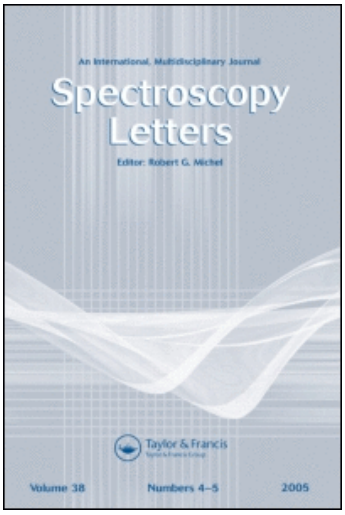

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MOLECULAR FLEXIBILITY OF *N*-ACYL HETEROCYCLES STUDIED USING ^{13}C NMR SPECTROSCOPY AND COMPUTATIONAL CHEMISTRY

Keywords: *N*-acylheterocycles, conformation, molecular dynamics, NMR

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ABSTRACT

The ^{13}C NMR spectra of a series of *N*-acyl six-member ring nitrogen heterocycles have been measured as a function of temperature and the results interpreted in terms of restricted amide rotation and ring inversion. Slow rotation is observed on the NMR time scale around the N-CO bond whilst the ring inversion is fast at ambient temperature. High temperature experiments have been undertaken to investigate the free energy of activation for the amide rotation and low temperature NMR experiments were used to probe the ring inversion process. The experimental results have been compared with theoretical calculations using molecular orbital, molecular mechanics and molecular dynamics approaches and good agreement is observed in all cases.

INTRODUCTION

The conformations and rotational and inversion barriers in *N*-acyl heterocycles such as morpholine, piperazine and piperidine have been the subject of continued study[1-7] because the amide group in this type of molecule is an important structure in organic and biological chemistry.[6] Previous work using ultrasonics and ^{13}C NMR spectroscopy on *N*-formylmorpholine had suggested that the ring geometry was fixed on the NMR time-scale at 306 K and that observed splittings in the ^{13}C NMR

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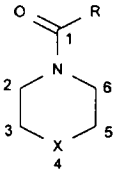
spectrum were due to different ring conformations and quadrupolar effects of the ^{14}N nucleus.[3] Llinares *et al*[2] have suggested from ^{13}C NMR studies that *N*-formylmorpholine and *N*-formylpiperidine exist in *syn* and *anti* amide conformations as a result of restricted amide rotation. Recently, ^{13}C NMR studies have been carried out on N-formylmorpholine[7] over a wide temperature range to elucidate the ring and amide dynamics and these showed that the ring conformation is fixed but that the formyl group exhibits slow rotation on the NMR time-scale at ambient temperature. In the present study , the work has been extended to include a variety of *N*-acetyl and *N*-formyl heterocyclic compounds and the results compared to those obtained from theoretical calculations.

All the molecules studied have the general structure shown below.



(I) R = H, X = O *N*-formylmorpholine
(II) R = CH_3, X = O *N*-acetylmorpholine
(III) R = H, X = NH *N*-formylpiperazine
(IV) R = H, X = CH_2 *N*-formylpiperidine

EXPERIMENTAL

All samples were of commercial origin (Aldrich) and were used without further purification. Solutions were prepared in either dmso-d_6 or ethanol-d_6 as approximately 10% *w/v* solutions and were not degassed. NMR spectra were measured on a Bruker AC-200 spectrometer operating at 50.3 MHz for ^{13}C observation over the temperature range 163-433 K. Typical ^{13}C NMR parameters comprised a spectral width of 12500 Hz, an acquisition time of 1.31 s corresponding to 32768 time domain points, a relaxation delay of 1.7 s, broadband ^{1}H decoupling and the application of a 1 Hz linebroadening before Fourier transformation. Chemical shifts were referenced to the ^{13}C shifts of dmso-d_6 at 39.50 ppm or the methyl carbon of ethanol-d_6 at 17.31 ppm. Molecules were constructed using SYBYL and the geometry was optimised using molecular dynamics with the Tripos force field[8] and with charges calculated empirically using the Gasteiger and Marisili method.[9] The dielectric constant was fixed at $\varepsilon = 1$. To determine the barrier to rotation about the amide bond a grid search was conducted. This consisted of constraining the rotatable bond torsion angle at a fixed value and allowing geometry optimisation of the rest of the molecule, this procedure being repeated at 5° intervals. The torsion angle τ(C2-N-C1-O), τ(MM) was calculated for the minimum energy form. The same angle was also calculated by MO optimisation τ(MO) with the AM1 Hamiltonian at the semi-empirical level using MOPAC.[10] The barrier height to amide rotation, ΔE, was calculated using the molecular mechanics grid search. Molecular dynamics calculations were carried out using SYBYL to investigate ring flip motion. Simulation were carried out for 50 ps sampling every 1 fs at 300K. The angle N-C2-C3-X4 was used to monitor any ring inversion processes.

