Supramolecular Similarity in Polymorphs: Use of Similarity Indices (I^X)

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ABSTRACT: A systematic investigation to assess the degree of similarity between polymorphs was carried out. A similarity indices (I^S) approach was applied in ten series of polymorphs with different characteristics and number of molecules in the asymmetric unit. Geometric (I^G), contact area (I^C), and stabilization energy (I^E) parameters were used. It was possible to situate each polymorph in different regions of similarity within the polymorphism phenomenon and determine the boundaries between quasi-isostuctural polymorphs and polymorphs of low similarity. The multiparameter I^DCG index was used as a robust tool to determine the total similarity within the polymorphism phenomenon. The highest contribution of the stabilization energy parameter (45%) toward the final value of similarity (I^DCG) was observed, followed by the contact area index (32%). The geometric index contributed approximately 23% to the final value of I^DCG. This information reinforces the importance of the contact area and stabilization energy in assessing the degree of similarity between crystalline structures. A new descriptor (I^Q) based on the comparison of the energetic contribution of intermolecular interaction types present in each crystal structure is presented. I^Q can be a versatile tool and applicable even for systems that do not share any similarity.

INTRODUCTION

The main definitions used to describe similarity in complete structures use a geometric parameter, mainly indicating concepts of isostructurality. Kálmán et al.⁰ (1993) defined isostructurality as the similarity of spatial arrangements of molecules of different compounds in their crystals and the IUCr definition" follows the same line. This is a phenomenon that can be interpreted in three dimensions (isostructurality), and it is also possible to extend into one-dimensional (1D) and two-dimensional (2D) directions. The capability to compare sets of crystal structures to identify degrees of similarity can find applications for a wide range of studies, such as polymorphs⁵−⁶ and multicomponent crystals.⁶,⁷ However, there is a lack of reliable tools to compare and classify complete crystal structures to indicate the existence of boundaries between high and low similarity.

Polymorphs were defined by McCrone in 1965 as a solid crystalline form of a given compound, resulting from the possibility of at least two crystalline arrangements of molecules of the same solid-state compound.⁸ As the properties of a material in the solid state depend on its crystalline form, polymorphs usually have different physicochemical properties.⁹ Thus, polymorphism is well known for its impact on properties such as melting temperature, solubility, dissolution rate, stability, bioavailability, and mechanical properties.⁹−¹¹

In this sense, polymorphism is a phenomenon in which significant differences between crystalline forms are expected, while high geometric similarity is expected in isostructurality. However, these two antagonistic concepts are entangled, since polymorphs that share a certain degree of similarity have been reported, even being included in a classification of quasi-isostuctural polymorphism.¹² Katrusiak et al.⁴ (2007) reported isostructurality in polymorphs of ethynylbenzene that presents a Z’ value higher than one, which is generated by cooling under pressure. Dey et al.¹² (2016) presented high-Z’ polymorphs of (Z)-2-fluoro-N’-phenyl-benzyldiamide, in which these systems were observed to produce very similar characteristics of packing and intermolecular interactions, where the interaction, C···H···F, played a significant role. For this case, the authors classified these polymorphs as quasi-isostuctural supramolecular architectures. The authors indicated a nearly isostructurial behavior for crystal structures formed under ambient conditions. Moreover, the authors also used the “energy framework” method to qualitatively indicate structural similarities in the interactions of crystalline forms. Coles et al.¹³ (2014) showed a high level of geometric similarity in 3-
chloromandelic acid polymorphs obtained by a temperature-dependent phase transition. The study was performed mainly using the XPac program. The authors reported an isostructural behavior for this kind of polymorphs.

From the studies that describe the interpretation of structure similarity, we are brought to the "problem of induction" formulated by Hume in the mid-18th century. The most notable response to the problem of induction was formulated by Popper two centuries later. Popper’s concept about the falsifiability of the proposed claims and their validity to verifiable evidence supports the basis of the modern definition of science. Thus, it is the most accepted answer for the problem of demarcation between science and non-science. The studies published in this area fall into the hypothesis of induction and mainly present a lack of demarcation for the system to be studied. Some studies have considered the average energy data of the crystalline network (energy framework analysis), which reproduces the unit cell “x” number of times and does not clearly identify which molecules are interacting. On the other hand, other studies that consider supramolecular constructs (or subclusters) neglect important information regarding the whole crystal structure.

In this sense, our research group recently proposed quantitative similarity indices $I^X$ (X = D, C, or G) — based on geometric ($I^D$), contact area ($I^C$), and stabilization energy ($I^G$) parameters15— using nine 5-aryl-1-(1,1-dimethylhet-yl)-1H-pyrazoles as a model to assess the packing similarity of complete crystal structures. The proposed indices demonstrated that the similarity between two crystalline structures can be estimated and classified into three different regions of similarity.16 Results indicated that supramolecular structures with high similarity must have high values for all three indices ($I^D$, $I^C$, and $I^G$). Recently, these indices have been used to compare crystalline structures of [2]rotaxanes.25 The normalized data used allow the results to be compared between different crystallographic data, see Supporting Information (SI), Figure S1 and Table S1.

Table 1. X-ray Crystallographic Data for 1IA and 1IIA Polymorphs

| Polymorph | Crystal system | Space group | Cell volume ($Å^3$) | Z |
|-----------|----------------|-------------|---------------------|---|
| 1IA       | monoclinic     | $P2_1$      | 522.70              | 2 |
| 1IIA      | monoclinic     | $P2_1/c$    | 1048.63             | 4 |

Both structures crystallize in the monoclinic crystal system. The asymmetric unit contains one molecule in each crystalline phase, and molecular conformations are virtually identical and found to be flat in both forms (Figure 3). As a result, this polymorph is not classified as a conformational polymorph but as a packing polymorph.

Powder X-ray diffraction (PXRD) is commonly used to identify polymorphic forms of polycrystalline samples.25,26 This method was applied to identify which is the predominant form or whether there is more than one crystalline phase in the system to be studied. Some studies have considered the average energy data of the crystalline network (energy framework analysis), which reproduces the unit cell “x” number of times and does not clearly identify which molecules are interacting. On the other hand, other studies that consider supramolecular constructs (or subclusters) neglect important information regarding the whole crystal structure.

