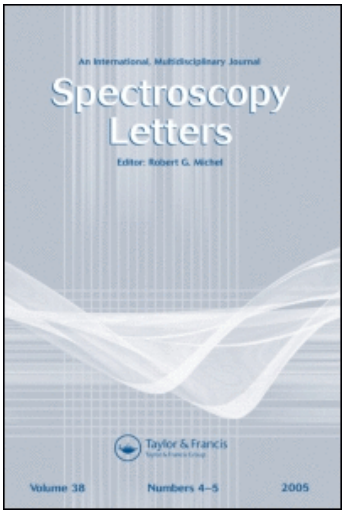

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Proton Nuclear Magnetic Resonance Spectroscopy: Significant Barriers to Rotation About N-N Bonds in 3-Acylaminoquinazolin-4(3*H*)-One Derivatives

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PROTON NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY: SIGNIFICANT BARRIERS TO ROTATION ABOUT N-N BONDS IN 3-ACYLAMINOQUINAZOLIN-4(3*H*)-ONE DERIVATIVES

keywords: quinazolin-4(3*H*)-ones, ^{1}H NMR spectra, hindered rotation, free energy of activation, stereochemical process, chiral axis, orthogonal conformation, coalescence temperatures.

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ABSTRACT

The proton NMR spectra of several 3-acylaminoquinazolin-4(3*H*)-one derivatives have been studied as a function of temperature. The changes, which were found to occur in the spectra at high temperatures, are discussed in terms of hindered rotation about the nitrogen-nitrogen bond. The free energies of activation for the rate-determining stereochemical process were calculated to be as high as (14.7~20.6 Kcal mol^{-1}) for hydrazine derivatives.

INTRODUCTION

Surprisingly large barriers have been observed for rotation about P-N bonds in aminophosphines[1,2], N-Si bonds in silylated hydrazines[3], N-As bonds in aminoarsines[1], and about N-S[4] and N-O[5] bonds.

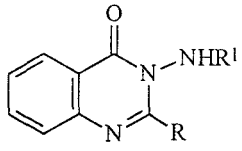
The conformational stereochemistry of several heterocyclic systems and hydrazines and the barriers in them to inversion of nitrogen and rotation about the N-N bond have been reported[6]. Studies by microwave spectroscopy and electron diffraction of hydrazine[7] and some substituted hydrazines[8] have shown that the preferred conformation is one with the nitrogen lone pairs gauche to one another. Also, the barriers to inversion of nitrogen in tetrafluorohyrazine[9] and in cyclic hydrazines[10] have been measured. Barriers to rotation have been reported for di- and tetraacylhydrazines, where both nitrogen atoms are of amide type[11], and in hydrazones[12], triazines[13] and tetrazines[14].

Recently, barrier to rotation was reported for 3-(diacylamino)quinazolin-4(3*H*)-ones[15]. We now report on the orthogonal conformation and estimation of free-energy barriers to rotation about the N-N bond in 3-acylaminoquinazolin-4(3*H*)-ones.

RESULTS AND DISCUSSION

During the course of current investigations of the syntheses of quinazolin-4(3*H*)-one derivatives[16], interesting features were observed in the NMR spectra of the products. We have now examined the ^{1}H NMR spectra of quinazolin-4(3*H*)-one derivatives **1-7** in more detail in order to understand the features better.

HINDERED ROTATION IN QUINAZOLIN-4(3*H*)-ONES



1 R = $CH_2C(OH)Ph_2$, R^1 = $COBu^t$
2 R = $CH_2SCSNPr^i_2$, R^1 = COMe
3 R = Et, R^1 = COMe
4 R = Et, R^1 = Me
5 R = Et, R^1 = $COPr^i$
6 R = Pr^i, R^1 = $COBu^t$
7 R = Pr^i, R^1 = COMe

