The chemistry of
Hydroxylamines, Oximes and Hydroxamic Acids

Part 1

Edited by

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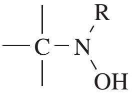

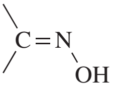

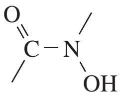

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Dedicated to the memory of

Professor Tuvia Sheradsky

and

to

Kifele bat TC $^{+}$ C, and Moische ben A * C

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Foreword

The present book, *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*, deals with the chemistry of three related functional groups that were not hitherto treated in 'The Chemistry of Functional Groups' series. Professor Artem Melman, then at the Hebrew University, who felt that such a book would be valuable, suggested the title and we followed his advice; he also contributed a chapter. We will be grateful to other readers who suggest other topics which, in their opinion, deserve to be included in new volumes in the series.

The two parts of the present volume contain 18 chapters written by experts from 14 countries. They include theoretical aspects, structural analysis, thermochemistry and NMR spectra of the three groups, chapters on the synthesis of the groups and on synthetic aspects, such as their use for synthesis of a variety of heterocyclic systems, the use of hydroxylamines and oximes for electrophilic amination, their use as analytical reagents, their electrochemistry and rearrangements both in the laboratory and in large-scale industry. Biological properties and use as therapeutic agents as well as the iron transfer ability of natural hydroxamic acids are covered in several chapters. Mechanistic aspects of these systems, including their effect as substituents, with emphasis on their α-effects, which are important both theoretically and as anti-toxic agents, are covered in two chapters. One sub-group, the N-heteroatom-substituted hydroxamic acids, is covered extensively from the synthetic, theoretical and biological aspects. Special chapters are devoted to related topics such as nitroxyl radicals, nitrosomethanides and their acids.

A few of the originally planned topics not covered in the present book are organometallic derivatives, analysis of, mass spectrometry, photochemistry and acidities and basicities of the title groups. We hope that these topics will soon be covered in an additional volume.

The literature coverage is up to the end of 2007, and extends in several chapters into 2008.

One of the editors (J. F. L.) is especially pleased to participate in this volume because the classes of compounds encompassed in the volume figured prominently in his chemical upbringing.

We would be grateful to readers who draw our attention to mistakes in the present volume and to omissions of important chapters related to the three groups.

Jerusalem and Baltimore
October 2008

ZVI RAPPOPORT
JOEL F. LIEBMAN

The Chemistry of Functional Groups
Preface to the series

The series 'The Chemistry of Functional Groups' was originally planned to cover in each volume all aspects of the chemistry of one of the important functional groups in organic chemistry. The emphasis is laid on the preparation, properties and reactions of the functional group treated and on the effects which it exerts both in the immediate vicinity of the group in question and in the whole molecule.

A voluntary restriction on the treatment of the various functional groups in these volumes is that material included in easily and generally available secondary or tertiary sources, such as Chemical Reviews, Quarterly Reviews, Organic Reactions, various 'Advances' and 'Progress' series and in textbooks (i.e. in books which are usually found in the chemical libraries of most universities and research institutes), should not, as a rule, be repeated in detail, unless it is necessary for the balanced treatment of the topic. Therefore each of the authors is asked not to give an encyclopaedic coverage of his subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself to a reader who is assumed to be at a fairly advanced postgraduate level.

It is realized that no plan can be devised for a volume that would give a complete coverage of the field with no overlap between chapters, while at the same time preserving the readability of the text. The Editors set themselves the goal of attaining reasonable coverage with moderate overlap, with a minimum of cross-references between the chapters. In this manner, sufficient freedom is given to the authors to produce readable quasi-monographic chapters.

The general plan of each volume includes the following main sections:

(a) An introductory chapter deals with the general and theoretical aspects of the group.

(b) Chapters discuss the characterization and characteristics of the functional groups, i.e. qualitative and quantitative methods of determination including chemical and physical methods, MS, UV, IR, NMR, ESR and PES—as well as activating and directive effects exerted by the group, and its basicity, acidity and complex-forming ability.

