Computers in Organic Chemistry*

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Until about a decade or so, till the fast-paced development and usage of computers, organic chemistry students often chose experimental projects during an internship. Presently, there are software packages that solve quantum chemical equations and present the possibility of a ‘black-box’ type of approach to getting exposed to computational organic chemistry. Encouraging as this may seem, Indian university students can find the entry to and an understanding of computational chemistry daunting due to a lack of exposure to research. This article attempts to bridge the gap for such students by providing a gentle introduction to the field of quantum chemistry.

1. Organic Chemistry in the Bachelor’s Program

Students doing a Bachelor’s degree in chemistry in India are first introduced to the ‘traditional’ branches of chemistry namely organic, inorganic, physical and analytical chemistry throughout their program. A significant amount of effort and time is spent on imbibing various concepts such as bonding, spectroscopy, reactions, reagents, synthetic strategies and the intricacies of reaction outcomes due to the complexity of the carbon skeletons and the presence of functional groups and their relative positions. Students are taught how to ‘push’ electrons and build intuition about why certain reactions will be favoured over the others, and how one can optimize the conditions to maximize the yield in a reaction. While this is mostly self-sufficient, every once in a while, the experimentalist observes a product that cannot be explained by simply working out an electron-pushing mechanism and deeper insights in terms of theoretical calculations are re-

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quired to unravel the unexpected outcome. One needs to work out the mechanism in such cases whose details eventually help in rationalizing the unexpected outcome. This started becoming evident especially in the 1960s where seemingly similar reactions gave unexpected products.

For instance, alkenes are not expected to react under thermal conditions to given cyclobutanes. Yet, an alkene and diene will add to give cyclohexenes—this is the famous Diels–Alder reaction. The reader is directed to a detailed discussion of various developments in the mechanistic understanding of this reaction in the comprehensive book by Steven Bachrach [1]. Here, we only outline the usefulness of computational chemistry in the knowledge acquired about this reaction. The activation barrier for this reaction was determined to be ∼27.5 kcal/mol [2] in early 1951 and about ∼23.3 kcal/mol in the 1980s [3] and in order to explain the mechanism, an attempt was made by computational chemists to reproduce this barrier value using theoretical approaches. After several important improvements [4–17], an activation barrier of 26–28 kcal/mol was obtained, depending on the accuracy of the methods used. While in excellent agreement with the experiment, the stepwise mechanism could not be ruled out. Experiments provided evidence for the concerted mechanism in greater favour compared to the stepwise mechanism by at least 3.7 kcal/mol [3] in terms of the barrier energy value. Accurate computational methods also suggested that the stepwise mechanism had higher barriers [6–10], and in the mid-1980s, the mechanistic question seem to have been resolved for the Diels–Alder reaction. In 1984 however, Dewar [18] proposed that in reactions involving multiple bond breaking and making, the degree of bond making and breaking is not synchronous. The resolution to this controversy came from secondary kinetic isotope effects (KIEs) in this reaction [19–25]. The substitution with isotopes changes the vibrational frequencies for all vibrations in which that atom is involved. This leads to a different vibrational partition function that, in turn, can be used to estimate a reaction rate using the Eyring transition state theory [20]. This is true of the terminal carbons of the diene and
the dienophile because of the change in hybridization from \( sp^2 \) to \( sp^3 \). The ratio of the original to the isotope-substituted (\( kH/kD \), for example) being > 1 (normal KIE) or < 1 (inverse KIE) can be directly compared to the experiment. The predicted KIEs for the concerted pathway were in better agreement with the experiment than the KIEs for the stepwise pathway for several reactions [22, 23]. However, the degree of synchronicity is not discernible from experiments, and this seems to depend on the system under consideration. In summary, we see that for a seemingly simple reaction such as Diels–Alder reaction, we find intricacies that are not easily addressed by experiment, and we find that experiment and computations have to work hand-in-hand to reveal the full picture.

Rationalizing unusual products aside, recent efforts are directed not just towards achieving high yield in a reaction but also designing catalysts that will selectively drive the reaction towards forming a certain enantiomer. These three scenarios (mechanism, rationalization and design) broadly constitute areas of organic chemistry where theoretical input is often required. We will discuss examples of these areas in a way that an undergraduate student can relate to, in terms of what is learnt from the classroom to what forms part of the modern-day research in computational organic chemistry.

