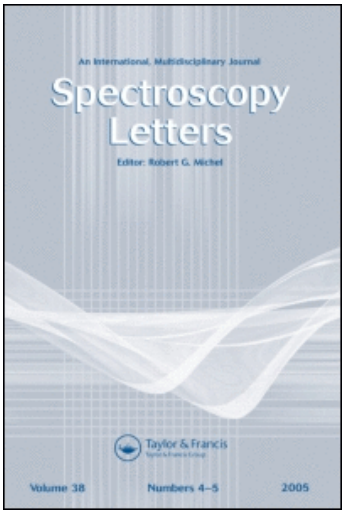

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Analysis of Hindered Rotation and Magnetic Anisotropy by NMR. Models for Drugs and Agricultural Compounds. The Diels-Alder Adduct of Phencyclone with N-Carbamoylmaleimide

Kevin Bynurn[a]; Robert Rothchild[ab]
[a] Science Department, The City University of New York, John Jay College of Criminal Justice, New York, NY [b] The Doctoral Faculty, The Graduate School and University Center, City University of New York,

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ANALYSIS OF HINDERED ROTATION AND MAGNETIC ANISOTROPY BY NMR. MODELS FOR DRUGS AND AGRICULTURAL COMPOUNDS. THE DIELS-ALDER ADDUCT OF PHENCYCLONE WITH N-CARBAMOYLMALEIMIDE

Key Words: Dynamic NMR, ^{1}H NMR, ^{13}C NMR, One- and two-dimensional NMR, COSY, DEPT, Restricted rotation, Stereochemistry, Anisotropy, Pharmaceuticals, Analysis.

Kevin Bynum[a] and Robert Rothchild[a,b]*

a) The City University of New York, John Jay College of Criminal Justice, Science Department, 445 West 59th Street, New York NY 10019-1199; b) The Doctoral Faculty, The Graduate School and University Center, City University of New York.

ABSTRACT

Analysis of NMR spectra of selected model compounds can be of great value in understanding aspects of hindered rotation and magnetic anisotropy in drugs and other compounds of much intrinsic importance. One- and two-dimensional ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) studies have been performed at ambient temperatures on the Diels-Alder adduct of N-carbamoylmaleimide with phencyclone, 1. The data for the adduct, 2, are interpreted as being consistent with: a) essentially slow exchange limit (SEL) spectra with respect to rotation about the $C(sp^2)-C(sp^3)$ bonds to the unsubstituted bridgehead phenyls, b) slow

*To whom correspondence should be sent at John Jay College.

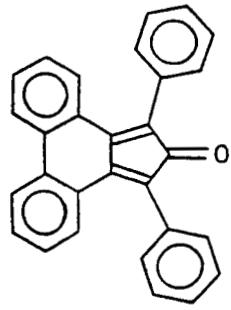
rotation on the NMR timescale for the amide NH_2 group, and c) fast rotation about the amide N-$CONH_2$ bond to the ring nitrogen. The assigned endo stereochemistry for adduct 2 and the conclusions regarding bond rotation rates are based on numbers of observed NMR signals and magnetic anisotropic effects. Full ^1H NMR spectral assignments and preliminary ^{13}C assignments are presented.

INTRODUCTION

For some time, we have been studying the NMR spectra of pharmaceuticals, agricultural compounds and analogs, regarding possible NMR methods for enantiomeric excess determinations and special aspects of hindered group rotations and magnetic anisotropy. Recently, we have focussed on a class of compounds as models for these effects. Hindered rotations, for example, can result in enantiomerism due to axial chirality, as in methaqualone (a sedative/hypnotic), afloqualone (a skeletal muscle relaxant), or Schering SCH40120 (potential antipsoriatic agent), and may also lead to unexpected anisochrony or NMR spectral line broadening, as in ketazolam (an anxiolytic). The detailed analysis of NMR spectra of relevant model compounds can produce considerable insight into the molecular behavior and spectral properties of drugs or other compounds of great intrinsic importance.

Phencyclone, 1, is a potent Diels-Alder diene component (1). We have reported that 1 forms Diels-Alder adducts with norbornadiene (2,3), 1,4-benzoquinone (4), maleic anhydride (5), N-n-propylmaleimide (6) and N-n-butylmaleimide (7) in which a remarkable degree of steric crowding results in hindered rotation about $C(sp^2)$-$C(sp^3)$ bonds to unsubstituted bridgehead phenyls. The hindered rotation is implied by slow exchange limit (SEL) ^1H and ^{13}C NMR spectra with the dispersion provided by medium field spectrometers, at ambient temperatures.

We report here the synthesis of the adduct, 2, of N-carbamoylmaleimide with 1, and the characterization of this adduct with one- and two-dimensional (1D and 2D) NMR



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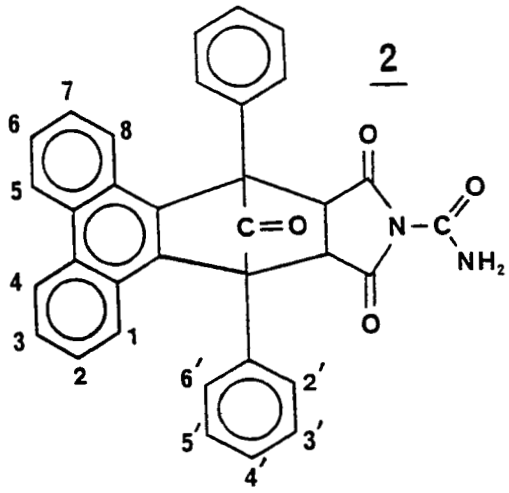

2

techniques at 300 MHz (for ^{1}H) and 75 MHz (for ^{13}C). Studies of this compound provide a significant extension of earlier work in this series by allowing a simultaneous examination of potential hindered rotations of the adduct's bridgehead phenyls as well as rotations about the two N-C=O bonds of the N-carbamoyl group.