(c) One or more chapters deal with the formation of the functional group in question, either from other groups already present in the molecule or by introducing the new group directly or indirectly. This is usually followed by a description of the synthetic uses of the group, including its reactions, transformations and rearrangements.

(d) Additional chapters deal with special topics such as electrochemistry, photochemistry, radiation chemistry, thermochemistry, syntheses and uses of isotopically labeled compounds, as well as with biochemistry, pharmacology and toxicology. Whenever applicable, unique chapters relevant only to single functional groups are also included (e.g. 'Polyethers', 'Tetraaminoethylenes' or 'Siloxanes').

This plan entails that the breadth, depth and thought-provoking nature of each chapter will differ with the views and inclinations of the authors and the presentation will necessarily be somewhat uneven. Moreover, a serious problem is caused by authors who deliver their manuscript late or not at all. In order to overcome this problem at least to some extent, some volumes may be published without giving consideration to the originally planned logical order of the chapters.

Since the beginning of the Series in 1964, two main developments have occurred. The first of these is the publication of supplementary volumes which contain material relating to several kindred functional groups (Supplements A, B, C, D, E, F and S). The second ramification is the publication of a series of 'Updates', which contain in each volume selected and related chapters, reprinted in the original form in which they were published, together with an extensive updating of the subjects, if possible, by the authors of the original chapters. Unfortunately, the publication of the 'Updates' has been discontinued for economic reasons.

Advice or criticism regarding the plan and execution of this series will be welcomed by the Editors.

The publication of this series would never have been started, let alone continued, without the support of many persons in Israel and overseas, including colleagues, friends and family. The efficient and patient co-operation of staff-members of the Publisher also rendered us invaluable aid. Our sincere thanks are due to all of them.

The Hebrew University
Jerusalem, Israel

SAUL PATAI
ZVI RAPPOPORT

Sadly, Saul Patai who founded 'The Chemistry of Functional Groups' series died in 1998, just after we started to work on the 100th volume of the series. As a long-term collaborator and co-editor of many volumes of the series, I undertook the editorship and I plan to continue editing the series along the same lines that served for the preceeding volumes. I hope that the continuing series will be a living memorial to its founder.

The Hebrew University
Jerusalem, Israel
May 2000

ZVI RAPPOPORT

Contents

List of abbreviations used

Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
AIBN	azoisobutyronitrile
Alk	alkyl
All	allyl
An	anisyl
Ar	aryl
Bn	benzyl
Bu	butyl (C_4H_9)
Bz	benzoyl (C_6H_5CO)
c-	cyclo
CD	circular dichroism
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
Cp	η^5-cyclopentadienyl
Cp*	η^5-pentamethylcyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAH	diisobutylaluminium hydride
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulphoxide
E-	entgegen
ee	enantiomeric excess
EI	electron impact
ESCA	electron spectroscopy for chemical analysis
ESR	electron spin resonance
Et	ethyl
eV	electron volt

Fc	ferrocenyl
FD	field desorption
FI	field ionization
FT	Fourier transform
Fu	furyl(OC_4H_3)
GLC	gas liquid chromatography
Hex	hexyl(C_6H_{13})
c-Hex	cyclohexyl(c-C_6H_{11})
HMPA	hexamethylphosphortriamide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
i-	iso
ICR	ion cyclotron resonance
Ip	ionization potential
IR	infrared
LAH	lithium aluminium hydride
LCAO	linear combination of atomic orbitals
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
M	metal
M	parent molecule
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
MNDO	modified neglect of diatomic overlap
MS	mass spectrum
n-	normal
Naph	naphthyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
Pen	pentyl(C_5H_{11})
Ph	phenyl
Pip	piperidyl($C_5H_{10}N$)
ppm	parts per million
Pr	propyl (C_3H_7)
PTC	phase transfer catalysis or phase transfer conditions
Py	pyridine (C_5H_5N)
Pyr	pyridyl (C_5H_4N)
R	any radical
RT	room temperature

