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An Infrared Study of Tautomerism in Acetohexamide Polymorphs

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Abstract—Infrared data determined for known polymorphic forms and some new derivatives of acetohexamide and related compounds support the view that acetohexamide polymorphs exhibit keto-enol tautomerism. They indicate that type A polymorphs exist in the enol form, probably stabilized by intramolecular bonding between an O—H and S=O group to form a six-membered ring. Type B polymorphs exist in the keto form with the urea carbonyl group intermolecularly bonded to a sulphonamide N—H. The new evidence disputes previous interpretations of the data.

The first report of polymorphism in acetohexamide (Girgis-Takla & Chroneos 1977) showed the occurrence of two forms, A and B, which are distinguishable by infrared spectroscopy and differential scanning calorimetry. Both forms were stable at room temperature (ca 20°C).

Since then, several physicochemical studies of acetohexamide polymorphs have been made. The identity of polymorphs A and B has been confirmed in all the published data, and it is possible that other polymorphic forms may also exist. Graf et al (1984), to avoid confusion over differences in nomenclature used for the same polymorphs, have tabulated all the reported forms, and have provided X-ray data which indicate the existence of at least 4 polymorphs. Infrared spectra of the two new polymorphic forms show that one form closely resembles polymorph A while the other is closely similar to polymorph B. It is still possible that a more detailed examination of the X-ray data could show them to be mixtures.

There is general agreement that form A is physically stable towards heat. Several workers have found that form B on heating undergoes a transformation to form A (Girgis-Takla & Chroneos 1977; Burger 1978; Kuroda et al 1978; Müller & Lagas 1979). This is disputed by Graf et al (1984) who believe that form B is converted by heat into one of the new polymorphic forms (V) having an almost identical infrared spectrum. Al-Saieq & Riley (1982) found both forms A and B stable towards heat. Both forms A and B are stable when suspended in water.

Because of the existence of two stable forms of acetohexamide, Graf et al (1984) have suggested that the compound exhibits keto-enol tautomerism, and that the B type polymorphs are in an enol form stabilized by the formation of a 6-membered ring formed by hydrogen bonding of the enolic-OH group to an oxygen of the SO_2 group.

Tautomerism and intramolecular bonding have also been shown to cause polymorphism in the butyrophenone tranquillizer drug, benperidol (Gassim et al 1985, 1986). With benperidol, however, there was clear evidence from infrared and ultraviolet spectral data to show which polymorph corresponded to which molecular structure. In the case of acetohexamide, there is no firm evidence as to which polymorph (or polymorphic series) is in the keto and which is in the enol form. The structures proposed by Graf et al (1984) could not be confirmed by the X-ray diffraction data, and no confidence limits are provided to support their thermodynamic data.

In this paper, the infrared spectra of acetohexamide polymorphs A and B and some acetohexamide derivatives are compared with spectra obtained for chlorpropamide and tolbutamide which have been studed in detail by X-ray diffraction methods. The findings suggest that polymorph A in fact is the enol form of acetohexamide, and polymorph B is the keto form.

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Materials and Methods

Preparation of polymorphs A and B

A commercial sample of acetohexamide (kindly supplied by Eli Lilly & Co. Ltd) was used to prepare these forms, as previously described (Girgis-Takla & Chroneos 1977).

Preparation of polymorph A2

Acetohexamide (50 mg) was dissolved in 12 mL hot benzene, and the solution left to crystallize at room temperature, as described by Graf et al (1979) for the preparation of polymorph IV. The crystals were stored in a desiccator over silica gel, m.p. 184–186°C.

Preparation of polymorph B2

Acetohexamide (200 mg) was dissolved in 40 mL hot isobutanol, and the solution was evaporated slowly at room temperature with the aid of a current of air, as described by Al-Saieq & Riley (1982) for the preparation of polymorph II. The crystals were stored in a desiccator over silica gel, m.p. 176–178°C.

