



CHAPTER 1

Introduction to the Book

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1.1 Introduction

This is a multi-author book, and as such it cannot be uniform in terms of the style or language. This variability is augmented by the different aspects of the topics of EFs in chemistry, its interplay of theory and experiment, and its overlaps with physics. As such, the present chapter tries to introduce some uniformity by outlining briefly the essence of the various chapters and the invisible thread that links them. Much of this link has to do with the chemical/physical insights that the book tries to derive for the sake of the community. At the end of this chapter, we provide a glossary of abbreviations and acronyms, which are uniformly used by all authors. However, by necessity, there will be a host of terms and symbols that are typical to each chapter. Nevertheless, we are hopeful that the final product is a coherent book that shows the many facets of applying EFs to molecules, reactions, molecules, and aggregates.

1.1.1 The Chapters that Make this Book

The chapter that follows this introductory chapter is written by the two editors, K. D. Dubey and D. Danovich. It deals with the impact of EEFs/LEFs on chemical structure and reactivity. It introduces valence bond reactivity

diagrams¹ as a tool that enables qualitative understanding of the impact of an EF and its directionality on bonds and chemical reactions.^{2,3} Among other aspects, it demonstrates how application of EFs lowers or raises energy barriers (depending on the field's directionality), controls regioselectivity, stereoselectivity, chiral discrimination, molecular orientation in space, and reaction mechanisms. A subsection of the chapter deals with the application of EFs in the presence of solvents. Importantly, the chapter derives also the selection rules that govern and control these effects.

As is discussed, these means of control depend on the orientation of the EEF *vis-à-vis* the reacting molecules or the bond in question.^{2,3} One of these rules is “the reaction-axis rule”. The reaction-axis defines the natural direction of electron flow between the molecules throughout the reaction, so old bonds can break and can be replaced by new ones. This, like the curly arrow mnemonic in organic chemistry, sets the favourable direction for delivering an EEF and obtaining catalysis or inhibition at will.

The following chapter, by S. Ciampi, I. Diez-Perez, M. L. Coote and N. Darwish,⁴ describes the manners by which EEFs and interfacial EFs (IEFs) are harnessed by experiment to impact chemical reactivity. It describes the usage of a scanning-tunnelling microscopic (STM) tip coupled to a charged surface to deliver an oriented EEF through molecules. This STM setup is designed to obey the “reaction-axis rule”.

The chapter further discusses the IEF that is formed near polarized electrode–electrolyte interfaces due to the imbalance of charged species (generally salts and excess surface charges).^{5,6} It describes other EEF types and their applications in chemical reactions, such as those delivered in the vicinity of statically charged insulators, air–liquid interfaces, charged biomolecules, or within molten salts and ionic liquids. The advantages/disadvantages of these EEF/IEF methods, and their potential for scalability is discussed.

The chapter by M. L. Coote and her co-worker, M. T. Blyth, describes the recent developments in designed LEFs (D-LEF)^{4,7–9} A D-LEF is an electric field that is built by design into the reacting molecules. One of the simplest ways of doing so is by pH-switchable charges. Thus, for example, using a carboxylic acid substituent on the reactant can “switch on” a negative charge upon increase of the pH. Similarly, using an amine substituent can create a switchable positive charge by lowering the pH. As this chapter describes, this strategy has an impact on bond energies, and reactivity/selectivity in Diels–Alder reactions, S_N1/S_N2 mechanistic selectivity, *etc.* More recent applications will be discussed, in which the strategy is carried over to photochemical reactions, catalytic cycles, and so on.

