described for Form E, resulting in a two-phase system: the neutral free base (common to both decomposition processes) and, in the present case, a novel Zolpidem tartrate monohydrate, unique to the "aging driven" decomposition. Our R.T. single crystal analysis gives for the free base comparable results as the H.T. XRPD ones already reported: orthorhombic, Pcba, a= 9.6360 (10)Å, b= 18.2690 (5)Å, c= 18.4980 (11)Å, V= 3256.4 (4)Å^3. The unreported Zolpiden tartrate monohydrate, instead, crystallizes in monoclinic $P2_1$, which for comparison purposes we treated in the non-standard setting $P112_1$ with a= 20.7582 (9)Å, b=15.2331 (5)Å; c= 7.2420 (2)Å, γ= 90.826 (2)°, V= 2289.73 (14) Å^3. The structure presents two complete moieties in the asymmetric unit (z=4, z'=2). The different phases obtained in both decompositions are readily explained considering the diverse genesis of both processes.

[1] I. Halasz, R.E. Dinnebier, *J. Pharm. Sc*. **2010**, *99*, 2, 871-874.

Keywords: polymorphism

MS53.P25

Acta Cryst. (2011) A**67,** C568

Exploring phases of a physiologically-active nitronyl nitroxide free radical

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Nitronyl nitroxides are free radicals that are interesting both in biology and magnetism [1], [2], [3]. Their crystal structures have been largely studied: over 300 are reported. The study of different phases (polymorphs, salts, co-crystals) is relevant because properties strongly depend on crystal structure; therefore, about 13% of the structures quoted above are polymorph. In one remarkable case, 10 polymorphs have been found for a single compound [4].

Derivatives of 2-phenyl-4,4,5,5-tetramethyimidazoline-1-oxyl 3-oxide (PTIO) react with ·NO to form the corresponding iminonitroxides (PTIs) and $\cdot NO_2$. Under inflammatory conditions, ·NO is produced in much greater amount than normally, undergoing transformations which cause tissue damage, therefore the ·NO scavenger behaviour of nitronyl nitroxides is interesting to be used as potential therapeutic agents [1], [2].

2-(4-Carboxyphenyl)-4,4,5,5-tetramethyimidazoline-1-oxyl-3-oxide (cPTIO) is a compound similar to PTIO studied by some of us [5]. It has been shown that cPTIO exerts beneficial actions on systemic inflammatory response.

Some crystal phases of cPTIO have been described including co-crystals and salts [6], [7]. In the context of a study on cPTIO crystal phases, it is presented here the new crystal structure of the cPTIO perchlorate whose free radical nature has been stated by means of EPR. Suitable single crystals of cPTIO perchlorate (intense orange colour) have been studied using X-ray diffraction. Crystals are monoclinic ($P2_1/n$, Z=4) having the following unit-cell parameters: a=7.815(2), 20.736(4), 10.478(2) Å, β =91.83(3)º.

The comparison with cPTIO crystal structure [8] shows that N-O bond lengths are shorter (1.22 *vs.*1.30 Å) being the rest of bond distances very similar. The imidazoline ring is plane whereas in cPTIO adopts a half-chair conformation. The crystal packing is also different, in cPTIO, molecules are linked by COOH···O-N(nitroxide) H-bonding and form infinite zigzag chains whereas in the present structure, organic ion is surrounded by perchlorate groups and no chains are formed.

[1] T. Akaike, M. Yoshida, Y. Miyamoto, K. Sato, M. Kohno, K. Sasamoto, K. Miyazaki, S. Ueda, H. Maeda, *Biochemistry* **1993**, *32*, 827-832. [2] S. Goldstein, A. Ruso, A. Samuni, *Journal Biolog. Chem.* **2003,** 50949-50955. [3] S. Greve, V. Vill, W. Friedrichsen, *Z. Naturforsch*. **2002,** *57b***,** 677-684. [4] M. Tamura, Y. Hosokoshi, D. Shiomi, M. Kinoshita, Y. Nakasawa, M. Ishikawa, H. Sawa, T. Kitazawa, A. Eguchi, Y. Nishio, K. Kajita, *J. Phys. Soc. Jpn.* **2003**, 1735. [5] M. Soler, A.M. Molins, L. Vila, *Journal of Infectious Diseases* **2001**, *183*, 105-112. [6] H. Hayashi, S. Karasawa, N. Koga, *J. Org. Chem* **2008**, *73*, 8683. [7] T. Otsuka, T. Okuno. M. Ohkawa, K. Awaga, *Mol. Cryst. Liq. Cryst. Sci. Technol., Section A* **1997**, *306*, 285. [8] C. Batz, P. Amann, H.J. Deiseroth, L. Dulog, *Liebigs Ann.* **1994**, 739.

