INTERMOLECULAR INTERACTIONS IN CRYSTALS: VIA EXPERIMENT AND THEORY TO INDUSTRIAL APPLICATION
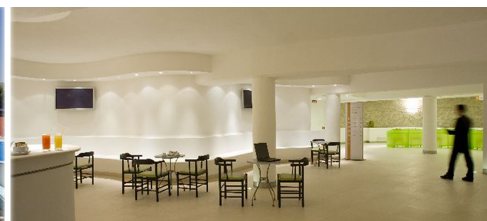
INTERNATIONAL CONFERENCE

APRIL 28. - 30. 2013

Pula (CA), Sardinia – Italy

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Session 1

The World is Flat – and Atoms are Round

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We are conditioned to believe that non-covalent interactions (e.g. Coulomb or dispersion) cannot result in directional preferences. The best known example is that a "covalent component" (aka "donor-acceptor interaction") is assumed to be important in hydrogen bonding because the preferred angle at the donor hydrogen is 180°. In fact, a purely electrostatic model reproduces the angle preference quite well[i]. Our use of isotropic atom-based models for non-covalent interactions (e.g. net atomic charges with Coulomb's law or Lennard-Jones potentials for repulsion/dispersion) leads us to assume that any directional preference must be due to covalent interactions, even though Price called the *"assumption that the charge distribution around each atom is spherical"* a *"travesty of bonding theory"* 27 years ago[ii].

Just how good (or how bad) are isotropic atom-atom models? The question is especially important today because many density-functional theory (DFT) techniques are supplemented by isotropic atom-atom potentials to compensate for the missing dispersion interaction in DFT. Like electrostatics, dispersion is generally assumed to be isotropic, but Stone has shown that both repulsion[iii] and dispersion[iv] are significantly anisotropic. Can DFT, for instance, reproduce the energy contour diagram for the interaction of an argon atom with a bromine molecule shown below?
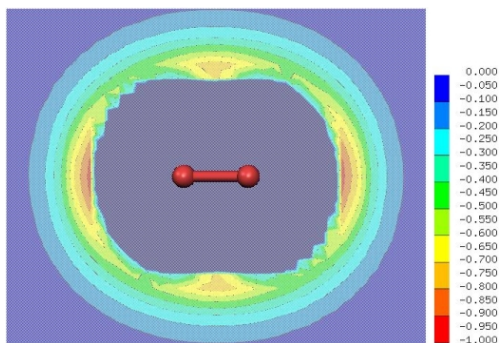

Figure: The calculated (CCSD(T)/aug-cc-pVQZ) Born-Oppenheimer interaction energy (kcal mol^{-1}) between an argon atom and a bromine molecule. The repulsive areas of the potential are colored gray.

The lecture will discuss some historical examples of how the spherical atom assumption has led to false conclusions and describe new attempts to analyze intermolecular interactions uniquely and rationally.

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iii.*Anisotropy of Atom-Atom Repulsions*, A. J. Stone and C.-S. Tong, *J. Comput. Chem.*, **1994**, *15*, 1377-1392.
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Predicting new compounds using global ab initio energy landscape explorations

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A fundamental issue in solid state chemistry and materials science is the rational planning of syntheses, analogous to the high degree of control already attained in molecular chemistry.[1] The basic requirements for success in this endeavor are the ability to predict possible target compounds, including metastable modifications at real thermodynamic conditions, and to devise synthesis routes to access these predicted compounds. Here, we focus on the first step, the prediction of new modifications.

Predicting which crystalline modifications can exist in a chemical system requires the global exploration of its energy landscape.[1] Due to the large computational effort involved, in the past this search for sufficiently stable minima has been performed employing a variety of empirical potentials and cost functions followed by a local optimization on the ab initio level.[1] However, this might introduce some bias favoring certain types of chemical bonding and entails the risk of overlooking important modifications that are not modeled accurately using empirical potentials. In order to overcome this critical limitation, it is necessary to employ ab initio energy functions during the global optimization phase of the structure prediction.[2]

Thus, we have applied several global exploration tools to the study of the ab initio energy landscape of a number of prototypical systems, LiF [3], BN [4], PbS [5], CaC_2 [6], Li [7], and several pernitrides MN_2 (M = Ca, La, Ti) [8], exhibiting various types of chemical bonding. The low-energy modifications found are in good agreement with the experimentally known structures, and in addition a number of new promising modifications at standard and elevated pressure are predicted.

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Prediction of Metal-organic Frameworks by First Principles Parametrized Force Fields and a Genetic Algorithm based Screening Procedure

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Porous coordination polymers (usually referred to as metal-organic frameworks or MOFs), as well as the related covalent organic frameworks (COFs), are a very fascinating new class of porous materials. They are highly ordered and crystalline polymers, but their properties are dominated by the molecular like building blocks. Especially fascinating is their variability and structural flexibility.

In this contribution, a procedure termed Reversed Topological Approach (RTA) will be explained, which is used to predict the structure and the most stable supramolecular isomer of a MOF or COF, starting from given building blocks. The method is built on accurate first principles parametrized force fields. Using a Genetic Algorithm, force field parameters are calibrated to DFT computed reference data [1]. A completely reparametrized force field MOF-FF has been developed in a consistent form for a wide range of MOFs and COFs [2]. In the RTA method, again a Genetic Algorithm is used to systematically screen the range of potential isoreticular isomers, which is a specific type of isomerism typical for MOFs. It allows to locate the most stable structure for a given topology and reveals possible disorder or even the presence of different phases. The approach will be exemplified for certain COFs [3] and MOFs, including hypothetical structures which are not synthesized yet.
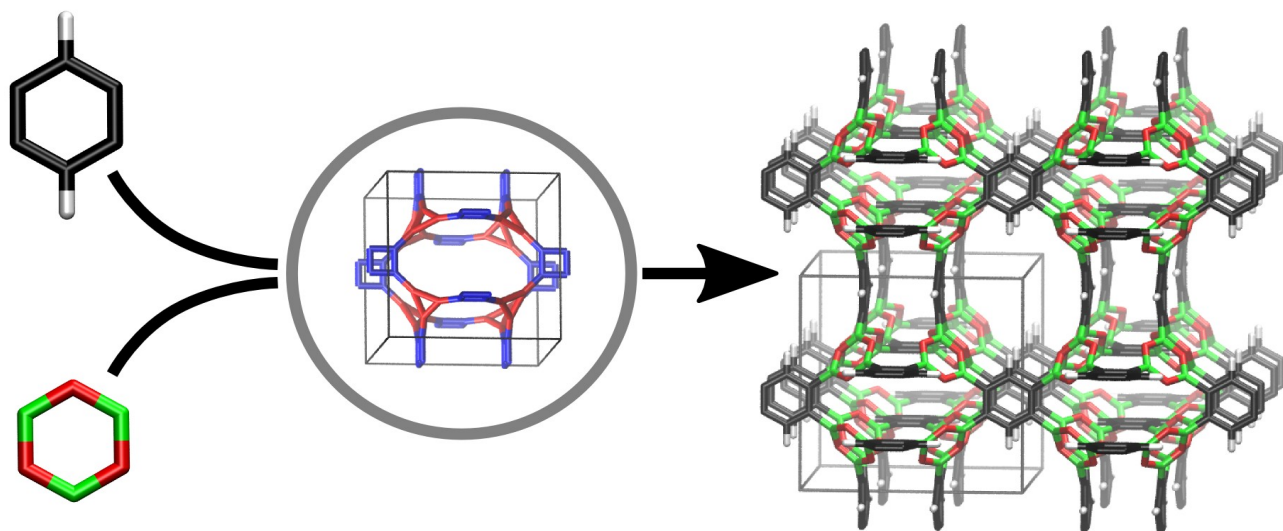
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Session 2

"In silico filter in cocrystal screening"

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The term 'cocrystal' is not clearly defined. A minimum consensus refers to a multicomponent stoichiometric crystalline material made of molecular components. It has well-defined physicochemical properties which are distinctly different from the individual components it was made from. If at least one of them is an active pharmaceutical ingredient such entities are called pharmaceutical cocrystals. This inherently produces the problem of choice for the cocrystal partner(s).

Selection of the partner(s) in view of the expected essential properties requests well-designed strategies being discussed in this presentation. The main interest is always to achieve a stable cocrystal out of the numerous combinations. Many options exist, but as so often, an adaptive balanced mixture usually turns out to be the most promising.

