Conformational Study of N-Methyl-5,6-dihydro-7H,12H-dibenz[c, f]azocine by Nuclear Magnetic Resonance Spectroscopy¹

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A study of the n.m.r. spectra of N-methyl-5,6-dihydro-7H,12H-dibenz[c,f]azocine, its deuterated derivative, and its conjugate acid in deuteriochloroform and in trifluoracetic acid at 27 and at -62° has shown that the molecule prefers the rigid "crown" conformation. From the equilibrium constant for the equilibrium flexible \rightleftharpoons crown at 27 and at -62° , ΔH and ΔS values of -3.2 ± 0.5 kcal/mol and 7 ± 2.0 s kcal/mol and in trifluoracetic acid at 27 hereing and the prefers the angle of the

 -7 ± 3 e.u. respectively were determined, indicating the preference for the crown conformer. A barrier to interconversion of the flexible to crown form at -62° was determined to be 15.3 \pm 0.3 kcal/mol.

These parameters provide the first experimental data pertinent to the conformational properties of the 1,4-cyclooctadiene system.

Une étude des spectres de résonance magnétique nucléaire du N-méthyl dihydro-5,6-7H,12H dibenz-[c,f] azocine, de son dérivé deutérié et de son acide conjugué dans le deutériochloroforme et dans l'acide trifluoroacétique, à 27 et -60° , montre que la molécule adopte préférentiellement la conformation rigide en couronne. A partir de la constante de l'équilibre forme flexible \neq couronne à 27 et -62° , les valeurs de ΔH et ΔS de -3.2 ± 0.5 kcal/mol et -7 ± 3 u.e. ont été déterminées, respectivement, indiquant une préférence pour le conformère couronne. Une barrière d'interconversion de la forme flexible à la forme couronne a été déterminée à -62° et vaut 15.3 ± 0.3 kcal/mol. Ces paramètres fournissent les premières données expérimentales pertinentes sur les propriétés conformationnelles du système cyclooctadiene-1,4. [Traduit par le journal]

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Introduction

In the last decade, eight-membered ring compounds have been the object of extensive investigation, including molecular orbital calculations (3), dipole moment studies (4), X-ray crystallography (5–7), and n.m.r. spectroscopy (8–11). By far, n.m.r. has proved to be the most powerful tool in the conformational determination of cyclic molecules in solution (10, 12, 13). Among the eight-membered rings, the cyclooctanes and cyclooctatetraenes are the two classes on which the majority of conformational analyses have been conducted (10, 14). The conformations of the cyclooctatrienes (17), on the other hand, have been less extensively investigated.

Of the three cyclooctadiene isomers only the 1,5-diene has been the object of experimental study (18). The cycloocta-1,4-diene has, however, been recently discussed from the point of view of

possible conformations. Dunitz and Waser (16) have proposed that this compound should exist as flexible 1 and crown 2 isomers. Experimental efforts to examine this claim by n.m.r. would undoubtedly be hampered by the spectral complexity of such multi-spin systems. Spectral simplification, though, can be achieved by a number of current techniques such as substitution of one or more protons on the ring by deuterium (9), fluorine (11), heteroatoms (19, 20), and/or aromatic rings (14).

We have undertaken an n.m.r. study of the conformational properties of an hetero analogue of cycloocta-1,4-diene, namely *N*-methyl-5,6-dihydro-7*H*,12*H*-dibenz[c,f]azocine (3) (21, 22), with a view to determining its most favorable ground state. The presence of the aromatic rings and nitrogen in the molecule provides a simple n.m.r. spectrum³ from which its conformational properties ought to be determinable.

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 $^{^{3}}$ A qualitative description of the n.m.r. spectrum of 3 was reported earlier (21).

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The parent compound **3** has been prepared by Pala and co-workers (22) utilizing an intermediate previously prepared by Bergmann and Pelchowicz (23), 2,2'-bis(bromomethyl)-diphenylmethane. It was our belief that their yield of this compound (22% after eight steps) could be improved by the choice of a better synthon (38) for its generation. Consequently, we utilized the readily available dibenzsuberone **4** (Scheme 1) as starting material and, after a sequence of five steps, obtained the desired intermediate in a yield of 53\%. Treatment of 2,2'-bis(bromomethyl)-diphenylmethane with methylamine gave **3** in 57\% yield.

Experimental

All melting points are uncorrected. All i.r. spectra were recorded on a Perkin-Elmer 237 Grating Spectrometer. Only the characteristic bands are reported (cm^{-1}). Routine n.m.r. spectra were measured using a Varian A-60 spectrometer. Precise studies on the title compound were carried out using a Varian HA-100 spectrometer. All coupling constants were determined with an accuracy of ± 0.1 Hz. The n.m.r. spectra were measured in deuteriochloroform unless otherwise specified and the chemical shifts are reported on the scale.

