

Identification of diastereomeric cyclobutyl dimers in a mixture by NMR

E RAJANARENDAR¹, A KRISHNAMURTHY*¹ and
J N SHOOLERY²

¹Department of Chemistry, Kakatiya University, Warangal, India

²NMR Applications Laboratory, Varian Instruments Division, Palo Alto, California, USA

MS received 19 February 1994; revised 12 May 1994

Abstract. The product obtained in a reaction of 3-methyl-4-nitro-5-styrylisoxazole (**1**) has been shown to be a diastereomeric mixture of two cyclobutyl dimers by NMR. A combination of ¹H, ¹³C spectra including DEPT, ASIS, 2D COSY and nOe techniques has established that centrosymmetric cyclobutane (**7**) and the isomer (**8**) with plane of symmetry are in 2:1 proportion.

Keywords. ASIS; diastereomeric mixture; cyclobutyl dimers; cetyl trimethyl ammonium permanganate (CTAP).

1. Introduction

In this paper, we report the use of NMR for the qualitative as well as quantitative analysis of a mixture which was earlier considered to be a single compound. It is an interesting example showing how much can be learned from NMR spectroscopy alone using techniques currently available.

2. Results and discussion

With the intention of converting the olefinic double bond in (**1**) (Morgan and Burgess 1921 to a glycol (**2**), the former has been treated with CTAP (Bhushan *et al* 1984). The reaction took an unexpected course as **1** underwent dimerisation. Column chromatography of the product furnished a substance which has been shown by NMR to be a diastereomeric mixture of two cyclobutanes. The very first evidence that the starting material has undergone dimerisation has come from mass spectra which showed the molecular ion peak at *m/z* 520.

¹H-NMR (CDCl₃) showed peaks between 2.3 and 2.4 and 4.8 and 5.5 in addition to those in the aromatic region. No peaks disappear on D₂O exchange, ruling out hydroxyl groups or other exchangeable protons. The DEPT spectrum shows, in addition to some CHs, two methyl peaks at 2.35 and 2.34 whose integrals are in 2:1 ratio. The peaks in the region 4.8–5.5 are far too complex for a simple AB spin system which is what would be expected from the adjacent CH groups with OH protons replaced by deuterium. Some of the multiplets are triplets, suggesting at least two equivalent spins coupling with the observed spin.

*For correspondence

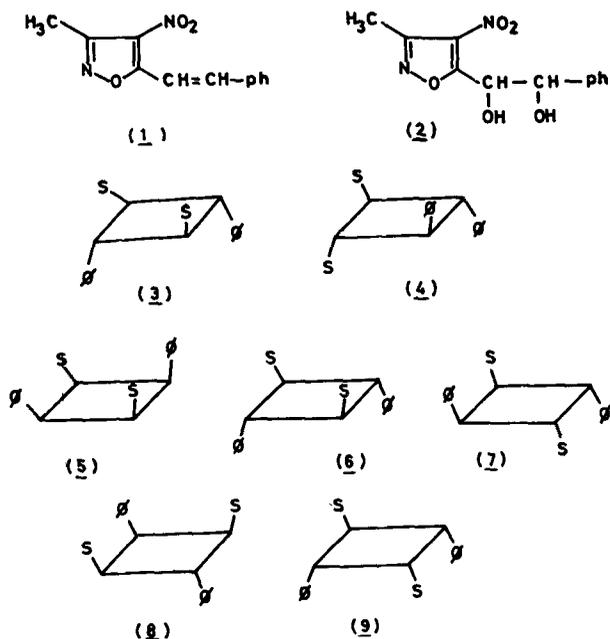


Chart 1.

A homonuclear cosy spectrum (figure 1) of the substance shows the expanded portion of the 4-8-5-5 region which has 4 triplets and an irregular quartet. Two strong central distorted triplets b and c couple to one another, while the small triplet a at the left couples to the triplet e at the right which in turn is coupled to another triplet with fine structure d. The integrals of these triplets are in the ratio 1:4:4:1:2 for a:b:c:d:e.

