STEREOCHEMISTRY OF 11,12-DIHYDRODIBENZ[b,f]AZOCIN-6(5H)-ONES

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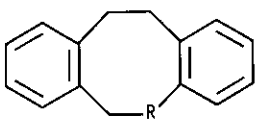
Abstract - The preferred conformation in solution of 11,12-dihydrodibenz-[b,f]azocin-6(5H)-ones has been assigned by means of LIS assisted ^{1}H nmr spectroscopy. The ^{1}H nmr temperature-dependent behaviour of the 8-membered ring has been investigated; the activation parameters have been determined and the influence of N-5 substitution on the ring mobility is discussed.

In recent years dibenzazocine derivatives have found wide application as pharmacological agents[1], especially for their psycotropic properties[2].

A lot of papers concerning the stereochemistry of hydrocarbon and heterocyclic medium-sized rings have appeared[3], which deal deeply with the complex problems arised by the existence of several conformations with an apparently little difference in energy through a process involving principally torsion about the single bonds of the eight-membered ring: this situation is analogous to the energetically inexpensive pseudorotation of the boat conformation of the 6-membered ring[4]. For 5,6,11,12-tetrahydrodibenzo[a,e]cyclooctenes and their thia- and aza-analogues 1, three possible conformations, chair, boat and twist-boat, are reported in solution[5], whereas in the solid state the 8-membered ring assumes a chair conformation. However it is also possible to postulate the existence in solution of several transition state geometries for the interconversion between any two of the conformers.

The 1,2:5,6-dibenzocyclooctadienones 2 exist in solution in a twist-tub conformation for the existence of considerable conjugation between the carbonyl and the aromatic ring[6].



R = CH_2, NH, S

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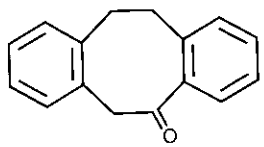

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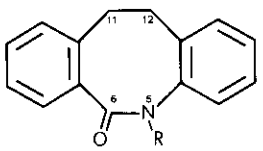
At present, very little informations have been published concerning the conformational behaviour adopted in solution by the 11,12-dihydrodibenz[b,f] azocin-6(5H)-one system. For some N-substituted derivatives the barriers to ring inversion have been calculated by dynamic nmr spectroscopy: the results are compatible with the suggested inversion boat-boat[7]. The conformational behaviour of dibenzazocinone system is still complex because of the large number of available conformers of comparable energy.

According to the hypothesis that the stereochemistry of the eight-membered ring could be correlated with the biological activity of these derivatives, we have examined the 11,12-dihydrodibenz [b,f] azocin-6(5H)-one 3 and its methylated homologue 4 using the nmr lineshape methods[8] which have been demonstrated to be



3, R = H

4, R = CH_3

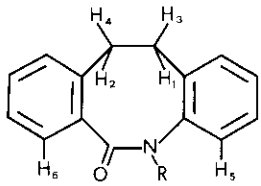
a powerful technique for solving the subtle problems posed by the conformational behaviour of mobile cyclic compounds in solution. The temperature dependence of nmr spectra and the computer simulation of $Eu(fod)_3$ induced shifts (LIS) allowed us to determine the configurational and conformational preferences of the system.

RESULTS AND DISCUSSION

In the ^1H nmr spectrum of 11,12-dihydrodibenz[b,f]azocin-6(5H)-one 3 at room temperature (Table I), the alicyclic region is characterized by a broad signal at 3.24δ corresponding to the ethylene-bridge. Moreover the spectrum shows a single-proton singlet at 7.72δ due to NH proton which disappears on deuteration and an eight proton aromatic multiplet at 7.00-7.35δ. These spectral features can be explained in terms of a fast ring inversion between two limiting conformers 3a and 3b (Figure 1): the observed singlet for the four methylene protons is a mean value owing to a rapid exchange between two conformers existing at room temperature. These conclusions are supported by temperature dependence of the nmr spectrum and at 10°C and below, the protons of the ethane fragment appear as non-equivalent and form an ABCD spin system which gives rise to two complex unsymmetrical groups of signals.

