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Probing transferability of intermolecular interactions by their features: a nitro group case study

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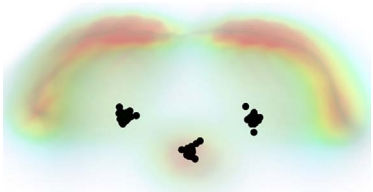
Based on the processing of supramolecular environments of nitro group from Cambridge Structural Database by means of the 'Atoms in Molecules' analysis of promolecular electron density function, it is demonstrated that the topological stability of intermolecular bonding within one associate reflects trends in prevalence of interactions with particular geometry in real crystals.



Probability to find intermolecular interaction in real crystals hides in its features

Keywords: electron density, topological analysis, promolecule, intermolecular interactions, structural database, transferability.

Intermolecular interactions play a crucial role in determining the properties of materials and chemical systems.[1,2] These interactions influence various aspects such as stability, solubility, and reactivity of molecules and are of uttermost importance in design of catalysts,[3,4] drugs,[5,6] functional[7,8] and high energy materials.[9,10] As most of these applications deal with crystalline phases, the studies of intermolecular interactions and their influence on the desired property have long been one of the main goals of organic crystallography.[11]

To study intermolecular interactions in crystals, the scientific community worked out a standard methodology which consists in evaluating of nature and strength of an interaction and determining its transferability. The nature of an interaction is understood as the combination of chemical theory based features attributing it to a specific type (see, for instance, refs. 12–14). A special attention is paid to estimate the degree of covalency of an interaction which determines its ability to form bonded (in a chemical sense) supramolecular complex. In its turn, the interaction's strength implies either the corresponding energetic contribution into crystal lattice energy[15,16] or the rigidity of interaction's geometry with respect to crystal field influence or external conditions (temperature, pressure, *etc.*).[17–20] Finally, the transferability of an interaction, though being weakly defined and reflecting the desire to consider multiatomic species in the paradigm of classical mechanics,[21,22] is usually understood as the possibility to use the interaction with particular features (*e.g.*, geometry) as a crystal structure directing pattern. Whereas the nature and strength of an interaction are commonly probed by electronic structure calculations supplemented by a simple geometrical analysis, the only existing way to check transferability is by the processing of structural databases containing relevant information on existing crystals.

All the three properties are believed to be interrelated that can be easily verified for strong intermolecular interactions with pronounced covalency such as hydrogen and halogen bonds: both these types can result in stable supramolecular entities with the structure being hardly flexible and readily formed in various crystals. These types of intermolecular interactions can lead to the formation of supramolecular synthons[23–26] which are so stable that they play the role of building blocks in the 'synthesis' of the desired crystal structure. However, even for relatively strong interactions there are cases when these properties seemingly contradict with each other. For instance, the geometry of π···π stacking interaction within the same pair of molecular fragments can vary substantially while nearly conserving its energetics.[27] The situation becomes even worse once weak intermolecular interactions are under consideration. For example, while the H···H interactions are commonly attributed to dispersive forces and have negligible covalent contribution, they occur in many organic crystals and are often responsible for the supramolecular conformation of hydrocarbon fragments.[28] This demonstrates the urge for all the three properties of an interaction under study to be analyzed and compared in each case.

From the experimentalist's point of view, among all the three properties the transferability probably plays the most important role. First, all the theoretical considerations regarding nature and strength of intermolecular interactions in crystals are by all means of model character and can be disproved by choosing another theoretical framework. Second, for practical purposes one only needs to design crystal structure with predictable physical or chemical properties. This task could be easily accomplished once the statistics on transferability of interactions between real crystal systems is large enough and a suitable prognostic model is trained. In the real (at least present) world though, the prevalence of an interaction in experimentally studied crystals is affected by available statistical sample which may be limited by scientific trends in many interesting cases.[29] It is this problem of statistics, as well as the historical path of chemical theory, that is the reason for quantifying the nature and strength of interactions.

Besides two obvious ways to overcome current statistical limitations (experimental studies of new samples and *in silico* modelling of putative crystal structures), one more root can be suggested by utilizing ever-present frameworks of chemical theory. That is to seek for a reflection of the whole statistics or its most representative features in theoretical peculiarities of an

interaction. Such a reflection, if exists, would be similar to the ergodic hypothesis and could allow 'single point' estimations of interaction's transferability.

In this contribution, we will try to show that there indeed exists a relationship between theoretical attributes and transferability even for weak intermolecular interactions. The object of research was the whole bunch of intermolecular interactions formed by nitro groups in organic crystals. The choice of the NO_2 group is due to its accessibility for various types of weak intermolecular interactions and its invaluable importance in many practical instances including the design of high-energy materials. The consideration of a functional group with its all-possible interactions rather than the specific interaction between two fragments widens the statistics and, hence, allows to neglect poorly defined ranking of interactions (O···π, O···O, π···π, *etc.*) while still demonstrating the relationship between the analysis of electronic structure and sampling of real crystal systems.

