PAPER

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Towards the use of experimental electron densities to estimate reliable lattice energies

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We examine the reliability of lattice energies (and by inference, intermolecular interaction energies) estimated from experimental electron densities. Based on the modest number of results published to date, lattice energies obtained in this fashion typically overestimate more reliable values, sometimes by hundreds of kJ mol^{-1}. The causes of this behaviour are explored in detail, and include a misunderstanding of the contribution of the polarization energy, the failure to recognise the important link to a sublimation process, and the use of inappropriate atom–atom potentials to estimate dispersion and exchange-repulsion energies. It is hoped that this contribution will encourage further research of this nature, and a more critical evaluation of energies derived from high-quality diffraction experiments on molecular crystals.

Introduction

The computation of intermolecular interaction energies and lattice energies for molecular crystals is essential to the prediction of their structure, rationalization of relative stabilities, as well as gaining insight into a number of chemical and physical properties, and the calculation of organic crystal lattice energies with "chemical accuracy" remains a challenge.[1]

At the same time, modern experimental charge density studies on molecular crystals are increasingly focusing on materials and problems relevant to crystal engineering,[2] in particular studies of crystal polymorphism and related topics associated with molecules of pharmaceutical relevance. For example, recent studies have examined two conformational polymorphs of coumarin 314 dye,[3] compared molecular charge densities of piroxicam in its β-polymorph with that in the monohydrate,[4] explored the use of experimental electron densities to predict synthon formation in a 2 : 1 co-crystal of 4-hydroxybenzoic acid (4HBA) and 4,4′-bipyridine (44BP),[5] and attempted to rationalise the observed structure of the 1 : 1 co-crystal of paracetamol and 44BP.[6]

In a small – but important – number of these studies, intermolecular interaction energies and lattice energies are being reported, based ultimately on the classical electrostatic interaction between molecular charge densities derived by modelling of the experimental X-ray diffraction data. This work aims to highlight recent attempts of this kind, critically assess some of the results, identify overall trends and shortcomings of various kinds, and hopefully encourage further

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research of this nature by laying a solid foundation for future work.

Results and discussion

The intermolecular interaction energy

Before discussing published results, it is important to establish precisely what is meant by the interaction energy between molecules in a crystal, and its relationship to the charge distributions of the interacting molecules, especially in the context of experimental molecular electron densities. For the past 50 years or so (see, for example, ref. 7 and references therein) the interaction energy between two molecules has been conveniently expressed as a sum of several discrete terms, the main ones being electrostatic, polarization (or induction), dispersion and exchange-repulsion:

$$E_{tot} = E_{ele} + E_{pol} + E_{dis} + E_{rep} \tag{1}$$

The first term is the classical Coulombic interaction between the two unperturbed molecular charge distributions (electrons and nuclei), and it can be positive (de-stabilising) or negative (stabilising). The second term is also electrostatic in nature, being the energy lowering associated with the perturbation (polarization) of the electron density of each molecule by the other, and is always negative. The dispersion term arises from non-classical effects and is also always negative, while the last term is always positive (as its name implies), and arises from the overlap of the two molecular wavefunctions.

There are several important points to note when applying this expression to experimental charge density studies:

• Only the first two terms are accessible from the electron density of a molecule extracted from its crystal environment.

• The electron distribution of a molecule extracted from a crystal by modelling of experimental X-ray diffraction data necessarily reflects the perturbation due to its surrounding crystal environment. Because of this it is commonly assumed (and often stated emphatically) that the calculation of the electrostatic energy between two perturbed molecules yields the first two terms above, $E_{ele}(polarized) = E_{ele} + E_{pol}$. This is not true. Detailed analysis[8,9] has shown that it overestimates the 'true' electrostatic energy, and in fact $E_{ele}(polarized)$ is closer to $E_{ele} + 2E_{pol}$.

• There are many possible model electron densities that will provide only slightly different fits to the experimental observations, so any one that is chosen as the 'best' has associated systematic and random errors. Estimating the uncertainty of the experimentally-derived electrostatic energy is essential. Without an idea of the magnitude of this uncertainty, comparison with other results, experimental or theoretical, is compromised.

• E_{dis} and E_{rep} are typically estimated *via* an atom–atom potential, usually of exp-6 form, and commonly those due to Spackman[10] or Williams, Hsu and Cox.[11,12] This is an approximation, as the representation of dispersion and repulsion energies with atom–atom potentials depends intimately on whether the electrostatic energy is calculated accurately, or estimated from distributed atomic moments (see below).

