autodE: Automated Calculation of Reaction Energy Profiles – Application to Organic and Organometallic Reactions

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ABSTRACT: Calculating reaction profiles to aid in mechanistic elucidation has long been the domain of the expert computational chemist. Here, we introduce *autodE*, an open-source tool capable of locating transition states and minima and delivering a full reaction energy profile with minimal human effort (<https://github.com/duartegroup/autodE>). *autodE* is broadly applicable to study organic and organometallic reaction classes, including addition, substitution, elimination, migratory insertion, oxidative addition and reductive elimination; it accounts for conformational sampling of both minima and TSs, and is compatible with many electronic structure packages. The general applicability of *autodE* is demonstrated in complex multi-step reactions, including metal-catalyzed cobalt- and rhodium-catalyzed hydroformylation, and an Ireland-Claisen rearrangement.

1. Introduction

Automating the search for new chemical reactions is seen as one of the ‘grand challenges’ in computational chemistry.^{1,2} Discovering such thermodynamically and kinetically accessible reactions requires knowledge of the underlying potential energy surface (PES), which to a first approximation, involves the characterization of reactants, products, intermediates, and transition states (TSs).^{3–5} While this has been routine for computational chemists for decades, locating TSs remains time consuming and a highly non-systematic endeavour.⁶ To this end, many automated TS-search algorithms have been developed which may be broadly classified into *single* and *double-ended* methods.^{7,8} The former requires a single chemical structure from which TSs, intermediates, and products are located with no *a priori* information. Representative examples include the *ab initio* nanoreactor (AINR),⁹ which employs high temperature and pressure molecular dynamics (MD) simulations to identify chemical transformations; the single-ended growing-string method (SE-GSM),¹⁰ which iteratively generates structures along the PES and optimizes them until a TS and minima at each side of the string are found; the artificial force induced reaction (AFIR) method,¹¹ which adds artificial external forces to the original PES of the target system, and the TSSCDS which uses high-energy dynamics simulations and a geometry-based algorithm to identify reactive pathways.¹² While they allow for free exploration of unknown pathways, these methods remain costly and limited to small systems (~10 reactant atoms) if left to freely explore all transformations.

On the other hand, *double-ended* methods use knowledge of both reactants and products. Depending on the specific method either single or multiple steps can be studied. The latter uses reaction network enumeration algorithms, which allow for a systematic search of the reaction space; but hit an exponential wall of complexity if arbitrarily many intermediates are permitted.^{13,14} Single-step methods, although seemingly limited in scope, remain a powerful and affordable approach to explore many chemical processes determined by elementary steps. This is the case, for example, when the goal is to elucidate the origin of regio- or enantioselectivity or compare different synthetically-plausible pathways for a given transformation. Several methods have been developed following this philosophy, from linear and quasi-synchronous transit^{15,16} and related approaches^{17,18} to more recent developments based on growing¹⁹ and freezing string methods^{20,21} (GSM/FSM, **Figure 1**). Finally, heuristic approaches guided by either graph-based chemical rules or electronic-structure theory have been

employed to explore a wide range of chemical reactions; including the Reaction Mechanism Generator²², which follows approaches pioneered by NetGen²³, and other reaction network approaches.^{24,25}

Figure 1. Comparison of approaches to generate reaction profiles.

Here, we introduce *autodE*, which combines elements of previously reported double-ended methods with the development of a general, easy to use, and freely available framework to automate the characterization of reaction pathways. The *autodE* algorithm takes inspiration from related methods, such as AutoTS²⁶ developed by Schrodinger® and the Reaction Mechanism Generator developed by Green et al.,²² and aims to overcome current limitations in applicability, conformational sampling and accessibility; specifically (1) it provides a broadly applicable framework to study organic and organometallic reaction classes; (2) it accounts for conformational sampling of both minima and transition states, which is essential particularly when exploring flexible systems; (3) it is freely available (open-source Python package under a MIT license) and requires minimal user input and expertise. Moreover, it is compatible with several electronic structure theory packages

and extensible to others. This work describes the algorithm and implementation of *autodE* and demonstrates its capabilities in a range of representative organic and organometallic reactions. We demonstrate that *autodE* is capable of localizing the different TSs and minima along the PES and delivering a full reaction energy profile using only SMILES representations as inputs and with a minimal human effort. To illustrate the functionality and general applicability of *autodE*, we apply it to a range of reactions classes, including complex organic and metal-catalyzed reactions.