These concern the different steps, which starts with the 'rational design', applying the knowledge of supramolecular synthons for selecting the most promising partners out of a pool from suitable candidates. Next we suggest ranking the promising partners, based on the calculated free energy of the expected cocrystals. Such calculations, based on 'data mining' strategies as developed by Detlef Hofmann[1] provide the 'theoretically best candidates' for which the likelihood to achieve a cocrystal is the highest. Therefore it is worth to apply the highest experimental efforts for such a candidate by increasing the number of experimental variables, probably at the expense of the least favorable candidate. For distinct theoretical results defining certain candidates as totally improbable, it might be even wise to totally drop them from the list.

Further properties can now be considered as well. They might include pharmacological considerations or even marketing preferences. Calculations of the expected solubility as introduced by D. Hofmann during this conference can lead to a combination of two or more ranking lists.

We hope to initiate an open and fruitful discussion in this fundamental research which is totally based on weak intermolecular interactions.
Although likewise important, here we will exclude further stages such as the optimum experimental syntheses, the analytic tools for the products, the evaluation of the physico-chemical properties and finally the most economical procedures.

1 "Data Mining in Crystallography" by D.W.M. Hofmann and L.N. Kuleshova, Springer Verlag 2012

Co-Crystal Formation During Pharmaceutical Formulation Development: An Industry Case Study

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Co-crystal formation is an emerging area in the pharmaceutical industry, which essentially broadens the options upon solid-state selection beyond salt formation. Hence, API co-crystals are typically looked at during API form optimisation in the Drug Substance process.
However, the recent FDA draft guidance on regulatory co-crystal classification addresses pharmaceutical co-crystals in the Drug Product process.
Although this viewpoint will be rather surprising for many, it does highlight one aspect which is often overlooked, namely the potential for API co-crystal formation with pharmaceutical excipients during formulation development.
The presentation will illustrate in detail the aspect of un-intended co-crystal formation during formulation processes with a comprehensive case study, also touching on monitoring tools to identify solid-state form changes in the Drug Product matrix, as well as presenting some practical aspects for risk assessment if such form conversions are observed.

Utilizing Chiral Information In Diastereomeric Co-Crystals

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Diastereomeric co-crystals like diastereomeric molecules are expected to differ in their physical and chemical properties. While enantiomeric pairs show different properties only in a chiral environment (e. g. polarized light), diastereomeric pairs show differences in achiral environments as well. Diastereomeric co-crystals involving chiral pharmaceutically active ingredients in combination with chiral excipients or a second chiral API offer the opportunity to tailor solubility rates and bioavailability.

Pairs of diastereomeric co-crystals are formed between two different chiral components whereby the handedness of one component remains constant, while for the other component both enantiomers are used successively. Reducing this scheme to practice often fails, since the two components don't form a co-crystal, when crystallized from solution. However, by means of solvent assisted ball milling numerous pairs of diastereomeric co-crystals affording the amide-acid motif have been prepared. In these cases crystal structure determination has to be based on the polycrystalline material obtained after ball milling. Modern algorithms for indexing powder diffractograms and for solving crystal structures via global optimization methods followed by Rietveld refinement have advanced this field substantially.

An added crystallographic benefit of this approach is the determination of the absolute structure of one of the two components based on the known absolute structure of the other component, for which both enantiomers are used in separate ball milling experiments.

Session 3

The role of CF₃-substituents in self recognition processes of organic compounds

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Supramolecular synthons, which involve strong intermolecular interactions, namely hydrogen bonds, had early been recognized as important intermolecular linkages. Attention is being given both to supramolecular synthons, which involve strong intermolecular interactions like hydrogen bonds, and to weak intermolecular interactions like C-H⋯X, CH⋯π and X⋯X. In the case of X = F, a number of reports in the literature conclude that organic fluorine hardly accepts hydrogen bonds. In previous studies we have shown the considerably influence of fluorine substituents on the self recognition processes of fluorine-substituted benzonitriles and pyridines.

Continuing our investigations on aggregation of substituted aromatic molecules in the solid state, we are now especially interested in the aggregation behaviour of CF₃- and CHF₂- substitueted arenes. These compounds are well known building blocks in the preparative organic chemistry. A detailed X-ray investigation of in situ crystallized CF₃-substitueted compounds allow analyzing the role of the weak directing CF₃, and CHF₂ and F subsituents on the aggregation of molecules in solid state.
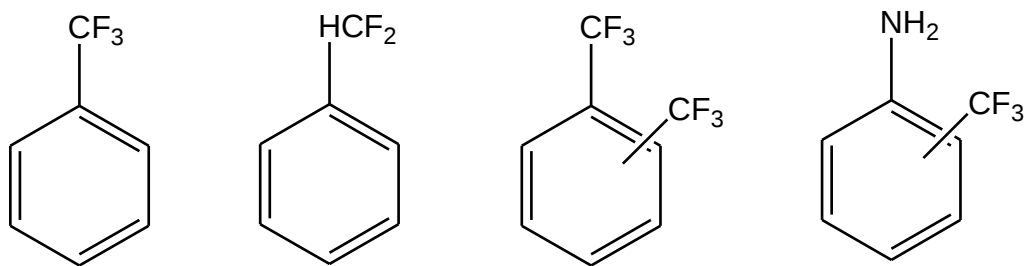
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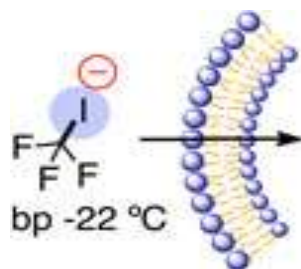
Halogen Bonding Defined!

Pierangelo Metrangolo[1,2], Gabriella Cavallo[1,2], Tullio Pilati[1], Giuseppe Resnati[1,2] and Giancarlo Terraneo[1,2]

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A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity[1]. It will be shown how halogen bonding is a strong, reliable, and specific interaction that can be successfully employed to drive recognition phenomena and self-assembly of various multi-component supramolecular architectures[2,3]. Heuristic principles will be presented to design complex and functional systems proving how the structure and topology of a supramolecular architecture can be anticipated from the structure and geometry of the starting tectons[4]. Similarities and differences between hydrogen and halogen bonding will be described[5] as well as their simultaneous use in driving the orthogonal self-assembly of purely organic frameworks [6]. The impact of halogen bonding in materials and life sciences will also be demonstrated in applications ranging from industrial separations[7] and supramolecular gels[8], to anion transport systems[9] (see Figure) and biomimetic catalysts [10].

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Hydrogen & halogen bonding in coordination compounds: structure & theory

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Well implemented are the multidentate N- and O-donor ligands as building blocks in the construction of metal complexes and coordination polymers. The interest is also arising from its usage as functional materials in many applications (i.e.host-guest reactions, luminecence,etc) [1].
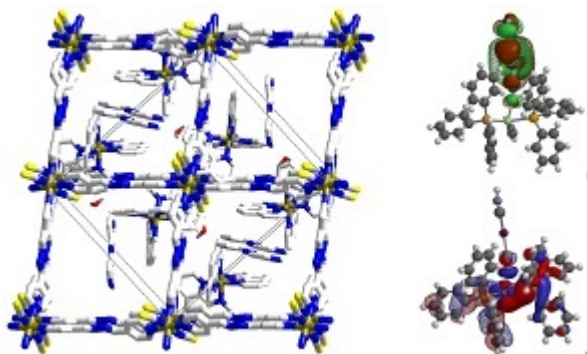
The intercalated compound in [2]   HOMO/LUMOs in [3]

Among other results is the one-pot molecular-scale crystal engineering of FeII-based grid-like framework self-assembly reaction involving structurally directed supramolecular synthons between molecular components [2]. A mutitude of different intermolecular synthons observed in these and others from our research are exploited and will be presented, with a perspective is given for structural and theoretical analysis [3-5].