Keywords: radical, salt, anti-inflammatory

MS53.P26

Acta Cryst. (2011) A**67,** C568-C569

X-ray powder diffraction study of malic acid

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The system of two malic acid enantiomers (components of the system) is typical example of a binary chiral system. It forms limited solid solutions as well as racemic modification at the equimolar composition [1]. Racemic malic acid is able to crystallize in different polymorphic modifications that complicates investigations of the system.

The molecule of malic acid $C_4H_6O_5$ (HOOC–CH_2–HCOH–COOH) has one chiral centre. Accordingly this compound can exist in the forms of two enantiomers *R* (+) and *S* (–). The database ICDD (Intern. Centre for Diffraction Data) contains characteristics of malic acid for its (–)-enantiomer ($P2_1$) and two monoclinic polymorph modifications of (*R,S*)-racemate ($P2_1/c$ и *Cc*). Referring to [2], (*R,S*)-malic acid grown from acetone solution is the stable modification, while that grown from water solution is the metastable modification. Unfortunately, these authors [2] did not indicate crystallochemical data (crystal system, space group, indices *hkl*, elementary cell parameters, etc.) for the phases of malic acid they synthesized.

We studied the polymorphic variety and structural deformations of racemic malic acid by means of X-ray and thermo-X-ray powder diffraction methods.

Initial samples of the enantiomers and racemate belong to the space groups $P2_1$ and $P2_1/c$ respectively. Besides, samples of malic acid obtained at different conditions were investigated at room temperature. Samples of the racemate (*R,S*), enantiomers (*R* and *S*), and mechanic mixture of the enantiomers (*R*+*S*) were grown from water, ethanol, and acetone solutions. Samples of the racemate (*R,S*) and equimolar mixture of enantiomers (*R*+*S*) were obtained after washing initial samples in heptane. Samples of crystallized melts of the racemate (*R,S*) and equimolar mixture of enantiomers (*R*+*S*) were obtained.

We found that (*R,S*)-malic acid could crystallize at least in three (probably in four) polymorph modifications: I ($P2_1/c$), II (*Cc*), III and supposedly IV (the space groups of III and IV ones were not identified for the present). Besides, X-ray characteristics (interplanar distances, *hkl* indices, parameters of monoclinic elementary cells, etc.) of two known (ICDD et al.) polymorphic modifications of racemic (*R,S*)-malic acid (I and II) were defined. Thermal phase transformations of *R*-enantiomer ($P2_1$), (*R,S*)-racemic modification I ($P2_1/c$), and equimolar mechanic mixture of malic acid (*R*+*S*) enantiomers were investigated at heating (the range was 50–140ºC, the temperature step was 2–10ºC). It was revealed that *R*-enantiomer and racemic modification I undergo only structural (thermal) deformations at heating: all the linear parameters *a*, *b*, and *c* (Å) and volume (Å^3) increase monotonously but angular parameter β decreases.

It is indicative that the equimolar mechanic mixture of enantiomers (*R*+*S*) undergoes a solid phase transformation into (*R,S*)-racemic modification I ($P2_1/c$). The transformation being extended in temperature starts at 90°C and finishes close to the melting point (118°C).

The work is granted by RFBR (10-05-00891, 10-02-01303).

[1] M. Kuhnert-Brandstatter, L. Friedl, *Microchimica Acta* **1977**, *II*, 507-516. [2] H. Kaemmerer, S.N. Lorenz, A. Black, Seidel-Morgenstern *Crystal Growth & Design* **2009**, *9*, *4*, 1851-1852.

Keywords: polymorphism, chirality, racemic

MS53.P27

Acta Cryst. (2011) A**67,** C569

Physical Form Screening of Olanzapine and Amoxapine

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The pharmaceutical field is frequently confronted with the phenomenon of multiple solid forms (polymorphs, solvates, salts and co-crystals) of the same chemical entity. Sometimes the properties of two solid forms of a drug are quite similar but can, and often do, vary substantially with potentially significant impact on pharmacokinetics, ease of manufacturing and stability of drug in dosage form and bioavailability. Hence, it becomes critical to have in depth knowledge of solid forms of a candidate molecule, so that the appropriate solid form can be taken forward as a clinical candidate.

