

Contents

Preface *XV*

List of Contributors *XVII*

1	Interaction of Radiation with Matter	1
	<i>Ignacio Pérez-Juste and Olalla Nieto Faza</i>	
1.1	Introduction	1
1.2	Spectroscopy: A Definition	1
1.3	Electromagnetic Radiation	2
1.4	Electromagnetic Spectrum	4
1.5	Interaction of Radiation with Matter	6
1.6	Magnetic Spectroscopies	12
1.7	Pulse Techniques in NMR Spectroscopy	14
1.8	Line Widths	15
1.9	Selection Rules	17
1.10	Summary of Spectroscopic Techniques	18
1.10.1	Absorption-Based Methods	19
1.10.2	Emission-Based Methods	20
1.10.3	Scattering and Diffraction Methods	21
	References	23
2	Computational Spectroscopy Tools for Molecular Structure Analysis	27
	<i>Cristina Puzzarini and Malgorzata Biczysko</i>	
2.1	Introduction	27
2.2	Potential Energy Surface and Molecular Structure	29
2.2.1	Minima and Conformational Analysis	29
2.2.2	Spectroscopic Tools for Structure Determination	31
2.3	Computational Aspects for Spectroscopic Techniques	32
2.3.1	DFT and Hybrid Approaches for Spectroscopic Applications	32
2.3.2	Rotational Spectroscopy	33
2.3.3	Vibrational Spectroscopy: Infrared (IR), Vibrational Circular Dichroism (VCD), Raman	34

2.3.4	Electronic Spectroscopy: One-Photon Absorption (OPA) and Electronic Circular Dichroism (ECD)	36
2.3.5	Magnetic Resonance Spectroscopy: Electronic Spin Resonance (ESR)	38
2.4	Application and Case Studies	40
2.4.1	Semi-Experimental Equilibrium Structure	40
2.4.2	Identification of Conformers/Tautomers	42
2.4.2.1	Rotational Spectrum of Proteinogenic Glutamic Acid	43
2.4.2.2	IR Spectrum of Glycine	43
2.4.2.3	Vibrational (IR/VCD) and Electronic (OPA/ECD) Spectra of (Z)-8-Methoxy-4-Cyclooctenone	47
2.4.2.4	ESR Spectra of Uracil Anion	48
2.4.3	3D Structure: Molecular Complexes and Flexible Macromolecules	50
2.4.3.1	Molecular Structure of Anisole Complexes	50
2.4.3.2	ESR Spectrum of Peptides	53
	Acknowledgments	55
	References	55
3	Absolute Configuration and Conformational Analysis of Chiral Compounds via Experimental and Theoretical Prediction of Chiroptical Properties: ORD, ECD, and VCD	65
	<i>Ana G. Petrovic, Nina Berova, and José Lorenzo Alonso-Gómez</i>	
3.1	Introduction	65
3.2	Chirality	65
3.3	What is a Chiroptical Method?	66
3.4	Quantum Mechanical (<i>Ab Initio</i>) Methods for Predicting Chiroptical Properties	71
3.5	Electronic Circular Dichroism (ECD)	73
3.5.1	Advantages of ECD	73
3.5.2	Limitations of ECD	73
3.5.3	Applications of ECD	74
3.5.3.1	Empirical Methods	74
3.5.3.2	Exciton Coupling	75
3.5.3.3	ECD Simulation via <i>Ab Initio</i> Methods: Conformational Analysis and Determination of AC	77
3.5.4	Challenge due to Vibronic Coupling	82
3.6	Vibrational Circular Dichroism (VCD)	82
3.6.1	Advantages of VCD	85
3.6.2	Limitations of VCD	86
3.6.3	Application of VCD	86
3.6.3.1	AC Assignment of Moderately Flexible Molecules with One Chiral Center	86
3.6.3.2	AC Assignment of Flexible Molecules with More Than One Chiral Center	88