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Systematic analysis of the weak interactions offered by F, Cl and Br in halogen substituted N-benzylideneanilines

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The interactions involving "organic fluorine"[1] have always been a controversial topic in contemporary research.[2] In spite of having high electronegativity, the role played by organic fluorine in crystal packing becomes doubtful due to its low polarizabilty.[3] Some of the research groups indicate that fluorine is not capable enough to alter the supramolecular motifs, which are capable of building the crystal lattice.[4] Whereas some other groups have proven that substantial role is being played by fluorine in constructing the lattice through C- H···F, C-F···F and C-F···π interactions in the presence and absence of strong hydrogen bond donor and acceptor groups.[5] The nature of these interactions is quite important to understand because drug molecules containing one or more fluorine atom show significant biological activity compared to their non-fluorinated analogues.[6] Its small size makes it as a good substituent in cases where there is a need to change the electronic properties of molecule without much change in the stearic hindrance at receptor site on cells or enzyme and its lipophilic character results in the increase of bioavailability of fluorinated drug molecules.[7] Therefore, fluorine as a part of the drug molecules has the capability to interact with the receptor site in our body. So there is a need for appropriate understanding of the intermolecular interactions offered by the fluorine atom. Our aim is to comprehend the nature and strength of fluorine mediated interactions in guiding the packing of small organic molecules in the crystal lattice. Hence, we have chosen a model system of different halogen substituted N-benzylideneanilines. In this system, first the packing in the lattice is analysed by having fluorine substituent in both the phenyl rings. Then one or the other substituent is replaced by chlorine and bromine successively in both the rings and effect of this replacement of the substituent on packing was examined. It has been observed that supramolecular motifs designed by organic fluorine are quite robust (figure 1) and these have not been altered by replacing the other substituent by chlorine or bromine with some exceptions. This indicates the robustness of the synthons formed by organic fluorine.
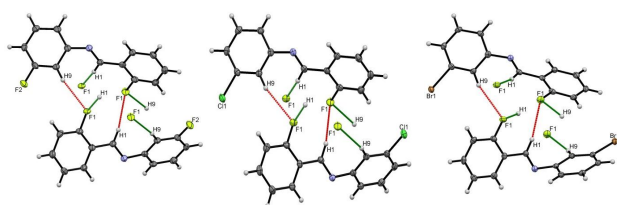

Figure 1: The steadiness of the supramolecular motif formed by utilizing ortho fluorine on the aldehyde ring with the imine hydrogen, which has not been altered even by replacing the meta fluorine on the aniline ring by Chlorine or Bromine.

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Session 4

Charge Density in Crystals from High Resolution X-ray Diffraction Experiments:

Toward a Deep Understanding of Intermolecular Interactions

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Two approaches are available to get the electron density of molecules: quantum mechanical calculations (Hartree-Fock (HF), Density Functional Theory (DFT)) and high resolution X-ray diffraction experiments. Both approaches yield electron density distributions of high quality for molecules in gas-phase or embedded in the crystal lattice. In the last decades, the confrontation of theoretical and experimental results has permitted to improve the methodologies used in the two approaches. From high resolution X-ray diffraction, the structure factors are modelized using the pseudo-atom model of Hansen-Coppens.[1,2] From this model, both spherical and deformation densities of each atom in the molecule can be parametrized. Then, the electron density of the molecule or a cluster of molecules in the crystal lattice can be analyzed by using the "Atoms in Molecule" topological theory of R.F. Bader.[3] Ionic, covalent bonds and even weak interactions like hydrogen bonds can be accurately characterized. This analysis is based on the gradient field and the Laplacian of the electron density. Other electrostatic properties like charges, electric moments and electrostatic potential or field can also be derived from the electron density distribution. From the atomic electron density parameters the electrostatic energy can be estimated in order to quantify the interaction between molecules in the crystal. [2] For more than ten years we are involved in the characterization of the interactions between pharmaceutical active molecules in the solid state. The methodology used for the determination of the electron and electrostatic properties from the X-ray diffraction will be presented. Applications to the pharmaceutical molecules will be extensively illustrated and compared to the theoretical calculation results.
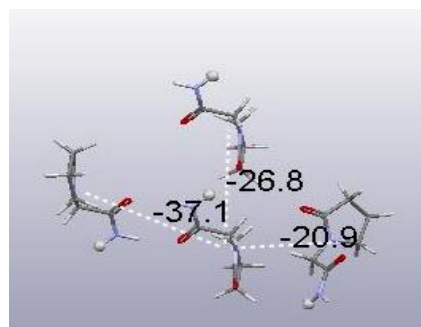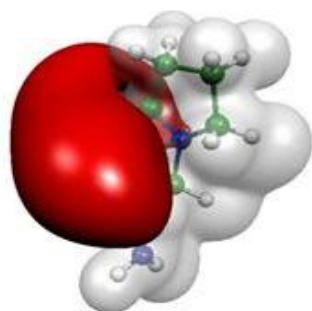
Electrostatic Potential (left) and interaction energies (right) of piracetam

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Experimental charge density studies: a tool for understanding the nature of interactions?

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X-ray diffraction provides an insight into the electron density distribution in crystals. Standard methods are based on independent atom model (IAM) approximation, which assume the spherically-averaged, neutral atoms. This model is the basis of unprecedent success of X-ray crystallography as a tool for "looking at the molecules". However, the details of electron density distribution (bonding density, lone pairs etc.) are outside the possibilities of standard model.

The expansion of IAM into the non-sphercial 'pseudoatom' model allows to analyze the fine details of the electron density distribution. This procedure is highly demanding experimentally, but it offers – often together with Atoms-in-molecules approach – the possibility of deeper understanding of the nature of bonds and other interactions. During the talk the general procedure will be described together with some results, ranging from small organic molecules to DNA and protein structures.

NON-COVALENT INTERACTIONS IN CRYSTALS REVEALED THROUGH THEIR EXPERIMENTAL ELECTRON DENSITY

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Nucleation and growth of molecular crystals, both from thermodynamic and kinetic point of view, is mainly driven by intermolecular interactions, which have mostly non-covalent character. The presence of Non-Covalent Interactions (NCI) can be detected by making use of theoretical and/or experimental techniques. As the Electron Density (ED) is an observable and measurable quantity (from X-ray diffraction experiments) which, at the same time, can be straightforwardly obtained from the wavefunction, it provides a direct bridge between experiment and theory. In 2010 Johnson et al.[1] introduced an ED-based NCI descriptor which exploits a quantity largely employed in DFT: the Reduced Density Gradient (RDG). In particular, they demonstrated that by building low-RDG isosurfaces in (relatively) low ED-region it is possible to detect the presence of NCI. Moreover, to allow a better characterization of various NCI, the quantity ED*sign λ_2 (where λ_2 is the second greatest eigenvalue of ED Hessian matrix) is mapped onto isosurfaces: the sign of λ_2 is used to distinguish between supposedly attractive and allegedly repulsive interactions, while ED is considered as a measure of their strength. We have recently applied such descriptor, for the first time, to experimentally derived ED (from single crystal X-ray diffraction) [2], showing that it allows an easy-to-catch visualization of NCI in crystals (Fig.1). Moreover, by comparing the experimental results with those obtained from fully-periodical DFT calculations, we could demonstrate that the experimentally-derived RDG-based NCI picture is reliable. By contrasting

the NCI picture achieved from the RDG-based descriptor with that obtained from the Quantum Theory of Atoms in Molecules(QTAIM [3]), we could also show how the two approaches may fruitfully complement each other in providing additional insight into the nature of a given NCI. In a separate work, we did explore to what extent the NCI description obtained using the true experimental ED differs from that retrieved using the simpler model of the promolecular ED, given by superposing the atomic densities. Our detailed analysis [4] challenges in part the belief that the NCI picture retrieved from the promolecular density almost matches that derived from the true density, as previously suggested [1]. Although the ED*sign(λ2) was the only quantity mapped onto isosurfaces in the original formulation of the RDG-based NCI descriptor, other choices are obviously possible. The energy density bears the advantage of being a physically rooted quantity (as the integral over the whole space gives the electronic energy of the system). Moreover, by mapping such quantity, the arbitrary distinction between attractive and repulsive interactions is avoided. We show that, when mapped onto RDG-isosurfaces, energy density is able to rank the strength of the various interactions. In addition, the possibility of partitioning the total energy density into potential and kinetic contributions, allows one to gain more insight into the different kinds of NCI and to distinguish better their specific nature. The exact energy density can be obtained only from the wavefunction, but, in the case of the experiment, we overcame this limitation using the functional introduced by Abramov [5], which enables one to derive an approximate energy density directly from the ED distribution; in the regions where NCI RDG-isosurfaces appear, the "exact" and approximate energy match almost perfectly. Eventually, we present the feature of the fortran90 code developed by us for the calculation of RDG, ED*sign(λ2)
and energy density grid files[6]. The code reads grid files in output from common commercial codes such as Gaussian 03/09, XD2006 and Crystal 06/09; moreover, it allows one to calculate ED, its derivative and energy density grid files directly from Gaussian wave function file.
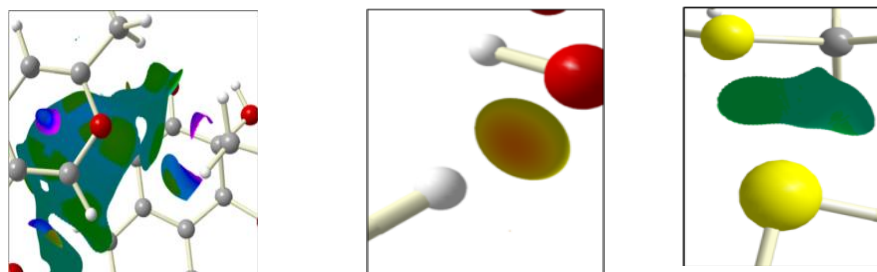
Figure 1. 0.6 RDG-isosurfaces in Austdiol and Famotidine molecular crystals. From left to right: van der Waals interaction in austdiol, O-H···O hydrogen bond in Austdiol, S···S key-lock interaction in Famotidine. ED*sign(λ2) is mapped onto isosurfaces and colour scale range from red (-0.30) to violet (+0.35) through light blue (0.0)

