Syntheses of Phencyclone Analogues. Applications for NMR Studies of Hindered Rotations and Magnetic Anisotropy in Crowded Diels–Alder Adducts

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Abstract: Undergraduate organic chemistry special laboratory projects based upon the synthesis of phencyclone, **1** (a potent Diels–Alder diene), and the preparation of a series of highly hindered Diels–Alder adducts of the phencyclone, were described earlier. Details of the synthesis of an analogue of **1** are presented here as an extension of these projects. The analogue, 3,6-dibromophencyclone, **2**, and adducts from a wide range of dienophiles, can be prepared by undergraduate organic chemistry students. These adducts (from **1** or **2**) are eminently suitable for student characterization by NMR to examine aspects of hindered rotation, magnetic anisotropy, and dynamic NMR spectroscopy, using modern one- and two-dimensional multinuclear methods with a medium-field instrument (7 T), to observe ^{1}H, ^{13}C, and ^{19}F. Use of **2** effectively doubles the range of potential target compounds for students. The Diels–Alder adducts (and their precursors) have been studied by molecular modeling methods. This present paper describes the reaction of **2** with **4**, the dienophile *N*-(4-dimethylamino-3,5-dinitrophenyl)maleimide ("Tuppy's maleimide"), to form the adduct **5**. Compound **5** has been well-characterized by 1D and 2D ^{1}H and ^{13}C NMR, and is illustrative of the wide range of adducts that can be made from **2** by students. The structure of **5**, as determined by geometry optimization at the semiempirical (AM-1) level, is included here.

Introduction

For several years, we have studied a series of adducts derived from phencyclone, **1**, a potent Diels–Alder diene. Our interest in these compounds results from their crowded structures, which lead to hindered rotations and striking examples of magnetic anisotropy when the adducts are characterized by medium-field (7 T) nuclear magnetic resonance (NMR) spectroscopy. Preparation of **1**, together with syntheses of varied dienophiles, and formation of a substantial series of the phencyclone-derived adducts have become major components in our two-semester undergraduate organic chemistry laboratory. A 7–8 week "special project" in the second-term laboratory has been implemented in which every student can be assigned unique target adducts. Many of these compounds had not previously been reported in the literature, so that our students enjoyed the excitement of true chemical research, trying to synthesize new compounds. The project has proven to be an exceptionally effective way of introducing concepts of stereochemistry, hindered rotations, and dynamic NMR spectroscopy while focusing on the Diels–Alder reaction, arguably one of the most important reactions for organic chemists. In particular, we have used this project as a basis for presenting modern one-dimensional (1D) and two-dimensional (2D) multinuclear NMR techniques observing ^{1}H, ^{13}C, and ^{19}F. Quite a few students took part in undergraduate research based on these studies following their exposure to the special project in the organic chemistry course; these students have routinely received coauthorships on numerous published and presented research papers describing their investigations. Recently, we have published the special project results based on **1** in two chemical education journals [1, 2] and have presented the results at science education meetings [3, 4].

We report here the synthesis of a symmetrical analogue of phencyclone suitable for preparation in undergraduate organic chemistry laboratories, 3,6-dibromophencyclone, **2**. This substituted derivative of phencyclone is readily prepared from 9,10-phenanthrenequinone, and provides an alternative Diels–Alder diene for potential generation of novel adducts from various dienophiles. Its availability and use essentially double the number of unique target compounds for students in the organic laboratory. The adducts derived from **2**, based on NMR characterization, exhibit fascinating opportunities for NMR studies of hindered rotation and magnetic anisotropy, comparable to those provided by adducts of **1**. More extended details of our results will be reported elsewhere.

This article intentionally focuses on the preparation of a single Diels–Alder diene and a single adduct derived from this diene so that we could provide detailed experimental procedures for their preparations, and extensive discussions of their NMR characterizations. The safe and reliable synthesis of the diene, **2**, doubles the number of accessible target Diels–Alder adducts that can be assigned to students, and complements use of the parent phencyclone itself. In particular, we note here that our attempts to synthesize several

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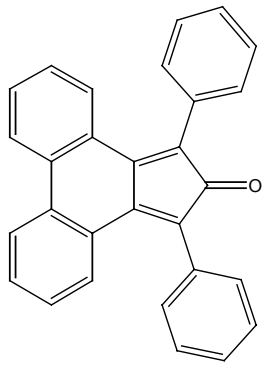

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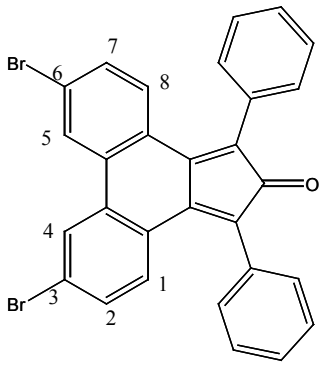

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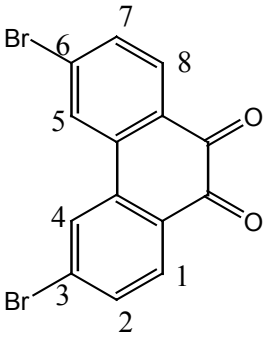

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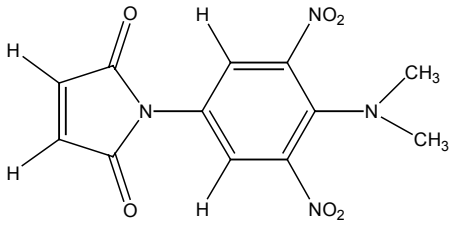