2. Methodology

In general, human-guided characterization of TSs and reaction pathways requires: (1) locating reactants and products; (2) locating the TS, usually starting from a guess TS structure generated by chemical intuition; (3*) once reactants, TSs, and products have been characterized, perform a conformational search to identify the lowest energy conformer in each case; and (4*) performing single point energy evaluations to refine energies. While the starred steps are not always performed, they are usually necessary to achieve meaningful conclusion about the reactivity and selectivity of a given reaction step. Our method follows this workflow, which is described in detail in the following sections, along with representative examples (**Figure 2**).

Figure 2. Diagrammatic workflow used by *autodE* to plot a reaction profile from a set of reactant(s) and product(s) SMILES strings. TSA = transition state analogue; where active bonds are constrained at distances found at the TS found in the step above or saved in the TS database.

With a view to generating reaction profiles efficiently using currently available quantum mechanics methods, our implementation makes use of two levels of theory: a lower-level (*lmethod*) and higher-level method

(*hmethod*). Both methods have default settings (**Table 1**) which can be modified by the user depending on the methods available in the respective software; for example, DFT methods can be used as *lmethod* for optimizations, and wavefunction methods as *hmethod* for single point energy evaluations. *autodE* is readily extensible to many other electronic structure theory codes and forcefields in addition to those with currently implemented wrappers (ORCA,²⁷ NWChem,²⁸ Gaussian09,²⁹ MOPAC,³⁰ GFN-XTB,³¹ see discussion in the SI and **Figure S1**). In the following paragraphs we describe the key features and implementation of *autodE*.

Table 1. Default methods used in *autodE* calculations. *sp* = single point energy, *opt* = optimization, *low_opt* = low level optimization, *optts* = transition state optimization, *hess* = Hessian. ^a. Uses D3 rather than D3BJ dispersion.

Software Package	Calculation	Default Method
ORCA, Gaussian09, NWChem ^a	<i>low_opt</i>	PBE-D3BJ/def2-SVP
	<i>opt, optts, hess</i>	PBE0-D3BJ/def2-SVP
	<i>sp</i>	PBE0-D3BJ/def2-TZVP
MOPAC	<i>low_opt, opt, sp</i>	PM7
XTB	<i>low_opt, opt, sp</i>	GFN2-XTB

2.1. Finding Lowest Energy Conformers for Reactant and Products

Locating the global minimum, or a structure close to it, on a PES is challenging but essential in estimating the feasibility of a reaction.³² To characterize the lowest energy conformer at a given level of theory requires transforming the 1D SMILES representation into a 3D geometry and searching the conformational space. Several open-source tools are available including RDKit³³ and CONFAB³⁴ implemented in OpenBabel, but are generally limited to organic species. *autodE* uses the ETKDGv2³⁵ algorithm implemented in RDKit, which is known to perform well for organic species, along with its SMILES parser.³⁶ To determine optimal parameters for the number of conformers generated and the root mean squared (RMSD) threshold used to exclude identical conformers, a set of 20 amino acids were considered. Using CREST³⁷ as the benchmark method, the generation of 600 conformers and RMSD threshold = 0.1 Å was sufficient to obtain reliable minima, rendering a conformer within 1 kcal mol⁻¹ of the most stable CREST conformer in 90% of the cases (18/20) (**Figure S2**). Therefore, this inexpensive conformer search was kept as the default for organic molecules and allows for *autodE* to remain method agnostic (i.e. *lmethod/hmethod* can be chosen by the user).

For metal complexes, where OpenBabel and RDKit fail to interpret the SMILES string and/or generate a sensible 3D geometry, we utilize our own SMILES parser and a simple repulsion+bonded (RB) forcefield (equation 1).

$$U_{\text{RB}}(\mathbf{x}) = \sum_{ij \in \text{bonds}} k_1 (r_{ij} - r_{ij}^0)^2 + \sum_{i > j} \frac{k_2}{r_{ij}^n} \quad (1)$$

The first harmonic term describes bonds between atoms, and the second term introduces a non-physical repulsion that enforces a notion of steric repulsion. Parameters $k_1 = 1$ and $k_2 = 0.01$ were selected based on empirical experience and comparison to optimized structures (**Figure S3**) while ideal bond lengths (r^0) are obtained as averages from the Cambridge Structural Database.³⁸