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Climbing the Jacob's ladder of dispersion-corrected DFT: accurate models for the prediction of molecular crystal polymorphism

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Periodic Density Functional Theory (DFT) calculations employing the PBE, PBE0 and B3LYP functionals coupled with different dispersion-correction schemes (-D and -TS) have been applied to the para-diiodobenzene (p-DIB) molecular crystal in order to determine how they perform in reproducing the energetic and crystal geometry of its two well known polymorphs. Our results [1] showed that, when properly corrected, DFT calculations successfully predict the relative stability of the α (Fig.1) and β phases at zero temperature, in good agreement with Diffusion Monte-Carlo (DMC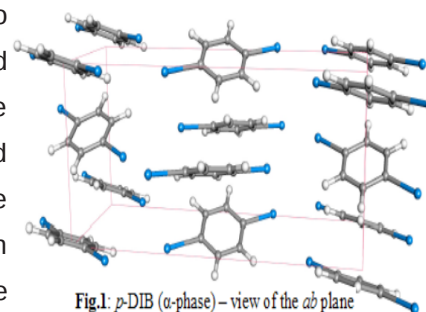) calculations [2]. Among the two dispersion corrections employed, the recently proposed Tkatchenko and Scheffler (TS) scheme [3] performs much better than the original Grimme scheme (D) [4]. This is imputable to the accurate nonempirical method used to obtain the effective dispersion coefficients in the former approach. We are currently benchmarking [5] the TS scheme also against a polar system, such as the oxalyl dihydrazide (Fig.2). This simple molecule gives rise to five

Fig.1: *p*-DIB (α-phase) – view of the *ab* plane

different phases, in which the competition of intermolecular H-bond and dispersive interactions makes the prediction of the relative stability very challenging. The TS scheme leads to a nice agreement with experiment both for structures and thermodynamics. Even high-level periodic MP2 calculations are ongoing for a further comparative purpose. The TS and other analogous models (e.g. XDM [6,7]) for dispersion-correction are still not commonly used in computational chemistry but the first results reported in literature denote the accuracy of such methods to describe long-range interactions, with respect to more approximated ones. An important advantage of employing the TS is the relatively low request of computational time, if compared with accurate post-Hartree-Fock or

Fig.2: α-phase of oxalyl dihydrazide

Quantum Monte-Carlo methods. An interesting review by Klimes et al., about the state-of-the-art of dispersion-correction schemes, which are classified according to a "Jacob's ladder ", appeared recently in J. Chem. Phys 137, 2012, 120901. In our opinion, such schemes can play a fundamental role to better understand the chemical and physical nature of weak interactions – not only in the field of molecular crystals – opening a new era for the design and the prediction of increasingly complex systems, as requested from the market.

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Session 5

M.DynaMix studies of solvation, solubility, permeability
and solid-liquid phase transitions

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This talk contains selected simulation studies to investigate to ability of current interaction potentials and force fields models to describe phenomena such as melting, dissolution, coordination, assembly, aggregation, hydration, solvation and permeation of small molecules including organic drug-like substances. Nearly all interaction potentials today are designed and parameterized for bulk liquids and aqueous solutions. Therefore they are always put to a critical test when used in other non-standard conditions. Solvation free energy is very sensitive to the used molecular models and a reliable test of different interaction potentials. All studies presented here are carried out using simulation software package "M.DynaMix" which is particularly suited for detailed and accurate studies molecular interactions with applications from climate modeling and chemical engineering to drug design. All carried out in intimate connection to experiments.

Laaksonen A., Lyubartsev A., Mocci F., (2012)

"M.DynaMix Studies of Solvation, Solubility and Permeability"

in "Molecular Dynamics – Studies of Synthetic and Biological Macromolecules",

(Ed. Wang L.), InTech, ISBN: 978-953-51-0444-5)

Jämbeck, Joakim P. M.; Mocci, Francesca; Lyubartsev, Alexander P.; Laaksonen, Aatto

Partial atomic charges and their impact on the free energy of solvation

Journal of Computational Chemistry (2013), 34(3), 187-197.

Egorov, Andrei V.; Brodskaya, Elena N.; Laaksonen, Aatto

Computer simulations studies of solid-liquid phase transitions in solid water nano particles

From Journal of Computational and Theoretical Nanoscience (2008), 5(9), 1914-1922

Calculation of Molecular Properties by Data Mining: the aProf approach.

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The multitude of crystallographic data on molecular structures deposited in public databases [1,2,3,4] is ever increasing and this fact is already exploited in many way in synthetic molecular design to calculate molecular relevant properties [5,6,7,8]. We have developed (Patent Deposit Request N. MI2012A001457, "Metodo per determinare valori di proprietà molecolari", 30-08-2012) a novel method that, applying data mining techniques to structural databases, is able to predict various molecular properties. The method is based on the new and fruitful definition of two entities: the atomic profile and the similarity index between profiles, leading to simple calculations and resulting in flexible, tunable and very accurate predictions of molecular properties. The method aProf is based on five steps:

1) Structural DB Parsing . 2) Atomic profile evaluation and classification to extract atomic types . 3) Training DB analysis . 4) Optimization and weight estimation .5) Prediction

First we parse a structural database of molecules and extract relevant information for each atom, in each of the molecule, in the form of an original atomic profile. Second, through the use of an ad-hoc originally defined similarity index inspired by the work of some authors [9], we classify all the calculated atomic profiles, in such a way to extract the really distinct atomic types [10,11,12] present in the initial data-base. A greater number of atomic types will increase the computational effort but in the meanwhile increase the accuracy of the predictions. Atomic types [10,11,12] can be interpreted as the chemical atoms present in the molecule, eventually with specific coordination capabilities, but can also be used to define united atoms, depending on the level of coarse graining indirectly obtained in the classification stage. Third, we select a database of molecules with the specific property under interest experimentally characterized, and we assign to each of them the atomic types according to our similarity index. Fourth, now that we have a set of reference molecule with known molecular property values and assigned atomic types, we can build a system of equations assigning to each atomic type a contribution to the property under study for all the known molecules. The solution of the system of equation parametrizes the value of each molecule in terms of the atomic types. The accuracy of this calculation is directly linked to the quality and number of molecules in both the databases we have parsed. Last step, the calculated atomic types are used to assign atomic types to the new, yet uncharacterized molecule, through the use of our similarity index. We can now add the atomic type contributions obtained in the fourth step and predict the property value for the molecule under study. We have applied our method aProf to the calculation of solubility of a large set of molecules, comparing the results obtained by other authors [8], and show that the method is not only viable and effective but also very accurate and fast. The fields of application of the method is very large, including solubility in water, densities in crystal phase, logP for drugs, and we are currently in the process of fully engineering our method and testing it with bigger and distinct databases.

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Water and ion parameters effects on the base sequence specificity of ion binding to DNA in MD simulations

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Nucleic acids are highly charged polyelectrolytes. Their interactions with counterions are of great importance for their structural stability, conformational behaviour and biological functions. Molecular modelling and simulation techniques, particularly Molecular Dynamics, have been highly useful for studies of interactions between DNA, water and ions at the molecular level, allowing to explain many experimental observations, or to obtain information not accessible experimentally [1]. Monovalent counterions, like Na + and K+, are among the physiological counterions of DNA. In recent years it has been shown that they can bind directly to DNA, partially losing their hydration water. These studies revised the common view of monovalent cations binding to the DNA double helix in a delocalized manner, without dehydration and irrespective of the base sequence. Obtaining detailed information at the atomistic level on the binding of ions like Na+ or K+ is tricky, and often the experimental data leave space to several interpretations. Very detailed information on counterion/DNA interaction can be obtained by Molecular Dynamics simulations, but to what extent the information obtained are dependent on the Force Field parameters used is yet to be fully understood. Here we present our studies [2] concerning the sequence specific binding of Na+ to three DNA sequence, containing either A-tracts of different length or no A-tract, and we compare the results obtained using different water models (flexible-SPC or TIP3P) and different ions parameters (Smith&Dang [3], Åqvist – amber adapted [4], Joung&Cheatham [5]).

