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Laboratories and Demonstrations

Synthesis of Diels–Alder Adducts of Phencyclone and NMR Studies of Hindered Rotations of Unsubstituted Bridgehead Phenyls: Microscale Experiments in Organic Chemistry

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…although this kind of "first-time-ever" innovative group of experiments puts tremendous demands on the instructors, the rewards are great and the excitement is infectious.

Synthesis of Diels–Alder adducts of phencyclone with diverse dienophiles provides the basis for a major extended module in the second-semester laboratory of an organic chemistry course. With many accessible target compounds, students can have individual novel compounds to prepare. Especially attractive for students, the adducts are highly hindered, resulting in slow rotation about the C–C sp^2–sp^3 single bond to the unsubstituted bridgehead phenyl groups. Slow-exchange-limit NMR spectra (^{1}H at 300 MHz and ^{13}C at 75 MHz) are obtained at ambient temperatures for these phenyl groups. The highly crystalline products are easily prepared and offer excellent opportunities to integrate modern 1-D and 2-D NMR techniques into this synthesis

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experiment, while introducing concepts of dynamic NMR spectroscopy. The synthetic reactions are readily carried out at the microscale level.

Background

Recently, following some earlier research in our laboratories, we have introduced a new major component in the second-semester laboratory of our year-long organic chemistry course. The module, about 8 weeks long, has provided an effective and highly rewarding laboratory experience for participating students and instructors. The module is based upon a series of microscale or semimicroscale organic syntheses of a rather diverse series of novel, highly hindered compounds. A sufficient number of target compounds have proven to be readily available from easily prepared or commercially available precursors, making individual synthetic goals possible for every student in a group of 15–20. Students can have several possible compounds as synthetic goals, or may individually employ distinct, different procedures to try to determine preferred conditions. Most of the target compounds appear to have been previously unreported, so we did not have "guaranteed" assurance of success, but an emphasis was placed on the class as a whole preparing the new compounds, even if an individual student's reaction might prove unsuccessful. The positive results obtained prompt this present report.

Phencyclone, **1** (Figure 1), is an effective diene component for the Diels–Alder reaction, and is reported to react via [4+2] cycloaddition with a wide range of dienophiles, with both electron-poor (normal Diels–Alder) as well as electron-rich dienophiles (inverse-electron-demand Diels–Alder) [1]. Simple syntheses of phencyclone have been reported as especially suitable for students [2–4], and it is commercially available (Lancaster Synthesis). We have incorporated a student synthesis of **1**, via KOH-promoted condensation of 9,10-phenanthrenequinone with 1,3-diphenylacetone in refluxing methanol, into this experimental module.

Earlier, in studies of the adduct of norbornadiene with **1**, we had concluded that there was remarkable steric hindrance in the adduct, leading to slow rotation of the unsubstituted bridgehead phenyls about the C–C sp^2–sp^3 bonds [5, 6]. The hindered rotation resulted in slow-exchange-limit (SEL) NMR spectra using medium-field instruments, initially at 200 MHz for ^{1}H (50 MHz for ^{13}C) and later at 300 MHz for ^{1}H

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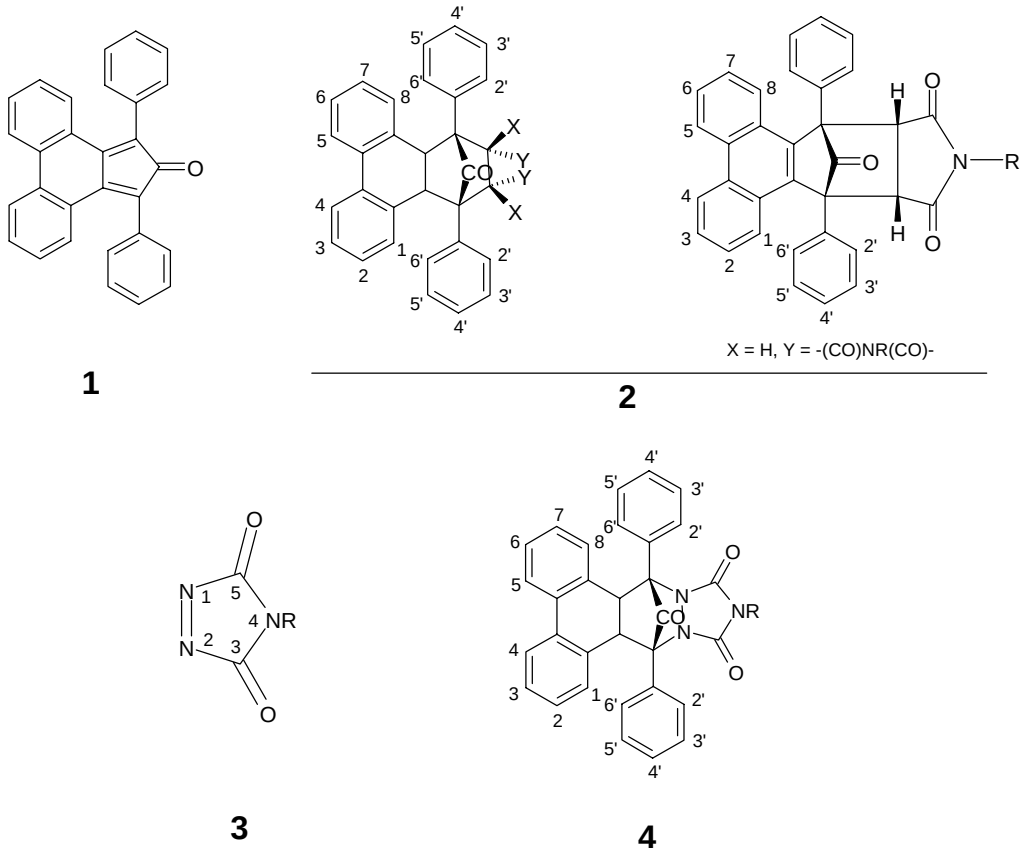

FIGURE 1. PHENCYCLONE: 1; GENERALIZED ADDUCT OF PHENCYCLONE WITH "ALKENE-TYPE" DIENOPHILE:2 (LEFT) AND WITH MALEIMIDE: 2 (RIGHT); 1,2,4-TRIAZOLINE-3,5-DIONE: ADDUCT OF 1 AND 3: 4.

(75 MHz for ^{13}C). The low-field (1.4 Tesla, 60 MHz for ^{1}H) spectrometers used for earlier characterization of these Diels–Alder adducts of **1** had insufficient dispersion to make the slow-rotation phenomenon clear [1–3, 7]. With medium-field FT-NMR spectrometers (200–300 MHz for ^{1}H) increasingly available for undergraduate organic chemistry laboratories, examination of these adducts and interpretation of the spectra provide an exceptionally rich experience for students to consider the physical organic chemistry aspects associated with rate processes of hindered rotations, and concepts of dynamic NMR. Further, while the one-dimensional (1-D) ^{1}H NMR spectra of these compounds may at the outset appear intimidating, some two-dimensional (2-D) spectral techniques such as ^{1}H-^{1}H chemical shift correlation spectroscopy (COSY) can provide such dramatic and facile interpretation that students gain a wonderful opportunity to appreciate the use of 2-D NMR techniques that are, too often, inadequately addressed in the basic course (see references cited in the Appendix 32rr1897.pdf).

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Inspection of simple Dreiding stereomodels (Brinkmann Instruments) suggests that hindered bridgehead phenyl rotation could have its origin in repulsions between the ortho protons (H2′ and H6′) of the phenyl groups, and H1 and H8 of the phenanthrene moiety in the adducts of **1**. Closest approach distance appears to be as little as 0.1–0.2 Å. These repulsions could be avoided if the bridgehead phenyls adopt a conformation roughly perpendicular to the phenanthrene moiety. With slow rotation, the asymmetry of the environment can result in nonequivalence of the two ortho positions (2′ and 6′); likewise the two meta positions (3′ and 5′) can become nonequivalent. This could potentially lead to anisochrony (different chemical shifts) for these nuclei (^{1}H or ^{13}C NMR) if the spectrometer has adequate dispersion. Note that rapid phenyl rotations interchange (and could render equivalent) the two ortho positions, 2′ = 6′, as well as the meta positions, H3′ = 5′. Fast-exchange-limit (FEL) spectra would show these nuclei as isochronous (and with double intensity).

