

A Solid-State NMR Study of Ring-Chain Tautomerism in 1,3-*O,N*-Heterocycles¹

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Dedicated to Professor Gábor Fodor on the occasion of his 75th birthday.

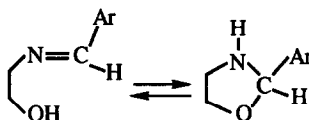
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ABSTRACT. The solid-state ¹³C CP/MAS nmr spectra of nineteen tetrahydrooxazines and oxazolidines have been recorded to determine their preferences for the ring or chain tautomeric form in the solid state. The chain form is preferred for those cases in which <80% of the ring tautomer is found in solution. The ring form is exclusively found only in derivatives with >93% preference for the ring tautomer in solution. In one case the solid-state reaction converting the open chain to the ring was observed to take place over a time-scale of several days.

INTRODUCTION

The ring-chain tautomerism in 1,3-*O,N*-heterocycles has been intensively studied in recent years, with special attention being paid to the tetrahydro-1,3-oxazine and 1,3-oxazolidine ring systems. These rings exhibit tautomerism in both solution²⁻⁶ and gas phases.^{7,8} The current paper extends this work into the solid state by means of solid-state nmr spectroscopy.

These systems are of particular interest because the ring formation of oxazolidines is an unfavoured 5-*endo-trig* process according to Baldwin's rules. Despite this, a rapid equilibrium reaction is observed to exist in solution:

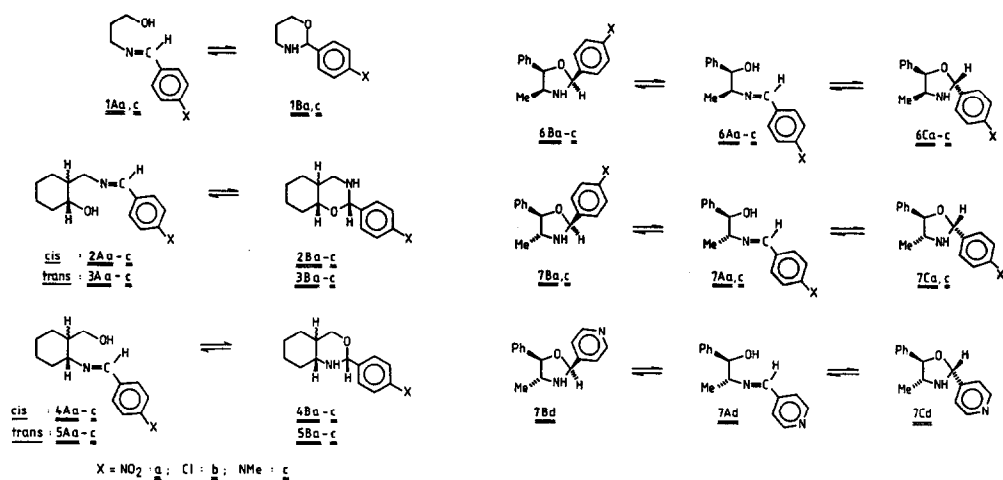


The equilibrium between the ring and chain forms can be described accurately by the simple equation:

$$\log K_X = \rho \sigma^+ + \log K_{X=H} \quad (1)$$

where $K = [\text{ring}]/[\text{chain}]$, ρ is a constant characteristic of the ring system and σ^+ is the Hammett-Brown electrophilic substitution constant.² In solution the constant ρ depends only weakly on the nature of the solvent, whereas $\log K$ has a strong solvent dependence. With the aid of the above equation it has recently proved possible to determine the electrophilic substituent constants for 3- and 4-pyridyl substituents.⁴ Studies in the gas phase using mass spectrometry show that the above equation also holds for the gas phase equilibrium.⁸

For the solid state, one might expect that the stronger crystal packing interactions should predominate over the smaller solution free energy differences, forcing the equilibrium to one extreme or the other, and that, therefore, only one form should be seen. This is borne out in the limited number of cases where X-ray crystallography has been applied. Alva Astudillo *et al.* found³ that the products from the reaction of 2-amino-2-methyl-1-propanol with *p*-tolualdehyde and *m*-bromobenzaldehyde exist only in the open chain form in the solid state. In contrast, in CDCl₃ solution the ring form predominates (63% and 79%, respectively).^{3,6} Two of the current compounds (**2a** and **3a**) have been shown by X-ray crystallography to exist in the ring form in the solid state,⁹ a result confirmed by the current work. These compounds also exist predominantly in the ring form in CDCl₃ solution (Table 1).²



It is of interest to see to what extent the forms that predominate in solution are also found in the solid-state. To what extent is the free energy difference between ring and chain forms of the free molecule (as represented by solution data) a determinant of the form the molecule adopts in the solid state? Solid-state nmr offers a rapid answer to this question since the spectra of ring and chain forms of the molecule are readily distinguished, primarily by the chemical shift of the C(2) ring carbon, or the open chain imine carbon (ca 160 ppm open chain, ca 86 ppm ring). The compounds investigated in the present paper were selected with the aim of covering a wide range of ring:chain ratios in CDCl₃ solution. We also included some compounds for which three component equilibria are possible.

