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DISCUSSIONS

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# Solid-state chemistry and applications: general discussion

Christer B. Aakeröy, Saman Alavi, Ngong Kodiah Beyeh, Lee Brammer, Mathieu Branca, David L. Bryce, Jan-Constantin Christopherson, Timothy Clark, Simon J. Cottrell, Janet E. Del Bene, Valentina Dichiarante, Alison J. Edwards, Mate Erdelyi, Catharine Esterhuysen, Marc Fourmigué, Tomislav Friščić, Pierre Kennepohl, Anthony C. Legon, Gareth O. Lloyd, Jane S. Murray, Chantal L. Mustoe, William T. Pennington, Sergiy V. Rosokha, Angshuman Roy Choudhury, Steve Scheiner, Patrick M. J. Szell, Mark S. Taylor and Seiji Tsuzuki

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**Alison Edwards** opened a general discussion of the paper by Christer Aakeröy: In the first crystal structure depicted, the imidazole nitrogen which is not making a supramolecular interaction looks to be making an electrostatically favourable (if not hydrogen bonded) interaction to an adjacent ring – is this the case?

**Christer Aakeröy** answered: That could be the case, but it is probably difficult to discern if the orientation is due to a specific individual interaction or if it is the result of a collection of forces.

**Alison Edwards** said: Is this perhaps a packing effect? It may differ in solution, which is my concern, particularly as nucleation events are occurring.

**Christer Aakeröy** answered: Again, that is possible, but we have not performed any solution studies that would allow us to make any definite statements regarding the specific influence of "packing effects".

**David Bryce** asked: Can you speculate on the consistency of the outcomes of your experiments if they were all conducted in a different solvent, or all conducted with mechanochemical approaches?

**Christer Aakeröy** answered: Based on the consistency of the molecular-recognition preferences displayed by the compounds in this study (and in combination with our previously reported results), I would be surprised if the

structural outcomes observed herein would be substantially altered by the solvent or by a mechanochemical approach.

**Alison Edwards** said: If you have not done the solvent dependence, to what extent have you looked at the concentration dependence? If the binding agent is at high concentration, do you get interaction from both sides? Have you thought about the fact that once you have made the first interaction it changes the nature of the acceptor – *i.e.* causing an effect?

**Christer Aakeröy** answered: In previous studies we have shown that by changing the relative concentrations of reactants it is possible to alter the stoichiometry of the product from, let us say 1 : 1 to 2 : 1, if the target substrate has multiple binding sites that are geometrically accessible. In some systems this variability is not possible, because the second binding site is "deactivated" as a result of the first binding event.

**Marc Fourmigué** commented: In hydrogen bonded systems, there is usually a tendency that all hydrogen bond donors would be satisfied. Do you get this here? What happens with the remaining iodine atoms, are they all involved in the bonding?

**Christer Aakeröy** answered: In three of the five halogen-bonded co-crystals presented herein all XB-donor atoms are engaged in halogen-bond interactions. Unsurprisingly, in the co-crystal with tri-fluoro tri-iodobenzene, only two of the three sites are involved.

**Seiji Tsuzuki** remarked: In the crystals of neutral molecules, the dispersion interactions are the primary source of the attraction in general. If the crystals are composed of ionic species, the contribution of electrostatic interactions is large. The polarization energy is proportional to the square of the electric field. Small ions and divalent and trivalent ions have large electric field. In such cases the contribution of the polarization (induction) is significant. The directionality of dispersion interactions is weak. On the other hand the electrostatic interactions of neutral molecules have strong directionality. Therefore the electrostatic interactions often play crucial roles in determining molecular orientation in crystals, although the electrostatic interactions are weaker than the dispersion interactions. The evaluation of total interaction energy and the contribution of each energy term (electrostatic, polarization, dispersion, *etc.*) by theoretical calculations is not difficult at present, such evaluation will be helpful for understanding the roles of intermolecular interactions in determining crystal structures.

**Christer Aakeröy** replied: In our paper we did not discuss or examine any aspect related to the total cohesive or lattice energy of a fully formed crystal. We focused our attention on the pair-wise assembly of molecules in systems where two different and well-defined interactions are possible. Given the directionality and long-range effects of electrostatic interactions of neutral molecules, we made the assumption that such forces will dominate the energy landscape at longer distances. In fact, it turns out that this electrostatic focus provides very helpful

indications as to where a specific hydrogen bond or halogen bond will form if there is a choice of binding sites, and the experimentally observed interactions can be readily rationalized accordingly. We have not made any statements or comments about the relative contributions of different energy terms in crystals or in intermolecular bonds at equilibrium distances. Despite the complexity of chemical bonds we have shown that an electrostatic picture is very helpful for predicting directional binding preferences as different molecules come together.

**William Pennington** asked: In the structures of **A2:XBD3** and **A3:XBD1**, tetramers are formed, but only one of the iodine atoms of the XB donor in each case is involved in N···I halogen bonding. Are there any close contacts between the other iodine atoms with those of neighboring molecules?

**Christer Aakeröy** answered: In **A2:XBD3** the second iodine atom makes a relatively short contact with the equatorial region of another iodine atom, and the third iodine atom makes a short contact with the π-system of an imidazole ring.

In **A3:XBD1**, (which is particularly complicated as there are four unique halogen-bond donors in the unit cell), the second iodine atom forms a short contact with the π-system of an adjacent pyridine ring in all four cases.

**William Pennington** asked: As you point out in your paper, hydrogen-bonded cocrystals often exhibit proton transfer. Is this observed in the heterodimers of any of your hydrogen-bonded systems?

**Christer Aakeröy** answered: In this particular study, we observed proton transfer in two of the nine crystal structures that were obtained with hydrogen-bond donors. Proton transfer cannot, in these cases, be explained *via* $pK_a$ differences between acid and base.

**Anthony Legon** opened a general discussion of the paper by Marc Fourmigué: Professor Fourmigué and co-workers have identified the partial transfer of the bromine atom of *N*-bromosaccharin to 4-picoline when they form an adduct. We have also observed such transfer in other circumstances in the gas phase. In 1997, we reported[1] the rotational spectrum of a complex formed by trimethylamine (as the Lewis base) with difluorine (as the halogen bond donor). Various observations about the nature of the observed rotational spectra of three isotopologues of the complex and the derived spectroscopic constants (including an estimated electric dipole moment of ~10 Debye which is greatly enhanced compared with the sum of those of its two components, a large change in the $^{14}N$ nuclear quadrupole coupling constant, and unexpected changes in the rotational constants on isotopic substitution) led to the surprising conclusion that the complex is best described as the ion–pair $(CH_3)_3N^+F\cdots F^-$, *i.e.* one in which there is a substantial extent of transfer of $F^+$ from $F_2$ to $(CH_3)_3N$. Significant partial transfer of $Cl^+$ from ClF was also identified in the gas-phase complex of $(CH_3)_3N$ and ClF, which is likewise strongly bound.[2] By contrast, the complex $H_3N\cdots F_2$ formed by difluorine and ammonia is very weakly bound and shows no large enhancement of electric dipole moment relative to the sum of those of its two separate components. These conclusions are supported by *ab initio* calculations.[3,4]

1 H. I. Bloemink, S. A. Cooke, J. H. Holloway and A. C. Legon, *Angew. Chem., Int. Ed.*, 1997, **36**, 1340–1342.
2 H. I. Bloemink, J. H. Holloway and A. C. Legon, *Chem. Phys. Lett.*, 1996, **254**, 59–68.
3 C. Domene, P. W. Fowler and A. C. Legon, *Chem. Phys. Lett.*, 1999, **309**, 463–470.
4 A. Karpfen, *Chem. Phys. Lett.*, **299**, 1999, 493–502.

**Janet Del Bene** said: Very nice work, I think basically that what you call neutral, intermediate and ionic, we call traditional, shared and transferred. When we get the F to move, we change the R group, so if you do that here you could determine the position of the halogen in the halogen bond. So it is a very neat thing to be able to do. I would say that your work also shows that it can indeed happen if you choose the right R groups.

**Lee Brammer** asked: Why is the interaction involving Br more covalent (stronger) than that involving I, contrary to what we would expect?