In this context, the main goal of this study is to investigate and quantitatively identify different degrees of similarity between polymorphs. For this, four new crystalline structures are reported: two 1,3-diphenyltriaz-1-ene polymorphs (2D geometric similarity) and two polymorphs of a triazene N-oxide copper complex (1D geometric similarity). Together, a systematic analysis of eight representative series of already reported polymorphs was used to identify similarities between supramolecular structures and ensure that a whole range of similarities in polymorphs is covered. The similarity indices approach was employed to assess the comparison between clusters in a quantitative and comparable manner. A new descriptor ($I^S$) based on the comparison of the stabilization energy contribution of intermolecular interaction types present in each crystal structure is presented.

# RESULTS AND DISCUSSION

Several models are presented in this investigation to better understand the different degrees of similarity between polymorphic systems. The structures used in this investigation were named in a form such that the representation of the crystalline phase and molecule in the asymmetric unit ($Z'$) is inferred. In this sense, the structure code is defined as shown in Figure 1.

![Figure 1. Representation of crystalline structure codes used in this investigation.](image)

The first model presented in this investigation is compound 1 (Figure 2a), which is a 1,3-diphenyltriaz-1-ene with two crystalline structures: the α and β forms. This model was chosen because the crystal structures presented qualitative geometric similarity in their crystalline lattice. Each polymorphic form is classified as I and II and, in both cases, there is only one molecule in the asymmetric unit, named as molecule A. Therefore, the polymorphs received the codes, 1IA and 1IIA, and will now be addressed this way.

![Figure 2. Representation of the molecular structure of compound 1 (a) and oak ridge thermal ellipsoid plot (ORTEP) diagram of polymorph 1IA. Ellipsoids are drawn at the 50% probability level (b).](image)

![Figure 3. Molecular overlay of 1IA (red) and 1IIA (green) phases. Overlay using N1-N2-N3 atoms (RMS: 0.008).](image)
X-ray diffraction (SC-XRD) data (Figure 4). In this manner, it is observed that the bulk sample has a diffraction pattern with probable predominance of crystalline phase 1IA.

![Figure 4. PXRD patterns for the experimental bulk sample and simulated patterns from SC-XRD data for forms 1IA and 1IIA.](Image)

Raman spectroscopy provides information on molecular structures and their crystal lattice, which is an effective technique to characterize polymorphs.27,28 Geometric structural changes in the crystal can cause band shifts in the spectra, as recently reported by our research group, in an example of rotaxane polymorphs.5 In this sense, Raman spectroscopy was performed to characterize forms 1IA and 1IIA at wavelengths of 532 and 785 nm (see SI, Figures S2 and S3). However, this technique could not be used as a screening tool to distinguish between crystalline phases. The crystallization temperatures of 1IA and 1IIA presented different values probably due to different organization adopted during the crystallization cycle. Fingerprints using Hirshfeld surfaces were generated for polymorphs 1IA and 1IIA (see SI, Figure S7). In general, both fingerprint plots are almost identical (isostructural) and do not furnish quantitative insights regarding the subtle differences in crystal packing. Two sharp spikes were observed for both forms, which shows the presence of hydrogen bonds (N–H···N). In this sense, this technique, which is widespread in the literature,30–33 did not provide definitive quantitative data regarding the differences in the crystalline packing of these two polymorphs. Since the highly qualitative similarity data of both polymorphs persisted in almost all characterizations, it was necessary to go further with a supramolecular approach to acquire additional quantitative data to observe the subtle differences.

**Supramolecular Comparison.** Our previously reported interpretation of the crystal16,17,20 considers both a linear interpretation of parts (dimers) and a systemic interpretation of the whole structure (supramolecular cluster). In previous studies,18–23 we showed that the supramolecular cluster can be defined as the smallest portion of the crystalline lattice in which all necessary energetic and contact area information is represented to understand the whole crystal.

In this sense, the supramolecular cluster of each polymorph was constructed to evaluate the differences between polymorphs (for additional information, see Supporting Information). The clusters demonstrated a high level of resemblance between both polymorphs. The contact area and energetic parameters were obtained for both polymorphic phases. Voronoi–Dirichlet polyhedral (VDP) analysis in the ToposPro software was used17 to construct the supramolecular cluster and obtain the molecular coordination number (N) for each polymorphic phase. The supramolecular cluster for forms 1IA and 1IIA presented N = 18 (see SI, Figures S17, S18 and Table S3). The VDP analysis was used to determine the contact area between the M1 molecule and MN molecules (C_{M1–MN}) from the clusters. Then, crystal energy stability was determined based on the stabilization energy of the different dimers formed between the M1 and MN molecules by using quantum mechanical calculations. Results for polymorphs 1IA and 1IIA are shown in Table S3 (for further information, see Supporting Information).

A strong linear correlation between G_{M1–MN} and G_{C_{M1–MN}} was observed (r = 0.94 for 1IA and r = 0.94 for 1IIA), which shows the narrow relationship between these two parameters. Therefore, the stabilization energy between the molecules of the crystal may be directly related to the contact area (surface complementarity). A subtle difference between phases 1IA and 1IIA was observed in the G_{cluster} data (Table 3) regarding the stability of the supramolecular structure. Polymorph 1IIA presented a higher stabilization energy when compared to 1IA.

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**Table 2. Thermal Analysis Data Obtained by DSC for the Single Crystals of Polymorphs 1IA, 1IIA, and Bulk Form**

| form | T_m<sup>a</sup> (°C) | ΔH<sub>m</sub><sup>b</sup> (kcal mol<sup>-1</sup>) | T<sub>c</sub> (°C) | ΔH<sub>c</sub> (kcal mol<sup>-1</sup>) |
|------|---------------------|-----------------|-----------------|-----------------|
| bulk | 98.65 | 4.79 | 50.68 | 3.68 |
| 1IA  | 92.62 | 5.95 | 51.54 | 4.06 |
| 1IIA | 96.57 | 5.47 | 51.77 | 5.43 |

