

***cis-trans* Isomerization in Biochemistry**

Edited by
Christophe Dugave



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Contents

	Preface	<i>XI</i>
	List of Contributors	<i>XIII</i>
1	Nomenclature	<i>1</i>
	<i>Christophe Dugave</i>	
2	General Mechanisms of <i>Cis-Trans</i> Isomerization: A Rapid Survey	<i>7</i>
	<i>Christophe Dugave</i>	
2.1	Introduction	<i>7</i>
2.2	Homolytic <i>Cis-Trans</i> Isomerization	<i>7</i>
2.3	Heterolytic <i>Cis-Trans</i> Isomerization	<i>10</i>
3	Mechanisms of <i>Cis-Trans</i> Isomerization around the Carbon–Carbon Double Bonds via the Triplet State	<i>15</i>
	<i>Yasushi Koyama, Yoshinori Kakitani, and Hiroyoshi Nagae</i>	
3.1	A Concept of a Triplet-Excited Region	<i>15</i>
3.2	Triplet-State Isomerization in Retinal	<i>17</i>
3.2.1	<i>Cis-Trans</i> Isomerization Examined by Electronic Absorption and Raman Spectroscopies and by High-Performance Liquid Chromatography Analysis	<i>17</i>
3.2.2	Triplet-Excited Region in All- <i>trans</i> -Retinal Shown in Terms of Stretching Force Constants Determined by Raman Spectroscopy and Normal Coordinate Analysis	<i>22</i>
3.2.3	Dynamic Triplet-Excited Region in Retinal As Revealed by Deuteration Effects on the Quantum Yields of Isomerization via the T ₁ State	<i>24</i>
3.2.4	Summary and Future Trends	<i>26</i>
3.3	Triplet-State Isomerization in β -Carotene and Spheroidene	<i>27</i>
3.3.1	<i>Cis-Trans</i> Isomerization in β -Carotene Studied by Electronic Absorption and Raman Spectroscopies and by HPLC Analysis	<i>27</i>

3.3.2	<i>Cis-Trans</i> Isomerization in Spheroidene Studied by Time-Resolved Absorption Spectroscopy and by HPLC Analysis	32
3.3.3	The Triplet-Excited Region of All- <i>trans</i> -Spheroidene in Solution and the Triplet-State Structure of 15- <i>cis</i> -Spheroidene Bound to the Bacterial Reaction Center Determined by Raman Spectroscopy and Normal Coordinate Analysis	35
3.3.3.1	All- <i>trans</i> -Spheroidene in Solution	35
3.3.3.2	15- <i>cis</i> -Spheroidene Bound to the Reaction Center	37
3.3.4	Conformational Changes and the Inversion of Spin-Polarization Identified by Low-Temperature Electron Paramagnetic Resonance Spectroscopy of the Reaction Center-Bound 15- <i>cis</i> -Spheroidene: A Hypothetical Mechanism of Triplet-Energy Dissipation	39
3.3.5	Summary and Future Trends	46
3.4	Spectroscopic and Analytical Techniques for Studying <i>Cis-Trans</i> Isomerization in the T ₁ State	47
3.4.1	Spectroscopic Techniques: Electronic Absorption, Raman, and Magnetic Resonance Spectroscopies	47
3.4.2	A Useful Analytical Technique: Singular-Value Decomposition Followed by Global Fitting	48
4	Retinal Binding Proteins	53
	<i>Hideki Kandori</i>	
4.1	Retinal Chromophore in Rhodopsins	53
4.1.1	Specific Color Regulation of the Retinal Chromophore in Protein	53
4.1.2	Unique Photochemistry of the Retinal Chromophore in Protein	56
4.2	Photoisomerization in Visual Rhodopsins	57
4.2.1	Structure and Function of Visual Rhodopsins	57
4.2.2	Primary Process in Vision Studied by Ultrafast Spectroscopy	59
4.2.3	Structural Changes of the Chromophore and Protein upon Retinal Photoisomerization	64
4.3	Photoisomerization in Archaeal Rhodopsins	66
4.3.1	Structure and Function of Archaeal Rhodopsin	66
4.3.2	Primary Process in Bacterial Photosynthesis and Light Sensor Studied by Ultrafast Spectroscopy	68
4.3.3	Structural Changes of the Chromophore and Protein upon Retinal Photoisomerization	69
4.4	Summary and Prospects	72
5	Non-Retinal Chromophoric Proteins	77
	<i>Marc Zimmer</i>	
5.1	Introduction	77
5.2	Photoactive Yellow Protein	77
5.3	Green Fluorescent Protein and Other GFP-like Proteins	79
5.4	Phytochromes	89