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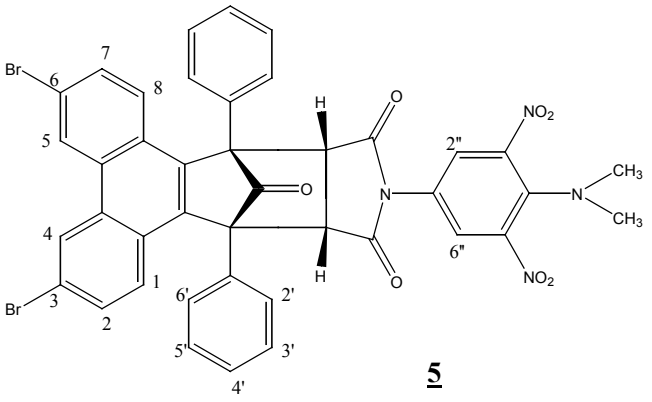

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other symmetrically substituted phencyclones for use as broadly effective Diels–Alder dienes suggested their more limited suitability for undergraduate lab experiments. Alternative dienes, with substituents on the phenanthrenoid moiety (e.g., 2,7-dinitrophencyclone) or with substituents on the phenyl rings (e.g., the 2,2',6,6'-tetrafluoro-, the *para*, *para*'-dimethoxy-, or the *para*, *para*'-dinitro analogues) were found to be more difficult or hazardous to prepare, or gave lower or less pure adduct yields with selected dienophiles, and were less attractive for our purposes. In contrast, 3,6-dibromophencyclone is easily made and has good reactivity with a wide range of dienophiles. We have already synthesized and characterized (by NMR) the Diels–Alder adducts of **2** with *N*-alkyl maleimides (R = ethyl, *n*-propyl, or *n*-butyl), *cis*-2-butene-1,4-diol, *cis*-1,4-diacetoxy-2-butene, and 4-methyl-1,2,4-triazoline-3,5-dione.

Experimental

Many of the solvents and reagents used are TOXIC and HAZARDOUS. Procedures involving these materials should be performed within an efficient fume hood, and appropriate protective garments must be required at all times, including safety goggles and proper chemically resistant gloves. We suggest having sodium bisulfite available (as solid or aqueous solution) to neutralize bromine spills, and sodium bicarbonate to neutralize spills of acetic acid.

Commercial reagents and solvents were obtained from Sigma-Aldrich and were used without further purification. Melting points were determined on a Mel-Temp apparatus.

NMR spectra were obtained on a Bruker ACF300 (7 T) spectrometer, equipped with an Aspect A3000 computer and a "quad nuclear" probe (QNP), at ambient temperatures in 5-mm sample tubes, using standard Bruker microprograms. Proton chemical shifts are expressed in parts per million (ppm) relative to a tetramethylsilane (TMS) internal standard at 0.0 ppm; chemical shifts for ^{13}C spectra recorded in $CDCl_3$ were referenced to the central peak of the solvent signal at 77 ppm. Absorption signals are described as s, d, t, q, dd, or mult to denote singlet, doublet, triplet, quartet, double doublet, or multiplet, respectively. Coupling constants are expressed in Hz. For carbon NMR, CH indicates a methine signal, and Q indicates a nonprotonated (quaternary) signal.

Preparation of 3,6-Dibromophenanthrene-9,10-quinone, 3. In a hood, liquid bromine (31.96 g, 0.2 mol) was weighed into a 500-mL Erlenmeyer flask equipped with a 24/40 standard taper joint. (*CAUTION! Bromine is corrosive! Wear protective gloves and goggles!* The high density and vapor pressure of bromine cause it to drip from pipets.) Nitrobenzene (200 mL) was added to the flask, followed by 9,10-phenanthrenequinone (20.82 g, 0.1 mol). The flask was equipped with a magnetic stirbar and a condenser topped with a drying tube (anhyd calcium sulfate), and heated directly on a hotplate/magnetic stirrer, maintaining the reaction mixture temperature at 100–120 °C. Temperature may be monitored with a thermometer in an aluminum block on the hotplate, and the reaction mixture temperature can be further monitored by intermittently removing the drying tube and carefully lowering a thermometer through the top of the condenser into the reaction mixture. Excessively high temperatures can lead to more highly brominated products. After overnight reflux (ca. 22 h), some light-colored solid was visible at the bottom of the flask, and after cooling to room temperature (ice-slush bath), more solid was apparent. About 100 mL of 3% aqueous sodium bisulfite ($NaHSO_3$) was added through the top of the condenser to remove residual bromine, and the crude solid product was collected by suction filtration, washed with ca. 2 x 50-mL portions of ice water to remove salts. The crude solid product, **3**, was dried on a Büchner funnel (aspirator suction) for 2 h, and then dried overnight between two large sheets of filter paper in a hood. Golden-brownish-yellow crystals of **3**, mp 268–279 °C (dec?), were obtained in 60–70% yield,

and >92% purity (based on proton NMR integrations). This is completely acceptable for use directly in the next step.