s-	secondary
SET	single electron transfer
SOMO	singly occupied molecular orbital
t-	tertiary
TCNE	tetracyanoethylene
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
Thi	thienyl(SC_4H_3)
TLC	thin layer chromatography
TMEDA	tetramethylethylene diamine
TMS	trimethylsilyl or tetramethylsilane
Tol	tolyl(MeC_6H_4)
Tos or Ts	tosyl(*p*-toluenesulphonyl)
Trityl	triphenylmethyl(Ph_3C)
Vi	vinyl
XRD	X-ray diffraction
Xyl	xylyl($Me_2C_6H_3$)
Z-	zusammen

In addition, entries in the ‘List of Radical Names’ in *IUPAC Nomenclature of Organic Chemistry*, 1979 Edition, Pergamon Press, Oxford, 1979, p. 305–322, will also be used in their unabbreviated forms, both in the text and in formulae instead of explicitly drawn structures.

CHAPTER 1

Some intrinsic features of hydroxylamines, oximes and hydroxamic acids: Integration of theory and experiment

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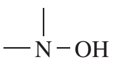
The chemistry of hydroxylamines, oximes and hydroxamic acids
Edited by Z. Rappoport and J. F. Liebman

I. INTRODUCTION

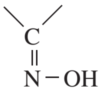
A. The Compounds

The structural link between hydroxylamines (**1**), oximes (**2**) and hydroxamic acids (**3**) is the N−OH group:

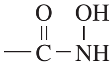


$$-\overset{|}{N}-OH$$

(**1**)



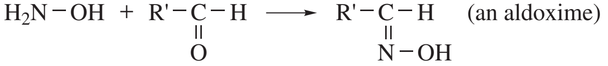
(**2**)



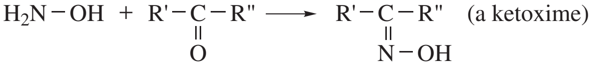
$$-\overset{\substack{O\\ \|}}{C}-\overset{\substack{OH\\ |}}{NH}$$

(**3**)

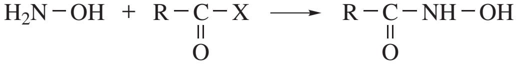
Formally, they can all be viewed as derivatives of hydroxylamine, $H_2N{-}OH$; indeed, oximes can be prepared by the addition of hydroxylamine to aldehydes and ketones (equations 1 and 2), and hydroxamic acids by its reactions with acetyl halides and esters (equations 3 and 4)[1].



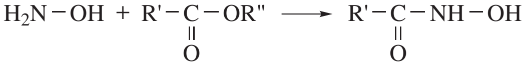
$$H_2N-OH + R'-\underset{\substack{\| \\ O}}{C}-H \longrightarrow R'-\underset{\substack{\| \\ N-OH}}{C}-H \quad \text{(an aldoxime)} \tag{1}$$



$$H_2N-OH + R'-\underset{\substack{\| \\ O}}{C}-R'' \longrightarrow R'-\underset{\substack{\| \\ N-OH}}{C}-R'' \quad \text{(a ketoxime)} \tag{2}$$



$$H_2N-OH + R-\underset{\substack{\| \\ O}}{C}-X \longrightarrow R-\underset{\substack{\| \\ O}}{C}-NH-OH \tag{3}$$



$$H_2N-OH + R'-\underset{\substack{\| \\ O}}{C}-OR'' \longrightarrow R'-\underset{\substack{\| \\ O}}{C}-NH-OH \tag{4}$$

However, there are also important features that very significantly differentiate between hydroxylamines, oximes and hydroxamic acids: the C=N double bond in **2** and the acetyl group in **3**.

In this chapter, our objective will be to integrate theory and experiment in relating chemical and physical properties of these three classes of compounds to electronic and structural factors. We will begin with an overview and comparison of some computational approaches.