^{13}C -spectrum readily confirms the conclusions. There are two methyl carbons at 11.02 and 11.11 ppm, four peaks between 40 and 48 ppm and a complex aromatic region which could not possibly arise from just one phenyl group which could display a maximum of 4 lines and the isoxazole ring which could display no more than 3 lines. Six resonances (171.5 and 171.0; 156.0 and 155.5; 136.5 and 136.0) for isoxazole ring carbons (Rao and Murthy 1983) obviously indicate isoxazole moiety is present in two different environments due to which they are non-equivalent. These three pairs of signals are assignable respectively to carbon 5, 3 and 4. A plot expansion of the aromatic protonated carbon region between 126.4 and 129.7 ppm showed a total of nine lines with the intensities which could be assigned in groups of three (representing the ortho, meta and para) carbons as 1, 2, 2; 1, 2, 2 and 4, 8, 8. The chemical shifts of these lines are at 126.85, 127.55, 128.05 (para carbon); 128.12, 128.16, 128.20 (ortho carbon); and 128.20, 128.88, 129.05 (meta carbon). Likewise, the signals at 139.56, 139.58 and 139.62 are due to the non-protonated carbon of the benzene ring (Silverstein *et al* 1981). These lines are consistent with the presence of two non-equivalent monosubstituted benzene rings in one molecular species and two equivalent mono-substituted benzene rings present in another species with twice the abundance of the first. Another 2D HET-COSY spectrum (figure 2) for the sp^3 region of the carbon spectrum shows a strong peak at 43 ppm which is close to a weak peak. The three weak carbon peaks correlate with the two weak triplets and an irregular quartet in the proton spectrum,

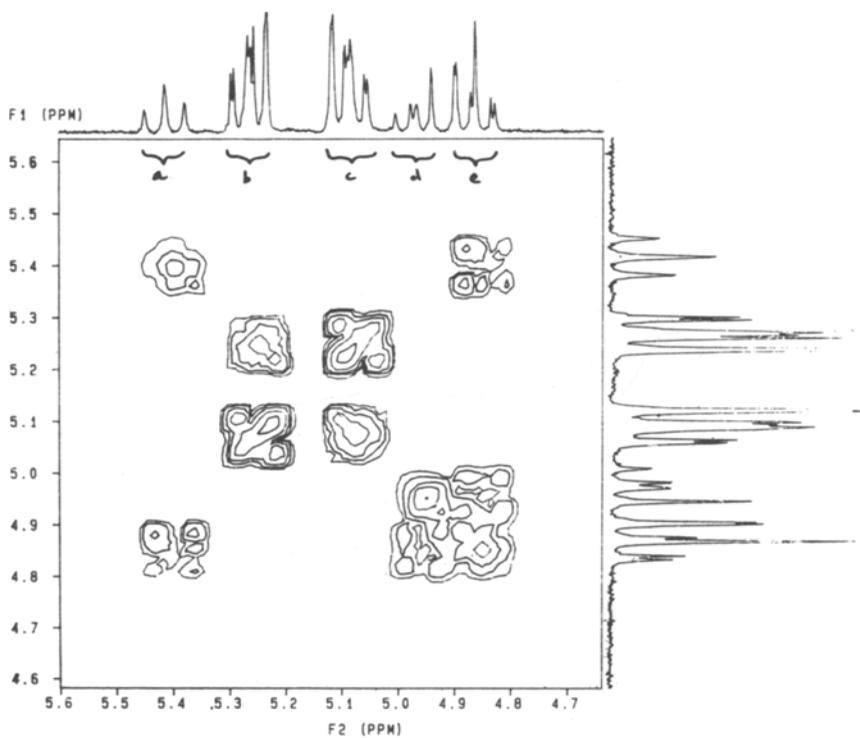


Figure 1. Homo-Cosy spectrum in CDCl₃.

