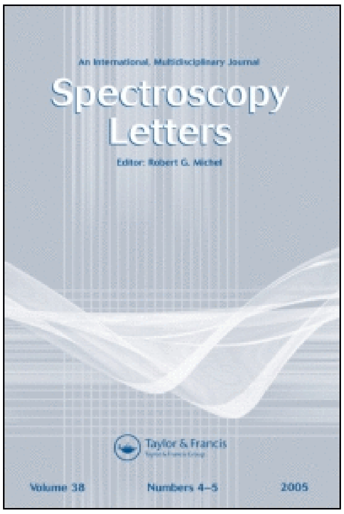

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

NMR Studies of Crowded Diels-Alder Adducts of Phencyclone with *N*-(2,6-Dialkylphenyl)maleimides. Hindered Rotations and Magnetic Anisotropy

Orlando Ramirez III[ab]; Robert Tokhunts[a]; Robert Rothchild[ac]
[a] Science Department, John Jay College of Criminal Justice, The City University of New York, New York, New York, USA [b] Chemistry Department, Queens College, The City University of New York, Flushing, New York, USA [c] The Doctoral Faculty, The Graduate School and University Center, City University of New York, USA

To cite this Article Ramirez III, Orlando , Tokhunts, Robert and Rothchild, Robert(2004) 'NMR Studies of Crowded Diels-Alder Adducts of Phencyclone with *N*-(2,6-Dialkylphenyl)maleimides. Hindered Rotations and Magnetic Anisotropy', Spectroscopy Letters, 37: 4, 421 — 436

To link to this Article: DOI: 10.1081/SL-120039591

URL: http://dx.doi.org/10.1081/SL-120039591

SPECTROSCOPY LETTERS
Vol. 37, No. 4, pp. 421–436, 2004

NMR Studies of Crowded Diels–Alder Adducts of Phencyclone with *N*-(2,6-Dialkylphenyl)maleimides. Hindered Rotations and Magnetic Anisotropy

Orlando Ramirez III,[1,2] Robert Tokhunts,[1]
and Robert Rothchild[1,3,*]

[1]Science Department, John Jay College of Criminal Justice, The City University of New York, New York, New York, USA
[2]Chemistry Department, Queens College, The City University of New York, Flushing, New York, USA
[3]The Doctoral Faculty, The Graduate School and University Center, City University of New York, USA

ABSTRACT

Phencyclone, **1**, 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

---

*Correspondence: Robert Rothchild, Science Department, John Jay College of Criminal Justice, The City University of New York, 445 West 59th Street, New York, NY 10019, USA; E-mail: rrothchild@jjay.cuny.edu.

DOI: 10.1081/SL-120039591
0038-7010 (Print); 1532-2289 (Online)

Diels–Alder adducts, **3a–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 **3a** exhibits a proton resonance at −0.13 ppm, upfield of tetramethylsilane (TMS); the "inner" ethyl group signals from **3b** appear at 0.026 ppm (CH_2, quartet), and −0.21 ppm (CH_3, triplet); and the "inner" isopropyl group from **3c** is seen at −0.06 ppm (methine, approx. septet) and −0.39 ppm (CH_3, doublet). Proton NMR of the crude *N*-(2,6-dialkylphenyl)maleamic acids (used as precursors of the maleimides, **2a–c**) exhibited two sets of AB quartet signals, suggesting possible conformers from hindered rotation in the amide groups about the HN–C=O bonds.

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; Maleamic acids.

INTRODUCTION

For some time, we have studied various hindered Diels–Alder adducts of phencyclone, **1**, 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 within 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 anisotropic effects can result. Some theoretical studies of related systems have recently been reported, and have relevance to important pharmaceuticals and drugs of abuse.[7,8] In this present report, we discuss the NMR results from one- and two-dimensional (1D and 2D) proton and carbon-13 ambient temperature spectral studies (at T) of the Diels–Alder adducts of **1** with *N*-(2,6-dialkylphenyl)maleimides, **2a** (R = methyl), **2b** (R = ethyl), and **2c** (R = isopropyl). The product adducts are designated **3a** (from **1** with *N*-2,6-dimethylphenylmaleimide), **3b** (from **1** with *N*-2,6-diethylphenylmaleimide), and **3c** (from **1** with 2,6-diisopropylphenylmaleimide).

EXPERIMENTAL

General discussions of NMR methods and synthetic techniques have been described in our earlier papers and references cited therein.[1–6] NMR spectra 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 standard 1D 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 2 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), 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. Abbreviations used in reporting NMR data include: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), Q (non-protonated or quaternary carbon signal), and conf. (conformer). Relative signal integrals for the maleamic acid conformers are shown as 1H, 2H, 3H, etc., for the major conformer, reflecting the sum of signals from minor and major conformations. For the minor conformers of the maleamic acids, assignments for proton signals other than the AB quartets must be considered tentative; see Results and Discussion. Observed coupling constants are given in hertz. Commercial reagents were obtained from Aldrich Chemical (Milwaukee, WI) or, for phencyclone, Lancaster Synthesis (Windham, NH) 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.