**Marc Fourmigué** answered: The "classical" ordering with I > Br comes from the ESP calculations which systematically (and also here) show a larger sigma-hole amplitude with iodine. With normal XB, the electrostatic contribution dominates and this ranking holds very well. However, we are in a situation here where we cannot rely only on the sigma-hole amplitude, because the interaction has a strong covalent contribution. We can even ask the question if this should still be called an halogen bond.

**Janet Del Bene** remarked: Could what you are seeing simply be a size effect?

**Marc Fourmigué** replied: This is a difficult question. I will say it in other words. A N–Br bond is for sure (shorter) and stronger than a N–I bond. In the situation here where we have a strong shared-shell character, the interactions with Br are therefore stronger than with iodine. The analysis of the critical points of the Laplacian under electric fields also shows an intermediate situation for bromine at all fields while with iodine, we move from the iodine on one side to the iodine on the other side.

**Steve Scheiner** asked: There is an extensive literature on proton transfers. One of the important elements is the p*K*'s of the pair of units, as well as the bond strength of the monomers. How much energy would it take to pull the Br off? In proton language, they talk about p*K*'s, could an analogous description be used here? For each molecule, on the left and right how much energy does it take to pull the Br off, as in an ionisation? You could then compare the energy of the left and right units, this may give you some way of thinking about why the Br behaves differently than the I.

**Marc Fourmigué** replied: This is a very good suggestion. Such calculations can be performed indeed.

**Timothy Clark** commented: The dominant energy is the ion pairing energy (see ref. 1), it may be that Janet Del Bene is right that the size effect could be large. However, the difference in size between bromine and iodine is surprisingly small.

Steve Scheiner's suggestion is very relevant but we must also take the electrostatic attraction in the ion pair into account.

1 A. Alex, E. Hänsele and T. Clark, *J. Mol. Model.*, 2006, **12**, 621–629.

**Sergiy Rosokha** asked: What is the distance between N and N in the case of I and Br? Probably, it is smaller with the bromine atoms. Perhaps you have a stronger interaction in this case which results in a deeper well and put Br in the middle?

**Marc Fourmigué** replied: You are right, the distance between the two N atoms is indeed shorter in the Br derivative. When we compared different systems involving different pyridines, we observed that the N···N′ distance decreases as the ionic character of the interaction increases. Your question prompts us now to perform energy calculations of the system, depending on the halogen position.

**Sergiy Rosokha** said: Formation of the adducts which you observed requires, in most cases, breaking the N–Br or N–I bonds. This would suggest a substantial activation energy – unless it is attenuated by halogen bonding. Did you observe how fast this process is and how fast your adducts are forming?

**Marc Fourmigué** replied: We have not performed any kinetic studies. I believe however that, as you suggest, we have here a concerted mechanism with limited, if any, activation energy.

**Sergiy Rosokha** said: Did you observe some colour changes in the process of this interaction?

**Marc Fourmigué** answered: We do not observe any colour changes, at least in the visible. A UV-vis characterization should be done to see if anything happens in the UV range.

**Gareth Lloyd** asked: I see you did the crystal structure at 150 K. The temperature can affect where the hydrogen is, is there perhaps a temperature dependence on where your halogens are?

**Marc Fourmigué** responded: When performed at different temperatures, at least between RT and 100 K, the N···N′ distance does not vary at all. It should be seen indeed as a covalent bond rather than an intermolecular interaction.

**Gareth Lloyd** remarked: Do you think you could design a system where it could jump between the two binding atoms, like we see in hydrogen bond examples in the solid state?

**Marc Fourmigué** replied: It is an interesting question but rather challenging. We should conceive a system where the N···N′ distance should be fixed very rigidly, at a distance slightly above that of the system at equilibrium!

**Mate Erdelyi** commented: We studied such N–X–N complexes for about eight years, and have computed that 58 kJ $mol^{-1}$ is needed to move the I from its covalent N–I bond distance to the N–I distance in an N–I–N complex, whereas 42 kJ $mol^{-1}$ is needed for Br to be moved from its covalent N–Br bond to the N–Br distance in an N–Br–N complex.[1] We have seen that the covalent character of the N–X bond increases when going from iodine through bromine to chlorine and fluorine, whereas the bond strength decreases. Thus the bond strength is determined by Coulombic attraction, which is the largest in the N–I–N complex, and weaker in the N–Br–N complex, and even weaker in the N–Cl–N complex. The less covalent to stronger bond.

We have seen single well behavior for the N–I–N and N–Br–N complexes, a possibly dynamic single well (wide flat minimum) for the N–Cl–N, whereas static asymmetric character for N–F–N.[1] These complexes are highly similar to those shown here.

1 A. Karim, M. Reitti, A.-C. C. Carlsson, J. Gräfenstein and M. Erdelyi, *Chem. Sci.*, 2014, **5**, 3226–3233.

**Patrick Szell** commented: Have you tried making the chlorine analogue of your compound? The $^{35}Cl$ solid-state NMR would be an interesting probe to the electronic structure and may offer additional insights. Unfortunately, bromine-79/81 and iodine-127 may be too broad to observe by solid-state NMR.

**Marc Fourmigué** replied: We have not tried with chlorine, but we already encountered several problems with the *N*-bromosaccharin (NBSac), which is much more reactive than the *N*-iodo analog (NISac). Indeed, we brominated electron-rich pyridines such as the *para*(dimethylamino)pyridine in *meta* position using NBSac, a reaction which does not occur with NISac.

**Mathieu Branca** asked: Considering the problematic reactivity of the positions 3 and 5 of the pyridine, maybe you could protect these positions with methyl groups?

**Marc Fourmigué** responded: Yes, this is a good suggestion. We are actually pursuing this work using a very electron rich pyridine with occupied *meta* positions, namely the azajulolidine.

**Steve Scheiner** opened the discussion of the papers by Christer Aakeröy and Marc Fourmigué: Probably a comment for everyone: the hydrogen bond field evolved so that proton transfer became important, perhaps halogen bonding is ripe for something similar? Following on from Janet Del Bene's work, what does it take to get a halogen atom to transfer from one site to another? We could think about the factors for this and the barriers. If there is a small barrier, are we going to see the halogen statistically, somewhere in between where in reality the halogen is moving rapidly between the sites?

**Pierre Kennepohl** replied: I agree that the evolution of the H-bonding literature may presage an equivalent shift in focus from "structure" to "function", *i.e.* reactivity in this field. In some cases, the structure is the function, but more

generally it would be of great interest to consider halogen bonding more broadly. Although I am likely not the first to point this out, sigma-hole interactions are already prevalent in the literature and textbooks without them formally being identified as such. I would point to the classic $S_N2$ reaction (often the first reaction students learn about in any detail), which is nothing more than an interaction of a nucleophile with a sigma-hole. In cases where the leaving group is a halogen, it is formally an inverse halogen bond interaction that essentially initiates the concerted substitution process.

Cases of atom transfer reactions initiated through sigma-hole bonding interactions are situations where inherently the interaction between the electron donor and the electron acceptor must necessarily transition smoothly from being essentially a long-range weak electrostatic intermolecular interaction all the way through to being a fully formed covalent bond. In the end, in all of these cases, we have to be able to transition through the full range of possibilities in this 3c4e bond to get from one extreme to another. For this reason, I would suggest that experimental and theoretical studies on the nature of reactions such as those described by Marc Fourmigué, Janet Del Bene, and Sergiy Rosokha during this meeting, will be extremely important moving forward.

**Sergiy Rosokha** replied: It seems that at least in some cases, barriers and kinetics of halogen atom transfer could be accounted for (similar to the proton transfer) by application of the electron-transfer formalism. Specifically, such an approach worked well for the interaction of the bromosubstituted aliphatic electrophiles with iodide anions which we described earlier.[1] In these systems, electron transfer from iodide (halogen bond acceptor) to the strong brominated electrophile is accompanied by the concerted dissociation of C–Br bond and formation of Br–I bond, *i.e.* bromine atom transfer. This process occurs within halogen-bonded complexes and its barrier is decreased by the strong electron coupling of electrophile and iodide. Most notably, the barrier for this reaction evaluated using electron-transfer two-state model in which electronic coupling was determined from the spectral and structural characteristics of the halogen-bonded complexes using the Mulliken–Hush formulation was consistent with the kinetics of the process measured experimentally.

