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Designing Molecules by Optimizing Potentials

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Abstract: The astronomical number of accessible discrete chemical structures makes rational molecular design extremely challenging. We formulate the design of molecules with specific tailored properties as performing a continuous optimization in the space of electron−nuclear attraction potentials. The optimization is facilitated by using a linear combination of atomic potentials (LCAP), a general framework that creates a continuous property landscape from an otherwise unlinked set of discrete molecular-property values. A demonstration of this approach is given for the optimization of molecular electronic polarizability and hyperpolarizability. We show that the optimal structures can be determined without enumerating and separately evaluating the characteristics of the combinatorial number of possible structures, a process that would be much slower. The LCAP approach may be used with quantum or classical Hamiltonians, suggesting possible applications to drug design and new materials discovery.

The purposeful design of molecules with optimized properties is daunting because the number of accessible stable molecules is immense.[1,2] For example, the number of medium-sized organic molecules considered to be possible drug candidates exceeds Avogadro's number.[2] At present, there is no viable experimental or theoretical scheme to search this rich structural space in a systematic and purposeful manner. The tremendous challenge of molecular optimization in such a vast space arises from the discrete nature of molecules. Each molecule is unique in structure and properties, and no set of continuous variables categorizes properties in the molecular space. We introduce an approach that "smoothes out" the chemical properties in the space of discrete target structures and thus facilitates property optimization. Smoothing of the property surfaces is shown schematically in Figure 1.

Much molecular design currently relies on (a) modifying known favorable motifs and exploring property changes, (b) developing structure−function relations and using rational design strategies,[3,4] and (c) employing combinatorial methods.[5−7] These approaches are limited either in their scope or in their efficiency. Efforts that aim to control quantum dynamical processes and to design optical waveguides[8−12] confront similar design challenges to those of molecular design. However, dynamical control focuses on tuning field−matter interactions for specific molecules. For solids, average medium models, like the virtual crystal model (VCM),[13] employ "counterfeit" or average atom descriptions to explore how properties vary with stoichiometry, but VCMs do not address molecule design issues. Our goal is to establish a flexible framework for the theoretical design of optimized molecules.

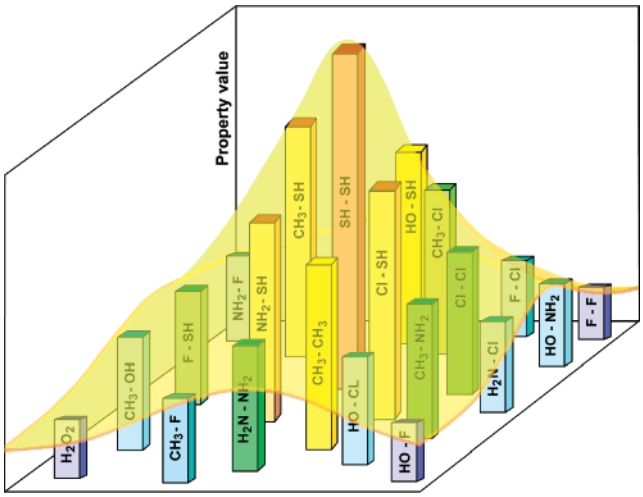

Figure 1. A schematic representation is shown of properties values. Bar heights represent electronic polarizabilities for 21 specific candidate structures (chemical structure is noted) and the smooth surface on which the property optimization is performed. Establishing a well behaved property surface that interpolates among the realizable molecules is a key aspect of the approach described here.

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Purposeful molecular property optimization is familiar in chemistry. Examples of organic nonlinear optical chromophore optimization, ligand−receptor binding free energy optimization, structure prediction of binary alloys, catalyst design, and molecular building block design for self-assembled nanostructures are familiar.[4−7] Progress is made using the power of chemical intuition and combinatorial approaches. The force of modern theory is largely used to interpret known results and to build up the base of chemical intuition in the context of a particular chemical design challenge. Our aim is to establish schemes that will allow theory to lead the discovery of new molecular and material structures optimized with respect to their properties and functions. To the best of our knowledge, there is a paucity of approaches to this challenge, the challenge of moving in the "inverse direction" from target property to molecule. As such, the aim of this paper is to set forth one strategy that can begin to address the open challenge of the inverse design of optimized molecular structures.