The ^1H nmr spectrum of compound 4 (Table II) shows that only one conformation is populated to a significant amount at room temperature and that it does not interconvert. The spectrum shows an ABCD-like spin system, which can be ascribed

Table I. Chemical shifts for 11,12-dihydrodibenz[b,f]azocin-6(5H)-ones 3 and 4.



3, R = H
4, R = CH_3

Compd.	N-H	N-CH_3	H-1	H-2	H-3	H-4	H-5	H-6	%	AF[9]
3	7.72		3.24	3.24	3.24	3.24	7.24	7.31	0.56	0.1023
	1.43		0.25	0.46	0.25	0.46	0.33	1.00		
	1.43		0.30	0.40	0.21	0.51	0.26			
4		3.36	2.85	2.97	3.30	3.42	7.08	7.20	1.00	0.0224
		1.29	0.66	0.69	0.33	0.36	0.58	1.00		
		1.28	0.67	0.34	0.35	0.55				

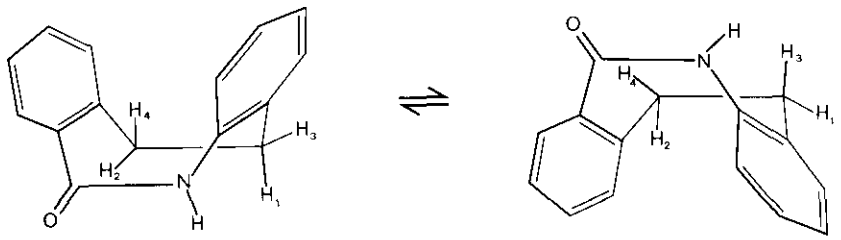
a) Figures in the first row indicate chemical shifts in $CDCl_3$ of undoped spectra; figures in the second row indicate the observed molar induced shifts; figures in the third row indicate the calculated molar induced shifts.

Table II. Chemical shifts (ppm), coupling constants (Hz) of ethylenic protons in the low exchange limit and calculated activation parameters for 3 and 4.

Compd.	ν_1	ν_2	ν_3	ν_4	Tc °K	ΔG^* Kcal/mol	ΔH^* Kcal/mol	ΔS^* cal/mol
3	2.95	3.07	3.45	3.59	283	13.9±0.9	16.8±1.9	10.2±3.8
	$J_{1,2}$ 8.0	$J_{2,3}$ 5.5	$J_{3,4}$ 4.0					
	$J_{1,3}$ -14.5	$J_{2,4}$ -14.5						
	$J_{1,4}$ 4.5							
4	2.85	2.97	3.30	3.42	438	21.2±1.2	16.1±1.8	-11.6±4.4
	$J_{1,2}$ 8.5	$J_{2,3}$ 5.5	$J_{3,4}$ 3.0					
	$J_{1,3}$ -13.0	$J_{2,4}$ -13.0						
	$J_{1,4}$ 5.5							

to the four diastereotopic methylene protons of the azocinone ring, besides a singlet at 3.36 ppm for the methyl group and a multiplet at 6.80-7.26δ for the aromatic protons. As the temperature is raised, the ABCD pattern is gradually transformed into an almost AA'BB' spin system, which appears as two groups of nearly symmetrical absorptions at 2.9δ and 3.36δ.

Chemical shifts and coupling constants have been extracted by iterative analysis of the spectra in condition of slow exchange, with a version of the program LAOCN3[10] (Table II). Inspection of the couplings in the spectra of compounds 3 and 4 shows that the upfield resonances ν_1 and ν_2 can be assigned to the methylene hydrogens situated on two different carbon atoms (Figure 1) and on the same side of the eight-membered ring, i.e. in a cis configuration: $J_{1,3}$ and $J_{2,4}$ have the characteristic sign and value of coupling between two geminal hydrogen atoms next to a phenyl ring[11].