Because the electrostatic energy is clearly the most important energetic quantity that can be derived from experimental charge density analysis, it is essential to fully appreciate the different ways in which this term has been calculated in practice – now, as well as in the past. To see these differences most clearly, note that the Coulombic interaction energy between two molecules A and B, with charge densities $\rho_A(r_A)$ and $\rho_B(r_B)$, is

$$E_{ele} = \iint \rho_A(r_A)\rho_B(r_B)|r_A - r_B|^{-1}dr_A dr_B \qquad (2)$$

These charge densities include point nuclear charges and continuous electron distributions, and they can be partitioned into atom-centred pseudoatoms, each consisting of a spherical atomic term including a nucleus (the promolecule) and a deformation term:

$$\rho_A = \sum_{i \in A}\left\{\rho_{A,i}^{atomic} + \Delta\rho_{A,i}\right\}$$
$$= \rho_A^{promolecule} + \Delta\rho_A \qquad (3)$$

The electrostatic potential of the promolecule is positive everywhere and relatively unstructured, and it is the deformation terms – which describe the redistribution of electron density on bonding – that give rise to the rich structure in the electrostatic potential. From this partitioning the product of molecular charge densities in (1) can be expanded to give

$$\rho_A\rho_B = \rho_A^{pro}\rho_B^{pro} + (\rho_A^{pro}\Delta\rho_B + \rho_B^{pro}\Delta\rho_A) + \Delta\rho_A\Delta\rho_B$$

and substituting this into (2) results in an expression like this for the energy:

$$E_{ele} = E_{ele}^{pro-pro} + E_{ele}^{pro-def} + E_{ele}^{def-def} \qquad (4)$$

Early attempts to calculate electrostatic energies from experimental electron densities approximated the electron distribution by a sum of atom-centred multipole moments (point charges, dipoles, quadrupoles, *etc.* on each atom), and used expressions due to Buckingham[13] to compute the electrostatic energy. But the spherical atomic charge densities have zero multipole moments, so this approximation amounts to ignoring the first two terms in (4). Numerous examples are available where this approach was used,[9,14,15] but the promolecule contribution to the electrostatic energy in (4), $E_{ele}^{pro-pro}$, is always negative at intermolecular separations,† and typically in the range −10 to −70 kJ mol^{-1} for nearest neighbour intermolecular interactions.[16] As such, it is essential to include that contribution, and several studies have been reported that corrected the multipole-moment term in (4) by adding a close approximation to $E_{ele}^{pro-pro} + E_{ele}^{pro-def}$.[17,18]

The accurate calculation of electrostatic interaction energies (2) from experimental charge densities was significantly advanced by the development of the 'exact potential and multipole method' (EP/MM),[19] which "combines numerical quadrature evaluation of integrals involving the electron density and potentials for short-range pseudoatom–pseudoatom interactions with the standard Buckingham-type multipole approximation for long-range interactions". Incorporation of this method into the popular software package XD[20] has resulted in the reporting of 'experimental' intermolecular interaction energies – and lattice energies – as outcomes of the charge density analysis of X-ray diffraction data, and these results are the focus of this contribution. Numerical calculation of accurate electrostatic energies, (2), can also be performed with VMoPro, a properties visualization part of the MoPro charge density analysis package,[21] but there appear to be only two reports[22,23] of experimental electrostatic energies using that software, and neither included lattice energies.

The lattice energy

Rather than discuss numerous examples of interaction energies for individual molecular pairs with different orientations, arising from something like twenty recent charge density studies, the focus here is on the sum of those energies – the lattice energy. Although one quantity per crystal structure makes for a more succinct discussion, this is not simply a matter of convenience. The logic here is that the lattice energy is closely related to a thermodynamic quantity – the

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† This appears not to be widely recognised, and can seem counterintuitive. It arises from the penetration of the electron distribution of one spherical atom inside that of another, resulting in a negative electron-nuclear interaction energy, which is only offset by the sum of positive nuclear-nuclear and electron–electron terms at much shorter separations, as described in considerable detail in ref. 49.

sublimation enthalpy, ΔH_{sub} – for which experimental measurements are available for a very large number of crystalline materials.[24,25] And of course lattice energies are vitally important for understanding the relative stability of polymorphs and co-crystals.