The dream of establishing "molecular property functionals" is a long standing one. Parr noted that chemistry can be thought of as the study of property functionals of the number of atoms present, the atomic number of each atom, and the number of electrons. Indeed, he suggested that these parameters could be thought of as continuous variables.[14] Mezey further explored atomic number dependent theory.[15] These were employed to examine molecular potential energy surfaces, but they do not seem to have been used to examine other molecular properties or, more importantly, to optimize those properties (the goal of the study described here). Allowing a moderately large number of atoms to vary in type and position without chemical constraint, while a general approach to optimization, seems to be a daunting starting point (although an approach that may eventually prove to be appealing).

Rather than considering an inaccessibly large library of possible structures, we cast the design of molecules as a problem requiring the search for the optimum nuclear−electron interaction potential function, $v(\mathbf{r})$, that generates a molecular system with associated target properties. The atom types and the nuclear positions determine $v(\mathbf{r})$. As such, all molecular properties are determined by $v(\mathbf{r})$ and the number of electrons N, because their knowledge allows, in principle, solution of the molecular Schrödinger equation. The potential function $v(\mathbf{r})$ thus encodes all of the chemical information for a given N. The richness and complexity of molecular phenomena in chemistry, biology, and materials science arise, almost miraculously, from variations in $v(\mathbf{r})$ and N. Analogous simplicity is seen in the density functional theory (DFT) of electronic structure in which molecular properties are functionals of the electron density, also a function of three spatial coordinates, just like $v(\mathbf{r})$. The Hohenberg−Kohn theorem states that the potential $v(\mathbf{r})$ is determined (to within an arbitrary constant) by the ground-state electron density.[16] In the study here, we construct a smooth surface that facilitates $v(\mathbf{r})$ optimization and that enables linking optimum potentials to real molecules.

The potential function $v(\mathbf{r})$ was also treated as a variable in earlier studies of molecular optimization and molecular property computation. Molecular hyperpolarizabilities were shown to change smoothly as the molecular Hamiltonian was varied.[17] Recently, DFT was formulated in the space of potential functions, the potential functional approach for DFT,[18] which establishes the theoretical underpinnings for the optimized effective potential approach.[19] Furthermore, optimization in the $v(\mathbf{r})$ space has been formulated to produce a target electron density (rather than the more conventional opposite case).[20] These observations motivate us to pose the hypothesis that a systematic optimization approach might be developed to design potential functions that generate molecules with optimized properties.

The advantages of optimization based on the potential arise from both the potential's "smoothness" and the favorable scaling of the computational cost with system size. The complexity of the potential function grows linearly with the molecular size. This is in stark contrast to the combinatorial explosion of possible molecular structures that would fill a growing molecular volume.[1,2] The challenge at hand is how best to carry out the potential-function optimization; it is essential that the optimized potential be linked to real molecules. While all molecules lie within the space of all $v(\mathbf{r})$'s, not all potentials map back to chemical structures or are C-representable (CR). A potential is CR (i.e., the potentials corresponding to the colored bars in Figure 1) only if it arises from a set of Coulombic attractions between electrons and nuclei of integer charge, as in chemical species. Indeed, the optimal Hamiltonians determined in earlier studies were difficult to link directly to specific chemical structures.[17] A full optimization in potential space most likely will lead to a potential that is not CR, since CR potentials are limited to a sum of Coulombic terms arising from integer nuclear charges.

To address the CR challenge, we develop here a construction for $v(\mathbf{r})$ as a linear combination of atomic potentials (LCAP):

$$v(\mathbf{r}) = \sum_{\mathbf{R},\mathrm{A}} b_{\mathrm{A}}^{\mathbf{R}}\, v_{\mathrm{A}}^{\mathbf{R}}(\mathbf{r}) \tag{1}$$

where $v_{\mathrm{A}}^{\mathbf{R}}(\mathbf{r})$ can be the potential of atom A at position $\mathbf{R}$ or can arise from a collection of terms, $v_{\mathrm{A}}^{\mathbf{R}}(\mathbf{r}) = \sum_{\mathrm{B}} v_{\mathrm{B}}(\mathbf{r})$, built from atoms {B} that form chemical building blocks. The parameter $b_{\mathrm{A}}^{\mathbf{R}}$ defines the mixing strength of a part of the potential. The constraints on $b_{\mathrm{A}}^{\mathbf{R}}$ are $\sum_{\mathrm{A}} b_{\mathrm{A}}^{\mathbf{R}} = 1$ and $0 \le b_{\mathrm{A}}^{\mathbf{R}} \le 1$ when an atom of type A is present at position $\mathbf{R}$ with probability $b_{\mathrm{A}}^{\mathbf{R}}$. The site could be given the freedom to be "vacant" by adding a corresponding term to the summation. Since an atom (or vacancy) is present at each specified site, the sum of all coefficients for the site is one, and each corresponding probability is between zero and one. It is sometimes convenient to use pseudopotential methods to solve many-electron problems. In that case, the atomic potentials are usually nonlocal. Thus the LCAP function consists of parts centered at many possible sites (the sum over $\mathbf{R}$), and each site accommodates a convex linear combination of possible $v_{\mathrm{A}}^{\mathbf{R}}(\mathbf{r})$. A LCAP is CR if $b_{\mathrm{A}}^{\mathbf{R}}$ values equal 0 or 1 for each $\mathbf{R}$ (species are either present or absent) and if no more than one $b_{\mathrm{A}}^{\mathbf{R}}$ value is equal to one for

