*-(2,6-dialkylphenyl) moieties of the adducts, one of the alkyl groups is directed "into" the adduct cavity, toward the phenanthrenoid portion, and these "inner" alkyl proton NMR signals were shifted upfield. Thus, in $CDCl_3$, the inner methyl of adduct **4a** exhibits a proton resonance at −0.05 ppm, upfield of tetramethylsilane (TMS); the inner ethyl group signals from **4b** appear at 0.09 ppm (CH_2, quartet) and −0.11 ppm (CH_3, triplet); and the inner isopropyl group from **4c** is seen at −0.10 ppm (methine, approx. septet) and, −0.28 ppm (CH_3, doublet). Ab initio molecular modeling results are presented for the precursor maleimides, **2**, and their adducts, **3**, from the parent phencyclone, **1a**, at the restricted Hartree–Fock level using the 6-31G* basis set. Results for the dibromoadducts, **4**, used the LAV3P* basis set.

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

INTRODUCTION

For some time, we have studied various hindered Diels–Alder adducts of phencyclone, **1a**, (i.e., 1,3-diphenyl-2*H*-cyclopenta[*l*]phenanthren-2-one) and analogs, with various dienophiles.[1–6] The adduct systems have been of particular interest for examination of hindered rotations, e.g., the slow rotations of the unsubstituted bridgehead phenyl groups of the adducts about the $C(sp^3)$–C(aryl sp^2) bonds. At ambient temperatures, medium field strength NMR spectrometers have shown slow exchange limit (SEL) spectra for the bridgehead phenyl protons (at 200 or 300 MHz) and carbons (50 or 75 MHz). These

hindered adducts have also evidenced rather striking examples of magnetic anisotropy. When N-substituted aryl maleimides, **2**, are used as the Diels–Alder dienophiles, we are able to consider potential hindered rotations about the adduct's N(sp^2)–C(aryl sp^2) bond in addition to the rotations about the bridgehead phenyls. Substantial hindrance about the N–C(aryl) bond of the maleimide adduct results from repulsions with the pyrrolidinedione moiety of the adduct, that is, interactions between the carbonyl oxygens and the ortho (2″ and 6″) substituents of the N-aryl group. Quite dramatic magnetic anisotropic effects can result. Some theoretical studies of related systems have been reported recently, and have relevance to important pharmaceuticals and drugs of abuse.[7,8] An improved understanding of molecular motions, such as bond rotations in hindered systems is, of course, of considerable importance for comprehending molecular structures and behavior. Rotations about bonds to aromatic rings, especially C-aryl and N-aryl rotations, have been particularly significant for numerous drug systems. Some examples include the C-aryl rotation in the benzodiazepine, ketazolam[9] and the N-aryl rotations in the potential antipsoriatic, Sch40120,[10] the muscle relaxant, afloqualone,[11] famprofazone (an analog of amphetamine)[12] and antipyrine.[13,14] N-Aryl rotations have also been important in the strictly controlled (Schedule I of the Controlled Substances Act) sedative-hypnotics, methaqualone,[15] and mecloqualone.[16] In these latter two compounds, the N-aryl rotation results in enantiomerization. In our earlier studies,[17] we discussed the NMR results from one- and two-dimensional (1D and 2D) proton and carbon-13 ambient temperature spectral studies (at 7 T) of the Diels–Alder adducts of **1a** with *N*-(2,6-dialkylphenyl)maleimides, **2a** (R = methyl), **2b** (R = ethyl), and **2c** (R = isopropyl). The product adducts are designated **3a** (from **1a** with *N*-2,6-dimethylphenylmaleimide); **3b** (from **1a** with *N*-2,6-diethylphenylmaleimide); and **3c** (from **1a** with 2,6-diisopropylphenylmaleimide). In this present report, we extend these studies by using the phencyclone analog, 3,6-dibromophencyclone, **1b** (i.e., 6,9-dibromo-1,3-diphenyl-*2H*-cyclopenta[*l*]phenanthren-2-one) to form Diels–Alder adducts **4a–c**, for NMR studies. Compound structures are shown in Figs. 1 and 2, with the preparation of **1b** outlined in Fig. 1, and the formation of adducts in Fig. 2. In addition to the NMR studies, we performed ab initio computational studies of the precursor maleimides, **2**, as well as their adducts from both the parent phencyclone and 3,6-dibromophencyclone.

EXPERIMENTAL

General discussions of NMR methods and synthetic techniques have been described in our earlier papers and references cited therein.[1–6] NMR spectra

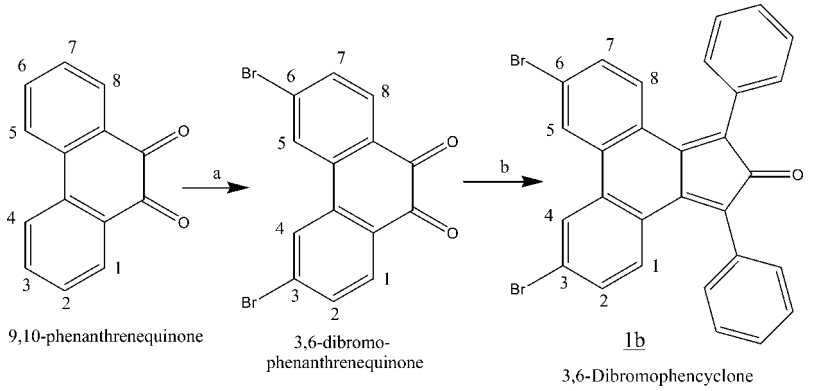

Figure 1. Preparation of 3,6-dibromophencyclone. Reagents. (a) Br_2, nitrobenzene, 100–120°, (b) 1,3-diphenylacetone, KOH, MeOH, reflux.