6	Fatty Acids and Phospholipids	95
	<i>Chrysostomos Chatgililoglu and Carla Ferreri</i>	
6.1	Introduction	95
6.2	Enzyme-Catalyzed <i>Cis-Trans</i> Isomerization of Unsaturated Fatty Acid Residues in Bacteria	97
6.3	Radical-Catalyzed <i>Cis-Trans</i> Isomerization of Unsaturated Lipids and its Effect on Biological Membranes	101
6.3.1	Geometric Isomerization of Unsaturated Fatty Acids in Solution	101
6.3.2	Isomerization of Phosphatidylcholine in Large Unilamellar Vesicles	103
6.3.3	Biological Consequences	106
6.4	Perspectives and Future Research	110
7	In Silico Dynamic Studies of <i>Cis-Trans</i> Isomerization in Organic and Biological Systems	113
	<i>Ute F. Röhrig, Ivano Tavernelli, and Ursula Rothlisberger</i>	
7.1	Introduction	113
7.2	Computational Methods	116
7.2.1	Time-Dependent Density Functional Theory (TDDFT)	116
7.2.2	Restricted Open-Shell Kohn–Sham Theory (ROKS)	120
7.3	Theoretical Aspects of CTI	122
7.3.1	Protonated Schiff Bases	123
7.3.2	Formalimine	124
7.4	CTI in PSB5 and Formalimine	124
7.4.1	Protonated Schiff Base (PSB5)	124
7.4.2	Formalimine	129
7.5	CTI in Rhodopsin	132
7.5.1	Introduction	132
7.5.2	Classical and QM/MM Studies of the CTI in Rhodopsin	133
7.6	Summary and Conclusions	137
8	Chemical Aspects of the Restricted Rotation of Esters, Amides, and Related Compounds	143
	<i>Christophe Dugave</i>	
8.1	Thermodynamic and Kinetic Aspects of <i>Cis-Trans</i> Isomerization	143
8.1.1	Esters and Thioesters	144
8.1.2	Amides and Thioamides	145
8.1.3	Oxalamides and Hydrazides	147
8.1.4	Carbamates and Ureas	148
8.2	Influence of the Environment on CTI	150
8.2.1	Solvent and Concentration	150
8.2.2	pH and Salts	152
8.2.3	Temperature	153

8.3	The Study of CTI of Amides and other Conjugated π -Systems	154
8.3.1	Spectroscopic Techniques	154
8.3.1.1	NMR Spectroscopy	154
8.3.1.2	Spectrometric and Fluorimetric Assays	155
8.3.1.3	Other Spectroscopic Techniques	157
8.3.2	Separation of <i>Z</i> and <i>E</i> Isomers	158
8.3.3	Models and Mimics for the Study of Amide CTI: Towards Multiple CTI Pathways	159
8.3.3.1	Acid/H-Bond-Catalyzed CTI	160
8.3.3.2	Nucleophilic/Basic Catalysis of CTI	161
8.3.3.3	Cation-Catalyzed CTI	161
8.3.3.4	Light-Induced CTI	161
9	Amide <i>Cis-Trans</i> Isomerization in Peptides and Proteins	167
	<i>Stephan Wawra and Gunter Fischer</i>	
9.1	Imidic and Secondary Amide Peptide Bond Conformation	167
9.1.1	Simple Amides	167
9.1.2	Secondary Amide Peptide Bonds	169
9.1.3	Imidic Peptide Bonds	171
9.1.4	Solvent and pH Effects	173
9.1.5	Sequence-Specific Effects	174
9.1.6	Secondary Structure Formation and CTI	178
9.2	Amide Relevant Conformations in Proteins	181
9.3	Native State Peptide Bond Isomerization	183
9.4	Biological Consequences	187
10	Enzymes Catalyzing Peptide Bond <i>Cis-Trans</i> Isomerizations	195
	<i>Gunter Fischer</i>	
10.1	Introduction	195
10.2	Cyclophilins	199
10.3	FK506 Binding Proteins (FKBPs)	204
10.4	Trigger Factor	209
10.5	Parvulins	210
10.6	Secondary Amide Peptide Bond <i>Cis-Trans</i> Isomerases	213
10.7	Catalytic Mechanism of Peptide Bond <i>Cis-Trans</i> Isomerases	215
11	Tailoring the <i>Cis-Trans</i> Isomerization of Amides	225
	<i>Luis Moroder and Christian Renner</i>	
	<i>John J. Lopez, Gabriele Tuchscherer and Manfred Mutter</i>	
11.1	Introduction	225
11.2	Substituted Prolines	225
11.2.1	Hydroxyprolines	226
11.2.2	Mercaptoproline	229