3.6.3.3	Establishing Solute–Solvent and Solute–Solute Intermolecular Interactions of Chiral Molecules	90
3.6.3.4	AC Assignment via VCD Exciton Coupling Methodology–The Future Perspective	94
3.7	Optical Rotatory Dispersion (ORD)	95
3.7.1	Advantages of ORD	96
3.7.2	Limitations of ORD	96
3.8	When More than One Method is Needed	97
3.8.1	Combination of ECD and VCD	97
3.8.2	Combination of ECD and ORD	97
3.8.3	Combination of VCD and ORD	99
3.9	Concluding Remarks	100
	References	100
 4	 Mass Spectrometry Strategies in the Assignment of Molecular Structure: Breaking Chemical Bonds before Bringing the Pieces of the Puzzle Together	 105
	<i>Wilfried M.A. Niessen and Maarten Honing</i>	
4.1	Introduction	105
4.2	Instrumentation and Technology	106
4.2.1	Ionization Techniques	107
4.2.2	Mass Analyzers	109
4.2.3	Tandem Mass Spectrometry Technologies	111
4.2.4	Data Acquisition Strategies in Tandem Mass Spectrometry	115
4.3	Breaking Chemical Bonds–Fragmentation Reactions	116
4.3.1	Fragmentation of Odd-Electron Ions	116
4.3.2	Fragmentation of Even-Electron Ions	118
4.3.3	Additional Strategies and Tools	123
4.4	Confirmation of Identity	125
4.4.1	Retrieving Compound Identity by Library Searching	126
4.4.2	Multiple SRM Transitions in Residue Screening	126
4.4.3	Confirming the Identity of Synthetic Products	127
4.5	Putting the Puzzle Together–Structure Elucidation of Unknowns	128
4.5.1	Strategies for Identification of Related Substances	128
4.5.2	Identification of Unknowns	131
4.6	Conclusions and Perspectives	136
	Abbreviations	136
	References	137
 5	 Basic Principles of IR/Raman: Applications in Small Molecules Structural Elucidation	 145
	<i>Ricardo F. Aroca</i>	
5.1	Introduction	145

5.2	Characteristic Vibrational Modes: Diatomics and Chemical Bonds	148
5.2.1	The Diatomic Example	150
5.2.2	Equilibrium Properties: Dipole Moment and Polarizability	153
5.3	Fundamental Vibrational Modes and Molecular Structure	158
5.4	Selection Rules and Finding the Number of Normal Modes in Each Symmetry Species	159
5.5	The Vibrational Assignment of Raman and Infrared Spectra	163
5.6	Conclusions	169
	References	169
6	Solid-State NMR Applications in the Structural Elucidation of Small Molecules	173
	<i>Mariana Sardo, João Rocha, and Luís Mafra</i>	
6.1	Introduction	173
6.2	Line-Narrowing and Sensitivity Enhancement Methods in ssNMR Spectroscopy	174
6.3	Probing Dynamics in Solids	175
6.4	Application of ssNMR Spectroscopy to Small Molecules	178
6.4.1	Hydrogen Bonding	178
6.4.2	Guest Molecules Adsorbed in Porous Materials	180
6.4.2.1	Probe Molecules to Study the Acidity of Catalysts	181
6.4.2.2	Other Molecules Anchored on Materials	188
6.4.2.3	The Special Case of CO ₂	191
6.4.3	Energy-Related Compounds	194
6.4.4	Pharmaceuticals	197
6.4.5	Biomolecules	206
6.5	NMR of Molecules on Surfaces (DNP)	214
6.6	NMR Crystallography	217
	Acronyms	228
	References	229
7	Simplified NMR Procedures for the Assignment of the Absolute Configuration	241
	<i>José Manuel Seco, Emilio Quiñoá, and Ricardo Riguera</i>	
7.1	Introduction	241
7.2	Single Derivatization Methods for Mono- and Polyfunctional Compounds	243
7.2.1	Low Temperature	243
7.2.2	Selective Complexation	252
7.2.3	Esterification Shifts	254
7.3	Resin-Bound Chiral Derivatizing Agents (Mix and Shake Method)	257
7.4	Non-resin in Tube Assignment (BPG and BINOL Borates)	260

7.5	Tandem HPLC-NMR: Simultaneous Enantioresolution and Configurational Assignment	262
7.6	Assignment Based on the Chemical Shifts from the Auxiliaries	264
7.7	Scope and Conclusions	272
	References	273
8	Structural Elucidation of Small Organic Molecules Assisted by NMR in Aligned Media	279
	<i>Roberto R. Gil, Christian Griesinger, Armando Navarro-Vázquez, and Han Sun</i>	
8.1	Introduction	279
8.2	Aligning Media	284
8.2.1	Magnetic Susceptibility	284
8.2.2	Paramagnetic Systems	288
8.2.3	Mechanically Strained Polymer Gels	290
8.2.3.1	Strained Gels for Polar Solvents	290
8.3	Measurement of RDCs	291
8.3.1	Measurement of $^1D_{CH}$ RDCs	292
8.3.1.1	^{13}C Detected Experiments	292
8.3.1.2	1H Detected Experiments	292
8.3.2	1H – 1H Couplings E.COSY and P.E.HSQC Experiments	296
8.4	Computational Methodology	297
8.4.1	Determination of the Alignment Tensor	297
8.4.2	Symmetrical Rotors	299
8.5	Data Analysis: Use of RDCs as Structural Constraints in Small Molecules	300
8.5.1	Determination of Configuration for Rigid Molecules	300
8.5.2	Assignment of Diastereotopic Groups	303
8.5.3	RC Assignment in Molecules with Conformational Flexibility	305
8.5.3.1	Multitensor Approaches to the Flexibility Problem	307
8.5.3.2	Multiple-Tensors Analysis: Dimers and Pseudo-Dimers	308
8.6	RDCs and Determination of Absolute Configuration	311
8.6.1	Assignment of the Absolute Configuration: Combination of Residual Dipolar Couplings and Chiroptical Techniques	312
8.7	Conclusions and Perspectives	316
	Acknowledgments	316
	References	316
9	NMR Techniques for the Study of Transient Intermolecular Interactions	325
	<i>Jesús Angulo, Ana Ardá, Eurico J. Cabrita, Manuel Martín-Pastor, Jesús Jiménez-Barbero, and Pedro M. Nieto</i>	
9.1	Introduction	325
9.2	Nuclear Overhauser Effect	326
9.2.1	Introduction to NOE-Based Methods	326
9.2.2	Transferred NOE	328

