Solving the inverse materials design problem with alchemical chirality

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Massive brute-force compute campaigns relying on demanding ab initio calculations routinely search for novel materials in chemical compound space, the vast virtual set of all conceivable stable combinations of elements and structural configurations which form matter. Here we demonstrate that 4-dimensional chirality, due to an ‘alchemical’ reflection plane in the nuclear charge space of the electronic Hamiltonian, dissects that space, defining approximate ranks among sub-sets which effectively reduce its formal dimensionality, and enable us to break down its combinatorial scaling. According to perturbation theory, distinct ‘alchemical’ enantiomers must share the exact same electronic energy up to third order — independent of their respective covalent bond topology, imposing relevant constraints on chemical bonding. Alchemical chirality enables the ‘on-the-fly’ establishment and exploitation of new trends throughout compound space without empiricism—as demonstrated by accurate predictions of chemical bond energies, by perturbed electron density analysis of BN doped benzene, and by ranking stability estimates for exhaustive BN doping in over 2,000 naphthalene and over 400 million picene derivatives on the proverbial back-on-the-envelope.

I. INTRODUCTION

The computationally demanding virtual simulation of molecules and materials, performed to predict their physical, materials and chemical properties, has become a routine tool in the molecular and materials sciences. Current efforts geared towards computational materials and molecular design might enable one day the realization of the holy grail of automatized experimental design and discovery. Driven by the accelerating progress of compute hardware and statistical learning (artificial intelligence), first seminal examples of integrating sophisticated software and robotics to perform experimental sequences and to establish rules and trends among properties and materials, as well as their synthesis, in real life have recently been introduced [1–5]. However, the lofty goal of ‘materials on demand’ has still remained elusive, even when doing it just in silico.

The use of empirical trends to guide experimental design has had a long tradition in the chemical sciences. Popular examples include Mendeleev’s discovery of the periodic table, Hammett’s relationship, Pettifor’s numbering scheme, Bell-Evans-Polanyi principle, Hammond’s postulate, or Pauling’s covalent bond postulate [6]. Modern systematic attempts to establish and exploit such rules in terms of quantitative structure-property relationships have led to computationally advanced bio-, chem-, and materials-informatics methodologies [7]. Unfortunately, these methods are typically inherently limited to certain applicability domains, and do not scale due to their empirical nature [8]. To rigorously explore the high-dimensional chemical compound space (CCS) [9], i.e. the combinatorially scaling number of all conceivable molecules or materials (usually defined by composition, constitution, and conformation), the quantum mechanics of electrons ought to be invoked.

It is thus not surprising that ab initio based materials design approaches have been at the forefront for more than 20 years [10–14], and have played a major role in popularizing the use of efficient and accurate quantum methods, such as density functional theory [15–19]. Sampling CCS from scratch, even when done within efficient optimization algorithms, is typically encyclopedic in nature, and ignores the many underlying relations among different properties and materials. Quantum machine learning models [20] statistically exploit such implicit correlations, hidden in the data, and have been successfully accelerated CCS exploration campaigns [21]. Machine learning efficiency and transferability demonstrably benefits greatly from explicitly enforcing known relationships (e.g. translational, rotational, or atom index invariances) directly in the model construction, rather than having to learn them agnostically from data [22]. Specific examples include explicitly imposing forces and curvatures in the loss function [23–25], spatial symmetry relations [26, 27], or arbitrary differential relations [28]. But even for the most efficient and transferable statistical models, e.g. the atom-in-molecule fragment based approach [29], the acquisition of training data in sufficient quantity and quality requires considerable up-front investments.

In this paper, we introduce the fundamental notion of a new symmetry relation in CCS which is fully consistent with the ab initio view of matter [30], and effectively enables us to solve the inverse materials design problem in a non-empirical and highly efficient manner. Spatial symmetry considerations have been crucial for the unravelling of some of the most fundamental laws of nature and are heavily used in many fields. In ab initio calculations, for example, symmetry group theory arguments are common to reduce computational complexity and load.