The above chapters delineate a coherent description of the principles that govern reactivity, and selectivity control and the practical ways to implement these principles by experimental designs. A related chapter, written by I. Diez-Pérez, N. Darwish, C. Foroutan-Nejad, L. Domulevicz, and J. Hihath, deals with molecular devices fuelled and/or controlled by either LEFs or EEFs.^{10–12} There is a broad range of molecular devices whose functionality is based on electric fields such as switches (*e.g.*, molecular isomerization by

the OEEF), and various memory devices, logic-gates, molecular machines, *etc.*¹⁰ This chapter deals also with these devices as means of controlling single molecule reactions, thus connecting to the chapter by Ciampi *et al.*, which describes the electrostatic catalysis of the Diels–Alder reaction in an STM junction.¹¹

The devices chapter describes how similar device architectures can be exploited for the design of a plethora of functionalities in molecular electronics. The chapter starts by describing a molecular field-effect transistor (molecular FET), where the well-established FET concept is implemented in a molecular junction in both solid-state and wet (electrochemical) environments. Next, the chapter shows more advanced functionalities, which are achieved by a subtle interplay between the intrinsic molecular LEF and the operative OEEF of the device.¹² The chapter concludes with the latest advances in the use of local OEEFs in molecular junctions as a tool to obtain molecular spectroscopic fingerprints in low-dimensional systems.

A second general topic of the book is discussed in the next two chapters that describe theoretical approaches that enable fruitful interplay between theory and experiment by quantifying EFs from charge distributions.

The chapter by T. Stuyver, J. Joy, D. Danovich and S. Shaik,¹³ describes the available theoretical approaches to quantify, generate and manipulate electric fields. Among these methods is the software TITAN, which was developed by the Jerusalem group.¹³ TITAN is both an electric field generator and quantifier; it can convert any molecular structure into a charge distribution and quantify the resulting LEF (*e.g.* the LEF associated to the protein environment of enzymes), or it can set up any desired EEF to augment or modify the LEF of a catalyst or an enzyme. The chapter describes a few applications of TITAN, *e.g.* the impact of the LEF embedded within cytochrome P450 OleT_{JE} and the effect of an additional EEF on the reactivity exhibited by this enzyme, the role of salt additives on catalytic oxidative addition reactions by a palladium complex, and the role of LEFs in experimentally designed models of active species of the enzyme cytochrome P450.

In addition, the chapter describes other methods and computational codes that focus on electric field quantification and generation. For example, the pioneering work by Sokalski *et al.*¹⁴ on the design of optimal catalytic fields, and the recent implementation of this bottom-up approach by Hartke *et al.*¹⁵ are discussed. Finally, the chapter provides a short overview of the alternative top-down long-range electric field optimization strategy developed by Head-Gordon and co-workers.¹⁶

Some related topics connected to the quantification of the effects of applied external field within the context of biophysical chemistry are discussed by C. F. Matta. Matta reviews the vibrational Stark effect on small molecules in intense fields,^{17–19} of intensities akin to those present in enzyme active sites or in cell organelles such as the mitochondrion, and in nanoelectronics devices.^{17,18} He and his co-workers (S. Sowlati-Hashjin and M. Karttunen) also discuss recent results on the response of the electron density to imposed field within the framework of “quantum theory of

atoms in molecules" (QTAIM). The chapter then proceeds to discuss the effect of the natural chemiosmotic electric field on the structure and reactivity of molecules belonging to electron transport chains. Subsequently, the author describes the latest results on the electric field of the electron transport chain enzymes.

Finally, Matta discusses some applications to enzymes in which the electric fields in the binding sites with and without their hosts (whether cofactors, substrates, inhibitors, or combinations of those) were quantified from experimental electron densities. This strategy yields key information about the electrostatic characteristics necessary for optimal inhibition which can guide drug-design by "reverse engineering" in a striking visualization and use of the "lock-and-key" hypothesis.¹⁹

An EEF may well have, depending on conditions, a very substantial impact on the dynamic behaviour of molecular and mesoscopic species in solution, which change both the 3D structure and the electronic structure in response to the field. This may occur in a manner that brings about a gamut of effects, spanning from well-understood chemical and biological changes all the way to health-related effects. These aspects are outlined in the chapter by N. J. English, who describes non-equilibrium molecular-dynamics (NEMD) simulations of molecular systems in solution in the presence of EEFs – both static and time-varying and electromagnetic fields (EMFs).^{20–22}

English reviews also the limitations and potential impact and prospects for exploitation of such simulations for both real-world and industrial end-use. He devotes attention to recent progress and advances in *ab initio* molecular simulation and dynamics in external fields, as well as challenges thereof (and, to some extent, for MD from empirical potentials), such as timescales required to observe low-frequency effects; indeed, the period of the respective molecular modes may be much longer than the presently available microsecond MD. The challenge in sampling phase space is described, along with prospects for application of fields in enhanced-sampling simulations, and polarisable force fields.