11.2.3	Halogenated Prolines	230
11.2.4	Other Proline Analogs	232
11.2.5	Alkylated Proline Analogs	233
11.2.6	Bridged Bicyclic Proline Analogs	235
11.2.7	Locked Proline Mimetics	237
11.3	Pseudoprolines in Chemical Synthesis and Biology	240
11.3.1	From Proline to Pseudoproline	240
11.3.2	Synthesis of Pseudoprolines	242
11.3.3	Pseudoprolines for the Synthesis of Difficult Sequences	244
11.3.4	Pseudoprolines in Bioactive Peptides	245
11.3.5	Pseudoprolines for Enhancing Peptide Cyclization and Turn Induction	246
11.3.6	Pseudoprolines for Modulating Polyproline Helices	247
11.3.7	Pseudoprolines for Modulating Structure and Function of Cyclosporins	249
11.3.8	Pseudoprolines for Targeting <i>Cis</i> Bonds in Peptides and Proteins	251
11.4	Conclusions and Perspectives	252
12	Peptidyl Prolyl Isomerases: New Targets for Novel Therapeutics?	261
	<i>Christophe Dugave</i>	
12.1	Introduction	261
12.2	Implication of PPIases in Biological Processes and Diseases	262
12.2.1	PPIases and Protein Folding and Trafficking	262
12.2.2	Immunosuppressive Pathways Through Formation of PPIase:Ligand Complexes	263
12.2.3	Modulation of Ion Channels by PPIases	265
12.2.4	Chaperone Activity of Immunophilins in Steroid Receptor Signaling	265
12.2.5	Immunophilins and Neurodegenerative Disorders	266
12.2.6	PPIases and Cell Multiplication	267
12.2.7	Implication of PPIases in Apoptosis	270
12.2.8	PPIases and Infectious Diseases	270
12.3	Structure and SAR studies of PPIases: Structural Evidence and Putative Catalytic Mechanism	272
12.3.1	Generalities	272
12.3.2	Cyclophilins and FKBP: Similar Molecular Basis for Distinct Catalytic Mechanisms	273
12.3.3	Parvulins	276
12.4	PPIase Inhibitors: From In Vitro Inhibitors to Novel Therapeutics	277
12.4.1	Natural PPIase Inhibitors and Their Analogs	277
12.4.2	Mechanism-Based Inhibitors	282

- 12.4.3 Library Screening Versus in Silico Design: Current Status and Future Prospects 284
- 12.5 Conclusion and Perspectives 288

13 **Other *Cis-Trans* Isomerizations in Organic Molecules and Biomolecules** 295

Muriel Gondry and Christophe Dugave

- 13.1 Introduction 295
- 13.2 *Cis-Trans* Isomerization around Single Bonds 295
 - 13.2.1 *Cis-Trans* Isomerism of Aryl Compounds 295
 - 13.2.2 Disulfide Bonds 297
 - 13.2.3 Amide Surrogates with Restricted Rotation of a σ -Bond 298
- 13.3 C=N-containing Compounds 300
 - 13.3.1 Oximes and Nitroso Compounds 300
 - 13.3.2 Imines and Schiff Bases 300
- 13.4 Dehydroamino Acids and Dehydropeptides 303
 - 13.4.1 Acryloyl Peptides, Acrylates and Related Molecules 303
 - 13.4.2 Naturally Occurring Dehydroamino Acids and Dehydropeptides 305
 - 13.4.3 Synthetic Dehydroamino Acids and Dehydropeptides 308
- 13.5 Phototunable Biomolecules Containing an Azobenzene Moiety 310
 - 13.5.1 Phototunable Ligands 310
 - 13.5.2 Phototunable Conformation of Peptides 312
 - 13.5.3 Modifications of Proteins with Photoisomerizable Motifs 313
 - 13.5.4 Other Phototunable Biomolecules 315

