

Reply to “Comment on ‘Crystal Structure Prediction by Global Optimization as a Tool for Evaluating Potentials: Role of the Dipole Moment Correction Term in Successful Predictions’” by B. P. van Eijck and J. Kroon

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We thank van Eijck and Kroon for pointing out some unintended ambiguities in our paper¹ and for giving us the opportunity to eliminate them. We hope that the following comments will clarify our position and how it diverges from that of van Eijck and Kroon.^{2,3}

This reply is organized as follows. In the first section, we describe the point of contention, namely, whether crystal-structure predictions should consider a correction to the electrostatic energy of polar crystals. (Consistent with normal usage, a *polar crystal* denotes a crystal whose unit cell has a nonzero dipole moment.) In the second section, we summarize and assess van Eijck and Kroon's arguments in favor of eliminating this correction a priori. In the third section, we describe our own protocol for crystal-structure prediction and consider briefly the three polymorphs of glycine mentioned by van Eijck and Kroon in their comment. In the final section, we address two other points raised by van Eijck and Kroon.

The Lorentz–Ewald Correction for Polar Crystals. The controversy between our two groups arises from a correction to the electrostatic energy of polar crystals (denoted as U^{outer} by van Eijck and Kroon), corresponding to the electrostatic interactions between an internal unit-cell dipole and the (uncompensated) charges of the unit-cell dipoles on the boundary surface of the crystal. Not surprisingly, the magnitude of this energy correction depends on the shape of the boundary surface and its orientation relative to the direction of the internal unit-cell dipole. For large crystals, this energy correction adopts the simple form

$$\frac{1}{2V} \int \frac{(\mathbf{p} \cdot \mathbf{r})(\mathbf{p} \cdot d\mathbf{S})}{r^3}$$

where the integration is carried out over the crystal boundary surface, and where \mathbf{p} and V represent the dipole moment and volume of the unit cell, $d\mathbf{S}$ represents an infinitesimal area on the crystal surface, and \mathbf{r} is the distance vector between the given internal unit cell and the infinitesimal surface area. This correction energy equals $p^2(2\pi/3V)$ for cubical and spherical crystal surfaces and attains its maximal value of $p^2(2\pi/V)$ for plate-like crystals in which the unit-cell dipole is perpendicular to the plate. This surface/bulk interaction energy was first computed by Lorentz,⁴ and has long been recognized as a subtle correction to the normal Ewald summation;^{3,5–21} hence, we denote this correction energy as the *Lorentz–Ewald correction*.

Both of our groups agree that the Lorentz–Ewald correction represents a physical, electrostatic energy that contributes to the total energy of the crystal. Unfortunately, this correction is not widely known, and one of the goals of our article was to call it to the attention of a wider audience. It should be stressed that, contrary to some presentations, this correction is *not* an artifact of taking the mathematical limit of infinite crystals. For example, the corrected energy is also obtained when using a simple spherical cutoff scheme.

The Lorentz–Ewald correction is also *not* included implicitly in the parametrization of the present generation of energy functions such as AMBER²² and OPLS-AA.²³ These energy functions were parametrized from data on the liquid state (such as heats of vaporization and density) and, thus, are independent of the Lorentz–Ewald correction, since this correction arises only from long-range crystalline order, which is absent in the liquid state. Therefore, it is appropriate to consider this correction in crystal structure predictions based on such potentials. However, it should be noted that other potentials have been parametrized using crystal data (such as heats of sublimation) that may include the Lorentz–Ewald correction implicitly. For such potentials, it may be difficult to discern in what way this correction has influenced the parameters.

The Arguments of van Eijck and Kroon Against the Lorentz–Ewald Correction. The principal disagreement between our two groups is whether the Lorentz–Ewald correction should be considered in the prediction of crystal structures, or whether other physical and structural features of crystals always conspire to cancel this term, at least to within the error of the empirical energy functions themselves. van Eijck and Kroon have argued consistently for the latter interpretation,^{2,3} based on three arguments described below. By contrast, we adopt a more conservative approach, in which we calculate both the corrected and uncorrected energies and apply physical reasoning to assess which predicted structures are more plausible for the particular crystal-growth conditions.

The first argument of van Eijck and Kroon is that the Lorentz–Ewald correction should not be included because it depends on the shape of the crystal, which is not known a priori. However, this argument is not compelling for two reasons. First, reliable crystal structure predictions can be made even without knowing the specific crystal shape, since the Lorentz–Ewald correction is bounded between two well-defined values: zero and the maximal correction. (This point is discussed below in more detail.) Second, it is conceivable that the macroscopic shape of the crystal may be included in the prediction algorithm through additional variables, particularly if some knowledge of the kinetics of crystal growth is added to the simulations.