EXPERIMENTAL

Experimental procedures followed those described earlier (6,7) unless stated otherwise. NMR spectra were obtained on a Bruker ACF300 spectrometer (Billerica MA) with Aspect 3000 data system on undegassed samples at ambient temperatures, with observe frequencies of 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C. The spectra normally employed standard Bruker microprograms, e.g., for COSY90 and DEPT45. Reagent phencyclone and N-carbamoylmaleimide were obtained from Lancaster Synthesis Inc. (Windham NH 03087-9977). Chloroform-d (99.8. at. % D, containing 0.03% tetramethylsilane [TMS] as internal standard) was obtained from Aldrich Chemical Co., Inc. (Milwaukee WI 53233) and acetone-d_6 (99.9. at. % D) from Cambridge Isotope Labs. (Woburn MA 01801). Reagents were used as supplied. NMR chemical shifts are reported in δ units (ppm) relative to TMS at 0.0 ppm; for ^{13}C spectra, shifts were referenced to the center line of the $CDCl_3$ triplet at 77.0 ppm.

Preparation of the N-Carbamoylmaleimide Adduct, 2, from Phencyclone:

N-Carbamoylmaleimide (150 mg, 1.07 mmol) was suspended in 60 ml of CH_2Cl_2 in a 100 ml r.b.S.N. flask equipped with a magnetic stirbar. Phencyclone (364.8 mg, 0.954 mmol) was added all at once to give an opaque dark olive green suspension. The flask was then stoppered, protected from light by covering with Al foil, and stirred at ambient temperature for 21.5 hours to yield a milky white suspension of crystals of the adduct 2. About 50 ml of CH_2Cl_2 was removed on a rotary evaporator (aspirator pressure, water bath below 30°). The suspension was then cooled in an ice slush, the crystals collected by vacuum filtration, washed with three 1 ml portions of ice cold CH_2Cl_2 and dried to yield 376.2 mg (75.5% yield) of fine white crystals. This sample was used directly for subsequent NMR studies. Mp (dec) 303-306°. Infrared data, selected peaks (phase, cm^{-1}): (KBr): 1793.7 (strained ketone carbonyl); 1757.8, 1718.0, 1580, 1302.9, 1182.1, 755.2, 724.9, 698.1; ($CHCl_3$): 1802.3

(strained ketone carbonyl), 1761.7, 1712.4, 1610, 1570.1, 1499.8, 1448.3, 1303.9, 1180.5.

RESULTS AND DISCUSSION

The 300 MHz ^{1}H NMR spectrum for the adduct 2 in $CDCl_3$ at ambient temperature is shown in Figure 1, with the final spectral assignments and details collected in Table 1. In this series of Diels-Alder adducts of phencyclone that we have previously reported, hindered rotation about the $C(sp^2)$-$C(sp^3)$ bonds from the unsubstituted phenyls to the bridgehead carbons appears to result from potential severe crowding between the phenyl ortho protons, 2′ and 6′, and H-1,8 of the adduct phenanthrene moiety. Closest approach distances as little as ca. 0.1-0.2 Å for these protons are indicated by inspection of Dreiding stereomodels (8), and the ^{1}H NMR spectra of these adducts (at 200 or 300 MHz) as well as the ^{13}C spectra (at 50 or 75 MHz) have been interpretable as consistent with SEL spectra due to bridgehead phenyl rotations that are slow on the respective NMR timescales. In the phencyclone adducts of norbornadiene, maleic anhydride or 1,4-benzoquinone, the products all have a mirror plane of symmetry which renders the two phenyls enantiotopic; the phenanthrene moiety positions 1/8, 2/7, 3/6, 4/5, etc., are also enantiotopic pairs. For the two N-n-alkylmaleimide adducts of 1 that we have studied, rapid rotation on the NMR timescale of the N-n-propyl and N-n-butyl groups (about the N-CH_2 bonds) effectively generates a comparable plane of mirror symmetry. The presence of the sigma symmetry plane in the adducts, on the NMR timescale, dramatically simplifies the expected NMR spectra of the adducts. For example, the aryl ^{1}H region should show nine equal intensity (2H) signals, consisting of four gross doublets and five gross triplets, if phenyl rotation is slow. If the rotation of the bridgehead phenyls were fast on the NMR timescale, the phenyl ortho positions 2′/6′ would be interchanged and averaged; the meta positions 3′/5′ would likewise be averaged. A fast exchange limit (FEL) spectrum could show two 4H intensity signals (a gross