^{1}H NMR (300 MHz) in $CDCl_3$: δ = 8.12 (2H, d [^4J = 1.68]), H-4,5; 8.08 (2H, d [^3J = 8.34]), H-1,8; 7.67 (2H, dd [^3J = 8.33, ^4J = 1.66]), H-2,7. In DMSO-d_6: δ = 8.67 (2H, d [^4J = 1.48]), H-4,5; 7.93 (2H, d [^3J = 8.32]), H-1,8; 7.76 (2H, dd [^3J = 8.30, ^4J = 1.44]), H-2,7. ^{13}C NMR (75 MHz) in DMSO-d_6: δ = 177.52 (C=O), 135.79 (Q), 132.63 (CH), 130.70 (CH), 130.63 (Q), 129.84 (Q), 127.62 (CH). In $CDCl_3$: 178.88 (C=O), 135.96 (Q), 133.44 (CH), 132.10 (CH), 129.90 (Q), 127.41 (CH). (Note that the third quaternary aryl carbon signal is coincidently overlapped with one of the methine CH signals.) In mixed solvent (56.5 mg acetone-d_6 with 722.0 mg $CDCl_3$): δ = 178.95 (C=O), 136.09 (Q), 133.48 (CH), 132.11 (Q), 132.05 (CH), 130.00 (Q), 127.59 (CH).

In a synthesis run at smaller scale, liquid bromine (3.19 g 20.0 mmol), nitrobenzene (20 mL), and 9,10-phenanthrenequinone (2.00 g, 9.61 mmol) were sequentially added to a 50-mL flask equipped with a reflux condenser and a drying tube, and allowed to reflux (ca. 100–120 °C oil bath temperature) for 22 hours. After cooling to room temperature and washing with ca. 15 mL 3% aq sodium bisulfite, the crude solid product was collected by suction filtration, washed with ice cold water (2 x 10 mL) and dried (Büchner funnel, aspirator suction). The crude solid appeared to be about 75% pure by NMR integration. Recrystallization of a portion was achieved using glacial acetic acid, about 35 mL acetic acid to 600 mg of sample. Two kinds of product crystals appeared to form, one portion settled to the bottom and the other portion floated. The two portions were separately collected, dried, and examined by NMR spectroscopy, which indicated that they were essentially the same, though the floating portion was slightly cleaner (ca. 90% purity by NMR integration). The overall yield was about 60%, mp 268–279 °C (dec?).

Preparation of 3,6-Dibromophencyclone, 2. In a 500-mL round-bottom flask were placed 3,6-dibromophenanthrene-9,10-quinone (22.02 g, 60.1 mmol, prepared as above), 1,3-diphenylacetone (13.25 g, 63.0 mmol, 5% molar excess), and 250 mL anhydrous methanol. A magnetic stirbar was added, the flask was fitted with a reflux condenser topped with a drying tube, and the reaction mixture was brought to gentle reflux using a heating mantle. While at reflux, a solution of potassium hydroxide (3.2 g) in 12.8 mL methanol was added dropwise through the top of the condenser. After 20 min, the mixture had turned dark greenish-black, and reflux was stopped. The mixture was cooled in an ice slush, and solid was apparent at the bottom of the flask. Suction filtration and drying yielded fine, dark greenish-yellow crystals in a crude yield of ca. 98%, mp 260–268 °C (dec?).

This material was highly insoluble in numerous common NMR solvents (see Discussion below), but a satisfactory proton spectrum could be obtained in $CDCl_3$ using a large number of scans (i.e., 512). NMR (300 MHz): δ = 7.87 (2H, d [^4J = 1.83]), H-4,5; 7.34-7.43 (12H, mult), H-1,8 and phenyls; 7.11 (2H, dd [^3J = 8.46, ^4J = 1.81]), H-2,7. This material appeared to be about 85% pure (by NMR integration), and was satisfactory for subsequent Diels–Alder adduct production.

In a separate run at smaller scale, dibromophenanthrenequinone (198.4 mg, 0.539 mmol), 1,3-diphenylacetone (119.6 mg, 0.569 mmol, 5% molar excess), and methanol (15 mL) were brought to reflux in a 50-mL round-bottom flask equipped with magnetic stirbar, reflux condenser, and drying tube. A solution of KOH (69 mg) in methanol (2 mL) was added dropwise as soon as the reaction mixture came to reflux. After 20 minutes, the dark green-black mixture was cooled (ice bath), and the crude product was collected by suction filtration. The fine, dark greenish-yellow crystals were obtained in about 80% yield after drying, mp 260–268 °C (dec?).