14 ***Cis-Trans* Isomerism in Metal Complexes** 321

Alzir Azevedo Batista and Salete Linhares Queiroz

- 14.1 Introduction 321
 - 14.1.1 *Trans* Effect 324
 - 14.1.2 Protonation of the Leaving Group 326
 - 14.1.3 Separation or Purification of *Cis-Trans* Isomers 327
 - 14.1.4 Identification of *Cis-Trans* Isomers 327
- 14.2 The *Cis-Trans* Isomerization of Metal Complexes: Mechanisms and Effects 330
 - 14.2.1 *Cis* or *Trans* Isomer? 330
 - 14.2.2 Isomerization Processes 331
- 14.3 *Cis-Trans* Isomers of Metal Complexes as Potential Therapeutics 334
- 14.4 Applications of *Cis-Trans* Isomerization of Metal Complexes in Supramolecular Chemistry 337
- 14.5 Final Remarks 341

Index 345

Preface

Life is governed by a relatively small number of chemical reactions that exploit a limited variety of simple concepts. However, their combination has led to an amazing chemical diversity which is still beyond the reach of the organic chemist, even in the most complex supramolecular systems, despite a huge set of synthetic methods. Among these basic processes and reactions, *cis-trans* isomerization (CTI) is undoubtedly one of the finest ways to tune the physical and chemical properties of biomolecules and hence to control their biological activities. Moreover, CTI of simple molecules generates molecular diversity in the form of geometric isomers with particular structures and properties.

Surprisingly, chemists were rather slow to study CTI, and it is only fairly recently that it has been taken into account in attempts to understand biological processes at the molecular level. The Swiss chemist Alfred Berthoud first investigated the light-driven CTI of alkenes and proposed a radical mechanism that accounted for the reversibility of the phenomenon, a theory which is still taught today.

Since the first attempts to understand CTI in simple molecular systems, a huge amount of work has been done to investigate CTI processes in biology, such as chromophore isomerization in chromoproteins. The finding that CTI concerns not only double bonds but also pseudo double bonds and restrained single bonds has led to extensive study of protein folding, modulation of the activity of peptides and proteins, and the construction of sophisticated supramolecular structures. CTI was also found to be implicated in the organization of metal complexes and supramolecular systems, though the mechanisms are basically different from those proposed for CTI of organic molecules.

The study of CTI has given rise to a large number of publications, which are the fruit of active collaborations between scientific teams whose expertise ranges from *in silico* quantum molecular mechanics to medicine. For these reasons, CTI processes concern not only chemists and biochemists, but also physicists and physicians.

Over the past 20 years there have been considerable changes in the way we consider CTI. In view of the results obtained in chemistry and biochemistry, CTI appears to be much more than a simple tuning of the properties of the molecule itself, and important remote effects have been highlighted. It is now obvious that

the inversion about either a double bond or a restrained single bond generates extensive changes in molecular size and shape, and in stereoelectronic properties, all of which function cooperatively. This has considerable consequences for the behavior of larger molecular systems such as membranes and proteins, and is suspected to be a particular way of storing potential energy usable not only for chemical reactions but also for macroscopic movement.

Light-driven CTI also plays a central role in the transduction of light into a chemical signal and so is the starting point of light perception in primitive organisms and in the vision of more complex organisms. CTI has also emerged as the basic concept underpinning holographic information storage of extraordinary capacity and resolution. However, we should never forget that billions of years before chemists utilized CTI to tune gel–sol phase transitions, nature used this simple reaction to modulate membrane permeability to enable adaptive responses to stress and environmental change.

Beyond protein folding, the discovery of peptidyl prolyl isomerases (PPIases) and related proteins has opened the way to novel concepts in biology: the notion of chaperone-assisted receptor binding is an emerging field of research which sheds light on receptor function and protein–protein interactions. The recent discovery of a secondary amide peptide bond *cis-trans* isomerase (APIase) heralds new advances in this field.