For the purpose of this discussion we assume that we can calculate E_{tot} in (1) from a pseudoatom model (or X-ray constrained wavefunctions[26]) for any pair of molecules A and B in a crystal. This requires the accurate calculation of E_{ele}(polarized), as well as some choice of atom–atom potential to approximate the dispersion and repulsion energies. Then the lattice energy can be estimated *via* a sum of pairwise energies:‡

$$E_{lat} = \frac{1}{2} \sum_{R_{AB} < R} E_{tot}^{AB} \tag{5}$$

E_{lat} can be related to the sublimation enthalpy by taking into account the electronic relaxation energy associated with the crystal to gas transition, ΔE_{rel}, as well as the difference between vibrational energies for the two phases, ΔE_{vib},

$$\Delta H_{sub}(T) = -E_{lat} + \Delta E_{rel} + \Delta E_{vib} + 4RT \tag{6}$$

and this can be approximated reasonably well[27] by

$$\Delta H_{sub}(T) = -E_{lat} + \Delta E_{rel} - 2RT \tag{7}$$

The important point here is that for crystals where little molecular geometry change occurs between crystal and gas phase, the sublimation enthalpy (a positive quantity) is less than the magnitude of the lattice energy at room temperature by ~5 kJ mol^{-1}. This provides a very useful primary benchmark against which to validate lattice energies (and, by inference, pairwise interaction energies) derived from X-ray diffraction data – bearing in mind of course the inherent experimental uncertainty of ~5 kJ mol^{-1} in these thermodynamic measurements.[28]

CrystalExplorer model energies

Although the latest compilations of phase transition enthalpies are comprehensive, sublimation enthalpies are not always available for molecular crystals of interest. However, CE-B3LYP lattice energies can be used as secondary benchmarks where sublimation data are lacking, and the individual energy components in the CE-B3LYP model can be used to inform us about the 'experimental' electrostatic energy.

CE-B3LYP model energies[29] incorporated in CrystalExplorer[30] utilise B3LYP/6-31G(d,p) quantum mechanical charge distributions for unperturbed monomers (obtained using Gaussian[31]), and separate the interaction energy between pairs of molecules or ions into electrostatic, po-

larization, dispersion and exchange-repulsion terms, in the manner of (1):

$$E_{tot} = k_{ele}E_{ele} + k_{pol}E_{pol} + k_{dis}E_{dis} + k_{rep}E_{rep}. \tag{8}$$

Here E_{ele} is the same as in (1), and E_{pol} is a sum of terms of the kind $\frac{1}{2}\alpha F^2$, where α are isotropic polarizabilities and F the electric field magnitude computed at each atomic nucleus resulting from the charge distribution of the other monomer. The other two terms are described in detail elsewhere[29,32] and optimum values of the scale factors k_{ele}, *etc.* in (8) have been determined by calibration against counterpoise-corrected B3LYP-D2/6-31G(d,p) interaction energies for a very large number of molecule/ion pairs. The mean absolute deviation (MAD) of these CE-B3LYP model pairwise energies from the DFT benchmark values is 2.4 kJ mol^{-1} for energies of molecule/ion pairs that span a range of 3.75 MJ mol^{-1}.[32] The same model energies yield lattice energies with a MAD from benchmark values of 6.6 kJ mol^{-1}.[33]

Comparison between EP/MM (XD) and CE-B3LYP lattice energies

Table 1 compares lattice energies reported using the EP/MM approach in XD for the electrostatic energy, and atom–atom potentials as indicated, with CE-B3LYP lattice energies based on the crystal structures tabulated. Experimental sublimation enthalpies are also listed for a subset of results. The table reveals that CE-B3LYP lattice energies are consistent with sublimation enthalpies, bearing in mind the inherent uncertainty in both quantities, and the fact that the relaxation energy has been ignored in these CE-B3LYP estimates.

Fig. 1 shows that (superficially at least) these experimental and CE-B3LYP lattice energies are poorly correlated. Almost all EP/MM (XD) lattice energies are greater in magnitude than CE-B3LYP results (*i.e.* they lie above the dashed line in the figure) – and sometimes much greater. There are several conspicuous outliers: 44BP and form II of the $(4HBA)_2(44BP)$ co-crystal, β-piroxicam and piroxicam monohydrate.

