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Investigación

Hindered Rotation in *N*-Carbomethoxylated Indole Derivatives

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Dedicated to Dr. Fernando Walls in occasion of its seventy anniversary

Abstract. *N*-Carbomethoxyindole derivatives display ^{1}H NMR dynamic processes arising from the hindered rotation about the N-C carbamate bond. Theoretical modeling by Molecular Mechanics predicts two conformational minima **A** and **B**, owing to the *E* and *Z* isomers of the carbamate group. Conformer **A**, with the carbonyl carbamate group oriented towards the benzene ring is, in most cases, more stable than the **B** conformer. A hydrogen bond provides an explanation for the preference of the **B** conformer in **2**. The energy profiles reveal that, between the molecules investigated, compound **3** has the lowest barrier to rotation for the interconversion of the **A** and **B** conformers. The relative energies of **3** favored the **A** conformer in large proportion (97:3). These results are consistent with the observed sharp signals in the ^{1}H NMR spectrum of **3**, while compounds **2**, **6** and **7** show some significantly broadened signals in their ^{1}H and ^{13}C NMR spectra.
Keywords: *N*-carbomethoxyindoles, hindered rotation, dynamic processes, NMR.

Resumen. Los derivados de indoles *N*-carbometoxilados exhiben procesos dinámicos en RMN ^{1}H resultantes de la rotación restringida alrededor del enlace N-C del carbamato. El modelado teórico por mecánica molecular predice dos mínimos conformacionales **A** y **B**, debido a los isómeros *E* y *Z* del grupo carbamato. El confórmero **A**, que presenta al carbonilo del carbamato orientado hacia el anillo de benceno es, en la mayoría de los casos, más estable que el confórmero **B**. La preferencia del confórmero **B** en **2** se atribuye a la presencia de un puente de hidrógeno. Los perfiles energéticos indican que, entre las moléculas investigadas, el compuesto **3** tiene la menor barrera rotacional para la interconversión de los confórmeros **A** y **B**. Las energías relativas de **3** favorecen al confórmero **A** en amplia proporción (97:3). Estos resultados son consistentes con las señales agudas observadas en el espectro de RMN ^{1}H de **3**, mientras que los compuestos **2**, **6** y **7** muestran algunas señales significativamente anchas en sus espectros de RMN de ^{1}H y ^{13}C.
Palabras clave: indoles *N*-carbometoxilados, rotación restringida, procesos dinámicos, RMN.

Introduction

Dynamic NMR studies about the barriers to internal rotation related to amide bonds have shown *E* and *Z* conformers in *N*-formylindoles [1]. However, for *N*-acetylindole derivatives a single favored conformer (more than 90 %) has been observed, even at low temperatures [2]. In these cases, the carbonyl group was preferentially oriented towards the benzene ring, with the H-7 proton laying in the deshielding current, provided steric or hydrogen bonding effects are not operative [2, 3]. On the other hand, the existence of equilibrating rotamers due to the carbomethoxyl substituent on the indole nitrogen has been well documented [4].

As part of an ongoing study of *N*-carbomethoxyindole derivatives, as intermediates for the total synthesis of bioactive physostigmine type alkaloids [5], as outlined in Scheme 1, we became interested in exploring which structural changes could influence the hindered rotation that some of these compounds evidenced in their ^{1}H and ^{13}C NMR spectra [6]. For these purposes the *N*-carbomethoxylated indole derivatives **2**, **3**, **6** and **7** were investigated.

Results and discussion

Compounds **2**, **6** and **7** were found to display dynamic effects in their ^{1}H and ^{13}C NMR spectra. The proton NMR spectrum of **2**, measured at room temperature in DMSO-d_6, showed broad H-7 (7.75 ppm) and carbamate methyl (3.79 ppm) signals, whereas H-2 bonded to an sp^3 hybridized carbon atom remained sharp. On heating, both H-7 and the carbamate methyl signals became sharp, indicating that the rotational barrier was exceeded at the C-N carbamate linkage. Theoretical data (Molecular Mechanics [7]) predict that conformers **A** and **B** (Fig. 1) are within an energy range of only 0.4 kcal mol^{-1} in favor of **B** (Table 1). The formation of a weak hydrogen bond between the hydroxyl group, attached to an sp^3 hybridized C-2 atom, and the carbonyl oxygen of the carbamate group could be at the origin of the slightly more stable **B** conformation. The hydrogen-oxygen distance was calculated to be 2.2 Å (Fig. 1), which is in the range for intramolecular hydrogen bonding.