were obtained at ambient temperatures on a Bruker ACF300 spectrometer (7.05 T) at ca. 300 MHz for proton or 75 MHz for carbon-13 using a QNP "quad" probe and Aspect 3000 data system. Chemical shifts in proton spectra were referenced to internal tetramethylsilane (TMS) at 0.0 ppm, and to the central line of the $CDCl_3$ triplet at 77.0 ppm for carbon-13 spectra. Standard Bruker microprograms were used for acquisitions. For normal 1D

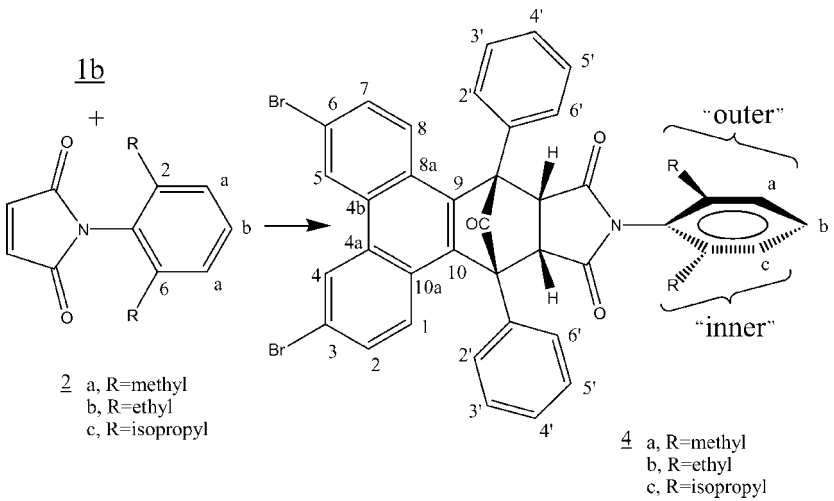

Figure 2. Adduct preparation from **1b**.

carbon-13 spectra, protons were decoupled using composite pulse decoupling (WALTZ16) with a relaxation delay of 3 sec; with this relaxation delay, integrated carbon signals for proton-bearing carbons were roughly proportional to the numbers of carbons. For the "high resolution" COSY45 spectra of the aryl proton regions, the spectral width in F_2 was typically ca. 2.5 ppm (750 Hz). The magnitude mode spectra were acquired with two dummy scans and 16 acquisitions for each of 256 t_1 increments, zero-filling once in F_1 and F_2 for a final data matrix of 512 × 1024. Data were processed with unshifted sine-bell apodization in both dimensions and symmetrized. For the XHCORR experiments [heteronuclear chemical shift correlation spectra (HETCOR)], typically 256 transients were obtained for each of 128 increments in the t_1 (proton) dimension, zero-filling twice in the t_1 dimension for a final data matrix of 512 × 4K; 1024 transients for each increment were acquired for **4c**. Abbreviations used in reporting NMR data include: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), and Q (non-protonated or quaternary carbon signal). Observed coupling constants are given in hertz. Commercial reagents were obtained from Aldrich Chemical (Milwaukee, WI) and were used without further purification. Infrared spectra were obtained with a Perkin Elmer 1640 FTIR with DTGS detector as KBr pellets. Reported melting points are uncorrected. The maleimides were prepared as described earlier[17] and were available from the earlier work. 3,6-Dibromophencyclone, **1b**, was synthesized as described earlier (See Fig. 1).[2] Katz and co-workers have pointed out the ease of preparing substantial amounts of the intermediate 3,6-dibromophenanthrene-9,10-quinone.[18]

Preparation of the Adduct, 4a, of 3,6-Dibromophencyclone with *N*-(2,6-Dimethylphenyl)maleimide

3,6-Dibromophencyclone, **1b** (405.2 mg, 0.75 mmol), **2a** (157.0 mg, 0.78 mmol, ca. 4% molar excess), ca. 3 mg of 2,6-di-*t*-butyl-4-methylphenol (BHT, see Results and Discussion), and 100 mL 1,2-dichloroethane were stirred and refluxed with a drying tube (anh. $CaCl_2$) on top of the condenser. After 10 min, the near-black mixture had become dark green, turning yellow as the reaction neared completion. After overnight reflux, preliminary solvent removal on the rotary evaporator (aspirator pressure, bath to 70°C) gave crude yellow solid which contained substantial residual solvent (by proton NMR), 76% crude yield. (Formation of complexes between adducts of **1a** and various solvents has been discussed.[19–21]) Successive addition and removal (by rotary evaporator) of 3 × 50 mL portions of CH_2Cl_2 permitted displacement of the dichloroethane. Recrystallization of the crude adduct from 2 : 1 hexanes/CH_2Cl_2 and slow evaporation of solvent (N_2 stream)