RESULTS:

***N*-formylmorpholine (I):** The ^{13}C NMR spectrum of *N*-formylmorpholine has been reported previously[7] and shows 5 carbon resonances at ambient temperature, one for the formyl carbon at high frequency and 4 others arising from the ring carbons. The ^{13}C chemical shifts determined here are given in Table 1.

Table 1: ^{13}C NMR Chemical Shifts (ppm) for (I) - (IV)

	(I)	(II)	(III)	(IV)
R	H	CH_3	H	H
X	O	O	NH	CH_2
C1	160.84	168.28	160.98	160.28
C2	39.98	41.15	40.63	40.33
C3*	65.75	66.01	46.17	24.80
C4	-	-	-	24.16
C5*	66.77	66.01	46.29	26.17
C6	45.14	46.01	45.07	45.62

C2/C6 were assigned on the basis that carbons *syn* to the carbonyl oxygen are more shielded than those *anti*.[2] * resonances not specifically assigned.

The slow rotation of the formyl group on the NMR time scale renders the chemical shifts of the pairs of nuclei C2/C6 and C3/C5 non-equivalent. The shifts at 66.77 and 65.75 ppm arise from C3 and C5 and have not been assigned specifically as *syn* or *anti* to the formyl oxygen. At 45.14 and 39.98 ppm are seen the resonances for C2 and C6. Here, on the basis of previous work,[2] the more shielded of the resonances can be assigned as the carbon *syn* to the formyl oxygen. On the basis of variable temperature NMR experiments which produced coalescence of the C3/C5 signals at 408±3 K, and from a knowledge of their chemical shifts in the absence of exchange (51.5 Hz), it was possible to calculate a free energy of activation $\Delta G^{\neq}$ for the conformational motion of 92.7 $kJ.mol^{-1}$. In addition, low temperature NMR spectroscopy down to 163K showed no changes from the ambient temperature spectrum indicating that ring inversion was still fast on the NMR time scale or that only one ring conformer is populated at all temperatures. This latter possibility is unlikely in view of the known rapid ring motion in *N*-alkylpiperidines which is fast on the NMR time scale.[1]

We had earlier carried out molecular dynamics simulations of this molecule which agreed with the NMR experiments showing that the formyl group was hindered in rotation but that the ring was flexible, averaging over a range of conformations with proportions of the two main forms corresponding to the chair forms having proportions of about 10:1, that being most populated having a torsion angle N-C2-C3-O of about - 60°.

***N*-acetylmorpholine (II)** : For this compound, similar chemical shifts to those of **(I)** were observed and are given in Table 1, and again the NMR evidence from low and high temperature studies was of slow amide group rotation and rapid ring inversion. At a temperature of 193K, the resonances of the ring carbons show increased broadening whilst the two resonances from the acetyl group remain sharp providing an indication of the slowing down of the ring conformational motion. For the acetyl group rotation, only one measurement of $\Delta G^{\neq}$ is possible in this molecule because the signals from C3 and C5 are coincident. Thus the signals from C2 and C6 coalesce

at 380±3K and have a chemical shift difference of 244.5 Hz in the absence of exchange. This allows the calculation of the lifetime at the coalescence temperature and the exchange rate of at this temperature. From this, $\Delta G^{\neq}$ is then calculated to be 73.9 kJ.mol^{-1}.

N-**formylpiperazine (III)** : The ^{13}C NMR spectrum at ambient temperature shows 5 carbon resonances as before, one for the formyl carbon at high frequency and four others arising from the ring carbons with shifts given in Table 1. The slow rotation of the formyl group on the NMR time scale renders the chemical shifts of the pairs of nuclei C3/C5 and C2/C6 non-equivalent. The assignments in this molecule are difficult to confirm absolutely as the 4 shifts are very close together being at 40.63, 45.07, 46.17 and 46.29 ppm. The shift at 40.63 ppm can be assigned to C2 based on the other molecules in the series and the shielding effect of the *syn* carbonyl group. The two closely situated resonances at 46.29 and 46.17 ppm coalesce at 360±3K and therefore arise from C3 and C5 and the signal at 45.07 ppm must come from C6. The coalescence behaviour of the C3 and C5 signals gives a $\Delta G^{\neq}$ value of 80.9 kJ.mol^{-1}. At low temperatures the ring carbons begin to broaden at 203K whilst the formyl carbon remains sharp, indicating a slowing down of the ring conformational motion. The lowest temperature which could be reached with this solution was 203K.