B. Survey of Computational Procedures

The purpose of this section is to present a short overview, with relevant examples, of some aspects of molecular computations. In-depth treatments can be found in textbooks such as that by Levine[2], and in the overview by Irikura and Frurip[3].

Tables 1 and 2 compare the experimental values of several properties of hydroxylamine and acetaldoxime, $H_3C{-}C(H){=}NOH$, with the results obtained by nine different computational procedures. These are of three general types:

(a) Hartree–Fock (HF): Until a few years ago, this was the most widely used *ab initio* method. It does not account for electronic correlation (i.e. the repulsions between electrons are treated in an average rather than instantaneous manner) and therefore is not reliable for predicting interaction energies. However, properties that depend upon the average electronic density distribution $\rho(\mathbf{r})$, such as the dipole moment and the electrostatic potential, are generally reasonably satisfactory. We have used the Hartree–Fock approach in analyzing the electrostatic potentials of carbon and boron/nitrogen model nanotubes with as many as 120 atoms[4].

(b) MP2-FC: Moeller–Plesset second-order perturbation theory is an extension of Hartree–Fock that takes some account of electronic correlation, although not for inner-shell electrons (FC = frozen core). MP2-FC requires more computer time and space, and thus is limited to smaller molecules (25–50 first-row atoms[4]).

(c) B3LYP: This is one of the Kohn–Sham density functional theory (DFT) procedures that have had such a dramatic impact upon computational chemistry since about 1990. Kohn–Sham DFT methods have evolved from the local density approximation, based upon the concept of a uniform electron gas, to gradient-corrected DFT, which recognizes that $\rho(\mathbf{r})$ is not constant, to hybrid gradient-corrected DFT, such as B3LYP, which introduces the Hartree–Fock exchange term into the density functional[2]. Density functional theory does include electronic correlation, to varying degrees, and in the Kohn–Sham formalism it is only somewhat more demanding of computer resources than is Hartree–Fock and therefore can treat equally large systems. Hybrid density functional techniques (e.g. B3LYP, B3PW91) are now very extensively used for molecular calculations.

After choosing a computational procedure, the next decision generally concerns the basis set, by which is meant the mathematical functions (usually corresponding to atomic orbitals) in terms of which the system is to be described. The computed results in Tables 1 and 2 are for three different basis sets; in order of increasing size, they are $6\text{-}31G^* < 6\text{-}311G^{**} \ll \text{cc-pVTZ}$. While a bigger basis set should permit a better description of the system, the processor time and space requirements increase very rapidly with size; furthermore, as will be seen, the variations in the values of computed properties, other than the energy, do not necessarily improve as the basis set becomes larger. For a given *ab initio* or DFT method, the molecular energy can be expected to decrease monotonically as the basis set increases in size (see Tables 1 and 2).

It seems fair to say that one of the consequences of the evolution and success of Kohn–Sham density functional methodology has been a diminished role for semi-empirical procedures (AM1, PM3, INDO etc.). While these can still be very useful, the capability of DFT to treat relatively large systems, and at an overall higher level of accuracy, has led to its being the method of choice in cases that earlier would have been treated semi-empirically.

Proceeding now to Tables 1 and 2, it is seen that bond lengths and bond angles are predicted well by both B3LYP and MP2-FC, Hartree–Fock being less effective. These results depend relatively little upon the basis set for the three that were used, which can be viewed as medium to large in size.

The atomization enthalpies show sharper distinctions between the nine approaches. The Hartree–Fock are very poor, as expected given the non-inclusion of electronic correlation. The MP2-FC are much better, but do not match the B3LYP, which actually achieve essentially 0% error in the two best cases. (Such perfection should not be expected regularly!) The atomization enthalpies do show a steady improvement as the basis set is increased.