In the variable temperature ^{1}H NMR spectra of **6** measured in DMSO-d_6, the signals of H-7 (7.60 ppm) and the car-

Table 1. MMFF calculation results for the low-energy conformations **A** and **B** of **2**, **3**, **6** and **7**.

Comp	Rel energy (kcal mol^{-1})		% Calcd popln[a] (T = 298 K)		Rotn barrier (kcal mol^{-1})
	A	**B**	**A**	**B**	
2	0.4	0.0	34	66	11.8
3	0.0	2.0	97	3	9.8
6	0.0	1.5	93	7	12.8
7	0.0	1.2	88	12	11.5

[a] From $\Delta G° = -RT \ln K$.

bamate methyl (3.83 ppm) group are significantly broadened at temperatures between 298 and 333 K. Clear sharpening was observed for these resonances above 343 K. At 353 K the signal owing to H-7 appears as doublet with J_{ortho} = 8.8 Hz (Fig. 2). The ^{13}C NMR spectrum of **6**, measured at room temperature, showed considerable broadening for the resonances owing to the two carbons of the *N*-carbomethoxyl group (152.4 and 53.2 ppm), C-7a (137.2 ppm), C-3b (132.3 ppm) C-7 (115.2 ppm), C-8a (96.7 ppm) and C-3a (48.3 ppm), which sharpened at 343 K (Fig. 3). For compound **6**, theoretical calculations predict that conformation **A** (Fig. 1), with the carbonyl carbamate group oriented towards the benzene ring, is preferred over **B** in a 13:1 ratio and with a relative energy difference of 1.5 kcal mol^{-1} (Table 1). The lower stability of **B** appears to result from the electrostatic repulsion between the electron lone pairs of the oxygen C=O carbamate group and those of the oxygen furan ring.

Examination of the proton NMR spectrum of **7**, measured at ambient temperature (298 K) in $CDCl_3$, reveals that the signals due to H-7 (8.00 ppm), H-2 (7.32 ppm) and the carbamate methyl (3.98 ppm) group are very broad. When measurements were carried out in DMSO-d_6 the signals were significantly sharpened, suggesting a fast rotation at the C-N carbamate linkage on the NMR time scale. For compound **7** theoretical calculations predict two conformational minima, **A** and **B** (Fig. 1). Conformation **A** with the carbonyl carbamate group oriented towards the benzene ring is preferred over **B** by a relative energy difference of 1.2 kcal mol^{-1}, which corresponds to the 7:1 ratio (Table 1).

The proton NMR spectrum of **3**, measured at room temperature in both $CDCl_3$ and DMSO-d_6, showed sharp signals for all resonances, which fits with fast interconverting conformers on the NMR time scale. For compound **3**, calculations for both conformational minima, **A** and **B**, suggest that the one with *E* arrangement is the most stable by 2.0 kcal mol^{-1}.

The dihedral drive option in the Spartan Pro program allowed us to calculate barriers to rotation of the carbamate group in **2**, **3**, **6** and **7**, the corresponding data are collected in Table 1. As shown in figure 4, the two ground state conformations **A** and **B** of compounds **2**, **3**, **6** and **7**, can be converted into each other by overcoming energy barriers of 11.8, 9.8, 12.8 and 11.5 kcal mol^{-1}, respectively. These barriers are smaller than the activation barriers determined for *E*-*Z* isomerisation in amides, which lies in the 14.6-21.5 kcal mol^{-1} range [8]. As in amides, the carbamate group prefers to be planar (**A** or **B** conformations). Experimental evidence for this lies in crystal structure determinations carried out in *N*-carbomethoxylated indoles [9]. Twisting is accompanied by pyramidalisation at nitrogen as n–$\pi^*_{C=O}$– delocalization is progressively turned off, until it disappears completely at a twist of ca. 90° (270°), where the lone pair lies in the nodal plane of the π-system of the carbonyl group (Fig 5). The 90° (270°) rotamer represents a higher energy conformation. For compound **3**, the corresponding computed barrier to rotation is the lowest, by *ca.* 2 to 3 kcal mol^{-1}, allowing the molecule to exists in a fast equilibrium of conformers **A** and **B**, with the weighted average strongly in favor of **A**. These results are in good agreement with the observed sharp signals in the ^{1}H NMR spectrum of **3**, measured at 298 K.