2. Relevance of Computers in Organic Chemistry

The discussion of computers in chemistry is a broad topic and will include computer technology developments for applications in experimental chemistry, such as the use of complex analysis methods for X-ray crystallography, Fourier–transform spectroscopy, mass spectrometry, etc. In this article, we will focus on the use of computers in theoretical chemistry, namely how computers help in answering fundamental questions about molecular behaviour in chemical reactions.

The field of computational chemistry is much more recent compared to classical mechanics (17th century) and quantum mechanics (1920s).
ics (1920s). Though solving the electronic Schrödinger equation for molecules (see Section 3.1) accurately and efficiently is one of the core problems in chemistry, it has taken several decades to make progress. One may recall that the Schrödinger equation for the hydrogen atom is exactly solvable, while for lithium and other multi-electron systems, it is not, and only an approximate solution can be obtained. The seed of using computers to address this problem in chemistry was sown after the invention of computers and the subsequent technological sophistication (1940s–1950s). Important and notable landmarks include the first semi-empirical approach to solve the electronic Schrödinger equation in the 1950s [26], the first fully ab initio approach to solve the same using the Hartree–Fock method in 1956 [27] and the first configuration interaction calculation by Boys and co-workers during 1950s [28]. The impact of such efforts is immense! We can now focus on the science of a chemical problem rather than the technical aspects of numerically solving an equation (which is not a chemical question at all) at multiple length scales and timescales (Nobel Prizes in 1966, 1998 and 2013).

Figure 1 gives an overview of how computational chemistry impacts several frontier research areas today. Although we have outlined two broad areas of organic chemistry (reaction mechanisms and photochemistry) where computational chemistry finds a place, this area has spawned several subareas that have become specializations in their own right. For example, photochemistry is the study of chemical reactions and other physicochemical phenomena induced by light absorption. Enzyme catalysis and catalyst design have different emphasis: while the former deals with how enzymes catalyze several important biochemical reactions in the natural world, catalyst design is the ‘holy grail’ (see Section 4) of organic chemistry, dealing with designing enzymes for specific purposes, particularly catalyzing reactions that do not necessarily happen in nature. The use of computational methods to simulate molecular spectra, such as those acquired using nuclear magnetic resonance, infrared light, UV-visible light, and microwave radiation, increased by leaps and bounds as the accuracy of the
numerical solutions to the electronic Schrödinger equation also improved in the 1980s [29]. It is now routine to use computed spectra to assign structures to the molecules of interest, so much so that one can deconvolute a spectrum into those of multiple structures that contribute to the overall envelope of the observed curve. Finally, computational chemistry remains invaluable in what it originally set out to do for chemists—understanding reaction mechanisms and the accompanying reaction dynamics. The current set of programs and software not only allows us to map a ‘minimum energy path’ from the reactant to the product (reaction mechanism) but also allows us to map various other paths that the reactant molecule can visit before it transforms into the product (reaction dynamics). Overall, the societal impact of research in these areas manifests in drug discovery and synthetic biology (using organisms instead of test tubes to carry out chemical reactions of interest).
3. Computational Organic Chemistry Research: Concepts

Molecules are ultimately quantum mechanical objects. The electrons being about 1800 times lighter than the nuclei, the nuclei only ‘see’ an average cloud of electrons and electrons have the ability to adjust to any change in the nuclear positions instantaneously. This difference in the masses is exploited in the description of molecules. Instead of attempting to solve the molecular Schrödinger equation, we make the Born–Oppenheimer approximation [30] to separate the solution procedure for electrons and nuclei. Figure 2 shows the connection between several fields of computational chemistry in terms of its subareas. The solution to the molecular Schrödinger equation for equilibrium and dynamical investigations requires a tremendous amount of effort, of which quantum chemistry is only a part. Once the solutions are obtained, a whole range of analysis methods is available to the computational chemist to interpret the experimental data at hand. Analysis methods include assignment of spectra, explaining reaction mechanisms, predicting reaction barriers and rates, estimating free energy reaction profiles, analyzing changes in electron density during the reaction, electronic population analysis, etc. We will now briefly examine the steps that lead to the solutions to the electronic Schrödinger equation in particular—this encompasses the field of quantum chemistry.