Incidentally, it is noteworthy that in addition to using powerful NMR methods to demonstrate adduct structure, infrared (IR) spectroscopy provides a quick and convenient indicator of successful Diels–Alder adduct formation. The bridging carbonyl in the desired products characteristically produces a strong, high-frequency absorption (ca. 1780-1805 cm^{-1}) for the C=O in a strained ring. Presence of this band demonstrates that decarbonylation has not occurred.

Although our first studies of these adducts involved norbornadiene as the dienophile [5, 6], use of norbornadiene does not provide the simplest case to study the adducts. It is actually a somewhat more complex system since the issues of exo vs. endo stereochemistry in the adduct arise with respect to both Diels–Alder components; there are formally four possible diastereoisomeric products. Subsequently, we have focused on phencyclone adducts with simpler, planar dienophiles, so that only a single pair of product stereoisomers is possible. These generalized adducts and the positional numbering used here are represented in structure **2** (Figure 1). The proton NMR studies were reported a few years ago for adducts from maleic anhydride [8] and 1,4-benzoquinone [9]. More recently, NMR studies have been published of adducts of phencyclone with *N*-propylmaleimide [10], *N*-butylmaleimide [11], *N*-carbamoylmaleimide [12] and 4-methyl-1,2,4-triazoline-3,5-dione [13]. (Please see the Appendix (32rr1897.pdf) for listings of other adducts of phencyclone.)

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The Student Laboratory Project

For the student laboratory project, a wide assortment of potentially suitable, simple Diels–Alder dienophiles are commercially available; use of different dienophiles can provide unique phencyclone adducts for each laboratory student. We suggest that a crucial consideration in selection of potential dienophiles should be sufficient symmetry that the product possesses a mirror plane of symmetry. If this holds true, the two bridgehead phenyls will be enantiotopic and one half of the phenanthrene moiety will be the mirror image of the other half (i.e., equivalent nuclei at positions 1 and 8, 2 and 7, 3 and 6, and 4 and 5). The mirror plane in the adducts greatly simplifies the resulting spectra and vastly aids interpretation.

Selection of diverse dienophiles leads to a wide range of reactivity with **1**. We had the students set up scouting runs, setting up reactions on a ca. 1.0-mmol scale using methylene chloride as the solvent in screw-cap vials that were capped (PTFE cap liners) and magnetically stirred at ambient temperature. The volatility of methylene chloride permits its facile removal and avoids possible ^{1}H or ^{13}C NMR spectral interferences in the aryl region that would typically result if benzene, toluene, or xylene were used as solvent. In some cases, it appears that phencyclone adducts prepared in aromatic solvents (benzene or toluene) often contain some solvent of crystallization. We have not observed this to be as troublesome with methylene chloride. Phencyclone is intensely colored (green–black) and has limited solubility in methylene chloride. Using the dienophile in a few percent molar excess allows the discharge of the phencyclone color to serve as a convenient indicator for the reaction's completion. If each student sets up 2–4 different reaction mixtures (using different dienophiles or solvents), the class can be rewarded by the gradual disappearance of the green-black color over the next couple of months. Productive discussions can be held to try to rationalize relative reactivities of different dienophiles.

In addition to having students apply a shotgun approach to discovering a broad range of suitable dienophiles, we simultaneously had students concentrate their efforts upon a more narrowly defined series of dienophiles. The students used an extended series of *N*-alkylmaleimides, either synthesized themselves or purchased commercially. There were several reasons for this. We had observed that simple *N*-alkylmaleimides react rapidly with **1** in CH_2Cl_2 at room temperature, often within a couple of hours or appreciably faster. Several of the simplest *N*-alkylmaleimides can be purchased, including the *N*-methyl, *N*-ethyl, *N*-propyl, *N*-butyl, *N*-*tert*-butyl, and *N*-cyclohexyl

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analogues. We have had our students prepare many others (Appendix 32rr1897.pdf). Noting that the preparation of *N*-phenylmaleimide (and its use as a Diels–Alder dienophile) has been used as an undergraduate experiment [14], we initially had students follow a modified procedure to make *N*-alkylmaleimides.

Lower primary alkylamines react almost instantly with solutions of maleic anhydride in CH_2Cl_2 (somewhat exothermically, so ice-bath cooling is useful). Although the intermediate, *N*-phenylmaleamic acid, and the product, *N*-phenylmaleimide, crystallize easily, the corresponding *N*-alkyl compounds appear less willing to do so, presumably because of their lower melting points. However, the crystalline *N*-alkylmaleamic acids can be isolated (if desired) by thorough removal of CH_2Cl_2 (rotary evaporator, aspirator pressure) since the reaction of amine and maleic anhydride seems both quantitative and fast. Following CH_2Cl_2 removal, the dehydration and cyclization of the maleamic acids to the desired *N*-alkylmaleimides is achievable by the addition of excess acetic anhydride with anhydrous sodium acetate and gentle warming (hot water bath). At this stage there is a significant difference between the *N*-phenylmaleimide (which easily crystallizes on workup) and the diverse *N*-alkylmaleimides we prepared. The *N*-alkylmaleimides are typically low-melting solids (e.g., mp 20 °C for *N*-butylmaleimide).

Although purification via (aspirator) vacuum fractional distillation is probably practical for several of these analogues, this can be a slow and tedious technique for the undergraduate organic chemistry laboratory. While elegant PTFE spinning band columns [15] are available (Ace Glass) for the microscale laboratory, providing enough equipment for a laboratory section would be expensive. We decided to use the crude *N*-alkylmaleimide oils directly for reaction with phencyclone following a brief series of washings and extractions to get rid of expected likely contaminants (e.g., unreacted amine, acetic anhydride, acetic acid, sodium acetate, and maleamic acids). Portions of the *N*-alkylmaleimide oils, along with portions of crystalline *N*-alkylmaleamic acids, were reserved for NMR and IR (NaCl plates or 3M disposable IR cards) characterization.

The virtue of the *N*-alkylmaleimide analogues as a series is that they react rapidly with phencyclone. Even the crude oils can be roughly titrated against the phencyclone by adding portions batchwise and awaiting gross decolorization. Often as little as 15 min is sufficient for reaction. After the consumption of phencyclone, we find that gradual

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solvent evaporation and scratching with a glass rod usually resulted (after filtration, washing, and recrystallization) in modest yields of light-to-white-colored crude adducts that were directly usable for NMR studies. Thus, the oily liquid nature of the crude *N*-alkylmaleimides could simplify their being washed from the crystalline Diels–Alder adducts. The light color of the adducts confirms the removal of **1**.

We found that a few primary amines reacted slowly, or not at all, with maleic anhydride. For example, pentachloroaniline appeared intractably unreactive, even when melted directly with maleic anhydride in the absence of solvent. Evidently, steric and electronic effects of the pentachlorophenyl group render the nitrogen essentially nonbasic and nonnucleophilic. In contrast, pentafluoroaniline reacted exothermically in CH_2Cl_2 at ambient temperatures, and the resulting maleamic acid was cyclized with acetic anhydride containing anhydrous sodium acetate simply by heating for 0.5 hour in a hot water bath. We also examined a few other compounds as sources of possible *N*-alkylmaleimides, including 2,2,2-trifluoroethylamine hydrochloride. (Fluorinated target compounds were of interest for ^{19}F NMR studies. See Appendix 32rr1897.pdf.) The one constraint we employed in selection of alkylamines for potential conversion to *N*-alkylmaleimides was to avoid chiral centers in the alkyl group, since this could potentially break the desired symmetry (mirror plane) in the target adducts, leading to added spectral complexity.