The difference between the two results for the $(4HBA)_2(44BP)$ co-crystal form II is 248 kJ mol^{-1}, well outside any reasonable experimental error, and it merits closer inspection, as the difference for 4,4′-bipyridine (44BP) in the same publication[5] is 212 kJ mol^{-1}, but of opposite sign. A plausible explanation is that these values do not properly reflect the stoichiometry of these two crystals. 44BP has two molecules in the asymmetric unit, and the chemical formula for 44BP is reported in the original work as $C_{20}H_{16}N_4$, rather than $C_{10}H_8N_2$. It makes little sense to report a lattice energy per two identical molecules, as this ignores the connection with the sublimation process, where the molecules are indistinguishable in the gas phase. The co-crystal form II (EPUPUB03) has formula $C_{10}H_8N_2 \cdot 2(C_7H_6O_3)$, but the asymmetric unit consists of one molecule of 4HBA and one-half of a 44BP molecule.

‡ For unit cells with nonzero dipole moments (*i.e.*, polar space groups such as $P2_1$, $Pna2_1$ and $Fdd2$) the summation in (5) is not representative of the entire crystal, and a cell dipole energy term is required.[50]

Table 1 EP/MM (XD) lattice energies estimated from X-ray diffraction data, $E_{\text{lat}}^{\text{XD}}$, compared with those using CE-B3LYP model energies, $E_{\text{lat}}^{\text{CE-B3LYP}}$, and experimental sublimation enthalpies, ΔH_{sub}, where available. [a] The electrostatic components of the EP/MM (XD) lattice energies, $E_{\text{lat,ele}}^{\text{XD}}$, are also given, along with the sum $E_{\text{lat,ele}}^{\text{CE-B3LYP}} + 2E_{\text{lat,pol}}^{\text{CE-B3LYP}}$. All energies are in kJ mol^{-1}

Compound	exp-6 potential	CSD refcode	Total lattice energies		Electrostatic components		ΔH_{sub}
			$E_{\text{lat}}^{\text{XD}}$	$E_{\text{lat}}^{\text{CE-B3LYP}}$	$E_{\text{lat,ele}}^{\text{XD}}$	$E_{\text{lat,ele}}^{\text{CE-B3LYP}} + 2E_{\text{lat,pol}}^{\text{CE-B3LYP}}$	
Dimethyl 3-(4-nitrophenyl) aziridine-2,2-dicarboxylate[34]	W&C	WIGJAY01	−178	−163	−100	−116	—
Dimethyl 2-(4-nitrophenyl) ethene-1,1-dicarboxylate[34]	W&C	XOCYOE	−182	−145	−85	−93	—
(±)-8′-Benzhydrylideneamino-1,1′-binaphthyl-2-ol[35]	W&C	WUFJOW01	−274	−188			—
Oxirane[36]	W&C	DUFBOV11	−51	−43	−34	−28	41 (ref. 37)
Dimethyl oxirane-2,3-dicarboxylate[36]	W&C	EYIJAY	−106	−105	−69	−77	—
Dimethyl 3-(4-nitrophenyl) oxirane-2,2-dicarboxylate[36]	W&C	XOCYUK	−192	−151	−103	−97	—
Oxirane-2,2,3,3-tetracarbonitrile[36]	W&C	TCYNEO04	−101	−85	−70	−77	—
Sulfathiazole form I[38]	W&C	SUTHAZ43	−183	−206	—	—	—
Sulfathiazole form II[38]	W&C	SUTHAZ30	−205	−218	—	—	—
Sulfathiazole form III[38]	W&C	SUTHAZ33	−230	−219	—	—	—
Sulfathiazole form IV[38]	W&C	SUTHAZ36	−206	−218	—	—	—
Sulfathiazole form V	—[b]	SUTHAZ05	—	−202	—	—	—
Pyrazinamide[39]	S	PYRZIN22	−99	−110	−93	−114	116(4)[24]
Rubrene (100 K)[40]	W&C	QQQCIG17	−264	−218	−64	−55	181 (ref. 41)
Rubrene (20 K)[40]	W&C	QQQCIG23	−268	−220	−70	−53	181 (ref. 41)
Carbamazepine form III[42]	—	CBMZPN22	−230	−152	—	—	—
β-Piroxicam[4]	—	BIYSEH14	−304	−161	—	—	—
Piroxicam monohydrate[4]	—	CIDYAP05	−571	−329	—	—	—
4-Hydroxybenzoic acid (4HBA)[5]	S	JOZZIH01	−181	−137	—	—	117(4)[24]
4,4′-Bipyridine (44BP)[5]	S	HIQWEJ03	−311	−99	—	—	106(3)[24]
(4HBA)$_2$(44BP) co-crystal form II[5]	S	EPUPUB03	−138	−386	—	—	—
(4HBA)$_2$(44BP) co-crystal form I	—	EPUPUB	—	−396	—	—	—
Paracetamol (PCM)[6]	—	HXACAN07	−189	−138	—	—	126(6)[24]
(PCM)(44BP) co-crystal[6]	—	MUPQAP	−271	−246	—	—	—
Benzene[34]	W&C	—[c]	−56	−48	−21	−20	45 (ref. 41)