Up to 10517 C–NO_2 fragments and their supramolecular environment were retrieved from the well-defined structures composed by C, H, N and O atoms and deposited in the Cambridge Structural Database[30] (having R-factor less than 5%, no errors and no formal disordering). Each supramolecular environment was composed by atoms forming geometrical contacts with the central NO_2 group (contact's length less than the sum of van der Waals radii and 0.5 Å; the normalization of X–H bond lengths).

To correlate the prevalence of interaction with specific geometry and the characteristics of electronic structure we utilized the 'Atoms in Molecules' theory[31] which not only reveals intermolecular bonding interactions by means of the electron density $\rho(\mathbf{r})$ topological analysis[16,32] but also provides insights into their nature and strength.[19,33–41] The promolecule model[42] implemented in the MultiWFN program[43] was used to construct the $\rho(\mathbf{r})$ function for each supramolecular associate. Note that this model was previously shown to provide a reasonable picture of bonding in both intra- and intermolecular regimes.[44–46] The further analysis of bonding was made in terms of the (3,–1) critical points of $\rho(\mathbf{r})$ corresponding to intermolecular interactions between NO_2 group and its surrounding.

In the spirit of the 'clouds of critical point variation' approach[47,48] we aggregated all the critical points into one 'cloud' by superposing all the NO_2 groups (lowering the root mean square deviation between groups). This 'cloud' is composed by 46877 points and reflects the 3D distribution of (3,–1) critical points of promolecular $\rho(\mathbf{r})$ with the coordinate $\mathbf{r}^{3,-1}_{\text{cloud}}$ denoting the geometry of each critical points (and, hence, bonding interaction) with respect to the averaged NO_2 group. The density of the 'cloud' [estimated, for instance, by the Gaussian kernel,[49] $\rho_{\text{KDE}}(\mathbf{r}^{3,-1}_{\text{cloud}})$] can serve as an estimate of the prevalence of specific geometry of intermolecular interaction. The denser is distribution of critical points – the more often (among existing crystals) bonding interactions occur in this region. In its turn, for each supramolecular cluster the local properties at intermolecular critical points serve as theoretical descriptors of bonding interactions. A detailed description of the approach is given in Online Supplementary Materials.

First of all, it should be mentioned that the form of the 'cloud' of critical points obtained by processing of statistical ensemble replicate the expected 3D shape of nitro group (Figure 1). We have also found that the density of critical points surrounding nitro groups has (1) two maxima near the oxygen atoms within the NO_2 plane, (2) maxima near the nitrogen atom above/below the NO_2 plane, (3) minima on the oxygen atoms near the X atom adjusted to the nitrogen atom, (4) minima in the middle of oxygen–oxygen and nitrogen–oxygen distances. If desired, this distribution can be regarded as an image of known types of intermolecular interactions formed by nitro group: the maximum

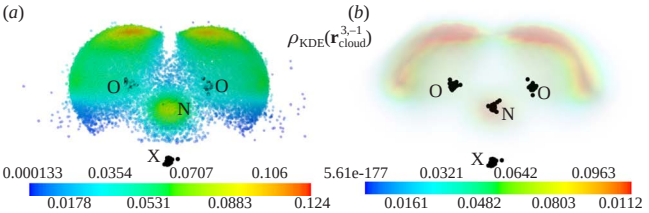


Figure 1 The distribution of (3,–1) critical points of $\rho(\mathbf{r})$ corresponding to intermolecular interactions of nitro group colored by the $\rho_{\text{KDE}}(\mathbf{r}^{3,-1}_{\text{cloud}})$ density function (*a*) and the isosurface plot of $\rho_{\text{KDE}}(\mathbf{r}^{3,-1}_{\text{cloud}})$ around the NO_2 group (*b*).

at oxygen atom reflects its role in the O···π and O···O interactions while the maximum at nitrogen atom corresponds to stacking and X···π interactions.

Whereas the strength of interaction [as revealed by the value of $\rho(\mathbf{r})$ at critical points, $\rho(\mathbf{r}^{3,-1}_{\text{cloud}})$] has nothing to do with the 'cloud' density (Figure 2), there is a descriptor which resembles the trends of statistical prevalence of interactions. Namely, the middle eigenvalue of the $\rho(\mathbf{r})$ Hessian [$\lambda_2(\mathbf{r}^{3,-1}_{\text{cloud}})$] tends to approach zero in the regions where the density of critical points distribution is small. It is widely known[50–54] that the λ_2 value demonstrates the 'catastrophic' character of the (3,–1) critical point: the $\lambda_2 = 0$ situation for the $\rho(\mathbf{r})$ function is a bifurcation at which the bonding interaction disappears. Hence, the topological unstability of atomic bonding graph in the area of intermolecular interactions of NO_2 group reflects to some extent the absence of bonding interactions with specific geometry (or, at least, their occasional character).