Another part of the synthesis module aimed to produce phencyclone Diels–Alder adducts derived from 4-alkyl-1,2,4-triazoline-3,5-diones, **3** (Figure 1). The heterocycle, 4-phenyl-1,2,4-triazoline-3,5-dione has been prepared by oxidation from 4-phenylurazole using lead tetraacetate at 0–5 °C [16], *tert*-butyl hypochlorite [17, 18], or *N*-bromosuccinimide [19]. The first method, using commercially available 4-alkylurazoles in CH_2Cl_2, seemed most attractive as an undergraduate procedure. The product triazolinediones can exhibit extraordinary reactivity as Diels–Alder dienophiles. We were able to have students try several variations of reaction conditions to make the *N*-methyl or *N*-*tert*-butyl-1,2,4-triazoline-3,5-diones for reaction with phencyclone; 4-methyltriazolinedione is commercially available (Aldrich Chemical). The near-instant discharge of the phencyclone color under selected conditions seemed to confirm the high reactivity of these dienophiles.

The resulting adducts, **4** (Figure 1), were of special interest to us since they provide systems in which the tetrahedral sp^3-hybridized bridgehead methines α to the imide

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carbonyls (present in the maleimide adducts) are replaced by nitrogen atoms. If these bridgehead nitrogen atoms are nearly planar in the triazolinedione adducts, then the imide ring moiety, $RN(CO)_2$, should be further from the phenanthrene moiety compared with the expected geometry in the maleimide adducts of **1** (with the usual endo stereochemistry of **2**). If the bridgehead nitrogen atoms were pyramidal rather than planar, students could consider the implications of possible slow or fast inversion of configuration at these potential stereocenters. Fast nitrogen inversions on the NMR timescale would be expected to produce a single set of NMR signals for a mixture of rapidly interconverting endo and exo adducts, i.e., a fast-exchange-limit (FEL) system. With higher energy barriers to nitrogen inversion, observation of two distinct sets of NMR resonances for the endo and exo isomers should be expected (for an SEL system), with the possible formation of one or both isolable products depending on inversion rates and reaction conditions. Indeed, a group of workers has reported obtaining the endo product at ambient temperatures (from 4-phenyl-1,2,4-triazoline-3,5-dione and phencyclone), which was converted to exo material at elevated temperatures [20], but these workers may have relied, in part, on unconventional IR assignments. The X-ray structure of a Diels–Alder adduct of 4-phenyl-1,2,4-triazoline-3,5-dione indicated pyramidal bridgehead nitrogen atoms [21].

In the NMR studies of phencyclone adducts derived from *N*-alkylmaleimides or triazolinediones, we have observed rather dramatic examples of magnetic anisotropy in these compounds. Comparing ^{1}H NMR chemical shifts in the adducts to those in, for example, phenanthrene and the *N*-alkylmaleimides (as reference compounds), we have seen: (a) substantial shielding of the adduct's phenanthrene-moiety protons (H1, H8, H2, and H7) due to their location in the bridgehead phenyl's shielding cone; (b) deshielding of one of the phenyl ortho protons, presumably resulting from anisotropy or steric compression (van der Waals effect) due to the strained bridging carbonyl or the proximal carbonyls in the heterocyclic ring derived from the dienophile (in the presumed favored conformations); and (c) shielding of 1.5–2 ppm for some *N*-alkyl group protons that lie in the shielding region of the phenanthrene moiety for the adducts of **1** with substituted maleimides, supporting the expected endo stereochemistry.

We found that most simple *N*-alkylmaleimides (with alkyl groups that did not produce excessive steric hindrance or unusual electronic problems) seemed to react with phencyclone fairly quickly, within 1 hour or less. However, for nonmaleimide

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dienophiles, the reactivity with phencyclone may not be known in advance, and may be substantially slower. We recommend that students set up each reaction mixture to be tested (phencyclone–dienophile mixture) in tightly capped screw-cap vials (PTFE-lined cap), clearly labeled to show the dienophile structure and the date the reaction began. These vials should be set up at the earliest possible opportunity in a "public" (fume hood) area of the lab so that students can routinely follow the progress of the reaction in each vial (via phencyclone decolorization) at the start of each laboratory period. Several minutes of commentary generated by the students and instructor during each laboratory period can address the relative dienophilicity suggested by the observed rates of color discharge in each mixture. It is quite intriguing for students to observe the slow and gradual reaction of a mixture that may have initially exhibited no sign of decolorization. Even slow reactions that may require months for full completion offer considerable insight and stimulation.

In passing, we note that with respect to potentially slow-reacting dienophiles, some students have isolated 9,10-dibenzoylphenanthrene from reaction mixtures in which the green-black phencyclone color was discharged over a period of days or weeks. Infrared spectra ($CHCl_3$ solution) provide the tip-off: the desired Diels–Alder adducts exhibit the strong 1780–1790-cm^{-1} band of the strained ring carbonyl, as noted above. The 9,10-dibenzoylphenanthrene lacks this distinctive band, and shows a very strong absorption at 1666–1670 cm^{-1} (diaryl ketone). Indeed, a sample of phencyclone in benzene without added dienophile was decolorized after stirring at room temperature for eight days, providing a ca. 15% isolated yield of 9,10-dibenzoylphenanthrene. It appears that this may be the result of oxidative decarbonylation due to reaction with oxygen. While this side reaction should be avoidable by running the phencyclone reactions under an inert atmosphere (nitrogen or argon), this is probably an unnecessary complication. The problem does not arise if fast-reacting dienophiles are employed. It very likely can be minimized when running the Diels–Alder reactions in screw-cap vials if enough solvent is added so that there is minimal head space over the reaction mixture; with little trapped air in the vial, the oxidation side reaction should be prevented. A possible mechanism for this oxidative decarbonylation is described in the Appendix (32rr1897.pdf).

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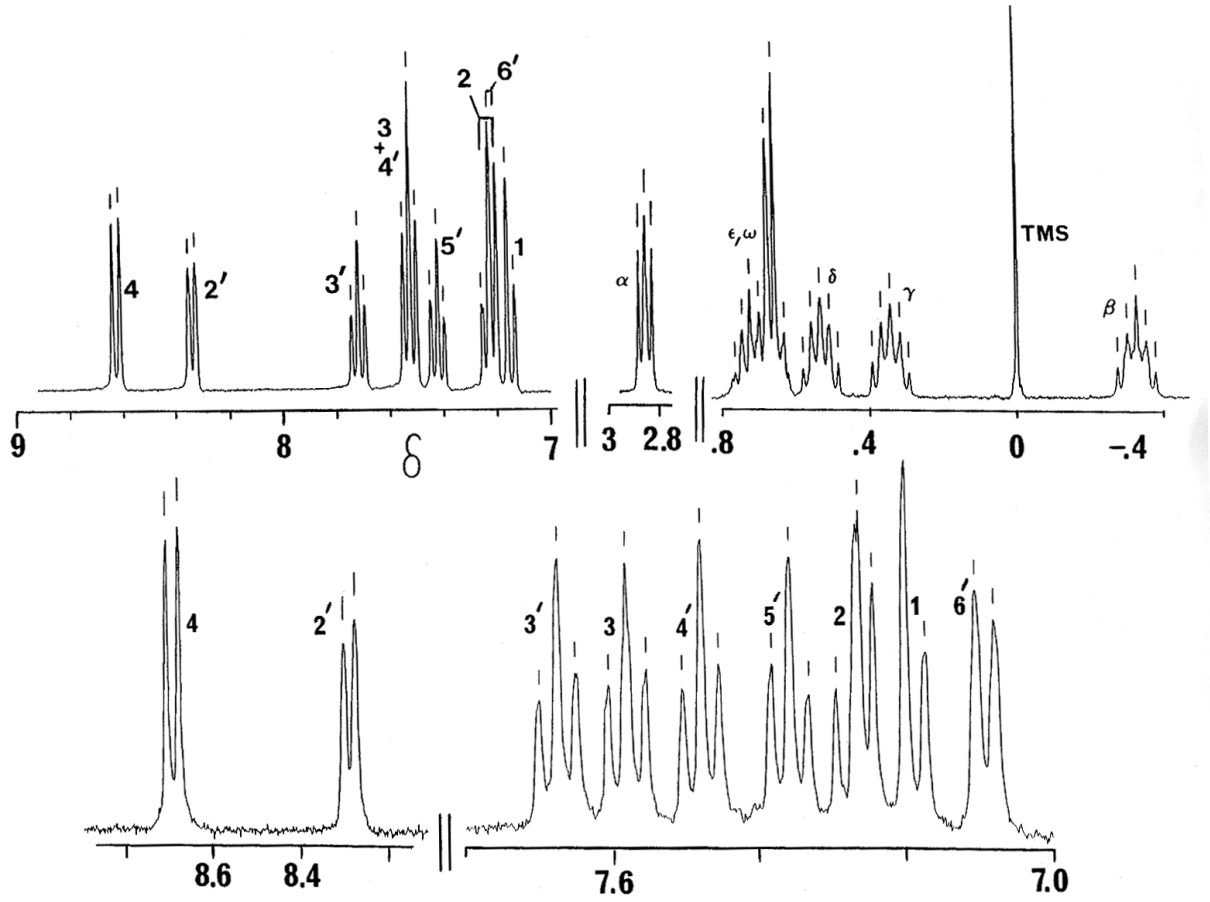