Recently, the French Nobel prizewinner Jean-Marie Lehn proposed the use of CTI as a source of molecular diversity in dynamic combinatorial chemistry. The prospect of using a dynamic fully reversible process such as CTI for the evolutionary selection of ligands is extremely attractive and should lead to fundamental advances in this field of research.

Although this book will not tackle the technological uses of CTI nor its application in supramolecular chemistry, the impressive advances in the development of molecular devices that produce a microscopic motion as well as a macroscopic movement must be cited herein.

Progress in the study of CTI should lead not only to better understanding of one of the main molecular bases of life, but also to the development of fascinating tools for studying biomolecules. These main lines of research are not incompatible, since one talks of supramolecular systems able to release bioactive molecules at the right place through a controlled CTI process. I am confident that work on CTI will yield important applications beneficial to humankind, and I sincerely hope that this book, which collates most of the recent data on CTI in biology, organic and inorganic chemistry, will help scientists to work with this aim in mind.

Saclay, January 6th 2006

Christophe Dugave

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1

Nomenclature

Christophe Dugave

Molecules in which free rotation around one or more bonds is restricted may exist as distinct stable rotamers in proportions that depend on the free enthalpy difference ΔG° of each rotamer. They can interconvert provided the intrinsic rotational barrier ΔG^\ddagger is not too high (Fig. 1.1). In the simplest case, there are two marked energy minima separated by energy barriers to rotation, which often implies either the effective breaking of a chemical bond (i.e. C=C photoisomerization in ethylene derivatives) or a disruption of conjugation (i.e. isomerization of a Y-C=X system, X and Y being heteroatoms). Therefore, there are only two geometrical isomers for one given system and theoretically 2^n possible isomers for a molecule that contains n isomerizable systems (e.g. retinal).

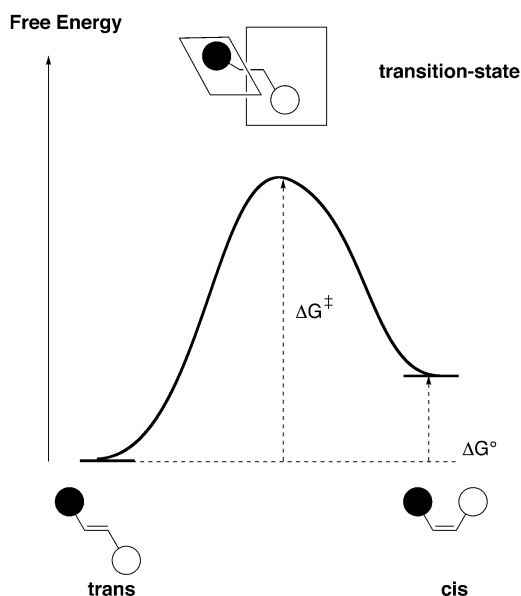


Fig. 1.1 Schematic representation of general *cis-trans* isomerism of a double bond.

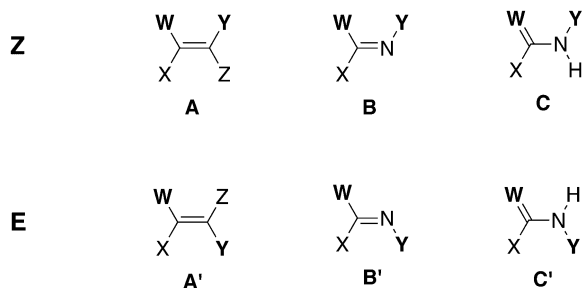


Fig. 1.2 General *Z/E* nomenclature for the description of geometrical isomers in π -systems.

The first proposed nomenclature suggested that isomers should be called *cis* when W and Y are on the same side of the double bond and *trans* when they are on the opposite side (Fig. 1.2), provided $W \neq X$ and $Y \neq Z$. However, this nomenclature was limited to the particular case where W and Y are identical. The more recent nomenclature of Cahn–Ingold–Prelog, based on the German *Zusammen* (*Z*) and *Entgegen* (*E*) notation, was extended to systems where W and Y are different substituents (Fig. 1.2). There is no direct relation between the two nomenclatures since they depend on the nature of substituents; and so the *Z* isomer is not necessarily *cis*. Moreover, the order of priority is determined by the atomic number of each atom connected to the C=C double bond [1]. Although the *E/Z* nomenclature may also be applied to compounds B/B' and C/C', these are considered as conformational isomers, whereas compounds A/A' are configurational isomers.