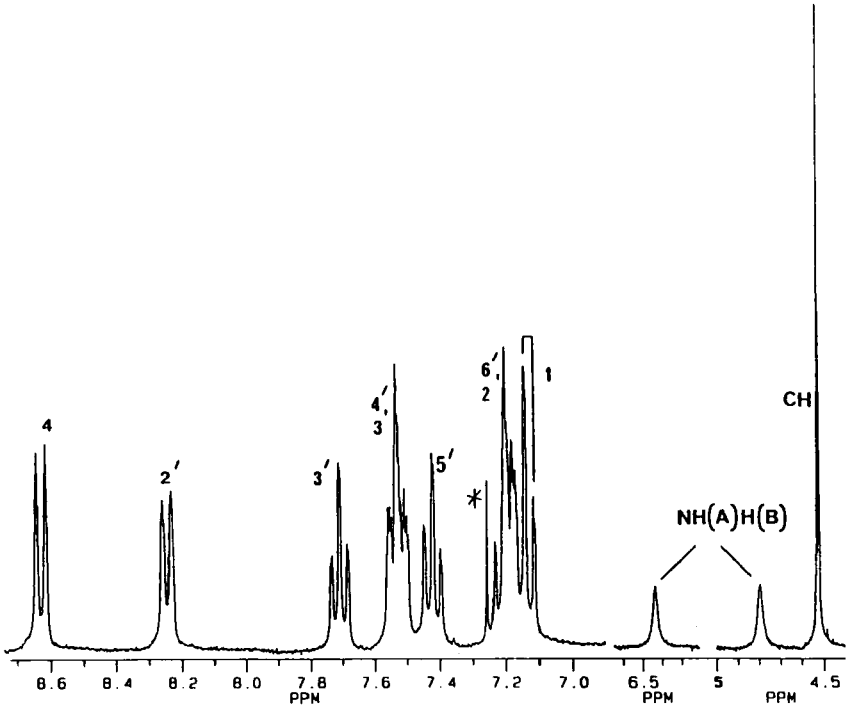

Figure 1. The 300 MHz ^{1}H spectrum of adduct 2 in $CDCl_3$ at ambient temperatures. Note that different chemical shift scales have been used for the various spectral regions; one division in each region is 0.1 ppm. ($CHCl_3$ impurity marked by asterisk.)

doublet for H-2′/6′ and a gross triplet for H-3′/5′) and five 2H intensity signals (two doublets and three triplets). Coincidental peak overlaps could reduce the number of observed signals. For ^{13}C NMR, the SEL case could show nine protonated and four unprotonated aryl carbon signals. The FEL case could show two "double intensity" (4C) and five additional (2C) signals for the protonated aryl carbons, as well as four unprotonated aryl carbon signals. Our earlier reports were consistent with the SEL case. In this present study of the adduct of 1 with N-carbamoylmaleimide, the

effective presence of a plane of mirror symmetry in the product 2 could not be taken for granted. Effective mirror symmetry of adduct 2 on the NMR timescale would require rapid rotation about the "amide"-type bond, N-$CONH_2$. Without such a rapid rotation of the carbamoyl group, the two phenyls would no longer be enantiotopic, since one phenyl would be close to the carbamoyl oxygen and the other phenyl would be further away (assuming that the carbamoyl group would preferentially be in a conformation coplanar with the pyrrolidinedione ring). This "coplanar carbamoyl conformation" would be favored electronically since it would maximize resonance delocalization of this system. It would also be favored by permitting intramolecular hydrogen bonding via a six-membered ring, between the NH_2 group and the proximal carbonyl of the pyrrolidinedione ring. Alternatively, if the carbamoyl group, $CONH_2$, preferentially existed in a plane perpendicular to the plane of the pyrrolidinedione ring (due, perhaps, to steric repulsions with the dione carbonyls), a plane of mirror symmetry could be present in the adduct molecule, but two distinct rotamers might exist in which anisochronicity could lead to substantial spectral complexity. Even simple amides such as N-N-dimethylacetamide are well known for exhibiting hindered rotation about the amide bond, N-CO, resulting in observed anisochronous signals for the NR_2 groups even with low spectrometer frequency (9a,10). The potential hindered rotations on both sides of the carbamoyl carbonyl, and their implications for the NMR spectra of the phencyclone adduct, 2, generated considerable interest in this system.

The 1D ^1H NMR spectrum of a $CDCl_3$ solution of 2 (Fig. 1) in the aryl region shows only six absorption regions due to coincidental near-overlaps. Two 2H intensity doublets are centered at 8.630 and 8.246 ppm with observed couplings of 8.36 and 7.81 Hz, respectively. Two 2H intensity approximate triplets are centered at 7.711 and 7.423 ppm with couplings of 7.70 and 1.12 Hz for the former, and 7.47 and ca. 1 Hz for the latter. A 4H multiplet is centered

near 7.53 ppm and a 6H multiplet appeared near 7.20 ppm. Detailed assignments of the aryl ^1H region relied on a "high resolution" COSY spectrum (^1H-^1H homonuclear 2D correlation), and 1D homonuclear decoupling experiments, discussed below. In addition, two broad 1H singlets appeared at 6.439 and 4.796 ppm, assigned to the two protons of the NH_2, nonequivalent due to slow rotation of the amide NH_2 on the NMR timescale. A sharp 2H intensity singlet at 4.524 was assigned to the two bridgehead methines alpha to carbonyl. Note that isochrony of these methines is consistent with FEL averaging as a result of rapid rotation of the carbamoyl group about the bond to the pyrrolidinedione nitrogen, N-$CONH_2$. If the carbamoyl group conformation(s) corresponding to local energy minima involved orientations in a plane perpendicular to the pyrrolidinedione ring, either fast carbamoyl group rotation is required, or only one of the two possible rotamers exists, in order to have chemical shift equivalence of the bridgehead methines. It seems unlikely that one such rotamer would be so strongly favored over the other. We therefore favor fast carbamoyl rotation to achieve isochronicity of the bridgehead methines, but cannot formally distinguish fast interconversions of degenerate rotamers with carbamoyl coplanar with the heterocyclic ring from interconversions of rotamers of unequal energy (i.e., "exo" versus "endo") with the carbamoyl perpendicular to the heterocyclic ring plane. The only other NMR signals in these regions are attributable to CH_2Cl_2 (which was used as the reaction solvent), and $CHCl_3$ (impurity in the NMR solvent).