with ice-slush cooling provided fine white crystals, collected and air-dried (20% recovery), with mp 251–255°C (dec., shrinkage, darkening, gas evolution). IR (KBr, cm^{-1}): 1793 (sharp, m, strained bridging ketone C═O); 1715 (sharp, strong, imide carbonyls). Proton NMR ($CDCl_3$, ppm): 8.69 (2H, d [$^4J = 1.73$], H(4/5)); 8.36 (2H, d [$^3J = 7.79$], H(2′)); 7.71 (2H, t [$^3J = 7.25$], H(3′)); 7.53 (2H, t [$^3J = 7.37$], H(4′)); 7.43 (2H, t [$^3J = 8.79$], H(5′)); 7.33 (2H, dd [$^3J = 8.93$, $^4J = 1.70$], H(2/7)); 7.15 (2H, d [$^3J = 7.70$], H(6′)); 7.03 (2H, d [$^3J = 8.97$], H(1/8)); 6.99 (2H, approx. d, $H_{a,b}$); 6.62 (1H, approx. *t* due to virtual coupling to near-isochronous $H_{a,b}$, apparent [*J* ca. 4.5], H_c); 4.66 (2H, s, bridgehead CH); 2.10 (3H, s, outer CH_3); −0.05 (3H, s, inner CH_3).

Carbon-13 NMR ($CDCl_3$, ppm) (see Results and Discussion): 195.41 (C═O, ketone); 173.04 (C═O, imide); 135.59 (Q); 134.44 (Q); 133.97 (Q); 133.14 (Q); 132.11 (Q); 130.80 (6′); 130.72 (2/7); 129.71 (Q); 129.57 (3′); 129.44 (tent. C_b [or C_a]); 129.29 (2′); 128.75 (coincidental overlap of 4′ and 5′); 128.24 and 128.20 (tent. C_c and C_a [or C_b], assignment can be reversed; 127.53 (1/8); 125.83 (4/5); 125.50 (Q); 122.38 (Q); 63.58 (*C*-C_6H_5); 45.02 (CH bridgehead methine); 17.92 (CH_3 "outer"); 15.52 (CH_3 "inner").

Preparation of the Adduct, 4b, of 3,6-Dibromophencyclone with *N*-(2,6-Diethylphenyl)maleimide

Similarly to the above, 3,6-dibromophencyclone (540.0 mg, 1.00 mmol), the diethylphenylmaleimide **2b** (240.7 mg, 1.05 mmol, 5% molar excess), ca. 3 mg BHT, and 100 mL 1,2-dichloroethane were added to a flask equipped with magnetic stirrer and reflux condenser topped with a drying tube (anh. $CaCl_2$). During reflux for 22 hr, the initially black mixture decolorized to a bright yellow solution. Solvent removal (rotary evaporator, aspirator pressure, 40°C bath temperature) left 946 mg crude product. Three portions of CH_2Cl_2 (50 mL each) were added and repeatedly removed (rotary evaporator) to remove traces of the initial dichloroethane solvent by co-distillation. Recrystallization of the remaining yellow impure product from a mixture of ca. 94 mL hexanes and 40 mL CH_2Cl_2 was achieved after cooling and partial solvent evaporation to give fine yellow crystals of **4b** (first crop 465 mg, ca. 60% yield), mp 270–274°C (dec., shrinkage, darkening, gas evolution). After standing at room temperature for several days, the mother liquor deposited 128 mg of fluffy white crystals which were found by NMR to be impure material which was not further characterized. The first crop material was used for spectral studies. IR (KBr, cm^{-1}): 1792 (sharp, m, strained bridging ketone C═O); 1715 (sharp, strong, imide C═O). Proton NMR ($CDCl_3$, ppm): 8.74 (2H, d [$^4J = 1.74$], H-4,5); 8.37 (2H, d [$^3J = 7.79$], H-2′); 7.71 (2H, t

[$^3J = 7.19$], H-3′); 7.53 (2H, t [$^3J = 7.40$], H-4′); 7.43 (2H, t [$^3J = 7.58$], H-5′); 7.32 (2H, dd [$^3J = 8.94$, $^4J = 1.72$], H-2,7); 7.14 (1H, t [$^3J = 7.71$], H_b), overlapped with 7.13 (2H, d [$^3J = 7.65$], H-6′); 7.04 (1H, d [$^3J = 6.64$], H_a, meta to N, outer), overlapped with 7.03 (2H, d [$^3J = 8.98$], H-1,8); 6.71 (1H, d [$^3J = 7.53$]), H_c, meta to N, inner); 4.68 (2H, s, CH bridgehead methine); 2.40 (2H, q [$^3J = 7.54$], CH_2CH_3, outer); 1.19 (3H, t [$^3J = 7.55$], CH_2CH_3, outer); 0.09 (2H, q [$^3J = 7.40$], CH_2CH_3, inner); −0.11 (3H, t [$^3J = 7.34$], CH_2CH_3, inner). Carbon-13 NMR ($CDCl_3$, ppm): 195.26 (C═O, ketone); 173.62 (C═O, imide); 140.92 (Q); 139.77 (Q); 134.08 (Q); 133.12 (Q); 131.96 (Q); 130.80 (C-6′); 130.66 (C-2,7); 129.75 (C_b, para to N); 129.54 (C-3′), 129.32 (C-2′); 128.71 (C-4′ and 5′) overlapped; 128.49 (Q); 127.66 (C-1,8); 126.02 (C_a, meta to N, outer); 125.83 (C-4,5); 125.68 (C_c, meta to N, inner); 125.38 (Q); 122.34 (Q); 63.57 (C-C_6H_5); 45.15 (CH-bridgehead methine); 24.49 (CH_2CH_3, outer); 21.56 (CH_2CH_3, inner); 14.10 (CH_2CH_3, outer); 12.40 (CH_2CH_3, inner).

