Azithromycin is the most important macrolide of *azalide* class (derived from erythromycin A by insertion of an N-methyl group in the lactone ring), and shows higher antibiotic effect than the parent compound, particularly against Gram-negative bacteria. Its synthesis is based on the Beckmann rearrangement of eryrhromycin A oxime to yield the imino ether, and several ways have been reported to reduce the imino ether and finally achieve the azithromycin. One of these routes involve the synthesis of a precursor of the azithromycin, the azithromycin 11,12-hydrogen borate [1], whose acid hidrolysis affords azithromycin.

This structure was studied in solution state through NMR spectroscopy [2], but no study was done so far in solid state, to know the accurate structure and the molecular conformation

In the present communication, we show the results of the analysis by x-ray diffraction of the crystals obtained in different conditions of crystallization: solving the borate in hot acetone and slowly cooling, or solving the borate in acetone and changing the polarity by adding water.

Both solids are crystalline, as is shown on their powder patterns, with different structural parameters, and including the second sample a percentage of amorphous material.

Controling the conditions of crystallization, we can decide what crystal obtain. The knowledge of its crystal structure and composition can give us information about the role of the solvent in controling the final crystal form.

[1] Bayod-Jasanada M, Carbajo R.J., López-Ortiz F., *J. Org. Chem*., 1997, **62**, 7479-7481. [2] Bayod-Jasanada M, Carbajo R.J., López-Ortiz F., *Magn. Reson. Chem*., 1998, **36**, 217- 225.

Keywords: crystallization, azithromycin, hydrogenborate

P.06.10.9

Acta Cryst. (2005). A**61**, C292

Modelling Disorder in 3,3'-dimethoxybenzil, $C_{16}H_{14}O_4$

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This work is part of an extended study of benzil ($C_{14}H_{10}O_2$) and derivatives which aims to understand the role that molecular flexibility plays in determining crystal packing and polymorphism [1,2]. In this study diffuse X-ray scattering is used to probe both the inter- and intra-molecular correlated motions of a series of similar compounds in order to gain insight into how molecular motion influences crystal packing. In future studies it is hoped to apply the methodology to compounds of pharmaceutical interest which display polymorphism. In the present paper we present results for the compound 3,3'-dimethoxybenzil, $C_{16}H_{14}O_4$, 33'DMOB. For this molecule the molecular flexibility is afforded by rotations about three C–C and two C–O single bonds, defined by the dihedral angles, ϕ_1–ϕ_5. Other molecular groups are considered rigid. Diffuse scattering arises from differences between the local structure of a crystal and the underlying *average* structure. Such differences (termed disorder) may be either static or dynamic in origin. The disorder in 33'DMOB is purely thermal, and conventional crystal structure determination using Bragg scattering yields a perfectly normal average structure with no anomalous atomic displacement patterns. Nevertheless all studies have observed strong and highly structured thermal diffuse scattering.

[1] Welberry T. R., Goossens D. J., Edwards A. J., David W. I. F., *Acta Cryst.*, 2001, **A57**, 101–109. [2] Welberry T. R., Heerdegen A. P., *Acta Cryst.*, 2003, **B59**, 760–769.

Keywords: diffuse scattering, molecular flexibility, monte carlo simulation

P.06.10.10

Acta Cryst. (2005). A**61**, C292

Serendipitous Rediscovery of Three Polymorphs of Benzidine

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The search for a co-crystal of benzidine (4, 4'-biphenyldiamine) as a donor with potential acceptors has revealed three polymorphs of the source material benzidine for which, somewhat surprisingly, no structure has been reported according to a CSD search Nov. 2003.

For about 130 years, benzidine and its derivatives had very wide industrial use, mainly as dyes and pigments in a variety of applications. By the middle 1970's the use of benzidine totaled 0.5-1 million kg. At that time the compound itself was found to be carcinogenic, and its commercial use has essentially been abandoned, apparently along with interest in its structure and properties.

The biphenyls attracted the attention of many crystallographers [1 and references therein]. One of the principle reasons for interest in this compound was the fact that in the gas phase the molecule had been shown to be non-planar, while in the crystal the molecule's presence on a crystallographic inversion center requires it to be planar.

The three reported structures are characterized by the molecules packing of Z'>1 (1.5, 3 and 4.5), which according to the CSD are found in only 0.25%, 0.4% and 0.002% of the total structures.

The three forms were grown from two component solutions (one is benzidine) as well as from solutions of benzidine only. In some crystallization experiments the polymorphs grew concomitantly [2].

[1] a) Brock C. P., Minton R. P., *J. Am. Chem. Soc.*, 1989, **111**, 4586-4593; b) Brock C. P., *J. Res. Natl. Inst. Stand. Technol*., 1996, **101**, 321-325. [2] Bernstein J., Davey R. J., Henck J. -O., *Angew. Chem. Int. Ed.*, 1999, **38**, 3440-61.