The COSY spectrum in Figure 2 showed weak crosspeak correlations between the two broad singlets assigned to the NH_2 protons, corresponding to a two-bond geminal coupling H(A)-N-H(B). No splitting is observable in the 1D ^1H spectrum, but COSY spectra (or variants) are capable of showing correlations even in cases where the coupling magnitude is smaller than the natural linewidth or where

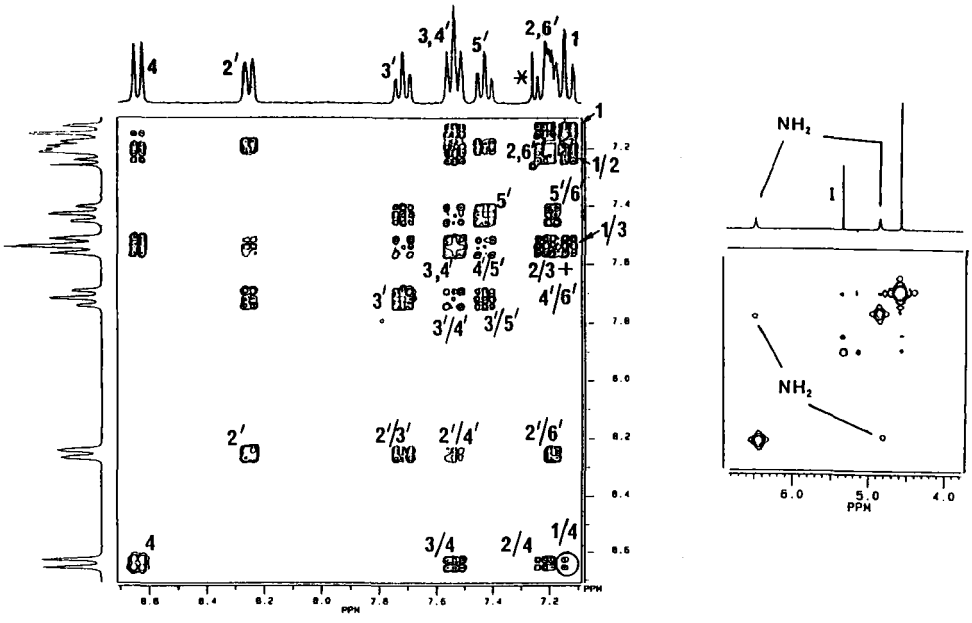

Figure 2. Two-dimensional homonuclear ^{1}H chemical shift correlation spectrum (COSY) of 2. The expanded aryl region ("high-resolution COSY") and upfield regions are shown; note that different scales have been employed for chemical shifts and contour levels. Assignments for crosspeaks are indicated. ($CHCl_3$ impurity marked by asterisk; CH_2Cl_2 by I.)

lines are broadened (13,14). For an amide NH_2, considerable broadening is expected due to ^{14}N quadrupolar moment relaxation of the protons.

The "high resolution COSY" of the aryl ^{1}H region showed three crosspeaks for the lowest field doublet at 8.63 ppm, assigned to H-4,5. The strongest of these crosspeaks, assigned as the vicinal ^{3}J(H-3/4) was centered at ca. 7.54 ppm and a slightly weaker crosspeak at ca. 7.22 ppm is assigned as ^{4}J(H-2/4). A very weak crosspeak correlated to the highest field doublet near 7.13 ppm was then assigned as

the long range ^5J (H-1/4) correlation, thus mapping out the phenanthrene moiety $(CH)_4$ system. The doublet near 8.25 ppm, assigned as the bridgehead phenyl ortho proton H-2′ (roughly syn to the ketone carbonyl in the presumed favored conformation) showed two strong crosspeaks. A 2x3 crosspeak correlated to the triplet at 7.71 ppm, assigned as the vicinal ^3J (H-2′/3′) coupling. An intense crosspeak which appeared as a 2x2 pattern at ca. 7.18 ppm could then be assigned as the ^4J "W" coupling (H-2′/6′). A third, weaker correlation at ca. 7.54 ppm was then assignable as ^4J (H-2′/4′). Note that ^5J crosspeaks for the bridgehead phenyls, i.e., H-2′/5′ and H-3′/6′, are too weak to see. COSY crosspeak assignments are included in Fig. 2, permitting assignments for the phenyl $(CH)_5$ system. Our assignments suggest two near-coincidental overlaps, with the approximate triplet (4H intensity) near 7.53 ppm due to H-3 and H-4′, and the 4H intensity multiplet near 7.2 ppm arising from H-2 and H-6′.

The one starting assumption normally made in aryl ^1H NMR assignments for these adducts of **1** is that the lowest field doublet, ca. 8.5-8.8 ppm, is the phenanthrene moiety H-4,5. One of the bridgehead phenyl ortho protons, designated H-2′, is assigned as the proton proximal to the strained ketone carbonyl when the phenyls are in their presumed low energy conformation, near coplanarity with the ketone carbonyl and roughly perpendicular to the phenanthrene moiety. This proximity to the carbonyl is thought to provide anisotropic deshielding (9b,11b,15) and H-2′ in these adducts has been assigned as the doublet ca. 8.2 ppm. Selective irradiation at the center of the lowest field H-4,5 doublet produced the results shown in Figure 3. No changes were observed in the doublet at 8.246 ppm (H-2′) or in the two 2H triplets, but distinct spectral sharpening or spectral simplification has occurred in the 4H multiplet from 7.49-7.53 ppm and the 6H multiplet from 7.10-7.25 ppm. The 4H lower field multiplet of the unirradiated spectrum grossly appears as a 1:2:1 triplet with extensive fine