FIGURE 2. EXPANSIONS OF THE 300-MHz ^{1}H NMR SPECTRA ($CDCl_3$) OF PHENCYCLONE ADDUCTS. (NOTE THAT PEAK AMPLITUDE AND CHEMICAL SHIFT SCALES MAY DIFFER IN EACH REGION.) UPPER TRACES: *N*-HEXYLMALEIMIDE ADDUCT, SHOWING ARYL, NCH_2 (α), AND UPFIELD REGIONS; THE BRIDGEHEAD METHINES' SINGLET AT 4.40 PPM IS NOT SHOWN. LOWER TRACES: 1,4-BENZOQUINONE 1:1 ADDUCT ARYL REGIONS. THE OLEFINIC PROTON SINGLET AT 5.75 PPM AND THE BRIDGEHEAD METHINES SINGLET AT 4.60 PPM ARE OMITTED. ^{1}H ASSIGNMENTS ARE BASED ON THE COSY SPECTRUM, WHICH IS NOT SHOWN.

Selected NMR Spectra

With the accompanying figures (Figures 2–6), we show selected representative NMR spectra (300 MHz for ^{1}H, 75 MHz for ^{13}C, and 282 MHz for ^{19}F) and spectral assignments for some of the Diels–Alder adducts with phencyclone. Most of the spectra define the phencyclone adduct of *N*-hexylmaleimide, discussed in detail in the Experimental section, but we include (Figure 5) some data for the *N*-hexylmaleimide itself, since rigorous ^{1}H NMR assignments in the maleimide and its adduct are required to estimate anisotropy magnitudes in the *N*-hexyl group of the adduct. The ^{19}F NMR of the phencyclone adduct of *N*-pentafluorophenylmaleimide (Figure 6) shows the surprising result of five separate fluorine signals.

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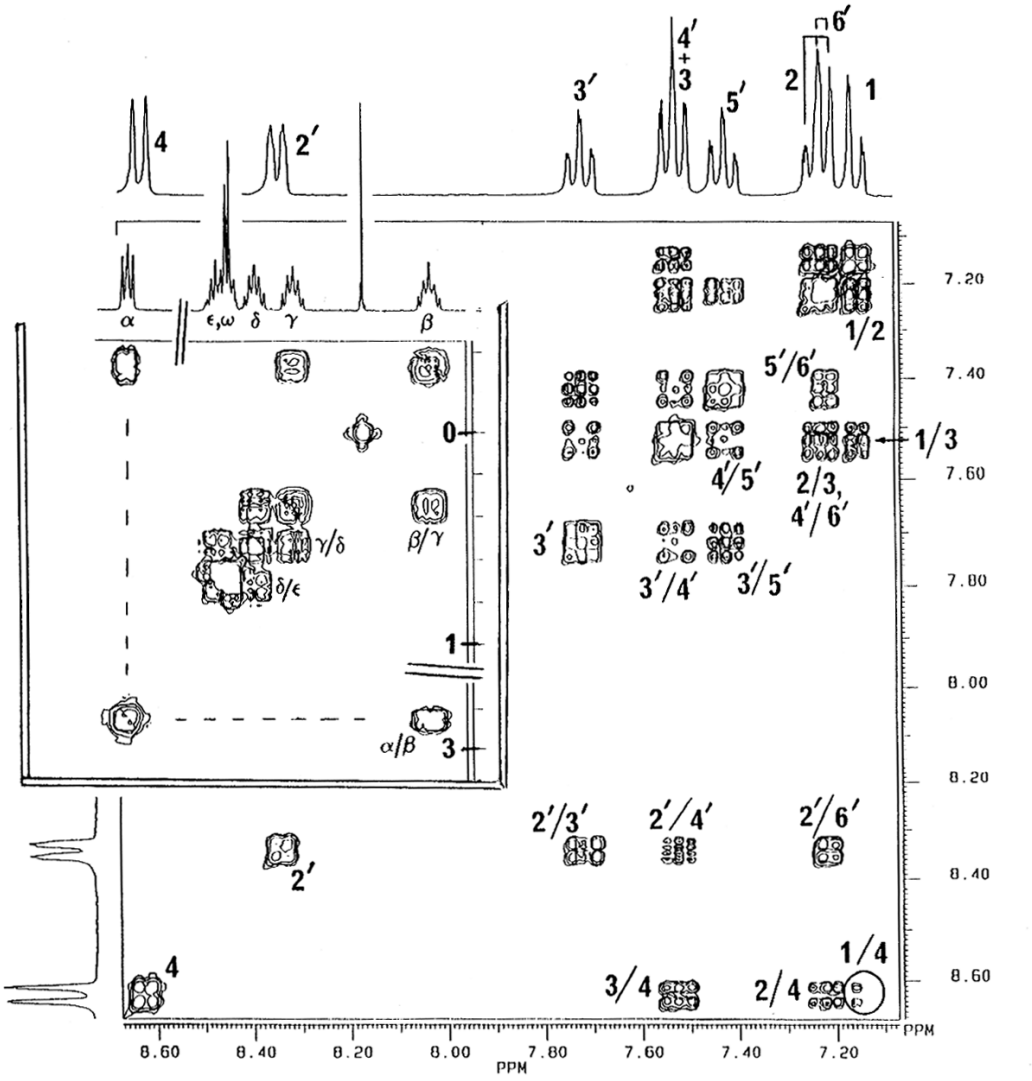

FIGURE 3. THE 300-MHz ^{1}H–^{1}H CHEMICAL SHIFT CORRELATION SPECTRA (COSY) OF THE PHENCYCLONE ADDUCT OF *N*-HEXYLMALEIMIDE (IN $CDCl_3$). (NOTE THAT PEAK AMPLITUDE AND CHEMICAL SHIFT SCALES MAY DIFFER IN EACH REGION.)

In Figure 3 the inset displays an expansion of the upfield region of the *n*-hexyl group. The cross peak labeled α/β allows assignment of the $NCH_2\underline{C}H_2$ (β) quintet based on its vicinal coupling to the α NCH_2 resonance. Note that anisotropic shielding results in appearance of the β CH_2 upfield of TMS. Under the inset is shown the high-resolution COSY expansion of the aryl ^{1}H region of this adduct, by which it is possible to map out the $(CH)_4$ spin system of the adduct phenanthrene moiety and the $(CH)_5$ spin system of the bridgehead phenyls. The 1-D ^{1}H spectra are shown as projections for each COSY spectrum.

