Pervasive Delocalisation Error Causes Spurious Proton Transfer in Organic Acid-Base Co-Crystals

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Abstract: Dispersion-corrected density-functional theory (DFT-D) methods have become the workhorse of many computational protocols for molecular crystal structure prediction due to their efficiency and convenience. However, certain limitations of DFT, such as delocalisation error, are often overlooked or are too expensive to remedy in solid-state applications. This error can lead to artificial stabilisation of charge-transfer and, in this work, it is found to affect the correct identification of the protonation site in multicomponent acid-base crystals. As such, commonly used DFT-D methods cannot be applied with any reliability to the study of acid-base co-crystals or salts, while hybrid functionals remain too restrictive for routine use. This presents an impetus for the development of new functionals with reduced delocalisation error for solid-state applications; the structures studied herein constitute an excellent benchmark for this purpose.

The crystalline structures adopted by organic molecules often involve a compromise between many competing weak interactions. Thus, the area of crystal structure prediction (CSP) presents a stringent challenge for computational methods, where the relative energies between different packing arrangements must often be assessed to within accuracies of a few kJ mol^{-1} or less.[1] The goal of reliable CSP, which has potential applications in pharmaceutical solid-form screening[2] and the discovery of functional materials,[3, 4] has demonstrated the effectiveness of solid-state density functional theory (DFT) for obtaining accurate structures and energetics of molecular crystals. The impressive success of dispersion-corrected DFT methods in CSP blind tests has led to increased use of these methods for modelling the organic molecular solid state.[1] However, a source of error that is not commonly acknowledged in this application area of DFT is delocalisation error.

It has long been established that delocalisation error in local density functionals results in over-stabilisation of charge-transfer complexes and other species with separated charges.[5, 6] This error is not seen in correlated-wavefunction theories and can be reduced for density-functional approximations (DFAs) through mixing of large amounts of exact (or Hartree-Fock, HF) exchange. Typically ca. 50% exact-exchange mixing is required to obtain accurate energetics for charge-transfer complexes,[7, 8, 9] charge-transfer excitation energies,[10, 11, 12] halogen-bonded complexes,[13] barrier heights of radical reactions,[14, 15] and other cases where delocalisation error plagues local functionals.

Several examples of density-driven delocalisation error have been noted, in which the improper density leads to significant errors in optimised geometries. This has been observed for the pre-reaction complex for H-atom abstraction from 1,4-diazabicyclo[2.2.2]octane (DABCO) by the benzyloxyl radical, where delocalisation error results in excessive stretching of one of the benzyloxyl C–H bonds.[16] Even more dramatic is the example of the carbanion intermediate for the Michael addition reaction of a thiolate to an olefin. In this case, a geometry optimisation can yield either the thiolate anion or carbanion, depending on the degree of exact-exchange mixing.[17] This is an excellent challenge for testing new functionals designed to reduce delocalisation error.[18]

Unlike for molecular systems, correlated wavefunction calculations on solid-state systems are uncommon and are restricted to the smallest unit cells.[19, 20] Therefore, accurate reference data for comparison is scarce. Indeed, performing efficient exact-exchange calculations using plane-wave basis sets is an ongoing challenge.[21] Consequently, dramatic examples of delocalisation error have not yet been illustrated for solid-state applications, with the exception of the consistent underestimation of band gaps.[6, 22, 23] While such energy-driven delocalisation errors exist, even the local density approximation (LDA) and generalised gradient approximation (GGA) functionals typically give reliable geometries for network solids. Moreover, dispersion-corrected GGAs perform extremely well in prediction of geometries of molecular solids, although organic salts have proved challenging[1, 24, 25] and exhibit fractionally charged ions.[26]