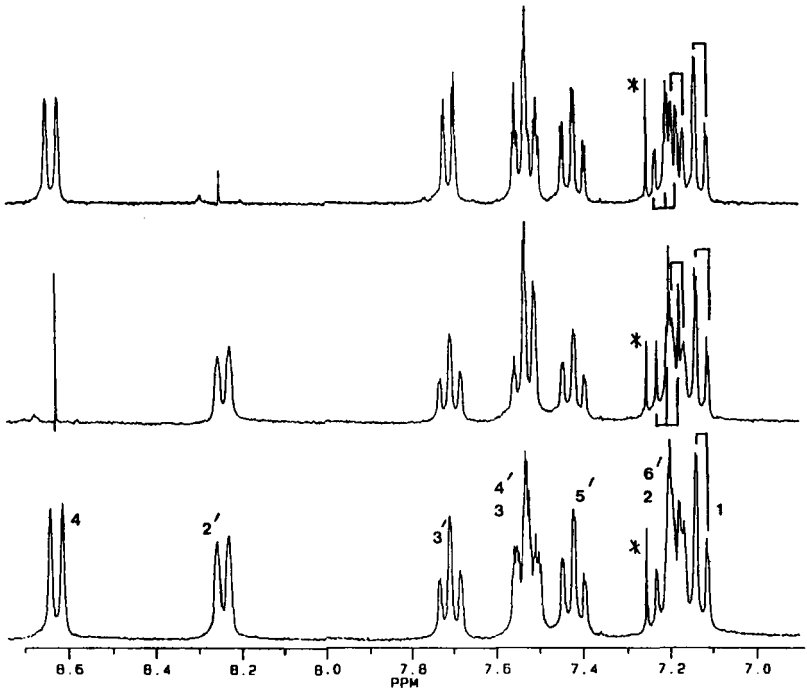

Figure 3. Expansions of part of the aryl ^{1}H spectral region of 2 with selective homodecoupling (irradiation of the H-4,5 doublet at 8.63 ppm) shown in the middle trace. The normal undecoupled spectrum is shown below. Decoupling of the H-2′ doublet at 8.25 ppm produced the top spectrum.

structure, but with decoupling of H-4,5, in addition to removal of much fine structure, the two higher field branches have become substantially greater than the low field branch. This could be interpreted as an approximate 2H doublet roughly overlying the two higher field branches of a 2H triplet. Irradiating H-4,5 would leave H-3,6 with only one large vicinal coupling (to H-2,7) and the smaller ^{4}J coupling to H-1,8; thus, H-3,6 would simplify to a gross doublet, assigned here as ca. 7.53 ppm. In the higher field 6H multiplet from 7.10-7.25 ppm note that the sharp peak at

7.26 ppm results from $CHCl_3$ impurity in the solvent), decoupling H-4,5 results in the appearance of three sharp peaks constituting an apparent triplet centered at 7.21 ppm. This could be assigned as H-2,7, with two vicinal neighbors, if the three bond couplings $^3J(1/2)$ and (2/3) were approximately equal. The highest field signals in this 6H multiplet region are clearly characterized as a distinct double doublet (dd) in the 7.10-7.15 ppm region. This dd pattern is distinctly sharper than in the undecoupled spectrum based on lower valley heights (when H-4,5 is irradiated). The last protons of the phenanthrene moiety of the adduct 2, i.e., H-1,8, should be assigned to this gross doublet centered at 7.13 ppm. H-1,8 should be split into a gross doublet by their single vicinal neighbors H-2,7 (^3J ca. 8 Hz), with a smaller ^4J coupling to H-3,6 (estimated ca. 1.5 Hz). A very small long range ^5J coupling to H-4,5 (probably about 0.5 Hz) is removed by decoupling of H-4,5, resulting in the sharpening of the H-1,8 signal to the well resolved dd. Evidently there is a gross doublet centered at ca. 7.18 ppm partly overlapping the H-2,7 signal; this final doublet would have to be H-6′ on the phenyl rings. This single selective decoupling experiment serves to fully map out the $(CH)_4$ spin system of the phenanthrene moiety of 2, allows numerical shift assignments (but not unambiguous label designations) to all aryl proton signals, permits identification of the phenyl H-6′ resonance, and supports the slow rotation of the bridgehead phenyls with an SEL spectral regime based on the apparent presence of four 2H gross doublets and five 2H gross triplets. These results seem fully consistent with the COSY results. Rapid rotation of the carbamoyl group about the $N\text{-}CONH_2$ bond is further supported by these results.

A second selective homonuclear decoupling experiment was performed with irradiation of the H-2′ doublet. The major change was in the gross triplet at 7.71 ppm, which appeared as a gross doublet (actually dd) with H-2′ decoupling, confirming the assignment of H-3′. The

remaining spectral changes were somewhat subtle. The 4H multiplet from 7.49-7.56 ppm appeared as a sharpened distinct triplet of triplets. This multiplet results from the near-coincidental overlap of two gross triplets from H-3 and H-4′; with H-2′ irradiation, the four bond coupling H-2′,4′, ca. 2 Hz, is removed, leading to some sharpening. H-4′ remains as a gross triplet because of two vicinal couplings to H-3′ and H-5′. The H-5′ signal at ca. 7.42 ppm sharpens to a well-resolved triplet of doublets with H-2′ irradiation, due to removal of the long range ^{5}J (H-2′,5′) coupling. Simplification of the 4H multiplet from 7.16-7.24 ppm upon H-2′ decoupling allows this region to be more clearly seen as an overlapping of an approximate doublet (H-6′) and the gross triplet (actually dt) of H-2. Essentially no change is seen in the approximate doublet centered near 7.13 ppm, assigned to H-1 of the phenanthrene moiety, when H-2′ is irradiated.