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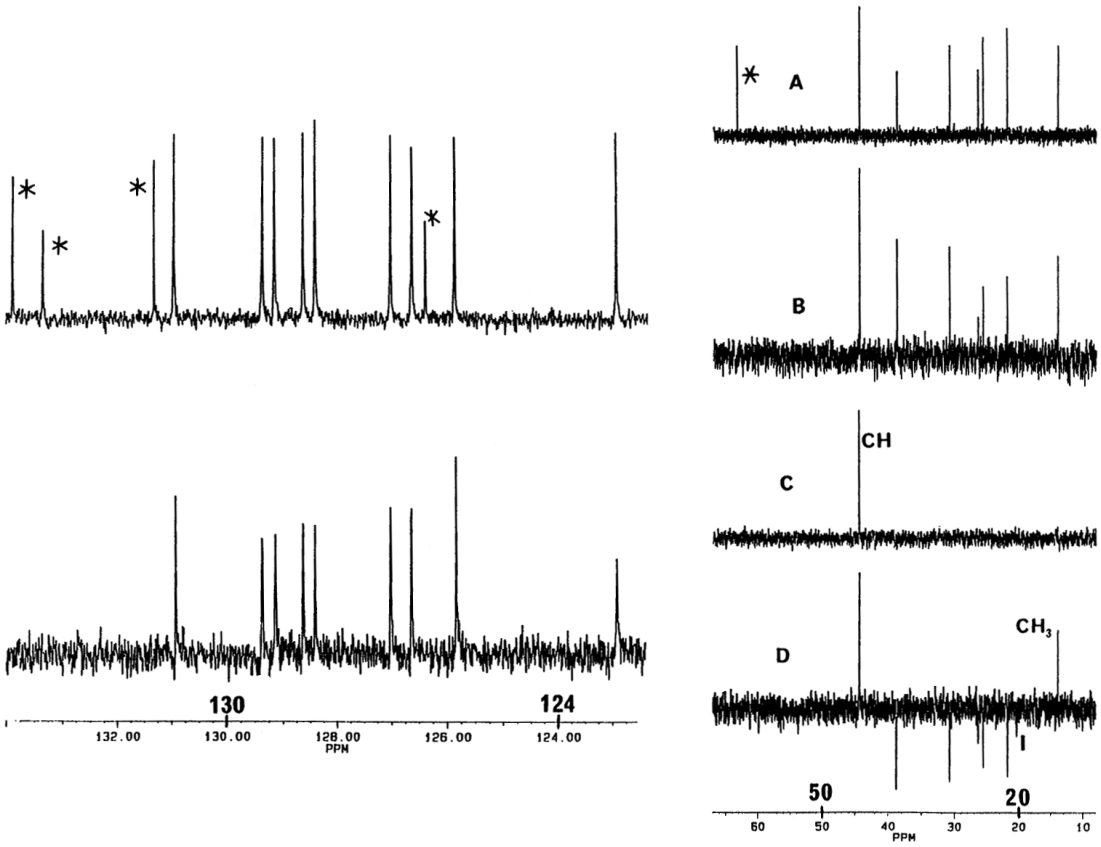

FIGURE 4. THE 75-MHz ^{13}C NMR AND DEPT SPECTRA FOR THE *N*-HEXYLMALEIMIDE ADDUCT OF PHENCYCLONE.

The 75-MHz ^{13}C NMR and DEPT spectra shown in Figure 4 are for the *N*-hexylmaleimide adduct of phencyclone. The upper left spectrum of the aryl region ^{13}C shows 13 signals expected for SEL bridgehead phenyl rotation. The aryl region DEPT-45 spectrum (lower left) shows only nine protonated carbon signals; the four absent peaks were from quaternary carbon atoms (shown by asterisks). The right side is the upfield region of the spectrum. From top to bottom: (A) the normal ^{13}C NMR spectrum shows six signals for the hexyl group, and signals for quaternary and CH bridgehead atoms; (B) the DEPT-45 spectrum shows only protonated carbon atoms: missing peak was $C_6H_5\underline{C}$ (asterisk); (C) the DEPT-90 spectrum shows only the methine (CH) bridgeheads; (D) the DEPT-135 spectrum shows CH and CH_3 signals as positive peaks, with the CH_2 signals appearing as negative peaks; (I = noise spike). Five methylene (CH_2) peaks are seen. The carbonyl signals at 196.8 ppm (ketone) and 174.3 ppm (imide) are not shown.

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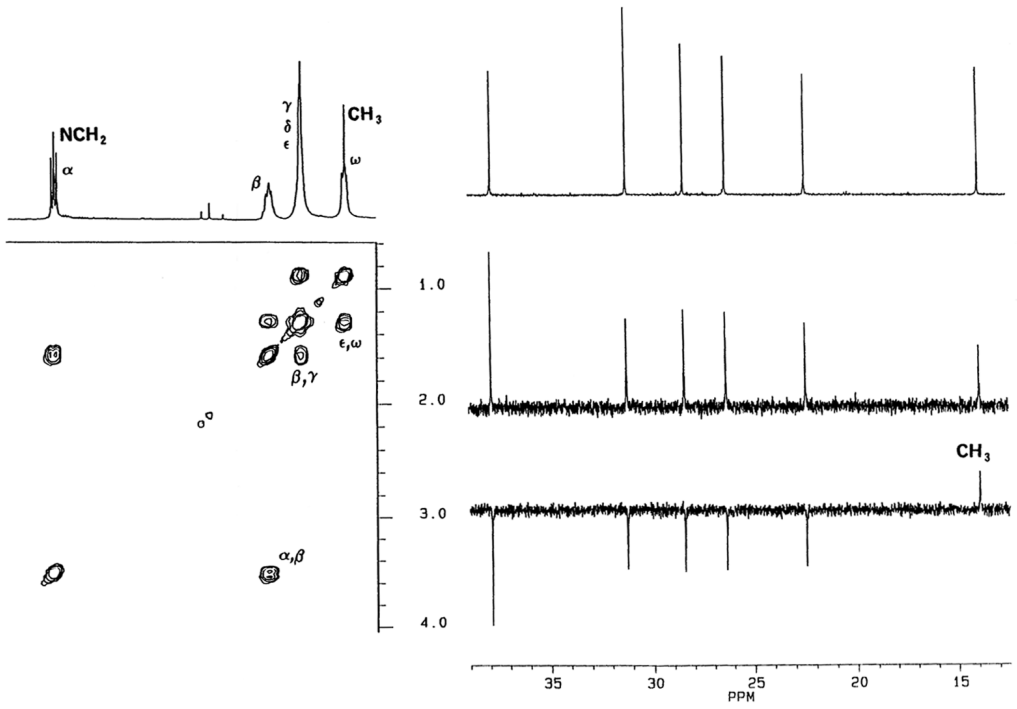

FIGURE 5. NMR SPECTRA OF *N*-HEXYLMALEIMIDE ($CDCl_3$) FOR COMPARISONS WITH THE CORRESPONDING PHENCYCLONE ADDUCT.