Along with methodological issues, the author reviews applications of EEFs to a wide variety of issues: (i) heating, (ii) structural (*e.g.* of aqueous systems), thermodynamic, and dielectric properties, (iii) dynamical properties, (iv) directed diffusion, (v) insights into spectroscopy, (vi) biomolecular simulation (*e.g.* influencing protein folding), (vii) potential technological applications, (viii) crystallisation/alignment,²² as well as (ix) the prospect of tailoring chemical reactivity.

All of these are described with the aim of extracting molecular-level understanding of field effects in terms of microscopic mechanisms, and of gaining some measure of control over these effects. Finally, there follows discussions of future prospects of improving MD simulations in the presence of EEFs in a variety of ways. Indeed, what may appear as heroic today in such MD simulations may well become routinely accessible in the not-too-distant future.

Three of the book chapters involve theoretical descriptions of time-dependent electric fields, which are formed by the oscillating dipoles in laser fields, fields in metallic nano-cavities, or generally in oscillating external-electric fields (OsEFs), as opposed to static ones.

In his chapter on manipulation of molecules by combined permanent and induced dipole forces, B. Friedrich describes a versatile technique to control molecular rotation and translation.^{23–26} The technique is based on the combined effect of external electric fields that act concurrently on the molecular permanent and induced dipole moments.²³ This synergistic effect of the combined fields arises for any polar molecule, as only an anisotropic polarizability, along with a permanent dipole moment, is required. This is always available in polar molecules. The effect of the combined fields can be achieved either by superimposing an electrostatic and a far-off resonant optical field (*i.e.* one that supplies electric field strength but does not cause transitions) that act, respectively, on the molecule's permanent and induced electric dipole,²⁴ or by making use of a unipolar electromagnetic pulse that seizes the permanent and induced dipole moments simultaneously.²⁵ If the combined electric fields are homogeneous, only molecular rotation is affected, whereas inhomogeneous fields affect both molecular rotation and translation.²⁶ As discussed and illustrated in the chapter, the ability to manipulate molecular rotation and translation has wide-ranging applications in research areas as diverse as reaction dynamics, spectroscopy, higher harmonic generation and molecular orbital imaging, the focusing and trapping of molecules, as well as quantum simulation and computing.

Another type of EF is described in the chapter by C. Climent, F. J. Garcia-Vidal, and J. Feist.^{27,28} Climent *et al.* describe a way of manipulating individual molecules within plasmonic nanocavities. Such metallic nanostructures support plasmons that are electromagnetic excitations localized near the metal surface and originate from the reorganization of “free electrons” of the metal. These plasmonic modes possess intense electric fields. When polarizable molecules having permanent dipole moments are placed inside the cavity, they induce dipoles in the metal and interact with them. Such interaction, which can be understood in terms of Debye and London forces, modifies the molecular energy landscape and can lower the energy barriers of a variety of regular thermal reactions. The authors show that these interactions with plasmonic modes are capable of catalysing organic reactions, like S_N1 and S_N2 , and also of modifying the transition temperature of spin-crossover Fe(II) complexes. This capability of plasmonic modes to modify molecular properties adds a powerful tool to the repertoire of electric field effects on chemical properties and reactions.

In the final chapter by C. F. Matta and A. D. Bandrauk, the authors describe the effects of intense laser fields in the infra-red (IR) region on chemical reactions.^{29–31} Matta and Bandrauk show how the “intensity” and “phase” of a plane polarized beam of two-colour laser pulses can be tuned to “invert” the potential energy surface (PES) for co-linear collisions of methane with either

halogens³⁰ or metal ions. In this way, a transition state on the PES can be converted into a radiation-stabilized bound state. The effective potential of the field-molecule system is approximated as the sum of the field-free potential, a linear phase dependent field-dipole term, and a quadratic phase dependent field-polarizability term. Peaks in the dipole moment and polarizability of the system are found near the transition state,³¹ so that the effects of the field are maximized near this stationary point in the PES. The phase and the intensity of the external laser field can be adjusted to eliminate or even invert the potential energy barrier converting a transition state into a bound state. More recent results are also touched upon in this chapter.