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each **R** (only pure species appear). Importantly, introducing the continuous values, $b_A^{\mathbf{R}}$, in the LCAP formulates the optimization as occurring on a continuous hypersurface. Mapping onto a continuous surface avoids the need to enumerate the astronomical number of discrete chemical structures. Performing the optimization on this hypersurface may require, at the end of the analysis, rounding the optimal $b_A^{\mathbf{R}}$ values to the nearest integer to obtain one or more CR structures.

The variables in a LCAP computation are the set of sites **R**, the set of possible atoms or functional groups at each site as defined by $v_A^{\mathbf{R}}(\mathbf{r})$, and the set of weighting coefficients $b_A^{\mathbf{R}}$. The astronomical number of structures accessible for moderate-size organic molecules is based on counting the number of unique chemical substituents and considering linking together several of them using known covalent-bond chemistry.[2] Employing a similar approach in the construction of the potentials, fragments library groups would determine available $v_A^{\mathbf{R}}(\mathbf{r})$ functions for each molecular site, and the fragments would be placed at positions (**R**) consistent with known rules of covalent bonding.

The LCAP thus continuously links all possible molecules, each site with a set of possible atoms or functional groups, through the variation in $b_A^{\mathbf{R}}$. Note that the number of electrons present in the systems may also change continuously as the weighting coefficients vary.

Within the LCAP framework, the design of molecules with an optimized targeted property becomes the optimization of $b_A^{\mathbf{R}}$ values for given sets of **R** and $v_A^{\mathbf{R}}(\mathbf{r})$ (which themselves could be variables in the optimization). If the property surface is sufficiently smooth, the optimization should be efficient. If the optimal answer is close to a CR potential, then the design strategy is successful. We demonstrate that these two criteria are indeed met and that the LCAP approach provides a promising strategy for molecular design.

The LCAP approach is not a fragmentation strategy like the "divide and conquer" method. Rather, it is a scheme to build up libraries of chemical potential functions that can be "snapped together" to build the analytically exact electron−nuclear attraction potential for a whole molecule put together from the chemical groups: just as a wire framework molecular model is snapped together from a library of pieces. The electronic structure calculation for a given LCAP does not make any additional approximation beyond those present in the standard density functional theory. The approach provides convenience and removes the need (at an early phase of the property optimization, see Supporting Information) of having to optimize geometry and composition simultaneously.

An illustrative example is given for the optimization of electronic polarizability and hyperpolarizability with DFT calculations. The LCAP approach achieves this landscape smoothing by introducing the possibility of placing many nuclei, or groups of nuclei, simultaneously at a specific site and having many such designable sites. As such, the admixture of the potential terms is adjusted to optimize the target property. The values of the optimized coefficients define a real optimized structure, or a family of structures. As an example, the optimal structures that will be discovered are chosen to be built from a few well-defined chemical species. Figure 2 shows a two-site optimization with six possible chemical groups on each of the sites.

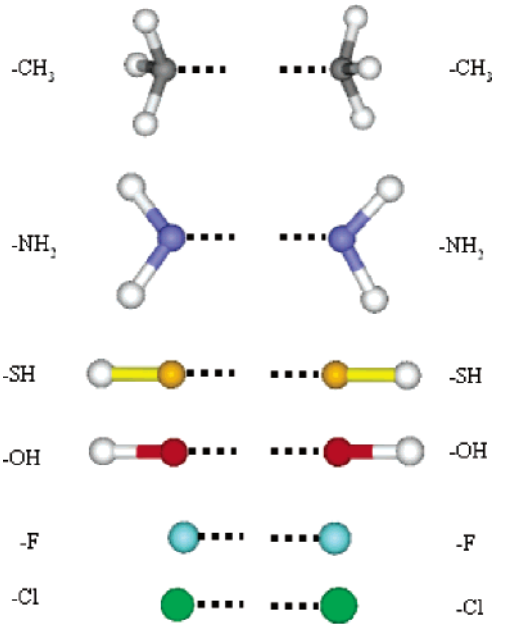

Figure 2. LCAP based on six different chemical substituents (−CH_3, −OH, −NH_2, −F, −Cl, and −SH) at two sites.