Preparation of *N*-(2,6-Diethylphenyl)maleamic Acid and *N*-(2,6-Diethylphenyl)maleimide (2b)

To a magnetically stirred slurry of maleic anhydride (2.96 g, 30.17 mmol, freshly crushed briquettes) in methylene chloride (100 mL) was added a solution of 2,6-diethylaniline (4.577 g, 30.67 mmol, ca. 1.7% molar excess) in methylene chloride (50 mL). After 15 min, the mixture had become clear reddish-brown, and was refluxed 15 hr using a condenser topped with a drying tube (anh. $CaSO_4$). Solvent removal gave the crude maleamic acid. Proton NMR ($CDCl_3$) suggested 2–3% of the corresponding maleimide, **2b** (see below), and signals assigned to major and minor conformers of the desired *N*-(2,6-diethylphenyl)maleamic acid, about 6.4 : 1 ratio based on integrals of the AB q signals, respectively, assigned as follows (ppm): 9.28 (1H, br s, NH of major conf.); 7.69 (br s, NH of minor conf.); 7.36 (approx. t, $^3J = 7.6$, H_b of minor conf.); 7.29 (1H, approx. t, $^3J = 7.7$, H_b of major conf.); 7.21 (d, $^3J = 7.6$, H_a minor conf.); 7.15 (2H, d, $^3J = 7.6$, H_a major conf.); 6.80 (1H, d, $^3J = 12.8$, half of AB q, major conf. vinyl proton); 6.41 (1H, d, $^3J = 12.8$, half of AB q, major conf. vinyl proton); 6.29 (d, $^3J = 13.0$, half of AB q, minor conf. vinyl proton); 6.07 (d, $^3J = 13.0$, half of AB q, minor conf. vinyl proton); 2.58 (approx. q, $^3J = \sim 7.6$, minor conf. $C\underline{H}_2CH_3$); 2.55 (4H, approx. q, $^3J = \sim 7.6$, major conf. $C\underline{H}_2CH_3$); 1.26 (t, $^3J = 7.5$, minor conf. $CH_2C\underline{H}_3$); 1.17 (6H, t, $^3J = 7.5$, major conf. $CH_2C\underline{H}_3$). Peaks from traces of the precursor aniline were tentatively assigned at (ppm): 7.01 (d, $^3J = 7.5$, H_a); 6.87 (t, $^3J = 7.5$, H_b); 6.35 (s, NH_2).

To the crude maleamic acid (ca. 30.1 mmol) in a rb flask equipped with condenser topped with a drying tube (anh. $CaSO_4$) was added freshly fused anhydrous sodium acetate (413.6 mg, 5.05 mmol), acetic anhydride (200 mL), and a trace of 2,6-di-*t*-butyl-4-methylphenol (BHT, ca. 3 mg). (BHT has routinely been used in our labs as a free radical trap to suppress potential polymerization of maleimides and also to suppress air oxidation of phencyclone to 9,10-dibenzoylphenanthrene.)[1] The mixture was heated in a boiling water bath ca. 3.5 hr, cooled and combined with 400 mL water, and extracted with CH_2Cl_2 (4 × 50 mL). The combined extracts were washed with saturated aq. $NaHCO_3$ (4 × 50 mL) and brine (100 mL), dried (anh. Na_2SO_4), and solvent removed on a rotary evaporator (aspirator pressure, 60°C bath temp.) The proton NMR of the crude maleimide product at this point revealed considerable remaining acetic anhydride, and the crude maleimide was dissolved in hexanes and washed with water (2 × 100 mL), causing separation of the product as crystals which were collected by filtration. Solvent removal from the remaining hexane solution gave a second crop of crystalline *N*-2,6-diethylphenylmaleimide, **2b**, combined yield 4.29 g, (62%), mp 68–72°C. IR (KBr): 1713.4 cm^{-1}, imide C=O. Proton NMR ($CDCl_3$, ppm): 7.36 (1H, t, $^3J = 7.66$, H_b); 7.20 (2H, d, $^3J = 7.67$, H_a); 6.88 (2H, s, vinyl protons); 2.40 (4H, q, $^3J = 7.58$, $C\underline{H_2}CH_3$); 1.13 (6H, t, $^3J = 7.61$, $C\underline{H_3}CH_2$).

Carbon-13 NMR ($CDCl_3$, ppm): 170.27 (C=O); 142.81 (Q); 134.29 (CH × 2); 129.98 (CH × 1); 127.86 (Q); 126.71 (CH × 2); 24.59 and 14.41 (CH_2CH_3).

Preparation of the Adduct, 3b, of Phencyclone with *N*-2,6-Diethylphenylmaleimide

To maleimide **2b** (674.2 mg, 2.940 mmol, prepared as above) was added phencyclone (1039.5 mg, 2.718 mmol, approx. **2b** : **1** molar ratio 1.08), BHT (ca. 3 mg), and CH_2Cl_2 (150 mL). The dark green-black mixture was refluxed 20 hr ($CaSO_4$ drying tube) to give a perfectly clear light yellow-green solution. Concentration to half-volume and chilling (ice slush) gave precipitate, which was collected by filtration and dried to yield the product **3b**. IR (KBr): 1789.9 cm^{-1} (strained bridging ketone C=O). Proton NMR ($CDCl_3$, ppm): 8.71 [2H, d, $^3J = 8.4$, H(4/5)]; 8.40 [2H, d, $^3J = 7.7$, H(2′)]; 7.71 [2H, t, $^3J = 7.3$, H(3′)]; 7.54 [2H, t, $^3J = 8.2$, H(3/6)]; 7.51 [2H, t, $^3J = 8.9$, H(4′)]; 7.40 [2H, t, $^3J = 7.1$, H(5′)]; 7.16–7.25 [6H, m, H(6′,1/8 and 2/7)]; 7.10 (1H, t, $^3J = 7.7$, H_b); 7.02 (1H, d, $^3J = 7.2$, H_a); 6.65 (1H, d, $^3J = 7.4$, H_c); 4.68 (2H, s, bridgehead CH); 2.40 (2H, q, $^3J = 7.5$, "outer" $C\underline{H_2}CH_3$);