TABLE 1. Comparison of experimental properties of hydroxylamine, H_2NOH, with results of various computational procedures[a]

Property	Experimental	Hartree–Fock			MP2-FC			B3LYP		
		6-31G*	6-311G**	cc-pVTZ	6-31G*	6-311G**	cc-pVTZ	6-31G*	6-311G**	cc-pVTZ
Energy (hartrees)[b]	—	−130.979	−131.028	−131.044	−131.325	−131.418	−131.508	−131.705	−131.757	−131.773
N−O distance (Å)	1.453[c]	1.404	1.397	1.398	1.452	1.436	1.441	1.447	—	1.447
H−N−O angle (deg)	103.2[c]	104.7	105.4	105.5	102.9	103.9	103.4	103.2	—	103.7
Atomization enthalpy (kcal mol^{-1})[d]	340.8[a]	177	184	188	290	310	330	331	336	340
Dipole moment (D)	0.59[e]	0.68	0.70	0.64	0.63	—	0.60	0.58	0.64	0.59
Atomic charges:										
Mulliken										
N	—	−0.525	—	−0.193	−0.528	—	—	−0.496	—	−0.203
O	—	−0.632	—	−0.366	−0.634	—	—	−0.547	—	−0.337
ESP										
N	—	−0.789	—	−0.755	−0.770	—	—	−0.737	—	−0.706
O	—	−0.486	—	−0.461	−0.464	—	—	−0.439	—	−0.434

[a] All computed and some experimental values are from NIST Computational Chemistry Comparison and Benchmark Database, NIST Standard Reference Database No. 101, Release 12 (Ed. R. D. Johnson III), 2005. http://srdata.nist.gov/cccbdb

[b] Energy minimum at 0 K; 1 hartree = 627.5 kcal mol^{-1}.

[c] M. D. Harmony, V. W. Laurie, R. L. Kuczkowski, R. H. Schwendeman, D. A. Ramsey, F. J. Lovas, W. J. Lafferty and A. G. Maki, *J. Phys. Chem. Ref. Data*, **8**, 619 (1979).

[d] Enthalpy required to separate molecule into atoms at 298 K.

[e] D. R. Lide (Ed.), *Handbook of Chemistry & Physics*, 87th edn., CRC Press, Boca Raton, 2006.

TABLE 2. Comparison of experimental properties of acetaldoxime, $CH_3C(H){=}NOH$, with results of various computational procedures[a]

Property	Experimental[a]	Hartree–Fock			MP2-FC			B3LYP		
		6-31G*	6-311G**	cc-pVTZ	6-31G*	6-311G**	cc-pVTZ	6-31G*	6-311G**	cc-pVTZ
Energy (hartrees)[b]	—	−207.884	−207.945	−207.970	−208.484	−208.612	−208.750	−209.131	−209.198	−209.221
N−O distance (Å)	1.408	1.375	1.369	1.370	1.417	1.400	1.406	1.409	—	1.407
C−N distance (Å)	1.276	1.251	1.248	1.246	1.286	1.282	1.278	1.276	—	1.268
C−N−O angle (deg)	110	111.8	112.1	112.4	110.0	110.7	110.4	110.9	—	111.5
N−O−H angle (deg)	103	104.3	104.5	104.6	101.7	101.5	101.6	102.2	—	102.6
Atomization enthalpy ($kcal\,mol^{-1}$)[c]	781.0	506	508	514	712	738	771	777	776	781
Dipole moment (D)	0.938	0.825	0.857	—	0.629	—	0.683	0.612	0.651	0.722
Atomic charges:										
Mulliken										
C[d]	—	0.090	0.073	−0.045	0.103	—	—	0.108	0.026	−0.028
N	—	−0.160	−0.149	−0.046	−0.176	—	—	−0.166	−0.132	−0.052
O	—	−0.609	−0.376	−0.310	−0.618	—	—	−0.510	−0.316	−0.254
ESP										
C[d]	—	0.436	—	0.445	−0.462	—	—	0.381	—	0.405
N	—	−0.374	—	−0.388	−0.351	—	—	−0.357	—	−0.375
O	—	−0.508	—	−0.485	−0.454	—	—	−0.430	—	−0.424

[a] All computed and experimental values are from NIST Computational Chemistry Comparison and Benchmark Database, NIST Standard Reference Database No. 101, Release 12 (Ed. R. D. Johnson III), 2005. http://srdata.nist.gov/cccbdb

[b] Energy minimum at 0 K; 1 hartree = 627.5 $kcal\,mol^{-1}$.