Figure 5 shows the NMR spectra of *N*-hexylmaleimide ($CDCl_3$) for comparisons with the corresponding phencyclone adduct. On the left the upfield region is shown, with the 300-MHz ^1H spectrum as a projection for the 2-D ^1H–^1H chemical shift correlation (COSY-45). Assignments are shown for the 1-D ^1H NMR peaks and the COSY cross peaks for the *n*-hexyl group. We can see the unexpected, nearly isochronous signals for the $NCH_2CH_2(C\underline{H}_2)_3$ (γ, δ, and ε protons); the deshielded approximate triplet for the NCH_2 (α); and the high-field near-triplet for the CH_3 group (ω). The olefinic proton singlet is not shown; it had no COSY cross peaks. The top right side of Figure 5 shows the normal 75-MHz ^{13}C spectrum for the upfield (*n*-hexyl) region (olefinic peak not shown). The middle trace is the DEPT-45 spectrum confirming that all six of these ^{13}C signals are from protonated carbon atoms (potentially CH, CH_2, or CH_3). The DEPT-90 spectrum, which would show only methine CH signals, exhibited no peaks in this region. The lower right DEPT-135 spectrum shows CH_2 signals inverted and positive peaks for methine (CH) (none are present here) and methyl (CH_3) signals. This confirms that the high-field carbon signal is the CH_3 (ω). Note that the accidental isochrony observed in the ^1H NMR for the γ, δ, and ε protons is not present in the ^{13}C NMR spectrum.

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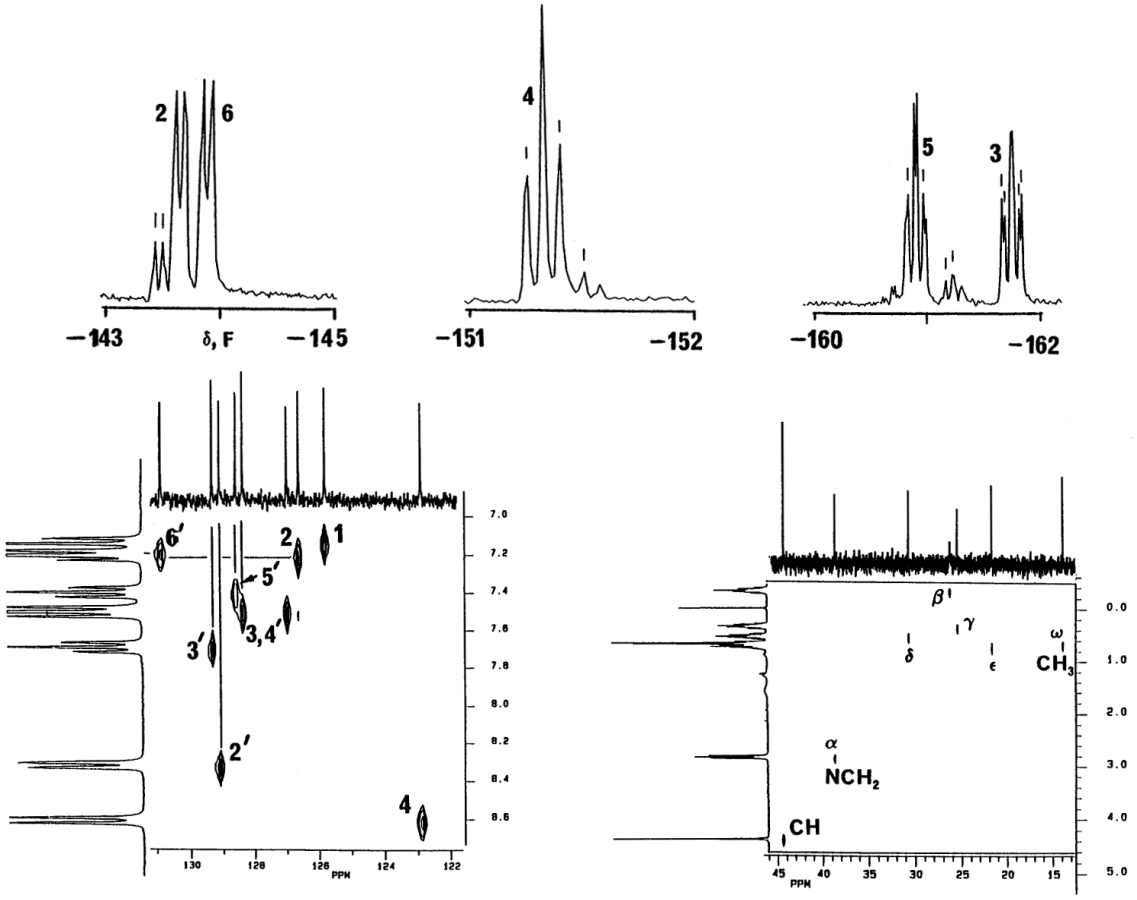

FIGURE 6. UPPER: EXPANSIONS OF THE 282-MHz ^{19}F NMR SPECTRUM OF THE *N*-PENTAFLUOROPHENYLMALEIMIDE ADDUCT OF PHENCYCLONE [REFERENCE 33 IN THE APPENDIX]. (NOTE THAT PEAK AMPLITUDE AND CHEMICAL SHIFT SCALES MAY DIFFER IN EACH REGION.) LOWER THE 2-D ^{1}H-^{13}CHETCOR SPECTRA FOR THE PHENCYCLONE ADDUCT OF *N*-HEXYLMALEIMIDE.

The three upper taces in Figure 6 show expansions of the 282-MHz ^{19}F NMR spectrum of the *N*-pentafluorophenylmaleimide adduct of phencyclone. The appearance of five separate fluorine signals (three gross triplets and two gross doublets) is consistent with the C_6F_5 group being roughly perpendicular to the pyrrolidinedione ring due to steric hindrance of the ortho fluorines with the “imide” carbonyls, in a slow-exchange-limit regime. The asymmetry of the environment results in anisochrony of the five fluorines. The gross doublets are assigned to the ortho fluorines (each with one vicinal ^{19}F neighbor) and the three gross triplets to the remaining fluorines (each with two vicinal ^{19}F neighbors). Some impurity peaks are present. The negative chemical shifts indicate that these aryl fluorine signals were upfield relative to the $CFCl_3$ internal standard at 0.0 ppm. F4 is the para fluorine. Unexpectedly, the lower-field ortho fluorine, F2, was

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shown to be vicinal to the higher-field meta fluorine, F3, based on cross peaks in the $^{19}F–^{19}F$ COSY-45 spectrum (not shown); F5 and F6 are also vicinal. Figure 6 (bottom): The two-dimensional $^{1}H–^{13}C$ heteronuclear chemical shift correlation experiment (XHCORR, HETCOR) for the phencyclone adduct of *N*-hexylmaleimide ($CDCl_3$) shows cross peaks that correlate ^{13}C peaks with their directly attached protons. Expansions for the aryl region (left) and upfield region (right) are shown (but note that chemical shift scales may be different in each region). The labeled cross peaks permit unequivocal assignments of all protonated carbon atoms with the exception of the aryl C3 and C4' (assignments may be reversed); also, assignments for C2 and C6' are tentative since the corresponding attached protons had very similar chemical shifts.

The numbers of absorption signals provide a simple and elegant demonstration of slow exchange limit spectra resulting from slow rotation of the bridgehead phenyls. SEL conditions are implied by nine aryl proton signals of equal intensity (area), consisting of four gross doublets for the phenanthrene moiety (H1, 8, and H4,5) and the phenyl ortho protons (H2' and H6') in addition to five gross triplets for the phenanthrene moiety (H2, 7, and H3, 6), the phenyl meta protons (H3' and H5'), and the phenyl para proton, (H4'). The gross doublet or triplet multiplicity reflects the number of vicinal proton neighbors. The actual numbers of signals and their appearance would reflect possible accidental overlaps and deviations from first-order spectra. With rapidly spinning bridgehead phenyls, FEL spectra result, due to averaging (interchange) of the two phenyl ortho positions (2' and 6') and the two meta positions (3' and 5'). The FEL ^{1}H NMR spectrum might therefore exhibit only seven aryl signals: two 2H doublets (H1 and H8, and H4 and H5), one 4H doublet (H2' and H6'), three 2H triplets (H2 and H7, H3 and H6, and H4'), and one 4H triplet (H3' and H5'). The 1-D ^{13}C NMR spectrum with broadband proton decoupling should show thirteen aryl carbon peaks under SEL conditions (nine methine and four quaternary carbon atoms). The two classes of carbon atoms, methine and quaternary, are readily distinguishable by spectral editing techniques, such as DEPT or APT. They can also be instructively differentiated by their peak intensities as a function of relaxation-delay times. For FEL conditions, only eleven aryl carbon peaks are expected (seven methine and four quaternary), since the two ortho positions (C2' and C6') of the phenyls are rendered equivalent by fast rotation, as are the two meta positions.