The 1D ^{13}C spectrum of adduct 2 is shown in Figure 4, for a $CDCl_3$ solution (undegassed) at ambient temperatures; 4500 FIDs were accumulated to achieve the favorable signal-to-noise ratio, using a relaxation delay of 10 sec and a 4 μsec pulse width (ca. 54^0 tip angle), so that unprotonated carbon peaks are readily seen. The lowest field signals of the carbonyls at 195.75, 172.64, and 155.27 ppm, are assignable to the strained ketone carbonyl, the two pyrrolidinedione carbonyls, O=CNC=O (rendered equivalent by rapid carbamoyl group rotation), and the $CONH_2$ carbamoyl carbonyl, respectively. With the indicated relaxation delay and pulse width, the two carbonyls of the maleimido ring produce a signal about three times greater (in height and integrated area) than the single carbonyls of the carbamoyl and ketone. At high field are seen the unprotonated bridgehead carbons, $C_6H_5\underline{C}$, at 63.56 ppm, and the threefold more intense (by integrated area) 44.66 ppm peak of the bridgehead methines. These shifts are consistent with previously studied adducts of 1 with other maleimides. The

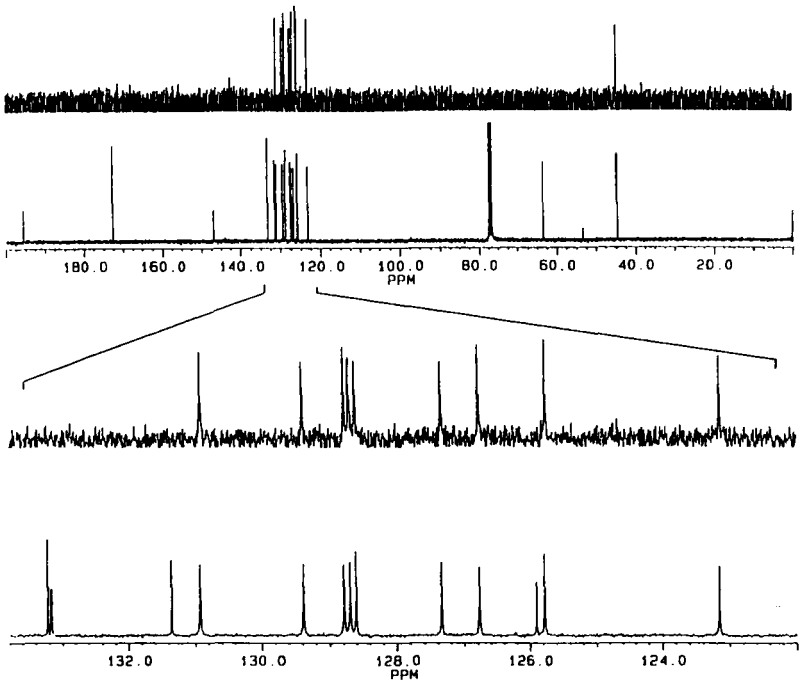

Figure 4. The 75 MHz ^{13}C NMR spectrum of 2 in $CDCl_3$ (ambient temperatures) with composite pulse decoupling (CPD) of protons. The "DEPT45" spectrum, displaying protonated carbon signals, is shown for comparison. See Results and Discussion. From top to bottom, the spectra are: (a) DEPT45 full spectrum, (b) full standard 1D ^{13}C spectrum (RD = 10 sec, 4500 acquisitions), (c) DEPT45 aryl region expansion, (d) 1D ^{13}C spectrum aryl region expansion.

impurity peak at 53.42 ppm is attributed to the reaction solvent, CH_2Cl_2.

Most significant is the aryl carbon signal region, which clearly exhibits thirteen peaks. Only two are appreciably shorter than the others, but by integrated area measurements, we unambiguously see nine large peaks (relative areas 1.02-1.15) and four small peaks (relative areas 0.28-0.53). This precisely fits the expectation for

an SEL system with slow bridgehead phenyl rotation and fast carbamoyl group rotation, for which nine protonated aryl carbon signals and four (weaker) unprotonated signals can be predicted. These results are summarized in Table 2. The DEPT45 spectrum (which should reveal all protonated carbons) was confirmatory, with the absence of the four low-area aryl peaks indicating that these were the unprotonated quaternary carbons; the three carbonyl signals and the $C_6H_5\underline{C}$ signals were also absent from the DEPT45 spectrum. The comparison of the aryl region DEPT and 1D ^{13}C spectra are included in Figure 4.

Comparisons of ^1H NMR chemical shifts for 2 with phenanthrene itself show substantial shifts to higher field for H-1,8 and H-2,7 of the adduct's phenanthrene moiety, about 1.0 ppm for H-1,8 and 0.6 ppm for H-2,7. This can be explained if these nuclei lay within the shielding cones of the bridgehead phenyls, which is consistent with a favored conformation of 2 in which the phenyls are rotated roughly perpendicular to the phenanthrene moiety plane (to relieve potential repulsions between the phenyl ortho protons and H-1,8). This conformation may equally account for substantial deshielding of the phenyl H-2', assigned as proximal and syn to the plane of the ketone carbonyl (9b,c,11b,15). H-2' is deshielded nearly 1.0 ppm relative to benzene. The similarity of the ^1H chemical shifts of the bridgehead methines of 2, at 4.52 ppm, to those in the analogous adducts of 1 with N-n-propylmaleimide (6) and N-n-butylmaleimide (7), which resonate at 4.40 and 4.41 ppm, respectively, support the same endo stereochemistry for these adducts. The ^{13}C chemical shifts for the bridgehead methines in these three adducts are 44.66 ppm for 2, and 44.50 and 44.45 ppm for the respective N-n-propyl and N-n-butyl analogs, suggesting a uniform stereochemistry.

Due to low solubility in $CDCl_3$, the reference spectrum of reagent N-carbamoylmaleimide was obtained in acetone-d_6. Two separate very broad signals were observed at 6.79 and 7.25 ppm, attributed to the NH(A)H(B) protons under slow

Table 1. NMR spectral data for 2, with chemical shifts in ppm. ^1H shifts[a] (observed coupling constants, in Hz)[b] for 2 and selected Reference Compounds.