1.18 (3H, t, $^3J = 7.5$, "outer" $CH_2C\underline{H}_3$); 0.026 (2H, q, $^3J = 7.4$, "inner" $C\underline{H}_2CH_3$); -0.21 (3H, t, $^3J = 7.4$, "inner" $CH_2C\underline{H}_3$).

Carbon-13 NMR ($CDCl_3$, ppm): 195.69 (ketone C=O); 173.86 (imide C=O); 141.19 Q; 139.82 Q; 133.83 Q; 133.78 Q; 131.64 Q; 131.01 (6′); 129.58 (b); 129.34 (3′); 129.31 (2′); 128.70 Q; 128.52 (5′); 128.40 (4′); 127.15 (3/6); 126.69 (1/8 or 2/7); 126.40 Q; 126.20 (2/7 or 1/8); 125.86 (a); 125.47 (c); 122.97 (4/5); 63.64 sp^3 bridgehead $C_6H_5{-}\underline{C}$; 45.34 (bridgehead CH); 24.47 "outer" $\underline{C}H_2CH_3$); 21.39 ("outer" $CH_2\underline{C}H_3$); 14.13 ("inner" $\underline{C}H_2CH_3$); 12.12 "inner" $CH_2\underline{C}H_3$)

Preparation of *N*-(2,6-Dimethylphenyl)maleamic Acid and *N*-(2,6-Dimethylphenyl)maleimide (2a)

To a magnetically stirred slurry of maleic anhydride (4.225 g, 43.1 mmol) in CH_2Cl_2 (100 mL) was added a solution of *N*-2,6-dimethylaniline (5.408 g, 44.6 mmol) in CH_2Cl_2 (50 mL). After 15 min, solid had dissolved to give a pale reddish-orange solution. The reaction flask was fitted with a condenser topped by a drying tube (anh. $CaSO_4$) and the mixture was refluxed for 3 hr, leading to a (slightly decolorized) yellow-orange solution. Solvent removal (rotary evaporator, aspirator pressure, water bath 60°C) gave the crude white maleamic acid crystals (ca. 9.8 g), mp 118.5–129.9°C; a second batch had mp 132–142°C. Proton NMR ($CDCl_3$) signals of two AB quartet patterns suggested a mixture of the two amide rotamers in about a 6 : 1 ratio. NMR ($CDCl_3$, ppm): 8.68 (1H, br s, NH, major conf.); 7.48 (br s, NH, minor conf.); 7.19 (1H, approx. t, H_b); 7.12 (2H, d, $^3J = 7.7$, H_a); 7.04 (trace of maleic anhydride); 6.88 (trace of maleimide vinyl H, see below); 6.70 (1H, $^3J = 12.9$, half of AB q, major conf. vinyl protons); 6.46 (1H, $^3J = 12.9$, half of AB q, major conf. vinyl protons); 6.33 ($^3J = 13.2$, half of AB q, minor conf. vinyl protons); 6.07 ($^3J = 12.9$, half of AB q, minor conf. vinyl protons); 2.26 (s, minor conf. CH_3); 2.24 (6H, s, major conf. CH_3). With a separate batch of the *N*-(2,6-dimethylphenyl)maleamic acid, using d_6-dimethyl sulfoxide (d_6-DMSO) as solvent, two sets of AB quartets were also observed, in a ratio of ca. 40 : 1. NMR (d_6-DMSO, ppm): 9.97 (1H, br s, NH, major conf.); 7.14–7.06 (3H, m, aryl H); 6.60 (1H, $^3J = 12.3$, half of AB q, major conf.); 6.30 (1H, $^3J = 12.2$, half of AB q, major conf.); 6.08 ($^3J = 12.4$, half of AB q, minor conf.); 5.91 ($^3J = 12.3$, half of AB q, minor conf.); 2.20 (s, CH_3, minor conf.); 2.17 (6H, s, CH_3, major conf.) [Small additional peaks, attributed to traces of 2,6-dimethylaniline, were seen for this sample at 6.81 (d, H_a); 6.46 (t, H_b); 6.23 (s, NH_2); 2.09 (s, methyl)].