1.1.2 Glossary of Electric Fields Types

Box 1.1 summarizes the range of EF types, which will be mentioned throughout the book. In addition, the box provides typical strengths of these fields in units of volts per Ångström (V \AA^{-1})

Box 1.1 Electric Fields Types and Their Magnitudes

I. Types of electric fields

There are various ways of generating electric fields, which effect chemical changes:

- **External electric fields (EEFs)** are generally uniform in space and are generated by a voltage bias, *e.g.*, in a capacitor.
- **Oriented external-electric fields (OEEFs)** are uniform and oriented in a given direction with respect to the molecule. These are generally dipolar fields, or ones generated by STM tips and charged surfaces. (Chapters 3, 2, and 5)
- **Oscillating electric fields (OseFs)** involve field vectors that oscillate in time, *e.g.* laser fields or AC fields. These are versatile fields, which can influence either only the polarizability of the reaction system (when the oscillation frequency is very high compared to the reaction rate), or also the dipole moment (when the frequency is moderate or low, *e.g.*, IR or MW). (Chapter 11)
- **Interfacial electric fields (IEFs)** are near-surface fields at electrified solids (conductors or insulators). In non-Faradic electrochemical cells (no current), the charged electrode surface causes the ions of the electrolyte to generate a charged double layer with an associate electric field. (Chapter 3)
- **Local electric fields (LEFs)** are generated inside supramolecular cavities due to oriented dipoles, and ions. For example, the LEF in the active sites of proteins. (Chapter 2)
- **Designed local electric fields (D-LEFs)** are local fields that are built into a molecule, *e.g.*, by adding an ion or ligands that have dipoles, or by a pH-switchable charge. (Chapter 4)
- **Tribo-electric fields (TEFs)** are generated by rubbing two tribo-electric layers against each other (*e.g.*, glass and fur), or by a metal-insulator contact. (Chapter 3)

- **Pulsed-electric fields (PEFs)** are short pulses of EFs, which may be alternating or unipolar.
- **Piezo-electric materials (PEMs)** are materials that develop charge separation, and hence a voltage build-up, due to anisotropic pressure (*e.g.*, by fast cooling), and catalysis.

II. Strengths of electric fields

One atomic unit (au) of electric field is the field generated by an electronic charge at a distance of 1 Bohr ($a_0 = 0.529 \text{ \AA}$). $1 \text{ au} = 51.4 \text{ V \AA}^{-1}$.

- **D-LEF** (due to ligand or charged ion): The field depends on the distance of the charge/ligand from the reaction centre. For example, CH_3CN non-covalently coordinated to ZnO^{+} (*i.e.* $\text{H}_3\text{CN-ZnO}^{+}$) generates near oxygen a **D-LEF** in excess of 1 V \AA^{-1} .
- **OEEF** (STM tip) $\approx 0.3\text{--}1.0 \text{ V \AA}^{-1}$. **OEEF** (in electron loss spectroscopy) may reach 5 V \AA^{-1} .
- **EEF** of 0.04 V \AA^{-1} can orient a protein in the gas phase. **EEF** of $\sim 0.5 \text{ V \AA}^{-1}$ orients I_2 in the gas phase.
- **IEF** (in the double layer near electrode surfaces) $\approx 0.01\text{--}0.1 \text{ V \AA}^{-1}$.
- **LEF** (in protein) $\approx 0.1\text{--}1.4 \text{ V \AA}^{-1}$. **LEF** (of a helix) $\approx 0.1 \text{ V \AA}^{-1}$. **LEF** (in DNA) $\approx 0.3 \text{ V \AA}^{-1}$.

Box 1.2 summarizes the field and dipole units and the energy changes due to field/dipole interactions.