Z/E isomerism is not limited to true double bonds and may be used when sp^2 electrons of a heteroatom are conjugated with a π -system to form a planar pseudo double bond. In particular, in the case of amides, the *cis* isomer is called *E*. Although the general tendency now is to use the *E/Z* nomenclature in chemistry, despite their inaccuracy *cis* and *trans* are still utilized by biochemists because they give a more readily understandable description of molecular shape, in particular for amides in peptides and proteins. When the chains are connected through a motif containing more than three dihedral angles (i.e. carbamates), the *syn-anti*

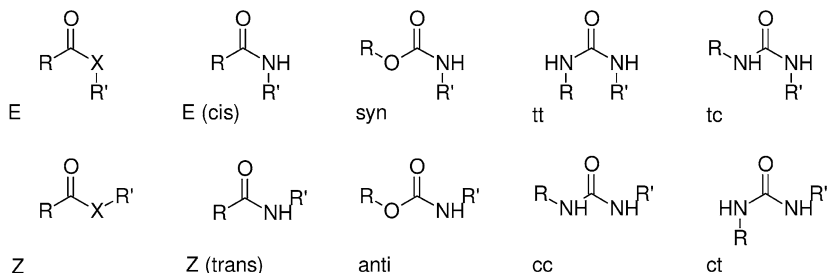


Fig. 1.3 Usual nomenclature for geometric isomers of esters, amides, carbamates, and ureas (*t*: *trans*, *c*: *cis*).

and *cis-trans* nomenclatures are usually applied since they refer to the relative position of substituents (Fig. 1.3).

Cis-trans isomerism may also occur with true single bonds. In fact, preferred conformational minima for $\omega = 180^\circ$ (*anti*) and $\pm 60^\circ$ (*gauche*) are usually found in alkanes (Fig. 1.4A). However, in severely crowded compounds, backbone valence angles are smaller than tetrahedral and therefore the Prelog–Klyne nomenclature is the standard (Fig. 1.4B) [2]. However, this notation is unhelpful for energy minima for ω of about 90° and 150° , a situation which is common for $\text{Si}_n\text{X}_{2n+2}$ polysilanes and which has resulted in a proliferation of nonstandard symbols and notations. Recently, Michl and West have suggested the use of new labels that account for particular conformations found in polymers, disulfides, etc. (Fig. 1.4C). They also recommend specifying the positive or negative sense (right or left) since these conformers are chiral. This notation also accounts for strongly deformed π -systems with the *syn* ($\omega \approx 0^\circ$) and *anti* ($\omega \approx 180^\circ$) configurations [3].

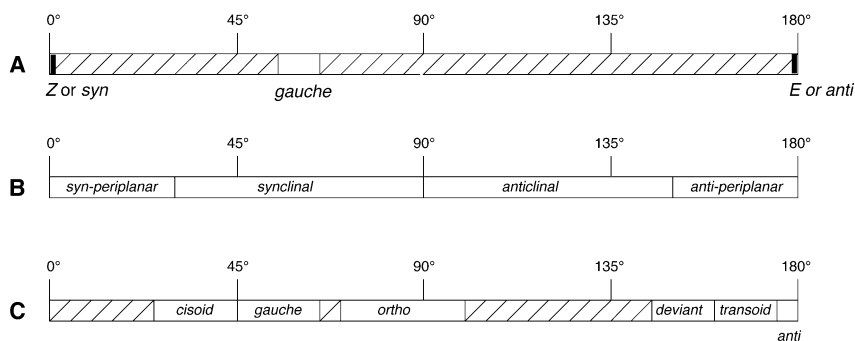


Fig. 1.4 Proposed labels for favored dihedral angles in the Cahn–Ingold–Prelog (A), Prelog–Klyne (B), and Michl–West (C) nomenclatures.