Nucleus	2	(Est'd J, Hz[b])	Phenanthrene (refs. 11a, 12)	
H-1,8	7.13	(8.44, 1.43)	8.12	
H-2,7	7.21	(ca. 7.6)	7.82	
H-3,6	7.525		7.88	
H-4,5	8.630	(8.36)	8.93	
			N-n-Carbamoyl-maleimide[c]	
CH	4.524		7.02	
NH_2 (A)	6.439	broad	7.25	broad
NH_2 (B)	4.796	broad	6.79	broad
H-2′	8.246	(7.81)		
H-3′	7.711	(7.64, 1.06)[b]		
H-4′	7.535			
H-5′	7.423	(7.45, ca. 1)[b]		
H-6′	7.18			

Notes: See Results and Discussion. (a) Chemical shift values for nuclei in overlapping multiplet regions (7.49-7.57 and 7.15-7.25 ppm) reflect some estimations, based on COSY and homonuclear decoupled data, with error estimated as ± 0.02 ppm. (b) Slight differences in couplings between tabulated and Discussion values reflect calculations based on standard 1D spectra and spectra with selective decoupling, e.g., with H-4,5 decoupled. Experimental error is estimated as 0.1 Hz. (c) Data from this present work, in CD_3COCD_3. In $CDCl_3$, the methine signal occurred at 6.87 ppm and two broad signals were tentatively assigned to the NH_2 at ca. 5.3 and 7.5 ppm.

rotation conditions. An apparent singlet at 7.021 ppm was assigned to the olefinic protons. We note that with $CDCl_3$ as solvent, the olefinic proton signal could be seen at 6.87 ppm. Two very broad and weak (poor signal-to-noise ratio) absorptions were tentatively assigned to the NH_2 at ca. 5.3 and 7.5 ppm (estimated). If solvent effects are neglected, we see that in the ^1H NMR spectra of N-carbamoylmaleimide and adduct 2, slow rotation is evidently present for the

Table 2. Carbon-13 chemical shift data (in ppm) for adduct 2. See Results and Discussion, Notes, and Experimental sections for details.

δ (ppm)	Assignment	Relative Area
195.75	ketone C=O	0.177
172.64	dione, 2 x C=O	0.509
147.02	carbamoyl $CONH_2$	0.162
133.22	Q	0.535
133.17	Q	0.291
131.36	Q	0.479
125.90	Q	0.323
130.93		1.104
129.38		1.138
128.79		1.104
128.70		1.099
128.60		1.111
127.34		1.093
126.78		1.094
125.78		1.022
123.15		1.147
63.56	C_6H_5C	0.417
44.66	2 x CHC=O	1.202

Notes: Q denotes quaternary unprotonated carbons based on absence from DEPT spectrum and low areas in 1D ^{13}C spectrum. Each signal corresponds to two carbons in adduct 2 except for the ketone and carbamoyl carbonyls which are each one carbon. Data obtained for an undegassed $CDCl_3$ solution at ambient temperature.

carbamoyl group CO-NH_2 bond, while fast rotation (FEL) is present about the bond from the ring nitrogen to the carbamoyl group, N-$CONH_2$. For adduct 2 in $CDCl_3$, the NH_2 peaks appeared at 4.80 and 6.44 ppm and in acetone-d_6 they appeared at ca. 6.30 and 6.55 ppm.

We have examined published ^1H and ^{13}C spectra from several major compilations (16-19) to look for evidence of fast or slow rotations in primary amides (i.e., RCO-NH_2 rotations) or simple tertiary amides (e.g., rotation of dimethylamino groups in N,N-dimethylformamide [DMF] or N,N-dimethylacetamide [DMA]). Similarly, we examined spectra of

ureas of the type $RR'NCONH_2$ or $RR'NCON(CH_3)_2$ or analogs. We looked at both 60 and 300 MHz ^1H spectra and 25 and 75 MHz ^{13}C spectra; solvents included DMSO-d_6, DMSO-d_6 + $CDCl_3$ (ca. 1 :1 v/v); $CDCl_3$, and dioxane. Where freedom from spectral overlaps permitted assignments, amides generally seemed to show hindered rotation about the CO-NH_2 bond in primary amides, with two separate peaks for the NH(A)H(B) protons. Tertiary amides such as DMF and DMA showed separate ^1H and separate ^{13}C signals, again supporting hindered rotations about the N-CO bond. This implies a high rotation barrier due to substantial double bond character between the nitrogen and the carbonyl, as a result of mesomeric electron release from the nitrogen.

In contrast, ureas almost always seemed to display fast rotations about both of the N-CO bonds, with, e.g., a single peak for the NH_2 group of monosubstituted ureas or a single peak for the $N(CH_3)_2$ groups of tetramethylurea in ^1H or ^{13}C NMR. It should be noted that the question of potential N-CO rotation rates in amides and ureas, as judged by the number of ^1H or ^{13}C NMR signals, is not at all trivial. We observed some primary amides that exhibited a single NH_2 peak (e.g., FCH_2CONH_2 and Cl_3CCONH_2 at 300 MHz in DMSO-d_6 + $CDCl_3$) and at least one "monosubstituted urea" that showed two separate peaks for the NH_2 (phenylacetylurea, 300 MHz, DMSO-d_6 + $CDCl_3$). Finally, there were examples that appeared to show a single broad peak for the NH_2 group at 60 MHz and two separate peaks at 300 MHz (e.g., $CH_3CH_2CONH_2$ in $CDCl_3$; $(CH_3)_3CCONH_2$ and $Cl_2CHCONH_2$ in DMSO-d_6 + $CDCl_3$; $ClCH_2CONH_2$ in DMSO-d_6). This could suggest that the N-CO bond rotation rates might be (in specific cases) rather delicately balanced with respect to the continuum of displaying a fast exchange limit spectrum at low spectrometer frequency and a slow exchange limit spectrum at the higher spectrometer frequency. Higher field NMR instruments can serve to "freeze out" dynamic chemical processes (20). A detailed treatment of the spectra of amides and ureas is beyond the scope of this communication.