Preparation of acetohexamide sodium salt

Acetohexamide (1·0 g) was dissolved in 100 mL of 1·5 M sodium hydroxide in 50% v/v methanol by warming gently. Sodium hydroxide (50 mL, 3 M) was added, and the solution left to crystallize at room temperature (20°C). The crystals

were dried under vacuum at 50°C and characterized by proton NMR (Müller & Lagas 1979).

The sodium salts of tolbutamide and chlorpropamide were prepared in a similar manner.

Preparation of N-*methylacetohexamide*

Methyl iodide (400 mg) was added to a cool solution of acetohexamide sodium salt (400 mg) in 10 mL of dry dimethylformamide. The solution was left overnight under reflux at 30°C, and then evaporated under vacuum. The residue was treated with 10 mL of water, and extracted with 4 volumes of benzene (15 mL). The benzene layers were combined and evaporated under vacuum, and the residue was re-crystallized from chloroform, m.p. 102-104°C. Analysis: Calc. for $C_{16}H_{22}N_2O_4S$: C, 56·79; H, 6·55; N, 8·28; S, 9.47. Found: C, 56·85; H, 6·61; N, 8·42; S, 9·21. The proton NMR spectrum was the same as reported by Kossoy & Occolowitz (1978).

Preparation of acetohexamide oxime

Absolute ethanol (20 mL) was added to a solution of hydroxylammonium chloride (1·0 g) and sodium acetate (2·0 g) in 10 mL of water. Acetohexamide (500 mg) was dissolved in the solution by heating to 70°C, and the solution allowed to crystallize in ice. The product was re-crystallized from 80% v/v ethanol, m.p. 185–187°C, and characterized by proton NMR.

Tolbutamide was from Sigma Chemical Co., chlorpropamide from Pfizer Ltd; phenylurea, 97% and acetophenone, 99% were from Aldrich Chemical Co. Ltd.

All the reagents and solvents employed were of analytical reagent grade. Infrared spectra were recorded from potassium bromide discs using a Perkin-Elmer Model 681 grating spectrometer. NMR spectra were recorded with Perkin-Elmer R32 (90MHz) spectrometer in d_6-dimethylsulphoxide. Melting points were determined in an Electrothermal melting point apparatus.

Results and Discussion

The assignments shown in Table 1, based on the evidence to be discussed below, lead to the assumption that acetohexamide polymorphs A and A2 exist in the enol form (IA), probably stabilized by intramolecular bonding, whilst the acetohexamide polymorphs B and B2 exist in the keto form (IB) probably stabilized by intermolecular bonding. The data given for polymorphs A and B in the Table can be applied equally well to the spectra of polymorphs A2 and B2, respectively. It is difficult to differentiate between polymorphs A and A2 using infrared data unless absorbance ratios be measured, and the spectrum of polymorph B2 closely resembles that of polymorph B (Graf et al 1979; Al-Saieq & Riley 1982).

Polymorph A (Fig. 1) gives rise to a sharp band at 3240 cm^{-1} characteristic of an intramolecularly bonded OH-group. This band is not seen in any of the other spectra studied. Both polymorphs A and B (Fig. 2) produce absorbance at 1685–1690 cm^{-1} due to the presence of an aryl ketone. The absorbance is shown by acetophenone, by *N*-methylacetohexamide (Fig. 3) and sodium acetohexamide (Fig. 4), but is not present in the spectra of tolbutamide and chlorpropamide (Fig. 5) whose molecular structures do not contain a ketone grouping. The band for acetohexamide, as expected, disappears when its oxime derivative (Fig. 6) is prepared, leaving a single band at 1655 cm^{-1} due to the urea carbonyl group, which is not affected by the hydroxylammonium chloride reagent. This band is found at 1660 cm^{-1} in the spectra of tolbutamide, chlorpropamide and acetohexamide, and appears to be characteristic of sulphonylureas. It is higher than the frequency of 1610 cm^{-1} measured for phenylurea (Table 1) and higher also than the frequencies reported by Bellamy (1975) for many di-substituted ureas, but agrees with the frequencies found by Nitta & Ando (1962) for a wide range of sulphonylurea compounds. It is higher also than the values found for the sodium salts of sulphonylureas (Table 1). The urea carbonyl band is absent from the spectrum of acetohexamide polymorph A due to enolization, and it is also absent, as expected, from the spectrum of acetophenone. Taken together, all the evidence makes it unlikely that the two carbonyl bands of acetohexamide could both absorb at 1685 cm^{-1}, as suggested by Graf et al (1979).