Metal complexes display a wide variety of coordination geometries that permit the existence of several geometric isomers. The situation is rather more complicated than with organic molecules since the three-dimensional arrangement of coordinates around the metal core leads to the multiplication of possible diastereomers. The *cis/trans* notation is usually employed but this nomenclature is based on a spatial reference: “*cis*” means “adjacent” while “*trans*” means “opposite” (Fig. 1.5) [4].

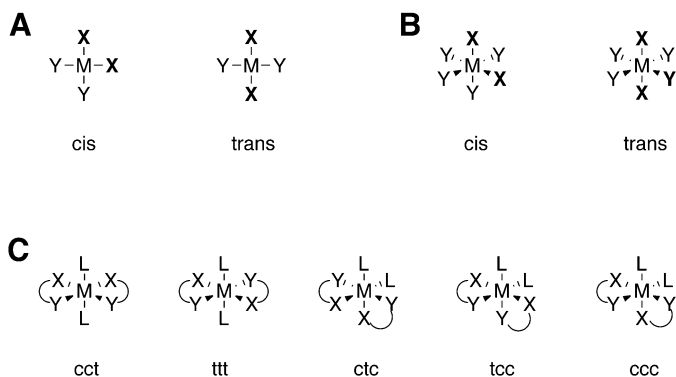


Fig. 1.5 Possible geometric isomerism around a metal core in a square planar (A) and two octahedral complexes (B, C).

The number of possible diastereomers depends on the variety of ligands and sometimes requires use of the one-letter code (*cis/trans* is noted *c/t*). This nomenclature may be applied to square planar complexes and to square planar pyramidal and octahedral complexes, but not to tetrahedral complexes where a given position is equivalent to any other. Moreover, geometric isomerism often implies the existence of optical isomerism.

The new labels *fac* and *mer* were introduced to reflect the relative position of three identical ligands around the octahedral structure. Thus, placing the three groups on one face of the octahedron gives rise to the facial isomer, and placing the three groups around the center gives rise to the meridional isomer (Fig. 1.6). When there are only two different ligands, the *cis/trans* and *fac/mer* nomenclature may be mixed in order to describe the complex geometry unambiguously [4].

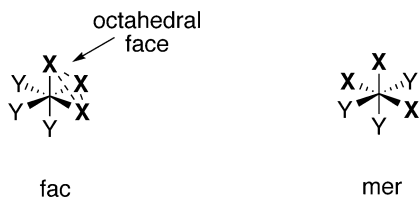


Fig. 1.6 *Fac* and *mer* isomers in octahedral metal complexes.

Syn/anti nomenclature is mainly employed for octahedral complexes when geometric isomerism arises from the presence of a fused ring. Therefore, the *syn* isomer has adjacent fused rings whereas the *anti* isomer has opposite fused rings [5].

In summary, molecular variety leads to a multiplicity of stereoisomerisms, which in turn has given rise to several specific nomenclatures. These will be utilized throughout this handbook with the overriding purpose of clarity, rather than strict accuracy.

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2

General Mechanisms of *Cis-Trans* Isomerization: A Rapid Survey

Christophe Dugave

2.1

Introduction

A database search yields more than 20 000 references that contain “*Z-E* isomerization,” “*cis-trans* isomerization,” or “geometric isomerization” as keywords, and the general tendency is an increase in the number of papers devoted to the kinetic aspects of *cis-trans* isomerization (CTI) in all fields. The main isomerization pathways have probably been discovered, though many remain the object of intense theoretical (see Chapter 7) and experimental research (see Chapters 4–6, 8–10, 13, and 14). In the present chapter, general CTI mechanisms will be divided into homolytic and heterolytic cleavage of the π -bond which allows isomerization, though some molecular motifs such as amides are able to switch from *cis* to *trans* via both processes. An overview of CTI in metal complex (mainly thermal, photochemical, and oxidative isomerizations) will be the purpose of Chapter 14 and will not be detailed here.