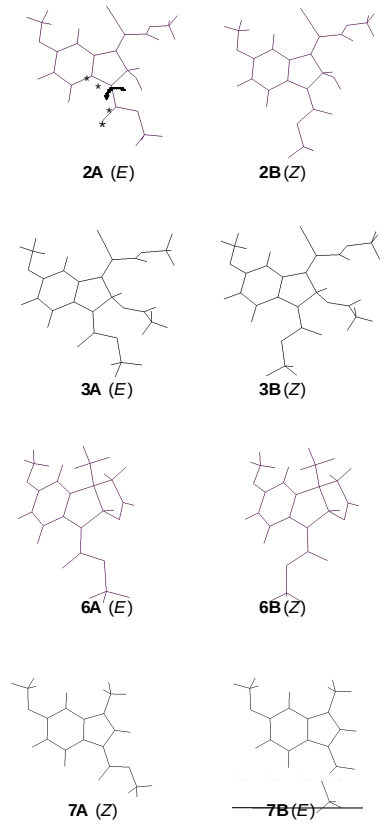


Fig. 1. Computed geometries **A** and **B** of **2**, **3**, **6** and **7** optimized at the MMFF level.

Experimental

Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained using

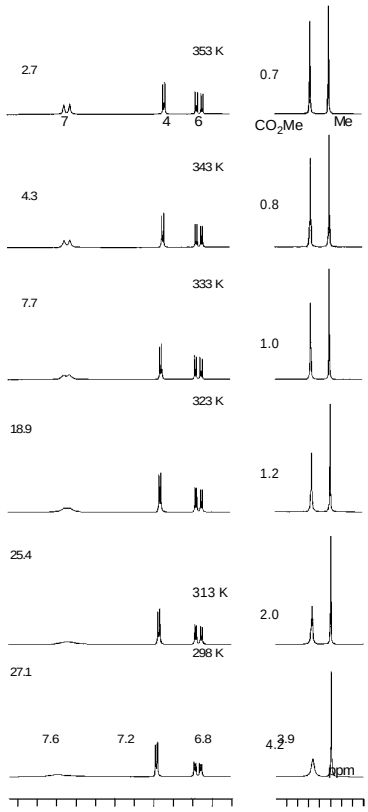


Fig. 2. 300 MHz ^{1}H NMR spectra (DMSO-d_6) of the aromatic (left) and methoxyl (right) regions of **6**, measured at various temperatures. Line widths at half height (in Hz) for H-7 and the carbomethoxyl protons are given at each temperature.

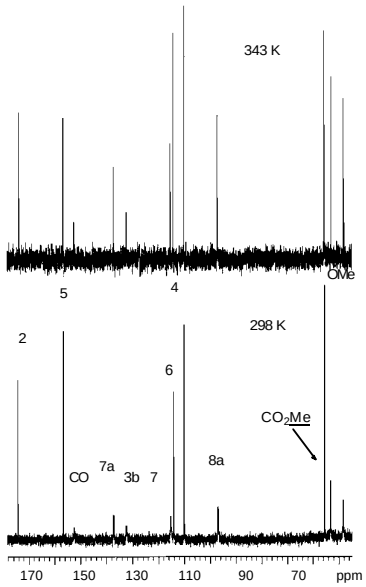


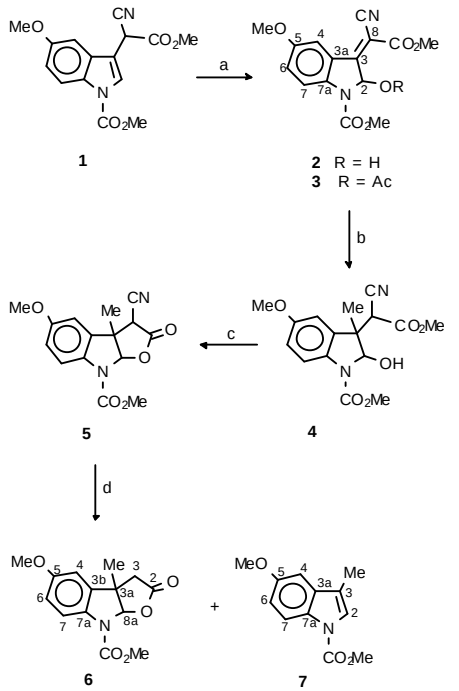
Fig. 3. 75 MHz ^{13}C NMR spectra (DMSO-d_6) of **6**, measured at 298 K (bottom) and at 343 K (top). The C-methyl signal at 23.6 ppm is not shown.