1 S. V. Rosokha and A. Traversa, *Phys. Chem. Chem. Phys.*, 2015, **17**, 4989–4999.

**Janet Del Bene** replied: If the barrier between two minima is small, the potential curve in that region will be relatively flat. This allows for movement of the halogen atom, and means that it is the vibrationally averaged structure that will be observed.

**Anthony Legon** replied: There is evidence of $F^+$ transfer from difluorine to trimethylamine on formation of the trimethylamine$\cdots F_2$ complex. On the other hand, the complex of ammonia with $F_2$ is very weak and shows no evidence of $F^+$ transfer. There is also evidence of partial Cl+ transfer in the complex of trimethylamine with ClF.[1–3] This parallels the identification of gradual proton transfer along the series $(CH_3)_3N\cdots HX$ from X = F to X = I to $(CH_3)_3N\cdots HI$. By the time $(CH_3)_3NH^+\,I^-$ is reached the proton is almost completely transferred even in the gas phase.[4]

1 H. I. Bloemink, S. A. Cooke, J. H. Holloway and A. C. Legon, *Angew. Chem., Int. Ed.*, 1997, **36**, 1340–1342.
2 H. I. Bloemink, J. H. Holloway and A. C. Legon, *Chem. Phys. Lett.*, 1996, **254**, 59–68.
3 C. Domene, P. W. Fowler and A. C. Legon, *Chem. Phys. Lett.*, 1999, **309**, 463–470.
4 A. C. Legon, *Chem. Soc. Rev.*, 1993, **22**, 153–163.

**Jane Murray** commented: This is certainly an interesting point to consider. Some work along these lines has been done, *e.g.* by Grabowski. We believe that this can be addressed in terms of the electric fields and polarizabilities of the participants (note that these are both physical observables). One could also invoke ionization energies (another physical observable) since it is well established that these often vary inversely to polarizabilities. We have discussed some of this in ref. 1 and 2.

1 J. S. Murray, P. Lane, T. Clark, K. E. Riley and P. Politzer, *J. Mol. Model.*, 2012, **18**, 541–548.
2 J. S. Murray and P. Politzer, *Theor. Chem. Acc.*, 2012, **131**, 1114.

**David Bryce** asked: I wanted to mention a paper by Shing Ho *et al.*[1] where he discusses a reverse hierarchy for bromine and iodine halogen bonds in DNA junctions. I am not sure if this is relevant to the reversal that you have observed, but could you comment on this?

1 M. Carter, A. R. Voth, M. R. Scholfield, B. Rummel, L. C. Sowers and P. Shing Ho, *Biochemistry*, 2013, **52**, 4891–4903.

**Marc Fourmigué** responded: Looking at the paper that you suggested,[1] I have noted that in their conclusions the authors state "*We find that bromine has the optimal balance between enthalpic and entropic energy components, resulting in the lowest free energy for X-bonding in this DNA system. The X-bond formed by iodine is more enthalpically stable, but this comes with an entropic cost, which we attribute to crowding effects. Thus, the overall free energy of an X-bonding interaction balances the stabilizing electrostatic effects of the σ-hole against the competing effects on the local structural dynamics of the system.*" We come back again to the question of Janet Del Bene related to the effect of the size of Br *vs.* I. Clearly here in these constrained biomolecular systems, the size plays an important role through the entropic effect.

1 M. Carter, A. R. Voth, M. R. Scholfield, B. Rummel, L. C. Sowers and P. Shing Ho, *Biochemistry*, 2013, **52**, 4891–4903.

**Mark Taylor** commented: It seems that the extract that David Bryce mentioned was referring to a free energy change, for a relatively complex system in aqueous solvent. This may not be a direct reflection of the strength of the halogen bond.

**David Bryce** answered: Yes, Mark Taylor is correct. It is my understanding that Shing Ho noted a reversal in free energy, not in bond enthalpy.

**Pierre Kennepohl** remarked: Referring back to the earlier question regarding the analogy with hydrogen bonding dynamics. Although you have a single potential well in the solid state system, this is likely an artefact of having a fixed N–N distance in the solid state structure. In solution, your systems may be well designed to observe halogen transfer from one molecule to the other. Therefore I

think it would be interesting to look at these molecules in solution and investigate the halogen transfer reactivity.

**Alison Edwards** commented: I am struck by the use of the word "anomalously". I have looked at some structures where the Br was considered "anomalous" but in my case with respect to similarity to distance to comparable Cl. Charge effects, bonding and distance are often surprising but the application of the term anomalous often serves to delineate what we do not know about the system. We hold expectations about the variations in separations which are not fulfilled and this then demonstrates shortcomings in the model.



**Janet Del Bene** answered: I think the word anomalous is anomalous. When we use this word we mean that we see something that we did not expect, which means we do not understand everything that is going on. So anomalous things broaden our understanding. I agree with Alison Edwards that it is not really anomalous, just unexpected. There is a statement by Einstein that says "*if we knew what we were doing, it wouldn't be called research*".

**Steve Scheiner** asked Marc Fourmigué: Regarding the distance between the two N atoms and proton transfers. As the proton is moving from one molecule to the other, the heavy atoms are far apart. As the proton is at the mid-distance, the heavy atoms shrink together. They then move apart again as the proton moves further along. Do you see something similar?

**Marc Fourmigué** responded: We have not looked at this from this perspective in this system but it is a very good suggestion. If you look at the evolutions with the *N*-iodosaccharin and various pyridines,[1] we note indeed that the N···N' distance decreases as the system becomes more ionic.

1 O. Makhotkina, J. Lieffrig, O. Jeannin, M. Fourmigué, E. Aubert and E. Espinosa, *Cryst. Growth Des.*, 2015, **15**, 3464–3473.

**Chantal Mustoe** asked: To return again to the fact that bromine is often an anomaly in the trends observed, we have recently done some work in collaboration with the Berlinguette group at the University of British Columbia[1] which showed that in systems with chloride as the halogen bond acceptor, a higher degree of covalency was observed when bromine was the halogen bond donor than when iodine was the halogen bond donor. We attributed this discrepancy to a better orbital overlap between Br and $Cl^-$ than I and $Cl^-$. Perhaps this could also be the case with your systems?

1 F. G. L. Parlane, C. L. Mustoe, C. Kellett, S. J. Simon, W. B. Swords, G. J. Meyer, P. Kennepohl and C. P. Berlinguette, *submitted*.

**Saman Alavi** commented: The work studied single "halide" transfer between donor and acceptor species, namely, A–X···B → A···X–B. The analogy to proton transfer between two bases was mentioned in the discussions, (A–H···B → A···H–B).

There are double hydrogen bonded systems, such as the well known diacid and DNA base complexes. Concerted double proton transfer can occur and has been

characterized in these complexes. There may be a possibility of designing double halogen bonded complexes where each molecule acts as a halogen bond donor and acceptor. This could lead to some interesting structural properties in the resulting complexes.

**William Pennington** opened a general discussion of the paper by Valentina Dichiarante: Have you compared the solid state properties as a function of the ionic liquid cation, and different chain lengths?

**Valentina Dichiarante** answered: Liquid crystalline behavior in these complexes was achieved only when ethyl-methyl-imidazolium iodide was used as halogen bond acceptor. Imidazolium iodides with longer alkyl chains gave crystals more easily, but did not afford liquid crystals (which were our targets).

**Catharine Esterhuysen** asked: Long chain systems are known to have an odd/even effect on the packing. Most of your compounds contain even-length chains, have you considered looking at odd-length chains to see if that affects the packing and properties of the liquid crystals?

**Valentina Dichiarante** responded: The main aim of our work was to combine liquid crystallinity, ionic character and photoresponsivity – by means of halogen bonding – in a unique platform, which must be a room temperature ionic liquid, showing at the same time thermotropic LC behavior and light-induced phase transitions. To achieve this goal, we selected synthons that already proved successful in our previous papers and exploited the supramolecular modular approach to join their different functionalities in one single material. Up to now, the only two complexes that fulfilled all these requirements were obtained from 1-ethyl-3-methyl-imidazolium iodide, whereas longer-chain derivatives were used only to get single crystals for structural confirmation of XB and stoichiometry. Hence, we did not study odd-length chains or look for possible odd/even effect in our systems. This could surely represent a further upgrade for future optimization, although we do not expect huge effects on their properties.