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We have been pursuing the syntheses of numerous related adducts for detailed NMR studies. Additional examples and references are cited in the Appendix (32rr1897.pdf). These, and our earlier papers, present detailed experimental information for adduct synthesis and spectral discussions.

The versatility and reactivity of phencyclone has suggested the use of numerous dienophile systems in addition to those noted above so that relevant ^{1}H, ^{13}C, and ^{19}F NMR examination of these adduct compounds, using 1-D and 2-D methods, is under way.

Conclusion

Although running the laboratories for this kind of “first-time-ever” innovative group of experiments puts tremendous demands on the instructors, the rewards are great and the excitement is infectious. Regular classroom discussions assure that the entire group is apprised of experimental results and can appreciate the overall progress being made by the class. Perhaps most gratifying and concrete is the interest expressed by many participating students in pursuing further studies in this area, as undergraduate research projects, after completing their organic chemistry course.

Experimental

We present here a detailed procedure for one adduct, prepared from *N*-hexylmaleimide and phencyclone, as a representative example of a sequence involving student preparation of the *N*-alkylmaleimide. Numerous lower *N*-alkylmaleimides are commercially available, and their purity normally permits their use in only a slight (3–5%) molar excess relative to phencyclone. With use of crude, student-prepared *N*-alkylmaleimide, a larger excess is appropriate, as indicated below. The particular dienophile employed may dictate appropriate modifications in the experimental details. The important point is that the basic reaction is quite robust and rather forgiving of specific procedural subtleties. Proper safety precautions should be employed, particularly eye protection, safety gloves, and fume hoods.

Preparation of N-*Hexylmaleamic Acid*

Freshly powdered (mortar and pestle) maleic anhydride (4.845 g, 49.4 mmol) (Caution: hazardous dust) is placed in a 250-mL conical flask, methylene chloride (12 mL) is

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added, and the mixture is cooled (ice-slush bath) with swirling. Most, but not all, of the maleic anhydride dissolves. A solution of *n*-hexylamine (5.000 g, 49.4 mmol) in CH_2Cl_2 (6 mL) is prepared (fume hood), and cautiously added in portions (Pasteur pipet) to the flask containing the maleic anhydride slurry. This reaction is somewhat exothermic, and occasional swirling of the reaction flask in the ice bath during the 3-5 min period of amine addition is recommended. During the addition of the amine, any undissolved particles of maleic anhydride dissolve completely. The resulting light-yellowish solution deposits near-white crystals upon standing at room temperature for 10 min. (Note that with other amines, the product maleamic acids may crystallize only after solvent removal). The crystalline maleamic acid is collected by vacuum filtration and washed with small portions of ice-cold CH_2Cl_2, and then allowed to suction-dry on the filter. Alternatively, the crystals may be allowed to air dry between laboratory periods. (This is a good stopping point.)

In this way, 6.556 g of a first crop of *N*-hexylmaleamic acid was obtained (66.7% yield). A second crop (2.827 g) was produced by evaporation of the CH_2Cl_2 from the filtrate (95.4% combined yield). This material is good enough for the next step (mp 76–78 °C).

IR ($CHCl_3$ solution, 2-cm^{-1} resolution, bands weak unless noted) (cm^{-1}): 3433.8, 3292.8 (br m), 3100.1 (br), 2958.0 (m), 2932.4 (m), 2860.2 (m), 2309 (v br, w), 1870 (v br, w), 1711.9 (s), 1633.6 (vs), 1576.3 (br vs), 1468.1 (shoulder), 1405.5, 1378.9, 1305.2 (br m), 1149.3, 1042.9, 959.1, 851.6 (m), 630.0, 598.9. IR (KBr pellet) (cm^{-1}): 3238.7 (br m), 2953.5 (m), 1708.1 (s), 1638.6 (s), 1500 (v br, vs), 1406.3 (m), 1251.0, 1197.7, 1148.9 (m), 1069.4 (m), 987.6, 958.5 (m), 903.9, 880.5, 851.6 (s), 796.8 (m), 760.6 (m), 726.3, 629.2 (s), 598.2 (m), 459.4 (s).

Preparation of N-*Hexylmaleimide*

N-Hexylmaleamic acid (6.000 g, 30.0 mmol), anhydrous sodium acetate (0.984 g, 12.0 mmol), and acetic anhydride (10.56 g, 104.0 mmol) are placed in a 100-mL round-bottom flask. (Caution: Acetic anhydride is a corrosive lachrymator. Use a fume hood and protective gloves.) The flask can be lightly corked (or topped with a drying tube of anhydrous $CaCl_2$) and the reaction mixture is heated for 0.5 h in a boiling water bath, during which time the reactants dissolve and form a reddish-brown solution (this is typical of the crude maleimides). This is a good stopping point as the reaction mixture can now stand for several days at room temperature.

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After standing at ambient temperatures, the solution may become a semisolid slurry. When this mixture is transferred to a 250-ml separatory funnel with 50 mL H_2O, the solids dissolve. (Evidently much of the crystalline material that may be observed after heating is sodium acetate.) The crude material is extracted twice with diethyl ether (50 mL, 10 mL) and the combined ether extracts are washed with saturated aqueous $NaHCO_3$ (3×40 mL) and with H_2O (40 mL) to remove maleic acid, maleamic acid, sodium acetate, acetic acid, and acetic anhydride. (CAUTION: Diethly ether is highly flammable. Do not use open flames in the laboratory while ether is being used.) The ether solution is transferred to a 250-mL conical flask and dried by addition of ca. 4 g anhydrous $MgSO_4$, and then allowing the corked flask to stand for 10 min with occasional swirling. The ether solution is decanted from the drying agent, which is rinsed with ether (10 mL), and the ether portions are combined. (Optionally, the ether solution may be treated with ca. 0.35g decolorizing carbon, and the decolorizing carbon removed by vacuum filtration through a pad of diatomaceous earth.) The ether solution is transferred to a tared 100-mL round-bottom flask and the solvent removed thoroughly on a rotary evaporator (aspirator pressure, water bath at ca. 40 °C), leaving 3.439 g of the crude *N*-hexylmaleimide as a red oil (nominal 63% yield based on crude weight). (Note that preparations of the maleamic acids and maleimides can be scaled down to "microscale," i.e., ca. 200–400-mg scale.)

IR ($CHCl_3$ solution) (cm^{-1}): 3452.2, 2957.9 (s), 2932.5 (s), 2860.0 (m), 1825.6 (m), 1752.9 (shoulder, m), 1699–1710 (vs), 1667.6 (shoulder, m), 1522.1, 1443.1 (m), 1410.1 (s), 1369.1 (m), 1126.4 (s), 1047.1, 996.6 (m), 898.6, 828.5 (s). IR (neat, NaCl plates, selected bands) (cm^{-1}): 3461.9, 3391.9 (br), 3099.2, 1826 (m), 1750 (shoulder, m), 1706–1717 (br vs), 1226.5 (s), 1171.0, 1156.5, 1125.5 (s), 996.9, 895.2, 830.1 (m), 696.3 (s). NMR (^1H, 300 MHz, $CDCl_3$, δ): 6.686 (s, 2H, HC=CH), 3.509 (apparent t, J = 7.3 Hz, 2H, NCH_2 [α]), 1.574 (apparent quint, J = 6.8 Hz, 2H, CH_2 [β]) , 1.280 (apparent br s, 6H, $(CH_2)_3$, [γ, δ, ε]), 0.876 (apparent t, J = 6.6 Hz, 3H, CH_3). NMR (^{13}C, 75 MHz, composite pulse decoupling of protons, δ): 168.86 (CO), 131.99 (C=C), 35.89, 29.24, 26.44, 24.34, 20.44, 11.91(CH_3).