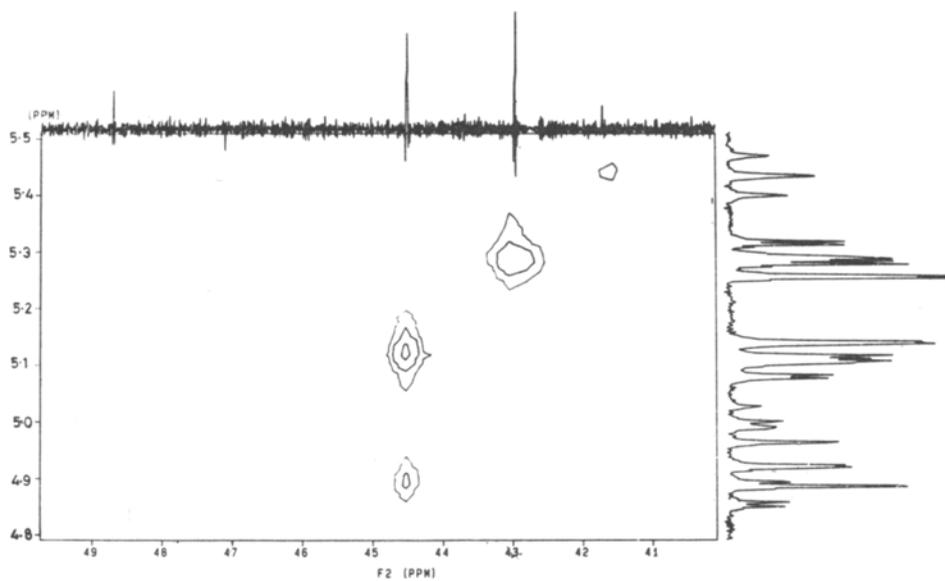


Figure 2. Het-Cosy spectrum.

while the two strong carbon peaks correlate with two strong distorted triplets in the proton spectrum.

Replacement of CDCl_3 by C_6D_6 as solvent brought about an interesting change in the resonance patterns (through ASIS). The two strong distorted triplets collapse into almost a singlet at 5 ppm, while the other triplets move apart and are found at 5.25, 4.78 and 4.4 ppm. The methyl peak is now clearly separated into two lines at 1.8 and 1.9 ppm. Some of the aromatic protons of the less abundant species have moved from 7.0 ppm to about 6.7 ppm. A 2D (homonuclear cosy) spectrum (figure 3) confirms that the strong multiplets at 5.0 ppm show no coupling to the three multiplets, but the three triplets all show coupling to one another, although the coupling between the weaker triplets show much less intense cross peaks. This is obviously due to quite a small value of the coupling constant between these protons. (This is consistent with the model that will be proposed in which these protons are on opposite corners of a cyclobutane ring.)

3. Interpretation of spectral data

All the data are in accord with the idea that the actual species present are dimers of the cyclobutane type with two phenyl substituents, ϕ , and two substituents corresponding to the isoxazole ring of the starting product, which will be designated S . Structures with alternating ϕ 's and S 's or structures with adjacent substituents of the same type are possible, with five stereoisomers of the first type and six of the second. To differentiate between these types it is necessary to consider the coupling constants for spin coupling

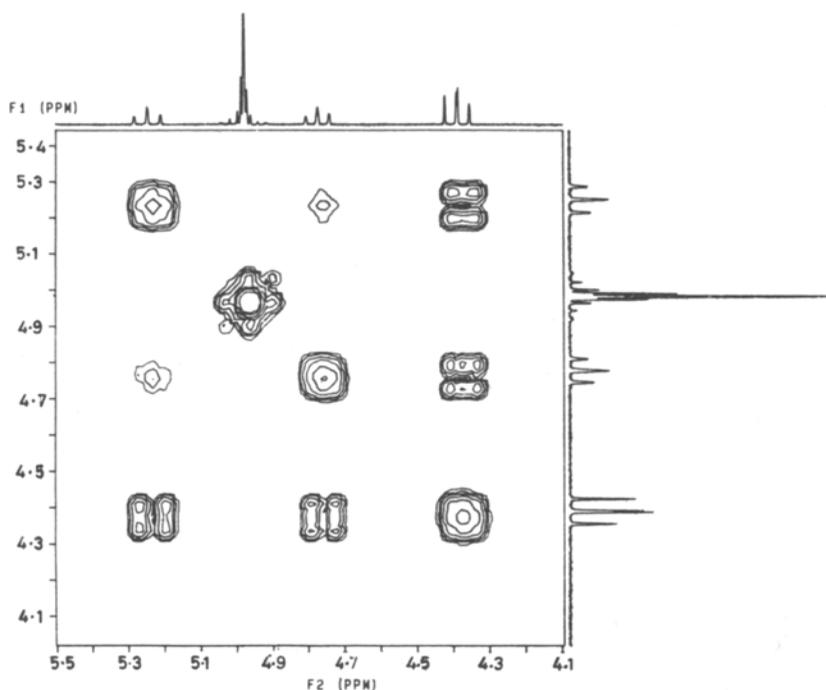


Figure 3. Homo-Cosy spectrum in C_6D_6 .

typical of protons on a cyclobutane ring. Cyclobutanes show approximately equal couplings between the proton on the substituted carbon and the adjacent *cis* or *trans* proton (Hasegawa *et al* 1984). The coupling constant is approximately 9 Hz. The spectra for the AA' BB' four-spin systems corresponding to the symmetrical structures 3 and 4 were simulated, using 9 Hz as the coupling constant for protons on adjacent carbons of the cyclobutane ring, and zero for all other couplings. The *cis* and *trans* coupling constants were assumed to be essentially the same. Figure 4 shows the simulated spectrum for the cyclobutane ring protons of 3 on the right, and for 4 on the left. Comparison with figure 5, a plot expansion showing the cyclobutane ring protons of the substance, confirms that the two strong distorted triplets in the centre must arise from a structure of type 3 with alternating and not adjacent ϕ 's and S's.