To generate reasonable 3D structures for organometallic complexes, each atom is added sequentially and randomly in a 10 Å cubic box, and the function U_{RB} is minimized with respect to all coordinates after each addition. Using a smooth potential with few local minima, $n = 2$ in Eq. 1, is required to obtain stable structures

for large complexes (**Figure S4**). For a test set of 20 metal-complexes with up to 100 atoms, our approach delivers a stable conformer in all cases, while RDKit successfully generates only 15 geometries and CONFAB failed in all cases (**Figure S5** and **Table S1**). With the analytic derivative of U_{RB} and a conjugate gradient algorithm implemented in *SciPy*,³⁹ an initial structure is available in a few seconds for complexes with more than 100 atoms. Stereodefined metal complexes are currently not supported, as random initialization does not respect any chirality.

An alternative and slightly faster approach used to generate conformers is to randomize all atoms by applying a random displacement vector (length ~ 3 Å) and then minimize the function U_{RB} with $n = 8$, as a more realistic surface (which is required to afford three minima in the butane dihedral PES, **Figure S4**). While simple, this strategy affords more conformers than both RDKit and CONFAB for the metal complex test set (**Figure S5** and **Table S1**). It is also worth noting that we found no advantage in using the EMBED algorithm⁴⁰ to generate initial coordinates for organic systems (**Figure S6** and **Table S2**). Moreover, conformers can be generated using arbitrary distance constraints specified by the user (e.g. to retain a square planar geometry given an 3D initial structure).

In *autodE*, for either organic molecules or metal complexes, the lowest energy conformer is found by optimizing each conformer at the *lmethod* and excluding non-unique structures based on an energy threshold (1 kJ mol⁻¹ default). The remaining structures are then optimized at the desired *low_opt* level with the *hmethod*, and the lowest energy is kept (**Figure S6**).

2.2. TS Location

Within *autodE*, each species has an associated molecular graph (X), in which the atoms correspond to vertices (V) and ‘bonds’ to edges (E). For a discussion of how bonds are defined, see the SI (**Figure S7**). From the set of reactant graphs $\{R_i\}$, the reactant graph (R) is formed as the graph union, and likewise with products $\{P_i\}$ to generate (P). This is represented in **Figure 3** for a Claisen rearrangement, where the graphs R and P are formed from a single reactant and product molecule. If R and P are isomorphic then the chemical transformation is not obvious from the graph transformation and the program will exit. Once this has been checked, to find a atom

mapping (bijection) from R to P , we generate $\{R'\}$, the set of transformations of R obtained by adding and/or removing edges [$g: E(R) \rightarrow E(R')$], where each function $\{g\}$ represents the bond rearrangement. The atom mapping(s) [$f: V(R') \rightarrow V(P)$] are then found where R' and P are isomorphic using NetworkX⁴¹. From this example, it is clear that a brute force search for all g obtained by enumerating over all possible edge additions/deletions becomes intractable quickly, as the number of operations grows as 2^N for a system with N atoms. However, chemical reactions usually involve a limited number of bonds that are formed and broken in a single elementary step, thereby substantially reducing the search space. We therefore limit the transformation to a maximum of four ‘active’ bonds where two edges are added and two removed, denoted (2, 2). For a graph X with b bonds ($b_X = |E(X)|$) the principle of microscopic reversibility is used to switch reactants and products if $b_R < b_P$. From these constraints, five scenarios exist:

- I. (1, 1) – substitution reactions e.g. S_N2 .
- II. (2,2) – substitution reactions e.g. peroxide epoxidation.
- III. (0, 1) – dissociation e.g. E1 eliminations.
- IV. (0, 2) – dissociations e.g. Diels-Alder cycloaddition.
- V. (1, 2) – eliminations e.g. E2 eliminations.