This material was used directly for conversion to the maleimide, **2a**. A portion of this crude maleamic acid (2.245 g, 10.24 mmol) was combined with acetic anhydride (30 mL), freshly fused anhydrous sodium acetate (204.3 mg, 2.491 mmol), and ca. 4 mg of 2,6-di-*t*-butyl-4-methylphenol (BHT) in a flask fitted with a condenser topped by a drying tube (anh. $CaSO_4$) and maintained at 90–100°C (boiling water bath) for 3.5 hr. Solvent was removed by rotary evaporator (aspirator pressure, water bath 80°C) for 1 hr. The residue was combined with water (350 mL) and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (4 × 50 mL), water (4 × 100 mL), and brine (100 mL). Drying the residue over anh. $CaSO_4$ and solvent removal gave the crude *N*-(2,6-dimethylphenyl)maleimide, **2a**, (1.56 g, 76% yield). When this crude material was combined with a mixture of CH_2Cl_2 (75 mL) and hexanes (150 mL), the addition of 500 mL water caused separation of the crude product as a solid. This whole mixture was further washed with water (3 × 200 mL), and solid was collected by filtration. A second crop was obtained from the mother liquor (after drying) by solvent removal to give a clear yellow oil, which crystallized after standing for several days. Proton NMR showed both crops of **2a** to have similar purity; mp 92–95°C. Combined yield 56%. Proton NMR ($CDCl_3$, ppm): 7.22–7.27 (1H, m, H_b overlapped with $CHCl_3$); 7.15 (2H, d, $^3J = 7.7$, H_a); 6.88 (2H, s, vinyl H); 2.11 (6H, s, CH_3).

Carbon NMR ($CDCl_3$, ppm): 169.53 (C=O); 136.97 (Q); 134.34 (2 × CH); 129.50 (1 × CH); 129.15 (Q); 128.51 (2 × CH); 17.93 (2 × CH_3).

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

Phencyclone (1.6009 g, 4.191 mmol) and **2a** (ca. 5% molar excess) in 150 mL CH_2Cl_2 were stirred and refluxed until the dark green-black color of the mixture was discharged to give a clear yellow solution (approx. 24 hr). The reaction mixture was concentrated to about half-volume and chilled to give the impure adduct, about 66.7% crude yield. A portion of this (993.8 mg) was recrystallized from 10 mL of CH_2Cl_2 : hexanes (1 : 1) to yield 526.2 mg of the adduct, **3a**, used for NMR studies, mp 270°C (darkening with gas evolution) major melting 278–287°C (further darkening and dec.). IR (KBr): 1789.8 cm^{-1} (strained bridging ketone C=O). Proton NMR ($CDCl_3$, ppm): 8.66 [2H, d, $^3J = 8.5$, H(4/5)]; 8.39 [2H, d, $^3J = 7.9$, H(2′)]; 7.71 [2H, approx. t, $^3J = 7.6$, H(3′)]; 7.50–7.56 [4H, m, H(3/6, 4′)]; 7.42 [2H, approx. t, $^3J = 7.6$, H(5′)]; 7.13–7.21 [6H, m, H(6′, 1/8, 2/7)]; 6.94–6.96 (2H, m, $H_{a,b}$); 6.54 (1H, approx. t, $^3J = 4.5$, H_c, apparent *t* due to virtual coupling to near-isochronous $H_{a,b}$); 4.67 (2H, s, bridgehead CH); 2.10 (3H, s, outer CH_3); −0.13 (3H, s, inner CH_3).

Proton NMR (d_6-acetone, ppm): 8.87 [2H, d, $^3J = 8.5$, H(4/5)]; 8.45 [2H, d, $^3J = 7.$, H(2′)]; 7.73 [2H, approx. t, $^3J = 7.5$, H(3′)]; 7.58–7.63 [2H, m, H(3/6)]; 7.55 [2H, t, $^3J = 7.4$, H(4′)]; 7.43 [2H, dt, $^4J = 1.0$, $^3J = 7.6$, H(5′)]; 7.26 [2H, d, $^3J = 7.8$, H(6′)]; 7.18–7.25 [4H, m, H(1/8, 2/7)]; 7.03 (1H, distorted d, $^3J = \sim 6$, H_a); 6.99 (1H, distorted t, $^3J = 7.4$, H_b); 6.59 (1H, approx. d, $^3J = 6.9$, H_c); 5.10 (2H, s, bridgehead CH); 2.14 (3H, s, outer CH_3); −0.13 (3H, s, inner CH_3).

Preparation of *N*-(2,6-Diisopropylphenyl)maleamic Acid and *N*-(2,6-Diisopropylphenyl)maleimide, (2c)

A mixture of maleic anhydride (2.2129 g, 22.57 mmol), 2,6-diisopropylaniline (4.1546 g, 23.43 mmol), BHT (ca. 4 mg), and toluene (100 mL), initially clear light yellow, was refluxed with stirring for 4 hr. Cooling to room temperature produced crystals, collected by vacuum filtration and air-dried, of the crude *N*-(2,6-diisopropylphenyl)maleamic acid (3.5789 g), subsequently used for direct conversion to the corresponding maleimide. The proton NMR of the maleamic acid was consistent with a mixture of the two conformers of amide HN–C═O rotation in about a 10 : 1 ratio based on integrals of the AB q peaks. Full integral intensities are given for the major conformer signals. Proton NMR ($CDCl_3$, ppm): 8.61 (1H, br s, N–H of major conf.); 7.48 (br s, NH of minor conf.); 7.43 (t, $^3J = 7.9$, minor conf.); 7.37 (1H, t, $^3J = 7.8$, H_b of major conf.); 7.25 [d, $^3J = \sim 8$, (overlapped with $CHCl_3$ and with doublet at 7.22 ppm), minor conf.]; 7.22 (2H, d, $^3J = 7.7$, H_a of major conf.); 6.70 (1H, d, $^3J = 12.8$, half of AB q, vinyl proton of major conf.); 6.45 (1H, d, $^3J = 12.8$, half of AB q, vinyl proton of major conf.); 6.31 (d, $^3J = 13.0$, half of AB q, vinyl H of minor conf.); 6.08 (d, $^3J = 13.0$, half of AB q, vinyl H of minor conf.); 2.96 [2H, approx. septet, $^3J = 6.9$, $C\underline{H}(CH_3)_2$ of major conf.]; 2.62 (approx. septet, $^3J = 6.8$, minor conf.); 1.19 [6H, d, $^3J = 6.8$, $CH(C\underline{H}_3)_2$ of major conf.]; 1.16 (d, $^3J = 6.9$, minor conf.). Signals for trace amounts of the 2,6-diisopropylaniline starting material were seen at 7.05 ppm (d, $^3J = 7.6$, H_a); 6.81 ppm (t, $^3J = 7.7$, H_b); 1.27 (d, $^3J = 6.8$, methyl); the isopropyl methine multiplet was overlapped with the corresponding resonance from the major conformer of the maleamic acid. Peaks consistent with some of the corresponding maleimide **2c** were also evident.