Preparation of the Adduct, 4c, of 3,6-Dibromophencyclone with *N*-(2,6-Diisopropylphenyl)maleimide

As above, 3,6-dibromophencyclone, **1b** (540 mg, 1.00 mmol), *N*-(2,6-diisopropylphenyl)maleimide, **2c** [ca. 1.05 mmol (Note: this sample of **2c** was known from its proton NMR to be somewhat impure, and sufficient excess of the crude material was used to provide the nominal slight molar excess)], ca. 3 mg BHT, and 100 mL 1,2-dichloroethane were added to a flask equipped with a magnetic stirrer and a reflux condenser topped with a drying tube (anh. $CaCl_2$). The mixture was refluxed for ca. 16 hr, during which time the decolorization of the initial black mixture to dark green and then to a clear greenish-yellow solution was seen. Solvent removal with a rotary evaporator (aspirator pressure, water bath ca. 40–50°C) produced yellow chunks of solid (349 mg, ca. 45% yield). The crude product was successively dissolved in 3 × 50 mL portions of CH_2Cl_2 and solvent removed each time (rotary evaporator) to remove the initial 1,2-dichloroethane solvent by co-distillation. Recrystallization of part of the yellow solid (179 mg) from hexanes/CH_2Cl_2 (ca. 2 : 1, v/v) gave, after cooling and evaporation of about 30% of the solution (N_2 stream) fine, pale yellow crystals (142 mg, ca. 79% recovery based on portion recrystallized), mp 270–274°C (dec., shrinkage, darkening, gas evolution). IR (KBr, cm^{-1}): 1792 (sharp, m, strained ketone C═O); 1716 (sharp, strong, imide C═O). Proton NMR ($CDCl_3$, ppm): 8.87 (2H, d [$^4J = 1.78$], H-4,5); 8.38 (2H, d [$^3J = 7.84$], H-2′); 7.72 (2H, t [$^3J = 7.19$], H-3′); 7.53 (2H, t [$^3J = 7.44$], H-4′); 7.41 (2H, approx. triplet of doublets [$^3J = 8.09$, $^4J = 1.02$], H-5′); 7.31 (2H, dd [$^3J = 8.98$, $^4J = 1.75$], H-2,7); 7.20

(1H, t [$^3J = 7.73$], H_b para to N); 7.11 (1H, dd, H_a meta to N outer), overlapped with 7.08 (2H, d, H-6′); 7.03 (2H, d [$^3J = 8.95$], H-1,8); 6.77 (1H, dd [$^3J = 7.71$, $^4J = 1.28$], H_c meta to N, inner); 4.70 (2H, s, CH bridgehead methine); 2.60 (1H, approx. septet [$^3J = 6.81$], C*H*$(CH_3)_2$, outer); 1.20 (6H, d [$^3J = 6.84$], CH(C*H*$_3)_2$, outer); −0.10 (1H, approx. septet [$^3J = 6.61$], C*H*$(CH_3)_2$, inner); −0.28 (6H, d [$^3J = 6.58$], CH(C*H*$_3)_2$ inner). Carbon NMR ($CDCl_3$, ppm): 195.03 (C═O, ketone); 173.87 (C═O, imide); 146.25 (Q); 144.56 (Q); 134.20 (Q); 133.10 (Q); 131.94 (Q); 130.81 (C-6′); 130.47 (C-2,7); 130.04 (C_b, para to N); 129.54 (C-3′); 129.35 (C-2′); 128.68 and 128.66 (split peak of C-4′ and 5′); 127.88 (C-1,8); 126.55 (Q); 125.88 (C-4,5); 125.20 (Q); 123.98 (C_c, meta to N, inner); 123.63 (C_a, meta to N, outer); 122.36 (Q); 63.59 (C–C_6H_5); 45.21 (CH bridgehead methine); 29.54 (*C*H$[CH_3]_2$, outer); 28.05 (*C*H$[CH_3]_2$, inner); 23.98 (CH[*C*H$_3]_2$, outer); 22.57 (CH[*C*H$_3]_2$, inner).

Key software used for molecular modeling included: (a) MacSpartan, v. 1.1, ©1996, Wavefunction Inc., (b) PC Spartan, v. 1.4c, ©1996–1997, Wavefunction Inc., (c) Titan, v. 1.0.5 (August 18, 2000) ©1999, Wavefunction Inc., Schrödinger Inc., (d) Spartan '02 for Windows, v. 1.0.2 (May 29, 2002) ©1991–2002, Wavefunction Inc., and (e) Spartan Essential (ES), v. 1.0.2 (May 31, 2002) ©1991–2002, Wavefunction Inc. All software was obtained from Wavefunction, Inc., Irvine, CA 92612.