3a ⇌ 3b

Figure 1 - Conformational equilibrium of compound 3

The proposed assignments agree also with the results obtained by computer simulation of the spectra recorded in presence of LSR (vide infra).

The observed temperature dependence is due to the activation of an internal molecular motion which is able to interchange the position of the protons in each methylene group (i.e. $\nu_1 \rightleftarrows \nu_3$ and $\nu_2 \rightleftarrows \nu_4$) between two sites with equal population. On the basis of the data reported for similar eight-membered flexible systems and of the examination of the geometrical characteristics of the system under investigation, it appears that the observed kinetic process can be attributed to the inversion of the central octatomic ring which involves a rigid chair and/or a mobile boat and twist-boat conformation with all the series of possible state geometries.

Another problem, when dealing with this type of molecule could arise from the superposition of ring inversion and nitrogen inversion and from the consequent presence of optical isomers, but since it is generally accepted that ring reversal

and not nitrogen pyramidal inversion is the slower process in azocine ring[1], we believe that the some should be true of the derivatives at hand. Thus the observed dynamic behaviour can be interpreted in terms of an exchange between two enantiomeric forms, the inversion motion of the nitrogen atom being fully averaged over the time of measurement.

For both compounds the inversion barriers have been determined as free energies of activation, ΔG^*, at the temperature where the ABCD spectra coalesce by a total linashape method; equal populations were chosen for two equilibrating conformers; the thermodynamic parameters are shown in table II. The ΔG^* values found in our compounds are close to those reported for some N-substituted dibenz[b,f]azocines[7], also as regards the parallel behaviour of substituents at N-5. Compound 3 shows a greater ring mobility (ΔG^*=13.9 Kcal) than the N-methyl substituted analogue (ΔG^*=21.2 Kcal). This behaviour might be attributed to the steric hindrance effect of the nitrogen substituent: the size of the R-group determines the extent of the peri-like interaction in the planar or nearly planar transition state, so contributing differently to the overall barrier.

Although the steric hindrance mechanism may play a significant role, it cannot be invoked as the only effect. Some other important factors can influence the potential barrier to ring inversion. ΔG^* values found for N-substituted derivative seem in fact very high if only steric effects were considered.

A considerable influence of solvent polarity on ΔG^* values is not to be expected for the system investigated because the transition state polarity does not differ greatly from that of the initial state[7,12].

The effect of the structure on the barriers can be extracted only on the basis of reliable data about the ring geometry. By application of LSR in nmr spectroscopy, information on the stereochemistry of the lanthanide-substrate complex has been obtained according to the McConnell-Robertson equation[13] which correlates the LIS to the geometric parameters of various protons.

With the addition of the paramagnetic reagent $Eu(fod)_3$ we obtained the expected resonance shifts: in compound 3 the N-5 and C-7 protons are respectively the most deshielded by LSR owing to their greater proximity to the carbonyl oxygen; the C-11 methylene protons, H_2 and H_4, which undergo a mutual exchange between their position by the 8-membered ring inversion are more shifted than C-12 ones, H_1 and H_3 (Table I). The obtained results suggested the presence in solution of two conformers 3a and 3b (Figure 1) in which the dibenzazocinone ring assumes a boat-boat conformation with N-5 which approaches sp^3 hybridization. The calculated LIS for the other possible conformers are too far away to be reconciled with the experimental values.

Different conclusions have been reached for N-methyl derivative 4: the best fit geometry of this molecule is a boat conformation, which does not interconvert at

room temperature, with an sp^2 hybridization of N-5. Only for this conformation and considering a planar geometry for the nitrogen atom, the LIS calculated were nearly coincident with the experimental values. The N-5 planarity in 4 can be attributed to the electron-donating effect of the methyl substituent, which delocalizes the partial positive charge existing on the trigonal N-5, thus contributing to the stabilization of the corresponding structure[14]. These conclusions are supported also by the different C-N bond distances 1.38 Å in 3 and 1.33 Å in 4, as obtained from the LIS simulation.