Diels–Alder Reaction of 3,6-Dibromophencyclone, 2, with Tuppy's Maleimide. In a screw-cap vial with a PTFE-lined cap were placed 3,6-dibromophencyclone, **2** (192.8 mg, 0.357 mmol), *N*-(4-dimethylamino-3,5-dinitrophenyl)maleimide ("Tuppy's maleimide", **4**, 125.7 mg, 0.410 mmol), 2,6-di-*tert*-butyl-4-methylphenol (BHT, ca. 2–3 mg), a magnetic stirbar, and sufficient methylene chloride solvent (ca. 15–20 mL) so that the reaction mixture level was about 0.5 cm from the vial lip. The vial was securely capped and stirred at room temperature for 15 min, by which time the dark suspension had almost completely decolorized to a light orange-yellow solution. Solvent removal on a rotary evaporator (aspirator pressure, water bath at 40–50 °C) gave 329.7 mg of crude product (mp 300–305 °C) which was adequate for NMR characterization without further purification. (Observed impurity peaks were mainly attributable to excess **4** and traces of methylene chloride.) The adduct, in contrast to plain 3,6-dibromophencyclone, is quite soluble in $CDCl_3$ (10.1 mg/803mg $CDCl_3$), so that 16 scans were sufficient for a reasonable signal-to-noise ratio. NMR: (^{1}H, 300 MHz, $CDCl_3$): δ = 8.72 (2H, d [^4J = 1.84]), H-4,5; 8.25 (2H, d [^3J = 7.53]), H-2'; 7.74 (2H, t [^3J = 7.65]), H-3'; 7.57 (2H, t [^3J = 7.40]), H-4'; 7.47 (2H, t [^3J = 7.58]), H-5'; 7.38 (2H, dd [^3J = 8.90, ^4J = 1.84]), H-2,7; 7.23 (overlapped with solvent peak) H-6'; 6.99 (2H, d [^3J = 8.98]), H-1,8; 6.43 (2H, s), H-2",6"; 4.63 (2H, s), C<u>H</u> (bridgehead methine); 2.66 (6H, s), N(C<u>H</u>$_3$)$_2$. (^{13}C, 75 MHz,$CDCl_3$): δ = 196.01 (C=O, ketone), 172.50 (C=O, imide), 143.75 (Q), 139.50 (Q), 133.39 (Q), 132.62 (Q), 131.42 (Q), 131.12 (C-2,7), 130.69 (C-6'), 129.66 (C-3'), 129.00 (C-4'), 128.98 (C-5'), 128.80 (C-2'), 127.08 (C-2",6"), 126.99 (C-1,8), 126.27 (C-4,5), 124.95 (Q), 122.96 (Q), 121.03 (Q), 63.52 (<u>C</u>-C=O), 44.67 (<u>C</u>HC=O), 42.09 (N-(<u>C</u>H$_3$)$_2$).

Results and Discussion

The use of symmetrically substituted phencyclones is essential so that the Diels–Alder adducts produced from these dienes will have a mirror plane of symmetry that ensures relatively simple and interpretable NMR spectra for the adducts. 3,6-Dibromophencyclone, **2**, appears to be an excellent choice for student preparation. The precursor of **2** is 3,6-dibromo-9,10-phenanthrenequinone, **3**. We note that the well-defined procedure reported here for synthesis of this precursor is derived from a 1932 German article [5] that provided quite sparse details for an undergraduate procedure. T. J. Katz and co-workers recently cited the earlier article as an efficient route to preparing as much as 185 grams of the 3,6-dibromophenanthrene-9,10-quinone in a single day, but did not present synthetic details or proton NMR data [6]. Actual orientation in 3,6-dibromophenanthrenequinone has rigorously been shown by the chemical transformations used by Katz for helicene synthesis. The orientation obtained on bromination of phenanthrenequinone is surprising, para to the electron-withdrawing carbonyl groups rather than meta. (Indeed, nitration gives the 2,7-dinitro product.) In our present report on the Diels–Alder adducts of dibromophencyclone, the observed very low field (high frequency) chemical shift assigned to H-4,5 of the adduct phenanthrenoid moiety is more consistent with 3,6-dibromo than with 2,7-dibromo substitution, based on the usually modest deshielding (ca. 0.2 ppm) substituent chemical shift effects for aryl bromine upon an ortho proton, and the usual low field position for H-4,5 in phenanthrene systems.

We found that **3** could readily be formed in ca. 75–90% purity (by ^{1}H NMR integrations), which was adequate for the subsequent aldol condensation; recrystallization from glacial acetic acid could improve the purity, if desired. The condensation of crude **3** with 1,3-diphenylacetone to form **2** proceeds in very high yield. The solubility of **2** in common NMR solvents is poor. We tried deuterated chloroform, benzene, acetone, dimethyl sulfoxide, acetonitrile, methanol, and trifluoroacetic acid, and observed very limited solubility.