Box 1.2 Units of Electric Fields and Interaction energies – Keeping it Simple

The field magnitude generated by a charge Q at a distance R , *e.g.*, along the Z -axis, is:

$$\vec{F} = \frac{k_e Q}{R^2}; k_e = \text{Coulomb's constant.} \quad (1.1)$$

The field is a vector. The direction of the vector is a convention (see Box 1.3). A commonly used unit for \vec{F} is V \AA^{-1} ($\text{V} = \text{volts}$). Conversion of the gas-phase value for k_e to these units leads to:

$$\vec{F} = \frac{14.4Q}{R^2}; Q \text{ in } e \text{ units, } R \text{ in } \text{\AA} \text{ units.} \quad (1.2)$$

At $R = 10 \text{ \AA}$, $\vec{F} = \pm 0.144 \text{ V \AA}^{-1}$, depending on the sign of Q . The interaction of this field with a charge Q' located at R in some direction, is given by:

$$\Delta E = \vec{F} \cdot Q' \vec{R} \quad (1.3)$$

(continued)

Box 1.2 (continued)

When the vectors \vec{F} and \vec{R} are mutually parallel and the charges Q (the generator of the field) and Q' are opposite, we get $\Delta E = -0.144 Q' R$ (eV), which for a unit charge Q' and $R = 10 \text{ \AA}$ becomes $\Delta E = -1.44 \text{ eV}$, i.e. $-33.21 \text{ kcal mol}^{-1}$.

A common interaction is that of a molecular dipole with a field. The corresponding interaction energy is given as a sum of a power series in the field, \vec{F}^n ($n = 1, 2, 3, \dots$), where $n = 1$ is the dipole-field interaction, the $n = 2$ term provides the energy due to the molecular polarisability, $n = 3$ refers to the hyperpolarisability, etc. (see Figure 4.5 in Chapter 4). Thus, if instead of $Q' \vec{R}$ in eqn (1.3) we use the moment $\vec{\mu}$:

$$\vec{\mu} = 4.8 Q' \vec{R} \text{ Debye } (R \text{ in } \text{\AA} \text{ and } Q' \text{ in e units}). \quad (1.4)$$

Then eqn (1.3) can be rewritten in terms of the dipole-moment vector ($\vec{\mu}$) in eqn (1.4) as:

$$\Delta E = \vec{F} \cdot \frac{\vec{\mu}}{4.8}; (\text{eV mol}^{-1}) = \pm 4.8 \vec{F} \cdot \vec{\mu} (\text{kcal mol}^{-1}). \quad (1.5)$$

Here ΔE is the interaction energy of the molecular dipole with the field, relative to a zero field. Both \vec{F} and $\vec{\mu}$ are vectors. When these vectors are parallel, the sign of the interaction energy will depend on the relative orientations of the two vectors – opposing vectors will lead to stabilization. Using $\vec{\mu} = 1 \text{ D}$ and $\vec{F} = 0.01 \text{ V \AA}^{-1}$, leads to:

$$\Delta E = \pm 0.048 \text{ kcal mol}^{-1} \quad (1.6)$$

In a chemical reaction within a field \vec{F} , both the reactant-cluster (RC) and the corresponding transition state (TS) have dipole moments. In such a case, we use in eqn (1.5) the difference of the dipoles, and the net stabilization energy (in kcal mol^{-1}) becomes,

$$\Delta \Delta E = 4.8 \vec{F} \cdot \Delta \vec{\mu}. \quad (1.7)$$

Thus, for example in a field of 1 V \AA^{-1} and a dipole difference of 10 D (due to a larger dipole for the TS), the interaction energy stabilizes the TS by $48.0 \text{ kcal mol}^{-1}$ relative to the reactant cluster.