[a] All experimental results employed the EP/MM approach in XD for the electrostatic energy, and atom–atom potentials from either Williams, Hsu and Cox[11,12] (W&C) or Spackman[10] (S) for dispersion and exchange-repulsion energies. The experimental values tabulated are unchanged from those reported in the original publications. CE-B3LYP lattice energies are based on the crystal structures indicated. [b] The choice of atom–atom potential was not indicated in the original work. [c] Based on X-ray data and crystal structure reported in ref. 43.

With reference to the sublimation process, one mole of the co-crystal will generate two moles of molecules of 4HBA and one of 44BP. This becomes clearer if we consider ΔE_{lat} for the hypothetical chemical process:

$$44\text{BP(s)} + 2 \times 4\text{HBA(s)} \rightarrow (4\text{HBA})_2(44\text{BP})(\text{s})$$
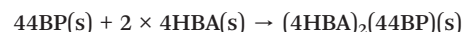
Assuming no changes in molecular geometries, we would expect this process to be accompanied by a lowering in inter-molecular energy, i.e. $\Delta E_{\text{lat}} < 0$.

$$\Delta E_{\text{lat}}(\text{form II}) = E_{\text{lat}}((4\text{HBA})_2(44\text{BP})) - [2E_{\text{lat}}(4\text{HBA}) + E_{\text{lat}}(44\text{BP})]$$
$$= -13 \text{ kJ mol}^{-1} \text{ (using CE-B3LYP results)}$$
$$= +535 \text{ kJ mol}^{-1} \text{ (EP/MM (XD) results)}$$

This makes it clear that the EP/MM (XD) lattice energies must be incorrect.

There are actually two known forms of the 2 : 1 co-crystal between 4-hydroxybenzoic acid and 4,4′-bipyridine,[44] and this discussion can be extended a little further by using CE-B3LYP energies to compare their relative stabilities. In the same manner pursued for form II, $\Delta E_{\text{lat}}(\text{form I})$ is −23 kJ mol^{-1} using CE-B3LYP results from Table 1, which suggests that form I is more stable than form II, in good agreement with the experimental observations.[44]

A similar analysis of the EP/MM (XD) lattice energies for the paracetamol (PCM) 1 : 1 co-crystal with 44BP yields ΔE_{lat} = +229 kJ mol^{-1},[6] but −9 kJ mol^{-1} using CE-B3LYP results. Here again the EP/MM (XD) lattice energies result in an
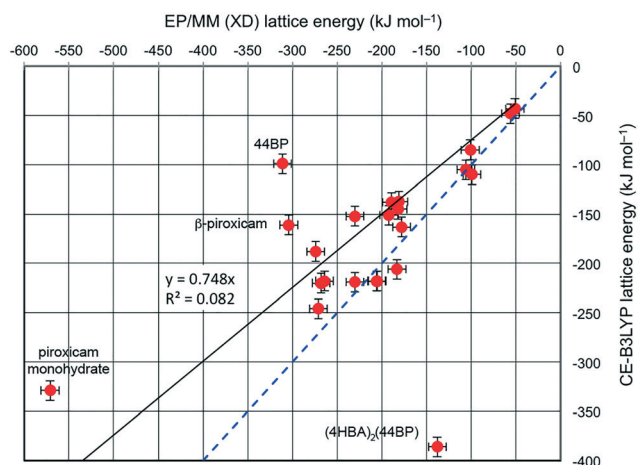

Fig. 1 EP/MM (XD) lattice energies compared with CE-B3LYP results from Table 1. The solid line is a linear regression, and the dashed line has unit slope, passing through the origin. Nominal uncertainties of ±10 kJ mol^{-1} are indicated for both quantities.

implausible estimate of the energy change for co-crystal formation.