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FIG. 1. A: Enantioselective catalysis enables the synthesis of either conventional enantiomer, related to its counterpart through spatial reflection symmetry. B: Alchemical (not spatial) chirality at four sites in a diamond cubic lattice relates BN doped alchemical enantiomers and through alchemical reflection (Boron, Nitrogen, and Carbon in red, blue, and gray, respectively). C: Predicted ($E_{\text{ACE}}$) from alchemical chirality estimation (ACE) versus true ($E_t$) single bond dissociation energies according to the 2-body rule for adjacent elements QRS using published DFT results for main-group elements in the 2nd and 3rd row of the periodic table and assuming all bond-distance to correspond to 2 Bohr. Predictions of bonding energies between QR and RS elements are denoted as LHS and RHS, respectively. Successive recursive application of the rule throughout either period is denoted by ‘rec’.

Symmetry constraints on compositional degrees of freedom would be highly desirable in order to establish general rules among distinct materials and properties, and to generally improve our understanding of chemical compound space [30].

Here, we propose to use a reflection plane in the nuclear charges of the external potential in the electronic Schrödinger equation to define ‘alchemical’ chirality. An illustrative comparison of conventional spatial and alchemical chirality is given in Fig. 1 for a tetra-valent carbon atom with four different substitutions and for doubly BN doped carbon in the diamond crystal structure, respectively. Exchange of the dopant atom sequence from NBBN → BNNB is tantamount to an alchemical reflection of corresponding nuclear charge differences around the perfectly symmetric nuclear charge reference plane $\tilde{\sigma}$ spanned by the carbon atoms in pristine diamond. No other spatial symmetry operation (rotation, translation, reflection) can interconvert these systems, thereby necessitating the concept of 4-dimensional alchemical chirality. Note that chirality crucially depends on dimensionality, e.g. the letter L is chiral within 2 dimensions.

II. BONDS

The external potential energy differences between the compound defining the reference reflection plane (such as carbon atoms in diamond in Fig. 1B) and either alchemical enantiomer are exactly mirrored in magnitude (opposite sign). As such, while the corresponding electronic Hamiltonians are alchemical mirror images of each other, their respective solutions to the electronic Schrödinger equation are not necessarily equal. More specifically, for reflections around atoms with identical chemical environments, we show that the electronic energy of corresponding alchemical enantiomers must be degenerate up to third order within alchemical perturbation density functional theory [31] (See Theory section below). As such, alchemical enantiomers are only approximately degenerate in their electronic energy.

It turns out, however, that this approximation is typically very fair, and that useful rules for chemical binding can be derived. For example, by enumerating all colored connected graphs that are sub-graphs of hexagonal lattices we obtain the following alchemical chirality estimate (ACE) of 2-body interatomic bonding for the electronic energy

$$E_{QR} \approx E_{SR} + (E_{QQ} - E_{SS})/2$$

where QRS correspond to three adjacent elements in the periodic table. While seemingly reminiscent of Pauling’s electronegativity based bond energy estimate [6], $E_{QS} = (E_{QQ} + E_{SS})/2 + \Delta \chi$, we stress the difference that this ACE relation is obtained from pure symmetry and perturbation theory based considerations, and is exact up
to third order within APDFT for alchemical enantiomers. Pauling, by contrast, merely postulated his Ansatz. Furthermore, our rule relies on bonding information involving three distinct and adjacent chemical elements rather than just two, and, maybe more importantly, it pertains to the electronic potential energy only, i.e., without the nuclear repulsion which is trivial to add a posteriori. This rule is easily verified for the example of BC and CN bonds in tetrahydrodiazadiborine (Fig. 4) by simply comparing the sum of all bond energies in either alchemical enantiomer (resulting in $E_{BC} \approx E_{NC} + (E_{BB} - E_{NN})/2$).

Subtracting nuclear repulsion estimates from published DFT data for all single bonds between main-group elements from the second and third period saturated by hydrogen [32], ACE yields bond energies of elements QR, i.e. solely based on bonding information of elements SR, QQ, and SS for adjacent elements QRS in the same period. As shown in Fig. 1, predicting bond dissociation energies among elements R and Q or S (to the left or right in the period) generates remarkably accurate predictions for bonds among elements in either period with a mean absolute error of $\sim 10$ kJ/mol, not far from the highly coveted ‘chemical accuracy’ of $\sim 4$ kJ/mol. A linear fit through all the diverse chemistries encountered yields a slope of 1.04, an off-set of $\sim 7$ kJ/mol, and a correlation coefficient of 0.981. Successive daisy-chaining across any given period represents a straightforward extension which dramatically reduces the number of reference bonds required for ACE—but only at the cost of reduced accuracy: The MAE increases to $\sim 22$ kJ/mol, i.e. still better or on par with common generalized gradient based approximations to the exchange correlation potential in DFT [33].

