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Journal of Molecular Structure 886 (2008) 24–31
Journal of MOLECULAR STRUCTURE
www.elsevier.com/locate/molstruc

Dynamic NMR studies of *N*-benzoyl pyrrolidine and *N*-benzoyl piperidine derivatives

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Received 11 October 2006; received in revised form 6 January 2007; accepted 9 January 2007
Available online 20 January 2007

Abstract

Variable-temperature ^{1}H and ^{13}C NMR spectroscopy are used to investigate barrier of C–N rotation in series of amides, such as *N*-benzoyl pyrrolidine, *N*-(4-chlorobenzoyl) pyrrolidine, *N*-(4-methoxybenzoyl) pyrrolidine, *N*-(4-chlorobenzoyl) piperidine, and *N*-(4-methoxybenzoyl) piperidine. $\Delta G^{\neq}_{298}$ of 65.2, 60.6, 58.8, 60.1, and 57.1 kJ mol^{-1}are found for the above compounds, respectively. Theoretical studies were done for these compounds and the results showed good agreement with the experimental results. Theoretical and experimental results showed that substituted methoxy group on the para position of benzene ring decreases the rotational barrier. Increasing steric effect and therefore unstabilizing the ground state (GS) in piperidine compare to pyrrolidine ring also decreases the rotational barrier. It was found out that the rotational barrier in the polar solvent is higher than non-polar solvent.
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Keywords: Amides; Rotational barrier; Dynamic NMR; Theoretical study

1. Introduction

The properties of amides have received much attention, not only they are a major functional group in organic chemistry [1–3], but they are key linkage in natural macromolecules such as proteins, polypeptides and synthetic macromolecules such as nylon and Kevlar. The C–N bond in amides is known to have relatively high rotational barrier of 54.4–83.7 kJ mol^{-1} due to the partial double bond character [4–6]. An important aspect of amides is their preference for a near-planar arrangement of amide group. By assuming sp^2 hybridization, the amide nitrogen can donate its lone pair electron density to the polarized carbonyl group This favorable interaction is lost as the amide bond rotates, raising the barrier to 75.3 kJ mol^{-1} in the case of formamide [7]. The resonance model has been quite successful in describing and predicting effects of nitrogen and carbonyl substitution on the magnitude of the rotational barriers [5,8–15]. In general, any substituent on the carbonyl larger than hydrogen, lower the rotational barrier due to unfavorable steric interaction with the nitrogen substituents, which causes destabilization of the planar ground state. Also, the electronegativity and capability to have resonance with the substituent attached to the carbonyl carbon has a marked effect on the magnitude of the rotational barrier. In general, increasing electron withdrawing groups decrease the barrier of C–N rotation in amides.

The slow exchange ^{1}H NMR spectra of all amides and thioamides systems show both conformational forms: *syn* (*N*-methyl or methylene group *syn* to the carbonyl oxygen) and *anti* (*N*-methyl or methylene group *anti* to the carbonyl oxygen). Observation of two separate *N*-alkyl resonances are the results of the magnetic anisotropy of the amide and thioamide groups. Previous studies of N-substituted oxoamides have shown that the *N*-methyl or methylene protons *anti* to the carbonyl oxygen, resonate at lower field than the *syn N*-methyl or methylene protons in formamide, trifluoroacetamide, acetamide and trifluoroacetyl pyrrolidine systems [5,8–17].

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doi:10.1016/j.molstruc.2007.01.019

Hirsch et al. have studied the variable-temperature ^{13}C and ^{1}H NMR of *N*-benzoyl piperidine and different substituted groups on piperidine ring in $CDCl_3$ [18]. They showed that the amide rotational barrier ($\Delta G^{\neq}_{T_c}$) in these compounds is *ca.* 60.7 kJ mol^{-1}. Suarez et al. have recently measured the gas and liquid-phase internal rotational barrier for *N*-(triflouroacetyl) pyrrolidine [19]. The present study examines the solution kinetic characterization of the hindered internal rotation around the C–N bond in *N*-benzoyl pyrrolidine, *N*-(4-chlorobenzoyl) pyrrolidine, *N*-(4-methoxybenzoyl) pyrrolidine, *N*-(4-chlorobenzoyl) piperidine ad *N*-(4-methoxybenzoyl) piperidine. These compounds have further interesting complication, in which the π-system in the phenyl ring plays as an electron donation and competes with nitrogen lone pair for resonance with carbonyl group and lowered the barrier height. In this study, we used both coalescence temperatures and slow exchange spectra to reports the Gibbs free energy ($\Delta G^{\neq}_{298}$), activation enthalpy ($\Delta H^{\neq}$) and activation entropy ($\Delta S^{\neq}$) differences describing the rotational barrier in these compounds. Also, we examined the effect of different solvents (DMSO-d_6, $CDCl_3$, Nitromethane-d_3 and Benzene-d_6) on rotational barrier in *N*-(4-chlorobenzoyl) pyrrolidine. Fig. 1 shows the compounds and carbon numbering used throughout this work.