Indeed, only a very few cases of ILs or ILCs with odd number alkyl chains are reported in the literature. For 1-alkyl-3-methyl-imidazolium tetrafluoroborates with less than 10 carbon atoms, for example, there is no overall difference in transition behaviour between odd and even chain lengths. For this reason, there seems to be no advantage in preparing the more expensive odd-chain length compounds. A small odd/even effect was observed in the melting points: odd-chain length compounds have melting points which are about 10 °C higher compared to those of their even-length neighbours. This is due to the deviation of the even chains from the linear all-*trans* configuration found for odd ones.[1] On the other hand, melting points of 1-alkyl-3-dodecyl-imidazolium bromides with even chains are reported to be higher than their immediate neighbours with odd lengths.[2]

1 J. D. Holbrey and K. R. Seddon, *J. Chem. Soc. Dalton Trans.*, 1999, 2133–2139.
2 M. Yang, B. Mallick and A.-V. Mudring, *Cryst. Growth Des.*, 2014, **14**, 1561–1571.

**David Bryce** asked: Are there any plans, or is it feasible, to explore the same sort of behaviour and structures using some of the other interactions we have discussed at this meeting (*e.g.*, tetrel, chalcogen, pnictogen bonds)? Or perhaps the required functional groups are not stable in solution for these applications? What are the pros and cons of moving away from halogen bonds to these other types of interactions?

**Valentina Dichiarante** responded: In principle, all these noncovalent interactions may be exploited to induce the self-assembly of non-mesomorphic building blocks into supramolecular photoresponsive ionic liquid crystals, even if up to now we have focused only on halogen bonds. Although the use of such interactions in functional materials is still quite limited, recent literature reports showed for example the potential of chalcogen bonds for anion transport applications.[1]

Undoubtedly, shifting from halogens to other elements will require optimization of several issues. First, the synthesis of properly tailored starting synthons (containing complementary donor and acceptor sites, ionic segments and a photoresponsive unit, at the same time) might be quite challenging. Furthermore, different geometrical constraints due to the choice of different bond donor atoms are expected to deeply influence the directionality of the resulting supramolecular mesogens. The presence of two sigma-holes on sulfur atoms, for example, would lead to a quite small angle between the deriving chalcogen bonds, with possible detrimental effects on the alignment of ionic channels and on the liquid crystalline properties of the complexes. The stoichiometry of the resulting complexes is also likely to change, and this will require to optimize again the molar ratios between the starting synthons. Finally, the thermal stability of these noncovalent assemblies may change significantly according to the nature of the interacting elements, creating additional problems if their mesogenicity is lost during phase transitions.

1 S. Benz, M. Macchione, Q. Verolet, J. Mareda, N. Sakai and S. Matile, *J. Am. Chem. Soc.*, 2016, **138**, 9093–9096.

**Angshuman Roy Choudhury** asked: On your structure slide (and Fig. 2 of your paper) showing the parallel packing, where are the imidazoles located? Are they in the ionic chain? My comment is about the imidazoliums with long chain. Ionic liquids with alkane chains with an odd number of C atoms are often more difficult to crystallise than those with an even number of C atoms. So I suspect that if you use an odd number of C atoms in the chain then you may have liquid crystalline properties but it will likely not crystallize, it would possibly go to a glass phase from the liquid crystalline state.

**Valentina Dichiarante** responded: The complexes that we were able to crystallize had six molecules in the asymmetric unit, two molecules of the imidazolium salt and four molecules of the XB donor (azocompound), respectively. The overall crystal packing was stabilized by segregation occurring between the charged and uncharged molecular fragments. Two distinct zones were visible in the adducts: a neutral area formed by the hydrocarbon moiety of the azobenzene and the alkyl tail of the imidazolium ring, and an ionic layer derived from the positively charged imidazolium ring and the iodide anion.

Concerning your comment, it is known that liquid crystals are flexible and mobile systems, that tend to crystallize in a waxy state with low degree of crystallinity. Changing the length of the imidazolium alkyl chain is surely a good strategy to affect their crystalline behavior. Actually, the main target of our paper was to find the best combination between ionic liquid crystalline properties and photoresponsivity of our adducts, in order to control phase transitions and ion alignment through light. Our attempts to grow single crystals simply aimed at elucidating the supramolecular organization of the LC complexes, confirming the driving role of halogen bonding and the stoichiometry seen in DSC measurements. For these reasons, we did not perform a systematic study on this topic yet, although future work will surely be planned to tune the phase behavior of our LCs.

**William Pennington** asked: Have you looked at systems in which the hydrocarbon chains have been replaced by perfluorocarbon chains?

**Valentina Dichiarante** replied: We have previously reported ionic LCs based on iodo-perfluoroalkanes.[1] In this previous paper, our group reported unconventional ionic liquid crystals, whose LC behavior was enabled by halogen-bonded supramolecular anions $[C_nF_{2n+1}\text{-}I\cdots I\cdots I\text{-}C_nF_{2n+1}]^-$ acting as rigid rod-like calamitic units. These unique materials were the first examples of ionic, halogen-bonded, imidazolium-based liquid crystals, in which liquid crystallinity was not driven by the cation's alkyl chains. It is also important that some of these complexes were mesomorphic even at room temperature, and may pave the way towards the design of totally new liquid-crystalline materials, as attractive platforms for novel functional materials.

1 G. Cavallo, G. Terraneo, A. Monfredini, M. Saccone, A. Priimagi, T. Pilati, G. Resnati, P. Metrangolo and D. W. Bruce, *Angew. Chem., Int. Ed.*, 2016, **55**, 6300–6304.

**William Pennington** commented: You indicated that chains with an odd number of carbon atoms did not crystallize well. Do you think that adding an oxygen into the chain would help, or would the flexibility be too plasticizing?

**Valentina Dichiarante** replied: The aim of our work was to obtain supramolecular room temperature ionic liquids with simultaneous liquid crystalline properties and photoresponsive behavior. Crystallization of two model complexes was done only to confirm the presence of the halogen bond.

**Alison Edwards** asked: If I am understanding you, you are using the liquid phase and getting crystals by cooling. Have you tried growing the crystals from a suitable solution? What about the odd-chain length molecules?

**Valentina Dichiarante** answered: Not exactly. The aim of our work was to obtain supramolecular room temperature ionic liquids with simultaneous liquid crystalline properties and photoresponsive behavior, so that we can drive phase transitions (and thus control ion channel alignment) through light. We mixed solutions of the starting (non-mesomorphic) building blocks in the proper stoichiometric ratio and evaporated the solvent under vacuum to get halogen-bonded complexes. Two of them were smectic liquid crystals. By irradiation with UV light

we were able to induce a liquid crystal-to-isotropic transition, whereas to go back (from isotropic to crystal phase) we had to cool the sample.

Single crystals were obtained from the same solutions by slow solvent evaporation, with the only purpose to confirm the presence of the halogen bond in our complex and the molar ratio between the starting azobenzene and imidazolium salt.

**Alison Edwards** commented: I would suggest going to very low temperature to crystallise from solution.

**William Pennington** asked: Do all the various methods of preparing your samples give the same phase?

**Valentina Dichiarante** replied: Yes. The complexes can be obtained by solution phase method or direct melting of the starting building blocks.

**Jan-Constantin Christopherson** said: I was wondering if upon irradiation to form the *cis*-isomer, you observe evidence that halogen bonding is presented, or would you surmise that the change in geometry has caused the halogen bond to separate?

**Valentina Dichiarante** responded: At the moment, we do not have a direct proof that XB is present after irradiation. Anyway, our previous study[1] showed that a nematic LC complex irradiated at 110 °C became isotropic, but after the light radiation was ceased, the LC phase was restored. Since the starting building blocks are not liquid crystalline, whereas the resulting complex is liquid crystalline, we think that XB survives during irradiation. The observed phase transition is due to the conformational change of the azobenzene, whose *cis*-isomer is unfavorable for mesogens alignment, but does not destroy the halogen-bonded complex.

In another experiment which we reported in the same paper,[1] the same complex (melting point = 95 °C) was irradiated at 90 °C (as a crystalline solid) and became isotropic. After illumination ceased, the backward isotropic-to-crystal transition occurred, showing an intermediate LC phase. This observation further confirms the presence of the halogen bond during phase transitions, since only the supramolecular complex is liquid crystalline.