The N—H stretching vibrations provide further evidence of the structures of the A and B type polymorphs. The absorption bands at 3310 cm^{-1} in polymorph A (the enol

Table 1. Infrared data of sulphonylurea derivatives, acetophenone and phenylurea.

	Stretching vibrations				
	N—H		O—H	C=O	
Compound	Urea	Sulphonamide	(Enol form)	Aryl	Urea
Acetohexamide, Polymorph A	3310	—	3240	1685	—
Acetophenone	—	—	—	1685	—
Acetohexamide, Polymorph B	3360	3160sh 3100b	—	1690	1660
Tolbutamide	3335	3180sh 3090b	—	—	1660
Chlorpropamide	3337	3190sh 3100b	—	—	1660
Acetohexamide oxime	3340	3140sh 3050b	—	—	1655
N-Methyl acetohexamide	3410	—		1710	1685
Acetohexamide sodium	3380	—	—	1690	1590
Tolbutamide sodium	ca 3410	—		—	1600
Chlorpropamide sodium	ca 3430	—		—	1610
Phenylurea	3420 3305	—	—	—	1610

sh: shoulder.
b: broad.

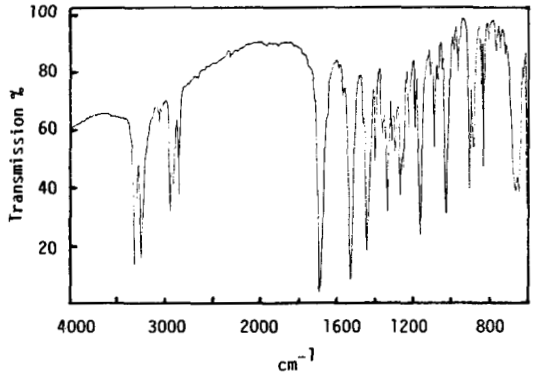


FIG. 1. Infrared spectrum of acetohexamide polymorph A.

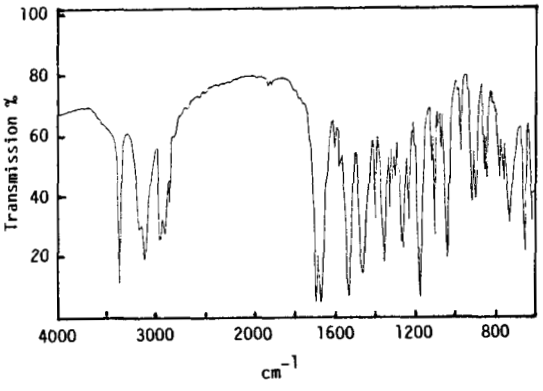


FIG. 2. Infrared spectrum of acetohexamide polymorph B.

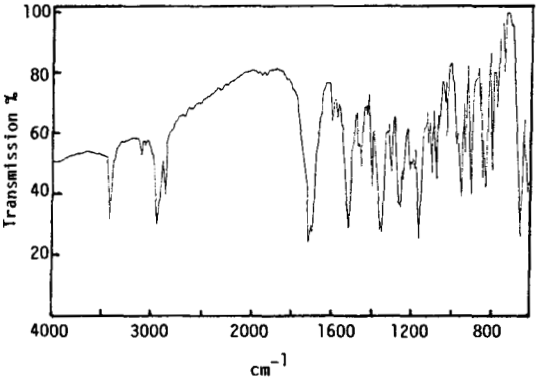


FIG. 3. Infrared spectrum of *N*-methylacetohexamide.