Laser fields are quantified in units of intensity, Watts per square centimetre (W cm^{-2}). The conversion to V \AA^{-1} units, is given by eqn (1.8), for chemical processes with a time scale longer than the oscillation period (see more in Chapter 11):

$$1 \text{ V \AA}^{-1} \approx 10^{13} \text{ W cm}^{-2} \quad (1.8)$$

Eqn (1.5) [also (1.7)] seemingly focuses only on the interaction energy of the electric field with the permanent dipole moment. However, this equation is also useful for computational chemists as a tool to estimate the entire interaction energy when one uses instead of the zero-order dipole moment the “*in situ* dipole moment”. The “*in situ* dipole moment” is the total dipole moment of the molecule exposed to the electric field F . Therefore, this dipole

moment includes all the effects due to the power series of the field effect on the molecular dipole (polarization and hyperpolarization, *etc.*). Thus, one can simply use the expression given in eqn (1.5) in Box 1.2, which is copied here as eqn (1.9):

$$\Delta E = \pm 4.8 \vec{F} \cdot \vec{\mu} \text{ (kcal mol}^{-1}\text{)}. \quad (1.9)$$

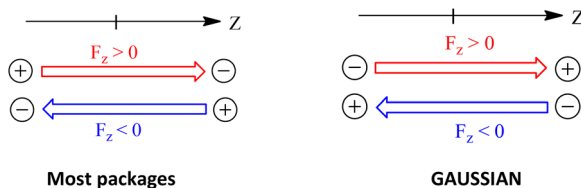
Here the field (F) is expressed in V \AA^{-1} units and the (*in situ*) dipole moment (μ) in Debye (D) units. When the two vectors are parallel, the direct product in eqn (1.9) is a simple numerical product, which leads to the total interaction energy (in kcal mol^{-1}) of the *in situ* molecular dipole with the external field, relative to the zero field situation.

Note that throughout Box 1.2 and in eqn (1.1) [eqn (1.5) and (1.7)], we focused on the gas phase. In other environments, the numerical values of the prefactors, in (1.5) and (1.7), *e.g.* 4.8, need to be modified by the corresponding relative permittivity, *e.g.* the dielectric constant of the solvent in the presence of an EEF. For the case of D-LEFs in a bulk solution environment the static dielectric constant of the solvent is used (*cf.* Figure 4.5 in Chapter 4).

Box 1.3 outlines the conventions used by quantum chemistry software to define positive/negative field vectors:

Box 1.3 Conventions for Field Vectors Representation

Be aware that software packages may not use the same convention for the OEEF. Consider an OEEF along the Z-axis. Most packages use the convention originating in physics, wherein the direction of the vector is from plus to minus. The convention in GAUSSIAN is opposite (minus to plus). We advise testing the convention of any software by placing a point charge in the positive Z direction and seeing if it gets stabilized, *vs.* its position in the negative Z direction.



Abbreviations and Glossary of Terms

BDE	Bond dissociation energy
BJ	Break junction
CT	Charge transfer
CTS	Charge transfer states
DFT	Density functional theory
e	Elementary charge

EA	Electron affinity
ϵ	Dielectric constant
μ	Dipole moment
ΔE^\ddagger	Reaction barrier height
EF	Electric field
EEF	External electric field
IEF	Interfacial electric fields
LEF	Local electric field (<i>e.g.</i> , in enzymes, catalysts, <i>etc.</i>)
OEEF	Oriented external-electric field
OsEF	Oscillating electric field
D-LEF	Designed local electric fields
PEF	Pulsed electric fields
PEM	Piezo-electric materials
TEF	Tribo-electric fields
F_Z	Electric field vector in the Z direction
IE	Ionization energy
IM	Intermediate
IR	Infrared
k_e	Coulomb's constant
MD	Molecular dynamics
MM	Molecular mechanics
MO	Molecular orbital
Orbitals	
AO	Atomic orbital
HOMO	Highest occupied molecular orbital
LUMO	Lowest unoccupied molecular orbital
MO	Molecular orbital
SOMO	Singly occupied orbital
P	Product
QM	Quantum mechanics
QM/MM	Quantum mechanics/molecular dynamics
q	Charge
R	Reactant
STM	Scanning tunnelling microscopy
TS	Transition state
$U(r)$	Electrostatic potential/interaction
VB	Valence bond
VBSCD	Valence bond state correlation diagram
VB CMD	Valence bond configuration mixing diagram

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