Defining the change in the number of bonds as $\Delta b = b_R - b_P$ as in references ²⁶ and ⁴², only when $\Delta b = 0$ does the full set of deleting and adding two edges need to be enumerated. Further acceleration is achieved by calculating $\{\Delta b_k\}$ where k is a bond type e.g. ‘C–C’ and ensuring any atom (a) doesn’t exceed a maximal valence i.e. $d(a) \leq 4$ for a carbon atom. For example, in a Claisen rearrangement $\Delta b_{C-C} = 1$ and $\Delta b_{C-O} = -1$ such that the enumeration over (1, 1) transformations is targeted to only C–C and C–O bonds. Once the set of valid $\{g\}$ is found, a TS is located for each of them (if it exists), and following conformational sampling, the lowest energy TS is taken for the calculation of a reaction profile. For the Claisen reaction shown in **Figure 3**, only one bond rearrangement is obtained while for the all-carbon analogue ($O \rightarrow CH_2$) two rearrangements are found ($g = \{g_1, g_2\}$). We are yet to find a reaction where the process of generating/checking R' and P isomorphisms and finding the bijection is comparable or more demanding than a DFT calculation.

Figure 3. Atom mappings between reactants and products for a Claisen rearrangement.

To generate a saddle point, while ensuring compatibility with multiple electronic structure codes, we favor finding a TS guess by performing a set of constrained geometry optimizations along a linear path between reactants and products. In general, *autodE* attempts 1D constrained searches over forming/breaking bonds except when $\Delta b = 2$ (e.g. Diels-Alder). If this procedure fails and the number of active bonds is more than one, a 2D PES exploration is performed by constrained optimizations and fitting a polynomial up to order 3.³⁹ From a 2D PES, the lowest energy saddle point is found by locating where the first derivative vanishes, and then using Dijkstra's algorithm⁴³ implemented in NetworkX.⁴¹ A constrained optimization at the saddle point is then performed to generate the TS guess. Once the TS guess is obtained, it is optimized with the TS optimizers implemented in the electronic structure theory package selected by the user. ‘Goodness’ of the TS is defined by an imaginary frequency mode ($|v_{imag}| > 45 \text{ cm}^{-1}$) and a significant contribution from the active bonds, or forward/backward displacement along the mode affords reactants/products (a quick reaction coordinate, QRC calculation⁴⁴). In cases where the reactant or product(s) are not isomorphic to R or P , conformers of the reactant and product complexes are generated (as outlined in §2.6) and isomorphisms checked for the

forwards/backwards displaced structures to all optimized conformers. This approach overcomes the limitation of NEB approaches that requires minimal structural difference between the initial and final states, which may be challenging when larger changes occur between the reactant and product complex or where the product is linked to P by one or more barrierless reactions e.g. some proton transfers.

2.3 Truncation

Performing tens of constrained optimizations along one or two coordinates in a large system is currently computationally demanding. To accelerate the generation of a TS guess in such systems, the system is truncated. Our implementation truncates over C–X bonds where the carbon atom is fully saturated and is at least two bonds away from the active atoms, and the truncated group is replaced by a hydrogen atom (**Figure S8**). The TS is then located using this truncated complex and saved in the template library from which the full non-truncated TS may be found using the templating method described below. For truncation to be utilized it must remove >10 atoms.

2.4. Finding Lowest Energy TS Conformers. TS conformers are located in a similar manner to the protocol described for metal complexes in §2.1 ($n=8$ in Eq. 3 and randomization using a displacement vector of ~ 3 Å). However, here the ‘active’ bonds are constrained at distances found at the TS using a harmonic potential with a force constant $k_1' = 10k_1$ (equation 2).

$$U_{\text{RB}}(\mathbf{x}) = \sum_{ij \in \text{bonds}} k_1 (r_{ij} - r_{ij}^0)^2 + \sum_{ij \in \text{const.}} k_1' (r_{ij} - r_{ij}^0)^2 + \sum_{i>j} \frac{k_2}{r_{ij}^8} \quad (2)$$

An identical method is then used to find the lowest energy transition state analogue (TSA) – as a model for the TS – performing optimizations with the active bonds constrained to their length in the TS. From the TSA a TS is found by rerunning the transition state optimization and checking that it is both a ‘good’ TS and is lower in energy than the previously found TS.