<sup>a</sup>Melting temperature (°C). <sup>b</sup>Melting enthalpy (kcal mol<sup>-1</sup>). <sup>c</sup>Crystallization temperature (°C). <sup>d</sup>Crystallization enthalpy (kcal mol<sup>-1</sup>).
Table 3. Contact Area and Stabilization Energy of the Dimers that Constitute the Supramolecular Clusters of Polymorphs 1IA and 1IIA

| dimer      | 1IA   | 1IIA  |
|------------|-------|-------|
|            | $C_{M1-MN}^a$ | $C_{M1-MN}^b$ |
| M1$\cdots$M2 | 43.18 | −9.48 |
| M1$\cdots$M3 | 43.18 | −9.48 |
| M1$\cdots$M4 | 12.66 | −2.15 |
| M1$\cdots$M5 | 12.66 | −2.15 |
| M1$\cdots$M6 | 13.20 | −1.54 |
| M1$\cdots$M7 | 16.40 | −2.15 |
| M1$\cdots$M8 | 16.40 | −2.15 |
| M1$\cdots$M9 | 13.20 | −1.54 |
| M1$\cdots$M10 | 10.14 | −1.79 |
| M1$\cdots$M11 | 4.12  | −0.40 |
| M1$\cdots$M12 | 13.49 | −2.41 |
| M1$\cdots$M13 | 13.49 | −2.41 |
| M1$\cdots$M14 | 11.40 | −1.66 |
| M1$\cdots$M15 | 18.68 | −6.19 |
| M1$\cdots$M16 | 18.68 | −6.19 |
| M1$\cdots$M17 | 11.40 | −1.66 |
| M1$\cdots$M18 | 4.12  | −0.40 |
| M1$\cdots$M19 | 10.14 | −1.79 |
| $G_{cluster}^a$ | 286.54 | 287.20 |
| $G_{cluster}^b$ | −55.52 | −56.25 |
| $G_{cluster}/C_{cluster}$ | −0.19 | −0.20 |

"Determined using software Topos through VDP analysis, in Å$^2$." $b$The energies (kcal mol$^{-1}$) were determined using the equation, $G_{M1-MN} = G_{M1-MN} = (G_{M1} + G_{MN})$. $c$Sum of all contact areas (Å$^2$). $d$Sum of all interaction energies (kcal mol$^{-1}$). $e$In kcal mol$^{-1}$ Å$^{-2}$.

This information suggests that phase 1IIA is the most favorable thermodynamically stable phase. However, it is worth mentioning that the difference between the stabilization energies is only 0.73 kcal mol$^{-1}$ and, due to such a low value, it is risky to classify which form is the "most stable" and, consequently, the most thermodynamically favored phase during crystallization. This low value in the energetic difference is in agreement with the expected range for packing polymorphs, and higher values are expected for conformational polymorphs.$^9,11$ This corroborates the findings obtained by Gavezotti,$^{35}$ according to which lattice cohesion energies of polymorphs are usually similar, with differences in a range of a few kJ mol$^{-1}$. $^{35}$

The high similarity observed in both parameters (contact area and stabilization energy) suggests classification of these polymorphs as isoenergetic and isocontact. The similarity is even more evident when the ratio between the stabilization energy and contact area of the cluster ($G_{cluster}/C_{cluster}$) is observed, which shows values of $-0.19$ and $-0.20$ kcal mol$^{-1}$ Å$^{-2}$ for 1IA and 1IIA, respectively. Moreover, the crystal packing efficiency$^{18}$ was obtained, and the results indicated another notable resemblance between the polymorphs with values of 0.74 and 0.77, for 1IA and 1IIA, respectively.

An overlay of both supramolecular clusters was used to assess the comparison between both crystal phases (Figure 5) by using the geometric parameter as the starting point. The overlay was applied by using the M1 molecule of each polymorph as reference. Then, the supramolecular cluster of each one was constructed.

High similarity between the two clusters is shown in Figure 5a and reveals an almost perfect overlap between systems from this viewpoint. The subtle difference in crystal packing is demonstrated in Figure 5b, showing that some molecules are “inverted” in the supramolecular cluster of 1IIA when compared to those in 1IA, without higher displacement of the molecular position. Moreover, it was possible to track eight dimers that are involved in this “inversion”, which is M1$\cdots$MN, where N = 4, 5, 10, 11, 12, 13, 18, and 19. At this point, it is possible to question: how significant is this inversion of eight molecules? To try to answer this question, the total difference in energy values of these eight dimers between the clusters was calculated. The result obtained was only $-0.24$ kcal mol$^{-1}$ ($-13.49$ and $-13.72$ kcal mol$^{-1}$ for 1IA and 1IIA, respectively). In this manner, this considerable geometric difference in crystalline packing did not promote any significant changes in stabilizing energy. The inversion of the molecules requires only a small amount of energy to occur, which demonstrates that there may not have been a big

Figure 5. Cluster overlay of polymorphs 1IA (red) and 1IIA (green), showing (a) high resemblance and the (b) subtle differences.
“energy barrier” to form both polymorphs. Despite obtaining such important quantitative information, it is still not possible to assess when this inversion occurs.

To establish the contribution (C and G) of each dimer in relation to the total supramolecular cluster, the raw data were normalized according to their N.17 The normalized stabilization energy (NGM1-MN) and normalized contact area (NCM1-MN) for both polymorphs are demonstrated in Figure 6. From the normalized values, the dimers can be classified into four types according to each profile,17,26 which can be used as indicators of possible major intermolecular interactions. Type I refers to directional interactions, with high stabilization energy (NG) in a small contact area (NC). Type II presents high stabilization energy in a large contact area. Type III presents small values of stabilization energy and contact area. And type IV presents small stabilization energy and high contact area.

After the normalization process, a remarkable resemblance between crystalline phases in relation to dimeric contribution in the contact area and stabilization energy aspects (Figure 6) was observed. It is worth mentioning that in this approach we compared all dimers involved in the crystalline lattice and not just some considered important dimers (synthons or motifs). Therefore, this approach allows a holistic analysis between polymorphs and furnishes a consistent and reliable method to analyze crystalline systems.

Most dimers presented values of NGM1-MN and NCM1-MN ≤ 1 (Figure 6) and both values correlated, which is typical behavior of type III. Two dimers presented type II characteristics with high stabilization values in both polymorphs, possibly related to π···π interactions. Two dimers showed values corresponding to type I, being characteristic of strong (directional) hydrogen bonds.

Even with the contact area and stabilization energy data, it was only possible to assess the resemblance and a few minor differences between polymorphic phases. Thus, it is necessary to examine even further where the differences between the polymorphs lie, the degree of similarity between these two polymorphic phases, and then compare to other reported polymorphs.