1 F. Fernandez-Palacio, M. Poutanen, M. Saccone, A. Siiskonen, G. Terraneo, G. Resnati, O. Ikkala, P. Metrangolo and A. Priimagi, *Chem. Mater.*, 2016, **28**, 8314–8321.

**Jan-Constantin Christopherson** asked: Did you perform any measurements to see how long the *cis* configuration remained, or was the change back to *trans* instantaneous? Despite the long lifetimes of the *cis*-form of these fluorinated azobenzenes, I would anticipate that, given the elevated temperatures (60 °C), the azobenzene may switch back quite quickly.

**Valentina Dichiarante** answered: Previous measurements[1] performed by our collaborators in Finland on the $\mathbf{AZO_{OC10}}$ compound showed that its thermal relaxation was exponential and had a half-life of *ca.* 51 s at 110 °C (while the half-

life at room temperature in a dilute DMF solution was *ca.* 12 days). Unpublished data on the $\mathbf{AZO_{OC12}}$ derivative showed that it has a lifetime of almost 13 days at 20 °C, so that single crystals of its *cis*-isomer could be isolated.

It is also reported in the literature that fluorination of benzene rings in azo-compounds stabilizes the *cis*-isomer.[2]

Although we do not have data at the moment on $\mathbf{AZO_{OC12}}$ at 60 °C, it is highly probable that after irradiation stops, it will go back to the more stable *trans*-form quickly (perhaps in a few minutes). By simple irradiation, we have not so far been able to control the system, which is bistable.

1 F. Fernandez-Palacio, M. Poutanen, M. Saccone, A. Siiskonen, G. Terraneo, G. Resnati, O. Ikkala, P. Metrangolo and A. Priimagi, *Chem. Mater.*, 2016, **28**, 8314–8321.
2 D. Bléger, J. Schwarz, A. M. Brouwer and S. Hecht, *J. Am. Chem. Soc.*, 2012, **134**, 20597–20600.



**Tomislav Friščić** opened a general discussion of the paper by Gareth Lloyd: Has anybody looked at the crystal structure prediction for phenylalanine?

**Gareth Lloyd** answered: We have indeed done this in collaboration with Graeme M. Day of Southampton University, UK, and published our results in the *Cryst. Growth Des.* special issue celebrating the contributions of Professor Bill Jones to Organic Solid-State Chemistry during his productive career. There are two key things to note from the crystal structure prediction, the structural landscape is complex with a number of polymorphs possible and that the hydrate is thermodynamically more stable than the known pure phases. Even though we are limited to $Z' = 1$ and 2, Graeme was still able to find all the polymorphs known to date, including the high energy empty phase of the hydrate forms.

1 K. P. Nartowski, S. M. Ramalhete, P. C. Martin, J. S. Foster, M. Heinrich, M. D. Eddleston, H. R. Green, G. M. Day, Y. Z. Khimyak and G. O. Lloyd, *Cryst. Growth Des.*, 2017, **17**, 4100–4109.

**Tomislav Friščić** asked: About phenylalanine, is this structure somehow special amongst other amino acids, forming hydrates?

**Gareth Lloyd** replied: The other amino acids do form hydrates quite regularly, so I would say phenylalanine is not special. In fact, it was only recently that the complete set of anhydrous crystal structures were determined for all the "common" 20 amino acids.[1]

1 P. A. Williams, C. H. Hughes and D. M. Harris, *Angew. Chem., Int. Ed.*, 2015, **54**, 3973–3977.

**William Pennington** asked: You are using sonication to induce gel formation. Have you ever tried using an inkjet printer to inject one reactant into the other? Sonication of amphiphilic molecules has traditionally been used to induce formation of liposomes, and we and others have found that this inkjet technique works better. Recently, we have replaced the inkjet with an air brush to inject a solution of the amphiphiles into water, with similarly good results.

**Gareth Lloyd** replied: That is a very good idea. We have not utilised these particular phenylalanine gels in these techniques as they have a temperature

based setting mechanism, making the procedure technically difficult. However, there are specific examples in industry where pH triggers are being used. Inkjet printing onto paper can certainly benefit from instantaneous gelation on contact with paper to help fix colour on printed paper better. In this case, the paper is slightly acidic allowing for the gelation through a pH change mechanism. 3D printing of cell growth media is certainly making use of printing technology, in most cases, the gelation trigger is chemical in nature, for example, uses Ca, or other metals, binding to cause crosslinking.

**Chantal Mustoe** commented: In your paper you said that the phenylalanine gels with F/Cl substituents have faster exchange dynamics at the fibre/solution interfaces. Are fast exchange dynamics at the gel/liquid barrier preferable and what are the potential applications of changing the rate of exchange?

**Gareth Lloyd** replied: Dynamics are definitely of interest. Mostly as these dynamic assemblies can be utilised as biological mimics and in applications as materials within industry. Properties such as self-healing, disassembly, and sensing are dependent on the dynamics of the gel assemblies. For self-healing, faster exchange would be preferred, but on the other hand, depending on the requirements of the materials, dynamics for disassembly (drug delivery for example) may be needed to be slower. As a research field, we are currently interested in making mimics of biological tissues in which the self-assembly and disassembly are controlled (mostly through enzymatic action and phosphorylation/dephosphorylation). It is often out-of-equilibrium, *i.e.* energy is required in either the self-assembly or disassembly. The dynamics of the gels would, therefore, be very important to enable chemical functionality to be "reacted" on or not, and energy utilised in the supramolecular constructs. Our interest in the phenylalanine dynamics is to utilise this as a means to disassembly the gel fibres, or prevent their formation, allowing for prevention of tissue damage in phenylketonuria.

**Chantal Mustoe** remarked: In your paper you say that there is a stepped change with the addition of Br and I substituents when compared to the F and Cl substituents resulting in the gels becoming metastable. Do you think that this change is simply due to the fact that Br and I are so much larger or is there something else going on?

**Gareth Lloyd** responded: This is an excellent point. I think the stepped change is probably a combination of both the strength of the interactions and size. We do have examples of other substitutions that are size based (methyl group) and in those cases, we do see some considerable differences in the hydrogels but not so much in the DMSO gels.

**Chantal Mustoe** asked: Would you not expect the halogenated FMOC phenylalanine gels to behave differently from the halogenated phenylalanine gels as a result of the bulky FMOC group?

**Gareth Lloyd** replied: Definitely. The FMOC series, and related gelators from, for example the work of Dave Adams,[1–3] have self-assembly in water that is

dominated by the amphiphilic character. The FMOC aromatic groups tend to π-stack and this is the predominate interaction compared to the phenylalanine structures that are electrostatic in nature. There is actually a recent paper by Metrangolo and coworkers that we cite in the paper that shows this well.[4] In this paper, the halogenation of FMOC-phenylalanine results in strong interactions not seen in phenylalanine and does not disrupt gelation in the same way, *i.e.* the iodo-FMOC-phenylalanine version gels whereas 4-iodophenylalanine does not.

1 D. J. Adams, M. F. Butler, W. J. Frith, M. Kirkland, L. Mullen and P. Sanderson, *Soft Matter*, 2009, **5**, 1856–1862.
2 L. Chen, K. Morris, A. Laybourn, D. Elias, M. R. Hicks, A. Rodger, L. Serpell and D. J. Adams, *Langmuir*, 2009, **26**, 5232–5242.
3 J. Raeburn, A. Z. Cardoso and D. J. Adams, *Chem. Soc. Rev.*, 2013, **42**, 5143–5156.
4 A. Pizzi, L. Lascialfari, N. Demitri, A. Bertolani, D. Maiolo, E. Carretti and P. Metrangolo, *CrystEngComm*, 2017, **19**, 1870–1874.



**Alison Edwards** asked: Have you looked at solid state NMR of the crystals and in particular, have you done 2D exchange experiments looking at the two molecules for ring flips? Following on from this, what aspects of the gel do you consider to be dynamic, what do you think is moving?

**Gareth Lloyd** replied: It is certainly something we have thought of doing. However, the experiments are quite time-consuming and we would be performing them on the gels. So it is part of our plans for further experiments to do in the future. In terms of dynamics, we have been investigating the dynamics of the movement between the solid, interface and solution. However, we have not characterised the dynamics within the crystals and how this may affect the dynamics we have explored.