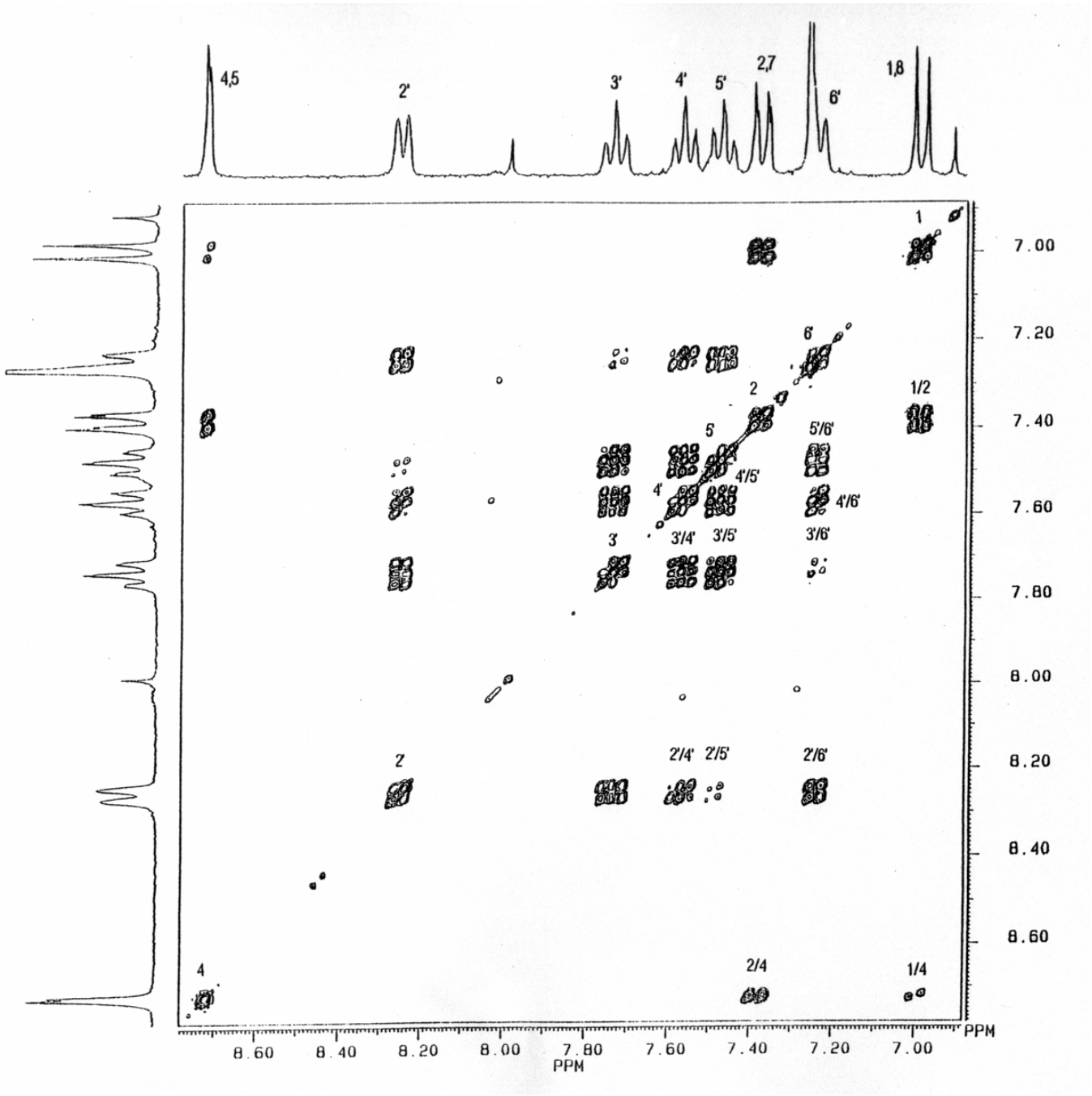

Figure 1. COSY45 spectrum of aromatic region of adduct **5**, 10.1 mg in 803 mg $CDCl_3$. For each of the 256 increments in t_1, two dummy scans and eight transients were acquired. Zero-filling once in both dimensions gave a final data matrix size of 1024 × 512. Data were processed with an exponential line broadening of 2 Hz and unshifted sine-bell apodization in both dimensions. Spectra were in the magnitude mode and were symmetrized. Standard Bruker microprograms, COSY.AU, were used. For this "high resolution" COSY45 spectrum, the spectral window was limited to the aryl region, ca. 6.9–8.8ppm (571 Hz). Note that crosspeaks corresponding to long-range couplings are seen.

An acceptable proton spectrum was obtained in $CDCl_3$ using 512 scans, but we could not get acceptable ^{13}C spectra, even with overnight accumulations (more than 13,000 FIDs acquired). Solubilities of the Diels–Alder adducts of **2** were better, allowing more extensive NMR characterization. The intermediate **3** is appreciably more soluble than **2**, so that the ^1H and ^{13}C NMR spectra were readily obtained using $CDCl_3$ or dimethyl sulfoxide-d_6. Interestingly, in $CDCl_3$, there is a coincidental overlap of two of the six aryl carbon signals of **3**, so that only five resonances are observed in the usual 120–140 ppm region. Addition of a few drops of acetone-d_6 to the $CDCl_3$ solvent (2.4 mg **3** in 722 mg $CDCl_3$ containing 57 mg acetone-d_6) broke the signal degeneracy to reveal all six aromatic carbon signals. With dimethyl sulfoxide-d_6, all six aryl carbon signals are resolved, but an apparent impurity in the solvent led to some interfering peaks; shorter relaxation delays of ca. 3 s suppressed these impurity peaks.

We note that the starting point for making the parent phencyclone and for the substituted derivative, **2**, reported here, is 9,10-phenanthrenequinone. We routinely used material

sold as 99+% pure (Sigma-Aldrich), but it might be possible to economize by starting with less-pure material, such as technical grade. Methods for purification of phenanthrenequinone as the bisulfite-addition compound have been described [7]. This potentially could be incorporated into the student project.

The formation of Diels–Alder adducts with the phencyclone analogue typically used a small molar excess of the dienophile so that completion of the addition reaction could be indicated by the near-decolorization of the phencyclone analogue. The slightly impure crude adducts were often acceptable for student use in NMR characterization and evaluation of hindered rotations, or the adducts could generally be recrystallized to higher purity. For reactions run at room temperature, we used screw-cap vials filled almost to the brim with solvent; our intention was to minimize the amount of atmospheric oxygen in the headspace of these mixtures. In some reactions of phencyclone or analogues, especially with slow-reacting dienophiles, we recovered 9,10-dibenzoylphenanthrene (from **1**) or 3,6-dibromo-9,10-dibenzoylphenanthrene (from **2**). It has been suggested that these are derived from an oxidative decarbonylation pathway, presumably involving free radicals; see Reference 1 and articles cited therein. We recommend addition of a trace of a free-radical trap, such as BHT or BHA, during the formation of the adducts, which might be expected to retard such oxidative pathways, and minimize other possible side-reactions, such as free-radical polymerization of the dienophile. Possible student miniprojects might explicitly explore the efficacy of these free-radical traps for reactions of specific dienophiles with **1** or **2**.