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Structural and Dynamical insights on HLA-DR2 complexes that confer susceptibility to Multiple Sclerosis in Sardinia: A Molecular Dynamics simulation study

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Sardinia is a major Island in the Mediterranean with a high incidence of Multiple Sclerosis (MS), a chronic autoimmune inflammatory disease of the central nervous system. MS susceptibility in Sardinian population has been associated with five alleles of major histocompatibility complex (MHC) class II DRB1 gene. We perform 120 ns of molecular dynamics simulation on two MS associated alleles, *15:01 (predisposing) and *16:01 (protective), unbound and in complex with the two relevant peptides: Myelin Basic Protein and Epstein Barr Virus derived peptides. In particular we focused on the MHC peptide binding groove dynamics. The predisposing allele was found to form a stable complex with both the peptides, while the protective allele displayed stability only when bound with myelin peptide. The local flexibility of the MHC was probed dividing the binding groove into four compartments covering the well-known peptide pockets. The predisposing allele in the first half cleft exhibits a narrower and more rigid groove conformation in the presence of myelin peptide. The protective allele shows a similar behavior, while in the second half cleft it displays a narrower and more flexible groove conformation in the presence of viral peptide. We further characterized these dynamical differences by evaluating H-bonds, hydrophobic
and stacking interaction networks, and finding striking similarities with super-type patterns emerging in other autoimmune diseases. The protective allele shows a defined preferential binding to myelin peptide, as confirmed by binding free energy calculations and in-silico residue mutation. On the other hand, the predisposing allele exhibits an higher degeneracy with regard to the myelin and viral peptides. All together, we believe the presented molecular analysis suggests that propensity to MS in Sardinia could be affordably linked to distinct peptide-MHC interaction and binding characteristics of the antigen presentation mechanism.

Session 6

Emulsion assisted solution crystallization of hydrogenated castor oil in an aqueous continuous phase.

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The crystallized form of hydrogenated castor oil (HCO) has a wide use as a rheology modifier in many consumer products, giving the desired constancy or preventing physical separation. The performance of HCO as a rheological modifier depends strongly on the shape and size distribution of the fat crystals and as such specific crystal shapes are preferred over others. There therefor is a high interest in industry to understand the impact of the crystallization conditions on polymorphism and morphology, and to manipulate the process to form the hydrogenated Castor oil into the desired microstructure. For this application the process is an emulsion assisted solution crystallization wherein the sparingly water soluble HCO is crystallized within the aqueous continuous phase rather than in the emulsified HCO droplets. The emulsion acts as a reservoir to feed the solution crystallization. Triacylglycerols such as HCO are typically crystallized in three different configurations or polymorphs, depending on the positioning of the three acyl groups. The three most common ones are α, β & β', although more polymorphisms are known to exist. Different polymorphs tend to crystallize into a preferred morphology, which is determined by the relative growth rate of the different crystal surfaces. For the discussed formulation and process, three distinct types of crystal morphologies have been observed; long fibrous crystals, spherulites and short needles. This worked has focused on how each can be formed under well-defined process conditions.

Insights from Crystal structures of Active Pharmaceutical Ingredients

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Most (small molecule) active pharmaceutical ingredients (APIs) can occur in different crystalline forms. The presentation outlines, why the knowledge of the crystal structures of these API solid forms is important and can be highly beneficial, not only to confirm phase identity and phase purity, but also to understand phase properties relevant for pharmaceutical development, crystallization behavior and thermodynamic stability relationships. Several real life examples from the last decade(s) are presented to illustrate the mentioned aspects.

Solubility and Crystal Structure Prediction

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The solubility is one of the crucial properties of drugs. From the thermodynamic point of view the prediction of the solubility is simple. The free energy of the drug molecule´s interactions must be the same in the crystal ($G_{lattice}$) and in the solution ($G_{hydration}$). In fact it is a tremendous theoretical problem. The free energy includes effects of temperature and pressure. However, quantum-mechanics gives a priori the enthalpy and the effect of
temperature and pressure has to be added in laborious calculations. It has been recently demonstrated, how to do this for the hydration energy [1].
Here we would like to show a simple way for the prediction of the free energy for the crystal. Data Mining Force Fields (DMFF) can fulfill this task very quickly and accurate. The basic idea of data mining on crystal structures is that any crystal structure is a global minimum in the free energy. The force field is obtained by optimization of the parameters, till it assigns always to the experimental structure lower energy as to virtual crystal structures produced during crystal structure prediction. A general description about the method can be found in the recently published textbook "Data mining in Crystallography" [2]. The free energy of the molecule in the crystal can be easily estimated by a crystal structure prediction with the data mining force field. The lowest energy of the predicted polymorphs corresponds to the free energy. This
is even true, if the predicted crystal structure does not coincide with the experimental crystal structure, and, instead of the experimental crystal structure, another polymorph is predicted nearby in energy rank. We performed a crystal structure prediction for all 30 drugs, where we did find accurate values for the free energy of hydration. A plot of the free energy interaction $\Delta G = G_{lattice} - G_{hydration}$ versus the solubility _log(S)_ shows a very high correlation with a coefficient of determination of 0.92. The linear regression holds over a range of 14 magnitudes of solubility.

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Lattice energy calculation – a quick tool for screening of stability and relative solubility of cocrystals.

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Cocrystals (or multicomponent crystals) have other physico-chemical properties, than pure crystals of one of the components. This is of large interest for drug developments, since the desired properties, e.g. solubility, stability, bioavailability, can be tailored by binding of two substances in a single crystal without chemical modification of an active component (API).

Here, with the aim to find a feasible approach for in silico screening of pharmaceutical cocrystals, FlexCryst program suit, implemented with Data Mining Force Field have been used. The very quick algorithm of _FlexCryst_ allows to predict correctly the typical hydrogen bonded motives (synthons) and to estimate properly (within +/- 3 kJ) the free energy of crystal lattice. The approach for a screening of cocrystals bases on the simple thermodynamic arguments that a cocrystal can be formed, if its total free lattice energy (G_{CC}) is lower than the sum of lattice energies of pure components: $-G_{CC} > -(G_{API}+G_{CF})$.

The free energy of cocrystals GCC and the pure components G_{API} and G_{CF} have been calculated for three classes of cocrystals: cocrystals of flavonoids, cocrystals of caffeine and cocrystals of agomelatine. All substances are able to form extended systems of intermolecular hydrogen bonds. This ability is recognized currently as one of the most important prerequisite for co-crystal formation. In the same time the flavonoids are known for the reason of difficulties in experimental formulation of their cocrystals The caffeine, vice versa, forms cocrystals relatively easily, but stability of obtained cocrystals stays relatively low. Agomelatine is an interesting example for the case of multiple polymorphic modification of API. The reasons of different behavior are discussed in terms of stability and solubility of pure components. The analysis of experimental and calculated data were performed.

It was found that present state of art of energy function of _FlexCryst_ allows a very good correlation between free energy of experimental and predicted crystal energy for all class of cocrystals and results in 80- 85% of successful predictions. The values $\Delta G = G_{cryst\_API} + G_{cryst\_CF} - 2G_{cryst\_CC}$, can be used as indication for probability of cocrystal formation. Taking into account that for the case of simple dissolution, solubility constant, _Ks_, depends on the balance between two kinds of interactions: G_{hydr} (how strongly the molecule associates with the solvent) and G_{cryst} (how tightly the molecule is bound to its own crystal lattice) , the values ΔG open the excellent opportunity to estimate also the relative solubility of cocrystals. These findings will allow to restrict experimental trials for cocrystallisation only with the "best" coformers admitting better probability of cocrystal formation with improved API solubility.

Poster Session

A QM:QM SCHEME FOR THE CALCULATION OF MOLECULAR CRYSTALS

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For crystalline material it is often important knowing the solid-state properties without access to crystal structure determinations. Methods exist for crystal structure prediction; however, a precise calculation of the structure and enthalpy is desired in any case. This allows calculating the X-ray powder patterns but also IR and Raman spectra, estimating solubility and many other properties.

Calculations based on quantum mechanical methods are superior to most other techniques which is why we introduce a QM:QM (quantum mechanical method in another quantum mechanical method) embedding scheme for calculating molecular solids, in which the inner shell is calculated by a quantum method of choice embedded into density functional theory including dispersion correction (DFT+D). The inner shell is divided in a fragment-based manner, in which all dimers and monomers are taken into account when optimizing the molecular solid. This way, we are able to fully optimize small to medium-sized molecular crystals.