The discrepancies between EP/MM (XD) and CE-B3LYP lattice energies for β-piroxicam and piroxicam monohydrate are also very large (Table 1). Although the origin of these differences is not obvious, it is notable that in this case the monohydrate has four molecules in the asymmetric unit: two of piroxicam (now in zwitterionic form, which is not the case in β-piroxicam) and two water molecules. Nevertheless, it is certainly not possible to use lattice energies, experimental or theoretical, accurate or imprecise, to conclude that "the zwitterionic, monohydrated form of piroxicam has a larger stabilisation (and thus is thermodynamically more stable)".[4]

Comments on the EP/MM (XD) electrostatic energy

The systematic overestimate of the lattice energy from experimental electron distributions provides a clue to a possible origin in the electrostatic term. As noted earlier, E_{ele}(polarized) is actually closer to the sum of $E_{ele} + 2E_{pol}$ than it is to $E_{ele} + E_{pol}$, and certainly greater in magnitude than E_{ele}.

Fortunately, many reports of EP/MM (XD) lattice energies also give a separate electrostatic term, and these results can be used to explore this overestimate. Fig. 2 compares $E_{lat,ele}^{XD}$ with $E_{lat,ele}^{CE-B3LYP} + 2E_{lat,pol}^{CE-B3LYP}$ for a subset of experimental estimates from Table 1. Results where the stoichiometry made little sense have been excluded, and nominal error estimates have been applied. The line of best fit passing through the origin suggests that the experimental electrostatic energy correlates strongly with the sum of $E_{lat,ele}^{CE-B3LYP} + 2E_{lat,pol}^{CE-B3LYP}$ from CE-B3LYP lattice energies. Note that the figure plots the sum of scaled CE-B3LYP energy terms (referring to the scale factors in (8)), which results in a MAD from the line of 9 kJ mol^{-1}; unscaled terms yield a slightly larger MAD of 11 kJ mol^{-1}. This analysis suggests that $E_{lat,pol}^{CE-B3LYP}$ is a rough measure of the overestimate in the true electrostatic energy when calculated using polarized charge distributions. Representative values of $E_{lat,pol}^{CE-B3LYP}$ are ~2 kJ mol^{-1} for benzene, ~9 kJ

mol^{-1} for rubrene, ~11 kJ mol^{-1} for oxirane-2,2,3,3-tetracarbonitrile and ~22 kJ mol^{-1} for dimethyl 3-(4-nitrophenyl)aziridine-2,2-dicarboxylate.

Comments on the atom–atom potentials

This analysis of electrostatic energies can partly explain the apparent experimental overestimate of lattice energies (and a possible correction for that), but the different atom–atom potentials used to provide corresponding estimates of dispersion and exchange-repulsion energies also deserve closer examination.

The 'Williams & Cox' atom–atom (nonbonded) potentials were originally derived by fitting to oxohydrocarbon[11] and azahydrocarbon[12] crystal structures, using atomic point charges to represent the electrostatic energies. Different refinements of these exp-6 potentials have been used extensively in crystal structure prediction, and a recent publication[45] summarizes the differences between the versions, and makes it clear that different versions are appropriate for use with different descriptions of the electrostatic energy: distributed atomic multipoles vs. atomic point charges fitted to the molecular electrostatic potential. The precise 'Williams & Cox' atom–atom potential terms used in XD are those for H, C, N and O reported in ref. 11 and 12.

In the 'Spackman' atom–atom potentials reported in 1986,[10] the exchange-repulsion terms were obtained using a rather simple density functional approach based on spherical atomic (promolecular) charge distributions. Empirical C_6 dispersion coefficients available at that time were added to yield a consistent set of exp-6 potentials for pairs of atoms up to and including Br. These were successfully applied to obtain geometries, interaction energies, force constants and vibrational frequencies of hydrogen bonded dimers of small linear molecules,[46] but it is important to recognise some of the assumptions in that model that may have been overlooked:

• The expression used for the exchange-repulsion energy[10] actually includes the electrostatic interaction between spherical atomic charge densities, $E_{ele}^{pro-pro}$. Because of this only the use of point atomic multipoles to compute the electrostatic component of the total interaction energy makes sense, along with an estimate of $E_{ele}^{pro-def}$ (labelled E_{pen} elsewhere[46]).