However, it is clear that observation of two separate signals for the NH_2 group of the adduct 2, and for the reagent N-carbamoyl maleimide, in both $CDCl_3$ and acetone-d_6, is highly unusual relative to spectra of "ordinary" ureas. We note that biuret, $H_2NCONHCONH_2$, (in DMSO-d_6 at 60 MHz) shows a single peak for the NH_2 protons (16) but that phenylacetylurea, $C_6H_5CH_2CONHCONH_2$, (in $CDCl_3$ + DMSO-d_6 at 300 MHz) clearly shows two peaks for the NH_2 (19). It may be that the observation of one or two ^1H NMR spectral peaks for the NH_2 group of simple ureas, $RR'NCONH_2$, as an indicator of rotation rates about the OC-NH_2 bond, is (in part) critically dependent on the electron withdrawing power of the substituents R and R'. Powerfully electron withdrawing groups might be expected to enhance mesomeric electron donation from the NH_2 to the carbonyl, increasing double bond character in the OC-NH_2 moiety. This should raise the bond rotation barrier and slow the OC-NH_2 rotation rate, leading to observation of two distinct NH_2 signals. That two signals are seen for the NH_2 in phenylacetylurea versus one peak for the NH_2 in biuret might simply reflect greater electron withdrawing character for the "ketone" group ($C_6H_5CH_2CO$) than for the carbamoyl group (H_2NCO). If both R and R' in $RR'NCONH_2$ are electron withdrawing (carbonyl) substituents, as in 2 and N-carbamoylmaleimide, this should certainly favor more double bond character in the OC-NH_2 moiety, resulting in the observed two peaks for the NH_2, as we see for these compounds. This explanation may be simplistic since the appearance of the NMR signal for, e.g., the OC-NH_2 of amides or ureas could also be influenced by: a) signal broadening from the ^{14}N quadrupole moment; b) possible accidental isochrony of the two NH_2 proton signals, for the nuclei syn or anti to the carbonyl; c) other chemical exchange processes, including intermolecular proton transfers competing with the N-CO bond rotation; d) potential presence of variable trace amounts of acidic or basic impurities in different NMR samples, which might lead to altered rates of chemical exchange processes (such as the

intermolecular proton transfer noted above). We have also not attempted to consider the role of the solvent or of possible intramolecular hydrogen-bonding within specific molecules.

Finally, we briefly consider the chemical shifts for the NH_2 protons in 2 and in N-carbamoylmaleimide. The chemical shifts of the NH_2 in both amides, $RCONH_2$, and ureas, $RR'NCONH_2$, seem to be somewhat solvent dependent, with lower field signals seen in DMSO-d_6 than for $CDCl_3$. This seems consistent with our observation of higher field NH_2 signals in $CDCl_3$ than in the more polar CD_3COCD_3 for both 2 and N-carbamoylmaleimide if the average shifts for NH(A)H(B) are considered. For 2, the average shifts are ca. 5.6 and 6.4 ppm, and for N-carbamoylmaleimide, ca. 6.4 and 7.0 ppm, in $CDCl_3$ and CD_3COCD_3, respectively. Much less separation in chemical shift of the NH(A)H(B) signals was seen in CD_3COCD_3, only ca. 0.25 ppm for 2 and 0.46 ppm for N-carbamoylmaleimide, compared with 1.64 and ca. 2.2 ppm in $CDCl_3$. We might speculate that at least some part of the higher field position for the mean chemical shifts of the NH_2 group of 2 compared to the N-carbamoylmaleimide (in either solvent) could reflect magnetic anisotropic shielding by the phenanthrene moiety in adduct 2, which is consistent with endo adduct stereochemistry. Solution concentration may also play a role in the NMR signal appearance and chemical shifts of these compounds but this was not examined here.

We believe that the study and conclusions presented here should be of special importance for two reasons. Firstly, this study of the adduct, 2, is part of an examination of a series of phencyclone adducts, with long-range goals of: (a) quantitatively mapping out the magnetic anisotropic effects throughout the space around these molecules, and (b) more precisely understanding the influence on the hindered rotations by different substituents. Secondly, and perhaps more important, 2 and related adducts serve as models for compounds of high

intrinsic importance. Our Introduction noted several drugs in which hindered aryl rotations were significant. We point out here several additional compounds in which the hindered "amide" rotation is quite relevant, including drugs such as carbamazepine (analgesic/anticonvulsant), carbuterol (bronchodilator), carbutamide (antidiabetic), carfimate and capuride (both hypnotics), carmofur and carmustine (both antineoplastics), carbiphene (analgesic), carpipramine (antipsychotic), and carisoprodol (skeletal muscle relaxant), as well as insecticides (carbaryl, cartap) and fungicides (carbendazim)!

CONCLUSIONS

The Diels-Alder adduct of phencyclone, 1, with N-carbamoylmaleimide, is reported. This adduct, 2, has been characterized by ^{1}H and ^{13}C NMR studies at 300 and 75 MHz, respectively. Bridgehead phenyl rotation in the adduct appears to be slow. The presence of effective mirror plane symmetry in the adduct, indicated by the relative spectral simplicity, is consistent with fast rotation of the carbamoyl group about the N-$CONH_2$ bond. Two separate equal intensity (1H) broad peaks in the adduct's ^{1}H spectrum (in CD_3COCD_3 or $CDCl_3$) suggest slow rotation of the NH_2 group. Shielding of H-1,8 and H-2,7 of the phenanthrene moiety of 2 (relative to the parent phenanthrene) is consistent with anisotropic effects due to a preferred conformation of the bridgehead phenyls of 2 placing the phenyls roughly perpendicular to the plane of the phenanthrene moiety. Such a conformation would also account for strong anisotropic deshielding for one of the phenyl ortho protons, H-2', syn to the ketone carbonyl. Endo adduct stereochemistry is tentatively assigned based on similarity of bridgehead methine chemical shifts to other phencyclone adducts of N-substituted maleimides.

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