We have found that *N*-(4-dimethylamino-3,5-dinitrophenyl)maleimide, known as *Tuppy's maleimide*, **4**, is an efficient dienophile for phencyclone and analogues. With **2**, it readily forms the adduct, **5**. This adduct exhibits a striking example of magnetic anisotropic shielding in its proton NMR ($CDCl_3$ solution), with the *N*-aryl protons of **5** resonating at 6.43 ppm (2H, s) compared to their position at 7.99 ppm in **4** itself. The shielding in the adduct is attributed to endo stereochemistry of the Diels–Alder adduct, placing the *N*-aryl group in the shielding region of the phenanthrenoid moiety. The 2D COSY45 experiment for homonuclear proton–proton chemical shift correlation readily allows assignments for all the proton signals of adduct **5**. Figure 1 shows the 2D COSY45 spectrum of **5** with the assignments for the crosspeaks. No coincidental proton signal overlaps were observed. In addition, the proton signals for the starting material, **4**, are also well separated, with absorptions at 7.99 (2H, s, aryl H), 6.92 (2H, s, vinyl HC=CH), and 2.84 (6H, s, NMe_2) ppm.

^{13}C NMR spectroscopy of **5** in $CDCl_3$ was performed with short (3-s) and long (60-s) relaxation delays. With the short relaxation delays, nonprotonated (quaternary) carbons exhibit reduced signal intensity (peak heights or areas) relative to protonated carbons. The latter carbons showed peak areas roughly in proportion to their relative numbers. With the long (60-s) relaxation delay, nonprotonated carbon signals often approach the response from protonated carbons, making it easier to directly observe peaks from the nonprotonated carbons, which might otherwise exhibit a response as little as 10–20% of that from protonated carbons. DEPT (distortionless enhancement by polarization transfer) spectra can also be used for rigorous distinction of quaternary carbons, and methine (CH), methylene (CH_2), and methyl (CH_3) groups. Despite the lower sensitivity and longer experiment time for the plain 1D ^{13}C spectra (especially with long relaxation delays) versus the faster DEPT experiments, there is some real pedagogic value to obtaining the simple ^{13}C spectra, for this allowed direct observation of the quaternary nonprotonated carbons, which are not detected by DEPT. In fact, the different experiments are most appropriately considered as complementary, since the DEPT subspectra allow distinguishing the different carbon classes, and the relative speed of DEPT spectroscopy allows more students to acquire spectra of their samples. Residual Tuppy's maleimide in our crude adduct sample showed protonated carbon signals at 126.16 and 134.56 ppm (for the sp^2 carbons) and at 42.24 ppm (for the methyl groups). We were able to largely assign all the protonated carbon resonances in the adduct by using 2D heteronuclear chemical shift correlation (HETCOR, XHCORR) spectroscopy. The resulting spectrum is shown in Figure 2. Adduct carbons 4' and 5' gave nearly isochronous signals (128.9846 and 128.9996 ppm), with valley height about 95%, but their crosspeaks for the directly bound protons are resolved. Nine crosspeaks for the aryl methines are seen, consistent with slow-exchange-limit rotation of the two unsubstituted bridgehead phenyls in the adduct, and fast-exchange-limit rotation of the *N*-aryl ring, on the NMR timescale. Note that for the *N*-aryl ring of the adduct, the simple protons (H-2",6") are not large enough to retard ring rotation past the imide carbonyls (at ambient temperatures), although for the bridgehead phenyls, which are more profoundly hindered by the phenanthrenoid H-1,8, slow rotation on the NMR time scale is observed (for proton and carbon). The expected 11 other carbon signals from the nonprotonated carbons of the adduct were also observed. At lowest field was the strained ketone carbonyl (196.01 ppm), with the imide carbonyls at higher field (172.50 ppm). In the high-field region, at 63.53 ppm, was the resonance for the benzylic sp^3 bridgeheads. The adduct structure exhibits eight nonprotonated aryl carbon resonances, but no attempt has been made to assign them by other NMR experiments. Lastly, we note that we have performed a 2D HETCOR experiment on Tuppy's maleimide itself (results not shown). Somewhat surprisingly, we found that the lower-field proton signal (7.99 ppm) correlated to the higher-field sp^2 carbon signal (126.16 ppm), and the vinyl proton signal (6.92 ppm) correlated to the lower-field carbon signal (134.56 ppm).

Previous reports have described the synthesis and NMR characterizations of a number of hindered Diels–Alder adducts derived from phencyclone with a series of diverse dienophiles [8–17]. Slow-exchange-limit spectra were found for ^1H and ^{13}C NMR (7 T, ambient temperatures) for the unsubstituted bridgehead phenyls. Several examples are included for the fluorine-containing compounds, providing the opportunity for students to use ^{19}F NMR. We have already successfully prepared several of the corresponding analogues from 3,6-dibromophencyclone; the results are being submitted elsewhere. Compound **2** appears quite promising as an effective Diels–Alder diene for undergraduate experiments.