Keywords: polymorph, co-crystal, concomitant crystallization

P.06.10.11

Acta Cryst. (2005). A**61**, C292

Structures of Some Hydroxynaphthaldehyde Schiff Bases

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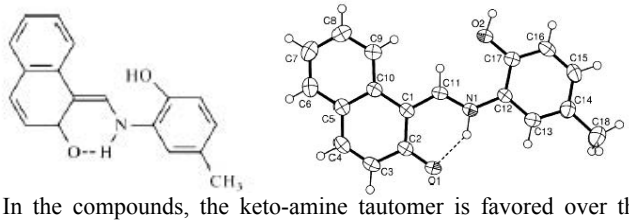
The molecules of compound, $C_{18}H_{15}N_1O_2$ (I) and $C_{17}H_{12}N_1O_2Cl_1$ (II) are not exactly planar, and adopts the keto-amine tautomeric form with an N---H…O and intermolecular O---H…O hydrogen bonds.



In the compounds, the keto-amine tautomer is favored over the phenol-imine form. The rather short C2-O1 and C1-C11 bonds can be considered as C=O and C=C double bonds, respectively. This fact, together with the very short C3-C4 bond, suggests the presence of a significant quinoidal effect. A similar quinoidal effect was observed in our previous work [1].

[1] Odabaşoğlu M., Albayrak C., Büyükgüngör O., *Acta Cryst*., 2004, **E60**, o142-o144.

Keywords: tautomerism, hydrogen bonds, diffraction structure analysis

P.06.10.12

Acta Cryst. (2005). A**61**, C292-C293

Two Polymorphs – Which One is Stable at Ambient Conditions?

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NN414 (6-chloro-3-(1-methylcyclopropyl)-amino-4*H*-thieno[3,2-*e*]-1,2,4-thiadiazine 1,1-dioxide) is an opener of ATP sensitive potassium channels, which attenuates hyperinsulinemia. The compound prevents diabetes and improves glucose tolerance without affecting body weight or body composition in preclinical studies. Apart from its therapeutic effects it is also interesting because of its

physico-chemical properties.

NN414 is a very weak acid with pK_a = 8.5, log P = 1.6, and molar weight M_w = 291.8 g/mol. Two true polymorphs, A and B, of this compound have been identified. Polymorph A crystallizes in needleshaped crystals with a triclinic unit cell by precipitation from a variety of solvents such as acetic acid, acetonitrile, diluted ammonia, methanol, N-methyl-pyrrolidone, 1-propanol, or 2-propanol [1]. Polymorph B forms prismatic crystals by precipitation from methanol or ethanol, and this unit cell is rhombohedral [1]. Mixtures of A and B can also be obtained. Both polymorphs are highly crystalline. Polymorph A melts at approximately 257ºC whereas polymorph B melts at approximately 269ºC [1].

To establish the thermodynamic relationship between A and B, different experiments concerning crystallization, density of mass, solubility and melting behaviour were carried out using hot stage microscopy, He-pycnometry, intrinsic solubility, and differential scanning calorimetry [2]. The results of these experiments unanimously point to an enantiotropic relationship between A and B, with A being thermodynamically stable at ambient conditions, and B being the stable polymorph at elevated temperatures. A transition point temperature between A and B has been estimated to T_{trans}= 215°C ± 15°C from the differences in melting enthalpies.

[1] Jensen A.F., Junager F., Jessen C. U., Kornø H. T., *International Patent Application*, 2004, WO2004005299. [2] Bernstein J., Davey R. J., Henck J.-O., *Ang. Chem. Intl. Ed*., 1999, **38**, 3440-3461.

Keywords: polymorphism, phase transition, drug molecule

P.06.10.13

Acta Cryst. (2005). A**61**, C293

Epimerization of α-amino Nitriles to Single Stereoisomers in the Solid State

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Enantiomeric or diastereomeric enrichment to a single isomer has had only limited success to date. We have found that a diastereomeric mixture of α-amino nitriles, which was prepared by the diastereo-selective Strecker reaction using the amino alcohol as a chiral auxiliary, thermally epimerizes to a single stereoisomer in the solid state. X-ray structure analyses have shown that the α-amino nitrile, [1*S*,2*R*,(*SR*)]-N-cyano(phenyl)methyl-1-aminoindan-2-ol, epimerizes at 65 °C to give a single diastereomer with an (*S*)-configureation ((*S*)-isomer) at the α position to the nitrile moiety. Namely the (*R*)-isomer is thermally unstable and the (*S*)-isomer is stable in the solid state. In DMSO solution, the diastereomerically pure (*S*)-isomer epimerizes at room temperature to give a 1 : 1 mixture of the (*S*)- and (*R*)-isomers. Therefore the cause of thermal unstability of (*R*)-isomer in the solid state should be ascribed to the crystal structure. In the (*R*)-isomer crystal there are two hydrogen bonds, an intramolecular N-H…O and an intermolecular CN…HO bonds which promote dissociation of the cyanide anion. On the other hand, the intramolecular O-H...N bond in the (*S*)-isomer crystal retards the dissociation of the cyanide anion. As a result, the (*R*)-isomer selectively epimerizes to the (*S*)-counterpart via an iminium or imine intermediate.