**Similarity Indices.** To understand the similarity between two supramolecular structures beyond qualitative comparisons, the recently proposed supramolecular similarity indices (I^G) were applied.16 The indices used geometric (I^G), contact area (I^C), and energetic (I^E) parameters, which were obtained by means of the supramolecular cluster, to compare the structures (for further information, see the Supporting Information). A value near one (1.0) indicates high similarity in the studied parameter, and lower values indicate a major difference between systems. Geometric analysis was carried out and considers the distances between all common non-hydrogen atoms between the reference M1 molecule and MN molecules in each considered cluster. Data were normalized by the product of the N value and the number of atom–atom distances between the monomers that constitute each considered dimer in the calculations.16 Correlation was obtained between the list of atom distances of each dimer in IIA with the list of atom distances of the corresponding equivalent dimers in IIIA. Each dimer has a unique value for contact area and stabilization energy, which is correlated with the equivalent dimer of the other clusters. The values for the similarity indices of the geometric, topological, and energetic parameters are presented in Table 4.

![Figure 6. Normalized contact area (NCM1-MN), normalized stabilization energy (NGM1-MN), and dimer classification of the supramolecular cluster of both polymorphic forms. Normalized data were obtained by NCM1-MN = N × (CM1-MN/∑CM1-MN) and NGM1-MN = N × (GM1-MN/∑GM1-MN).](image)

Table 4. Similarity Indices between IIA and IIIA for the Geometric (I^G), Contact Area (I^C), and Energetic (I^E) Parameters, and the Multiparameter Index of Similarity (I^PCG)

| comparison | I^G | I^C | I^E | I^PCG |
|------------|-----|-----|-----|-------|
| IIA vs IIIA| 0.670 | 0.980 | 0.977 | 0.809 |

A high level of contact area and stabilization energy similarity between polymorphs was observed, with values near 1.0 (Table 4), which quantitatively shows isocontact and isoenergetic behavior. Notably, this occurs regardless of the low geometric index value (I^G), which demonstrated an intermediate-to-low value (0.670). This low value suggests a higher level of difference between crystal phases. However, this is a result of the subtle difference resulting from the inversion of some molecules, as discussed in previous sections (Supramolecular Comparison).

The XPac software56,57 was used for the same comparison, as it uses only geometric data. A dissimilarity index value of 1.2 was obtained, which is considered a high level of similarity (values below 2.5).35 However, the same analysis showed that it is similar in two dimensions. This occurs because the software only considered a similar portion, i.e., the subcluster (supramolecular construct) consisting of 10 molecules, and neglected the other molecules constituting the crystal. Therefore, as demonstrated in a previous study,16 the dissimilarity index data, although quantitative, do not follow an appropriate trend of maximum and minimum. Systems of high similarity (three-dimensional, 3D) with values close to 10.0 and lower similarity values close to 1.0 are observed. This happens because a different number of molecules in each example is considered and does not allow a range of comparisons, as observed in recent studies.38,39 In other words, the x values do not provide clear quantitative information regarding complete crystal structure comparisons.16

The data furnished by the similarity indices can help quantitatively show any differences in the supramolecular cluster between polymorphic forms. A lower similarity in the geometric index (two-dimensional similarity) was observed, despite very high contact area and stabilization energy similarities. This analysis also indicates that the contact area and energetic parameters are vital in reliably indicating degrees
energetic parameters. The inheritance of the high resemblance in the contact area and triazene polymorphs (1IA used to expand the analysis (Figure 7). The case of bisphenyl similarity (between 0.8 and 0.6).16 IDCG provided a consistent considers the effect of the geometric difference and also carries the inheritance of the high resemblance in the contact area and energetic parameters.

**Application of the Similarity Indices (I²) to Other Examples.** To evaluate whether the supramolecular similarity indices (I²) are suitable to be used in polymorphs with different degrees of similarity, several additional examples were used to expand the analysis (Figure 7). The case of bisphenyl triazene polymorphs (1IA and 1IIA) has already been demonstrated, in which structures with \( Z' = 1 \) and 2D geometric similarity were compared. Therefore, it was necessary to select examples with higher \( Z' (Z' > 1) \) and that share higher geometric similarity to assess index performance. Examples that share 3D similarity, i.e., classified with the paradoxical classification of quasi-isosctructural polymorphs, were used. The phenomenon of structures with \( Z' \) higher than 1 shows great interest in the field of crystal engineering; therefore, use of these examples in the methodology of similarity indices is mandatory. Comparisons between systems with distinct \( N \) were also evaluated. Some of the models used are polymorphs that were reported in studies on degrees of isostructurality, whereas others were without any further discussions regarding the supramolecular environment or comparisons. The codes used for each molecule used here follow the previously described procedure (Figure 1).

The supramolecular clusters, contact area, stabilization energy, and overlays of all polymorphs used are described in the Supporting Information (Figures S17–S76 and Tables S3–S44). In the cases where the \( Z' \) values were higher than one, the reference molecule (M1) is indicated by its different torsions (Supporting Information, Figures S11–S16). Each \( Z' \) molecule was considered an independent reference molecule (M1) and a supramolecular cluster was constructed around each one. Compound 2 is a copper complex with an N-oxide bisphenyl triazene as the ligand. The choice for these two models relies on the observed crystal packing of each one, which shared similarities in only one dimension. Crystalline structure data can be found in the SI (Table S2).

Compounds 3 and 4, which were reported by Coles et al.13 and Chopra et al.,12 respectively, were chosen, since both studies present important highlights regarding polymorphs with high degrees of similarity. Coles et al.13 demonstrated a high level of geometric similarity between 3-chloromandelic acid polymorphs. The study was mainly performed using the XPac program. Chopra et al.12 reported a case of high \( Z' \) value for (Z)-2-fluoro-N'-phenylbenzimidamide polymorphs. The authors claimed that the reported system presents quasi-isosctructural structures (near-isostructurality) and strong similarities among the interactions involved. In this study, the average energy of neighboring molecules around the shell formed from each \( Z' \) was calculated. The energies of the neighboring shell present a similar concept to that of the supramolecular cluster17 and coordination spheres.40 These two series of polymorphs were selected because they are reported examples in the literature of polymorphs of high similarity (3D). Thus, using them for the application of similarity indices will aid in the pursuit for the frontiers of the phenomenon of quasi-isosctructurality in polymorphs. With the previous examples, all dimensions of similarity (1D, 2D, and 3D) are covered. Other examples were collected to possess enough structures in each region of similarity and, thus, have a systemic view of the phenomenon.