Experimental screening is often used to explore all possible physical forms and has been implemented at a variety of different scales and throughputs [1]. Whilst fully automated parallel crystallisation capabilities are available in our laboratory, these require 10s of grams of material for a comprehensive solution crystallisation search [2]. However, we have established a method of high throughput crystallisation (HTC) for physical form screening of compounds using quartz 96/48 multi well plate formats with an automated system for collecting high quality Raman spectra (Thermo DXR system). This methodology has various advantages including reduced material requirements, fast data collection, no separate sample preparation, and analysis of sample in suspension. Multi-well plate approaches are complementary to the larger scale automated methods as in high through put screening. It has various advantages in the context of solid form screening when only small amounts of compound are available. The analytical technique utilized in this methodology, Raman spectroscopy has emerged as an efficient analysis tool to differentiate between various solid forms like (polymorphs, solvates or amorphous) [3]. High throughput crystallisations of two marketed drugs, olanzapine and amoxapine were carried out on 96/48 multi well plates under various conditions i.e. solvents, antisolvents, concentrations, different counter ions. Raman spectra were collected automatically using array software. Various chemometric tools were used to classify the samples and to identify novel forms. In one example of olanzapine, 96 crystallizations utilizing 144 mg of olanzapine and ~20 ml of 48 solvents yielded 21 novel forms. The results of high throughput crystallisation were used as guide to scale up experiments to fully characterize the 30 novel physical forms.

[1] A.J. Florence, H.G. Brittain, *Informa Healthcare,* New York **2009,**. *2* 139-184. [2] A.J. Florence, A. Johnston, P. Fernandes et.al. *J. Appl. Cryst.* **2006**, *39*, 922–924. [3] S.L. Morissettea, O. Almarssona, L.M, Petersona, *Adv. Drug Deliv Rev,* **2004**, *56*, 275–300.

Keywords: solid state, physical form screening, high throughput crystallisation, raman spectroscopy

MS53.P28

Acta Cryst. (2011) A**67,** C569

New insight into the desmotropy of irbesartan

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Polymorphism, the ability of a compound to exist in more than one modification, is a widespread phenomenon of extreme importance in pharmaceutical development. Irbesartan, an anti-hypertensive agent (angiotensin II antagonist), crystallizes in two distinct solid state modifications because of a tautomerism, first established in solution by M. El-Hajji and J.-P. Bezard (1998). This special case of polymorphism is termed desmotropy and occurs within a tetrazole ring in which the unique hydrogen may be either on an α- (adjacent) or β-nitrogen (opposite) with respect to carbon. Even if the two desmotropes exhibit different sizes and morphologies, crystals of form A (trigonal, thin needles) and B (triclinic, large prisms) could be grown concomitantly from ethanol/water. Form A, analysed by synchrotron diffraction (ESRF Grenoble) at room temperature (RT), builds up sixfold helix-chains through non covalent N-HN hydrogen bonds (HB), and recent laboratory X-ray data showed that the channels in the molecular packing may contain non-stoichiometric water. The structure of form B consists of head-to-tail dimers also linked by N-HN HB.[1] Irbesartan has been studied by solid state NMR at RT and at 253K;[2] the authors easily distinguished the two modifications by ^{13}C CP/MAS. They also carried out ^{15}N CP/MAS studies and concluded that, in contrast to form A in which the 6 expected signals of the 6 molecular nitrogens are found at RT, only two sharp peaks appeared in the spectrum of form B at the same temperature (with a broad resonance region) and the 6 expected signal were only recovered at 253K for this modification. The NMR data of form B, together with the results of a ^{15}N CP/MAS dipolar dephasing experiment and of a 2D EXSY spectrum, allowed the authors to claim that form B undergoes, at RT, an exchange process consisting of simultaneous proton hopping (i.e. jumps from one β-nitrogen to the other) and internal rotation of the tetrazole ring. We present new RT and 125K diffraction data on Form B, using either X-rays or neutrons. X-ray data show that the triply disordered butyl-chain established at RT [1] perfectly locks in at 125K, Neutron diffraction data (ILL Grenoble), show that the hydrogen is perfectly localized on the nitrogen opposite the tetrazole-carbon such as to establish a HB with its neighbouring imidazole. This is corroborated by X-ray difference-maps also supporting a single tetrazole-protonation at RT. Atomic vibrational amplitudes can under no circumstances account for a 180° rotation of the tetrazole around the phenyl-tetrazole bond at RT.

Consequently, we do not believe Bauer and al.'s model for form B; we merely sustain that the unexpected ^{15}N resonances at RT are attributed to the vicinity of the tetrazole ring and the disordered butyl-chain, which was indeed revealed by diffraction methods.

[1] Z. Böcskei, K. Simon, R. Rao†, A. Caron, C.A. Rodger, M. Bauer, *Acta. Cryst.,* **1998**, C54, 808-810. [2] M. Bauer, R. Harris, R. Rao, D. Apperley, C.J. Rodger, *Chem. Soc. Perking Trans. II,* **1998,** 475-481.

Keywords: desmotropy, polymorphism, NMR

MS53.P29

Acta Cryst. (2011) A**67,** C569-C570

A new pharmaceutical co-crystal: (*S*)-naproxen-isonocotinamide

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