While in principle most of the adducts we have prepared could have formed with either endo or exo stereochemistry, we have not routinely encountered clear evidence for formation of the stereoisomeric exo Diels–Alder adducts from reaction of dienophiles with **1** or **2**. Since the key goal in these studies was

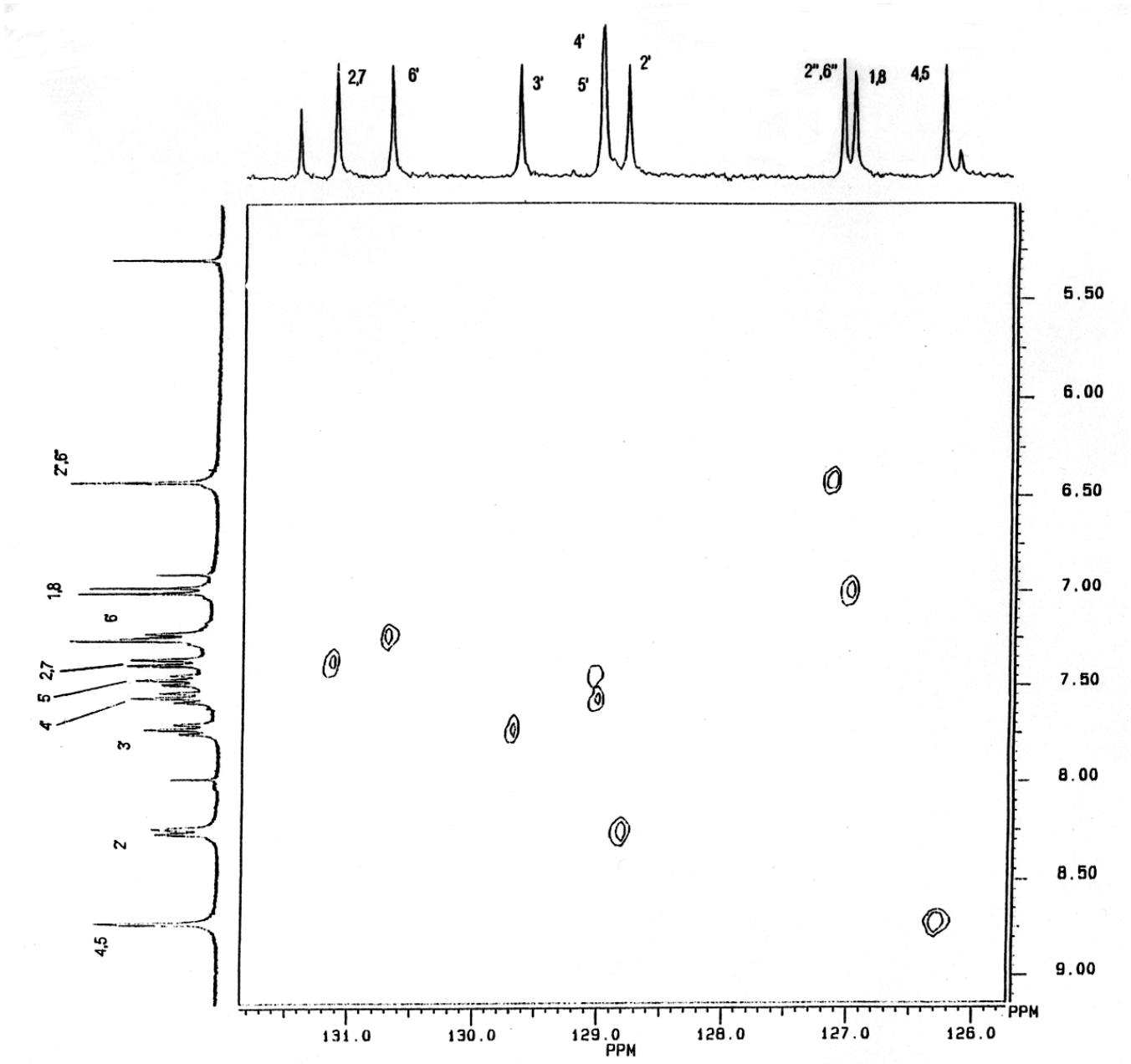

Figure 2. The Bruker microprogram XHCORR.AU was used for the one-bond ^{13}C–^{1}H chemical shift correlation experiment of adduct **5**. The ^{13}C spectral width was 7463 Hz over 4K points (the carbonyl region was omitted), for a digital resolution of 3.6 Hz/point in the f_2 (carbon) dimension. For the proton (f_1) dimension, two dummy scans and 256 transients were acquired for each of 128 increments in t_1. The proton spectral window was 2492 Hz (ca. 0.8–9.1 ppm). Zero-filling twice in the f_1 dimension gave a final data matrix size of 4096 x 512. Data were processed using a sine-bell window function in f_1 shifted by 18° (SSB = 10), and an unshifted sine-bell function for f_2. An exponential line-broadening of 2 Hz was used in each dimension. An expansion of the aryl region is shown.

to define suitability for undergraduate laboratories, NMR studies were overwhelmingly directed toward examination of the crystalline fractions that formed by gradual concentration of the reaction mixtures (or by recrystallization of the crude solid products) when decolorization of the mixture indicated disappearance of the initial diene. The possibility of small amounts of exo isomers in the mother liquors from these cycloadditions can not be ruled out. When solvent was completely removed from the reaction mixtures from different dienophiles for preliminary proton NMR spectra of the crude product mixtures, the anticipated second sets of peaks for the isomeric Diels–Alder adduct were certainly not apparent for the great majority of the dienophiles we tested. For maleimide-type dienophiles, observation of the sharp singlets assigned to the bridgehead methines in the pyrrolidinedione ring of the adducts (ca. 4–5 ppm) should allow facile detection of the isomer, since this spectral region was generally free from interfering peaks. A minor isomer (3–5%) should have been detectable. Recent X-ray crystal structure studies in this series showed endo stereochemistry [18]. Earlier studies of **1** as a Diels–Alder diene addressed stereochemistry and possible reversible adduct formation, but did not observe the striking hindered rotations of the unsubstituted bridgehead phenyls in