3.1 Electronic Structure Holds the Key to Chemical Reactions

One starts by learning about chemical reaction mechanisms by ‘pushing’ electrons. In essence, such an exercise implicitly assumes that the nuclei are more or less stationary (except maybe hydrogens). However, in this approach, we do not understand the underpinnings of why and how. A rigorous route to learning mechanisms is by gaining a theoretical understanding using quantum chemical principles. The theoretical premise of quantum chemistry lies in how electrons and nuclei behave. If we had a microscopic camera to observe their motion, we would find that the electrons, about 1800 times lighter than the nuclei, move...
much faster, and for every change of nuclear coordinates, they change their coordinates almost instantaneously (the fact that they need to change their coordinates is because of the change in the electric field created by the nuclei that in turn exerts a force on the electrons). Another way to understand the timescale separation in electronic and nuclear motion is to imagine using a microscopic camera with a very slow shutter speed. We will then need to take multiple shots of the molecular motion when the nuclei change their position each time and put together the shots to get a movie frame. This frame can be compared to the first camera above, which captured the molecular motion as is. Since the electrons adjust (almost) instantaneously to nuclear motion, the two movie frames will be nearly identical [31].

The molecular Schrödinger equation involves the molecular Hamiltonian:

\[
\hat{H}_{\text{molec}}(r, R) = \hat{T}_N + \hat{T}_e + \hat{V}_{ee}(r) + \hat{V}_{en}(r, R) + \hat{V}_{NN}(R),
\]

where \(\hat{T}_N\) is the nuclear kinetic energy, \(\hat{T}_e\) is the electronic kinetic energy, \(\hat{V}_{ee}\) is the electron-electron repulsion energy, \(\hat{V}_{en}\) is the electron-nuclear attraction energy and \(\hat{V}_{NN}\) is the nuclear-nuclear repulsion energy, and the variables \(r\) and \(R\) represent the set of electronic and nuclear coordinates respectively. The Born-
Oppljheimer approximation involves the separation of the electronic and nuclear motion due to their difference in masses and treating nuclei as particles with frozen coordinates. Instead of completely neglecting the effect of nuclear motion, we rewrite $\hat{V}_{eN}(r;R)$ as $\hat{V}_{eN}(r;R)$, where the arguments imply a parametric dependence of electronic energy on the nuclear coordinates instead of a joint dependence on both electronic and nuclear coordinates. By doing so, with a certain amount of algebra [32, 33], we can use a product representation of the wavefunction as

$$\Psi_{molecular}(r;R) = \chi(R)\Psi_{el}(r;R)$$

where we can solve the following equation first: $H_{el}(r;R)\Psi_{el}(r;R) = E_{el}(R)\Psi_{el}(r;R)$ and then solve the nuclear sub-system equation: $(\hat{T}_{N} + \hat{V}_{eN}(R)\chi(R) = E\chi(R)$ to get the molecular energy. Note that the $H_{el}(r;R) = (\hat{T}_{e}) + \hat{V}_{ee}(r) + \hat{V}_{eN}(r;R) + \hat{V}_{NN}(R)$. The electronic eigenvalues $E_{el}(R)$ are called potential energy surfaces (PESs); the dynamics of the nuclei in chemical reactions are described by the motion of the nuclei on these surfaces. When does this approximation break down? The approximation holds as long as the PESs are well-separated from each other; if they come close to each other (either by accident or due to molecular symmetry), then the nuclear kinetic energy becomes large, and one must consider coupled electron-nuclear dynamics. This is usually the case when the molecules are in their ground electronic state. In several photochemical reactions, however, this approximation often breaks down, and one has to go beyond the Born–Oppenheimer approximation to correctly explain the experimental observations.

Although the Born–Oppenheimer approximation came into place in 1927, theoretical chemistry had to wait for the mean-field approximation (Hartree–Fock method) to be implemented in the 1950s due to the high computational demands of the equations at hand. In the Hartree–Fock method, each electron is influenced by a mean field due to all other electrons (Figure 3) instead of being influenced instantaneously. This allows us to visualize the electronic wavefunctions in a way we understand the exact solutions of the hydrogen atom, namely the orbital functions. This is because of the reduction of the many-body electronic Schrödinger
equation to a set of one-electron equations that can be solved much more easily. The numerical solution of these equations are carried out typically using an atomic orbital basis set, the details of which the interested student is referred to a more thorough treatise [34]. One must note that the notion of orbitals, as much as it is central to understanding chemical reactions from a quantum perspective, is valid only within a mean-field description of the electrons. The orbital picture continues to provide deep insights; nevertheless, the users must appreciate the limitations and assumptions under which they are obtained and that electron correlation effects, which require us to go beyond the mean-field approximation, are crucial to explaining several chemical reactions.