RESULTS AND DISCUSSION

Synthetic aspects were straightforward, with the maleimides prepared by cyclodehydration of the maleamic acids derived from reaction of maleic anhydride with the corresponding 2,6-dialkylanilines.[17] Bromination of phenanthrenequinone in nitrobenzene gave 3,6-dibromophenanthrene-9,10-quinone, which underwent condensation with 1,3-diphenylpropanone using methanolic KOH to give the desired 3,6-dibromophencyclone, **1b**.[2] (See Fig. 1). The adducts **4** from **1b** (Fig. 2) formed in reasonable yields under mild conditions, indicating that **1b** is an effective Diels–Alder diene, probably comparable to the parent phencyclone, **1a**.[2,22] We usually add a trace of the free radical trap, BHT, when synthesizing maleimides or their phencyclone adducts in an effort to suppress possible free-radical side reactions.[1,2]

The dibromophencyclone adducts require eight kinds of 2H intensity aryl proton signals and three 1H aryl proton signals assuming adequate spectral dispersion and SEL spectra for the bridgehead phenyls and the N-aryl rings. For the aryl carbon signals, eight pairs of methines (2 × CH) and three single methines (1 × CH) are expected for proton-bearing carbons. For the non-protonated (quaternary) aryl carbons, there should be five signals

associated with carbon pairs, and three signals from individual carbons. For each of the three adducts described, **4a–c**, NMR proton signals were largely assigned based on results of the high resolution COSY45 homonuclear chemical shift correlation spectra. Even when overlaps occurred in the 1D proton spectra, separation into the second dimension with the COSY45 spectra allowed quite complete and explicit assignments, with rather accurate estimates of the chemical shifts of each proton made possible. These chemical shifts, as estimated from the COSY spectra, are given in the Experimental data. The five protons of the bridgehead phenyl $(CH)_5$ spin system are defined from the COSY experiment, but we cannot rigorously assign whether H-2′ or H-6′ (of the bridgehead phenyls) is proximal or distal with respect to the bridging ketone carbonyl. Under our conditions, we could observe off-diagonal crosspeaks not only for the vicinal ^3J couplings, but also the long-range ^4J and even ^5J couplings. "Tilting" of COSY45 crosspeaks assists in assignments. With the proton assignments available, the heteronuclear chemical shift correlation experiment directly gave the carbon-13 assignments for most protonated carbons. The adduct **4a** exhibits a proton NMR spectrum (in $CDCl_3$) free from overlaps among the bridgehead phenyls or phenanthrenoid signals, in contrast to the overlaps of the H(1/8 and 2/7) signals for the adducts **3**, from plain phencyclone, but there is an overlap of two of the methine signals of the N-aryl ring. We have tentatively assigned the 6.69 ppm signal as H_c (rather than H_b) based on the expected anisotropic shielding for the inner proton meta to the nitrogen.[19,20] We attribute the apparent triplet structure of this signal to a virtual coupling effect with the near-isochronous H_a and H_b, and note that the apparent splitting of ca. 4.5 Hz is much less than would be expected for a normal vicinal coupling between aryl protons. When the NMR signals of the three protons H_{a-c} of the N-aryl ring of an adduct are well-resolved from each other, as in the spectrum of **3a** in C_6D_6,[17] or in the spectra of **4b** or **4c** in $CDCl_3$ (see below), the highest-field aryl proton signal is clearly doublet character, assignable as H_c. Based on these proton assignments, we have made tentative carbon assignments. The crosspeaks in the heteronuclear chemical shift correlation spectrum do not exhibit sufficient separation in the carbon dimension to allow unambiguous distinction of the 128.24 and 128.20 ppm peaks and there is even slight uncertainty between the peaks at 130.80 and 130.72 ppm. The integrated intensity of the 128.75 ppm peak is consistent with a coincidental overlap of the 4′ and 5′ carbons. Despite the near-overlaps of some signals in the 1D spectra, the HETCOR spectrum of **4a** clearly shows all 11 required crosspeaks for the aryl signals, which positively shows the SEL slow rotation system (on the NMR timescale).

Adducts **4b** and **4c** have well-separated signals for the N-aryl protons based on the COSY45 crosspeaks, despite some overlaps in the 1D proton

spectra with other aryl proton absorptions of the adducts. The 1D carbon-13 spectra showed a coincidence of the signals for C-4′ and C-5′ for both **4a** and **4b**, but a noticeably split peak can be observed for the **4c** spectrum. For each of the dibromo adducts, 11 distinct crosspeaks are resolved for the 2D HETCOR spectra, unambiguously demonstrating the slow rotations on the NMR timescales for the unsubstituted bridgehead phenyl and the N-aryl rings. We have not attempted to assign the quaternary aryl carbon signals. Assignments for the carbonyls and the quaternary sp^3 $C-C_6H_5$ signals are made by analogy with the adducts of **1a**. One simplification in the proton spectra for the adducts of **1b** (vs. those of **1a**) is that there are no resonance overlaps for the phenanthrenoid signals of the dibromo adducts, whereas the H-2,7 and H-1,8 signals of the plain phencyclone adducts are virtually isochronous. In addition, the splitting patterns of the phenanthrenoid ring protons for the **1b** adducts permit rigorous assignments.