A mixture of the *N*-(2,6-diisopropylphenyl)maleamic acid (2.5213 g, 9.16 mmol), ca. 4 mg BHT, anh. sodium acetate (107.5 mg, 1.31 mmol), and acetic anhydride (25 mL) was stirred at 90–100°C (boiling water bath) for 4 hr. The mixture was combined with 500 mL water and extracted with CH_2Cl_2

(4 × 50 mL). The combined organic layers were washed with 5% aq. $NaHCO_3$ (4 × 100 mL) and 400 mL brine. After drying (anh. Na_2SO_4) and solvent removal, crude *N*-(2,6-diisopropylphenyl)maleimide, **2c**, was obtained (1.8753 g, 6.81 mmol, 74% yield), mp 78–90°C. IR (KBr): 1711.0 cm^{-1}, imide C=O. Proton NMR ($CDCl_3$, ppm): 7.43 (1H, t, $^3J = 7.8$, H_b); 7.25 (2H, d, $^3J = 7.8$, H_a); 6.88 (2H, s, vinyl protons); 2.62 [2H, approx. septet, $^3J = 6.9$, $C\underline{H}(CH_3)_2$]; 2.22 (s, trace of acetic anhydride); 1.16 [12H, d, $^3J = 6.8$, $CH(C\underline{H}_3)_2$].

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

A mixture of the crude *N*-(2,6-diisopropylphenyl)maleimide, **2c**, prepared as above (787.5 mg, 3.06 mmol), phencyclone (1.0657 g, 2.79 mmol), ca. 3 mg of BHT, and toluene (25 mL) was stirred under reflux using a condenser topped by a drying tube (anh. $CaCl_2$) for 12 hr. Although some green color was still present (suggesting unconsumed **1**), the reaction mixture was cooled to room temperature to deposit light-colored precipitate. Vacuum filtration of the solid and washing with chilled toluene gave white crystals, which were air-dried (1.438 g, 2.25 mmol, 80.6% yield based on **1**. Preliminary proton NMR of this material showed appreciable residual toluene to be present, which was removed by successively adding three small portions of CD_2Cl_2 to a sample of the adduct followed by repeated solvent removal by rotary evaporator. [Phencyclone adducts may form complexes with various solvents.][9] IR (KBr): 1788.7 cm^{-1} (strained bridging ketone C=O). Proton NMR ($CDCl_3$, ppm): 8.74 [2H, d, $^3J = 8.5$, H(4/5)]; 8.41 [2H, d, $^3J = 7.8$, H(2′)]; 7.72 [2H, t, $^3J = 7.2$, H(3′)]; 7.49–7.57 [total 4H, complex m, including m at ca. 7.55 for H(3) and overlapped t, $^3J =$ ca. 7.8, at ca. 7.51 for H(4′)]; 7.39 [2H, dt, $^4J = 1.0$, $^3J = 7.6$, H(5′)]; 7.07–7.19 [complex region, total app. 9H, consisting of narrow m, 7.16–7.19 for near-isochronous H_b, H(1/8 and 2/7); d, $^3J = 8.3$ at ca. 7.13 for H(6′); approx. dt, $^4J = 0.9$, $^3J = 6.9$ at 7.08 for H_a]; 6.71 (1H, dd, $^4J = 1.3$, $^3J = 7.7$ H_c); 4.71 (2H, s, bridgehead CH); 2.62 [1H, app. septet, $^3J = 6.9$, "outer" $C\underline{H}(CH_3)_2$]; 1.20 [6H, d, $^3J = 6.8$, "outer" $CH(C\underline{H}_3)_2$]; −0.06 ppm [1H, app. septet, $^3J = 6.7$, "inner" $C\underline{H}(CH_3)_2$]; −0.39 ppm [6H, d, $^3J = 6.7$, "inner" $CH(C\underline{H}_3)_2$]. Carbon-13 NMR ($CDCl_3$, ppm): 195.46 (ketone C=O); 174.13 (imide C=O); 146.64 Q; 144.65 Q; 133.97 Q; 133.79 Q; 131.64 Q; 131.04 (6′); 129.88 (b); 129.37 (2′ and 3′); 128.48 (5′); 128.38 (4′); 127.22 (3); 126.76 Q; 126.57 (1/8 or 2/7); 126.49 (2/7 or 1/8); 126.23 Q; 123.92 (c); 123.48 (a); 123.03 (4/5); 63.69 sp^3 bridgehead $C_6H_5{-}\underline{C}$; 45.45 (bridgehead CH); 29.53 ["outer" $\underline{C}H(CH_3)_2$]; 28.06 ["inner" $\underline{C}H(CH_3)_2$]; 24.02 ["outer" $CH(\underline{C}H_3)_2$]; 22.44 ["inner" $CH(\underline{C}H_3)_2$].