First example calculations for the alkane crystals of ethane, propane and butane using MP2 embedded into PBE+D2[1] are presented. As for other weakly bound molecular crystals[2], DFT+D in any of its variants[1,3] is underestimating experimentally determined cell volumes. MP2:PBE+D2, on the other hand, yields results much closer to the experimental values, making it a valuable addition to the current methods at hand.

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Properties of Asp, Glu, Gly and Leu on the Fe 3O4-(111)-surface:
A force field simulation study

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Magnetite (Fe_3O_4) crystallises in the inverse spinel structure [1]. In nature magnetite is an important biomineral. Magnetotactic bacterias, e.g., use magnetite single-crystals to orientate themselves in the earth magnetic field. The connection between the inorganic magnetite-(111)-surface and the organic parts of the animals is the magnetosome membrane (MM). The composition of the MM of the magnetotactic bacteria Magnetospirillum gryphiswaldense has been analysed [2,3] . The MM is built by different magnetosome membrane proteins (MMPs). Two of these MMPs are the proteins MamJ and MamG. The structure of MamJ is dominated by the amino acids aspartic acid (Asp) and glutamic acid (Glu) whereas MamG is dominated by glycine (Gly) and leucine (Leu). Forcefield simulations of the interaction of the magnetite-(111)-surface and the membrane offer the possibility to investigate if and how the amino acids interact with the surface. Additionally, it is possible to investigate the interactions and the adsorption distances between the surface atoms and the functional groups of the amino acids. We have chosen the COMPASS-forcefield because all parameters of the surface and of the amino acids are defined in this forcefield. As simulation software we used Forcite which is integrated in the Materials Studio 5.0 software package. In addition to that we use the magnetite-(111)-surface that had already experienced relaxation [4]. Based on the assumption the surface has been defined as a constraint. The amino acids may adsorb in a docking box built by a 47.49 Å x 47.77 Å magnetite-(111)-surface and a 19.28 Å vacuum slab. For every amino acid 10000 frames has been calculated. The results show that it is energetically favourable for the amino acids to adsorb on the surface. All of them adsorb in Fe-O-distances between 2.6 and 4.1 Å. The involved O-atoms belong to the carboxyl-group (Asp) or to the carboxylate-group (Gly, Glu and Leu). From this it follows that electrostatic interactions dominate. This conclusion can be proven by the results. Summing up we can show that it is energetically favourable for all of the amino acids to adsorb on the magnetite-(111)-
surface and that the electrostatic interaction dominates during adsorption.

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Mimicking peptides in silico

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We recently developed pep:MMs:MIMIC, a novel web-oriented peptidomimetic compound virtual screening tool based on a multi-conformers three-dimensional (3D)-similarity search strategy. pep:MMs:MIMIC, given a peptide three-dimensional structure, is able to automate a multiconformers three-dimensional similarity search among 17 million of conformers calculated from 3.9 million of commercially available chemicals collected in the MMsINC database. We now present an ameliorated version of the tool, with key improvements in the quality of the search algorithms and in the user interface. The version 2.0 of (our) tool is characterized by incorporation of partial charge and lipophilicity informations into the shape descriptors, extensive use of automated pharmacophore-based search, superposition of the query peptide with the top scoring candidate peptidomimetics, and full integration with the Pymol interface. Last, any private or public molecular database can be reprocessed by the user .

Insights Into the Charge Density of Carbamazepine Drug in Form III to Understand the Intermolecular Interactions.

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Carbamazepine is an essential drug used for the treatment of epilepsy. The experimental electron and electrostatic properties of carbamazepine drug molecule in form III were determined from accurate high resolution X-ray diffraction data collected at 100 K. The results are compared to quantum mechanics calculations for gas-phase molecule and dimers. The experimental electron density was refined using the Hansen-Coppens multipole formalism [1] and the deformation electron density maps are compared to the theoretical ones.

These results, in particular the topological analysis of carbamazepine using Bader's theory[2] and the electrostatic potential features will be presented. We will also discuss the electrostatic intermolecular interaction energies values calculated from the electrostatic potential, which show the equivalency of the strength of the hydrogen bonding and the aromatic-aromatic interaction of CBZ molecules in the crystal lattice [3]. Experimental Electrostatic Potential of Carbamazepine
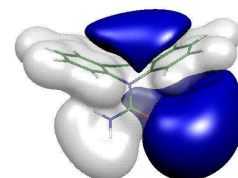
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Applying Efficiently Parameterized Molecular Models in Industrial Research Projects

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Molecular simulations relate macroscopic phenomena to their roots in molecular interactions. The practical applicability of these simulations within process engineering and material design requires the construction of appropriate molecular models for a wide range of chemicals. The key to a quantitative property prediction is the accuracy of the simulation's foundation, the force field. A force field describes the intra- and intermolecular interactions by a semi-empirical equation and its associated parameters. Manual adjustment and optimization of these parameters is, at best, extremely time consuming. Hence, an automated parameterization scheme is essential in our pursuit to create tailor-made models for specific investigations in a timely fashion.

Fraunhofer SCAI has developed two semi-automatic tools with user-steered scientific workflows: The Workflow for Force Field Optimization Package (Wolf2Pack) [1] was designed to optimize the intramolecular degrees of freedom. The GRadient-based Optimization Workflow (GROW) [2] addresses the intermolecular degrees of freedom, e.g. Lennard-Jones parameters. Together, these optimization tools enable us to create reliable and fast molecular model parameters capable of predicting quantitatively experimental physicochemical properties of chemicals over a wide range of temperatures and pressures. In this work we discuss the application of our numerical simulation methods to following industry projects: Development of new materials on the basis of Nanotubes embedded in hard matter matrixes [3] , Simulating cement based materials [4] , Calculating Octanol/Water partition coefficients , Calculating free energy profiles of Ionic Liquids moving through a biological membrane in order to predict their toxicity

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X-ray single crystal investigation on solid behaviour of methyl 3,5-bis(hydroxymethyl)- benzoate, its phenylethynyl extended derivative in polymorphous forms and corresponding carboxylic acids.

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The crystal structure of methyl 3,5-bis(hydroxymethyl)benzoate is compared to the phenylethynyl extended methyl 4-[3,5-bis(hydroxymethyl)phenylethynyl]benzoate (polymorph I) which crystallize in the same monoclinic space group. A corresponding polymorphous form of the latter compound (polymorph II) was isolated that features conspicuous differences concerning the conformation and the arrangement of the molecules in the crystal packing. The related carboxylic acids 3,5-bis(hydroxymethyl)benzoic acid and 4-[3,5-(hydroxymethyl)phenylethynyl]benzoic acid, show a carboxylic acid dimer based structure. All molecular structures are explicitly investigated regarding the conformational similarities and differences of the tolane frameworks and the hydroxymethyl substituents.[1]

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New frontiers in material modeling

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Particle simulation of condensed matter and simple liquids plays a key role in the discovery and prediction of their underlying physical and chemical properties. To this end, the availability of efficient programs for large-scale simulations and analysis tools is a issue of primary interest. In this presentation, latest advances by Computer Modelling Group of Chemistry Department in
Stockholm University are presented:
 A nonequilibrium molecular dynamics simulation of cholesteric liquid crystal, to investigate Lehmann effect and calculate   the cross coupling coefficient between the temperature gradient and the   director angular velocity.
 A porting on GPU architecture of MdynaMix molecular dynamic software, with the goal to boost efficiency thanks to the growth of high performance computing resources. Also a new linearly   scaling accurate and robust Ewald summation method, based on non-uniform fast Fourier transforms, is presented.
 The creation of PASYVAT software tool, that offers a visual approach to simulation data analysis, to manipulate a set of 3D coordinates,   obtain topological information and calculating radial distribution functions.