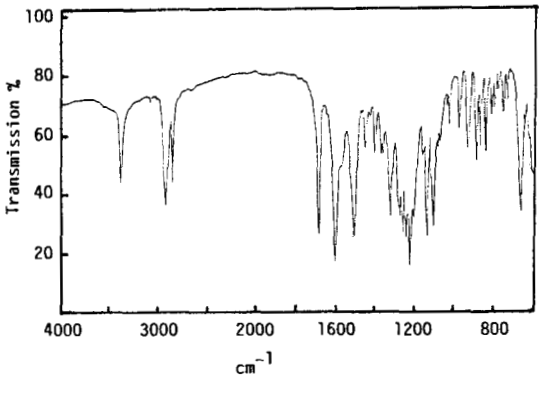


FIG. 4. Infrared spectrum of sodium acetohexamide.

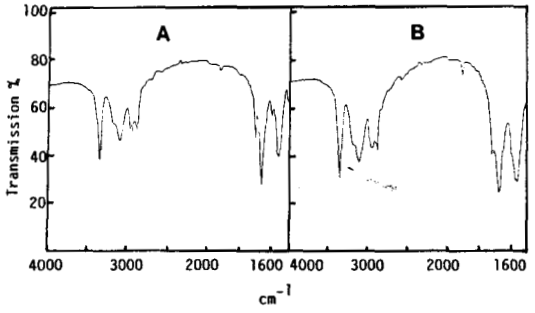


FIG. 5. Infrared spectra of (A) tolbutamide and (B) chlorpropamide.

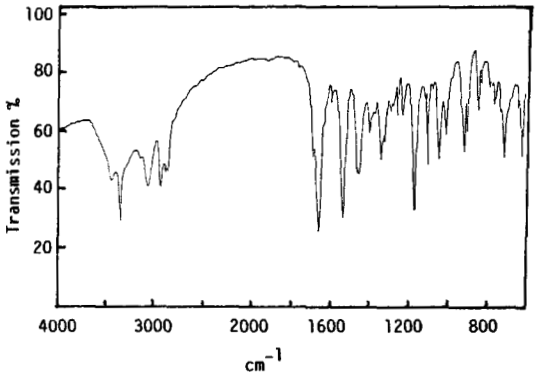
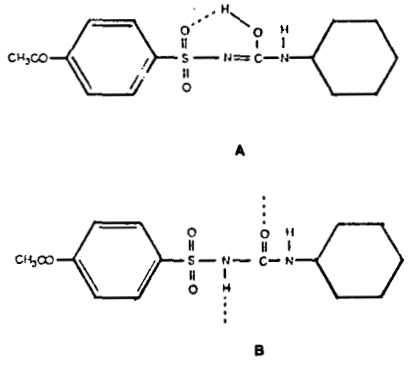


FIG. 6. Infrared spectrum of acetohexamide oxime.



(I). Acetohexamide polymorphs.

form) and 3360 cm^{-1} in polymorph B (the keto form) are almost certainly due to the urea N—H grouping. The shift in frequencies could be caused by increased conjugation in the enolized system. The sodium and *N*-methyl derivatives of acetohexamide show bands in this region at 3380 cm^{-1} and 3410 cm^{-1}, respectively, which must also be due to urea N—H stretching, since neither compound has a free sulphonamide N—H.

At the same time, a broad band near 3100 cm^{-1} (absent from polymorph A) occurs with polymorph B and in the spectra of the commercial forms of tolbutamide and chlorpropamide. In all cases, this band is characteristic of an intermolecularly hydrogen bonded sulphonamide N—H group. X-ray diffraction methods have been used to demonstrate that both chlorpropamide (Koo et al 1980) and the two stable polymorphs of tolbutamide (Nirmala & Gowda 1981;

Donaldson et al 1981) exhibit a urea carbonyl structure, and form two or three intermolecular hydrogen bonds between the urea N—H and sulphonamide S=O, between the urea N—H and urea C=O, and between the sulphonamide N—H and urea C=O in order of increasing bond strength. This supports the infrared evidence concerning the sulphonamide N—H, and suggests that acetohexamide polymorph B must possess a urea carbonyl structure intermolecularly bonded to a sulphonamide N—H.