Further ACE rules emerge when increasing the alchemical nuclear charge radius ($\Delta Z = \pm 1, \pm 2$) with PQRT corresponding to five adjacent elements in the periodic table: $E_{FR} \approx E_{TR} + (E_{PP} - E_{TT})/2$, $E_{PQ} + E_{QT} + 2E_{SR} \approx E_{PS} + E_{ST} + 2E_{QR}$, and $2E_{PR} + E_{QT} + E_{ST} \approx E_{PV} + E_{PS} + 2E_{TR}$. These rules are identical for the 3D diamond lattice and the 2D hexagonal graphene structure. Note that other graph lattices could yield additional rules, and that rules for interatomic 3- and n-body contributions to binding exist as well. For example, invoking $\Delta Z = \pm 1$ only, one finds the 3-body rule that $E_{SRQS} + 2E_{RQS} + E_{RQR} \approx E_{SRQS} + 2E_{BQS} + E_{BRS}$. A systematic enumeration of ACE rules for 2- and 3-body terms for graphene and diamond is given in the SI.

### III. SYMMETRY FLOW-CHART

To integrate alchemical chirality within the symmetry point-group flow-charts common to molecular or crystallographic studies, a flowchart is presented in Fig. 2. A necessary condition for alchemical enantiomers to occur is the absence of linearity, i.e. a $C_{\infty v}$ symmetry element. Furthermore, alchemical enantiomers exist only if pairs of distinct atoms can be mapped onto each other under a symmetry operation, a consequence of the reflection in nuclear charge space that defines alchemical enantiomers. If a compound has no spatial symmetry, atom sites with similar electron density derivatives $\partial^2 \rho$ constitute these pairs exactly as strictly symmetry-equivalent atoms do. At least two such pairs need to exist in a compound to obtain alchemical enantiomers which are different chemical objects. For a single pair of symmetry-equivalent atoms, the alchemical reflection in nuclear charge space would trivially connect two spatially equivalent compounds.

### IV. RANKING

To apply ACE to inverse materials design problems, we show-case in applications in well defined sub-regions of CCS and solve three specific and increasingly challenging design tasks. All three use-cases address the combinatorial design problem of how to dope planar hexagonal lattices to an increasing extent (6, 10, and 22 carbon atoms, respectively). Hexagonal lattices are archetypical scaffolds, e.g. relevant in the design of graphene-inspired materials for nano-technological devices [34], catalytic surfaces [35–37], porous BN-doped based nano-fibers for battery materials [38], or 2D materials in general [39]. Just doping with BN already results in a combinatorial explosion, already for the 77 smallest benzoid-like structures, the number of possible unique BN-doped derivatives exceeds 7 tera [40]. As such, we believe that it is warranted, and without loss of generality, to focus on constitutional isomers in rigid lattices for which thermal on geometrical distortions can be neglected. Note that relative off-sets in total energies due to differences in stoichiometry are straightforward to estimate, and typically occur on different orders of magnitude, and that subsequent inclusion of configurational degrees of freedom within alchemical predictions is possible, as already demonstrated for small molecules [41, 42] and ionic, metallic, and semiconducting solids [43–45]. As such, the focus of the fol-
approximately equal amount, leading to the near-degeneracy of the electronic energies of the two alchemical enantiomers. To quantify this effect, Fig. 4 also shows the corresponding APDFT based electronic energy estimates up to 5th order (within perturbation theory the energy order precedes the wave-function order), numerically demonstrating that the degeneracy is identical in 2nd order, and starts to deviate by ~0.01, 0.02, and 0.025 Ha for 3rd, 4th, and 5th order, respectively. The 5th order predictions deviate from the actual electronic energies by ~0.03 and 0.02 Ha, respectively. Addition of the nuclear repulsion terms typically lifts the approximate degeneracy, resulting in quantitative ACE estimates as well as simple inequality rules for total energies that $E_{\text{BNNBCC}} > E_{\text{NBBNCC}}$ due to the larger nuclear repulsion experienced when atoms with larger nuclear charges (nitrogens in this case) are closer in proximity to each other than atoms with lower nuclear charges (boron).