EXPERIMENTAL

Compounds **1-7** were prepared as described earlier^{2,4,5} and were recrystallised from hexane, with the exceptions of **3b** and **7c**, which were recrystallised from ethanol.

Preparation of Schiff base 2Aa. *cis*-2-Aminomethylcyclohexanol¹⁰ (0.65 g, 5 mmol) was dissolved in ethanol (10 cm³) and *p*-nitrobenzaldehyde (0.76 g, 5 mmol) was added. After the mixture had been allowed to stand for 30 min at room temperature, the solvent was evaporated off at reduced pressure with a max. water bath temperature of 40 °C. The crystalline residue was washed with hexane. Mp 91-93 °C. After one

recrystallisation from di-isopropyl ether the mp rose to 93-97 °C. Yield 72%. After three recrystallisations, the compound proved to be the pure oxazine **2Ba**, with mp 102-103 °C.

Preparation of oxazine 2Ba. *cis*-2-Aminomethylcyclohexanol¹⁰ (0.65g, 5 mmol) was dissolved in ethanol (10 cm³) and *p*-nitrobenzaldehyde (0.76 g, 5 mmol) was added. After the mixture had been allowed to stand for 2 hours at room temperature, the solvent was removed under reduced pressure at a water bath temperature of ca 60 °C. The crystalline residue was recrystallised from ethanol. Yield 82%, mp 102-103 °C.

When the benzylidene derivative **2Aa** was dissolved in ethanol and heated under reflux for 10 min. in ethanol followed by evaporation and recrystallisation from ethanol, the oxazine **2Ba** was obtained, mp 102-103 °C.

Solid-state nmr spectra were obtained on a Bruker MSL500 spectrometer operating at 125.758 MHz. Most spectra were obtained using the CP/MAS technique. Some spectra were obtained using 90° carbon pulses and high power ¹H decoupling. Typical spinning speeds using 4 mm rotors were between 5 and 10 kHz. Contact times for cross polarisation were typically 1 msec and recycle delays of 5-20 secs, sufficient for total or almost total ¹H relaxation, were employed. All samples were run at at least two different spinning speeds to allow identification of spinning side bands. Non-quaternary suppression (NQS) spectra were also obtained to allow identification of quaternary and methyl group carbon resonances. Chemical shifts are referenced to the CH₂ in adamantane at 38.56 ppm. A typical set of solid-state spectra is shown in Figure 1.

Solution-state spectra were obtained on a JEOL GX 400 FT-NMR spectrometer in CDCl₃ solution.^{2,4,5}

RESULTS AND DISCUSSION

Table 1 presents the results of the solution-state and the solid-state nmr experiments. In no case is evidence found that the equilibria observed in both the gas phase and in solution also exist in the solid state. In all cases except two, the solid-state spectra are consistent with a unique molecular species in the solid-state structure. The identity of the single solid-state species is found from the characteristic chemical shift of the carbon at C(2) in the ring. For compounds in the ring form, a shift of about 85 ppm is found for this carbon. For molecules in the open chain form, this carbon is present in an imine group, with a chemical shift of around 160 ppm.

Compound **2a** prepared and crystallised under mild conditions gives the kinetically controlled product, the imine **2Aa**. After transport from Szeged to St Andrews by post and waiting prior to running of the spectrum (ca 10 days), the solid state spectrum in Figure 2a was obtained, which shows evidence of two species present in the solid (peaks at 86.6 and 162.7 ppm). After standing at room temperature for two weeks the compound had almost completely converted to the cyclic form, as evidenced by the disappearance of the peak at 162.7 ppm and other spectral changes (Figure 2b). When **2a** was prepared under equilibrating conditions, the ring form **2Ba** was isolated and gave a characteristic ring form solid-state nmr spectrum.

Compound **7d**, which is in the chain form (**7Ad**), shows a doubling of most of the peaks in the solid-state spectrum (Figure 3). For example, the methyl peak is a doublet, at 20.9 and 23.9 ppm. It appears as if the intensities of the two doublet components are nearly equal at all sites, e.g. C(1) and C(2) in the aminoethanol section of the chain appear as equally intense doublets at around 79 and 76 ppm, respectively. This behaviour could arise from several causes, the most probable being (i) the coexistence of two solid phases, (ii) the existence of two molecules of **7Ad** in the asymmetric unit, or (iii) the existence of both *cis* and *trans* isomers in the solid.