a Perkin Elmer 16F PC FT-IR spectrophotometer. EIMS were obtained on Varian Saturn 2000 or Hewlett Packard 5989A spectrometers. NMR spectra were recorded on Varian Mercury spectrometers working at 300 and 75.4 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts are reported in ppm downfield from tetramethylsilane. Standard library pulse sequences were used for all NMR experiments. Dynamic NMR measurements were performed with samples thermostated by means of a stream of air heated to required temperatures. Molecular mechanics force field calculations [7] were performed using the PC Spartan Pro program [10]. Compounds **2** and **6** were obtained from **1** as intermediates in the formal total synthesis of the alkaloids physostigmine and physovenine [11], whereas **3** and **7** were obtained as by-products during the same syntheses (Scheme 1).

Methyl (*Z*)-3-(1-Cyano-2-methoxy-2-oxoethylidene)-2,3-dihydro-2-hydroxy-5-methoxy-1*H*-indole-1-carboxylate (2) and its *O*-acetyl derivative 3. To a precooled (0 °C) stirred solution of **1** [11] (3.9 g, 12.9 mmol) in glacial acetic acid (40 mL) was added dropwise a solution of chromium oxide (4.5 g) in water (25 mL). The reaction mixture was stirred for 1 h at 0 °C and then poured onto cracked ice. The crude precipitate, which had formed, was collected by suction filtration and washed with water (3 × 25 mL). The solid residue was dissolved in EtOAc (200 mL), washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was crystallized from EtOAc to afford **2**, as yellow solid (3.37 g, 82 %): mp 173-174 °C (EtOAc / hexane); R_f = 0.26 (4:6, EtOAc / hexane); IR ($CHCl_3$) ν_{max}: 3570, 3030, 2220, 1724 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.75 (1H, br s, H-7), 7.71 (1H, d, *J* = 2.6 Hz, H-4), 7.35 (1H, d, *J* = 7.9 Hz, OH), 7.27 (1H, dd, *J* = 9.1, 2.6 Hz, H-6), 6.55 (1H, d, *J* = 7.9 Hz, H-2), 3.84 (3H, s, *O*-CH_3), 3.79 (3H, br s, *O*-CH_3), 3.75 (3H, s, *O*-CH_3); ^{13}C NMR (DMSO-d_6) δ 162.8, 162.2, 155.2, 151.3, 141.3 (br), 124.1, 122.1, 116.0, 115.9, 108.0, 95.4, 82.8, 55.5, 53.0, 52.9 (br); EIMS *m/z* 318 [M]$^+$ (100), 286 (41), 258 (40).

The filtrate obtained after the isolation of **2** was allowed to stand at room temperature for 5 days. The formed red crystals were filtered to give the *O*-acetyl derivative **3** (0.11 g, 2 %): mp 145-147 °C (EtOAc / hexane); R_f = 0.43 (4:6, EtOAc / hexane); IR ($CHCl_3$) ν_{max}: 3032, 2218, 1728, 1256 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.85 (1H, d, *J* = 2.7 Hz, H-7), 7.81 (1H, d, *J* = 2.7 Hz, H-4), 7.59 (1H, s, H-2), 7.35 (1H, dd, *J* = 9.1, 2.7 Hz, H-6), 3.81 (3H, s, *O*-CH_3), 3.79 (3H, s, *O*-CH_3), 3.77 (3H, s, *O*-CH_3), 1.98 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 166.8, 160.9, 158.9, 155.6, 151.3, 141.5, 123.6, 123.2, 116.6, 115.6, 108.2, 97.0, 81.7, 55.7, 53.5, 53.3, 20.5; EIMS *m/z* 318 [M-42]$^+$ (8), 302 [M-58]$^+$ (63), 243 (100), 199 (49).