Such accuracy, while not on par with explicitly correlated quantum chemistry calculations in large basis sets, is on a similar scale as generalized gradient approximated DFT or semi-empirical quantum chemistry methods — typically sufficiently accurate for successful computational materials design studies as demonstrated for the many examples of successful computational discovery of heterogeneous catalysts [47], or the materials project data-set [48]. The following two use-cases explore this question for ACE based ranking in a more systematic and comprehensive fashion.

### A. BN doped benzene

As a first use-case we provide an in-depth but intuitive illustration of alchemical chirality with benzene, its six equivalent carbon atoms as the mirroring reflection plane, and the alchemical enantiomers corresponding to carborazine (C$_2$H$_6$B$_2$N$_2$, tetrahydrodiazadiborine (THDADB)). Since second order APDFT — resulting in alchemical normal modes to define a complete basis in certain sub-spaces of CCS — has already been applied to benzene [46], the occurrence of 6 degenerate estimates among the 11 constitutional isomers of tetrahydrodiazadiborine (C$_2$H$_6$B$_2$N$_2$) can now be readily explained thanks to alchemical chirality: They represent three pairs of alchemical enantiomers. For the select enantiomer pair BNNBCC/NBBNCC, a molecular planar analogue to the crystalline example (Fig. 1B) is given in Fig. 3, contrasting the conventional spatial reflection plane $\sigma$, with the alchemical reflection plane $\sigma_A$. While NBBNCC and BNNBCC are mutually achiral in the sense of conventional spatial 3D chirality, the alchemical chirality relation between the two becomes obvious, with regular benzene corresponding to the reflection plane.

In Fig. 4, the corresponding perturbing potentials (exact mirror images of each other) for the two benzene enantiomers from Fig. 3 are shown, as well as the resulting electron density derivatives of benzene up to 4th order. Corresponding figures for all other BN doped benzene mutants are provided in the SI. As it becomes obvious already by visual inspection, the perturbed densities are near identical for even orders, and alchemically镜ored for odd orders. This indicates that the perturbational series in APDFT [31] extrapolates to an approximately equal amount, leading to the near-degeneracy of the electronic energies of the two alchemical enantiomers. To quantify this effect, Fig. 4 also shows the corresponding APDFT based electronic energy estimates up to 5th order (within perturbation theory the energy order precedes the wave-function order), numerically demonstrating that the degeneracy is identical in 2nd order, and starts to deviate by ~0.01, 0.02, and 0.025 Ha for 3rd, 4th, and 5th order, respectively. The 5th order predictions deviate from the actual electronic energies by ~0.03 and 0.02 Ha, respectively. Addition of the nuclear repulsion terms typically lifts the approximate degeneracy, resulting in quantitative ACE estimates as well as simple inequality rules for total energies that $E_{\text{BNNBCC}} > E_{\text{NBBNCC}}$ due to the larger nuclear repulsion experienced when atoms with larger nuclear charges (nitrogens in this case) are closer in proximity to each other than atoms with lower nuclear charges (boron).

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### B. BN-doped naphthalene

Interestingly, since the equivalence of the electronic energies is transitive, having a second reference that connects one alchemical enantiomer with a third one allows us to build chains of alchemical enantiomers that must have similar electronic energies, consequently enabling a ranking of molecules within one such group solely by the magnitude nuclear-nuclear interaction. Fig. 5A illustrates the chaining of exact ($\sigma_A$) and approximate ($\tilde{\sigma}_A$) alchemical enantiomers for BN-doped naphthalene where four pairs of alchemical enantiomers could form such a chain. For reflections along the exact alchemical symmetry axis $\sigma_A$, the energy difference is 1 mHa or 8 mHa, respectively. For cases with approximate alchemical symmetries $\tilde{\sigma}_A$, this energy difference is notably larger (237 mHa), but typically still much smaller than the nuclear repulsion energy contributions.

Overall, exhaustive charge-neutral and iso-electronic BN doping in naphthalene leads to 2,285 unique derivatives for which we have used ACE based chaining to establish energetic ranks. Having identified all alchemical enantiomers through exhaustive scanning within one stoichiometry (stoichiometries as a whole can be ranked with existing relations[49]), we have ranked all possible molecules using ACE within groups of molecules approximately degenerate in electronic energy. These groups form the connected components of a graph where all
molecules are nodes and only alchemical enantiomers are connected, thus allowing us to exploit the transitivity of the electronic energy degeneracy. Within these groups, solely the nuclear-nuclear interaction induces the ranking. Among the groups, we rank based on averaged bond-counting results for their bond energies, where bond-energies have been obtained by fitting to the imposed energy degeneracies among all pairs.