It proved impossible to obtain a spectrum of compound **5c** using the cross polarisation technique. The data on this compound were obtained by pulsing at the carbon frequency and high power ¹H decoupling.

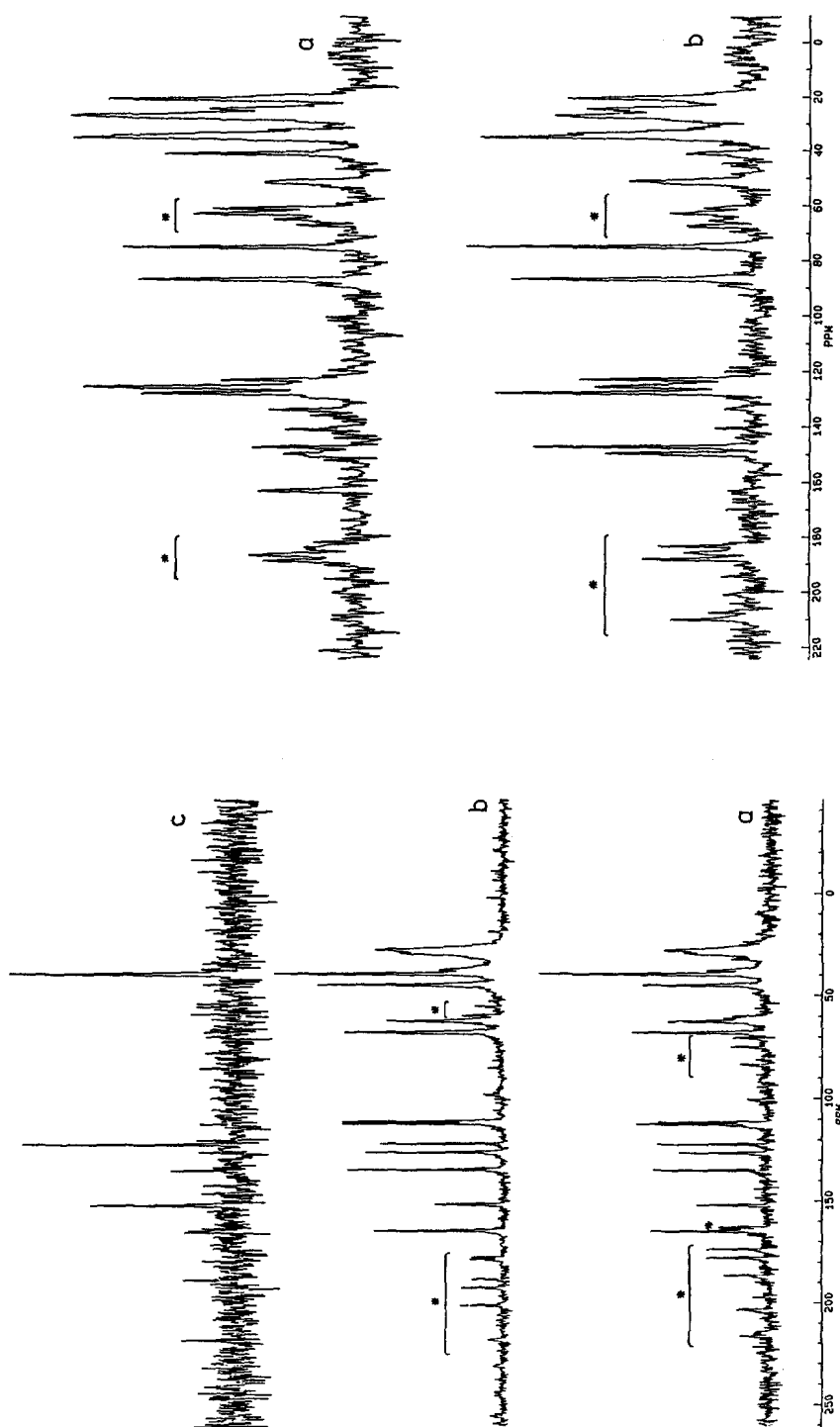


Figure 1. Typical solid state spectra obtained in this work for compound 5c. (a) at 6.45kHz, 16 transients, (b) at 8.34kHz, 56 transients, and (c) NQS spectrum at 8.34kHz allowing identification of the aromatic quaternary carbon resonances (122.2 and 151.8 ppm) and the NMe carbon resonance (39.7ppm) 16 transients. Peaks marked with stars are spinning side bands.

Figure 2. Spectra of compound 2a obtained at 7.5 kHz. (a) The initial spectrum showing evidence of the presence of both 2Aa and 2Ba. (b) The spectrum of the same material after two weeks in which all the 2Aa has converted to 2Ba. Peaks marked with stars are spinning side bands.