Preparation of the Diels–Alder Adduct of N-*Hexylmaleimide and Phencyclone*

The crude *N*-hexylmaleimide (above) is used directly without further purification. *N*-hexylmaleimide (0.992 g, nominally 5.48 mmol, ca. 2.2 equiv), 15 mL CH_2Cl_2, phencyclone (0.942 g, 2.47 mmol), and a small magnetic stirring bar are placed in a screw-cap vial (20–25 mL capacity) with a PTFE-lined cap. The near-black reaction

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mixture is magnetically stirred at room temperature until the intense green–black phencyclone color is discharged (about 35 min), leaving a deep-yellow solution. The mixture is transferred to a tared round-bottom flask and concentrated on a rotary evaporator to about one-quarter of its initial volume, to give a thick, semiopaque oil, which is induced to crystallize by scratching with a glass rod. Hexane (15 mL) is added to the oily yellow-orange crystals. Trituration induces further crystallization. (Note: we have since found that numerous adducts of phencyclone are readily crystallized from absolute ethanol–hexane.) Chilling and collection of the crystals by vacuum filtration, followed by washing with 30 mL ice-cold hexane and air-drying, results in 0.968 g of the light-beige crystalline adduct (69.6 % yield, mp 232–236 °C [dec.]), which was pure enough for the NMR studies.

IR ($CHCl_3$ solution, cm^{-1}): 2932.7 (m), 2860.6, 1790.6 (s, strained ketone C=O), 1700–1704 (vs, imide C=O), 1605.9, 1499.5 (m), 1448.5 (m), 1437.3 (m), 1396.8 (s), 1369.1 (m), 1346.9 (m), 1291.2, 1175.0, 1139.4, 1070.0, 1044.9, 1035.1, 911.5, 870.9, 642.3, 614.5, 555.0, 512.6. IR (CCl_4 solution, selected bands, cm^{-1}): 3066.0, 2932.9 (m), 2859, 1794.9 (s, strained ketone C=O), 1707.3 (vs, imide C=O), 1500.7 (m), 1448.5 (m), 1437.2, 1394.9 m, 1346.1, 1174.7, 1138.9, 1044.8, 696.9 s, 642.3, 614.9, 555.0, 512.9. IR (KBr pellet, selected bands): 2932.5 m, 1786.4 s (strained ketone C=O), 1701.6 (vs, imide C=O), 1396.3 (m), 1341.2 (m), 1222.3, 1165.3, 1135.6, 1035.2, 910.9, 871.8, 825.6, 779.2 (m), 758.0 (s), 724.1 m, 696.3 (s), 643.0, 614.2, 555.2, 510.9. NMR (^1H, 300 MHz, $CDCl_3$, δ): 8.626 (2H, d, J = 8.4 Hz, H4 and H5), 8.342 (2H, d, J = 7.9 Hz, H2'), 7.717 (2H, apparent t, J = 7.2 Hz, H3'), 7.524 (4H, t, J = 7.4 Hz, coincidental overlap of H3, H6, and H4'), 7.422 (2H, apparent t, J = 7.6 Hz, H5'), 7.211 (d, J = 7.3 Hz, H6' overlapped with the H2–H7 signal centered at 7.224, for a total of 4H), 7.147 (2H, d, J = 7.6 Hz, H1 and H8), 4.402 (2H, s, ring-junction methines), 2.847 (2H, t, J = 7.8 Hz, NCH_2 [α]), 0.6–0.8 (5H, complex multiplet, overlap of apparent sextet for CH_2 [ε] at 0.726 and apparent t for CH_3 [ω] at 0.659), 0.535 (2H, apparent quint, J = 7.2 Hz, CH_2 [δ]), 0.343 (2H, apparent quint, J = 7.5 Hz, CH_2 [γ]), –0.328 (2H, apparent quint, J = 7.8 Hz, CH_2 [β]). NMR (^{13}C, 75 MHz, $CDCl_3$, δ): 196.82 (ketone), 174.27 (imide), 133.88 (quaternary), 133.34 (quaternary), 131.29 (quaternary), 130.94, 129.35, 129.14, 128.62, 128.40, 127.00, 126.62, 126.38 (quaternary), 125.86, 122.91, 63.38 (quaternary, $C_6H_5\underline{C}$), 44.45 (CH), 38.75 (CH_2), 30.72 (CH_2), 26.31 (CH_2), 25.50 (CH_2), 21.72 (CH_2), 13.86 (CH_3).

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We would be pleased to provide relevant reprints, special assistance, and suggestions to instructors who may consider introducing these experiments.

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REFERENCES

1. Sasaki, T.; Kanematsu, K.; Iizuka, K. *J. Org. Chem.* **1976**, *41*(7), 1105–1112.
2. Harrison, E. A., Jr. *J. Chem. Educ.* **1991**, *68*(5), 426–427. See footnote 5 therein.
3. Harrison, E. A., Jr. *J. Chem. Educ.* **1992**, *69*(7), 571. See footnote 5 therein.
4. Forsyth, W. R.; Weisenburger, G. A.; Field, K. W. *Trans. Ill. State Acad. Sci.* **1996**, *89*, 37–40.
5. LaPlanche, L. A.; Xu, Y.; Benshafrut, R.; Rothchild, R.; Harrison, E. A., Jr. *Spectrosc. Lett.* **1993**, *26*(1), 79–101.
6. Xu, Y.; LaPlanche, L.; Rothchild, R. *Spectrosc. Lett.* **1993**, *26*(1), 179–196.
7. Plemenkov, V. V. *Dokl. Akad. Nauk. SSSR* **1978**, *240*(3), 608–611; *Chem. Abstr*. **1978,** *89*, 107827q.
8. Benshafrut, R.; Callahan, R.; Rothchild, R. *Spectrosc. Lett.* **1993**, *26*(10), 1875–1888.
9. Callahan, R.; Rothchild, R.; Wyss, H. *Spectrosc. Lett.* **1993**, *26*(9), 1681–1693.
10. Bynum, K.; Rothchild, R. *Spectrosc. Lett.* **1996**, *29*(8), 1599–1619.
11. Bynum, K.; Rothchild, R. *Spectrosc. Lett.* **1996**, *29*(8), 1621–1634.
12. Bynum, K.; Rothchild, R. *Spectrosc. Lett.* **1997**, *30* (4), 727–749.
13. Bynum, K.; Rothchild, R. *Spectrosc. Lett.* **1997**, *30*(8), 1713–1732.
14. Adams, R.; Johnson, J. R.; Wilcox, C. F. *Laboratory Experiments in Organic Chemistry*, 7th ed.; Macmillan: New York, 1979; pp 438–444. (Note that the experimental procedure at the top of p 442 contains an error due to misprinting, requiring the deletion of several lines.)

ISSN 1430-4171
http://journals.springer-ny.com/chedr
S 1430-4171 (98) 02192-4

15. Mayo, D. W.; Pike, R. M.; Butcher, S. S. *Microscale Organic Laboratory*, 2nd ed.; Wiley: New York, 1989; pp 61–63.

16. Gillis, B. T.; Hagarty, J. D. *J. Org. Chem.* **1967**, *32*, 330–333.

17. Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *Tetrahedron Lett.* **1962** (14), 615–618.

18. Cookson, R. C.; Gilani, S. S. H.; Stevens, I. D. R. *J. Chem. Soc. (C)* **1967**, 1905–1909.

19. Wamhoff, H.; Wald, K. *Org. Prepn. Proc. Int.* **1975**, *7*(5), 251–253.

20. Ried, W.; Lim, S.-H. *Liebigs Ann. Chem.* **1973**, *1*, 129–133.

21. Swarbrick, T. M.; Markó, I. E.; Kennard, L. *Tetrahedron Lett.* **1991**, *32*(22), 2549–2552.