RESULTS AND DISCUSSION

Syntheses of the desired adducts were achieved in a straightforward manner (Fig. 1). The commercially available 2,6-dialkylanilines were converted with maleic anhydride to the respective N-substituted maleamic acids in high yields. Cyclodehydration of the corresponding maleamic acids with acetic anhydride containing anhydrous sodium acetate at ca. 90–100°C gave reasonable yields of the maleimides, in adequate purity for adduct formation. 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. Use of a slight excess of the dienophile relative to phencyclone, e.g., typically 3–8% molar excess, allows the use of the discharge of the intense green-black phencyclone color to indicate reaction completion. Reaction of phencyclone with the respective maleimides, **2a**, **2b**, and **2c**, gave the desired Diels–Alder adducts, **3a**, **3b**, and **3c**. We note that the crude maleamic acid product reaction mixtures showed two sets of AB quartet NMR proton signals ($CDCl_3$ solvent) which we interpreted as consistent with the vinyl protons (HC=CH) of major and minor conformational isomers with respect to rotation about the amide HN–C=O bonds. We have not attempted to rigorously assign these conformers (as E or Z). The geometry about the C=C double bonds in the maleamic acids is established as cis configuration by the magnitude of the observed vicinal coupling constant (ca. 13 Hz) from the characteristic AB quartet patterns of the HC=CH moiety. (Rigorous assignments for other proton resonances of the proposed minor conformers were not always possible because of the potential presence of small amounts of the precursor anilines or traces of the corresponding maleimides.) Conversion of these maleamic acid mixtures to the maleimides, **2**, resulted in products having the expected single set of NMR absorption signals. Reaction of each maleimide with **1** gave the corresponding adduct. 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.[10–13] A "three-dimensional" representation of the adduct, **3a**, of phencyclone with 2,6-dimethylphenylmaleimide, is shown in Fig. 2; hydrogens have been hidden for clarity. 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

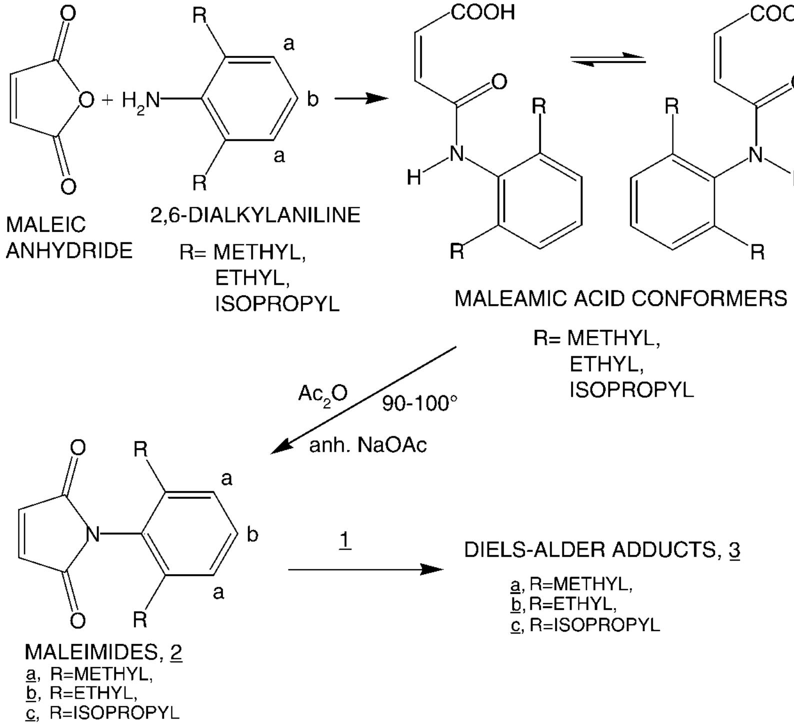

Figure 1. Synthetic scheme for preparation of Diels–Alder adducts of phencyclone.

alkyl group on the N-aryl group directed "into" the cavity of the endo adduct, and thereby anisotropically shielded by the phenanthrenoid moiety.