### 3.2 The Potential Energy Surface and Minimum Energy Path

The eigenvalues $E^i(R)$ of the electronic Schrödinger equation form a series of potential energy surfaces (PESs) for that molecule (where the word ‘series’ here refers to the superscript index $i$). For example, a diatomic molecule, having only one internal coordinate (bond coordinate), will have a series of potential curves (Figure 4) indexed by $i = 0, 1, 2$, etc. From triatomic molecules onwards, we will have a multi-dimensional PES as a function of $(3N-6)$ coordinates for nonlinear molecules and $(3N-5)$ for linear molecules. In the context of computational organic chemistry, the PES is the starting point for any meaningful analysis of chemical

**Figure 3.** A mean field picture of the electrons around an atom. Each electron feels only an effective potential due to the other electrons, making the Schrödinger equation essentially a series of one-electron equations.

The coordinates used for constructing PESs are not unique—one could use a combination of bond lengths, bond angles, dihedral angles, normal modes of vibration, or other sets of coordinates that might be intuitive to the problem of interest.
Figure 4. Potential curves of a typical diatomic molecule. Each point on a curve is the (approximate) energy eigenvalue of the electronic Schrödinger equation at a given internuclear distance.

reactions. The coordinates used for constructing PESs are not unique—one could use a combination of bond lengths, bond angles, dihedral angles, normal modes of vibration, or other sets of coordinates that might be intuitive to the problem of interest. Such a choice is often the domain of a theoretical chemist, who works out the details of the tools needed to decipher the mechanism behind a photochemical or photophysical reaction.

Shown in Figure 5 are two ways of representing multi-dimensional PESs, namely the surface plot as well as the contour plot; this set of plots in Figure 5 is for a triatomic molecule (using two bond length coordinates) where the minimum denotes the stable triatomic molecule. Any increase in one of the bond lengths increases the electronic energy; beyond a point, the bond breaks and dissociates into a diatomic molecule and an isolated atom. On the other hand, a similar construction of PES for the reaction A+BC→AB+C against the coordinates A-B and B-C bond coordinates will result in the triatomic species being in the transition state and not the minimum [35]. Therefore, PESs provide us with all the information needed to understand the reaction mechanism—both from a thermodynamic and kinetic point of
view—as long as we are considering molecules in the gas phase. The PESs are modified when we include a solvent’s effect, which is important to consider when it comes to the relative stabilities and kinetic aspects of a reaction. We will consider the effect of solvent in Section 3.4.

3.3 Free Energy of the Reaction and Rates

A transition ‘state’ in a reaction is pictorially depicted as the top of the barrier in a typical reaction (Figure 6A). The word ‘state’ here is originally introduced in a thermodynamic sense meaning an ensemble of structures and denotes a free energy maximum along the reaction coordinate. On the other hand, the transition ‘structure’ is a single structure on a theoretically calculated PES, where all first-order energy derivatives are zero and all second derivatives except one are positive. In other words, this state is a first-order saddle point (Figure 6B); the PES does not even include a vibrational description and denotes only the electronic contribution (and not vibrational, rotational, translation and entropic). Chemists often use the terms transition state and transition structure interchangeably, and while this does not imply equivalence, one should be aware of the difference and what it means in a reaction context. We will therefore use the more common term ‘transition state’ to keep things familiar to known

Figure 5. Two equivalent ways to viewing a potential energy surface of a poly-atomic molecule: (A) 3D surface plot and (B) 2D contour plot.

A transition ‘structure’ is a single structure on a theoretically calculated PES, where all first-order energy derivatives are zero and all second derivatives except one are positive.
chemical language. The transition state is the next most important topological feature of the PES after minima (reactant, product and intermediates) and, for a chemist, is the key to understanding reaction mechanisms. While we won’t go into further discussion of the transition state itself here, we will highlight its connection with the statistical description of reaction rates and how it helps us calculate the reaction rate constants.

One can think about reaction rates in two ways—absolute reaction rates, which require accurate knowledge of the PES and several molecular dynamics trajectory calculations, or statistical reaction rates, which use statistical approximations about the reaction constituents to estimate the rates (transition state theory (TST) [36], Rice–Ramsperger–Kassel–Marcus (RRKM) [37], variational TST [38]). Historically, statistical theories first developed in the 1920s and 1930s [39–41], building on the Arrhenius equation [42, 43] formulated in 1889. It is only in the last four decades that computational resources have become powerful enough to map out PESs accurately. The Eyring equation is one of the most important equations in the kinetic theory of reactions using statistical mechanics [44].