For the kinetic measurements at -62 °C intergrals were taken every 150 s and the rate constant obtained by a least squares analysis of the data. The standard deviation (1.5×10^{-5}) in the rate constant and the possible error in measurement of the probe temperature (2°) lead to an uncertainty in ΔG^+ of 0.3 kcal/mol. The above relatively accurate integral measurements are possible as we are monitoring the intensity of a sharp singlet as a function of time. Thus, systematic errors are minimized and only random errors produce scatter in the data.

Benzophenone-2,2'-dicarboxylic Acid

An acetone solution of dibenzsuberone (5 g) was oxidized with potassium permanganate (14 g) in the presence of sodium bicarbonate, according to the method of Smith and Rouault (24). Work-up and recrystallization from ethanol afforded 4.7 g (72%) of product: m.p. 213.5–2.4° (lit. (25) 212°); i.r. (Nujol) 3300–2200, 1700, 1670; n.m.r. (DMSO- d_6) 7.15–8.40 (8H, multiplet, aromatic), 10.15 (2H, broad singlet, OH).

Diphenylmethane-2,2'-dicarboxylic Acid

Benzophenone-2,2'-dicarboxylic acid (6.0 g) in ammonia was treated with zinc dust (19.0 g) over 20 h in a manner similar to that described by Bergmann and Pelchowicz (23). The yield of the diacid, m.p. 259-261° (lit. (23) 254.5°) was 5.4 g (94%): i.r. (Nujol) 3300-2200, 1720; n.m.r. (DMSO- d_6) 7.00-8.20 (10H, multiplet, aromatic and OH; elimination of 2H by exchange with D₂O), 4.88 (2H, singlet, methylene).

Dimethyl-diphenylmethane-2,2'-dicarboxylate

Diphenylmethane-2,2'-dicarboxylic acid (4.6 g) was esterified with methanol (240 ml) in presence of concentrated sulfuric acid (1 ml) under reflux for 36 h. Then, the product was freed from excess methanol and collected in ether. The ethereal solution was washed with a cold solution of sodium bicarbonate, dried over MgSO₄, filtered and the solvent removed to give 4.8 g (95%) of an oily residue which solidified on standing: m.p. $42-44^{\circ}$ (lit. (23) 44°); i.r. (CHCl₃) 1725; n.m.r. (DMSO- d_6) 7.00– 8.10 (8H, multiplet, aromatic), 4.82 (2H, singlet, methylene), 3.79 (6H, singlet, methyl).

2,2'-Bis(hydroxymethyl)-diphenylmethane

Dimethyl-diphenylmethane-2,2'-dicarboxylate (4.8 g)







FIG. 1. The ¹H n.m.r. spectrum of N-methyl-5,6-dihydro-7H,12H-dibenz[c,f]azocine (3) in deuteriochloroform.

was reduced to 2,2'-bis(hydroxymethyl)-diphenylmethane as described in the literature (23) in 91% yield: m.p. 162– 162.5° (lit. (23) 158–158.5°); i.r. (Nujol) 3350–2800; n.m.r. (DMSO- d_6) 6.8–7.8 (8H, multiplet, aromatic), 4.56 (4H, singlet, methylene), 4.10 (2H, singlet, methylene), 3.42 (2H, broad singlet, hydroxyl).

2,2'-Bis(bromomethyl)-diphenylmethane

2,2'-Bis(hydroxymethyl)-diphenylmethane (1.5 g) was reacted with phosphorous tribromide according to Bergmann and Pelchowicz (23). The pale yellow crystalline product was recrystallized from benzene to afford 2.1 g (90%) of solid melting at 92° (lit. (23) 93–94°): n.m.r. 7.0–7.7 (8H, multiplet, aromatic), 4.54 (4H, singlet, methylene), 4.37 (2H, singlet, methylene).

N-Methyl-5,6-dihydro-7H,12H-dibenz[c,f]azocine

2,2'-Bis(bromomethyl)-diphenylmethane (1.5 g was reacted with methylamine according to the procedure of Casadio *et al.* (22). There was obtained after sublimation of the crude product, 1.0 g (57%) of *N*-methyl-5,6-dihydro-7*H*,12*H*-dibenz-[*c*,*f*]azocine: m.p. 92° (lit. (22) 93°); n.m.r. 6.98–7.40 (8H, multiplet, aromatic), 4.26 (4H, quartet, methylene adjacent to N), 4.00 (2H, quartet, methylene), 1.90 (3H, singlet, methyl).