Using CCSD/cc-pVDZ as a ground-truth QM method for all naphthalene derivatives, we have performed an exhaustive validation of alchemical ranking, resulting in a Spearman correlation coefficient of 0.9899. Dissecting CCS in all the various possible stoichiometries of BN doped naphthalene, the scatter plot of ACE rank vs. QM rank results in a very reasonable correlation, as shown in Fig. 5B. To place ACE based ranking in perspective, the inset of Fig. 5B also reports corresponding sorted ranking errors (wrt. CCSD) when using PBE0 [50–52], PBE [16], xTB [53], PM6[54], bond-counting (BC), UFF [55] with respective Spearman correlation coefficients of 0.9998, 0.9983, 0.9966, 0.9592, 0.9562, and 0.9021. In terms of computational cost invested to rank all naphthalene derivatives, ACE ranking is slightly more expensive than bond counting, UFF or PM6 in terms of accuracy however, it clearly outperforms all three—without any need for empirical knowledge or fitting to external data! It is worth noting that bond counting is the only method that has been re-parametrized on this particular data set which explains its good performance compared to PM6. As also shown in Fig. 5B, ACE reproduces bond type frequency trends as a function of rank. While the accuracy of ACE itself is not on par with more advanced semi-empirical quantum chemistry (xTB) the sorted ranking error distribution suggests that alchemical ranking is closer to xTB than it is to PM6. However, in contrast to alchemical ranking, xTB relies on substantial empirical data for fitting. While PBE, B3LYP, and PBE0 are obviously more accurate, their computational cost is also three orders of magnitude larger than xTB (~ 40 s). As such, we conclude that alchemical ranking is superior to bond-counting and PM6, and could represent a viable alternative to xTB if accuracy thresholds are less stringent and computational load is high.

C. BN doped picene

As a third usecase we have used ACE to explore and deepen our understanding of the CCS spanned by the 413,887,189 unique k-fold BN doped derivatives of picene (See Fig. 6, with $k < 7$ and $k > 9$). Dissecting its CCS first by all stoichiometries, we can use the trends to map out obvious structural features as a function of rank in order to detect useful descriptors for structure-property relationships. Roughly speaking, results Fig. 6 suggest that the energy will typically decrease within any given stoichiometry as the number of CC, BN, NN, and BB bonds increases, increases, decreases, decreases, respectively. Differences in B and N counts in any ring (a measure of compositional homogeneity per ring), hardly affects the energy except for the heavily BN doped stoichiometries (11 and 10 BN pairs). The degree of clustering (as measured by root mean squared distances) varies wildly with little correlation for BB, BN and NN, as long as only few sites have been doped. As the degree of BN-doping increases, the strong stabilising effect of BN...
FIG. 5. (A) Chains of alchemical enantiomers used for ranking molecules. Each alchemical symmetry plane is denoted with a grey line and the reference molecule, the chiral center. Exact symmetries are denoted $\sigma_A$ while approximate symmetries are given as $\tilde{\sigma}_A$. All CCSD electronic energies given in Hartrees. (B) All 2,285 unique BN-doped naphthalene derivatives ranked by their total energy as obtained from quantum chemistry calculations compared to the ranking from alchemical chirality estimation (ACE). Histogram colored by number of molecules in a given bin. Energy scales shown in Hartree for each stoichiometry. Energies relative to the most stable molecule. Two representative molecules of same sum formula $\text{C}_4(\text{BN})_3$ and geometry are annotated. Inset shows the distribution of rank errors sorted in ascending order for different methods: the force field UFF, bond counting (BC), semi-empirical PM6, ACE (this work), semi-empirical xTB-GFN2 (xTB), and the DFT methods PBE, and PBE0, both with density-fitted cc-pVDZ basis set. Side panels show bond type frequencies. 

A common problem in materials design consists of identifying global optima. In Fig. 6, we also show the least and most stable BN doped derivatives for each stoichiometry, as identified by ACE. As more and more carbon sites are BN-doped, the sites interact more strongly and patterns emerge that are in line with the aforementioned summary observations, e.g. the energetically unfavourable nature of nitrogen clusters. Thus even if high accuracy is needed eventually, pre-filtering with ACE can dramatically accelerate the identification and discovery of candidate compound lists which are to be treated with higher level quantum methods subsequently.