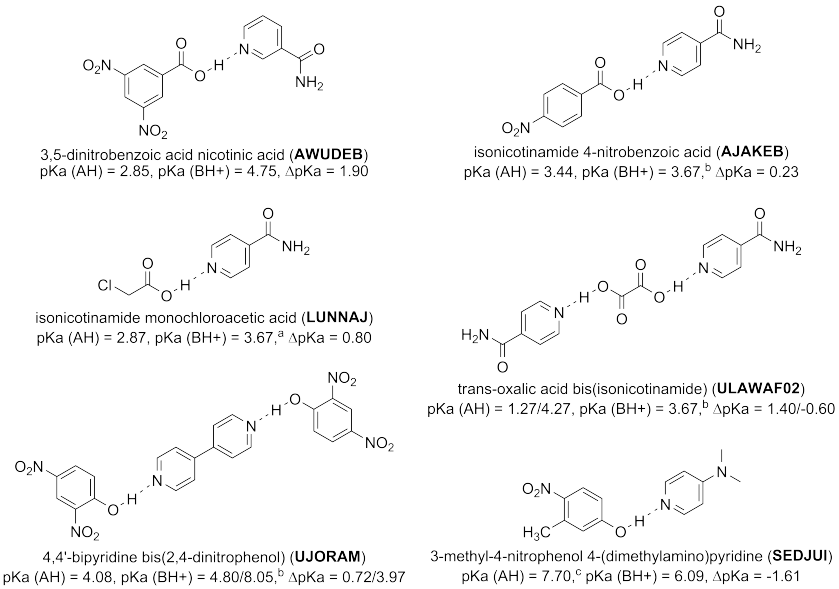
One area where delocalisation error may be prevalent in solids is for multi-component crystals, where significant charge transfer between the species may exist in nature, or falsely be predicted by DFAs. Multicomponent crystals consisting of an organic acid-base pair serve as a good example. Such materials can exist as a neutral co-crystal, or proton transfer from the acid to the base can result in the formation of an organic salt. This has importance in, for example, the pharmaceutical industry, where the solubility and bioavailablity of active pharmaceutical ingredients depends strongly on their crystalline form.[27, 28, 29, 30]

The extent of the proton transfer has been shown, in many cases, [31] to be predictable by the difference in pKa's (ΔpKa) of the acid and base components.[32] Generally, if this value is less than zero (or greater than ca. 3), a co-crystal (or salt) will likely form from the acid-base pair.[32, 33] However, reliable predictions cannot be made for intermediate ΔpKa's,[31, 32, 33] where the material can also possess a mixed ionisation state.[31, 32, 34, 35] It is thus beneficial to turn to computational methods as a means to determine whether a co-crystal or salt will form from a given pair (or group) of compounds.[36, 37]

Two of us recently conducted a study of the energetic driving forces for co-crystal formation[35] using a dispersion-corrected GGA functional, specifically PBE-D3.[38, 39] It was found that geometry optimisation of 6 of the 350 co-crystals considered resulted in spurious proton transfer to give the corresponding organic salt.[35] Similar conclusions were drawn by others for nicotinamide-based crystals and their analogues.[34] We have also performed B86bPBE-XDM[40] plane-wave calculations, which yielded identical results with respect to the spurious proton transfers, indicating that the choice of dispersion model is not the culprit for this erroneous stabilisation of salts over co-crystals. As a salt possesses delocalised charges, these results appear consistent with the delocalisation error inherent in GGAs, and in other local or semi-local DFAs.

In this work, we investigate the effect of exact-exchange mixing on the predicted geometries of the six co-crystals previously identified to form salts preferentially during the course of DFA geometry optimisations.[34, 35] For simplicity, crystal structures that were found to possess mixed ionisation states or had proton positions mis-assigned, have been excluded. The molecular diagrams and unit-cell structures of the crystals considered herein are depicted in Figures 1 and 2, respectively.