Crystallisation and Melting Behavior
of 9,10-Dihydroacridine and 9,10-Dihydroanthracene

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Keywords: CH_2/NH substitution; 9,10-Dihydroacridine; 9,10-Dihydroanthracene; small organic molecules

What is known about the influence of CH_2/NH substitution on the crystal structure of organic molecules so far? Within rigid aromatic systems like benzene and pyridine or anthracene and acridine the electronic distribution determines the crystal structure. Those cases show completely different crystal packing [1]. But what about flexible molecular structures? The comparison of cyclohexane and piperidine show similar aggregation behavior of at least one polymorph of cyclohexane and piperidine [2, 3]. To investigate whether the flexible or the rigid unit determines the formation of the solid state we synthesized 9,10-Dihydroacridine and compared the crystallisation and melting behavior to 9,10-Dihydroanthracene by using different techniques such as XRD, DSC and hot stage microscopy.
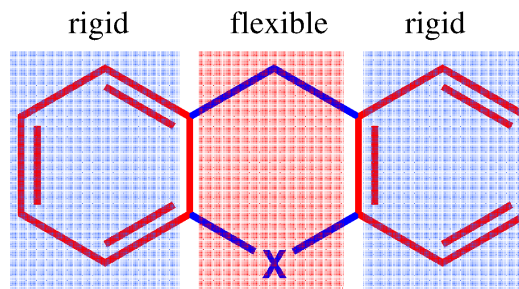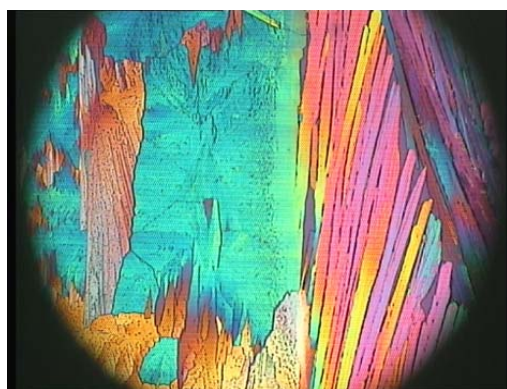
$$X = CH_2, NH$$

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Electron density study of a syn-facial Cr-Mn complex. Toward the understanding of the subtlety of a heterometalic bond.

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A few years ago, a peculiar class of air-stable electron-deficient syn-facial heterobimetallic compounds, accounted for as syn-facial Cr,Mn benzyl complexes, were synthesized by the sequential reaction of organolithium reagents and methyltriflate with cyclomanganated (η6-arene)Cr(CO)3 complexes [1]. Three limiting forms (A, B and C) are used to describe syn-facial heterobimetallic Cr, Mn benzyl complexes. Each form entails different consequences over the bonding modes of the organic ligand, oxidation state of the metals and over molecular geometry. Form A implies i) a significant shortening of the CAr−Cbenzyl as a result of its increased ethylenic character, ii) a significant shortening of the Mn-to-Cbenzyl bond, and iii) a pronounced folding of the Cr-bound arene ligand due to pentahapticity. In both limiting forms B and C, the Mn center binds the benzylic position through a σ-bond and the η6 bonding mode of the Cr-bound arene ligand is preserved.

We have performed two low temperature single crystal X-ray diffraction experiments on syn-facial Cr,Mn benzyl complex at synchrotron Soleil. Despite the difficulties encountered during the data reduction and the methanol disordered solvent, we have finally been able to determine the electron and electrostatic properties of the compound. The results will be discussed in order to better understand the subtlety of the heterometalic bond in this kind of compound.
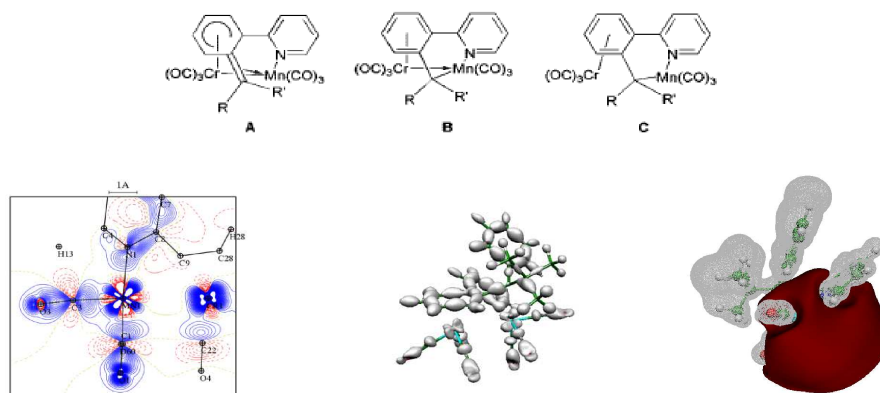
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Halogenated pyridines and pyridine N-oxides:
# Topological analysis of the intermolecular interactions in the solid state

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In recent years, halogen interactions, the so-called halogen bonding, involving C−Cl, C−Br, and C− I groups have become an important tool in crystal engineering. [1] The understanding of the possible modes of intermolecular interactions with participation of the chlorine, bromine, or iodine atoms provides suitable background for the prediction of the arrangement of neighboring molecules in the crystalline phase. In contrast the special aggregation behavior of

fluorinated arenes is controversially discussed. But do we really understand processes of the crystal formation involving halogen atoms on the molecular level? The interpretation of the crystal topology in the case of more or less weak intermolecular interactions actually depends on the specific viewpoint of the researcher. We consider two approaches for a description of crystal structures: geometrical approach, which is based on Kitaigorodskii's close packing principle,[2] Etter's rules for crystals containing hydrogen bonds, [3] and the supramolecular synthon concept,[4] which are the basis of crystal engineering. The latter approach includes the recognition of some strongly bonded motifs in the crystal structure based on strong intermolecular interactions using modern ab initio quantum chemical methods, in particular MP2/6-311 G(d,p). Selected low-melting halogenated pyridines and H/D/F-substituted pyridine N-oxides were crystalized by in situ cryo- crystallization using optical heating and cooling devise. Whereas the geometrical approach provides for 3-bromo- and

3-iodopyridine almost identical molecular organization of shortly Hal ...N-bonded chains, the energetical approach shows differences in basic structural motifs: layered structure vs. isotropic molecular packing respectively (Figure 1). [6,7,8]
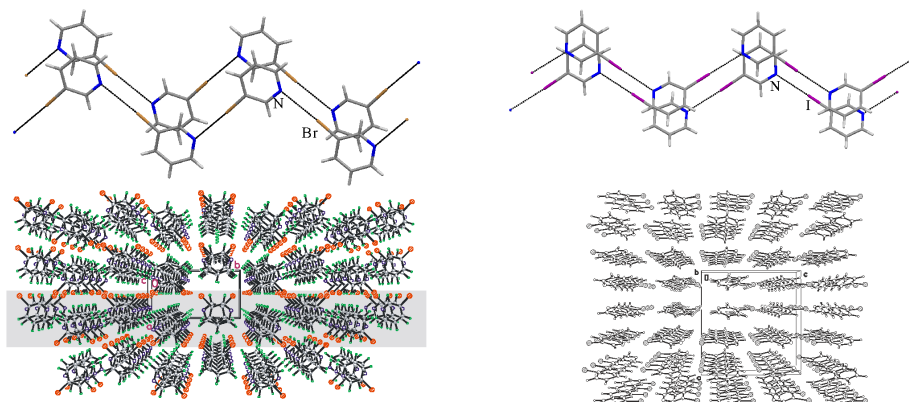
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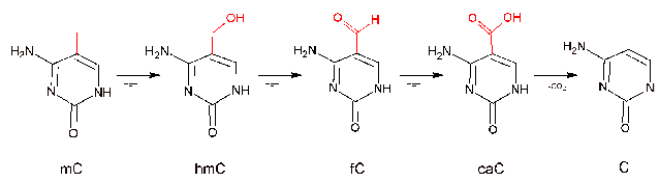
Keywords: crystal engineering, halogen bonding, ab initio quatum-chemical calculations

First X-ray structural study of supramolecular association in proton-transfer adducts and salts of 5-carboxylcytosine, the eighth DNA base.

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DNA is not merely a combination of adenine (A), cytosine (C), guanine (G), thymine (T) nucleobases. It also contains modifications that have profound impacts on gene expression and cellular identity. To date, four other forms of cytosine, known as the fifth, sixth, seventh, and eighth DNA bases, have been identified in mammalian cells: 5-methylcytosine (mC), 5-hydroxymethyl cytosine (hmC), 5-formylcytosine (fC) and 5-carboxylcytosine (caC). The mC and hmC modifications play critical roles in epigenetic regulation of gene expression and maintenance of cellular identity, as they are linked to key developmental events, as well as many types of cancer [1, 2]. The two most recently identified fC and caC, although much less abundant then mC and hmC, are proposed to be part of the cytosine oxidative demethylation pathway catalyzed by the ten-eleven translocation (TET) family dioxygenases [3-5].