2.5 Transition State Templates

To accelerate the location of TSs, if available, a template is employed to generate a TS guess structure. Templates are saved into a library following the successful location of a TS and contain a graph, solvent, charge and

multiplicity. For a template to be used, the reactant(complex) must have the same charge, multiplicity, and solvent parameters as the one used to obtain the template. In addition, the active bonds must match (same number and atoms) along with their nearest neighbors, based on their connectivity and atom type. If a matching template is found in the library, then a TS guess is generated by constrained optimization, where the active bonds are fixed at values found in the saved TS, from which TS optimization is performed. For example, a TS found for $\text{EtCl} + \text{F}^- \rightarrow \text{EtF} + \text{Cl}^-$ enables a 10 $\times$ faster characterization of the TS for the propyl analogue.

2.6 Non-covalent Complexes

In many chemical processes, the formation of a reactant/product complex precedes/follows the chemical step of interest, and are therefore fundamental to determine the kinetics of the process. In some cases, the molecular graph of the reactant and product complexes may not be isomorphic to the separated reactants (*R*) and products (*P*). For example, in the base-catalyzed hydrolysis of methyl acetate, loss of MeO^- from the tetrahedral intermediate proceeds with concurrent deprotonation of the acid (**Figure S9**). Thus, to successfully characterize the TS as ‘good’, reactant and product complex conformers are required from which isomorphisms can be checked to the forward/reverse displaced species from the TS. This approach allows the lowest energy conformer of a non-covalent interaction (NCI) complex to be located systematically. For a complex formed by molecule A and B, conformers of the A.B complex are constructed by adding molecule B to the current set of atoms of B recursively at points equally spaced on the surface of a sphere⁴⁵ in a random orientation around A then energy minimizing (**Figure S10**). For a complex with N_R reactants using N_S points on a sphere and N_T random rotations, this approach generates $(N_S \times N_T)^{N_R-1}$ conformers. To maintain efficiency, a maximum threshold number of conformers (1000 default) is set, which are subsequently optimized using at least semiempirical or DFT as the *lmethod*. This approach also provides an additional functionality, e.g. facilitating the generation of hydrogen bond complexes of relevance in anion-recognition without prior knowledge (**Figure S11**).

2.7 Reactive Reactant Complexes

For bimolecular reactions (substitution and elimination, not addition as $b_P > b_R$) an initial NCI complex on the PES must be found that favors a linear arrangement of the nucleophile and the leaving group, while also reducing

the required number of optimizations. For this reason, the energy function U_{RR} (equation 3) is minimized with respect to rigid-body rotation and translation of one reactive component with empirical parameters $c_1 = c_2 = c_3 = 1$, $c_4 = 10$ and $c_5 = 2.5$ (1.5) for charged (uncharged) complexes.

$$U_{\text{RR}}(\mathbf{x}_i) = \sum_{\{\text{ac}\}} c_1 (r_{\text{ac}} - c_5 r_{\text{ac}}^{\text{avg}})^2 + \sum_{\{\text{acx}\}} c_2 (1 - \cos \theta) + \sum_{\{\text{acx}\}} c_3 (1 - \cos \phi) + \sum_{\{\text{ij}\}} \frac{c_4}{r_{\text{ij}}^4} \quad (3)$$

This energy function has been designed to maximize the collinearity of vectors $\mathbf{v}_{\text{an}}$, $\mathbf{v}_{\text{ac}}$ and $\mathbf{v}_{\text{cx}}$ while maintaining both a low steric repulsion and distance ($r_{\text{ac}} = |\mathbf{v}_{\text{ac}}|$) close to that desired (**Figure 4**). This choice is guided by chemical intuition, and there are rare cases where this does not adhere to e.g. front-side $\text{S}_{\text{N}}2$ ^{1,46}. For example, for $\text{S}_{\text{N}}2$ substitution, E2 elimination and $\text{S}_{\text{N}}\text{Ar}$ reactions adequate initial geometries are obtained (**Figure 4**, **S12**). Note that there may be several minima on this surface; thus, the multiple initial random rotations and translations (~ 10) are performed to have a better chance of locating the global minimum while remaining computationally inexpensive (execution time $\sim$ seconds).

¹ A front side $\text{S}_{\text{N}}2$ mechanism is, however, found when conformers of a backside $\text{S}_{\text{N}}2$ TS are generated.

Figure 4. (a) Illustration of the geometric parameters used in equation 2 using the S_N2 reaction ($NH_3 + CH_3Cl$) as an example: v_{an} is the average of vectors $\{v_{am}\}$ where m is a nearest neighbor to a . (b) Minimization of the function $U(x_i)$ for an E2 reaction; the energy profile is qualitative as it depends on an initial random configuration. Initial and optimized structures are shown.