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.[19–23] 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 proton NMR signal of the ortho alkyl group on the N-aryl ring directed "into" the cavity of the endo adduct, and thereby anisotropically shielded by the phenanthrenoid moiety. The most striking feature of the proton NMR spectra of the dibromoadducts, **4**, is surely the upfield position of these inner alkyls. Thus, in $CDCl_3$, the inner methyl of adduct **4a** exhibits a proton resonance at −0.05 ppm, upfield of TMS; the inner ethyl group signals from **4b** appear at 0.09 ppm [(CH_2, quartet) and −0.11 ppm (CH_3, triplet); and the inner isopropyl group from **4c** is seen at −0.10 ppm (methine, approx. septet) and −0.28 ppm (CH_3, doublet)]. In addition to these anisotropic effects, the bridgehead phenyls also clearly exhibit the significant influence of nearby anisotropic groups, such as the ketone and imide carbonyls and the phenanthrenoid moieties. For example, based on the optimized structure of adduct **4a** (described below), we point out for illustrative purposes the calculated distances: (a) from H-2′ to the ketone C=*O* of 2.729 and 2.731 Å; (b) from H-6′ to the proximal imide C=*O* of 2.550 and 2.532 Å; and (c) from H-6′ to the ketone C=*O* of 4.535 and 4.535 Å. (We have arbitrarily designated the 2′ position of the bridgehead phenyls to be closer to the bridging ketone carbonyl for purposes of these geometric considerations.) It might also be noted that since the

simplicity of the NMR spectra of all of the adducts implies, in effect, a mirror symmetry plane, there must be "enantiomerization" processes occurring which are fast on the NMR timescale. No mirror plane of symmetry exists in any of the optimized structures (see below) because of the presence of axial chirality in, e.g., the N-aryl moiety. Achieving effective symmetry may predominantly involve small rotations about the N-aryl bond without requiring a high activation energy motion of alkyl groups past the imide carbonyls. For **3b** and **4b**, significant rotations about the aryl-C_2H_5 bonds would also be needed.

Ab Initio Computational Studies

Geometry optimization calculations (at the Hartree–Fock level, 6-31G* basis set) for maleimides were initially performed using PC Spartan or Mac-Spartan. High level calculations on the adducts could not be performed on these systems because of limits on the number of basic functions. The desired optimizations for adducts were subsequently first carried out 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 ESSENTIAL or Spartan '02 for Windows on Dell Pentium 4 platforms with 1.4, 2.4, or 3.06 GHz processor speeds and 524 or 1024 MB memory. These systems potentially allow up to 200 atoms or 2000 basis functions (for the TITAN Hartree–Fock module) and TITAN includes the pseudopotential basis sets for the heavy atoms (bromine), e.g., LAV3P*. Spartan ES and Spartan '02 do not provide the LAV3P* basis sets. For the calculations on the dibromo compounds, the pseudopotential basis set is used primarily to speed up the calculations by inclusion of fewer basis functions.[24–27]

Many of the calculations were routinely run several times with different software packages to confirm reproducibility, particularly in the case of the Diels–Alder adducts. Although normal expectations might predict essentially identical results, our observations for these and related systems indicated that this was not always true, especially with TITAN. It has been suggested that the final optimized energies from discrete calculations might differ if the relevant "energy surfaces" for these compounds were relatively flat, involving interconversion of slightly different rotational isomers, with shallow local minima that could make smooth convergence to the true global minimum somewhat problematic. Differing final energies for the repeated calculations could reflect the locations of different local minima. In addition, we frequently encountered "stuck" optimizations with TITAN, in which the desired smooth convergence to lower energies would fail to occur, and the calculation would halt. The resulting energies obtained during these stuck geometry

optimizations would generally *but not always* be higher than the energies obtained from runs which had fully and smoothly converged to a minimum. We regarded the calculated energies from the stuck optimizations as spurious, and did not use such values in the final data presented here. In calculations that had halted because of becoming stuck, it was sometimes possible to slightly rotate one of the groups, e.g., an aryl ring, by a few degrees, and to then resubmit the structure for satisfactory further optimization. It is possible that the particularly hindered systems described here (perhaps the result of repulsions of the inner alkyl groups) may have rendered the optimizations especially prone to becoming stuck. Fully converged and successfully completed optimizations for any given compound generally were in good agreement, and data presented here reflect the lowest energy calculations, regardless of the software or platform used.

Ab initio geometry optimizations for the maleimides showed the effects of severe repulsions between the imide carbonyls and the 2,6-dialkylphenyl groups. The N-aryl ring was almost perpendicular to the heterocyclic ring for each analog. Relevant dihedral angles are summarized in Table 1. For **2a**, one hydrogen of each methyl group is almost coplanar with the N-aryl ring and directed away from the maleimide ring. The average dihedral angle between the rings was 81.5°. Qualitatively, the diethyl analog, **2b**, was interesting in having the two ethyl groups oriented away from each other, directed to opposite faces of the N-aryl ring, in what may be referred to as an "anti" or "transoid" conformation. A higher energy local minimum conformation for *N*-(2,6-diethylphenyl)maleimide was also found in which both of the ethyl groups were approximately coplanar with the N-aryl, and directed away from the carbonyls; this conformation is designated **2b′**. The calculated energy of this "coplanar" **2b′** was 0.00245 au (1.54 kcal/mol) higher than for the anti, transoid **2b**. For the diisopropylphenylmaleimide, **2c**, both isopropyl groups were positioned so that the smallest groups on the benzylic carbons, i.e., the methine hydrogens, were roughly coplanar with the N-aryl ring, and directed toward the maleimide ring. The average dihedral angle between the rings was 87.5°.