Keywords: epimerization, solid state isomerization, diastereomeric enrichment

P.06.10.14

Acta Cryst. (2005). A**61**, C293

Two Oxime Derivatives Including Succinimid and Morpholin Groups

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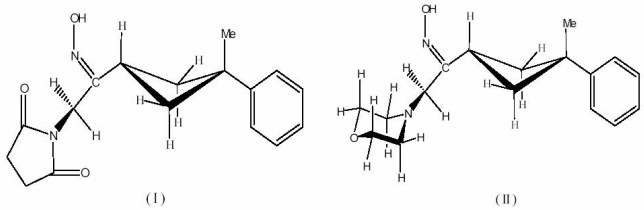
The title compounds, 1-methyl-1-phenyl-3-[1-hydroxyimino-2-succinimido) ethyl] cyclobutane, $C_{17}H_{20}N_2O_3$, (I), and 1-(3-methly-3-phenylcyclobutyl)-2-morpholin-4-yl-ethanone oxime, $C_{17}H_{24}N_2O_2$, (II), crystallize in space group $P2_1/c$, [1]. Each compound contains a cyclobutane ring, an oxime group and a benzene ring [2]. The cyclobutane ring in (II) is more puckered than in (I). In (II), morpholin ring adopts a chair conformation. Although the oxime moiety in (I) has an E configuration, the oxime moiety in (II) has a Z configuration The molecules in (I) are linked by O–H...O and C–H...π(benzene) interactions, forming a two-dimensional network, while the molecules in (II) are connected by O–H...N interaction.



(I) (II)

[1] Özdemir N., Dinçer M., Yılmaz İ., Çukurovalı A., *Acta Cryst*., 2004, **E60**, o145-o147. [2] Ahmedzade M., Çukurovalı A., Koparır M., *J. Chem. Soc. Pak*., 2003, **25**, 51-55.

Keywords: crystal structures, organic molecule, drug action

P.06.10.15

Acta Cryst. (2005). A**61**, C293

3-Methoxy-5-(4-methylphenyldiazenyl)salicylaldehyde and 3-methoxy-5-(2-methylphenyldiazenyl)salicylaldehyde

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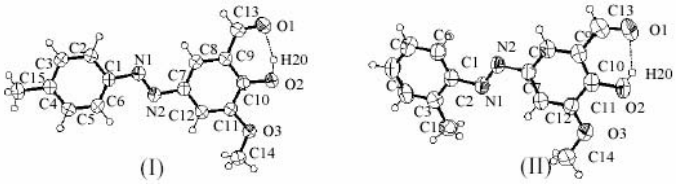
The two title molecules, both $C_{15}H_{14}N_2O_3$, are roughly planar and display a *trans* conformation with respect to the -N=N- double bond, as found for other diazene derivatives. In both compounds, there are intramolecular O–H...O hydrogen bonds and the crystal packing is governed by weak intermolecular C–H...O hydrogen bonds and π-π stacking.



(I) (II)

The structures of both (I) and (II) (Figs. 1 and 2) contain two essentially planar fragments, *viz*. one monosubstituted (C1-C6) and one trisubstituted phenyl ring (C7-C12). The aromatic rings are in a *trans* conformation with respect to the azo double bond. The C14–O3 bond length [1.413(2)Å in (I) and 1.429(4)Å in (II)] is approximately equal to that usually associated with a methyl C–O bond in a methoxy group attached to an aromatic ring (1.424Å; Allen *et al*., 1987).

[1] Allen F. H., Kennard O., Watson D. G., Brammer L., Orpen A. G., *J. Chem. Soc. Perkin Trans*., 1987, **2**, S1-19.

Keywords: azo groups, π-π stacking, aromatic ring

P.06.10.16

Acta Cryst. (2005). A**61**, C293-C294

Crystal Structure of 2-cyclohexyl-5-formyl-6-(4-bromophenyl) Imidazo[2,1-b] [1,3,4] Thiadiazole

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1,3,4-thiadizole nucleus is associated with a broad spectrum of biological activities, possibly due to built in toxophoric thioamide (S-C=N-) unit. Biosteric nature with biologically significant thiazole moiety and its non-carcinogenic nature. A lot of work on the synthesis and biological activities of condensed imidazo(b) thiazoles has been reported since the discovery of novel broad spectrum anthelmintic, Tetramisole. The trend has been shifted to explore the drugs containing biosteric thiadiazole ring in place of thiazole ring of tetramisole viz., imdizo (2,1-b) -1,3,4-thiadizoles and their derivaties. The title compound screens them for their pharmacological activities.