• The repulsion part of the exp-6 potential for a hydrogen atom involved in a hydrogen bond was set to zero.

These points imply that the 'Spackman' exp-6 potentials should not be used in combination with experimental electrostatic energies computed with the EP/MM approach (or any other essentially exact method). The second point is obviously problematic for general application to molecular crystals, as it requires making assumptions about which atoms are hydrogen bonded, and which are not.

This analysis reveals that neither of the 'Williams & Cox' or 'Spackman' exp-6 potentials is suited to providing dispersion and exchange-repulsion energies that complement experimental electrostatic energies calculated by accurate methods, such as EP/MM. This in turn clearly identifies a
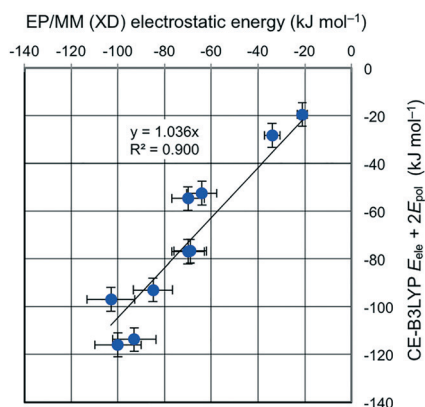

Fig. 2 Electrostatic components of ten EP/MM (XD) lattice energies[34,36,39,40] compared with the CE-B3LYP sum of scaled components $E_{ele} + 2E_{pol}$. Nominal uncertainties of ±5% are indicated for the experimental quantities, and ±5 kJ mol^{-1} for the CE-B3LYP sums.

need to develop an appropriate set of nonbonded potentials for this purpose. One attempt has been made to modify the 'Spackman' exp-6 potentials by fitting to *ab initio* repulsion energies and experimental dipole oscillator strength distributions (for the C_6 dispersion coefficients), but the results have not been reported in detail.[18]

Concluding remarks

A number of important observations emerge from this analysis, along with several suggestions for future research:

• The calculation of intermolecular interaction energies – and lattice energies – as an outcome of experimental charge density analysis based on X-ray diffraction data is still in its infancy, despite early studies dating back to the 1980s.[14]

• There is clear evidence that the pseudoatom multipole model is capable of providing reliable estimates of the electrostatic interaction energy between polarized molecules in crystals. However, future studies of this kind need to recognise that the electrostatic energy calculated between polarized molecules does not simply "include the effects of polarization". It actually overestimates them, sometimes by a large margin, and this overestimate should be taken into account.

• Improvements need to be made to the nonbonded atom–atom potentials used to approximate the dispersion and repulsion energies. A first step in this direction may be to use dispersion models such as the simpler D2 model due to Grimme,[47] as successfully incorporated in the CE-B3LYP model energies in CrystalExplorer.

• Realistic estimates of the experimental error in the computed experimental electrostatic energy are not just desirable; they are essential for a critical evaluation of the results. The method outlined recently by Jelsch and co-workers[22] to estimate statistical errors in pseudoatom-derived properties, including the electrostatic energy, is an important development.

• Ignoring basic thermochemical processes in presenting and discussing the EP/MM (XD) lattice energies is unhelpful. The relationship of lattice energies to experimental sublimation enthalpies, and the widespread availability of the latter quantities, needs to be exploited as much as possible. If experimental values make little sense compared with PIXEL[48] or CE-B3LYP results, those discrepancies are surely telling us something important.

This work has focused on energies based on electron distributions derived from the pseudoatom model fitted to X-ray diffraction data. This model has well known limitations that give rise to inherent systematic uncertainties, which in turn can be hard to quantify. What if instead X-ray constrained wavefunctions[26] were used to compute all quantum mechanical energy terms (especially electrostatic and exchange-repulsion, in the same manner as the CE-B3LYP model), coupled with a modern model of the dispersion energy? This question is yet to be answered, but it is hoped that this contribution will encourage studies aimed at critically assessing the relative merits of the two approaches for deriving intermolecular interaction energies and lattice energies from high-quality diffraction experiments on molecular crystals.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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