5,5,7,7-Tetradeuterio-N-methyl-5,6-dihydro-7H,12Hdibenz[c,f]azocine

Using a procedure analogous to that quoted above, dimethyl-diphenylmethane-2,2'-dicarboxylate was reduced with lithium aluminum deuteride. The tetradeuterated product of that reaction was converted in an identical manner to that described above into 5,5,7,7-tetradeuterio-N-methyl-5,6-dihydro-7H,12H-dibenz-[c,f]azocine. The isotopic purity was estimated by n.m.r. spectroscopy to be better than 95%.

Results and Discussion

A. Nuclear Magnetic Resonance Spectral Parameters

The n.m.r. spectrum of **3** in deuteriochloroform exhibits two well-defined AB quartets in a ratio of 2:1 (Fig. 1). These quartets, centered at δ 4.30 (J = 14.9 Hz)⁴ and δ 4.09 (J = 12.7 Hz), correspond to the protons on C-5 and C-7, and on C-12 respectively. The *N*-methyl region of the spectrum shows that more than one isomer is present. At room temperature a sharp singlet at δ 1.94 represents the major isomer (91.7% of methyl absorption) and a small broad peak at δ 2.44 represents the minor isomer (8.3% of methyl absorption). Absorptions due to the methylene protons of the minor isomer were too weak to be observed.

When trifluoroacetic acid (TFA) is added gradually to the sample in deuteriochloroform, the low field protons of the quartet, centered at δ 4.30, shift slowly downfield and finally appear at δ 5.26 (J = 14.0 Hz) in pure TFA. This shift to low field is typical of protons α to nitrogen because of a decreasing shielding of the adjacent protons by the positively charged nitrogen in the

⁴All the geminal coupling constants discussed herein are assumed to be negative as has been found for the benzylic methylene protons of 2,3-diphenylpropionic acid (27).

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FIG. 2. The ¹H n.m.r. spectrum of (A) 3-H⁺ in TFA and (B) 3-H⁺ (5,5,7,7-d₄) in TFA-d₁.

conjugate acid 3-H⁺ (26). Of particular significance is the fact that in pure TFA this signal is still a doublet, *i.e.* $J_{H-N-C-H}$ must be less than 1 Hz since all the other protons α to nitrogen show vicinal (H-N-C-H) splittings that indicate the exchange of the N-H proton with solvent is slow on the n.m.r. time scale. We have previously established the presence of a Karplus relationship between the magnitude of vicinal H—H coupling for the H—N—C—H fragment of amines in TFA (28) and the dihedral angle between the vicinal protons. The lack of vicinal coupling in the low field absorption of **3** in TFA shows, therefore, that the angle between the proton on nitrogen and these protons on the α carbons is $\approx 90^{\circ}$.

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Examination of Dreiding models shows that the geometry of the flexible conformer permits

both of the H-N-C-H bond angles⁵ to vary

between 0 and 120°. Thus, for the flexible form, one must expect, on the average, a coupling of some magnitude between the proton on nitrogen and both of the adjacent methylene protons. In the rigid crown conformer, however, the H-N-C-H bond angles are fixed at 90 and 30° for the non-equivalent protons. As a result, the absence of observable H-N-C-H splitting indicates a 90° dihedral angle and is consistent only with assignment of the crown conformation⁶ to the major isomer.

The relative intensities of the two methyl peaks are also affected by the presence of acid. The addition of TFA to the sample in deuteriochloroform causes a downfield shift of both *N*methyl groups (26). Concomitantly, the smaller peak increases in intensity as the concentration of TFA increases until, in pure TFA, it accounts for 28% of the total methyl absorption and appears at δ 2.98: The other *N*-methyl peak has

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⁵In general, the Dreiding models are too rigid and estimated bond angles are only accurate to within 5°. Bond angles reported in this paper are to be considered within this range.

⁶An X-ray crystallographic examination of the azocine 3 (37) has since shown that the preferred conformer in the crystal state is also the crown form.

shifted to δ 2.39. Both peaks are doublets and display the characteristic H—N—C—H coupling of 5.3 Hz (26).⁷

The remainder of the methylene proton absorption of the two isomers of 3 in TFA is not sufficiently resolved to allow individual assignments to be made (Fig. 2A). However, the assignment of the methylene bridge protons of the two isomers is made possible by the examination of the deuterated derivative of 3 in which the hydrogens at C-5 and C-7 have been replaced by deuterium.