Polymorphs of compounds 5–8 were used in two studies involving isostructurality. Coles et al.13 (2014) used XPac to obtain the similarity dimensions and dissimilarity index (x) value of each comparison. In addition, the authors compared them to a first study in which the indices proposed by Fábián and Kálmán33 were used to identify the dimensions of isostructurality. Thus, it is convenient to add these examples, which already have values for the two methods reported in the literature, and apply the similarity indices (I²). Structures that present high disorder in their structures were not selected, which made any comparison unfeasible. The structures of these polymorphs were reported in different studies.44–48

Structures of compound 9 were obtained from a study by Kubicki (2004).39 The author reported new polymorphs through temperature variation experiments, in which qualitative analysis of the crystalline networks indicated high similarity. Examples from compound 10 were reported by Katrusiak et al.30 (2015) in a study in which temperature and
pressure varied in obtaining different crystalline phases of pyrimidine molecules.

In examples with \( Z′ > 1 \), it is necessary to generate a cluster for each molecule of the asymmetric unit and compare all clusters with each other. Only one cluster for a structure whose \( Z′ = 2 \), for example, will not be enough to represent all minimal information necessary to understand it as a whole. Obviously, the two clusters of this example should have redundant dimers, since part of a cluster will be present inside the other cluster. However, this is the most practical approach to analyze these types of systems and is conducted in this manner in other studies related to the phenomenon. 17

For structures with \( Z′ > 1 \), a discussion about the structures of compound 3 is shown as an example. The contact area and energetic data from the supramolecular cluster show a significant similarity between clusters. Compound 3IA, when compared to 3IIA, has an energetic difference of only \(-1.02 \text{ kcal mol}^{-1} \) and \(-2.46 \text{ kcal mol}^{-1} \), when compared to 3IIA and 3IIIB, respectively. The \( G_{\text{cluster}}/C_{\text{cluster}} \) parameter showed a difference of \(-0.009 \text{ kcal mol}^{-1} \) and \(-0.014 \text{ kcal mol}^{-1} \) \( \AA^{-2} \) when comparing 3IA to 3IIA and 3IIIB, respectively. The relation between energy and contact area assesses the high degree of similarity in these systems regarding the isocontact and isoenergetic behavior.

The similarity indices between supramolecular clusters were calculated to determine the degree of similarity between the forms of each compound. Index data regarding the geometric (I\(^{D}\)), contact area (I\(^{C}\)), and stabilization energy (I\(^{G}\)) parameters are shown in Figure 8 and present values that are located at the top of the similarity range previously proposed by us. 16 All supramolecular comparisons of compound 3 showed indices with values above 0.9, which is an excellent value of similarity. In this sense, the similarity indices quantitatively reflected the “reality” of the cluster overlay of these polymorphs (for further information, see Supporting Information—Table S45, Figures S77 and S78).

The 30 comparisons presented by the series of 10 polymorphs demonstrate that the geometric index (I\(^{D}\)) presents a certain stability in its values, regardless of the general degree of similarity. This result corroborates the behavior already observed in our previous study that proposed new descriptors, and also when applied to some crystalline structures of rotaxanes. 23 The range of values for I\(^{D}\) is somewhat narrow and indicates that the real minimum for this index should be somewhere between 0.6 and 0.7. Once again, this demonstrates that for a quantitative comparative index the sole use of the geometric parameter has its limitations. The advantage of the geometric parameter is that it defines the levels of isostructurality, whether in one, two, or three dimensions. However, for further analysis, other parameters that reflect the characteristics of supramolecular structures must be taken into consideration, such as the contact area and stabilization energy.

In general, the values of contact area and stabilization energy indices presented similar behavior (Figure 8b,c). Some systems showed high values of similarity for contact area and energy, often presenting isoenergetic and isocontact character, despite the low value for the geometric index. This was the case of 1IA and 1IIA and some examples of structures 4I and 4II.

To facilitate interpretation of the comparisons, only one final value was used to reflect general similarity furnishing the final contribution of each parameter to the phenomenon of structural similarity in polymorphs, i.e., the multiparameter index, IDCG, was performed (see the SI, Figure S78 and Table S45). Salbego et al. 16 (2018) proposed three distinct regions of similarity, in which we can observe that the largest portion of the comparisons remained in the intermediate region (14) or high-similarity region (14) and the remaining two in the low similarity region. As a result, two questions emerge from this analysis: the first involves the issue that many comparisons are in border regions of the proposed regions. At least five systems, which can be considered between 1D and 2D in the isostructural question, present values between 0.7 and 0.6. The question is whether the proposed regions in the first investigation are still viable.

The second question is the set of different comparisons for the same structure, a consequence of the presence of more than one molecule (\( Z′ > 1 \)), leading to the necessity of more than one supramolecular cluster comparison. In these cases, we...
should look for one final value to reflect all structure comparisons (i.e., compare the whole system). The values were observed in different regions of similarity when using molecule A or molecule B of a considered structure. One of the cases is the comparison of 4I and 4II, which are six comparisons and presented in regions of high (2) and intermediate similarity (4). These two structures were reported as quasi-isostuctural by Dey et al. (2016) and have $Z' = 2$ and $Z' = 3$ in each structure, respectively. All comparisons were expected to fall in the region of high similarity, as indicated by the authors, although the obtained indices do not represent this behavior in most of the comparisons. On the other hand, 3I and 3II presented all values in the region of high similarity, which is in accordance with the isostructurality reported by Coles et al. (2014).

This second question is regarding the problem of analyzing structures with $Z' > 1$ when comparing the clusters of all fragments, as is usually done in the literature. To avoid analyzing more than one comparison of the same structure and only compare the respective complete crystalline phases, a deviation calculation of all values involved in the same comparison between the crystalline phases (using the root mean square error) was performed. The values obtained for the IDCG index, with this new proposal, can be seen in Figure 9.

![Figure 9](https://example.com/figure9.png)

**Figure 9.** Multiparameter index (IDCG) considering unique values for each crystalline phase comparison.

There was a clear reduction in the comparisons: from 14 to 7 in the region of high similarity, 14 to 10 in the intermediate region, and maintaining 2 in the low-similarity region (Figure 9). Consequently, the letters representing the molecules in the asymmetric unit were removed because there was no further need. This new view of similarity data (Figure 9) showed a high correlation with the one observed qualitatively when cluster overlapping was observed (see the SI, Figures S48–S76), indicating that the index reflected the structural reality presented when comparing polymorphs. The values of the first six comparisons (Figure 9) reflect their isostructural character and, consequently, isoenergetic and isocontact behavior. The seventh comparison (II vs III) demonstrated a high level of similarity—despite being considered a geometrically similar system in only two dimensions—with IDCG of 0.809. This value falls close to a border region between the region of high similarity and intermediate ones. Again, the index reflects this unique case of a 2D structure, but with a highly similar character in the other two parameters.