The second argument of van Eijck and Kroon is that tin-foil boundary conditions are applicable “under most practical circumstances”, i.e., the surrounding medium cancels the surface charges, zeroing their interaction with the internal unit-cell dipole and, thus, eliminating the Lorentz–Ewald correction. Although van Eijck and Kroon cite no references to support their contention that tin-foil boundary conditions are nearly universally valid for crystals, our own survey of the literature (discussed below) indicates that such conditions are indeed valid for many polar crystals. This is consistent with the general correlation between the solubility of polar solutes and the dielectric constant of their solvent. However, we note that such crystals may also be grown in a vacuum by sublimation or in

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low-conductivity, low-dielectric organic solvents; in both cases, tin-foil boundary conditions do not hold. Therefore, tin-foil boundary conditions cannot be assumed to be universally valid.

The third argument of van Eijck and Kroon is that, in those cases where tin-foil boundary conditions fail, the crystal shape will naturally arrange itself to render the Lorentz–Ewald correction negligible. It is true that strongly dipolar crystals often grow in a needle-like shape that minimizes the Lorentz–Ewald correction. (More on this in the next paragraph.) However, we note that the crystal shape is defined by the slowest growing planes of the crystal, and that the crystal growth may be dominated by nonelectrostatic interactions (e.g., hydrophobic interactions and molecular shape complementarity), particularly for macromolecular crystals. Therefore, it seems inappropriate to assume that the crystal shape will always adjust to minimize the electrostatic interactions.

We do agree with van Eijck and Kroon that, under many conditions, the Lorentz–Ewald correction may be minimized by physical and/or structural features of the crystal. To assess the frequency with which this correction is canceled in crystal structures, we studied a randomly chosen sample of 135 polar crystal structures from the Cambridge Structural Database. The overwhelming majority (95%) of these crystals were grown in solutions of high dielectric constant, in which tin-foil boundary conditions are applicable, thus reducing the Lorentz–Ewald correction to negligible levels. Moreover, many of the remaining polar crystals adopted a crystal shape that minimized the Lorentz–Ewald correction (e.g., by forming needles). For a few other crystals, the polar form seems to be the only plausible geometrical packing; other competing structures would have very high energies. Thus, although the shape and surrounding medium of these polar crystals do require that a significant Lorentz–Ewald correction be added, its addition would not be likely to alter the relative energy rankings of the lowest-energy structures. Therefore, the Lorentz–Ewald correction makes a critical contribution to the energy of only a few native crystal structures. It remains to be established whether the Lorentz–Ewald correction plays a more significant role in nonnative structures that compete with the native structure.

Several other minimizing factors should be considered in addition to those cited by van Eijck and Kroon. Static and dynamic disorder, mosaicity, and anomalous surface structure in the crystal may serve to randomize the orientation of dipoles on the crystal surface; in the limit of complete decorrelation of the dipolar orientations on the surface, the Lorentz–Ewald correction would be zero. Twinning and similar phenomena can also effectively cancel the Lorentz–Ewald correction; for example, two or more crystal grains may grow in concert such that their net dipole moment would be close to zero, thus minimizing this correction. However, this twinning argument does not pertain to our predictions, since we purport to predict the structures of only monocrystals.

Our Protocol for Treating the Lorentz–Ewald Correction in Structure Predictions. Nevertheless, we do not agree with van Eijck and Kroon in their optimism that the Lorentz–Ewald correction will *always* be canceled completely. We adopt a more conservative approach, in which we calculate both the corrected and uncorrected energies, and apply physical reasoning to assess which predicted structures are more plausible for the particular crystal-growth conditions. We choose the spherical Lorentz–Ewald correction as representing the typical magnitude of this correction.

A key issue is how the relative energy rankings of the proposed crystal structures change upon adding the Lorentz–

Ewald correction. This correction is positive and bounded between zero and the maximal value given above. Therefore, if these relative energy rankings are robust upon the addition of an energy correction between these two extreme values, we may be confident in our predictions. Moreover, if such a predicted structure agrees with the experimental structure, we feel justified in saying that our prediction method succeeded.

By contrast, if the relative energy rankings change drastically with the addition of the Lorentz–Ewald correction, then we must consider whether other physical and/or structural factors are likely to cancel the correction. (The relevant factors are those cited above, such as the dielectric constant/conductivity of the surrounding medium, or the shape of the crystal and its orientation to the unit-cell dipole.) If such factors seem likely to cancel the Lorentz–Ewald correction, we propose the *uncorrected* minimal structure as our best prediction of the crystal structure, albeit with less confidence than in the first case. Conversely, if such factors do not seem likely to cancel this correction, we propose the *corrected* structures as our best prediction of the crystal structure, although again with less confidence than in the first case.