The sample is a mixture of two of the type 3 compound, which must be included in the five possible structures (5-9).

Structures 5, 6 and 7 have either a centre of symmetry or two intersecting planes of symmetry, while 8 and 9 have only a plane of symmetry and consequently have only two equivalent protons on the ring and two non-equivalent protons. The minor component is therefore either 8 or 9. Structure 5 can almost certainly be ruled out on the basis of steric crowding, leaving the structure of the major component as either 6 or 7.

A distinction between structures 8 and 9 for the less symmetrical component can be made on the basis of the nuclear Overhauser effect (nOe) which results from polarization transfer between protons which are close together in space. The nOe is dependent on the inverse sixth power of the internuclear distance, making it a sensitive test of molecular conformation.

In figure 5 the triplet and quartet centred at 4.96 ppm and 5.42 ppm respectively are assigned to the two non-equivalent cyclobutane ring protons, and the triplet centred at 4.86 ppm is assigned to the two equivalent ring protons. The equivalent ring protons must be on the same side of the ring, and they show an nOe of approximately 10% when the proton at 4.96 is irradiated, while the nOe is only about 2% if the proton at 5.42 ppm is irradiated. Measurements made from a Drieding model (which is not as accurate in strained systems as when a strain-free structure can be constructed) show that the ratio of the interproton distances for protons on opposite sides of the ring and

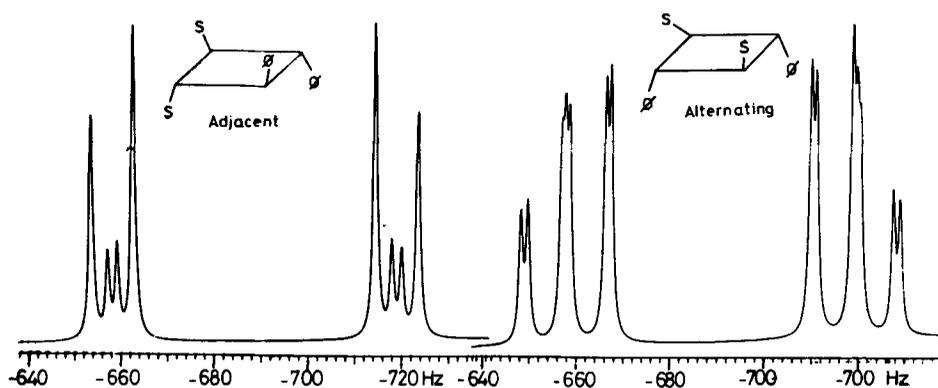


Figure 4. Simulated spectrum.