Synthesis and NMR studies of the Diels–Alder adducts, **3a–c**, from maleimides **2a–c** with the parent "plain" phencyclone, **1a**, have been reported.[17] NMR spectra of these adducts, **3**, showed slow rotation regimes for the bridgehead phenyls and N-aryl rings, and exhibited considerable anisotropic shielding of inner alkyl groups. Calculation of the equilibrium geometries for the adducts, **3**, converged smoothly when using Spartan '02 Essential (Spartan ES, v. 1.0.2) and suggested that the gross conformations of the *N*-(2,6-dialkylphenyl) groups of the adducts closely paralleled the orientations of the maleimides. The optimized structures for adducts **3b** and **4b** both exhibited the diethylphenyl moiety with the anti, transoid conformation. (See Table 1 for selected dihedral angles and Table 2 for selected distances from the inner

Table 1. Dihedral angles[a] in maleimides (**2a–c**) and adducts (**3a–c**, **4a–c**). (see Results and Discussion).

	2a	**2b** (anti)	**2b′** (coplanar)	**2c**		
Optimized structure energy (au)	−665.02415	−743.09028	−743.08783	−821.15586		
Basis functions[b]	247	285	285	323		
Calculation time[b] (hr)	1.5	3	3	5.5		
N-aryl dihedral angles						
O=*C*–N–C(ipso)–*C*	81.32, 81.64	83.37, 83.42	87.40, 87.56	−87.47, −87.51		
C(ipso)–C–CH_2–CH_3		91.44, 91.50	179.29, 179.65			
C(ipso)–C–C(Me_2)*H*				−0.81, −1.10		
	3a	**3b**	**3c**	**4a**	**4b**	**4c**
Optimized structure energy (au)	−1848.60108	−1926.66596	−2004.73238	−1873.27750	−1951.34165	−2029.40787
Basis functions	733	771	809	702	738	774
Calculation time (hr)	86	184	61	26	45	42

(*continued*)

Table 1. Continued.

	3a	**3b**	**3c**	**4a**	**4b**	**4c**
N-aryl dihedral angles						
O=*C*–N–C(ipso)–*C*(out)	96.82, −78.67	81.43, −93.78	82.40, −91.54	92.17, −83.90	96.22, −80.02	87.29, −86.60
O=*C*–N-C(ipso)–*C*(in)	101.66, −82.86	86.45, −98.33	88.54, −97.51	96.18, −87.74	100.75, −83.02	93.26, −92.85
C(ipso)–C–CH_2–*C*H_3 (out)		−104.15			−89.77	
C(ipso)–C–CH_2–*C*H_3 (in)		−107.44			−100.65	
C(ipso)–C–C(Me_2)*H*(out)			0.01			−3.87
C(ipso)–C–C(Me_2)*H*(in)			0.84			−1.59
C–C_6H_5 *dihedral angles*						
O=*C*–C–C(ipso)-*C*(2′)[c]	51.78, −51.48	50.54, −52.59	51.87, −52.55	52.22, −52.25	51.50, −52.83	52.43, −51.89

[a]Signs of some dihedral angles may reflect the "family" of enantiomer of a portion of the structure (as optimized) because of potential axial chirality and lack of perfect mirror symmetry.

[b]Approximate calculation times for each tabulated structure serve to provide a qualitative sense of processing times. These structures were obtained with TITAN, except for **3a** and **3b**, which used Spartan ES. The 6-31G* basis set was used for **2** and **3**, and LAV3P* was used for **4**.

[c]The 2′ position of the bridgehead phenyls is arbitrarily designated as being proximal to the bridging ketone carbonyl.

Table 2. Distances from adduct "inner" alkyl groups to selected phenanthrenoid bonds (angstroms).

	3a	**3b**	**3b**	**3c**	**4a**	**4b**	**4b**	**4c**
Bond	Inner CH_3	Inner CH_2	Inner CH_3	Inner $HCMe_2$	Inner CH_3	Inner CH_2	Inner CH_3	Inner $HCMe_2$
9,10	4.141	4.285	4.555	4.231	4.069	4.270	4.516	4.243
4a,10a (4b,8a)	4.044, 3.857	4.077, 4.153	4.047, 4.598	4.020, 4.102	3.778, 3.887	3.989, 4.236	3.833, 4.093	4.054, 4.063
4a,4b	3.904	4.089	4.064	4.038	3.786	4.065	3.843	4.033
4,4a (4b,5)	3.816, 3.845	3.972, 4.012	4.144, 4.438	3.931, 3.948	3.709, 3.731	3.985, 4.005,	3.843, 4.051	3.937, 3.939
10,10a (8a,9)	3.920, 4.160	4.135, 4.243	3.953, 5.041	4.079, 4.181	3.869, 4.014	4.033, 4.329	3.910, 4.537	4.129, 4.138

alkyl groups to the phenanthrenoid group.) Some representative optimized structures are shown in Fig. 3. 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. For the adducts, dihedral angles of the bridgehead