\[ k = \kappa \frac{k_B T}{h} e^{-\frac{\Delta G^+}{RT}}, \]

where \( \kappa \) is called the transmission coefficient, \( T \) is the temperature, \( \Delta G^+ \) is called the free energy of activation of the reaction, \( k_B \) is the Boltzmann’s constant, \( h \) is Planck’s constant and \( R \) is the universal gas constant (\textit{Figure 6A}). Although successful for many decades, the statistical theories could not account for the reaction rates in several experiments (see, for example, these references [45–46]). This stems primarily from the breakdown of the assumption in these theories that the initial energy provided in a reaction gets distributed faster than the timescale of the reaction. More examples of such non-statistical behaviour have been observed over the years, and the necessity of explicitly modelling the reaction using accurate PESs has increased alongside increased accuracy of experiments in detecting and charac-
terising transient species in a reaction.

In routine calculations by computational chemists, the estimates of absolute and relative free energies of reactants, products and the transition states are made using several algorithms, depending on whether the molecule is isolated (gas phase) or in solution. In the gas phase, an ideal gas model yields the translation contribution, a rigid rotor model yields the rotational contribution, and a harmonic oscillator model is assumed to obtain the vibrational contribution [47]. In solution, a recent treatise using an advanced treatment of the contributions from the solvent [48] is recommended to get meaningful free energy of solvation that can be further used to estimate the reaction free energies.

3.4 The Role of Solvent

Most chemical reactions and property measurements (like spectra) are carried out in a solvent. The solvent profoundly influences the properties of the solute in terms of the structures adopted, relative energies of conformers, reaction mechanisms (in terms of shifts in reaction, activation energies and paths) and its spectroscopic signatures. Classic examples include keto-enol tautomerism [49], where the enol form is stable in the gas phase. The tautomer dominates in solution because of a larger dipole moment and reversal in the acidity trends of aliphatic alcohols when going

**Figure 6.** (A) One-dimensional representation of a typical reaction coordinate, (B) The notion of the transition state as a first order saddle point on a potential energy surface.
from the gas phase to solution [50]. Hence the thermodynamics (equilibria) is altered by the introduction of solvent. Though not discussed here, the solvent also influences the kinetics of a reaction, thus affecting the rates and the outcome. In this section, we briefly introduce the tools from computational chemistry that simulate the solvent environment.

There are multiple ways to include the effects of a solvent environment. The continuum model of a solvent accounts for the polarization effects exerted by the solute and solvent on each other in terms of the changes in the local electric field surrounding the solute. This electric field is part of a ‘reaction field’ that is described by various approximations and involves the definition of a cavity around each atom in the molecule that uses this reaction field [51] (Figure 7). Recently such models have been further developed to account for non-electrostatic effects such as dispersion [52]. This model is the most efficient in terms of computational resources and is often used to test the effect of solvent before going on to include explicit solvent in the calculations. However, this approach fails if the solvent molecule is directly involved in the reaction chemistry (for example, in hydrogen bonding, coordination complex, etc.).

Explicit solvent models are much more challenging since one has to correctly estimate the number and orientation of the solvent molecules around the solute to capture the electronic effects within at least the first solvation shell. Why is this important? In several molecular problems, the solvent molecules within the first solvation shell interact the strongest with the solute, and the effect starts diminishing as we move further from the first shell (which is what we expect). If one does not account for all the solvent molecules, then the computational chemist is often bound to overestimate the electronic effects exerted by each solvent molecule [53]. Further, it has been shown recently that it is important to not only have the explicit solvent molecules but also have the continuum model effects and multiple configurations by doing molecular dynamics simulations, in addition to correctly reproducing the experimental trends in spectroscopic properties [54].
How accurate is the implicit solvent model? Ideally, the explicit solvent model will do better than the implicit solvent model, but how much can we get away with in terms of the description of the solvent as a bulk dielectric term? It all depends on how sensitive the molecular property is to the solvent polarity and hence is a system-specific answer. The interested reader is encouraged to read recent articles by the pioneers in this field to get a feel for the accuracy of such methods [55]. In summary, although the bulk of organic chemistry happens in solution, it is often common for a computational chemist to start looking at the reaction in the gas phase, then include the effect of solvent implicitly to test for the impact of bulk effects, and then think about the role of explicit solvent in tuning the free energy of the reaction.