The polymorphs that fall into the intermediate region reflect their 2D or 1D character observed in the cluster overlay, especially the so-called quasi-isostuctural polymorphs by Dey et al. (2016), which present more characteristics of intermediate similarity in this method. The similarity border that is most concerning for classification purposes is the lowest region, between intermediate and low similarity. The example of the polymorphs 7I, 7II, and 7III fall into this category. A comparison between phases I and II presented a value of 0.706, whereas the two involving the polymorphs in phase III presented values of 0.607 and 0.666. This discussion does not affect the conclusion of the proposal, since the region of interest and greater importance for studies that seek some application is the region of high similarity and the upper border. A possible change of the proposed similarity regions, shifting the border to 0.7 instead of 0.6, may be proposed after a larger number of examples and studies.

Multilinear correlation of all values of the indices (I$^G$, I$^C$, and I$^D$) and values of the final IDCG index was carried out to observe which parameter is the most relevant for investigating the similarity of polymorphs. The values in Figure 9 were used, considering only a value by crystalline phase comparison. The correlation obtained was $I^{DCG} = 0.438I^G + 0.313I^C + 0.227I^D + 0.017$; $R^2 = 0.9990$. From this correlation, it is possible to obtain important information regarding the high contribution of the energy parameter (45%) for the final value of similarity (IDCG), followed by the contact area index (32%). The geometric index contributes around 23% to the final value of IDCG. The multilinear correlation in the case of the polymorphs showed the same trend presented in the previous study that used a series of tert-butyl pyrazoles. A slight increase in geometric contribution in these systems and a consequent decrease in the energy parameter was observed. Contact area parameter contribution was the same in both investigations.

The results reinforced that the multiparameter index can provide the contribution of each of the parameters used (each distinct physical meaning) in the series of structures studied, as initially proposed. Thus, the data corroborate the previously presented conclusion, in which the geometric parameter alone did not provide reliable data on similarity, since a high value of I$^D$ can be observed even in less similar systems. The multilinear correlation shows that the contact area and stabilization energy parameters are more sensitive to reflect differences when comparing polymorphs.

**Investigation of Intermolecular Interactions.** A full data collection of each type of interaction contribution was carried out using stabilization energy fragmentation in atom–atom interaction ($G_{AI}$) analysis. For this, the polymorphs of compounds 1, 2, 3, and 4, which are structures that could represent the three main regions of similarity, were selected. Thus, the energy fragmentation in interaction types was performed for all dimers that constitute the cluster of each considered polymorph. The stabilization energies of each atom–atom interaction were obtained using the $G_{AI}$ analysis, following a procedure already reported in studies using different kinds of molecules. This analysis correlates the electron density at the bond critical point ($\rho$), obtained from quantum theory of atoms in molecules (QTAI) data, and the stabilization energy between monomers that constitute the dimers of the cluster.

The importance of this study at an interaction level is directly related to the possible properties of crystalline structures. Polymorphic phases that maintain the same kind and proportion of interaction types may be pointed out as systems with a high degree of similarity, and similar properties
may also be expected. Crystal structures that show different interaction types or contributions—such as polymorphs with bigger differences between phases—may lead to distinct properties. Due to some polymorph characteristics sharing a high energy similarity, the $G_{AI}$ analysis allowed us to observe, in these small differences of raw energy values, whether changes occur in the interactions involved. This kind of approach, in our understanding, provides an in-depth analysis to understand the similarity degree between crystal structures, since it considers all intermolecular interactions involved.

The energetic contribution of each interaction gave us helpful insight into the most important intermolecular interactions between molecules in the supramolecular cluster. The five different types of interactions present in IIA and IIIA can be seen in Figure 10a, and it is possible to observe the high degree of similarity between the two phases.

It is fascinating that, despite the geometric difference observed between the two phases (2D similarity) (Figure 5) and motivated by the subtle difference in the inversion of some molecules, differences in the types of interactions involved in the crystalline packing are not observed. Regarding the quantitative contribution of each interaction (Figure 10a), only a slight increase in the contribution of the H···C interaction was observed in IIA. In contrast, a lower contribution of the H···N interaction in the IIA form was observed when compared to IIA. In general, there is a clear domain of N···C and H···C interactions for stabilization of the supramolecular structure of both polymorphs, with contributions totalizing around 50% of the stabilization energy. The subtle differences in contribution and types of interaction in IIA and IIIA imply a characteristic close to isoenergetic behavior, in this case, isointeraction.

The contribution of the interactions of IIA and IIIA, from the fingerprints of the Hirshfeld molecular surface obtained by software CrystalExplorer, 29,54,55 is demonstrated in Figure 10b. From this approach, we return to the question of the quantitative data obtained, although it does not represent the true nature of the crystalline lattice. Different from the $G_{AI}$ analysis (Figure 10a), a higher contribution of the H···H contacts (55%) was observed, which is indicated, in this case, as the most relevant one. Using the fragmentation method, this interaction is indicated as the third interaction, with values close to 20%. Contrastingly, H···N and N···C with values close to 9% were lower when compared to the $G_{AI}$ analysis. The data from the other clusters of compounds 2, 3, and 4 (see Supporting Information, Figures S82–S85) showed similar behavior, in which an overestimation of the H···H contribution is observed. Contribution analysis of the contacts (interactions) across the Hirshfeld surface does not reflect the same results observed by the $G_{AI}$ analysis, in which all intermolecular interactions present in the crystal are considered. However, for further conclusions in this particular topic, an investigation with an even larger set of structures/models are needed.

Atom–atom interactions using the energetic fragmentation ($G_{AI}$ analysis) provide a good understanding of the energy contribution of each type of interaction in crystal stabilization. However, it depends on an extensive analysis of contribution distribution (Figure 10a) to try to understand the similarities and differences of interactions between two crystalline structures. When dealing with more than one comparative system and/or systems with a high number of intermolecular interactions, the difficulty in interpreting the results increases. Thus, a proposal to “summarize” the comparison of interaction contributions between two structures in only one final quantitative and comparable number becomes necessary. In this manner, a new descriptor called the similarity index of intermolecular interactions ($I^Q$) was proposed.