9.2.3	CORCEMA: Relaxation Matrix	331
9.2.4	Transfer-NOE Applications	332
9.2.5	Transfer-NOE: Quantitative Applications	334
9.3	Saturation Transfer Difference NMR	335
9.3.1	STD NMR Applications	337
9.3.1.1	Ligand Screening	337
9.3.1.2	Epitope Mapping	338
9.3.1.3	Quantitative Structural Analysis: CORCEMA-ST	339
9.3.1.4	Binding Constants from STD NMR	341
9.4	Diffusion NMR	345
9.4.1	Diffusion and Molecular Structure	345
9.4.2	Measuring Diffusion with NMR	345
9.4.3	Diffusion Coefficient in the Presence of Chemical Exchange	348
9.4.4	Diffusion NMR Applications	349
9.4.4.1	Diffusion NMR Screening	349
9.4.4.2	Diffusion NMR in the Study of Non-covalent Transient Intermolecular Interactions	349
9.4.4.3	Diffusion NMR in the Study of Self-aggregation	350
9.4.4.4	Diffusion NMR to Determine the Equilibrium Binding Constant	351
9.5	Conclusions	354
	References	354
10	Analysis of Molecular Interactions by Surface Plasmon Resonance Spectroscopy	361
	<i>Eva Muñoz and Daniel Ricklin</i>	
10.1	Introduction	361
10.2	General Aspects of the Surface Plasmon Resonance Principle	362
10.3	The SPR Experiment	363
10.3.1	Sensor Surface Design and Preparation	364
10.3.1.1	Covalent Immobilization	364
10.3.1.2	Non-covalent Immobilization	366
10.3.2	The Binding Experiment	367
10.4	The Information Contained in the SPR Experiment	369
10.4.1	Qualitative Information	369
10.4.2	Binding Affinity and Kinetics	370
10.4.3	Concentration Analysis	372
10.4.4	Thermodynamics	373
10.5	SPR Applications: From Large to Small Molecules	373
10.5.1	Working with SPR and Large Molecules	373
10.5.1.1	Protein–Protein/Peptide Interactions	373
10.5.1.2	Antibody–Antigen Interactions	376
10.5.1.3	Oligonucleotides	377
10.5.1.4	Larger Structures	378
10.5.2	Working with SPR and Small Molecules	378

10.5.2.1	Starting Up	379
10.5.2.2	Steric Hindrance	380
10.5.2.3	Mass Transport Limitation	381
10.5.2.4	Matrix Effects	382
10.5.2.5	Refractive Index Jumps and Baseline Drifting	383
10.5.2.6	Limited Solubility and Use of Organic Solvents	384
10.5.2.7	Changes of Refractive Index Increments	385
10.6	Beyond SPR—Orthogonal Interaction Biosensor Technologies	386
	References	387
11	Determination of Absolute Configurations by Electronic CD Exciton Chirality, Vibrational CD, ¹H NMR Anisotropy, and X-ray Crystallography Methods—Principles, Practices, and Reliability	393
	<i>Nobuyuki Harada</i>	
11.1	Introduction	393
11.2	Reliability in the AC Determination and Selection of Method	394
11.3	Non-empirical Method: AC Determination by the X-ray Bijvoet Method	395
11.4	Non-empirical Method: AC Determination by the ECD Exciton Chirality Method	396
11.4.1	Outline of the ECD Exciton Chirality Method	396
11.4.2	Molecular Exciton Theory of the CD Exciton Chirality Rule and Application to Steroidal Dibenzoate	398
11.4.3	The Most Ideal Exciton CD of (6 <i>R</i> ,15 <i>R</i>)-(+)-6,15-Dihydro-6,15-ethanonaphtho[2,3- <i>c</i>]pentaphene	400
11.4.4	Illustrative Cases: Application of the CD Exciton Chirality Rule	401
11.4.4.1	Acyclic 1,2-Glycols	401
11.4.4.2	Acetylene Alcohols	403
11.5	Non-empirical Method: AC Determination by VCD Spectroscopy and DFT MO Simulation	403
11.6	Empirical Method: AC Determination by ¹ H NMR Anisotropy Method Using M α NP Acid	408
11.6.1	Enantioresolution of Racemic Aliphatic Alcohols Using M α NP Acid and Simultaneous Determination of Their ACs	411
11.6.2	Application of the M α NP Acid Method to <i>cis</i> -2-Butyl-2-methyl-1-tetralol	411
11.6.3	Verification of the AC of <i>cis</i> -2-Butyl-2-methyl-1-tetralol by X-ray Crystallography	414
11.6.4	Verification of the AC of (S)-(-)-[VCD(+) ⁹⁸⁴]-4-Ethyl-4-methyloctane by Chemical Correlation	415
11.7	Relative Method: X-ray Crystallography Using Camphorsultam Dichlorophthalic Acid (CSDP Acid)	416
11.7.1	Application of the CSDP Acid Method to Other Racemic Alcohols	418