3. Results and Discussion

To demonstrate the applicability of *autodE* in multiple reaction classes, we explored some textbook organic reactions (S_N2 , E2, etc.) alongside industrially relevant organic and metal-catalyzed reactions involving more than 50 atoms. By way of example, we demonstrate that *autodE* is broadly applicable, efficient in exploring conformational space, and straightforward to use.

Even with a small amount of programming experience using *autodE* is as simple as declaring reactants and products involved in the reaction from their respective SMILES strings (or from xyz files) and optionally implicit solvent. To calculate the reaction profile for a simple S_N2 reaction the input and output are shown in **Figure 5**, where the calculation is parallelized over four processing cores, the reaction immersed in an implicit aqueous environment and reactant/product are defined as SMILES strings. Here, by calling the method `calculate_reaction_profile(with_complexes=True)`, the association complexes are also calculated along the energy profile. Alternatively, one can decide only to obtain the TS, with the function `locate_transition_state`.

Figure 5. Reaction energy profile for an S_N2 reaction calculated using *autode*. Electronic structure calculations were performed at the GFN2-XTB and DFT level in XTB/ORCA, respectively, for geometry optimization/energy calculations. Final energies quoted at the CPCM(H₂O)-PBE0-D3BJ/def2-TZVP//CPCM(H₂O)-PBE0-D3BJ/def2-SVP level of theory. Distances in Å.

Without specifying which electronic structure codes to use, *autode* employs first available *hmethod* and *lmethod*, (sequentially ORCA, Gaussian09, NWChem and XTB, MOPAC respectively), with the default DFT methodologies listed in **Table 1**. Using this setup, the reaction energy profile shown in **Figure 5** is obtained in less than 10 minutes. While it would be ideal to obtain reaction free energies, the cost and limitations associated with the calculation of entropy and thermal contributions using currently available models (ideal gas) mean that the addition of such corrections should be considered with care. For this reason, potential energies are set as the default in *autode*. However, free energies can be obtained by running frequency calculations which can be achieved within a Python environment using *autode* by performing a Hessian calculation (with e.g.

Calculation(molecule, method, keywords=method.keywords.hess, ..., see the documentation for examples: <https://duartegroup.github.io/autodE/>).

3.1 TS Conformers

A thorough exploration of the conformational space in order to find the lowest energy conformer for reactants and TSs is essential in characterizing the kinetic and thermodynamic parameters of a reaction. As discussed in §2.2, *autodE* provides two routes to locating TS conformers: The first uses reactant/product complex conformers, from which different TSs may be traversed, and the second locates TS conformers directly. If using templates, both approaches are efficient, generally requiring only one constrained optimization and one TS optimization per conformer once a TS has been found. Direct TS conformer searching is, however, faster as only the TSAs are optimized and the lowest energy found whereas full enumeration from reactant/product complexes can require rescanning over the PES.

For example, for an E2 elimination reaction, the initial search may locate a transition state in which the deprotonation occurs with the proton and the leaving group in a *syn* conformation, rather than the favored *anti* conformer. The latter TS is automatically found in *autodE* by employing the strategy outlined in §2.2 (**Figure 6a**). Similarly, the *autodE* algorithm correctly locates the lowest energy H-migration TS for the radical decomposition of 1-propanol, with an RMSD < 0.1 Å compared to the human-generated TS from ref ⁴⁷ (**Figure S13**). The importance of this unbiased TS conformer generation is highlighted in the Michael addition of nitromethyl acetate and methyl vinyl ketone, where several rotatable bonds exist (**Figure 6b**). For this reaction, an exhaustive search from product conformers generated 21 TS conformers, which upon optimization, led to a range in activation energies of more than 5 kcal mol⁻¹ and reaction energies that differ by up to 17 kcal mol⁻¹. The weak correlation between $\Delta E^\ddagger$ and ΔE_r highlights the importance of a systematic conformer search at both minima and transition states.

Figure 6. (a) Lowest energy transition state conformers found with *autode* for methoxide + chloroethane elimination. (b) TS and product conformer distributions for the reaction between nitromethyl acetate and methyl vinyl ketone addition.