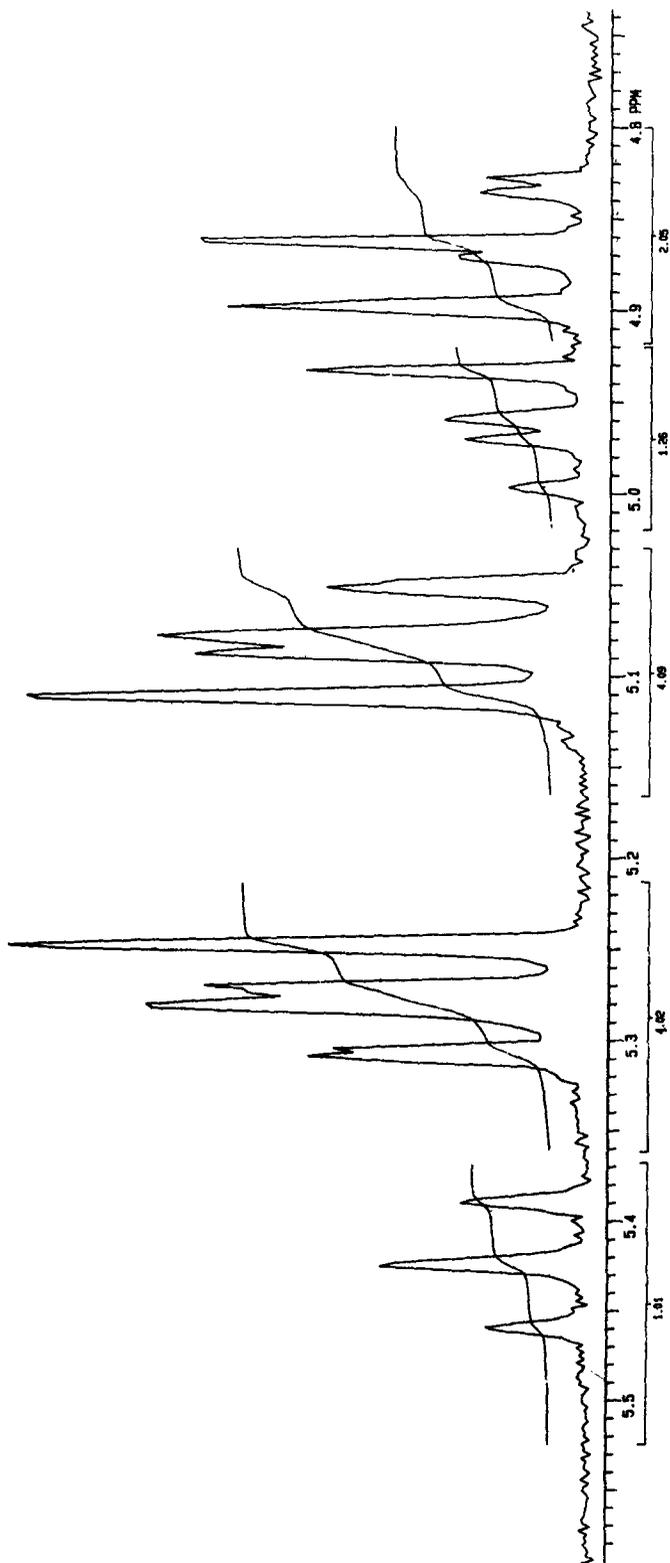


Figure 5. Plot expansion of aliphatic region of proton spectrum.

for those on the same side of the ring is 1.2, and the sixth power of 1.2 is greater than 4. Thus these measurements are in accord with assigning the proton at 4.96 ppm to the one on the same side of the ring as the two equivalent protons.

The reverse experiment, irradiating the triplet at 4.86 ppm, shows nOe effect 4 times larger for the proton at 4.96 ppm than for that at 5.42 ppm as expected. At the same time, an nOe comparable to that for the 4.96 ppm proton is observed for the ortho protons of one of the aromatic rings. This is interpreted to mean that this aromatic ring is on the same side of the cyclobutane ring as the two equivalent protons at 4.86 ppm, and this requires the structure of the component to be **8**.

The more symmetrical component of the mixture, present in twice the molar concentration of structure **8**, was also studied in the same way. When the triplet at 5.08 ppm is irradiated, the triplet at 5.27 shows an nOe greater than 10%, and the reverse is true if the triplet at 5.27 is irradiated. This means that the non-equivalent protons are on the same side of the cyclobutane ring, and if we exclude structure **5** from consideration, only structure **7** is possible for the more symmetrical component.

4. Experimental

Nucleus, ^1H ; frequency, 300 MHz; instrument, Varian XL-GEMA 300; solvent, CDCl_3 ; reference standard, TMS; temperature, 50°C ; mode of study, FT; pulse width, $12.0\ \mu\text{s}$; acquisition time, 1.778 seconds; spectral width, 4500.5 Hz; no. of transients, 16; Nucleus, ^{13}C ; spectral width, 18761.7; acquisition time, 0.800 s; pulse width, $6.0\ \mu\text{s}$; frequency, 75 MHz; Transients, 41984; pulse sequence, S2 PUL; decoupling conditions, decoupler mode (NNN), decoupler offset ($-450.0\ \text{Hz}$).

Acknowledgement

ERN and AKM thank Prof T V Padmanatha Rao of the Kakatiya University for encouragement.

References

- Bhushan V, Rathore R and Chandrasekaran S 1984 *J. Chem. Soc., Chem. Commun.* 431
Hasegawa M, Nohara M, Saigo K, Mori T and Nakanishi H 1984 *Tetrahedron Lett.* 25 561
Morgan G T and Burgess H 1921 *J. Chem. Soc.* 119 697
Rao C J and Murthy A K 1983 *Org. Magn. Reson.* 21 77
Silverstein R M, Bassler G C and Morrill T C 1981 *Spectrometric identification of organic compounds* 5 edn (New York: John Wiley and Sons) p. 265