Figure 1: Molecular diagrams for the six co-crystals considered in this work, together with their CCDC codes. pKa values for the acid (A), the protonated base (BH+), and their corresponding difference, ΔpKa, are given. pKa values were taken from Ref. 41 unless otherwise indicated; [a]Ref. 42, [b]Ref. 43, [c]The pKa listed has been averaged from the reported values for 4-nitrophenol (7.14) and 3,5-dimethyl-4-nitrophenol (8.25) from Ref. 41.

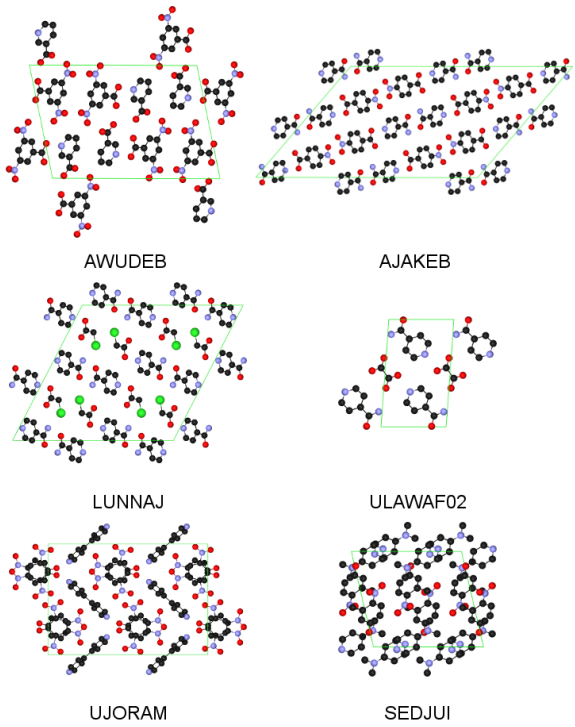


Geometry optimisations of these experimentally determined co-crystals were performed using the CRYSTAL17[44] software package. The PBE[38]-D3[39] dispersion-corrected GGA, the PBE0[45]-D3,[39] PBEh-3c,[46] and screened-exchange HSE-3c[47] hybrid functionals, and the scaled version of HF-3c[48, 49], "sHF-3c" (which reduces the overbinding of the unscaled method)[50] were used to probe exact exchange mixing (from 0 to 42%) as seen in typical DFAs.

The results of the DFA geometry optimisations are summarised in Table 1. As with the previous plane-wave calculations using the same dispersion-corrected functional,[35] PBE-D3 optimisation causes each of the co-crystals to undergo spontaneous proton transfer, from the acid to the base, forming the corresponding salts. Similar results are also obtained with PBE0-D3 (which contains 25% exact exchange). Conversely, sHF-3c, PBEh-3c (42% exact exchange), and HSE-3c (42% exact exchange in the short-range, gradually attenuated to 0% in the long-range) optimisations consistently preserve the neutral co-crystal when starting from the experimental geometry. Thus, relatively high fractions of exact exchange (in excess of 25% and possibly around 40%) are needed to predict a stable co-crystal.

To verify that the co-crystal is indeed the "correct" structure for these compounds, the C–O bond lengths are compared with the experimental X-ray crys-

Figure 2: The unit-cells of the six co-crystals considered in this work, together with their CCDC codes. Hydrogen atoms are omitted for clarity. Colours: black = carbon, blue = nitrogen, red = oxygen, green = chlorine.



tallographic data in Table 2. For the four carboxylic-acid containing crystals (AJAKEB, AWUDEB, LUNNAJ, and ULAWAF02), both PBE and PBE0 predict effectively equal C–O distances, implying the formation of a carboxylate group and a salt. Conversely, PBEh-3c, HSE-3c, and sHF-3c predict different C–O bond lengths, as are seen experimentally, implying formation of a carboxylic acid and a co-crystal. For the two alcohols, SEDJUI and UJORAM, assignment of the protonation state is slightly more difficult. However, the PBE and PBE0 C–O bond lengths are considerably shorter than experiment, implying formation of a phenoxide anion and salt, while the PBEh-3c, HSE-3c, and sHF-3c distances for the phenols are in better agreement, implying a stable alcohol and co-crystal.