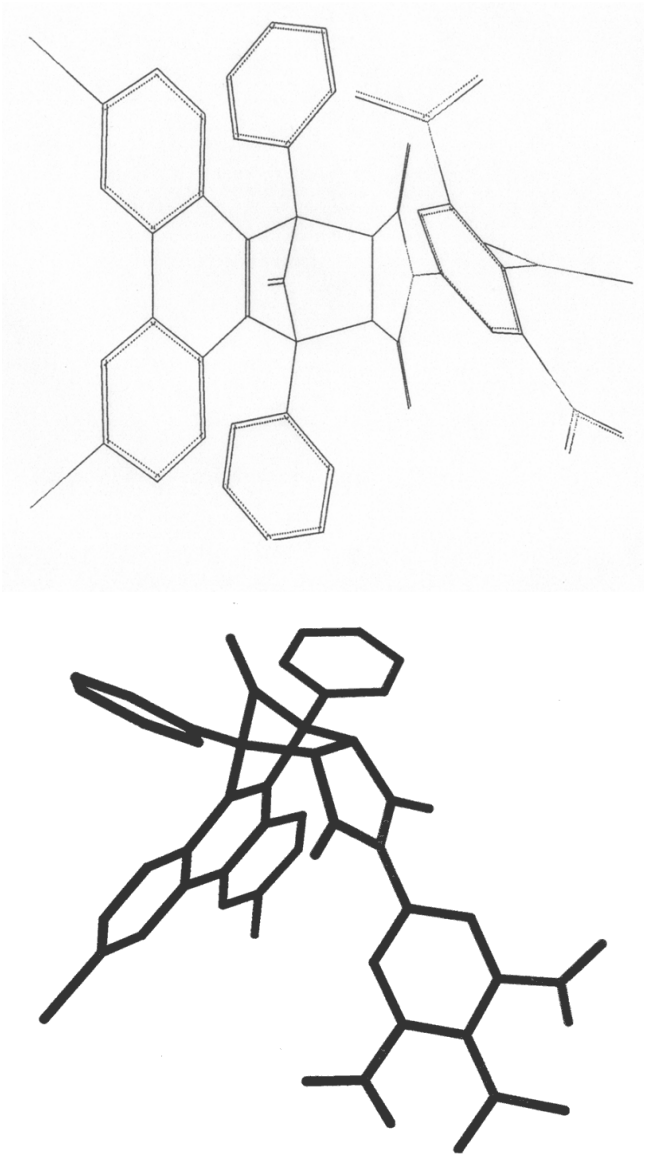

Figure 3. Representative views of adduct **5**, geometry optimized at the AM-1 level using the MacSpartan version 1.1 (semiempirical program: release 1.0) from Wavefunction Inc., Irvine CA 92612 (1996) running on a Power Macintosh 9500/200 (200-MHz CPU, 32 MB RAM, virtual memory on). The structure converged to a heat of formation of 146.647 kcal/mol in about 2.5 hours. For clarity, hydrogens have been omitted. (Atomic coordinates available on request.)

the adducts because of the low NMR spectrometer field strength and the resulting limited dispersion [19].

We have also used these compounds for molecular modeling studies, to gain an appreciation of potential interactions in these crowded systems, and to offer students the opportunity to integrate molecular modeling calculations with the experimental work of synthesis and spectroscopy. While the full adducts of **1** or **2** are rather large for ab initio calculations, we have completed some theoretical studies at the Hartree–Fock 3-21G* and 6-31G* levels using smaller model compounds [20] to examine the energetics of aryl group rotations. For semiempirical calculations at the AM-1 level, the full adduct structures can easily be optimized; representative structures for compound **5** are presented in Figure 3, based on the MacSpartan or PC Spartan packages (Wavefunction, Inc., Irvine, Calif.). Molecular modeling examination of **5** is especially interesting for students because of the substantial degree of crowding among many of the groups, involving nonbonded interactions and potential hindered rotations, influencing conformations of the bridgehead phenyls, the *N*-aryl imide group, and the dimethylamino and nitro groups of the *N*-aryl ring.

Conclusions

We have presented details of the synthesis and characterization of a versatile Diels–Alder diene, 3,6-dibromophencyclone, **2**. This diene is capable of forming Diels–Alder adducts with a wide range of dienophiles. Preparation and NMR studies of **2** and its adducts are very suitable for undergraduate organic chemistry students. The use of **2** is exemplified by its reaction with Tuppy's maleimide. The resulting adduct **5**, described here, exhibits slow-exchange-limit ^{1}H and ^{13}C NMR spectra (7 T, ambient temperatures) for the unsubstituted bridgehead phenyls, and fast-exchange-limit spectra for the *N*-aryl ring. Examples of 2D homonuclear and heteronuclear chemical shift correlation spectra for **5** are provided. Applications for molecular modeling studies by students are also described.

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