Methyl 5-Methoxy-3a-methyl-2-oxo-2,3,3a,8a-tetrahydro-8*H*-furo[2,3-*b*]indole-8-carboxylate (6) and its degradation product 7. Compound **5** was obtained from **4** by the procedure described in Ref. [11]. A mixture of **5** (132 mg, 0.44



(a) CrO_3/H_2O, AcOH, 0 °C, 1 h; **2**: 82%, **3**: 2%; (b) 4 equiv MeMgI, Et_2O-THF 1:1, rt, 15 min, 50%, from **2**; (c) 6% aq. KOH, THF, rt, 20 min, quant.; (d) Al_2O_3 10% aq. THF, reflux 30 min, **6**: 75%, **7**: 9%.

Scheme 1. Preparation of the compounds.

mmol) and alumina (1.18 g) in 10 % aqueous THF (6 mL) was stirred at reflux until TLC analysis showed complete disappearance of starting material (0.5 h). The alumina was filtered off and washed with EtOAc (5 × 20 mL). The filtrate and the eluates were combined, concentrated, and purified by flash chromatography on silica gel. Elution with increasing concentration of EtOAc in hexane gave indole **7** as pale yellow solid (9 mg, 9 %): mp 49-50 °C (DMSO); R_f = 0.83 (4:6, EtOAc / hexane); IR ($CHCl_3$) ν_{max}: 3012, 1728, 1376, 1266 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.93 (1H, br d, *J* = 8.8 Hz, H-7), 7.41 (1H, m, H-2), 7.06 (1H, d, *J* = 2.2 Hz, H-4), 6.94 (1H, dd, *J* = 8.8, 2.2 Hz, H-6), 4.95 (3H, s, *O*-CH_3), 3.82 (3H, s, *O*-CH_3), 2.20 (3H, d, *J* = 1.3 Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 155.6, 150.7, 131.8, 129.3, 123.0, 116.6, 115.2, 112.9, 101.9, 55.4, 53.7, 9.2; EIMS *m/z* 219 $[M]^+$ (100), 204 (46), 160 (26).

Further elution gave the principal reaction product, furoindole **6** (2:8, EtOAc / hexane), which was isolated as white solid (91 mg, 75 %): mp 136-137 °C ($CHCl_3$ / hexane); R_f = 0.31 (4:6, EtOAc / hexane); IR ($CHCl_3$) ν_{max}: 3018, 1784, 1722, 1212 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.77 (1H, br s, H-7), 6.83 (1H, br dd, *J* = 8.9, 2.3 Hz, H-6), 6.73 (1H, d, *J* = 2.3 Hz, H-4), 6.12 (1H, br s, H-8a), 3.90 (3H, br s, *O*-CH_3), 3.80 (3H, s, *O*-CH_3), 2.99 (1H, d, *J* = 17.9 Hz, H-3), 2.84 (1H, d, J = 17.9 Hz, H-3'), 1.43 (3H, s, CH_3); ^{13}C NMR (DMSO-d_6) δ 173.4, 157.0, 152.6 (br), 136.0 (br), 133.1 (br) 116.2, 114.0, 109.4, 97.5, 55.8, 53.2 (br), 48.1 (br), 41.3, 24.9; EIMS *m/z* 277 $[M]^+$ (100), 232 (20), 218 (26).

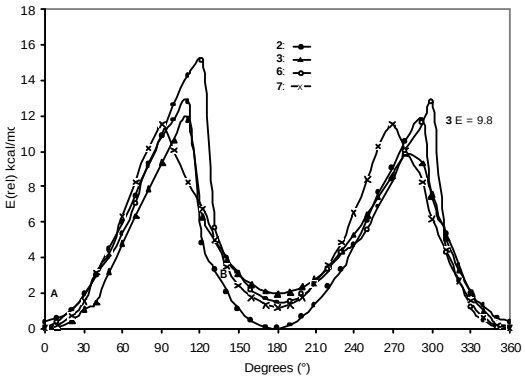


Fig. 4. Energy profiles for the interconversion of the **A** and **B** conformers in **2**, **3**, **6** and **7**, calculated at the MMFF level.

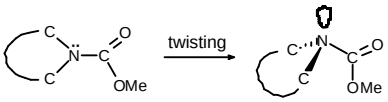


Fig. 5. The N-C carbamate bond twisting.

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