Presently, although the functional effects of fC and caC on the process of transcription have not yet been clarified, the existence in fC of a strong intramolecular hydrogen bond between the exocyclic amine and the formyl group was suggested to promote the mutagenic imino tautomer able to form a wrong base-pair with A [6]. Actually, no experimental or theoretical studies concerning caC have been reported in literature. This communication describes the first systematic analysis of the solid-state hydrogen-bond interactions in five proton-transfer adducts of caC, as proton-acceptor with hydrochloric (I), hydrobromic (II), nitric (III) acids, and caC, as proton-donor with benzamidine (IV) and phenylbiguanide (V), and in caC calcium salt (VI).
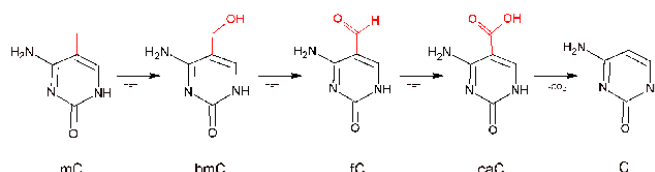
1. Jaenish R, Bird A (2003) Nat Genet 33:245-254 **2**. Law JA, Jacobsen SE (2010) Nat Rev Genet 11:204-220 **3.** Ito S, Shen L, Dai Q, Wu SC, Collins . LB, Swenberg JA, He C, Zhang Y (2011) Science 333:1300-1303 **4.** He Y-F, Li B-Z, Li Z, Liu P, Wang Y, Tang Q, Ding J, Jia Y, Chen Z, Li L, Sun Y, Li X, Dai Q, Song C-X, Zhang K, He C, Xu G-L (2011) Science 333:1303-1307 **5**. Pfaffeneder T, Hackner B, Truß M, Mǜnzel M, Mǜller M, Deiml CA, Hagemeier C, Carell T (2011) Angew Chem Int Ed 50:7008-7012. **6.** Karino N, Ueno Y, Matsuda A (2001) Nucl Ac Res 29:2456-2463.

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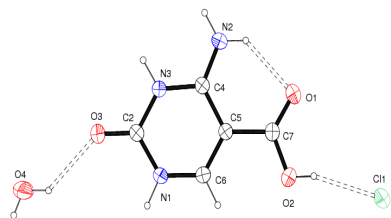
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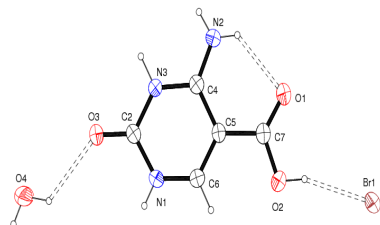

Presently, although the functional effects of fC and caC on the process of transcription have not yet been clarified, the existence in fC of a strong intramolecular hydrogen bond between the exocyclic amine and the formyl group was suggested to promote the mutagenic imino tautomer able to form a wrong base-pair with A [6]. Actually, no experimental or theoretical studies concerning caC have been reported in literature. This communication describes the first systematic analysis of the solid-state hydrogen-bond interactions in five proton-transfer adducts of caC, as proton-acceptor with hydrochloric (I), hydrobromic (II), nitric (III) acids, and caC, as proton-donor with benzamidine (IV) and phenylbiguanide (V), and in caC calcium salt (VI).

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(I)

(II)

(III)

(IV)

(V)

(VI)

List of participants:

Axel Becker, Merck, Germany   S2-6
Co-Crystal Formation During Formulation Development: An Industry Case Study

A. Daniel Boese Uni Potsdam, Germany   PS-22
Daniel.Boese@uni-potsdam.de
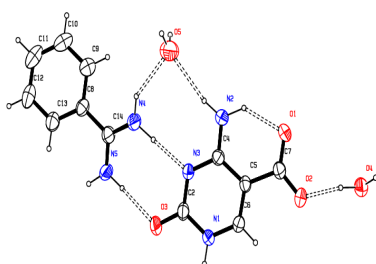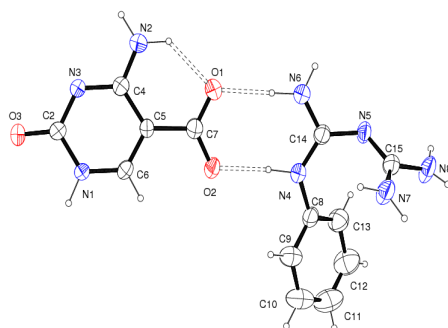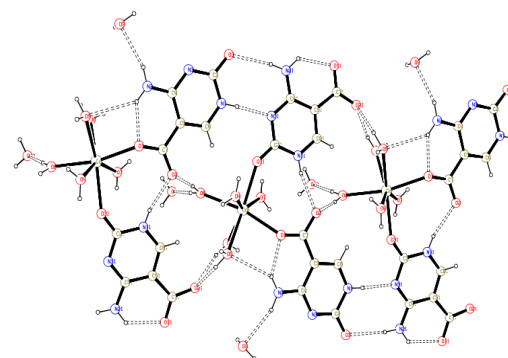A QM:QM SCHEME FOR THE CALCULATION OF MOLECULAR CRYSTALS

Roland Boese, SolidChem, Germany   P2-5
In silico filter for cocrystal screening

Walter Broeckx, P&G, Belgium   S6-19
Emulsion assisted solution crystallization of hydrogenated castor oil
 in an aqueous continuous phase

Andreas Buerger, RUB, Germany   PS-23
Properties of Asp, Glu, Gly and Leu on the Fe 3O4-(111)-surface: A force field simulation study

Timothy Clark, Uni Erlangen-Nuermberg, Germany   S1-2
The World is Flat – and Atoms are Round

Matteo Floris, CRS4, Italy   PS-24
Mimicking peptides in silico

Mohamed Ghazzali, Uni King Saud, Saudi Arab   S3-9
Hydrogen & halogen bonding in coordination compounds: structure & theory

Detlef Hofmann, CRS4 Italy   S6-20
Solubility and Crystal Structure Prediction

Felix Katsch, Uni Freiberg Germany   PS-26
X-ray single crystal investigation on solid behaviour of methyl 3,5-bis(hydroxymethyl)- benzoate, its
phenylethynyl extended derivative in polymorphous forms and corresponding carboxylic acids.

Gurpreet Kaur, IIS, Indien   S3-10
Systematic analysis of the weak interactions offered by F, Cl and Br in halogen substituted N-
benzylideneanilines

Thorsten Köddermann, SCAI Fraunhofer, Germany   PS-25
 Applying Efficiently Parameterized Molecular Models in Industrial Research Projects

Maciej Kubicki, Uni Poznan, Poland   S4-12
Experimental charge density studies: a tool for understanding the nature of interactions?

Amit Kumar, CRS4, Italy   S5-18
Structural and Dynamical insights on HLA-DR2 complexes that confer susceptibility to Multiple Sclerosis in
Sardinia:A Molecular Dynamics simulation study

Anna Kupka, RUB, Germany   PS-27
Crystallisation and Melting Behavior of 9,10-Dihydroacridine and 9,10-Dihydroanthracene

Liudmila Kuleshova, CRS4, Italy   S6-21
Lattice energy calculation – a quick tool for screening of stability and relative solubility of cocrystals.

Aatto Laaksonen,i Uni Stockholm   S5-15
M.DynaMix studies of solvation, solubility, permeability and solid-liquid phase transitions

Cristian Lehmann, MPI Muelheim, Germany   S2-6
Utilizing Chiral Information in Diastereomeric Co-Crystals

Klaus Merz, Uni Bochum, Germany   S3-7
Small organic molecules: Similar shape and size - similar aggregation behaviour?

Pierangelo Metrangolo, Polytech Milano   S3-8
Halogen Bonding Defined!

Francesca Mocci, Uni Cagliari, Italy   S5-17
Water and ion parameters effects on the base sequence specificity of ion binding to DNA in MD simulations

Norbert Nagel, Sanofi-Aventis, Germany   S6-19
Insights from crystals of Active Pharmaceutical Ingredients

Davide Presti. Uni Milano, Italy   S4-14
Climbing the Jacob's ladder of dispersion-corrected DFT: accurate models for the prediction of molecular crystal polymorphism

Massimiliano Porcu, Uni Cagliari, Italy   PS-26
New frontiers in material modeling

Gustavo Portalone, Uni Roma, Italy   PS-30
First X-ray structural study of supramolecular association in proton-transfer adducts and salts of 5-carboxylcytosine, the eighth DNA base.

Stephan Ruehl, FIZ, Karlsruhe, Germany

Gabriele Saleh, Uni Milano , Italy   S4-12
NON-COVALENT INTERACTIONS IN CRYSTALS REVEALED THROUGH THEIR EXPERIMENTAL ELECTRON DENSITY

Carsten Schauerte, SolidChem, Bochum **Germany**

Christian Schoen, FKF, Max Plank, Germany   S1-3
Predicting new compounds using global ab initio energy landscape explorations

Vera Vasylyeva, Uni Duesseldorf, Germany   PS28
Halogenated pyridines and pyridine N-oxides: Topological analysis of the intermolecular interactions in the solid state