Table 1. Ring-chain tautomeric ratios in CDCl₃ solution and the solid-state results^a.

Equilibrium	X	% of tautomers in CDCl ₃ ring		Solid	Characteristic chemical shift
1Aa ⇌ 1Ba	NO ₂	23	77	chain	157.1
1Ac ⇌ 1Bc	NMe ₂	95	5	chain	163.0
2Aa ⇌ 2Ba	NO ₂	7	93	ring	86.6
2Ab ⇌ 2Bb	Cl	25	75	chain	161.4
2Ac ⇌ 2Bc	NMe ₂	89	11	chain	165.9
3Aa ⇌ 3Ba	NO ₂	6	94	ring	85.5
3Ab ⇌ 3Bb	Cl	20	80	ring	86.7
3Ac ⇌ 3Bc	NMe ₂	85	15	chain	165.0
4Aa ⇌ 4Ba	NO ₂	3	97	ring	87.9
4Ab ⇌ 4Bb	Cl	12	88	ring	87.0
4Ac ⇌ 4Bc	NMe ₂	73	27	chain	162.1
5Aa ⇌ 5Ba	NO ₂	1	99	ring	86.6
5Ac ⇌ 5Bc	NMe ₂	40	60	chain	164.8
6Aa ⇌ 6Ba ⇌ 6Ca	NO ₂	44	56 ^b	chain	160.2
6Ab ⇌ 6Bb ⇌ 6Cb	Cl	65	35 ^b	chain	161.3
6Ac ⇌ 6Bc ⇌ 6Cc	NMe ₂	95	5 ^b	chain	162.0
7Aa ⇌ 7Ba ⇌ 7Ca	NO ₂	14	86 ^b	chain	159.6
7Ac ⇌ 7Bc ⇌ 7Cc	NMe ₂	79	21 ^b	chain	161.1
7Ad ⇌ 7Bd ⇌ 7Cd		8	92 ^b	chain	158.7

^a All spectra were obtained at ambient laboratory temperature.

^b The combined amounts of the C(2) epimers.

One of the most interesting features of the data is the predominance of the chain tautomer in the solid state, even in compounds found to prefer the ring form in solution. Only those cases where the ring is most strongly favoured, with >93% ring form in solution, give exclusively the ring form in the solid. For cases involving between 80% and 93% ring form in solution either form is found in the solid. Where the solution equilibrium contains <80% ring form in solution, the solid is composed exclusively of chain molecules.

It is interesting to speculate as to the reasons for this. Whilst there is no proof that recrystallisation of these compounds gives the thermodynamically most stable form of the solid, the evidence from compound **2a** in which one species in the solid changes into the other, suggests that this may be the case. The free energy difference between solids formed from ring or from chain molecules will contain a term arising from the ring-chain free energy difference of the free molecules, and also terms arising from intermolecular interactions in the solid. Our data suggest that where the ring form is 1.5 kcal.mole⁻¹ more stable than the chain form in solution (a model for the free molecules) this energy difference is sufficient to predominate over the intermolecular terms and ensure a ring form in the solid. Where the free energy difference in solution is less than 0.8 kcal.mole⁻¹, the energy difference is insufficient to overcome these terms. This idea merits further experimental examination.

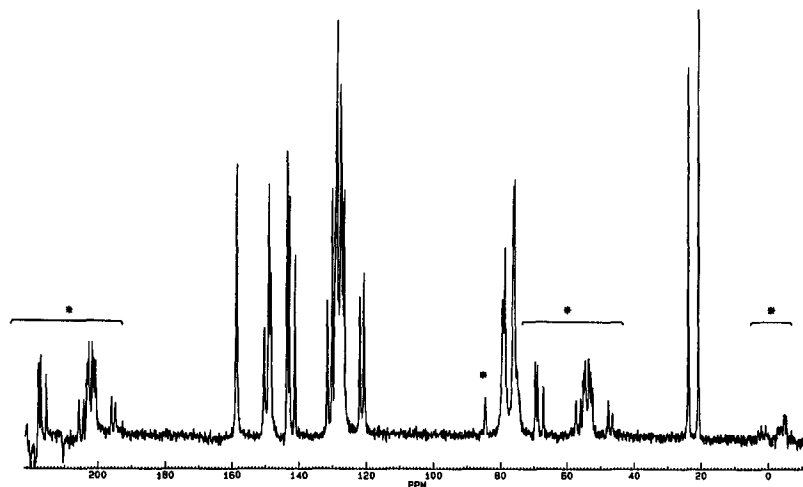


Figure 3. Spectrum of compound **7d** at 9.1 kHz, showing doubling of most bands, 128 transients. Peaks marked with stars are spinning side bands.

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