To propose the new similarity index regarding intermolecular interactions, the $G_{AI}$ analysis was considered (Figure 10a), except that the raw data (kcal mol$^{-1}$) were normalized by the number of total interactions types present in each cluster. This normalization process, once again, allows different systems to be compared. The similarity at the intermolecular interaction level ($I^Q$) between two supramolecular clusters A and B is obtained following eq 1.

$$I^Q = 1 - \frac{\sum (NG_{AI} - NG_{AIIpredict})^2}{n_{int}}$$  \hspace{1cm} (1)

In eq 1, $NG_{AI}$ is the normalized contribution of the considered interaction type observed in cluster A. $NG_{AIIpredict}$ is the normalized contribution of the considered interaction presented in cluster A and predicted from a linear equation from the equivalent interaction of cluster B. Moreover, $n_{int}$ is the number of the considered intermolecular interactions types. This index ($I^Q$) may contribute to act as a tool in the comparison of intermolecular interaction types contribution between two crystalline structures.

Using the quantitative data from the fragmentation, an index is established to show the change of interaction behavior.
between the two compared crystals. In a system with the same kind of interactions and similar contribution, the $I^{Q}$ index will show values close to 1.0. On the other hand, comparison between systems with different types of interactions and unrelated values of contribution will provide lower $I^{Q}$ values. The step-by-step process to achieve the $I^{Q}$ index is demonstrated in the Supporting Information (Figures S79–S82). $I^{Q}$ was determined for each of the comparisons between the different molecules of the asymmetric unit. Then, deviation among the values was calculated to obtain only one value per polymorph comparison (Figure 11), as already discussed for the $I^{DCG}$ index.

![Figure 11. Intermolecular interaction similarity index ($I^{Q}$) for the comparisons 1I vs 3II, 2I vs 3II, 4I vs 3II, and 4I vs 4II.](image)

The values obtained from $I^{Q}$ (Figure 11) correspond very well to the qualitative analysis and corroborate the quantitative data previously obtained. The three main regions of similarity defined for the other indices can also be used for the $I^{Q}$ index. The similarity of interactions was greater for quasi-isostructural systems, such as the 3I vs 3II comparison, indicating an isointeraction profile. The other polymorphs 4I, 4II, 2I, and 2IIA presented values consistent with their characteristics in their comparisons.

The comparison between 2I and 2II presented a very low value of $I^{Q}$, indicating significant changes both in the types of interactions and in proportion of the interactions common for both polymorphs (see the SI, Figure S82). The comparison between 4I and 4II indicated an intermediate level of similarity in intermolecular interactions, which is not as high as the similarity indicated by the authors. The well-defined regions by the $I^{Q}$ index showed the versatility of this index and its applications may be broader than the other indices.

The comparison between 1I and 3II indicated that the structural difference did not affect the similarity of the system in relation to intermolecular interactions, leading to a high value of 0.889 (isointeraction). This result corresponds well to the analysis of intermolecular interactions (Figure 10), in which, in spite of the geometric difference between crystalline phases, there was no change in the types of interactions involved and no significant modification in the contributions of the existing interactions. The $I^{G}$ value was slightly lower than the $I^{Q}$ index, and this is probably because $I^{Q}$ is more sensitive to small changes between systems. The $I^{Q}$ value considers the subtle differences in intermolecular interactions, whereas $I^{G}$ deals with a “general” energy value, considering only the energy between monomers that constitute the considered dimer.

To better understand the differences between these two indices, we can imagine a simpler system: two dimers A and B (one of cluster A and another of cluster B) with values of $-10.0 \text{ kcal mol}^{-1}$ and NG values of 2.1 and 2.0. At first sight, this particular comparison will lead to good correlation and high similarity, thus a high $I^{Q}$ value. Now we can consider that these same two imaginary dimers A and B have 4 and 2 interaction types, respectively, and that two interactions present in both clusters have different values. This will lead to a large difference in intermolecular interactions and, consequently, affect the $I^{Q}$ index.

This imaginary case helps us understand the importance of $I^{Q}$ in comparing crystalline structures, especially polymorphs, since changes in interactions are directly correlated with changes in the properties of materials. In the case of pharmaceuticals, the same idea is valid: polymorphs may or may not have activity due to subtle changes in intermolecular interactions. Therefore, having a tool that quantifies and compares systems considering intermolecular interactions and being able to be compared in the same range (metric) becomes relevant.

Considering that the multiparameter index ($I^{MP}$) allows the addition or subtraction of other parameters, one may question why not add the new $I^{Q}$ index to the $I^{DCG}$ index, for example, forming the $I^{DCGQ}$ index. This would result in a greater dilution of the contributions of each parameter in the final index, where each one would have an initial theoretical contribution of 25% of the total value (before 33% in $I^{DCG}$). For the example of 1IA and 1IIA, the multiparameter index $I^{DCGQ}$ would have a value of 0.829. This higher value, when compared to the $I^{DCG}$ value (0.809), is expected, since we are adding a high value parameter to an index that previously had two high values and one low (geometric) value. As a result, it can be inferred that this issue of dilution of parameter contribution, in a $I^{DCGQ}$ index, is reduced (from 33 to 25%) by the influence of the geometric parameter (which is the most distinct parameter in this case). In addition, the energy factor is overestimated, since both $I^{Q}$ and $I^{G}$ bring the inheritance of the energy profile (each with its characteristics) and present similar values in these polymorphs. This case would consider the use of two indices for the same parameter, which may lead to erroneous conclusions.

An additional issue to be considered is the validity of feeding an index with parameters of different natures. The original parameters ($I^{P}$, $I^{E}$, and $I^{G}$) come from dimer–dimer differences of two clusters A and B, taking into consideration geometric equivalence. In the case of $I^{G}$, the geometric equivalence is unnecessary, since the final data of the cluster as a whole are compared through the sum of the interactions present in all dimers that constitute the cluster, then considering cluster-to-cluster differences. Thus, the plausible and more coherent output is to use $I^{Q}$ as a single index.

The $I^{Q}$ index is an additional data point in the interpretation of conventional graphs of intermolecular interaction contribution (Figure 10). The graphs enable analysis by type of interactions, whereas the index provides a single final value for the entire comparison, promoting a rapid interpretation of the similarity region. Additionally, $I^{Q}$ can be used independently if the compared structures share some level of geometric similarity, since it is a global balance of interactions. For
example, in a series of structures in which one wants to analyze
which structure resembles more closely in interactions with a
certain standard structure, for use in a given application, the $I^2$ index can be used.