The position of the symmetric S=O stretching band is at 1157 cm^{-1} in polymorph A and at 1165 cm^{-1} in polymorph B, which would be consistent with stronger hydrogen bonding in polymorph A. A similar effect appears to be shown by the antisymmetric stretching bands which are at 1330 cm^{-1} for polymorph A and 1345 cm^{-1} for polymorph B, but these may not be resolved from the methyl deformation band in the same region. The significance of this observation is doubtful, however, since the symmetric S=O stretching absorption appears at 1155 cm^{-1} in *N*-methylacetohexamide and implies stronger intermolecular hydrogen bonding for this compound also. (The normal position of the band in solid-phase spectra of sulphanilamide derivatives is about 1180 cm^{-1}.)

Since the urea N—H stretching frequency remains unchanged in both polymorphic forms of tolbutamide (Leary et al 1981), it has been proposed by Donaldson et al (1981) that the different forms of tolbutamide may only undergo some changes in orientation, while maintaining the same intermolecularly bonded chain structure. It is possible that such changes in orientation could be responsible for the differences between polymorphs A and A2 and between polymorphs B and B2.

References

Al-Saieq, S. S., Riley, G. S. (1982) Polymorphism in sulphonylurea hypoglycaemic agents: III. Acetohexamide. Pharm. Acta Helv. 57: 43–46

Bellamy, L. J. (1975) The Infrared Spectra of Complex Molecules. Vol. 1. 3rd edn. Chapman and Hall, London, p. 250

Burger, A. (1978) Zur Polymorphie oraler Antidiabetika 4. Mitteilung Acetohexamid: thermodynamische und biopharmazeutische Aspekte. Sci. Pharm. 46: 207–222

Donaldson, J. D., Leary, J. R., Ross, S. D., Thomas, M. J. K., Smith, C. H. (1981) The structure of the orthorhombic form of tolbutamide. Acta Cryst. B37: 2245–2248

Gassim, A. E. H., Girgis Takla, P., James, K.C. (1985) Intramolecular bonding in some butyrophenones. J. Pharm. Pharmacol. (Suppl.) 37: 126P

Gassim, A. E. H., Girgis Takla, P., James, K. C. (1986) Ultraviolet spectrophotometry for the determination of benperidol by a difference procedure and for the elucidation of its polymorphic structures. Analyst. 111: 923–926

Girgis-Takla, P., Chroneos, I. (1977) The polymorphism of acetohexamide. J. Pharm. Pharmacol. 29: 640–642

Graf, E., Beyer, C., Abdallah, O. (1979) Polymorphie bei Acetohexamid. Acta Pharm. Techn. 25: 9–20

Graf, E., Beyer, C., Abdallah, O. (1984) On the polymorphism of acetohexamide. Pharm. Ind. 46: 955–959

Koo, C. H., Cho, S. I., Yeon, Y. H. (1980) The crystal and molecular structure of chlorpropamide. Arch. Pharm. Res. 3: 37–49

Kossoy, A. D., Occolowitz, J. D. (1978) Mass spectrometry of *N*-methylsulfonylureas. A re-examination. Biomed. Mass. Spectrom. 5: 123–127

Kuroda, K., Yokoyama, T., Umeda, T., Takagishi, Y. (1978) Studies on drug nonequivalence. VI. Physico-chemical studies on polymorphism of acetohexamide. Chem. Pharm. Bull. 26: 2565–2568

Leary, J. R., Ross, S. D., Thomas, M. K. J. (1981) On the characterisation of the polymorphs of tolbutamide. Pharm. Weekbl. (Sci. Ed.) 3: 62–66

Müller, B. W., Lagas, M. (1979) Some aspects of the polymorphism and stability of acetohexamide. Ibid. (Sci. Ed.) 1: 77–84

Nirmala, K. A., Gowda, D. S. S. (1981) Structure determination of tolbutamide. Acta Cryst. B37: 1597–1599

Nitta, Y., Ando, N. (1962) Studies of sulfonylurea derivatives. III. The infrared spectra of 1-p-tolylthio-3-alkylureas and corresponding sulfonyl compounds. Chem. Pharm. Bull. 10: 1081–1084