V. CONCLUSION

We have noted the existence of ‘alchemical’ chirality, a 4-dimensional chirality in the nuclear charge space which is spanned by external potentials in the electronic Hamiltonian. While the symmetry is exact for the perturbing Hamiltonians of the corresponding enantiomers, the corresponding variational electronic energies are degenerate only up to third order. This is similar, in concept, to parity violation [56] that yields slight energy differences between spatial enantiomers, even though this effect is orders of magnitude smaller. Our findings indicate that the range within which alchemical chirality estimates (ACE) hold is sufficiently large to be relevant for substantial swaths of CCS. From a practical point of view, both experiments and simulations have a resolution limit resulting from method uncertainty beyond which molecules or crystals are indistinguishable. Alchemical chirality offers a new way to find those symmetrically related enantiomers with practically identical energies from which only one needs to be considered in terms of measurements or calculations.

Specifically, we have provided novel ACE based bonding rules of chemical bonds and angles. Numerical bonds subdivides the constitutional isomers into groups of identical BN bond count within which boron clusters are stabilising while nitrogen clusters are destabilising. Since the BB bond effect is visible for any fixed number of BN bonds, we can conclude that the impact of BN bonds on stability is larger than the one of BB bonds. Following this concept of conditional order, and with the data shown in Fig. 6 and the extended version thereof in the SI, we can identify the following stabilising design patterns in decreasing order of strength: i) add BN pairs, ii) maximize CC bonds, iii) substitute sites shared between rings, iv) maximize BN bonds, v) avoid N substitutions on rings sharing a larger amount of bonds with other rings, and vi) balance BN substitutions in each ring. Note how ACE has given us access to a complete ranking without a single quantum chemistry calculation. While the individual rank might not be completely accurate, as shown in Fig. 5B, the emerging pattern yields relevant and novel structure property trends as a direct consequence of alchemical chirality.
FIG. 6. Trends among all 414 million BN-doped picenes of the select stoichiometries (top) ranked by their total energy based on ACE. Each row shows a geometric property for each stoichiometry as a function of the ACE rank and averaged over 200 bins. Those molecules that are the most or least stable for each stoichiometry are listed separately.

Evidence for single bonds of 2nd and 3rd row main-group elements even suggests that DFT level of accuracy can be reached with such rules. CCSD based perturbation theory results for tetrahydrodiazadiborine (and all other possible BN doped benzene derivatives) have served the illustration of alchemical chirality, indicating near-degeneracy for the electronic energies of alchemical enantiomers, deviating by roughly two orders of magnitude less than a covalent bond. Correspondingly, ACE can serve the energy ranking of more complex systems, as discussed for the two use-cases of BN doping in naphthalene and in picene. Using CCSD/cc-pVDZ as a reference, the comparison to bond-counting, semi-empirical DFT, generalized gradient approximated DFT, and hybrid DFT results for the over 2,000 naphthalene derivatives indicates that the alchemical chirality based ranking outperforms bond counting and common semi-empirical quantum chemistry (PM6), while approaching the performance of semi-empirical DFT (xTB) in terms of fidelity—at negligible computational cost and without empiricism. For the BN doping of picene, ACE of more than 400M unique derivatives has enabled the establishment of structural trends, as well as the identification of the least and most stable derivatives for each stoichiometry. We stress that for all the alchemical chirality derived results presented, not a single quantum chemistry calculation was necessary.

Overall, our arguments and numerical results indicate that the concept of alchemical chirality represents a novel, fundamental and useful symmetry relation in CCS. Its power to dissect, group, and rank throughout the CCS of constitutional isomers holds great promise to further
progress towards the overall goal of virtual computational materials discovery. Future work will deal with current limitations, such as the necessity to perform alchemical changes only in close vicinity in nuclear charge space, to restrict changes to be iso-electronic and neutral, or to rely on scaffold lattices with fixed nuclear positions. It would also be interesting to study how alchemical chirality can be exploited using quantum machine learning models.