***N*-formylpiperidine:** This molecule also exhibits slow amide rotation at room temperature giving 5 ring carbon resonances with ^{13}C chemical shifts as in Table 1. The most deshielded pair of these at 40.33 and 45.62 ppm are assigned to C2 and C6 on the basis of the arguments given earlier. The resonance at 24.16 ppm is assignable to C4 because it does not show any coalescence behaviour and thus the two other resonances at 24.80 and 26.17 ppm, arising from C3 and C5 are not assigned specifically. These latter resonances coalesce at 408K and at this temperature the resonances for C2 and C6 are broadened and have moved closer together but have not coalesced. The free energy of activation of the amide rotation has been calculated to be 88.5 kJ.mol^{-1} based on the C3/C5 coalescence. The C2/C6 resonances are at coalescence at 433K giving a value of $\Delta G^{\neq}$ of 83.9 kJ.mol^{-1}. The ring conformational motion could not be frozen out even at 163K, all signals broadening equally presumably due to increased viscosity.

Theoretical calculations: The result of the molecular mechanics and MO geometry optimisation are shown in Table 2. The molecular mechanics generally show the amidic nitrogen as nearly planar and thus the minimum energy torsion angle τ(MM) is close to 0. The corresponding value from MOPAC is larger and this is mainly because the nitrogen is no longer planar.

The amide rotation barrier heights are in fair agreement with the NMR-determined values given that molecular mechanics force fields are generally parameterised to reproduce molecular geometries rather than energies and that in addition calculations are performed *in vacuo*. The molecular dynamics results show that the 6-membered rings flip in all cases between the chair forms and given that the molecular mechanics calculations show that the nitrogen is virtually planar the two chair forms become equivalent and hence should show equal populations. The molecular dynamics was over 50 ps and showed that both chair forms are

Table 2: Amide torsion angles calculated by molecular mechanics (τ(MM)) and molecular orbital methods (τ(MO)) and amide rotation barrier heights calculated by molecular mechanics for (I) - (IV)

Molecule	τ(MM)°	τ(MO)°	ΔE(kJ.mol^{-1})
N-formylmorpholine (I)	0.0	3.9	98.5
N -acetylmorpholine (II)	4.5	5.7	89.7
N -formylpiperazine (III)	0.0	6.1	99.9
N -formylpiperidine (IV)	0.7	9.1	100.1

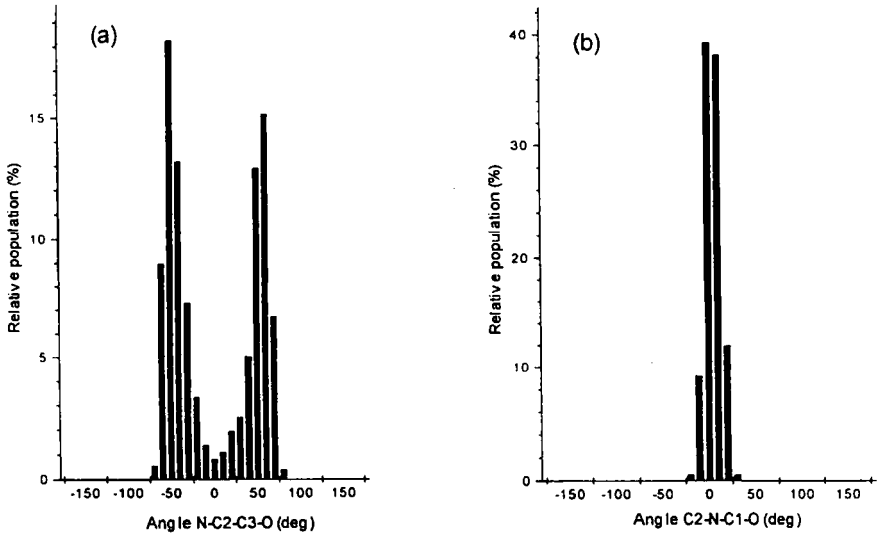


Figure 1. Histogram obtained for molecular dynamics calculation for (a) ring inversion and (b) acyl group rotation in N-formylmorpholine (I).

significantly populated (Figure 1(a), for *N*-formylmorpholine (I)) and extending the run time would probably tend to equalise the populations.

On the other hand the molecular dynamics simulations demonstrate the rigidity of the amide bond on the same time scale with only one conformation being populated (Figure 1(b)). The same behaviour is observed for all four molecules. Molecular dynamics could be run using a solvent shell but the effect of this would be to slow down any molecular motions and make the calculation excessively long. This was not carried out as all molecules behaved similarly. The calculations are in good agreement with the NMR spectroscopic results both in term of the facial ring inversion process and the more restricted amide rotation.

This combined NMR experimental and theoretical calculations approach thus provides confidence in the calculation of the behaviour of the molecular systems.

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