CONCLUSIONS

The bisphenyl triazene polymorphs $I_{IA}$ and $I_{IIA}$ were characterized regarding their physical properties. It was possible to observe the difficulty in identifying each phase with the available techniques due to the high similarity between them. Similarity indices were applied for these new polymorphs and eight other series of distinct polymorphs with different characteristics and number of molecules in the asymmetric unit. The same similarity range proposed in a previous investigation was confirmed in this study. The different regions of similarity were determined within the phenomenon of polymorphism, allowing the determination of the boundaries between the quasi-isostructural systems for the phenomenon of polymorphism, allowing the determination of
the boundaries between crystalline structures.

The multiparameter $I^{PCG}$ index was used as a robust tool to determine the total similarity within the polymorphism phenomenon. High contribution of the energy parameter (45%) to the final value of similarity ($I^{PCG}$) was observed, followed by the contact area index (32%). The geometric index contributed around 23% to the final $I^{PCG}$ value. This information reinforces the importance of the contact area and stabilization energy in assessing the degree of similarity between crystalline structures.

A new descriptor ($I^{F}$) based on the comparison of the energetic contribution of intermolecular interaction types present in each crystal structure was presented. Although only a few examples were carried out, our index provides a proof-of-principle that this descriptor reflects the nature of polymorphic intermolecular interaction similarity. This descriptor may be a versatile and applicable tool, since it can be used for systems that share no degree of similarity. In this way, the use of similarity indices to compare complete crystal structures may be a helpful tool for researchers in the crystal engineering area.

EXPERIMENTAL SECTION

Single Crystal X-ray Diffraction (SC-XRD). Single crystals of compounds $I$ and $I_{II}$ were obtained by slow evaporation of methanol at 25 °C. Diffraction measurement was performed using a Bruker D8 Venture with a Photom 100 CMOS detector with graphite monochromatized Mo $K\alpha$ radiation ($\lambda = 0.71073$ Å) for $I_{II}$, $I_{III}$ and $I_{II}$, and Ag $K\alpha$ radiation ($\lambda = 0.56087$ Å) for $I_{II}$. Absorption corrections were performed using multiscan methods. Anisotropic displacement parameters for non-hydrogen atoms were applied. The structure was solved and refined using the WinGX software package. The structures were refined based on the full-matrix least-squares method using the SHELXL program. The ORTEP projections of the molecular structures were generated using the ORTEP-3 program. Crystallographic information files (CIFs) for the novel structures were deposited at the Cambridge Crystallographic Data Centre (CCDC) under identification numbers 1885614 ($I_{II}$), 1885618 ($I_{III}$), 1885641 ($I_{II}$), and 1885683 ($I_{II}$). Crystallographic data can be observed in the Supporting Information (Figure S1, Tables S1 and S2). The other structures used for this investigation can be found at CCDC under the following identification numbers 970351, 970350, 970204, 1016402, 170329, 170330, 201620, 201621, 1209196, 1749773, 1749787, 179358, 179361, 2414649, 2414679, 2414699, 1059291, 1059297, 1059309, 1059311, and 1059311.

Thermal Analysis. The melting temperature and associated enthalpy of fusion of polymorphs $I_{IA}$ and $I_{IIA}$ were determined using differential scanning calorimetry (DSC) with a MDSC Q2000 (T-zeroTM DSC technology, TA Instruments Inc.). Dry high-purity (99.999%) nitrogen gas was used as the purge gas (50 mL min$^{-1}$). For each experiment, around 1 mg of sample was crimped in hermetic aluminum pans with lids. For each polymorphic phase, single crystals previously confirmed by SC-XRD analysis were used. The heating rate used for all samples was 5 °C min$^{-1}$. The samples were submitted to three heating–cooling cycles, with a temperature range of ±80 °C to the beginning of the decomposition temperature observed by thermogravimetric analysis (TGA). The TGA analysis was performed on a TGA Q5000 (TA Instruments Inc.). The heating rate used was 10 °C min$^{-1}$ under an inert atmosphere of N$_2$ (50 mL min$^{-1}$). The samples were weighed on a Sartorius scale (M500P) with an accuracy of ± 0.001 mg. Data were treated using TA Universal Analysis 2000 Software, version 4.5 (TA Instruments Inc.).

Raman Spectroscopy. For each analysis, one single crystal, which was previously confirmed by SC-XRD analysis, was spread on a mirror glass plate and analyzed with a Bruker Senterra micro-Raman spectrometer. The best spectra were collected using 532 and 785 nm wavelength lines with 2 and 10 mW of illumination power, respectively. The exposure time was 3.0 s and two coadditions were taken. The scattered beam was collected by an Olympus 20x objective.

Contact Area Analysis. Voronoi–Dirichlet polyhedra (VDP) was used in the ToposPro software for the construction of the supramolecular clusters. The face of the molecular VDP was considered a set of atomic VDP faces corresponding to the adjacent contacts between the atoms of two molecules. From this, we established that the area of the face of a VDP corresponds to the interaction between two molecules. The considered parameter granted by the software was the area (in Å$^2$) in contact between the molecules.

Quantum Mechanical Calculations. The stabilization energies of the intermolecular interactions of compounds were determined by single point calculations performed with geometries obtained from X-ray diffraction data. To obtain the interaction energy, density functional theory (DFT) calculations were performed using the Gaussian 09 software package at the $\omega$B97x-D/cc-pVQZ level of theory (restricted Hartree–Fock (RHF)) for structures of compounds 1, 3–10. For structures $I_{IIA}$ and $I_{IIIA}$, the calculations were performed at the $\omega$B97x-D/cc-pVQZ-PP level of theory (unrestricted Hartree–Fock (UHF)). The counterpoise method of Boys and Bernardi was employed to minimize the basis set superposition error. The energy value used was the electronic energy furnished by Gaussian. The dimer energies ($G_{M_{i}-M_{j}}$) were determined by the energy values of the dimer energy ($G_{M_{i+M_{j}}}$) minus the sum of the M1 molecule ($G_{M_{1}}$) and MN molecule ($G_{MN}$) energies. All QTAIM analyses were performed with the aid of the AIMALL program package. The wavefunctions used in the QTAIM analysis were generated at the above described level of theory.
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