**Alison Edwards** commented: In the crystalline materials with nicely resolved multiplicity, there should be no difficultly to observe the ring flips which would be invisible to X-ray (or indeed any diffraction method). I have some previous papers on this. Characterising the aromatic groups at the surface based on the ring flips[1,2] and exchange for 2-fold symmetric substituents, substantial molecular dynamics can occur completely unobserved in the crystalline state if the net motion creates no disorder.[3] Early attempts at assigning protein NMR spectra proposed using the presence of ring flips to identify aromatic residues at the surface of a globular protein because it was thought that such motions could not occur in the interior of proteins where the packing density was like that of a small molecule crystal. When this was found to be incorrect, Chris Dobson flipped the proposal and asked "who has ever looked to see if ring flips occur in small molecule crystals?" If you have 2 site exchange you can have substantial dynamics which could potentially be invisible to the diffraction methods.

1 J. Fattah, J. M. Twyman, S. J. Heyes, D. J. Watkin, A. J. Edwards, K. Prout and C. M. Dobson, Combination of cross polarization/magic angle spinning NMR and X-ray crystallography: structure and dynamics in a low-symmetry molecular crystal, potassium penicillin V, *J. Am. Chem. Soc.*, 1993, **115**(13), 5636–5650.
2 M. Wendeler, J. Fattah, J. M. Twyman, A. J. Edwards, C. M. Dobson, S. J. Heyes and K. Prout, Combination of CP/MAS NMR spectroscopy and X-ray crystallography: structure and dynamics in molecular crystals of hydrogen, lithium, sodium, rubidium, and cesium penicillin V, *J. Am. Chem. Soc.*, 1997, **119**(41), 9793–9803.

3 A. J. Edwards, N. J. Burke, C. M. Dobson, K. Prout and S. J. Heyes, Solid state NMR and X-ray diffraction studies of structure and molecular motion in ansa-titanocenes, *J. Am. Chem. Soc.*, 1995, **117**(16), 4637–4653.

**Gareth Lloyd** responded: The is great information to have, and I thank you for bringing this up. Work has been done on the phenylalanine·HCl crystals[1] and it is definitely the case that dynamics within crystals are important to know when it comes to some of the behaviour seen in them. And highlights what we think of modern crystals, they are not the "molecule cemetery" that is often quoted, but rather dynamic systems with interfaces that are constantly changing and the molecules within crystals often have significant motion.

1 W. Li and A. E. McDermott, *Concepts Magn. Reson., Part A*, 2013, **42A**, 14–22.

**Steve Scheiner** opened a general discussion of the paper by Tomislav Friščić: This may be an ambitious sort of question but can you explain why you get the structures that you do, what intermolecular forces might be dominating?

**Tomislav Friščić** answered: The predicted structures should correspond to a minimum of crystal and molecular energies. Structural motifs, *i.e.* particular orientations or arrangements of molecules (or ions) are usually a result of more directional forces, while the overall stability is usually determined by the large number of weaker, "van der Waals" type of interactions. But, as I am not an expert, maybe a better and more informative reference would be a review by Graeme Day entitled "Current approaches to predicting molecular organic crystal structures".[1]

1 G. M. Day, *Crystallogr. Rev.*, 2011, **17**, 3–52.

**Jane Murray** said: Your cradle stacking is very interesting. In the *cis* position, you should have accessible negative regions of electrostatic potential associated with the two azo nitrogens. Then the phenyl rings with the F's should have positive regions above and below them. This could be a very simple explanation for what you observe.

**Tomislav Friščić** answered: Indeed, I fully agree with your comment, and it provides an elegant and simple explanation of the stacking motifs found in structures of perfluorinated *cis*-azobenzenes. It has indeed also been confirmed by electrostatic potential calculations – for more information see ref. 1. This is, in our view, an interesting new motif to explore in crystal engineering and we continue active work on it.

1 O. S. Bushuyev, A. Tomberg, J. R. Vinden, N. Moitessier, C. J. Barrett and T. Friščić, *Chem. Commun.*, 2016, **52**, 2103–2106.

**Gareth Lloyd** commented: In the examples of the stacking of the azo groups one on top of each other – what happens when the azo compounds become asymmetric across the azo group?

**Tomislav Friščić** responded: This is something that we have not yet investigated, although we are starting to look into systems that are non-symmetrical across the azo moiety.

**Gareth Lloyd** commented: In terms of the *trans* structures, if they are not symmetric do you think it will still give you your dichroism?

**Tomislav Friščić** answered: Yes, I believe that dichroism should be observable, as long as the azo chromophores are aligned in parallel throughout the structure.

**Angshuman Roy Choudhury** commented: The packing of *trans* azobenzenes with symmetric substitution on either side follows a symmetric packing while the un-symmetrical ones have different way of packing. It is difficult to make and purify them. We have a few unsymmetrical halogen substituted azobenzenes, which I could send you for your experiments.

**Tomislav Friščić** answered: Thank you for your interest – we are looking forward to collaborating with you on this topic.

**Pierre Kennepohl** remarked: I am intrigued by the potential behaviour of these species under an applied magnetic field. I would expect some circular dichroic behaviour from the Au complex and therefore you might get interesting non-linear behaviour due to communication between the two components of the system. A relatively small field (1–2 Tesla) should be sufficient to probe this effect. Daniel Leznoff (at Simon Fraser University) would be a good person to talk to about this.

**Tomislav Friščić** responded: Thank you for the comment – it is very much spot-on. Our use of dicyanoaurate(I) anions is actually inspired by the work of the Leznoff group. The suggestion of looking for non-linear behavior in a magnetic field is intriguing and we would be definitely interested to look into this.

**William Pennington** commented: For compound **1**, with three crystallographically unique 15-crown-5 molecules, in which one is "empty" and the other two are associated with a potassium cation, is it possible to do a solid-state ion exchange of the cations?

**Tomislav Friščić** replied: This is an interesting question – we have not yet attempted to do such an experiment, but I feel it would be interesting and worthwhile.

**William Pennington** asked: Rather than sequestered metal cations, we have been using methyltriphenylphosphonium cations for crystallization of iodide-organoiodine hybrid salts. These cations often stack in columns, which might lead to parallel alignment of your azobenzene chromophores.

**Tomislav Friščić** replied: Thank you for your suggestion – I would really need to check on your previous work, and see how it might help us guide further studies – thanks!

 

**Ngong Kodiah Beyeh** commented: You said that you used the 15-crown-5 ether just to fish out the sodium cation. Is that the only role of the 15-crown-5 or does it play any additional roles?

**Tomislav Friščić** replied: Adding 15-crown-5 enabled the synthesis of the cocrystal salt, as just $K[Au(CN)_2]$ was non-reactive, presumably due to higher stabilization of the salt structure composed of small ions. We also find that there are molecules of 15-crown-5 that are contained in the structure of the dichroic four-component crystal, but do not complex with $K^+$. This means that they probably act as a "space-filling" or "structure supporting" components to a crystal structure that might be composed of incongruent cations (*i.e.* $K^+$ complexed with 15-crown-5) and anions (polymeric, halogen-bonded metal–organic anions).

**Gareth Lloyd** asked Tomislav Friščić: You say the crown ether is "space-filling"? Did you manage to get a single-crystal-to-single-crystal emptying/exchange and/or porosity that would show that you can remove it and it is space filling? What does the TGA for this look like? Do you see a step loss of guests?

**Tomislav Friščić** answered: We have so far been unable to remove the crown ether molecule without disrupting the overall material structure. The analysis by TGA (shown in Fig. 6a of our paper) reveals that the material breaks down by heating in one single broad step, without any clearly resolvable steps that could be ascribed to any of the components.

**Lee Brammer** said: In reference to the discussion of TGA studies, presumably you lose the ether first from your crystals as it is volatile and much of the remaining content is either charged or of greater molecular weight.

**Tomislav Friščić** responded: The thermal decomposition of the four-component crystal seems to take place in one single and broad step (Fig. 6a of our paper), after which the weight residue seems to correspond to $K[Au(CN)_2]$ only.

**Steve Scheiner** opened the discussion of the papers by Valentina Dichiarante, Gareth Lloyd and Tomislav Friščić: I have a question for everyone. Protein chemists have gotten to the point where they say "here's a sequence of amino acids, guess what is the structure of the protein." Quantum chemists have also done something similar. Are crystal structure determinations getting to the point where you could be given a couple of molecules and predict the structure? Are we getting to this point for halogen bonded systems?