All of the spectra showed a dependence on temperature that indicated significant barriers to rotation about the N-N bonds. In the case of compound **1**, the CH_2 protons at C-2 must be equivalent unless the plane of the aromatic ring is orthogonal to the plane of the pivaloylamino group, which renders the N-N bond as a chiral axis. At room temperature the corresponding ^1H NMR signal for the CH_2 group in compound **1** appears as two AB doublets (J_{AB} = 17 Hz) in [$^2H_6$]DMSO. These two doublets showed a single broadened line at 150 °C, so that a reasonable estimate of the free energy of activation ($\Delta G^{\ddagger}_C$) at the coalescence temperature (T_C) could be made by using the formula given in equation 1[5]. Similar calculation were made for the other compounds and the results are shown in Table 1.

$$\Delta G^{\ddagger}_C = 4.57\, T_C \left[9.67 + \log \frac{T_C}{(\Delta\nu^2_{AB} + 6\, J^2_{AB})^{1/2}} \right] \qquad (1)$$

In the case of compound **2**, the ^1H NMR signal for the CH_2 protons in [$^2H_6$]DMSO consisted of two AB doublets (J_{AB} = 15 Hz). On raising the temperature to 120 °C, the two AB doublets showed significant line-broadening indicative of the onset of equilibration. The ^1H NMR spectrum at -20 °C showed the presence of two diasteroisomers in unequal proportions (1:2), indicating restricted rotation about the N-N bond below room temperature.

The ^1H NMR spectra of compound **3** shows two separate double quartets (J = 7.0 and 15.5 Hz) at 20 °C which coalesced to perfect single quartets at 100 °C. Similarly the ^1H NMR spectra of compound **4** show two separate double quartets (J = 7.4 and 16.0 Hz) at -50 °C which coalesced to perfect single quartets at 60 °C. In the ^1H NMR spectrum of compound **5** recorded at room temperature the methyl protons of the isopropyl group appear as two separate doublets (J = 6.9 Hz) and the CH_2 protons at position 2 appear as two overlapping doublet quartets (J = 7.5 and 16.5

TABLE 1

^{1}H NMR Parameters and Free-Energy Barriers About the N-N Bond ($\Delta G^{\ddagger}_C$) Estimated from Coalescence Temperatures (T_C) for Compounds 1-7 [a].

Comp. No.	Solvent	$\Delta\nu_{AB}$[b](T), Hz ± 0.5 Hz	J_{AB}, Hz ± 0.5 Hz	T_C, °C ± 2 °C	$\Delta G^{\ddagger}_C$ at T_C[c] Kcal mole^{-1}
1	[$^2H_6$]DMSO	20 (20)	17.0	150	20.6
2	[$^2H_6$]DMSO	264 (23)	15.0	120	17.7
3	[$^2H_6$]DMSO	40 (20)	15.5	100	17.9
4	$CDCl_3$	180 (-50)	16.0	60	14.7
5	$CDCl_3$	16 (20)	16.5	58	16.0
6	$CDCl_3$	24 (20)	6.7	63	16.5
7	$CDCl_3$	22 (20)	6.7	63	16.5

[a] The table refers only to the CH_2 signals (compounds **1-5**) or CH signal (compounds **6** and **7**) at position 2 of the quinazolinone moiety.
[b] At 400 MHz
[c] Errors are difficult to estimate: they are probably less than ± 0.2 Kcal mole^{-1}.

Hz). However, at 58 °C, these signals coalesced to a doublet and a quartet, respectively, which indicates the onset of equilibration *via* rotation about the N-N bond. In the case of compounds **6** and **7**, the ^{1}H NMR spectra showed two doublets (J = 6.7 Hz) for the isopropyl methyl protons. On raising the temperature to 63 °C, these two doublets collapsed to a single perfect doublet.

From these results I conclude that this phenomenon results from the orthogonal arrangement of the two ends of the hydrazine system and a high barrier to rotation about the N-N bond. Orthogonal conformations are known to be significantly more stable than their coplanar counterparts for hydrazine derivatives[17].

EXPERIMENTAL

Compounds **1-7** were prepared as previously reported[16]. ^1H NMR spectra were recorded on a Bruker spectrometer operating at 400 MHz. Chemical shifts are reported in parts per million relative to tetramethylsilane.

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