The polarizability α is calculated using the finite-field method:[21,22]

$$\alpha = \sum_i \alpha_{ii}/3$$

$$\alpha_{ii} = -[E(F_i) + E(-F_i) - 2E(0)]/F^2$$

where $i = x$, y, or z. $E(F_i)$ is the DFT ground-state electronic energy of the system in the presence of a field F_i. The derivative of the polarizability with respect to the coefficients is calculated using $\partial E(F_i)/\partial b_A^{\mathbf{R}}$, which is computed using the Hellmann−Feynman theorem (see Supporting Information). We also change the LCAP coefficients to a new set of variables $t_A^{\mathbf{R}}$ where

$$b_A^{\mathbf{R}} = (t_A^{\mathbf{R}})^2/\sum_{\mathbf{R}} (t_A^{\mathbf{R}})^2$$

The constraints on $b_A^{\mathbf{R}}$ can be satisfied without constraining $t_A^{\mathbf{R}}$.

We used norm-conserving pseudopotentials produced with the FHI98PP program[23] in the local-density approximation. An energy cutoff of 100 Ry is used to determine the number of plane-wave basis functions. An external field of 0.02 au was applied to calculate the electronic polarizability. The molecule was placed in a cubic box with sides of length 8.5 Å. A quasi-Newton optimization algorithm was used to optimize the polarizability, and a system with two designable sites was studied. First, the two functional groups −CH_3 and −SH were placed at each of the two sites. The distance between the heavy atoms was fixed at 1.53 Å, a bond length typical of a single covalent bond. The bond and dihedral angles were chosen based on experimental geometries of the corresponding molecules. Figure 3 is a contour map of the polarizability as a function of the two weighting coefficients: one is associated with the presence of an −SH group on the left site, and one is associated with

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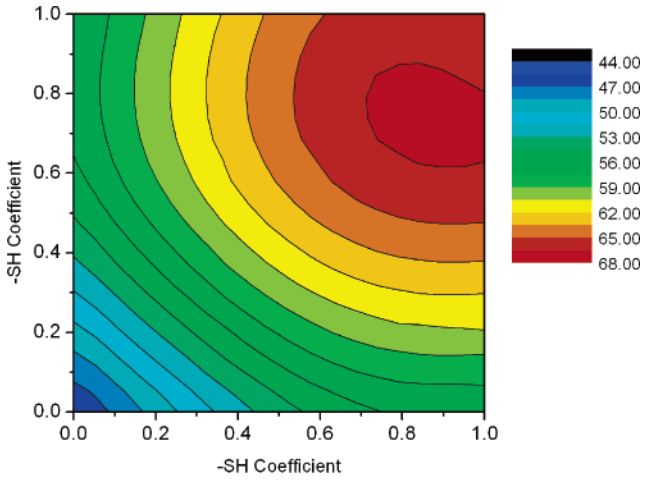

Figure 3. Polarizability contours. The contours (10^{-25} esu) are drawn as a function of the two −SH weighting coefficients. The lower left corner corresponds to CH_3CH_3, the upper right corresponds to H_2S_2 (fixed 90° torsion angle), and the two other corners correspond to CH_3SH.