**Tomislav Friščić** answered: Indeed, I would argue that there has been much progress towards the goal of sketching a few molecules and then figuring out the potential crystal structures. Maybe the best insight into the state-of-the-art procedures is provided by the results of the most recent, the 6$^{th}$, test of crystal structure prediction, see ref. 1.

1 A. M. Reilly *et al.*, *Acta Crystallogr.*, 2016, **B72**, 439–459.

**Gareth Lloyd** responded: Crystal structure prediction has certainly worked in some circumstances. The recent blind test[1] had some compounds that contained chloride groups, so this is starting to be part of "routine" crystal structure prediction. As with protein structure prediction, there are caveats and difficulties that are recognised by the community. Strangely, the most common issue is "predicting" the correct conformations of organic compounds that are then imputed into the crystal structure prediction. This is often done in the gas phase and often highlights that the gas phase is very different to the liquid and solid state meaning calculations need to be altered to take this into account. Please see the report on the most recent blind test of crystal structure prediction run by the CCDC (Cambridge Crystallographic Data Centre). There is also a Faraday Discussion on this exact topic in 2018 (*Methods and applications of crystal structure prediction: Faraday Discussion*, 11–13 July 2018, Cambridge, United Kingdom, http://www.rsc.org/events/detail/24508/methods-and-applications-of-crystal-structure-prediction-faraday-discussion).

1 A. M. Reilly *et al.*, *Acta Crystallogr.*, 2016, **B72**, 439–459.

**Alison Edwards** said: I am going to disagree with you profoundly. The problem is not properly addressed. When you have determined a crystal structure you have determined one crystal structure. Polymorphism is very well known, even without adding the complications of potential solvates *etc.* as a further complication – it is inherently difficult to predict this, for example cholesterol has over 30 polymorphs. It is an intellectually interesting question for some systems to think about possible crystal structures, but even in well studied systems, it is a very different matter to actually make a material by design. A thought experiment about a particular proposed crystal packing you may want to make is certainly intellectually stimulating and potentially scientifically and commercially important, but suggesting that you might be able to predict all possible crystal structures seems to be a peculiar notion to pursue.

**Tomislav Friščić** responded: The methods of Crystal Structure Prediction (CSP) are not directed towards providing one single crystal structure. Instead, they provide an increasingly good overview of the landscape of crystal structures and molecular packing motifs that are available to a particular system. From such a selection of structures it is possible to identify potential polymorphs, but also structures of possible host frameworks in inclusion compounds.

**Gareth Lloyd** replied: Correct, predicting all crystal structures would be a notion beyond most people and is certainly not something that would be claimed by any. The crystal structure prediction is still a "best" guess of what the potential structures would be for a given molecule or set of molecules, as would be the original question/statement of the "prediction" of the folding of a protein.

**Angshuman Roy Choudhury** said: Again regarding structure prediction, we tried to co-crystallise fluconazole with different acids.[1] We ended up getting four new polymorphs but not salt structures. When we tried to crystallize fluconazole alone, we ended up getting the monohydrate always. So the presence of reactants/

impurities/solvents will change the nucleation process and hence will yield a new crystal structure, where the prediction will fail.

1 M. Karanam, S. Dev, and A. Roy Choudhury, *Cryst. Growth Des.*, 2012, 240–252.

**Jane Murray** commented: The molecule fluconazole lacks symmetry and has hydrogens on the triazole rings that are likely quite positive and a hydrogen on the centrally-located OH group also quite positive, as well as the hydrogens on the phenyl ring (less positive). The fluorines on the phenyl ring are not candidates for halogen bonding, as they are likely to have completely negative surface electrostatic potentials (with negative sigma-holes).

For many reasons, including those listed above, the molecule fluconazole has many options for crystallizing. This is in contrast to perfluorinated iodo-compounds which have very positive electrostatic potentials on the outer sides of the iodine atoms which often strongly dictate their patterns of crystallization.

Your comment that the presence of reactants/impurities/solvents will change the nucleation process is valid.

**Tomislav Friščić** said: CSP is aimed towards a particular chemical composition, and cannot be aimed towards parameters that might not be readily controllable, such as presence of impurities and moisture. However, CSP techniques will provide an insight into the polymorphic landscape of a compound, allowing the prediction of possible polymorphic forms. So, why we cannot predict which polymorph will form from a particular experiment (especially if the nature of the impurities, or overall conditions are not well known), one can gain a pretty good idea what structures are possible. Again, I would accompany this answer with a reference to the latest blind test of CSP.[1] Also, it is possible to use CSP techniques to address hydrate formation, and one interesting reference in that context is the paper by S. L. Price entitled "Which, if any, hydrates will crystallise? Predicting hydrate formation of two dihydroxybenzoic acids".[2]

1 A. M. Reilly *et al.*, *Acta Crystallogr.*, 2016, **B72**, 439–459.
2 D. E. Braun, P. G. Karamertzanis and S. L. Price, *Chem. Commun.*, 2011, **47**, 5443–5445.

**Gareth Lloyd** responded: You are totally correct in bringing this up. Crystal growth still occurs in very complicated environments, and the more complicated the environment the more difficult the prediction.

**Angshuman Roy Choudhury** addressed Tomislav Friščić and Gareth Lloyd: We have analyzed the structural features of fluorinated flexible amides, where the strong hydrogen N–H···O=C bond holds the molecules in a linear fashion with parallel molecules. But when then terminal fluorine starts to interaction through various weak C–H···F hydrogen bonds then the molecules connected by N–H···O=C hydrogen bonds get arrange in antiparallel direction. Hence a different structure is generated.

**Tomislav Friščić** answered: Thank you for this information, the role of organic fluorine in solid-state molecular assembly is still poorly understood and a fascinating topic.

**Janet Del Bene** addressed Tomislav Friščić and Gareth Lloyd: I would like to comment on the word "predict". Theoreticians sometimes use the word "predict" improperly. Prediction is easy when the answer is known, but if it is known, then what is being presented is not a prediction. Having said this, it seems to me that in most cases, it is easier for a theorist to predict since the systems of interest have fewer degrees of freedom compared to your systems. The challenge is to predict correctly.

**Tomislav Friščić** responded: I would agree, but one needs to start somewhere. It is maybe fairly easy to obtain a complex multi-component crystalline structure, but that is still a major challenge for crystal structure prediction. Still, the complexity of systems addressed by the blind tests of CSP has been steadily increasing over years and the latest one also included a 3-component hydrate structure.[1]

1 A. M. Reilly *et al.*, *Acta Crystallogr.*, 2016, **B72**, 439–459.

**Gareth Lloyd** answered: The degrees of freedom are a very important aspect of crystal structure prediction, and computationally it becomes increasingly difficult with the increase in degrees of freedom. In some cases, there has been crystal structure prediction of experiments that have not been performed. The blind tests are experiments that have been done but are not publically known. A recent paper from the Cooper and Day groups have done this successfully studying porous molecular solids.[1]

1 A. Pulido, L. Chen, T. Kaczorowski, D. Holden, M. A. Little, S. Y. Chong, B. J. Slater, D. P. McMahon, B. Bonillo, C. J. Stackhouse, A. Stephenson, C. M. Kane, R. Clowes, T. Hasell, A. I. Cooper and G. M. Day, *Nature*, 2017, **543**, 657–664.

**Steve Scheiner** addressed Tomislav Friščić and Gareth Lloyd: Following up on this then, as a quantum chemist, for structure prediction what can we contribute? The energy of interaction between two species in the gas phase, that is probably only of marginal use to you. What else could we be evaluating to help you with this?

**Tomislav Friščić** responded: Evaluation of the broad range of van der Waals interactions would probably be a very useful contribution. Honestly, a simple means of analyzing individual interactions and their contributions to the overall stability and structural motifs in a solid-state (crystalline or non-crystalline) system would be very useful.

**Gareth Lloyd** answered: Good accurate calculations are always important and understanding of intermolecular bonds and conformations of molecules are crucial parts of the calculations required for crystal structure prediction. The high-speed steps of crystal structure prediction use force fields that can often be "trained" to highly accurate interactions determined by quantum chemists.

