

The N-Substituent Effect on the Internal Rotational Barrier in N-Alkyl-N-ethylacetamides.

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The barriers of internal rotation about the C(O)-N bond of four N-alkyl-N-ethylacetamides [$\text{CH}_3\text{C}(\text{O})\text{NEtCH}_2\text{R}$, $\text{R}=(1)\text{Me}$, $(2)\text{H}$, $(3)\text{CH}_2\text{OH}$, $(4)\text{CH}_2\text{OAc}$] were determined by ^{13}C DNMR Spectroscopy at coalescence temperature. The results allowed to conclude that the isomeric preference and the internal rotation barrier about the C(O)-N bond of the N-alkyl-N-ethylacetamides **1,2,4** depend mainly on the steric effects of the N-substituent R, while in the N-alkyl-N-ethylacetamide **3** they also depend on the intermolecular hydrogen bond effect.

As barreiras de rotação interna em torno da ligação C(O)-N de quatro N-alkil-N-metilacetamidas [$\text{CH}_3\text{C}(\text{O})\text{NEtCH}_2\text{R}$, $\text{R}=(1)\text{Me}$, $(2)\text{H}$, $(3)\text{CH}_2\text{OH}$, $(4)\text{CH}_2\text{OAc}$] foram determinadas por espectroscopia de RMN Dinâmica de ^{13}C na temperatura de coalescência. A partir dos resultados foi possível concluir que a preferência isomérica e a barreira de rotação interna em torno da ligação C(O)-N das N-alkil-N-metilacetamidas **1,2,4** dependem principalmente do efeito estérico do N-substituinte R, enquanto que na N-alkil-N-metilacetamida **3**, essas propriedades dependem também do efeito de pontes de hidrogênio inter-moleculares.

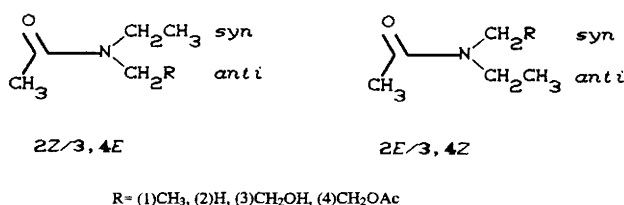
Key words: internal rotation barrier; amides; N- substituent effect.

Introduction

Hindered rotation about the C(O)-N bond in N,N-dialkylamides has been studied extensively¹⁻⁵. In symmetrical¹ amides, ^1H and ^{13}C NMR signals from N-substituents on each side of the nitrogen atom are generally non-equivalent at room temperature, but coalescence are observed at higher temperatures. Thus, Dynamic NMR methods have been used to determine the barrier of internal rotation of a variety of symmetrical tertiary amides^{1,6,7}. On the contrary, very few dynamic NMR studies of unsymmetrical amides have been reported⁸. In such compounds hindered rotation give rise to rotational isomers E and Z, the relative populations of which are determined mainly by both the nature of the N-substituents and α -carbonyl substituents. The primary objective of this study was to identify of the causing effect of N-substituents on the rotational barriers and the relative populations of the E/Z isomers of N-alkyl-N-ethylacetamides **2-4**. In order to trace these effects, the N,N-diethylacetamide **1** was studied also (Scheme 1).

Results and Discussion

The ^1H and ^{13}C NMR signals of the syn- and anti-N-ethyl-substituents of N,N-diethylacetamide **1** and the E and Z isomers of acetamides **2-4** have been unambiguously assigned by homonuclear and heteronuclear COSY experiments^{9,10}.



Scheme 1.

Conformational Equilibrium: the E/Z isomeric equilibrium of the compounds **2-4** was determined by digital integration of the ^1H NMR signals of the N- CH_3 and N-C- CH_3 groups. To select also non-superimposed signals, chloroform- d_1 and benzene- d_6 were used as solvents. The experiments showed that both the solvents and a moderate variation of temperature on the relative population of isomers can be neglected. The Gibbs energies, ΔG° , of compounds **2-4** were calculated⁸ using Eq. 1,

$$\Delta G^\circ = R T \ln K \quad (1)$$

where $K = m_Z/m_E$ is the equilibrium constant (m_Z and m_E are the molar fractions of isomers E and Z, respectively), R the gas constant ($1.9857 \text{ Kcal.K}^{-1}.\text{mol}^{-1}$), and T the temperature (298 K).