The spectrum of **3**-H⁺ (5,5,7,7- d_4) in TFA- d_1 shows a quartet for the major isomer centered at $\delta 4.08$ (J = 13.5 Hz) and a second isomer centered at δ 4.60 (J = 19.0 Hz) (Fig. 2B). The magnitudes of these two geminal coupling constants allow assignment of crown and flexible conformations to the major and minor isomers respectively. It is recognized that a benzene ring on a methylene group causes a negative shift on the geminal proton-proton coupling constant and that this shift varies with conformation. Empirical (29, 30) and theoretical (31, 32) evidence support this correlation and estimate the effect to be at least 4 Hz in the most favorable conformation 5 and zero in the conformation 6. achieved by a rotation of 90° about the phenyl— CH₂ bond. A Dreiding model of the crown form of 3 shows ϕ to be very close to 90° for both benzene rings, leading to the expectation that they should have a negligible influence on ^{2}J . On the other hand, a model of the flexible form allows one of the two methylene groups to be oriented at $\phi = 30^{\circ}$ and the other at $\phi = 90^{\circ}$ in either of two equivalent "twist-boat" types of conformation. Thus, an appreciable negative shift of the geminal coupling constant ought to be caused by the hyperconjugative effect of the benzene rings in the flexible conformation. The observed value ${}^{2}J$ of -13.5 Hz for the major isomer represents a normal value for a diphenylmethane-type methylene group possessing $\phi = 90^{\circ}$ for both benzenes to CH₂ bonds (33). The 5.6 Hz more negative value of ²J in the minor isomer is only consistent with a flexible conformation for this isomer.

B. Temperature Dependence of Equilibrium Constant

From integration of the peaks for the N-CH₃ groups of the two isomers at room temperature and -62° , the equilibrium constants K_{eq} (minor \rightleftharpoons major) were found to be 11.0 and 124 respectively. From such a temperature dependence, ΔS_{eq} is calculated to be -7 ± 3 e.u. and $\Delta H_{eq} = -3.2 \pm 0.5$ kcal/mol.⁸ The much greater entropy for the minor isomer is corroborative evidence that it possesses a flexible conformation. A comparable difference in entropy between the "crown" and "boat-chair" forms of tetroxocane has been found by Anet and Degen (20).

C. Barrier to Inversion

While it should be possible to determine the barrier to interconversion of the crown and flexible forms by DNMR (34), the strongly biased equilibrium makes line-shape measurements difficult and relatively less accurate. Since the two N-CH₃ peaks were observed to coalesce at about 40°, thus indicating a barrier of the order of 15 kcal/mol, we have undertaken a direct measurement of this interconversion by a "temperature-jump" experiment. A deuteriochloroform solution of 3 was plunged into liquid nitrogen. The sample after 5 min was warmed quickly to -62° and placed in the proble of the HA-100 spectrometer which was also held at -62° . Integration showed the proportion of isomers to be 96.5 and 3.5. The rate of relaxation to the equilibrium position of 99.2 to 0.8 at -62° , determined by repeated integrations, was found to be $6 \pm 1.2 \times 10^{-4} \text{ s}^{-1}$. This corresponds to a free energy of activation of 15.3 \pm 0.3 kcal/mol for conversion of the flexible to crown forms.

In conclusion, we have established the presence

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⁷A point to be noted here is that protonation of a crown-flexible conformer mixture could give rise to four different conjugate acids and thus four sets of methyl doublets. However, only two doublets are observed, indicating the presence of only two isomeric conjugate acids. The other two isomers (having the opposite but undetermined configuration at nitrogen) are presumably too unstable to populate the mixture in measurable quantity. Interconversion of all isomers occurs readily via the following equilibria: $\operatorname{crown}_1 \rightleftharpoons \operatorname{flexible}_1 \rightleftharpoons$ flexible $\rightleftharpoons \rightleftharpoons$ crown₂ (the subscripts indicating the configuration at nitrogen).

⁸The rather large uncertainty in ΔS results from the limits of accuracy in integration which we estimate to be $\pm 0.5\%$ for the measurement of well-resolved sharp singlets. There can be no doubt that there is a large entropy difference between conformers for, if ΔS were zero, the concentration of flexible form at -62 °C ought to have been 3.2%.

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of two conformations of the azocine 3 whose n.m.r. and thermodynamic properties allow assignment of a "crown" conformation to the energetically favored isomer and a "flexible" conformation to the less abundant isomer. Both the thermodynamic and kinetic parameters for this conformational equilibrium have been determined. It is tempting to propose the data for 3 as providing reasonable estimates of the conformational equilibrium in cis-1,4-cyclooctadiene. Indeed, substitution of aromatic rings in the place of double bonds does not appear to alter conformations significantly (18) nor alter the barrier to interconversion appreciably (35) unless the rings are adjacent to one another (14). Similarly, replacement of a CH₂ group by a nitrogen atom causes little change in bond length and resultant geometry (36). We can, therefore, propose that the conformational properties exhibited by 3 constitute a reasonable estimate of the analogous properties of 1,4-cyclooctadiene.

Finally, the predominant isomer, the crown conformation of 3, possesses some unique geometric features that should prove helpful in the study of other phenomena, in particular the study of substituent effects on geminal coupling constants (30) since the projected angle ϕ is 90°.

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Further work related to azocines having different alkyl groups on nitrogen is in progress. Hopefully, such studies will provide information on steric effects in these eight-membered rings.

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