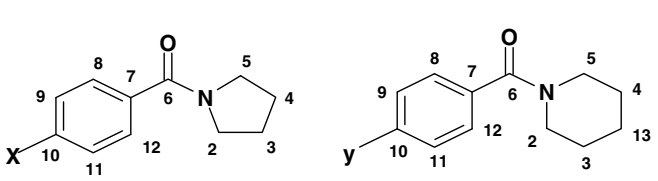
2. Experimental section

2.1. Synthesis of corresponding amides

The amides were prepared by the Schotten–Baumann method [20] and were purified by distillation or recrystallization. Chemicals were purchased from Merck and Aldrich Chemical companies.

2.2. Sample preparation

Solution-phase NMR samples for ^{1}H NMR and ^{13}C NMR were prepared with 0.1 M concentration and for studying solvent effect for compound **3**, the 0.05 M concentration was used. Deuteriated solvents were obtained from Merck with exception of nitromethane which was obtained from Aldrich. Bezene-d_6 and DMSO-d_6 were 99.5 atoms % D; chloroform-d_1 was 99.8 atom % D; nitromethane-d_3 was 99.0 atom % D. All solvents contained 1% of TMS.



X = H 1
X = Cl 2
X = OMe 3

y = Cl 4
y = OMe 5

Fig. 1. *N*-benzoyl pyrrolidine and *N*-benzoyl piperidine derivatives with carbon numbering.

2.3. NMR measurements

^{1}H NMR measurements were performed on a Bruker AMX500 using 5 mm variable temperatures (VT) probe with proton observation at 500.13 MHz. All measurements were made on spinning samples in the locked mode. In all measurements, acquisition time was 1.58 s/scan, with a pulse length of 9.65 μs, and pulse delay time of 10 s. Typically 16 scans were collected at each temperature and stored in 32 k of memory. Sweep width was 10330.58 Hz for all spectra, giving a digital resolution of 0.316 Hz/point. The resulting solution spectra for all compounds had typical S/N ratios greater than 500:1. The spectra line-width parameter, T_{2nat}, was determined for each spectrum by measuring the line width of the TMS. For ^{13}C NMR 3000 scans were collected at slow exchange and coalescence temperature. The resulting ^{13}C NMR spectra had typical signal-to-noise (S/N) ratios greater than 200:1. Probe temperatures (±0.5) were measured with a calibrated, digital thermocouple.

2.4. Rate analysis

Rate constants were calculated for exchange spectra by using the MEXICO [21] program, which uses an iterative nonlinear least squares regression analysis to obtain the best fit of the experimental spectrum. Rate constants were extracted from the ^{1}H NMR exchanging spectra using the $A_2 \leftrightarrow B_2$ portion (β protons relative to nitrogen) of the ring $A_2C_2 \leftrightarrow B_2D_2$ spin system of the two-site mutual coupled with the neighbor hydrogen's and equally populated. Also, from ^{13}C NMR spectrum at coalescence temperature, rate constants and $\Delta G^{\neq}_{T_c}$ were extracted.

The complete band shape (CBS) method of analysis first requires the measurement of chemical shifts and natural transverse relaxation times (T_{2nat}) in the absence of exchange to separate spectral changes due to natural temperature dependence from those due to exchange. The systems were all studied in temperature ranges in which exchange was apparently absent and the parameters of natural temperature dependence could be determined. Coupling constants showed no temperature dependence in any of the systems studied. On the other hand chemical shifts and T_{2nat} exhibited a dependence on temperature in most situations. Whenever a temperature dependence of either chemical shifts or T_{2nat} was found, a linear relationship was assumed and adjusted parameters were estimated for exchanging temperatures.

Although the CBS analysis provides a clear method for extracting rate constant from NMR line shape spectra, but it suffers from some limitations. For example, systems with high barriers which show only slow exchange or little differences in limiting chemical shifts of two sites of exchange data for slower rates are needed in order to get more accu-

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