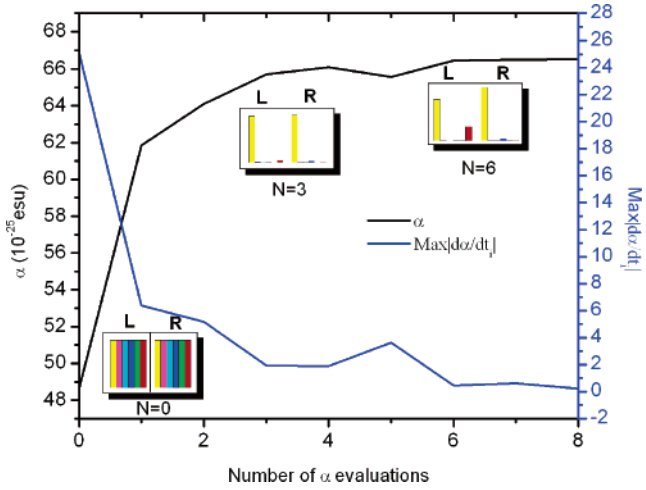

Figure 4. Polarizability and the maximum derivative $|d\alpha/dt_A^R|$. Values are plotted versus the number of function evaluations beginning with uniform coefficients on all six functional groups (−CH_3, −OH, −NH_2, −F, −Cl, and −SH). The red, green, blue, cyan, magenta, and yellow bars in the insets indicate the relative weights, respectively. L and R labels refer to the left and right chemical groups, respectively.

the presence of an −SH group on the right site. The contour map shows that the polarizability changes smoothly with variation of the two weighting coefficients. The maximum polarizability is found for b_A^R values of 0.87 and 0.74, when the system is composed of 87% −SH and 13% −CH_3 at one site and 74% −SH and 26% −CH_3 at the other site. The asymmetry in these values arises from the slightly different torsional interactions for the −SH groups with their −CH_3 partners at the other site in the two structures. Beginning with uniform initial coefficients, the calculation converges to the correct maximum point with a few polarizability evaluations. Ten additional runs, beginning with random initial guesses, were performed, and all converged to the same optimum point. The optimization indicates that the H_2S_2 molecule (fixed 90° torsion angle) is the structure with maximum polarizability among the four possible choices (representing three chemically distinct molecules).

Figure 4 shows the progress of the optimization beginning with uniform initial coefficients for six functional groups (−CH_3, −OH, −NH_2, −F, −Cl, −SH) at each of two sites. The results converge within a few polarizability calculations to the maximum point of the property surface with 100% of −SH at one site and 76% −SH at the other site. Ten additional runs beginning with random initial guesses converge to the same maximum. No other local maxima were found. Therefore, the calculation uniquely identifies the optimum molecule for the given property. The calculation indicates that the H_2S_2 (fixed 90° torsion angle) molecule is the structure with maximum polarizability among all possible choices, in agreement with direct enumeration and evaluation. Even in this simple case, the LCAP optimization identifies the optimum molecule much more efficiently than the conventional approach of enumerating and evaluating candidate molecules one by one. The LCAP optimization is essentially completed after four function evaluations, optimizing 10 degrees of freedom (5 on each site) in these calculations. As such, optimization avoids enumerating structures and evaluating properties for all 21 possible molecular structures.

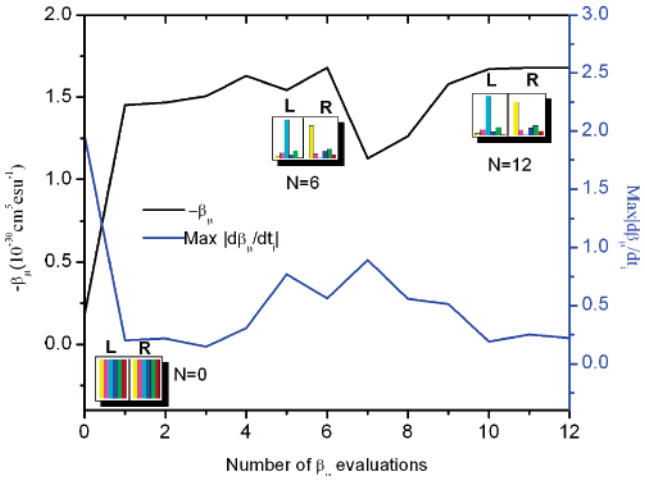

Figure 5. First electronic hyperpolarizability and the maximum derivative $|d\beta_\mu/dt_A^R|$. Values are plotted versus the number of function evaluations beginning with uniform coefficients on all six functional groups (−CH_3, −OH, −NH_2, −F, −Cl, and −SH). The red, green, blue, cyan, magenta, and yellow bars indicate the relative weights of the six functional groups, respectively.