3.5 Wavefunction Analysis Methods

Computational chemists primarily solve the electronic Schrödinger equation to get the electronic eigenfunctions; these, as explained in Section 3.1, are often within the mean-field approximation to
get ‘orbitals’, which are essentially one-electron functions. One gets a large number of such orbitals for a given molecule, and to a large extent, only a few are important to describe the reaction chemistry at hand. These are part of the ‘frontier orbitals’ comprising a few of the highest occupied orbitals and lowest unoccupied (or virtual) orbitals. It is useful to develop tools to visualise on the computer these orbitals, either directly or by using them to calculate specific properties such as atomic charges on the atoms or the electrostatic potential. Figure 8 shows an example of the ground electronic state density mapped with the electrostatic potential. We can see that such a plot clearly shows the electron-rich and electron-deficient regions in the molecule, which in turn can be used to assess the chemical reactivity. In the example shown here for methyl chloride, the methyl end of the molecule will be attacked by Lewis bases (nucleophiles), and the chloride end will approach Lewis acids. This and many more methods are at the disposal of the organic computational chemist to analyse a chemical reaction. The interested reader is referred to several features of the current quantum chemistry programs that describe the state-of-the-art wavefunction approaches in this area [56–58].

3.6 Advanced Considerations

Organic chemistry has evolved to include the study of not only organic compounds but also organometallic molecules such as catalysts containing heavy elements like Rb, Mo, Rh, Ru, etc., (for example, the Wilkinson’s catalyst Rh(PPh₃)₃Cl). Theoretical description of the electronic structure of heavy elements (atomic number greater than Ar) is an active area of research because of the relativistic effects of the electrons in these systems. With the introduction of the d and f shells, the electrons closer to the nucleus approaches the speed of light and hence have to be described appropriately in the electronic Schrödinger equation [55]. This is another area of quantum chemistry undergoing extensive method development and requires significant background in the physical sciences to be pursued as an academic career.
A lot of the deduction in the organic reaction mechanism is contained in analysing the critical points along the reaction path, namely the local energy minima (reactants, products and intermediates) and one or more transition states. However, the molecule is not always guaranteed to take the minimum energy path (i.e., along the intrinsic reaction coordinate) or follow a statistical dynamics route where the energy gets quickly redistributed in relation to structural changes from the transition state. For these cases, one cannot apply the standard TST or RRKM theories to predict the reaction rate and instead must use explicit nuclear dynamical methods to determine the mechanism of the reaction. This forms part of investigations by the dynamics community in theoretical chemistry and often involves advanced mathematical treatment of the time-dependent Schrödinger equation [59].

In the last two decades, routine computational chemistry has evolved to use density functional theory (DFT) methods to study organic reactions. While this is advantageous in terms of computational costs, the description is approximate at best. To improve the accuracy of the description of the electrons and how they bring about a reaction, one must include a better treatment of the electron correlation. The electronic structure theory development community handles this to produce methods such as MCSCF, MRCI, etc., [60].

4. Holy Grail(s) in Computational Organic Chemistry

One of the major goals of computational organic chemistry is to predict reagents that will make a reaction happen with high selectivity and desirable qualities in terms of its applications. What is daunting is to make sure that competing reactions do not occur in this case, and this is challenging to achieve in terms of computational efficiency and chemical accuracy. One often compromises accuracy in the interest of efficiency. It is only recently that developments in the field of density functional theory have allowed the possibility of these two desirable qualities to meet each other. Current state-of-the-art methods in reaction design include the ar-
tificial force-induced reaction method [61] and nano-reactor [62] method, and the interested reader may refer to these for further information.

We have not described the role of a catalyst in this article, but one is only too familiar with the effect of a catalyst on a reaction from high school chemistry. Catalysts have several advantages, especially in an industrial setting, since their ability to speed up reactions saves money (plant operational time) and energy (lower temperature). They are also reusable and hence can be exploited for several cycles until impurities or other factors ruin them. The downsides include the cost of making the catalyst in the first place and the narrow range of reactions for which each catalyst is useful. Nevertheless, the design of catalysts in synthetic chemistry is the second major goal of computational organic chemistry. Much of the recent efforts have gone into using enzymes [63] and solid-state catalysts [64]. In addition, if the reaction can be carried out in a natural organism setting, such as in a cellular environment, one would circumvent the environmental issues associated with large-scale synthetic chemistry issues.

In summary, students entering the field of computational organic chemistry will find a rich plethora of opportunities to contribute to society not only in terms of tackling biochemical problems leading to drug discovery and ‘clean’ materials but also by advancing the fundamental understanding of how chemistry works all around us.

Further Reading

This article provides a flavour of the concepts and background necessary to start a career in computational organic chemistry. For more comprehensive coverage, the interested reader is directed to several resources [1–65] with excellent examples of various case studies to pique curiosity.
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Suggested Reading


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