11.7.2	Application of the CSDP Acid Method to Asymmetric Reaction Products	430
11.8	Relative Method: X-ray Crystallography Using of M α NP Group as Internal Reference	432
11.8.1	Alternative Preparation of Enantiopure M α NP Acid	432
11.8.2	AC Determination of Other M α NP Esters by X-ray Crystallography	433
11.9	Conclusion	438
	Acknowledgments	439
	References	439
12	An Integrated Approach to Structure Verification Using Automated Procedures	445
	<i>Juan Carlos Cobas Gómez, Michael Bernstein, and Stanislav Sýkora</i>	
12.1	Introduction	445
12.1.1	Setting the Scene: The Need for an Automatic Structure Verification (ASV) Platform	445
12.1.2	Automatic Structure Verification: What It Is and What It Is Not	449
12.1.3	Background and Existing ASV System	451
12.2	Practical Aspects of NMR Automatic Verification	453
12.2.1	Digital Resolution	453
12.2.1.1	Zero Filling	454
12.2.2	Window Functions	457
12.2.2.1	Sensitivity Enhancement	458
12.2.2.2	Resolution Enhancement	459
12.2.2.3	Weighting Functions and Integration	460
12.2.3	Linear Prediction	462
12.2.4	Relaxation Times and Delays	464
12.2.5	Alignment of ^1H and HSQC Spectra	465
12.2.6	General Recommendations for the Choice of NMR Acquisition and Processing Parameters	466
12.2.6.1	^1H -NMR Spectra	466
12.2.6.2	Single Bond ^1H - ^{13}C 2D Heterocorrelation	466
12.3	The Architecture of the Automatic Verification Expert System	471
12.3.1	Introduction	471
12.3.2	The Scoring System	472
12.3.2.1	Score	473
12.3.2.2	Significance	473
12.3.2.3	Quality	473
12.3.3	NMR Prediction and Spectral Synthesis	474
12.3.3.1	^{13}C -NMR Prediction	474
12.3.3.2	^1H -NMR Prediction	475
12.3.3.3	^1H Spectral Synthesis	476
12.3.4	Automatic Importing and Processing of NMR Data Sets	476

12.3.5	Automatic Analysis: Spectral Deconvolution and Peaks Labeling	478
12.3.6	ASV Tests	483
12.3.6.1	Number of Nuclides Test (NN)	483
12.3.6.2	^1H Prediction Bounds Metrics	483
12.3.6.3	Automatic Assignments Test	484
12.4	Performance of the Automated Structure Verification Systems	485
12.4.1	Basic Definitions	485
12.4.2	Tests of Performance	488
12.5	Conclusions	490
	Acknowledgments	490
	References	490

13 On the Search for the Appropriate Techniques for Structural Elucidation of Small Molecules

Maria Magdalena Cid and Jorge Bravo

13.1	Introduction	493
13.2	The Challenge of Structural Determination	495
13.3	Tools: Mass Spectrometry (MS)	497
13.4	Tools: Solution NMR Spectroscopy	499
13.5	Tools: Solid-State NMR Spectroscopy	501
13.6	Chiroptical Spectroscopies	507
13.7	Theoretical Calculations: <i>Ab initio</i> Calculations of NMR Shifts	512
13.8	Theoretical Calculations: Computer-Assisted Structure Elucidation	514
13.9	Summary	515
	Acknowledgments	516
	References	516

Index 521

