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Investigación

A Non-sterically Preferred Conformation in Bis-1,4-(2-methyl-4, 5-dihydro-1*H*-benzo[g]indolyl)benzene

Luis Chacón-García, Roberto Martínez* and María Isabel Chávez

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán, 04510, México, D.F. E-mail: robmar@servidor.unam.mx

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Dedicated to Dr. Barbarín Arreguín

Resumen. Se describe el análisis conformacional del compuesto nombrado en el título. Los resultados muestran que la conformación preferida no es la esperada a partir de consideraciones estéricas. El cambio de disolvente de $CDCl_3$ a benceno-d_6 no tuvo efecto significativo en el equilibrio.
Palabras clave: Análisis conformacional, benceno 1,4-disubstituído, RMN ^{1}H.

Abstract. A conformational analysis of the title compound in solution is described. Results show that the preferred conformation is not the one expected from steric considerations. Change of the solvent from $CDCl_3$ to benzene-d_6 had no significant effect on the equilibrium.
Keywords: Conformational analysis, 1,4-disubstituted benzene, ^{1}H NMR.

Introduction

Biaryl compounds have attracted much attention because of their wide ranging utility [1-5] One of the most important properties of biaryls is their conformation, which is usually fixed due to a restriction of the free rotation between the rings (atropisomerism). This stereochemical property of biaryls has attracted interest from biological activity researchers because the vast majority of compounds that interact with biological systems require specific stereochemical characteristics. For this reason, specific atropisomers are biologically active, for example as components of antibiotics like vancomycin or in cardiovascular drugs like 4-aryl-1,4-dihydropyridines [6, 7]. Hence, study of the conformational properties of atropisomeric systems has become very important.

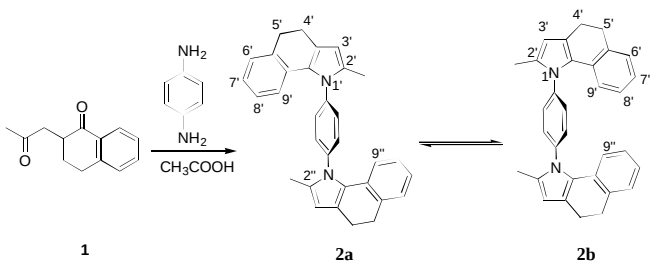
Since it was first reported in the 1920s, atropisomerism has been explained in terms of steric effects [8-11]. Although biaryls are the most common examples of atropisomerism, dipyrrylbenzene atropisomers have also been described [12]. It is noteworthy that *m*-substitution on the phenyl ring is considered to be the most important factor in freezing the conformation in all reported cases.

In order to study the conformation of molecules with potential cytotoxic activity, we describe here the conformational analysis of a bis 1,4-(2-methyl-4,5-dihydro-1 *H*-benzo [g]indolyl)benzene, a non previously described compound.

Results and Discussion

Compound **2** was prepared by a Paal-Knorr reaction between the 1,3-dicarbonyl derivative **1** and 1,4-phenylenediamine at reflux temperature (Scheme 1). Compound **1** was obtained from α-tetralone [13].

The ^{1}H NMR spectra of **2** at 300 ºK in $CDCl_3$ (Fig. 1b) showed duplicity in both of the signals (6.31 and 6.57 ppm). Integration of these signals suggested that a mixture of at least two detectable isomers was present, in the ratio 1.3:1. To confirm the presence of conformers the temperature was varied, and a coalescence of the two broad signals was found at 328 ºK (Fig. 1c). When the temperature was returned to 300 ºK the starting spectrum was recovered, with no detectable change. The ^{13}C NMR spectra did not show any duplicity at room tem-



Scheme 1. Synthesis of **2a** and **2b**.

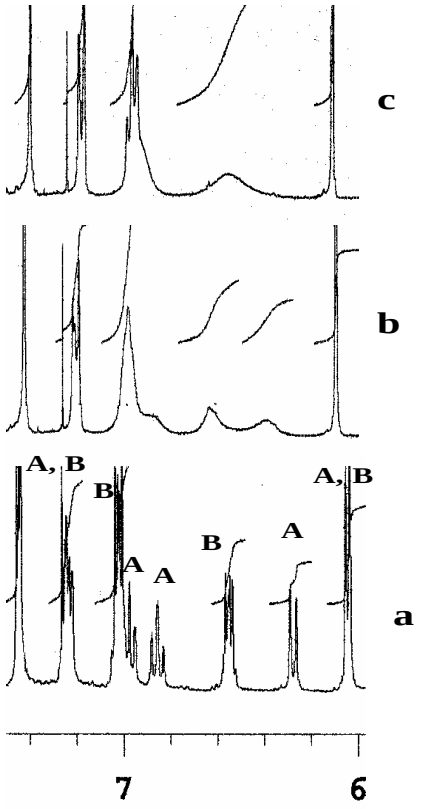


Fig. 1. ^{1}H NMR spectra at different temperatures: a) 218 ºK, b) 300 ºK and c) 328 ºK.