For each of the target adducts, assuming adequate dispersion in the NMR spectra, slow rotation of the bridgehead phenyls and the N-aryl groups should lead to nine aryl proton signals of 2H intensity and three 1H intensity aryl proton signals (total of 12 aryl proton signals). For the carbon-13 spectra of the aryl regions, signals of nine methine pairs (2 × CH), and three single intensity methines (1 × CH) are expected for the protonated aryl carbons. Seven signals for quaternary (non-proton-bearing) aryl carbon signals should be seen, including four "double intensity" and three "single intensity," for a total of 19 kinds of aryl carbons. Some effort was expended in trying to find solvents that would reveal this multitude of signals, but overlaps (particularly in the aryl proton spectral regions) were encountered. For example, ^{1}H spectra of **3a** were acquired in $CDCl_3$, CD_2Cl_2, CD_3CN, d_6-acetone, C_6D_6, and d_6-DMSO, but none of these allowed full separation of all 12 aryl proton signals. C_6D_6 was superior in providing essentially first order, fully resolved signals for each of the three protons on the N-aryl ring [with 1H doublets at 6.73 and 6.20 ppm, and a 1H triplet at 6.65 ppm] but produced substantial overlaps in the remaining aryl region (which was partly obscured by C_6HD_5 solvent impurity). The d_6-acetone seemed to be slightly better than the other solvents in providing at least partial separation of the three methines on the N-aryl ring while displaying only modest overlaps in the remaining aryl region; COSY45 spectra were acquired for **3a** in both $CDCl_3$ and in d_6-acetone. $CDCl_3$ was used for **3b**. For adduct **3c**, $CDCl_3$, C_6D_6, and d_6-acetone were tried, with $CDCl_3$ somewhat superior for aryl proton signal dispersion. For each of the three adducts described, **3a**, **3b**, and **3c**, NMR proton signals were largely assigned based on results of the "high resolution" COSY45 homonuclear chemical shift correlation spectra. Even when substantial overlaps occurred in the 1D proton spectra, separation into the second dimension with the COSY45 spectra usually 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 principal assumption was that the lowest field proton signal could be attributed to H-4, 5 of the phenanthrenoid moiety, deshielded by the multiple aromatic rings and by a mutual buttressing effect. Each proton of the phenanthrenoid $(CH)_4$ spin system can then be assigned; the H(1/8) and (2/7) usually were almost isochronous. The five protons of the bridgehead phenyl $(CH)_5$ spin system are also 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 HETCOR experiment directly gave the carbon-13 assignments for most protonated carbons. We did not attempt to rigorously assign non-protonated aryl carbons. Assignments for other non-protonated carbons, e.g., imide vs. ketone carbonyls, and the bridgehead sp^3 $C_6H_5-\underline{C}$ signal, are made by analogy with known systems.

Lastly, we would like to note several suggestions from the reviewers. A useful and informative website was recommended[14] regarding various types of weak interactions that could play a role in the Diels–Alder reactions and molecular conformations involved in these systems. Also, NMR techniques based on the nuclear Overhauser effect (NOE) have been suggested for potential utility in elucidation or confirmation of: (a) maleamic acid conformer structures; (b) endo adduct stereochemistry; and (c) rigorous distinction of the H-2′ vs. H-6′ protons of the bridgehead phenyls in the adducts. X-ray crystal structures for the adducts would establish the solid-

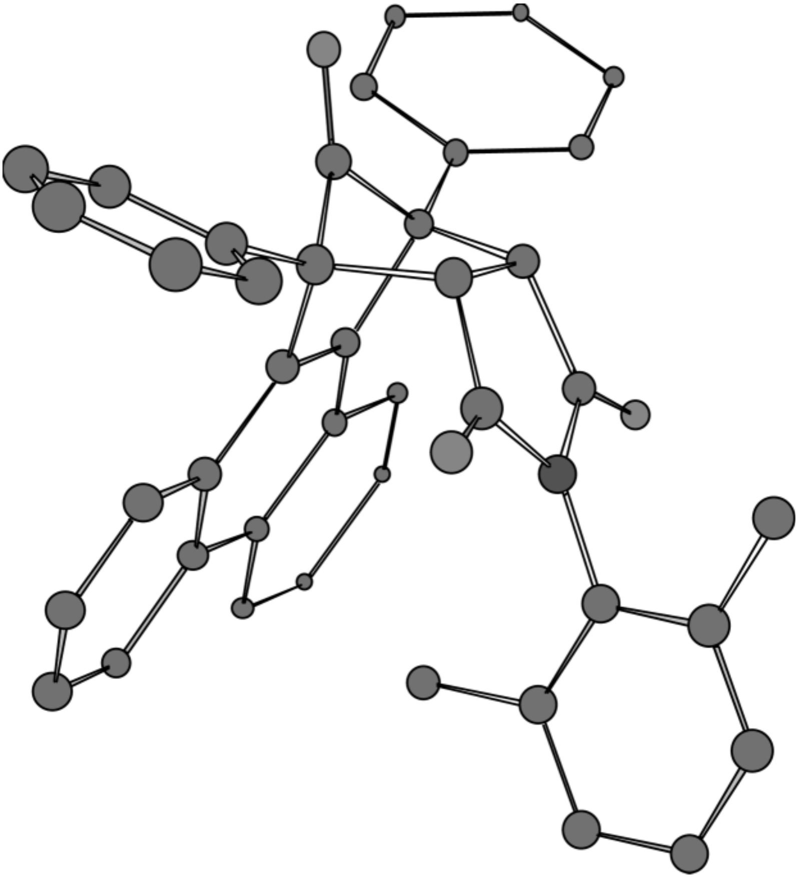

Figure 2. 3D representation of adduct **3a**, from phencyclone with *N*-(2,6-dimethylphenyl)maleimide, showing the endo stereochemistry. Twisting of the N-aryl group to reduce repulsions with the pyrrolidinedione carbonyls results in one of the methyl groups being directed "into" the adduct cavity, toward the phenanthrenoid moiety. This "inner" alkyl group is expected to experience appreciable anisotropic shielding. (Hydrogens have been "hidden" for clarity.)

state stereochemical structures. We are grateful for these suggestions for potential future investigations.