VI. THEORY

Previous methodological work tackling chemical compound space from first principles through variable ‘alchemical’ nuclear charges included 4-dimensional density functional theory [57], the use of thermodynamic integration [58], trends among vertical energies [49], entire potential energy surfaces [59], nuclear grand-canonical ensembles [60, 61], linear combinations of atomic potentials [62], and APDFT [31]. Starting in 1996 with stability of solid solutions [63], multiple promising applications, based on quantum alchemical changes, have been published over recent years, including thermodynamic integrations [64], mixtures in metal clusters [65, 66], reactivity estimates [67], water adsorption on BN-doped graphene [68], BN-doping in fullerenes [69], protonation energy predictions [70, 71]. However, apart from near-sightedness studies on chemical transferability [72], general rules, rooted in the quantum mechanical framework of variable composition are mostly still lacking. Here, we describe ‘alchemical’ chirality, defined by compositional reflection in the nuclear charge mirror plane of some reference system. Such a reflection defines alchemical enantiomers as distinct constitutional isomers with electronic energies being identical up to third order. Alchemical chirality relates distinct molecules and materials in ways which, to the best of our knowledge, have not yet been discussed before.

Calculating the total potential energy of any compound $U$, most commonly obtained within the Born-Oppenheimer approximation and neglecting relativistic effects, represents the probably most crucial step in any atomistic simulation study. It consists of two contributions, the nuclear repulsion which can be evaluated trivially, and the more involved electronic energy $E$ which, within the picture of density functional theory, sums up the electrons’ kinetic contributions as well as their interactions with each other and with the nuclear charges. As such, $E$ is key, and typically represents the principal goal of most modern electronic structure theory developments, including improved DFT approximations. But also text-book discussions, such as the virial theorem in physical chemistry, deal with the discussion of the chemical bond in terms of electronic energy.

The difference in electronic energy $E$ between a reference reflection molecule, constituting a maximum in electronic energy, with electron density $\rho_r$ and some “adjacent” iso-electronic alchemical enantiomer $i$, $\Delta E = E[\rho_r(r)] - E[\rho_i(r)]$, can be obtained through thermodynamic integration over the coupling constant $0 \leq \lambda_i \leq 1$ which linearly interpolates the nuclear charges between reflection molecule and alchemical enantiomer. According to Hellmann-Feynman, $\Delta E = \int_{-\infty}^{+\infty} dr \Delta v_{ri}(r) \int_0^1 d\lambda_i \rho(r, \lambda_i)$ with $\Delta v_{ri}(r)$ as difference in external potential between reflection molecule and alchemical enantiomer [31, 73].

Approximating this difference by a Taylor series expansion ($\approx \sum_{n=1}^{\infty} \frac{1}{n!} \int_{-\infty}^{+\infty} dr \Delta v_{ri}(r) \left. \frac{\partial^{n-1} \rho(r)}{\partial \lambda_i^{n-1}} \right|_{\lambda_i=0} )$, subtracting the energy of the other alchemical enantiomer $j$ (i.e., $\Delta v_{ri} = -\Delta v_{rj}$), and rearranging results in

$$\Delta E_{ij} \approx \sum_{n=1}^{\infty} \frac{1}{n!} \int_{-\infty}^{+\infty} dr \Delta v_{ri}(r) \left( \frac{\partial^{n-1} \rho_i(r)}{\partial \lambda_i^{n-1}} + \frac{\partial^{n-1} \rho_r(r)}{\partial \lambda_j^{n-1}} \right)$$

which is zero for all orders $n$ as long as $\frac{\partial^{n-1} \rho_r}{\partial \lambda_i^{n-1}} = -\frac{\partial^{n-1} \rho_i}{\partial \lambda_j^{n-1}}$. Eq. (2) must be exactly zero up to third order since (1) the zeroth order term $E[\rho_j]$ cancels, (2) the first order Hellmann-Feynman term $\int dr \Delta v_{ri} \rho_r$ is zero for highly symmetric systems (as necessary to define an alchemical reflection plane) due to $\Delta v$ and $\rho_r$ being odd and even functions [46], and (3) due to the second order term canceling since $\rho_i \rho_r = \sum_j \Delta Z_i \Delta Z_j \rho_i \rho_r$ differs for $i$ and $j$ only by the sign of $\Delta Z_i$. In other words: if a molecule contains a set of disjoint pairs of atoms of the same elements which share nearly the same chemical environments, it can bee seen as the nuclear charge reflection plane, or chiral center, of all corresponding alchemical enantiomers. For example, the benzene molecule is the chiral center for 3 pairs of alchemical enantiomers (for $\Delta Z = \pm 1$, i.e. BN doping). For iso-electronic charge-neutral mutations, alchemical enantiomers differ from their chiral center only in their nuclear charges such that the net nuclear charge difference of each atom pair is zero.

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