[c] Enthalpy required to separate molecule into atoms at 298 K.

[d] Carbon bonded to nitrogen.

The situation is quite different for the dipole moment. The Hartree–Fock values are comparable to the MP2-FC and B3LYP for hydroxylamine, and significantly better than the others for acetaldoxime. This reflects the fact that Hartree–Fock electronic density distributions $\rho(\mathbf{r})$ are, overall, reasonably good[5]. The errors in the MP2-FC and B3LYP results may seem rather large, especially on a percentage basis, but it should be noted that dipole moments are obtained as a small difference between two much larger numbers (the electronic and nuclear moments), so that any errors in these are greatly magnified in the former. (The same problem is encountered in computing ΔE or ΔH for chemical reactions. One way of addressing it in this context is by means of isodesmic and related types of equations[2].)

Calculated atomic charges are included in Tables 1 and 2, even though these are not physical observables and cannot be determined experimentally, because they are conceptually convenient and are widely used in analyzing molecular electronic structures and reactive properties. Numerous definitions of atomic charge have been proposed over the years, but all of them are arbitrary and purport to quantify something that has no experimental basis. In Tables 1 and 2 are listed two sets of atomic charges. The Mulliken, which are very popular due to ease of computation, result from partitioning the molecular orbital expression for the electronic density[6]; the ESP are designed to reproduce the electrostatic potential produced by the molecule's electrons and nuclei[7]. Mulliken charges can vary considerably with the basis set[2, 8], as is seen in Tables 1 and 2; note, for example, the B3LYP values. This is less of a problem for the ESP since they come from $\rho(\mathbf{r})$, which is much less dependent upon the basis set. What is particularly serious, however, is that the Mulliken and the ESP results actually differ even *qualitatively* in predicting whether the nitrogen or the oxygen in hydroxylamine is the more negative. This example illustrates the inherent uncertainty associated with trying to assign a charge to an atom in a molecule.

We conclude this section with a comment concerning notation. To identify a computational approach, it is customary to write 'procedure/basis set', e.g. MP2-FC/6-311G**. If the geometry is obtained by procedure 1 and basis set 1, and that geometry is then used in calculating a particular property with procedure 2 and basis set 2, this is designated by 'procedure 2/basis set 2//procedure 1/basis set 1'.

II. ANALYSIS OF COVALENT AND NONCOVALENT INTERACTIONS

Three fundamental properties that play key roles in determining covalent and/or noncovalent interactions are the electrostatic potential $V(\mathbf{r})$, the ionization energy I (sometimes written IE) and the polarizability α. All three can be obtained experimentally. It is primarily in terms of these properties that we will examine the inter- and intramolecular interactions of hydroxylamines, oximes and hydroxamic acids. Accordingly we shall first briefly discuss $V(\mathbf{r})$, I and α.

A. Electrostatic Potential

$V(\mathbf{r})$ is the electrostatic potential that is created throughout the space of a system by its nuclei and electrons. It is given by equation 5, which is simply a form of Coulomb's Law:

$$V(\mathbf{r}) = \sum_{\mathrm{A}} \frac{Z_{\mathrm{A}}}{|\mathbf{R}_{\mathrm{A}} - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')\mathrm{d}\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \tag{5}$$