Additionally, the positive value of ΔS^* found for compound 3 also indicates that the nearly planar transition state appears to be more likely. Therefore the activated complex for 3 has with respect to 4 a more disordered state compared to the limiting states as expected for the fast inversion of the pyramidal nitrogen. Even if the discussion of activation entropies may be somewhat intriguing for its higher degree of indetermination with respect to the other thermodynamic quantities there is no doubt that the greater mobility of 3 compared with 4 is mainly due to ΔS^*, while for 4 the very low value of ΔH^* is the dominant factor. We conclude that the DNMR study of the dibenzazocinone system and the determination of activation parameters for the ring inversion has allowed to verify some hypothesis about the stereochemistry and the conformational preferences of the octatomic ring: besides the steric requirements, also the electronic factors can play a role in determining the ring mobility of the eight-membered dibenzazocinone system.

EXPERIMENTAL

The ^1H nmr spectra of the title compounds were determined in deuteriochloroform with TMS as internal standard, at probe temperature (25°) and even at -20°C on a Bruker WP-200 SY at 200 MHz. All chemical shifts were given in (δ) ppm.

The $Eu(fod)_3$ tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)europium was used as lanthanide shift reagent (LSR) and was added stepwise up to a value of 0.4 L/S ratio. Each signal was followed in the spectra and the LIS's were found to be directly proportional to the L/S ratio present. A least-square fit for the experimental points was used to obtain the observed molar LIS. Calculation related to the simulation of the experimental LIS data were performed on an IBM 370/115 computer using the LISCA program[15].

The interatomic distances, bond angles and dihedral angles were taken from Dreiding molecular models. The methyl group was treated as twelve equivalent points over which calculated LIS values are averaged. In the title compuonds the lanthanide-oxygen distance was fixed at 3.0 Å, which is the most widely accepted value[16].

The total lineshape method was employed to determine exchange rates; the coalescence temperatures were calculated by first determining K_c from an approximate expression[17] and then interpolating T_c from the Arrhenius plot.

The ABCD pattern were analysed with the aid of a version of the LAOCN3 program modified by us to run on our IBM computer and to include a subroutine for plotting calculated spectra on a line printer (the rms errors were of 0.03 and 0.07 Hz for compounds 3 and 4 respectively).

11,12-Dihydrodibenz[b,f]azocin-6(5H)-one (3) This compound was prepared according to the literature[18]: mp 250-252°C. Ir (nujol): 3200 and 1650 cm^{-1}; ^1H nmr ($CDCl_3$): 3.24 (br.s, 4H, CH_2CH_2), 7.00-7.35 (m, 8H, ArH), 7.72 (s, 1H, NH) (Tables I and II)

5-Methyl-11,12-dihydrodibenz[b,f]azocin-6(5H)-one (4) To a solution of the compound 3 (3 mmol) in DMF was added dropwise a solution of methyl iodide (15 mmol) and of potassium carbonate (0.5 g) in DMF. The resulting mixture was heated under reflux for 5 h and then subjected to chromatography on preparative silica gel plates using ether/light petroleum (8:2) as eluent. From the highest band afforded 0.2 g of 5-methyl-11,12-dihydrodibenz[b,f]azocin-6(5H)-one (4) (from ethyl acetate) mp 95-97°C. Ir (nujol): 1640 cm^{-1}; ^1H nmr ($CDCl_3$): 3.36 (s, 3H, CH_3); 2.7-3.58 (m, 4H, CH_2CH_2), 6.8-7.26 (m, 8H, ArH)(Tables I and II); Anal. calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.80; H, 6.92; N, 6.19.

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