Additional calculations were performed with sHF-3c, PBEh-3c, and HSE-3c starting from the salt geometries obtained from PBE-D3. sHF-3c again consistently transfers the proton back to its original placement, returning to the neutral co-crystal. With PBEh-3c, this was also the case for AJAKEB, ULAWAF02, and SEDJUI. However, for the other three crystals, the salt could be obtained as a stable, minimum-energy structure. With HSE-3c, only AJAKEB and

Table 1: Summary of structures predicted by selected DFAs (c = co-crystal, s = salt). The initial input geometry was either the experimental co-crystal X-ray structure or the PBE-D3 optimised structure.

Method	PBE-D3/DZP	PBE0-D3/DZP	PBEh-3c		HSE-3c		sHF-3c	
Input Structure	exp	exp	exp	PBE-D3	exp	PBE-D3	exp	PBE-D3
AWUDEB	s	s	c	s	c	s	c	c
LUNNAJ	s	s	c	s	c	s	c	c
UJORAM	s	s	c	s	c	s	c	c
AJAKEB	s	s	c	c	c	c	c	c
ULAWAF02	s	s	c	c	c	c	c	c
SEDJUI	s	s	c	c	c	s	c	c

Table 2: Experimental and optimised C–O bond lengths (in Å); the initial geometry for the optimisations was either the experimental co-crystal structure, or the PBE-D3 optimised structure. The mean absolute error (MAE), with respect to the experimental reference data, is given for each method.

Method	Expt.	PBE-D3/DZP	PBE0-D3/DZP	PBEh-3c		HSE-3c		sHF-3c	
Input Structure		exp	exp	exp	PBE-D3	exp	PBE-D3	exp	PBE-D3
AWUDEB	1.219, 1.256	1.276, 1.282	1.262, 1.267	1.218, 1.287	1.239, 1.252	1.219, 1.286	1.240, 1.252	1.213, 1.326	1.213, 1.326
LUNNAJ	1.220, 1.293	1.273, 1.290	1.259, 1.275	1.212, 1.301	1.232, 1.267	1.212, 1.301	1.233, 1.267	1.210, 1.339	1.210, 1.339
UJORAM	1.313	1.290	1.278	1.306	1.267	1.304	1.265	1.318	1.316
AJAKEB	1.222, 1.307	1.281, 1.291	1.266, 1.275	1.218, 1.299	1.218, 1.299	1.219, 1.299	1.219, 1.299	1.217, 1.336	1.217, 1.336
ULAWAF02	1.223, 1.288	1.272, 1.289	1.257, 1.273	1.208, 1.294	1.208, 1.294	1.209, 1.293	1.209, 1.293	1.208, 1.332	1.209, 1.332
SEDJUI	1.328	1.305	1.291	1.317	1.318	1.316	1.282	1.337	1.337
MAE	–	0.031	0.031	0.010	0.015	0.009	0.019	0.024	0.024

ULAWAF02 returned to their co-crystal forms. The relative PBEh-3c and HSE-3c energies of the salt and co-crystal forms are given in Table 3. Similar to previous conclusions from the literature [31, 32, 33], there is only a weak correlation between these relative energies and the ΔpKa, and no correlation with the individual pKa's.

The present results illustrate the potential of delocalisation error to cause qualitative disagreements between calculated and reference crystal structures, resulting in differing ionisation states and chemical-bonding arrangements. Depending on the extent of exact-exchange mixing, either the organic salt, neutral co-crystal, or both, can be obtained from DFA geometry optimisation of the multicomponent crystals considered herein. The pure GGA (PBE-D3) and the low-%HF hybrid (PBE0-D3) both favour proton transfer, resulting in salt structures; this error can be understood by the tendency of GGA exchange to over-stabilise delocalised charges. Using full exact exchange, as in sHF-3c, correctly preserves the neutral co-crystal in all cases, but tends to overestimate the bond lengths, which is characteristic of HF theory. Using an intermediate exact-exchange mixing of 42%, as in PBEh-3c, or a screened exchange hybrid, such as HSE-3c, leads to prediction of both salt and co-crystal structures as local minima in 50% or more of the cases studied. The similarity of the PBEh-3c and HSE-3c results implies that the truncated Fock-exchange distance regime employed in HSE-3c is not severe enough to encourage charge transfer. Overall, the results clearly demonstrate the sensitivity to exact-exchange mixing that is