Z_{A} is the charge on nucleus A, located at $\mathbf{R}_{\mathrm{A}}$, and $\rho(\mathbf{r})$ is the electronic density of the system. Thus $V(\mathbf{r})$ is the net result at any point $\mathbf{r}$ of the positive contributions of the nuclei and the negative ones of the electrons. Although $V(\mathbf{r})$ is a potential, it is usually given in energy units, e.g. kcal mol^{-1}, which means that the value quoted is actually the interaction energy of the system with a $+1$ point charge placed at $\mathbf{r}$. The general interpretation of $V(\mathbf{r})$ is that regions in which it is positive will interact favorably with negative portions of the surroundings, such as lone pairs, π electrons, anions etc., and unfavorably with positive portions, e.g. hydrogens, cations etc.; negative regions of $V(\mathbf{r})$ will do the reverse.

The electrostatic potential $V(\mathbf{r})$ is a physical observable, which can be determined experimentally by diffraction methods[9, 10] as well as computationally. It directly reflects the distribution in space of the positive (nuclear) and the negative (electronic) charge in a system. $V(\mathbf{r})$ can also be related rigorously to its energy and its chemical potential, and further provides a means for defining covalent and ionic radii[11, 12].

Noncovalent interactions are primarily electrostatic in nature[13, 14], and thus can be interpreted and predicted via $V(\mathbf{r})$. For this purpose, it is commonly evaluated on the surfaces of the molecules, since it is through these surface potentials, labeled $V_S(\mathbf{r})$, that the molecules 'see' and 'feel' each other. We have shown that a number of condensed-phase physical properties that are governed by noncovalent interactions—heats of phase transitions, solubilities, boiling points and critical constants, viscosities, surface tensions, diffusion constants etc.—can be expressed analytically in terms of certain statistical quantities that characterize the patterns of positive and negative regions of $V_S(\mathbf{r})$[15, 16].

All of this is of course predicated upon finding some reasonable way to define the surface of a molecule, for which there is no rigorous physical basis. We follow the suggestion of Bader and coworkers[17] in taking this to be the 0.001 au (electrons bohr^{-3}) contour of the molecule's electronic density $\rho(\mathbf{r})$; this contour encompasses about 96% of the electronic charge. (1 bohr = 0.5292 Å.) In contrast to another approach to defining a molecular surface, involving fused 'atomic' spheres, the method of Bader and coworkers has the advantage of reflecting features specific to that molecule, such as lone pairs, π electrons and strained bonds. We have confirmed that other outer contours of $\rho(\mathbf{r})$, e.g. the 0.002 au, would be equally effective[18].

Our focus in this chapter shall be primarily upon the surface electrostatic potential, specifically its most positive and most negative values, denoted by $V_{S,\max}$ and $V_{S,\min}$, respectively. There may be several local and absolute maxima and minima on a given surface. They indicate the most positive and negative sites. The former are often associated with hydrogens, especially acidic ones, and the latter with lone pairs, π electrons of unsaturated molecules and strained bonds[5]. We have demonstrated that $V_{S,\max}$ and $V_{S,\min}$ correlate well with measures of hydrogen bond donating and accepting tendencies[19].

We will also refer in some instances to the overall most negative potentials, $V_{\min}$, associated with nitrogen and oxygen lone pairs. These can be viewed as indicating the effective 'center' of the lone pair. Such $V_{\min}$ are always more negative than the corresponding $V_{S,\min}$, and are located within the molecular surface.

B. Ionization Energy

The ionization energy I is the amount of energy required to remove an electron from an atom or molecule. This normally involves the least tightly held electron, which is in the highest occupied orbital. I is clearly a governing factor in any process involving charge transfer from the system.

Whereas $V(\mathbf{r})$ and $V_S(\mathbf{r})$ are local properties, i.e. have a different value at each point $\mathbf{r}$, I is global, in the sense that there is just a single value for the whole system (assuming that only the highest-energy electron is considered). Chemical reactions, however, are site-specific, and so there is a need for a *local* ionization energy, that gives the energy needed to remove an electron at each point $\mathbf{r}$ in the space of a system.