Table 1 presents the percentage values of the isomer Z, the equilibrium constants (K), and the Gibbs energy values (ΔG^0) for the compounds **2** - **4**, as determined by the Eq. 1. According to the calculated ΔG^0 values the following order for the isomeric preference was found: **3**<**2**<**4**.

Table 1. Thermodynamic parameters of *N*-alkyl-*N*-ethylacetamides **1** - **4**.

Compound	R ^a	%Z ^b	K ^c	$-\Delta G^0_{298}$ ^d
1	Me	50	1.00	0
2	H	53	1.13	0.07
3	CH ₂ OH	52	1.08	0.04
4	CH ₂ OAc	56	1.27	0.14

^aSee Scheme 1.

^bFrom integration of ¹H NMR peak areas. The error estimated is ± 1 %.

^c $K = m_Z/m_E$.

^dIn kcal.mol⁻¹. Standard deviations of each of these mean values do not exceeded ± 0.01 kcal. mol⁻¹.

The oxygen atom and the CH₃ groups can be considered as substituents of the carbonyl carbon in compounds **2** - **4**, where the latter has a larger volume. The nitrogen atom also exhibits substituents with different volumes. In the ground state, the substituents at the carbonyl carbon and the nitrogen atom can be found in the carboxamide plane. Therefore, one can suppose that the isomeric preference is given to the isomer that has the more spacious trans groups in the amide bond plane¹⁰. It could be shown previously that the *N*-ethyl-*N*-methylformamide has the isomeric preference E, and all the α -substituted *N*-ethyl-*N*-methylacetamides have an isomeric preference Z¹⁰. It was also shown that the increase of steric size of the carbonyl carbon substituent leads to an increase of ΔG^0 , that is, an increase of the relative population of Z. The results for the R group of the *N*-alkyl-*N*-ethylacetamides **2** - **4** have shown that compound **3** (R=CH₂OH) presents the Z isomeric preference and ΔG^0 value, just as expected from steric bulkiness arguments. This fact can be due to the existence of competitive effects: an intermolecular hydrogen-bonding of the OH group with the carbonyl oxygen atom of the other molecule. This effect is rather weak, but it is not sufficient to fix a given isomeric preference. Thus, the net result showed that the compound **3** has a similar trend of a symmetric compound, such as the *N,N*-diethylacetamide(**1**). One could expect intra-molecular hydrogen-bonding between the OH and the carbonyl oxygen, however, this fact would lead to the strong Z-isomeric preference, which has not been observed.

Rotational Barriers: the occurrence of non-equal isomeric population in *N*-ethyl-*N*-methylamides, requires that the activation energies (i.e., rotational barriers), for the conversion of one isomer to the other are different from those of the reverse process. We have calculated the activation parameters from the coalescence temperature using equations developed by Shanin-Atidi and Bar-Eli¹¹, which take into account the effect of unequal isomer populations (Eqs. 2,3 and 4).

$$\Delta G^{\#}_{EZ} = 4.57T_c [10.62 + \log[X/2\pi(1+\Delta P)] + \log(T_c/\Delta\nu)] \quad (2)$$

$$\Delta G^{\#}_{ZE} = 4.57T_c [10.62 + \log[X/2\pi(1-\Delta P)] + \log(T_c/\Delta\nu)] \quad (3)$$

$$\Delta P = \frac{[(X^2-2)/3]^{3/2}}{X} \quad (4)$$

In Eqs. 2 and 3, $\Delta G^{\#}_{EZ}$ and $\Delta G^{\#}_{ZE}$ are the Gibbs energies of activation for the conversion from E to Z isomer and from Z to E isomer, respectively, T_c is the coalescence temperature, where the ¹³C NMR signals for two isomers are collapsing, $\Delta\nu$ is the frequency difference (in Hertz) between the two NMR signals at T_c , ΔP is the population difference between the isomers ($m_Z - m_E$), and X is a value defined by Eq. 4.

Although line-shape analysis methods^{6,8,12} for the determination of activation parameters are more accurate, the coalescence temperature approach avoids complications arising from the temperature-dependent variation of NMR line widths^{7,13}. Moreover, it has been clearly demonstrated that the coalescence temperature approach leads to activation energies, $\Delta G^{\#}_{T_c}$, which are significant and reliable parameters for correlations of structures with barrier heights^{7,11,13,14}.

In Table 2, the values of coalescence temperatures (T_c) are presented, and the Gibbs energies of activation ($\Delta G^{\#}_{ZE}$) determined from Eqs. 3 and 4, along with the $\Delta\delta C^1$ values [$\Delta\delta C^1 = \delta_{N-C^1(anti)} - \delta_{N-C^1(syn)}$] of the N-CH₂ groups of the *N*-ethyl substituents. Compounds **1** - **4** show a qualitative trend where the $\Delta G^{\#}$ values, i.e., the magnitude of barrier to rotation, are **4** < **1** \approx **2** < **3**.