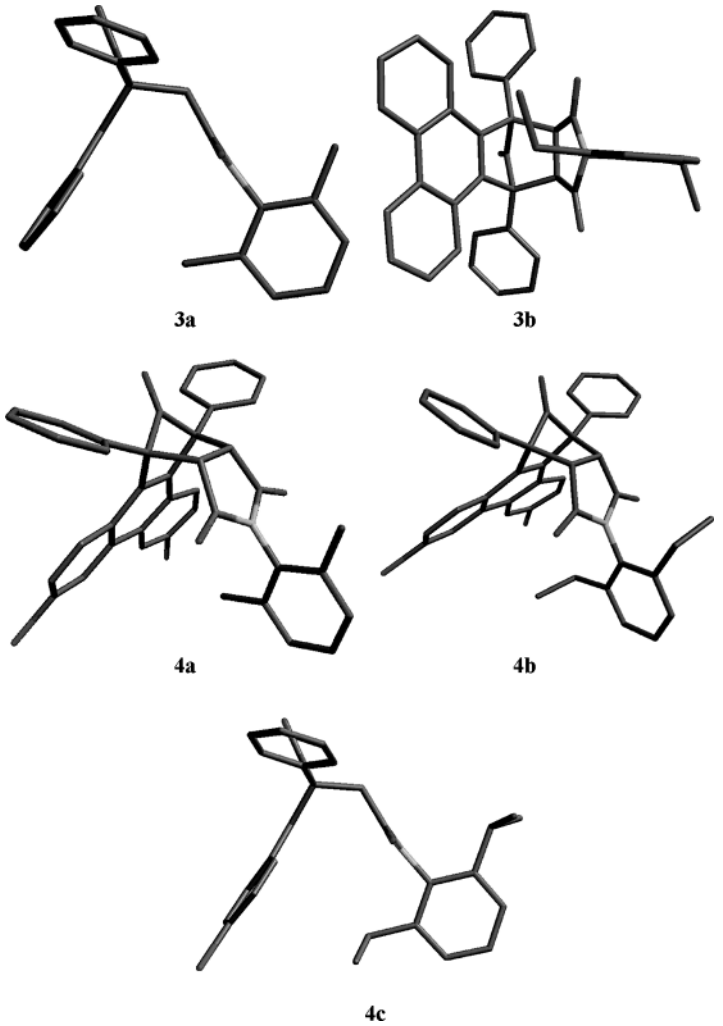

Figure 3. Representative optimized structures. For clarity, hydrogens are hidden: (a) compound **3a**; (b) compound **3b**; (c) compound **4a**; (d) compound **4b**; (e) compound **4c**. (*View this art in color at www.dekker.com.*)

phenyl groups are defined with C-2′ arbitrarily designated as proximal to the bridging ketone carbonyl.

Our present ab initio HF/6-31G* (or LAV3P*) calculations appear to be the highest level that has been applied to these compounds. Because of the heavy atoms (bromine) in the adducts of **1b**, the 6-31G* basis set alone was not applicable, and we used the LAV3P* basis set available in TITAN. LAV3P* applies the 6-31G* basis set to lighter elements.[24–27] In our hands, we encountered some difficulty in obtaining consistent convergence for the geometry optimizations of **4**. For example, in a series of eight calculations for **4a**, the optimization stuck seven times and successfully completed only once, yielding an optimized energy of −1873.27750 au [hartrees (1 hartree = 627.5 kcal/mol)] [Calculation parameters included the disabling of symmetry, turning convergence ON, and specifying highest accuracy cutoffs for the SCF (IACC = 1), as suggested by Wavefunction, Inc.] Approximate calculation times are shown in Table 1. 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. A few general observations that we made include: (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) particularly in the diisopropyl adducts, **3c** and **4c**, some pyramidalization at the nitrogen is seen, with the N-aryl portion folding away from the phenanthrenoid moiety; (c) the conformations of the bridgehead phenyls relative to the ketone carbonyl is very consistent in all of the adducts **3** and **4**, ca. 51–52° for the O=*C*–C–C(*ipso*)–*C*(2′) dihedral angle magnitudes.

CONCLUSIONS

In each of the three dibromophencyclone adducts, **4a**, **4b**, and **4c**, NMR results are consistent with SEL rotations on the NMR timescales for: (a) the *unsubstituted* bridgehead phenyl groups with respect to rotation about the C(sp^3)–C(aryl sp^2) bonds, and (b) the *N*-(2,6-dialkylphenyl) groups with respect to rotation about the N(sp^2)–C(aryl sp^2) bonds. Substantial magnetic anisotropic effects are evidenced from the bridgehead phenyls' proton NMR, with signals ranging from ca. 8.4 ppm for H-2′ to about 7.1 ppm for H-6′, a wide range of shifts for a phenyl that is neither substituted nor conjugated

to other groups. We believe that these effects result, in part, from anisotropy from the phenanthrenoid group as well as the ketone and imide carbonyls. Even more striking magnetic anisotropic effects are seen for the alkyl groups on the N-aryl portion. A rotation of 180° about the N-aryl bond interchanges the inner and outer alkyl groups as a two-site degenerate process, permitting direct comparisons of the proton shifts (and the carbon-13 shifts for **4a**, **4b**, and **4c**) for the alkyl groups in the two environments for each adduct. For the outer alkyl groups, the observed chemical shifts are considered relatively normal, in contrast to the inner alkyl groups with resonances that are substantially shielded by the phenanthrenoid moiety. High level ab initio Hartree–Fock geometry optimizations using the 6-31G* basis sets for the maleimides, **2a–c**, and for the adducts, **3a–c**, of plain phencyclone, were performed, and for the corresponding dibromoadducts, **4a–c**, using the LAV3P* basis sets, and key results have been presented, supporting our picture of these systems as being very hindered.

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