We introduced such a quantity, the average local ionization energy $\overline{I}(\mathbf{r})$[20], in equation 6:

$$\overline{I}(\mathbf{r}) = \sum_i \frac{\rho_i(\mathbf{r})|\varepsilon_i|}{\rho(\mathbf{r})} \tag{6}$$

In equation 6, $\rho_i(\mathbf{r})$ is the electronic density of orbital i, having energy ε_i. The formalism of Hartree–Fock theory (within the framework of which equation 6 was proposed) and Koopmans' theorem[21,22] provide support for interpreting $\overline{I}(\mathbf{r})$ as the local ionization energy, which focuses upon the point in space rather than an orbital.

In analyzing chemical reactivity, we compute $\overline{I}(\mathbf{r})$ on the 0.001 au surface of the molecule, just as we do $V(\mathbf{r})$. The lowest values of the resulting $\overline{I}_S(\mathbf{r})$, its local minima $\overline{I}_{S,\min}$, indicate the locations of the least tightly held, most reactive electrons, and are an effective means for identifying and ranking sites favorable for electrophilic attack. $\overline{I}_S(\mathbf{r})$ computed via Kohn–Sham density functional procedures are equally successful for this purpose[23]. It should be pointed out that the $\overline{I}_{S,\min}$ are invariably somewhat larger than the magnitude of the highest occupied orbital energy, because $\overline{I}(\mathbf{r})$ averages over *all* of the system's electrons, and there is always some probability of inner, more tightly held ones being at the point in question, even on an outer contour of $\rho(\mathbf{r})$.

The local maxima of $\overline{I}_S(\mathbf{r})$, the $\overline{I}_{S,\max}$, reveal the locations of the most strongly bound electrons. While we have found some evidence that these may be sites reactive toward nucleophiles, this is not well-established. Since $\overline{I}_{S,\min}$ and $\overline{I}_{S,\max}$ are local features, referring to specific points in space, it is quite possible to have one or more of each in the neighborhood of a given atom in a molecule; this simply means that there are both tightly and loosely held electrons in different regions around the atom. Some examples will be seen later in this chapter.

In addition to its role with regard to chemical reactivity, $\overline{I}(\mathbf{r})$ is also linked to atomic shell structure and electronegativity, local temperature (or kinetic energy), radical characterization, bond strain and local polarizability. For a recent overall review, see Politzer and Murray[24].

C. Polarizability

The extent to which an atom or molecule's charge distribution is affected by an external electric field $\mathbf{E}$ (which could be due to an approaching reactant) is governed, to first order, by its polarizability $\boldsymbol{\alpha}$. It was really $\boldsymbol{\alpha}$ to which Pearson was referring in his hard and soft acid–base theory[25], which rationalizes a large number of chemical reactions. The terms 'hard' and 'soft' refer, respectively, to low and high polarizability.

Specifically, the change in the system's dipole moment $\boldsymbol{\mu}$ is given by equation 7:

$$\boldsymbol{\mu}(\boldsymbol{\varepsilon}) - \boldsymbol{\mu}(0) = \boldsymbol{\alpha} \cdot \mathbf{E} \tag{7}$$

Whereas $\boldsymbol{\mu}$ is a vector, with three components, $\boldsymbol{\alpha}$ is a nine-component tensor, which can be represented by a symmetric 3×3 matrix[26] (equation 8):

$$\boldsymbol{\alpha} = \begin{pmatrix} \alpha_{xx} & \alpha_{xy} & \alpha_{xz} \\ \alpha_{xy} & \alpha_{yy} & \alpha_{yz} \\ \alpha_{xz} & \alpha_{yz} & \alpha_{zz} \end{pmatrix} \tag{8}$$

What this means is that a field along one axis, e.g. the x, can influence not only that component of $\boldsymbol{\mu}$, i.e. μ_x, but also the other two, μ_y and μ_z. This is done through α_{xy}