Table 3: Relative PBEh-3c and HSE-3c energies (in kcal/mol per proton transferred) for the co-crystal and salt forms (co-crystal energy – salt energy), together with literature pKa's (see Figure 1 for references). For AJAKEB, ULAWAF02, and SEDJUI, no stable salt form could be found with PBEh-3c.

Quantity	pKa (acid)	pKa (base)	ΔpKa	ΔE (PBEh-3c)	ΔE (HSE-3c)
AWUDEB	2.85	4.75	1.90	1.10	1.15
LUNNAJ	2.87	3.67	0.80	-1.42	-1.31
UJORAM	4.08	4.80	0.72	-1.69	-1.10
AJAKEB	3.44	3.67	0.23	–	–
ULAWAF02	4.27	3.67	-0.60	–	–
SEDJUI	7.70	6.09	-1.61	–	-1.69

the signature of delocalisation error.

The consistent failing of the GGA functional to stabilise the six co-crystals considered in this work is a significant issue because the success and convenience of dispersion-corrected GGAs has led to their widespread use in studying molecular crystals. For example, DFT-D optimisation has been suggested as a tool for validation of experimental crystal structures[51] and has been demonstrated to be among the most promising approaches to CSP.[25, 52, 53] Multicomponent acid-base crystals are common and are of great importance within the pharmaceutical industry,[32, 27] which is one of the main users of CSP. In this context, the formation of a multicomponent solid can modify the physical properties of an active pharmaceutical ingredient. The correct identification of protonation is important for understanding the resulting properties, as well as for regulatory and intellectual property reasons. The erroneous prediction of the ground protonation state means that GGA-based CSP approaches cannot be applied to multicomponent crystals capable of such acid-base equilibria with any expectation of reliability.

Finally, because the delocalisation error was found to affect the geometries of the multicomponent crystals, rather than simply energies or electron densities, density-corrected DFAs[54] are not a viable solution. Moreover, full HF exchange or hybrid functionals are not practical for large-scale applications with plane-wave/pseudopotential calculations, which are the workhorse of solid-state electronic-structure theory. Thus, new approaches to reduce delocalisation error using local-density ingredients are needed. The crystalline acid-base equilibria considered herein should constitute an excellent benchmark for development of functionals with reduced delocalisation error for solid-state applications.

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Keywords

Charge Transfer, Co-Crystals, Density Functional Calculations, Electronic Structure, Salts

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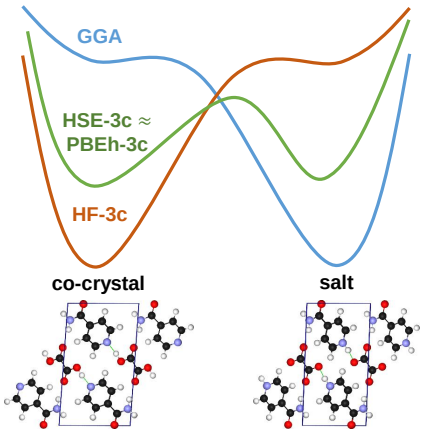

A commonly overlooked limitation of density-functional theory, **delocalisation error**, is found to affect the protonation sites in multicomponent acid-base crystals. This error greatly affects the reliability of these methods for validation of experimental (or the prediction of new) crystal structures. The results provide an impetus to develop alternative methods, if they are to be used routinely in industry.