The qualitative trends for compounds **1**, **2**, **4** can be rationalized by the steric effect model¹. In the steric model for rotational barriers in amides, it is assumed that an increase in size of the substituent at the carbonyl carbon or nitrogen will result in greater repulsive forces in the planar ground state relative to the transition state and will, therefore, produce a decrease of the rotational barrier. Therefore, the higher rotational barrier of compound **3** cannot be explained only with the steric model but also by the existence of a competitive effect caused by intermolecular hydrogen bonds of the OH group with carbonyl oxygen atoms of other molecules.

It was observed that $\Delta G^{\#}$ values of *N*-alkyl-*N*-ethylacetamides **1** - **4** exhibit a reasonable correlation with the ¹³C NMR $\Delta\delta C^1$ values ($\Delta\delta C^1 = \delta_{N-C^1(anti)} - \delta_{N-C^1(syn)}$, the N-CH₂ group of *N*-ethyl substituents), Table 2.

Finally, we conclude that the Gibbs energy (ΔG^0) and the Gibbs activation energy ($\Delta G^{\#}$) of compounds **1** - **4**, although depending mainly on the steric effect of the *N*-substituents, they are independent among themselves.

The isomeric preference of the *N*-ethyl-*N*-alkylacetamides depend on the rotational barrier about the C(O)-N bond. The Gibbs energy values can be found in range 0.04 to 0.14 kcal. mol⁻¹, and reflect the thermodynamic stability of the isomers E and Z. They can be negligible when compared with the $\Delta G^{\#}_{ZE}$ values for the rotation of the amid bond, 17.7 to 18.6 kcal. mol⁻¹).

Experimental

Compounds: compounds **1** - **4** were prepared by reaction of acetyl chloride with the corresponding substituted amine¹⁰.

NMR Measurements: ¹³C NMR spectra were recorded at 80 MHz using a Bruker AC-80 (20.15 MHz) spectrometer,

Table 2. Gibbs activation energy parameters for *N*-alkyl-*N*-ethylacetamides **1-4**.

Compound	R ^a	T _c (K) ^b	ΔG [#] _{ZE} ^c	ΔδC ¹ (ppm) ^d
1	Me	360	17.9	2.95
2	H	348 ^b	18.0	3.20
3	CH ₂ OH	379	18.6	4.18
4	CH ₂ OAc	356	17.7	3.19

^aSee Scheme 1.

^bThe error estimated is ± 1K. For compounds **1,3** and **4**, the *N*-CH₂ of *N*-ethyl substituent ¹³C signal collapse were observed, for compound **2** it was observed the *N*-C-CH₃ signal.

^cIn kcal.mol⁻¹. Standard deviations of each of these mean values do not exceed ± 0.02 kcal.mol⁻¹.

^dΔδC¹ = ^δ*N*-CH₂(*anti*)-^β*N*-CH₂(*syn*) (The *N*-CH₂ of the *N*-ethyl substituent).

for 1M solutions in 1,1,2,2-tetrachloro-1,2-dideuteroethane, containing 0.1% of tetramethylsilane, as solvent, in 5mm i.d. sample tubes. The conditions were as follows: deuterium internal lock, pulse width 1.6μs, flip angle 30°, acquisition time 1.6s, spectral width 5000Hz, pulse repetition time 1.3s, number of transients 7000, and number of data points 16384.

Coalescence temperatures were determined by recording the ¹³C NMR spectra on the Bruker AC-80(20.15 MHz) spectromete, in over the temperature range 20-130°C, using a calibrated ECO3-Bruker temperature control accessory. The coalescence temperatures (T_c) reported in this study are the minimum temperatures at which signals arising from corresponding *N*-CH₂ carbons of each rotamer are no more distinguishable. The precision of the T_c determinations was established by recording the ¹³C NMR spectra in 1°C increments in the T_c ± 5°C interval. In no case the precision of the determinations exceeded ± 1°C which corresponds to a maximum error of ± 0.2kcal. mol⁻¹ in the calculated values of ΔG[#]_{T_c}.

The frequency difference, Δν(Hz), between the two signals of *N*-CH₂ carbon atoms at coalescence temperature was estimated by extrapolation from the temperature versus Du curve (minimum five measuring values).

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