We have also applied the LCAP approach to optimize the first hyperpolarizability β_μ (see Supporting Information). Since the hyperpolarizability is more expensive to compute than the polarizability, ultrasoft pseudopotentials were used in the DFT analysis.[23] The molecule was placed in a cubic box with sides of length 18 a_0. An energy cutoff of 35 Ry was used to determine the size of the plane-wave basis set. An external field of 7.71×10^{-3} V/Å was applied to calculate the electronic first hyperpolarizability. Figure 5 shows the progress of the optimization beginning with uniform initial weighting coefficients. The gradients decrease rapidly within a few steps, and $|\beta_\mu|$ reaches a maximum. The optimized structure has 67% weighting of fluorine at one site and 57% weighting of −SH at the other (Figure 5), indicating F−SH is the optimal molecule. This optimized chemical structure is in agreement with the results of direct enumeration and evaluation of all hyperpolarizabilities. Our focus above has been on the optimization scheme, and we have not yet discussed issues of molecular geometry as fragments are brought together. In formulating the optimization scheme, we assumed that changes in bond lengths and bond

angles (including the bond linking the fragments), upon forming the composite molecule from a library of "standard" fragments, have a modest effect on the property values, especially on the relative values. This simplification is validated in the set of 21 structures of Figure 2 and the four push−pull polyenes studied in the Supporting Information. We have also assumed that considering only a single "standard" fragment geometry is sufficient to carry out the optimization (validated by the two specific families of structures examined). Indeed, both of these simplifications can be relaxed, as described in the following two schemes.

The first scheme addresses the issue of geometry relaxation caused by electronic changes in the molecule upon bonding the standard fragments: the output chemical structure can be geometry optimized and used as the starting point for another LCAP optimization cycle. This procedure can be iterated until self-consistency is obtained. Importantly, our aim is not to find a global energy minimum or absolute maximum property for a prescribed chemical formula. Rather, we intend to determine the most favorable chemical structure within a restricted family of structures that could be assembled from the standard molecular fragment library. A second scheme, completely within the LCAP optimization framework, aims to explore further the conformational space for a given chemical structure. This scheme, combined with the first, addresses changes in noncovalent interactions upon assembling the molecule from its fragments. This scheme would input a family of thermally accessible conformers for each standard fragment as independent variable units in the LCAP optimization. In this procedure, the optimization would identify not only the most favorable standard fragment but also its most satisfactory conformation from the perspective of the property. Both of these schemes should be accessible computationally. This discussion has focused on local geometries and geometry changes upon assembling a molecule from structural fragments. Following the identification of promising lead structures, thermal averaging could be pursued for the structures and the properties in the condensed-phase environment of interest.

The LCAP approach described here maps an intrinsically discrete molecular space onto a set of continuous variables, making efficient optimization possible. Framing our calculations in this way leads to optimized structures that can be realized chemically. In the examples examined here, optimal structures were identified much more rapidly than could be accomplished with exhaustive enumeration and evaluation of properties. Multiple property optima could result from this analysis: if multiple extrema were found in the property surfaces or if optima were found with comparable weightings of multiple chemical groups at the same site. In either case, several structures would be suggested, and a more detailed analysis could be carried out on this refined list of potential targets.

The specific calculations implemented here show that molecular electronic polarizability and hyperpolarizability are indeed smooth functions of the LCAP coefficients and that the optimal molecule can be determined efficiently. Importantly, the LCAP approach maps the molecular search problem onto a smooth hypersurface, avoiding the need for direct enumeration and evaluation of all candidate structures. The cost of the LCAP optimization will grow linearly with molecular size (and is also proportional to the cost of calculating the property of interest). This is a particular benefit over the combinatorial growth in the number of molecular structures, and hence the computational cost, with molecular weight. In this regard, the LCAP approach has similarities to neural-network optimizations of challenging NP-complete problems.[24]

Since the LCAP approach can be implemented with classical or quantum Hamiltonians, many kinds of property optimization can be explored with this scheme. As such, the LCAP approach appears to provide a promising theoretical framework to address broader challenges in molecular design. Combining LCAP methods with conformational sampling may provide a systematic approach to address open challenges in the design of biological ligands with tailored binding characteristics or new materials with optimized properties. The challenge now is to expand the library of chemical building blocks so that a large and diverse universe of structures can be explored and optimized.

Since our completing the study described above, a closely related and quite promising molecular design approach was very recently published by Rothlisberger and co-workers.[25] Defining a nuclear chemical potential, it explores the optimization of protein inhibitor binding energies based on atom-type variation in a fixed molecular framework. As such, the approach examines structures of a fixed "connectivity" and requires a somewhat different approach to satisfy chemical valency and to relax molecular configurations; it seems to fall within the framework of atomic number dependent functionals (vide supra).

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Supporting Information Available: Details of the density-functional calculations, optimization details, and computed and measured electronic polarizabilities and hyperpolarizabilities. This material is available free of charge via the Internet at http://pubs.acs.org.

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