3.2 Organic Reaction

For *autode* to become routinely used in mechanistic investigations, it must be applicable to synthetically relevant, and usually more complex, reactions. Here, we explored the unexpected Ireland–Claisen rearrangement of divinylcyclopropanes reported by the Stoltz group and explored computationally via trial-and-error (Houk group) and the AFIR method.⁴⁸ With known intermediates, processed as SMILES strings from Chemdraw®, *autode* was tested and compared to the human guided approach, which originally involved the testing of various conceivable mechanisms. *autode* delivered an essentially identical reaction profile and reduced the time from the year of human and compute effort reported in ref 47 to a few minutes of setup time and ~600 CPUh (one day

of computer time in 24 cores) (**Figure 7**). Interestingly, *autodE* deviates < 2 kcal mol⁻¹ from the trial and error-based search (blue), with **INT3** showing a larger difference of 5 kcal mol⁻¹ due to *autodE* finding a more stable than the one located previously.

This example demonstrates that a compilation of chemical knowledge, required to hypothesise reasonable mechanisms, and the use of *autodE*, can substantially speed up joint experimental and computational efforts to elucidate complex reaction mechanisms, and in this way advance the optimisation of synthetic routes and the design of novel catalysts.

Figure 7. Ireland–Claisen rearrangement calculated using *autodE* (black) and described in ref.⁴⁸ (blue) calculated at B3LYP-D3BJ/6-311++G(2d,2p)// B3LYP-D3BJ/6-31G(d). CPCM(hexane) solvent model used in ORCA (this work) and IEF-PCM(hexane) in Gaussian09 (ref.⁴⁸). 3D Structures of the most stable intermediates and transition states are shown in **Figure S14**.

3.3 Organometallic Reaction

The conversion of alkenes into aldehydes via addition of CO and H₂ is an exceptionally important industrial process, making catalyst optimization the subject of considerable study.⁴⁹ The mechanism was discovered by Heck and Breslow⁵⁰ and has been the subject of numerous computational studies (for an overview of these studies see ref.⁵¹ and references cited therein). Those works have provided significant insights into the

mechanism of the reaction, and have also highlighted the challenges associated with it. In fact, only finding the intermediates and transition states along the PES is already a laborious process, requiring extensive sampling, due to the presence of several conformers and isomeric forms (**Figure 8a**).

Applying *autodE* to study this catalytic cycle using only the SMILES strings of the catalyst, ethylene, intermediates and products, the full reaction profile was obtained in just under 26 hours (16 CPU cores, excluding electronically barrierless ligand association steps (**Figure 8b**).

Figure 8. (a) Heck-Breslow mechanism of hydroformylation in the absence of a phosphine catalyst. (b) Reaction profile calculated at PBE0-D3BJ/def2-TZVP//PBE0-D3BJ/def2-SVP in *autodE*.

autodE correctly identifies the most stable isomer of all intermediates, for example the axial isomer for strong σ -donors (H: **INT1**, alkyl: **INT3**, acyl: **INT5**). TSs for all steps in the cycle are located successfully, contain a single imaginary frequency and have geometries very similar to those found for analogous phosphine-based catalysts (**Figure S15**).⁵² The same process was applied to the analogous Co-catalyzed hydroformylation (**Figure S16**), which has been used as a representative example in other automated reaction generation algorithms.^{13,14,53} Once again, all TSs were successfully located with minutes of setup time.

With a view on expanding the use of *autodE* for catalyst design campaigns, and following previous efforts in this field,⁵⁴ we have also developed the *molfunc* tool (<https://github.com/duartegroup/molfunc>). Combining *autodE* with *molfunc* enables a rapid screening of different catalysts by performing functionalization of

hydrogenic or other monovalent atomic positions. For example, for the H-insertion step, *molfunc* facilitates the exploration of different groups at the *para* position of phosphine on the barrier (**Figure S17**). The obtained positive correlation between the enhanced electron withdrawing ability of the catalyst and rate agrees with the experimental observation.⁵¹