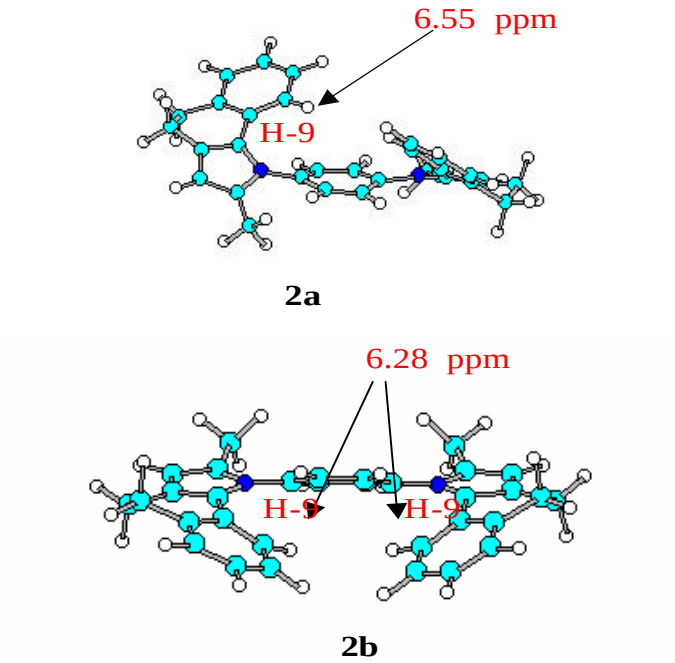


Fig. 2. Geometries obtained from PM3 calculations for compounds **2a** and **2b**. Chemical shifts of proton H-9 are shown.

Table I. ^{1}H NMR chemical shifts of conformers **2a** and **2b** at 328 ºK.

	2a	**2b**
Me	2.23	2.20
H-3'	6.06	6.04
H-4'	2.72	2.72
H-5'	2.96	2.96
H-6'	7.25	7.25
H-7'	6.98	7.03
H-8'	6.86	7.04
H-9'	6.28	6.55
H-2,3	7.44	7.46

perature. When the temperature was decreased at 218 ºK, however, a ^{1}H NMR spectrum with well-defined signals was obtained (Fig. 1a) that showed the expected duplicities. The broadness of the signals in the room temperature spectrum made assignation of the signals difficult; hence, the signals were assigned in the spectrum at 218 ºK. COSY and HETCOR experiments confirmed the presence of two different species, and allowed the assignation of the set of signals corresponding to each conformer. This analysis showed that the set of signals denoted A in Fig. 1a (6.28, 6.86, 6.98 ppm) corresponds to one species, and the signals denoted B correspond to the other species (6.55 and 7.04 ppm), which was more populated. The set of signals denoted B generate a second order spectrum (irradiation at 7.04 converts the multiplet at 6.55 to a singlet). ^{1}H NMR chemical shifts for compounds **2a** and **2b** are described in Table I.

The spectroscopic analysis outlined above demonstrates the presence of the two conformers **2a** and **2b**, which have a diastereomeric relationship. The next step was to determine which conformer represents the major population. While there is no direct way of knowing which of the signals corresponds to **2b**, it is possible to determine which signal corresponds to **2a** through the nuclear Overhauser effect (nOe). The nOe effect should be appreciable in **2a** between one of the methyl groups and the signal at 6.28 or 6.55 ppm, due to the proximity between CH_3 and H-8. This interaction is possible only in **2a**.

A NOESY experiment clearly showed that this interaction occurs between the signals at 6.28 and 2.23 ppm. It is surprising that these signals correspond to the less populated species. In other words, the major species in the equilibrium is **2b**, which is not the conformation that would be expected from steric considerations. Numerically, the preferred conformation of **2b** over **2a** is not as big to receive special attention, but if it is considered that **2b** is the less expected specie in the equilibrium, the matter becomes attractive. With the aim to compare the experimental results with theoretical methods, a semiempirical calculation with PM3 was carried out [14]. It was found that **2a** was the preferred conformer, although the energy difference was 1 kcal / mol. Structures are shown in Fig. 2. Distance between H-9' and the closer CH_3-C-2'' in **2a** was found to be 3.6 Å, whereas distance between H9' and H9'' in **2b** was 2.6 Å.

The spectrum of the same mixture obtained in benzene-d_6 gave almost the same diastereomeric relation as that obtained in $CDCl_3$, which indicates that the dipolar moment is not the main factor causing conformation **2b** to be the preferred over **2a**. Further studies to find the factors responsible for this preference are in process.

Experimental

To a stirred solution of **1** (0.1 g, 0.5 mmol) in 5 mL of acetic acid at 80 ºC, 1,4-diaminobenzene (0.027g, 0.25 mmol) was added. After 1h of reflux and magnetic stirring, acetic acid is neutralized with a solution of 5 % $NaHCO_3$ in water in a separation funnel with CH_2Cl_2. After reduction of the solvent, previously dried with Na_2SO_4, under reduced pressure, **2** was obtained pure, by chromatographic purification in silica gel 1:1 hexane/AcOEt (0.115g, 52 %) from the obtained mixture, as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, 300 ºK): δ 2.16 (s, 3H), 2.7 (t, J = 7 Hz, 1H), 2.99 (t, J = 7 Hz, 1H), 5.99 (s, 1H), 6.3 and 6.56 (broad, 1H), 6.82 and 6.94 (broad, 1H), 6.94 (m, 1H), 7.42 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 300 ºK): δ 12.9, 22.5, 30.9, 106.9, 120, 123, 126.6, 125.8, 128.2, 129.3, 129.7, 135.7, 139.6; IR ($CHCl_3$): 1516, 2937 cm^{-1}; HR-MS (EI): Estimated for $C_{32}H_{28}N_2$: 440.222; observed: 440.2274.

Acknowledgments

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