Moreover, this relation is observed even if the nitro group is considered without its supramolecular environment (Figure 3). According to the CCSD[55]/cc-pVTZ[56] calculations of the isolated $MeNO_2$ molecule (full geometry optimization to minimum on potential energy surface[57]), the λ_2 distribution over the so-called van der Waals isosurface[58,59] of $\rho(\mathbf{r})$ (0.001 a.u.) again resembles the pattern. Namely, there are regions of pronouncedly negative values of λ_2 near the oxygen atoms (especially within the NO_2 plane) and near the nitrogen atom above/below the NO_2 plane. These regions are altered by interlayer areas with flat electron density (green on the left panel of Figure 3). It is interesting to note that the electrostatic potential – a standard metric to seek for possible nucleophilic and electrophilic sites of a molecule when predicting its supramolecular behavior[60] – is characterized by a rather flat distribution with nearly zero values in the region close to the nitrogen atom (Figure 3, right). In other words, the electrostatic potential analysis does not reveal any pronounced tendency of the nitrogen atom to form peak-to-hole interactions which are commonly recognized as rather strong ones.

Despite the proposed methodology can be easily extended to analyze transferability of intermolecular interactions formed by other functional groups, two important issues regarding its applicability must be stressed. First of all, the promolecule model can provide misleading insights into the electron density topology for non-directional and multicenter interactions (stacking, *etc.*) and does not seem to be sufficient when estimating properties of strong intermolecular interactions such

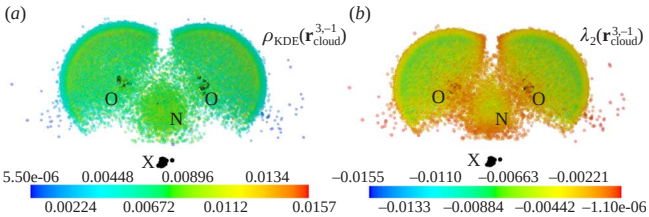


Figure 2 The distribution of (3,–1) critical points of $\rho(\mathbf{r})$ corresponding to intermolecular interactions of nitro group colored by the $\rho(\mathbf{r}^{3,-1}_{\text{cloud}})$ (*a*) and $\lambda_2(\mathbf{r}^{3,-1}_{\text{cloud}})$ (*b*) values.

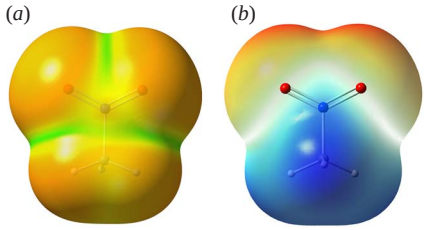


Figure 3 The 0.001 a.u. isosurface of $\rho(\mathbf{r})$ in the isolated equilibrium nitromethane molecule colored by the λ_2 values [(*a*), from –0.00243 a.u. in red to 0.0 a.u. in green] and electrostatic potential values [(*b*), from –0.05276 a.u. in red to +0.05276 a.u. in dark blue].

as H-bonds. It can be though believed that a large statistic on intermolecular bonding graphs may overcome this problem. Second, the size of a statistical sample describing some intermolecular interaction (or a functional group) in interest is always restricted by the data available *via* structural databases. This is partially solved when considering electron density in the isolated gas-phase state (as for $MeNO_2$ molecule discussed above), however one has to account for a potential redistribution of electron density and its Hessian upon the formation of strong intermolecular interactions.

Nevertheless, we claim that the analysis of Hessian of $\rho(\mathbf{r})$ can potentially be used to estimate the transferability of intermolecular interactions with particular geometry between different crystal systems. At least, one can anticipate that unstable bonding graphs having bifurcative critical points of $\rho(\mathbf{r})$ rarely occur in real crystal systems. To retrieve trends of transferability without processing structural databases, the analysis can be limited to only one functional group (and in isolated state) that opens a possibility to produce images of potential interactions and seek for complementary fragments.

Online Supplementary Materials

Supplementary data associated with this article (description of proposed methodology, Cartesian coordinates of CNO_2 fragments, Cartesian coordinates and other properties of (3,–1) critical points of promolecular electron density) can be found in the online version at doi: 10.1016/j.mencom.2024.06.023.

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