**Angshuman Roy Choudhury** asked: For structure prediction, one starts with the optimized geometry for the molecule and then tries to fit it inside a given cell with a range of space groups. In the gas phase we always try to optimise the geometry. In my system with 4 polymorphs and 7 different of conformers,[1] we

calculated the energies of the conformers and these were widely different. Then my student optimized all the conformers, which reduced to two unique conformations, which were different in energy. It is not always true that the most stable conformer will give the most stable crystal structure. So, structure prediction will face problems in handling more flexible molecules with a large range of possible intermolecular interactions and structural chemists will always need to determine the real structure.

1 M. Karanam, S. Dev, and A. Roy Choudhury, *Cryst. Growth Des.*, 2012, 240–252.

**Tomislav Friščić** answered: Indeed, the crystal structure prediction protocols can be expanded to work with molecular conformations that do not represent a gas-phase minimum. It is not done very often, as it increases computational costs. The total energy of a crystal structure is considered a combination of molecular (*e.g.* conformational) and crystal energies. Maybe the following paper, in which a molecule adopting a conformation that is not a gas-phase minimum, would be of interest.[1] Still, I do not think that experimental chemists will be made obsolete any time soon!

1 A. M. Belenguer, T. Friščić, G. M. Day and J. K. M. Sanders, *Chem. Sci.*, 2011, **2**, 696–700.

**Gareth Lloyd** responded: Conformers are an important issue in crystal structure prediction, as you say, and there is always a need to explore much more than just the one conformer during the procedures. And this is and will continue to be, an important aspect and a limiting step in the procedures. These kinds of results show why we still need experimentalists and theoreticians. Neither can predict what will happen and we need both to explain what occurs in the majority of experiments and results known and that will come in the future.

**Janet Del Bene** addressed Tomislav Friščić and Gareth Lloyd: It may well be that an experimentalist may probe a local minimum on a surface. This means that theorists should look for local minima as well as the global minimum.

**Tomislav Friščić** responded: Indeed, crystal structure prediction is able to provide a range of structures, corresponding to different minima and that can be related to structural motifs found in inclusion frameworks or other polymorphs.

**Gareth Lloyd** responded: I totally agree, and this is an important issue in crystal structure prediction.

**Simon Cottrell** addressed Tomislav Friščić and Gareth Lloyd: Most of the systems that have been discussed at this meeting are multi-component systems. How much harder do you think crystal structure prediction is for multi-component systems than for single-component systems?

**Tomislav Friščić** responded: CSP becomes increasingly demanding with the number of parameters involved in the process, and the number of distinct (chemically or crystallographically) molecular species is one of them. However, CSP of multi-component crystals is possible. While I am not an expert on the

topic, I have seen that CSP has made very significant progress into prediction of multi-component structures, *e.g.* salts and cocrystals, as well as their stoichiometric compositions. Some information on these topics can be found in a review by G. M. Day[1] and one example of work focusing on multi-component crystals and CSP is by A. J. Cruz-Cabeza, G. M. Day *et al.*[2]

1 G. M. Day, *Crystallogr. Rev.*, 2011, **17**, 3–52.
2 A. J. Cruz-Cabeza, K. Shyam, L. Fábián, T. Friščić, G. M. Day and W. Jones, *Chem. Commun.*, 2010, **46**, 2224–2226.



**Gareth Lloyd** responded: It is much harder, mostly due to two reasons. The first is that the conformation of the molecules are each separately determined, yet they will influence themselves in the crystal structure meaning many more conformations need to be considered, and certainly not just the minima of the conformational energy landscape in vacuum. Secondly, the increase in any degrees of freedom makes the calculations increasingly more difficult and time consuming. As an example, the phenylalanine monohydrate structure is very difficult to predict. The way we did it was to look for low density phases that could "include" the water resulting in a prediction of the "empty" phase. In this case the phenylalanine monohydrate can be "emptied" to this high energy polymorph. It is certainly likely that it would be impossible to directly synthesise this polymorph directly and the kinetic pathway utilising the formation of the monohydrate and hemihydrate is required for formation.

**Angshuman Roy Choudhury** asked Tomislav Friščić: As you have seen dipole–dipole interaction in *cis* azobenzene, and noticed a probable N$\cdots\pi$ contact; we have also noted N$\cdots\pi$ contact in fluorinated bis-benzyledeneanilines, where the packing is by $\pi$-stacking and N$\cdots\pi$ interactions. Examples of similar interactions can be found in the Cambridge Structural Database.

**Tomislav Friščić** replied: This is very useful information, we will continue to explore N$\cdots\pi$ systems in the Cambridge Structural Database (CSD) and would appreciate any more details that you could provide us.

**Saman Alavi** addressed Tomislav Friščić and Gareth Lloyd: For crystal structure prediction, our knowledge of intermolecular forces are the weak point. The representation of dispersion forces between molecules is not very accurate and for example usually does not include polarisability and there is the problem of assigning model partial atomic charges for intermolecular interaction. There are a wide range of water force fields, for example, and if we cannot figure out a unified model for water, what hope is there for more complicated molecules with polarization, partial charge transfer, conformational changes, *etc.*? The first weakness in crystal prediction is describing the intermolecular interactions (intramolecular forces are fine and are well represented by quantum chemical methods). The second problem in crystal structure determination is how to pick out proper minima in the free energy landscape that represent the solid phase formed under the synthetic and pressure/temperature conditions of the experiment. You can have one structure representing one local free energy minimum and then change some conditions and then go to another local minimum. The

global free energy minimum may be very complex to find and the experimentally different conditions may drive it to one local minimum over the global minimum. Metadynamics or other methods can help to sample different local minima of the free energy surface and direct us to a global minimum, but if the intermolecular potentials are not good, then this will still be a barrier. Therefore the predictions for solid state structures may not represent what is seen experimentally. If you introduce a second component to the mixture and try to predict the structures of co-crystal materials, then you have increased problems.

**Tomislav Friščić** replied: CSP is a highly advanced area, and structures of multi-component systems, solvates, cocrystals and salts have already been addressed in previous work. I highlight the work of A. J. Cruz-Cabeza, G. M. Day *et al.*[1,2] as well as the work on the 5th and 6th blind tests of CSP which included a solvate, a salt, a cocrystal and – what might be most relevant for this question – a three-component crystal hydrate.[3,4]

1 A. J. Cruz-Cabeza, K. Shyam, L. Fábián, T. Friščić, G. M. Day and W. Jones, *Chem. Commun.*, 2010, **46**, 2224–2226.
2 A. J. Cruz-Cabeza, G. M. Day and W. Jones, *Chem. Eur. J.*, 2008, **14**, 8830–8836.
3 D. A. Bardwell *et al.*, *Acta Crystallogr.*, 2011, **B67**, 535–551.
4 A. M. Reilly *et al.*, *Acta Crystallogr.*, 2016, **B72**, 439–459.

**Gareth Lloyd** replied: We agree. Your statement represents and summarises some of the issues in understanding and predicting crystal structures.

**Saman Alavi** addressed Gareth Lloyd and Tomislav Friščić: In terms of general feasibility of a crystal structure prediction, if one can reproducibly do an experiment and get a unique structure then computationally we should be able to predict this. But if impurities will give other types of structures or mixtures, then it may be too much to ask to expect computational models to predict things.

**Tomislav Friščić** replied: The procedures of CSP are not directed towards detecting the one crystal structure, but instead they provide a wide range of potential crystal structures, that can be ranked according to their energy and a parameter that indicates how "reasonable" a structure is (most often, density). So, CSP protocols can give an insight into not only what the most stable structure might be, but also what the structural landscape of potential polymorphs – or even inclusion compounds – might be.

**Gareth Lloyd** responded: This is certainly one of the issues I think divides experimentalists and theoreticians. There is no such thing as a "clean" crystal or 100% pure phase. Therefore, what we often represent as a single or multi-component crystallisation is often much more complicated. Heterogeneous crystallisation is the norm, compared to homogeneous crystallisation and this is not easy to reproduce in calculations. Not that it is stopping people from trying. Elegant works from S. L. Price of University College London are excellent examples of this.[1,2]

1 J.-B. Arlin, L. S. Price, S. L. Price and A. J. Florence, *Chem. Commun.*, 2011, **47**, 7074–7076.
2 V. K. Srirambhatla, R. Guo, S. L. Price and A. J. Florence, *Chem. Commun.*, 2016, **52**, 7384–7386.