Finally, if we find that the experimental structure has a much higher energy than our global minimum structure, regardless of whether the Lorentz–Ewald correction is added, then we feel justified in saying that the potential function failed to predict the crystal structure. If many crystals are studied, and the potential function fails to predict the experimental structure for a high percentage of them, then it seems fair to state that the potential function does not reproduce the physical energy well and needs to be reparametrized. We stress, however, that our study involved only six crystals and was meant primarily to illustrate our methods; no general conclusion should be drawn from our study about the validity of the potentials that we studied.

The Criterion for Success in Crystal Structure Prediction. We do not understand van Eijck and Kroon's argument that "one should not take the fact that an experimental structure has the lowest energy in a certain force field as proof that 'the predictions were successful'". We consider our prediction to have succeeded if the experimental structure is found within the few lowest-energy predicted structures. This criterion for success agrees with that adopted in the recent blind tests of ab initio crystal structure prediction organized by the Cambridge Crystallographic Data Centre. Even van Eijck and Kroon themselves appear to adopt this criterion: "the observed crystal structure should be present on the list of hypothetical crystal structures, not only with a good geometry but also with a reasonably low energy".²⁴

In particular, we do *not* claim that a crystal structure prediction succeeds if and only if the experimental structure is the lowest energy structure. It is true that we would consider it ideal if a potential function could be designed and parametrized such that its global minimum would always correspond to the experimental structure. However, this goal seems distant at present; flawed functional forms, imperfect parametrization, and sundry other approximations (such as the neglect of entropy) may cause discrepancies between the experimental and global minimum structures. We are keenly aware of these defects and make no claims about the absolute validity of the potentials that we studied nor about our method for global optimization.

Application to the Polymorphs of Glycine. For illustration, our methodology may be applied to the three polymorphs of glycine cited by van Eijck and Kroon. While the α polymorph is nonpolar,^{25,26} the β and γ polymorphs are both polar.^{27–29}

Hence, in the absence of compensating effects such as a surrounding medium of high dielectric constant, the expressed surface charges of these latter polymorphs would have strong electrostatic interactions with the dipole moment of an internal unit cell. However, all three of these polymorphs are grown in a medium of high dielectric constant ($\epsilon \approx 80$) where tin-foil boundary conditions are clearly applicable. Therefore, following the methodology described above, we would predict that the uncorrected energies would be more appropriate for assessing the relative stabilities of these polymorphs in aqueous solution, as indeed found by van Eijck and Kroon. This is supported by other physical considerations for these polymorphs. For example, the growth of the γ polymorph is favored by pH conditions near the pK_a values of the ammonium or carboxylate group, while the structure of the β polymorph favors rapid growth along the dipolar axis, leading to needle-like crystals whose Lorentz–Ewald correction is small.²⁷ Therefore, the observed polymorphs of glycine are consistent with our treatment of the Lorentz–Ewald correction.

Two Final Clarifications. van Eijck and Kroon seem to interpret our paper as suggesting that the Lorentz–Ewald correction should *always* be included in crystal structure prediction, regardless of the external conditions. Suffice it to say, that was not our intention. We are surprised that our paper was so misunderstood, particularly our statement “the crystal can therefore no longer be treated computationally in isolation from that medium”. van Eijck and Kroon seem to interpret this statement as meaning that we advocate that the Lorentz–Ewald correction should *always* be included in crystal structure predictions. However, we intended to convey exactly the opposite meaning, namely, that this correction was unnecessary for crystals grown in a high-dielectric/high-conductivity medium. That was the intended sense of the preceding clause, “If the crystal is surrounded by a medium of very high dielectric constant, ...external charges are ‘borrowed’ from that medium and compensate the surface effect”.

van Eijck and Kroon also point out that our published data do not provide compelling evidence that the Lorentz–Ewald correction should be added in crystal structure predictions. We concur with their assessment. However, it was never our intention to argue for this correction from our crystal structure predictions. Rather, our arguments were founded upon the physics of the crystal; specifically, we wished to point out that the Lorentz–Ewald correction represents a true electrostatic

energy (not a mathematical artifact) that may contribute significantly to the total crystal energy under appropriate conditions. It seemed important to call renewed attention to this correction, since even well-respected researchers seemed unaware of it and of the fact that the crystal energy may vary significantly with the surrounding medium through this term. Our observation that this correction may also serve as an effective penalty function (expediting our search for nonpolar structures) was merely incidental; this observation is irrelevant to deciding whether the Lorentz–Ewald correction should be included in the potential function, since it does not pertain to the physics of the crystal.

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