3.4 Further Examples

To demonstrate the generality of our method, we tested *autodE* on a set of 15 simple organic reactions of different classes. *autodE* finds all TSs in all cases and generates reactions profiles in a matter of hours (**Figure S18**). Further examples include metal-catalyzed carbonylation of methanol to generate acetic acid via the Monsanto (Rh, **Figure S19-20**) and Cativa (Ir, **Figure S21-22**) processes,⁵⁵ alkaline ester hydrolysis (**Figure S9**), a Houk–List TS (**Figure S23**),⁵⁶ and 57 carbene insertion reactions reported in ref ⁵⁷ (**Figure S24**). In this latter case *autodE* correctly locates 55/57 insertion TSs, with two failures occurring when a QRC+graph isomorphism check fails to confirm the TS as linking reactants and products, despite the TS being correct. Moreover, TSs for synthetically relevant reactions including a key Diels-Alder step in a total synthesis of Brevianamide A investigated by Domingo *et al.*⁵⁸ and a diastereoselective epoxidation⁵⁹ are presented in the SI (**Figure S25-26**).

3.5 Limitations

The graph-based approach affords two immediate limitations of the method: The need to define bonds, and checking stereochemistry. While bonds are generally well-defined in organic systems, they are not a rigid concept. Indeed, the energy required to overcome an interaction between atoms (i.e. a bond) does not necessarily correlate with the type of interaction (e.g. covalent or non-covalent) (**Figure S27**). This is partially alleviated by not regenerating the molecular graphs from the 3D structure and retaining the SMILES-defined connectivity but may afford an incorrect assignment of a ‘good’ TS, which actually does or does not lead to products/reactants. Furthermore, the isomorphism condition on reactants/products does not currently include a stereochemistry check – the algorithm simply finds the lowest energy TS. While this is often defined by the reaction type e.g. stereochemical inversion in S_N2 is generated by traversing the lowest energy TS there are reactions such as the Peterson olefination where this is not adhered to.

By enforcing a maximum connectivity change of four (up to 2 bonds breaking and forming) means that, for example, the TS in a synchronous Fritsch–Buttenberg–Wiechell rearrangement⁶⁰ mechanism cannot be found. In this case, chemical intuition is required to prevent the very slow enumeration of 10 2D PES scans if all combinations of coordinates are chosen i.e. here some human intervention is necessary.

Finally, we note a limitation in the current *lmethod* electronic structure theory methods used to generate conformers of reactant and product complexes. Reactions involving anions are particularly problematic, as at the TB-DFT level they are generally not sufficiently stable (even in implicit solvent) such that the reaction may be barrierless at the *lmethod* level. We hope that as semi-empirical/TB electronic structure methods become more accurate and/or DFT and WF methods become faster, this limitation will be mitigated. Because *autodE* does not rely on one specific method implementing novel methods should be only an afternoons work.

4. Conclusion

Converting a 2D representation of a reaction to a reaction profile has long been the domain of expert computational chemists. Here we have shown that our method, *autodE*, can largely automate this process and present a selection of both simple and synthetically interesting organic and organometallic reactions. By building *autodE* in a way that does not rely on a particular electronic structure theory method, future methods for calculating points on the potential energy surface are easy to include. Indeed, the dominant source of failure of the methodology is due to inaccuracies in electronic structure methods rather than issues associated with *autodE*. Crucially, *autodE* is open source, making the development faster, more collaborative and more robust. We believe *autodE* will facilitate faster computational investigation.

Computational Methods. All *autodE* calculations were performed with a development version of the code with the beta release distributed with this manuscript. Unless otherwise stated the *lmethod* used was GFN2-xTB v. 6.2³¹ and the *hmethod* ORCA v. 4.2.²⁷ All ORCA optimizations employed resolution of identity DFT (RI or RIJCOSX for hybrid functionals)^{61,62} using the PBE⁶³ or PBE0⁶⁴ functional, in combination with the D3BJ dispersion correction,^{65,66} def2-SVP or def2-TZVP basis set⁶⁷ (with effective core potentials for Rh⁶⁸) and the default auxiliary basis set.⁶⁹ Gaussian09⁷⁰ calculations employed identical methods without density fitting unless otherwise specified. NWChem v. 6.6³⁸ calculations used no dispersion correction as D3BJ is unavailable with PBE0. Default integration grids were used in all DFT calculations. Conformers generated with RDKit⁷¹ version 2020.03.1 and OpenBabel version 2.4.1.

Supporting Information. Compatibility of *autodE* with different electronic structure theory codes; details on the construction of molecular graphs, evaluation of conformer generation approaches, and further examples on the applicability of *autodE* on organic and organometallic processes.

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