CONCLUSIONS

In each of the three phencyclone adducts, 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 7.2 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 **3b** and **3c**) 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. That the N-aryl rotations in our systems correspond to two-site degenerate processes serves to distinguish our results from elegant earlier studies by Harano and co-workers, e.g., Ref.,[10] etc. Their reports included "less symmetrical" N-aryl groups, such as 2-alkylphenyl or 1-naphthyl. For such groups, N-aryl rotations would result in conformers of unequal energies (and presumably, unequal equilibrium abundances). In contrast, the 2,6-dialkylphenyl groups reported here allow rigorous recognition of the chemical shifts for "inner" vs. "outer" alkyl groups, without the complications of differing conformers. High level molecular modeling calculations applied to these systems should be of considerable interest.

ACKNOWLEDGMENTS

Partial support has been provided to R.R. by the U.S. Education Department (Hispanic-Serving Institutions — Title V, and the Minority Science and Engineering Improvement Program), National Science Foundation, and the Professional Staff Congress—City University of New York Research Award Program, and to O.R. and R.T. by the Project ASCEND/McNair Program.

REFERENCES

1. Callahan, R.; Bynum, K.; Prip, R.; Rothchild, R. Synthesis of Diels–Alder adducts of phencyclone and NMR studies of hindered rotations of unsubstituted bridgehead phenyls: microscale experiments in organic chemistry. [Chem Educator 1998 3 (2): S1430–4171 (98) 02192-4 Avail. URL: http://journals.springer-ny.com/chedr].
2. Callahan, R.; Marshall, K.; Rothchild, R.; Rosmarion, K. Syntheses of phencyclone analogs. Applications for NMR studies of hindered rotations and magnetic anisotropy in crowded Diels–Alder adducts. The Chemical Educator, [online] 2001, 6, 227234 DOI 10.1007/s00897010488a.
3. Bynum, K.; Rothchild, R. NMR studies of hindered rotation. The Diels–Alder adduct of phencyclone with *N*-*n*-propylmaleimide: restricted motion of bridgehead phenyls. Spectrosc. Lett. **1996**, *29* (8), 1599–1619.
4. Bynum, K.; Rothchild, R. NMR studies of hindered rotation. The Diels–Alder adduct of *N*-*n*-butylmaleimide with phencyclone: restricted motion of bridgehead phenyls. Spectrosc. Lett. **1996**, *29* (8), 1621–1634.
5. Bynum, K.; Rothchild, R. Analysis of hindered rotation and magnetic anisotropy by NMR. Models for drugs and agricultural compounds. The Diels–Alder adduct of phencyclone with *N*-carbamoylmaleimide. Spectrosc. Lett. **1997**, *30* (4), 727–749.
6. Amin, M.; Bynum, K.; Callahan, R.; Prip, R.; Rothchild, R. Studies of hindered rotation and magnetic anisotropy by ^{1}H, ^{13}C and ^{19}F NMR. The Diels–Alder adduct of *N*-pentafluorophenyl maleimide and phencyclone: a model for drugs. Spectrosc. Lett. **1998**, *31* (3), 673–692.
7. Langowski, B.; Rothchild, R.; Sapse, A.-M. Ab initio studies of hindered rotation of some aromatic rings in *N*-2,6-difluorophenyl imides and unsubstituted bridgehead phenyls. Spectrosc. Lett. **2001**, *34* (2), 235–251.
8. Azanli, E.; Rothchild, R.; Sapse, A.-M. Ab initio studies of hindered aryl rotations of methaqualone, mecloqualone and 3-(2,6-difluorophenyl)-2-methyl-4(3H)-quinazolinone. Spectrosc. Lett. **2002**, *35* (2), 257–274.
9. Eto, M.; Setoguchi, K.; Harada, A.; Sugiyama, E.; Harano, K. Phencyclone Diels–Alder adducts as a new crystalline host. Role of $C\text{–}H\cdots\pi$ and $C\text{–}H\cdots O$ interactions. Tetrahedron Lett. **1998**, *39* (52), 9751–9754.
10. Sasaki, T.; Kanematsu, K.; Iizuka, K. Molecular design by cycloaddition reactions. XXV. High peri- and regiospecificity of phencyclone. J. Org. Chem. **1976**, *41* (7), 1105–1112.
11. Yoshitake, Y.; Misaka, J.; Setoguchi, K.; Abe, M.; Kawaji, T.; Eto, M.; Harano, K. Non-hydroxylic clathrate hosts of $[4+2]\pi$ cycloadducts of phencyclone and *N*-arylmaleimides: recognition of aromatic guests. J. Chem. Soc. Perkin Trans. 2 **2002** (9), 1611–1619.

12. Yoshitake, Y.; Misaka, J.; Abe, M.; Yamasaki, M.; Eto, M.; Harano, K. Carboxylic acid clathrate hosts of Diels–Alder adducts of phencyclone and 2-alkenoic acids. Role of bidentate C–H···O hydrogen bonds between the phenanthrene and carbonyl groups in host–host networks. Org. Biomol. Chem. **2003**, *1* (7), 1240–1249.
13. Tan, R.Y.S.; Russell, R.A.; Warrener, R.A. The application of ^{13}C-NMR spectroscopy to the determination of the stereochemistry of Diels–Alder adducts. Tetrahedron Lett. **1979**, *20* (52), 5031–5034.
14. M. Nishio. The CH/π Interaction. http://www.tim.hi-ho.ne.jp/dionisio/.

Received October 7, 2003
Accepted April 9, 2004