2.2

Homolytic *Cis-Trans* Isomerization

Since the elucidation of the photoisomerization of alkenes in 1928, numerous CTI pathways have been proposed. In fact, many unsaturated compounds may isomerize via different pathways depending on the conditions. For example, polyenes may photoisomerize via either the π, π^* singlet or triplet excited states and also via photosensitization by singlet–singlet and triplet–triplet intersystem crossing [1] via a perpendicular radical transition state that accounts for the formation of the least stable *Z* isomer [2]. CTI of olefine and polyene systems has been thoroughly investigated using a wide variety of models including stilbenes and stilbene analogs, retinal derivatives and carotenoids, etc., as well as simple cycloalkenes (Fig. 2.1) [3], leading to the parallel emergence of novel theories and powerful techniques to probe the behavior of molecular systems in the 10^{-14} to 10^{-11} s range, such as femtosecond laser spectroscopy [4] (see Chapter 4).

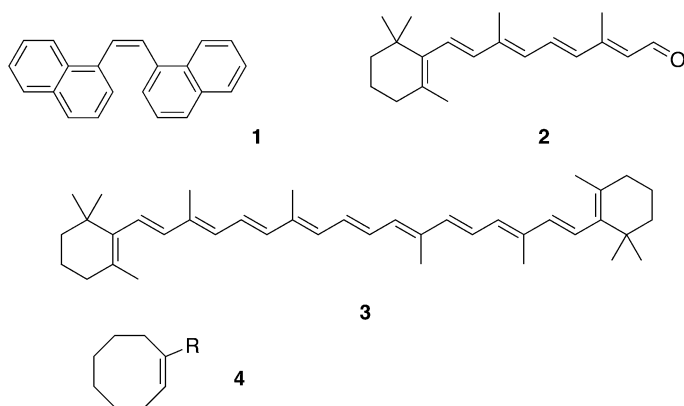


Fig. 2.1 Some model compounds used for studying photoisomerization processes: *Z*-1,2-bis- α -naphthylethylene **1**, retinal **2**, β -carotene **3**, cyclooctene **4**.

However, there are many other CTI pathways for the simple polyenes: aborted heterogeneous hydrogenation, radical reactions initiated by radical generators including photosensitization by ketones [5] and paramagnetic molecules (e.g. oxygen, atomic bromine and iodine, nitrogen oxide) and heat [6,7]. Recently, a new mechanism for the iodine/light-catalyzed CTI of stilbene has been proposed and seems to imply the formation of a complex between iodine and the alkene that leads to a single radical adduct [8]. A similar process was proposed for the thiyl radical-mediated CTI of polyenes [9]. A relevant example is retinal, which may isomerize experimentally through many of these distinct pathways. Moreover, many pathways play an important part in the CTI of polyenes *in vivo* where they have a central role in vision, metabolism, and accidental alteration of biomolecules, in particular phospholipids (Fig. 2.2).

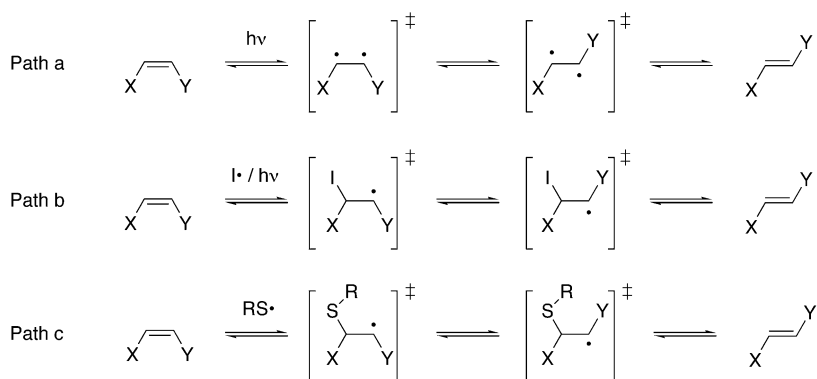


Fig. 2.2 Possible mechanisms of *cis-trans* (*Z-E*) isomerization of olefins and related compounds via heterolytic cleavage of the C=C bond: photoisomerization (path A).

As a general rule, the more the molecule is conjugated, the lower the energy barrier to isomerization. While nonconjugated alkenes require typically 97–164 kcal mol⁻¹ to isomerize via the lowest triplet state and the π, π^* singlet state, respectively, the calculated energy barrier to CTI of retinal Schiff bases lies between 23 and 60.6 kcal mol⁻¹ depending on the C=C bond and the protonation state of the imine [10]. It is well known that *cis*-polyacetylene isomerizes to the all-*trans* compound upon heating to 150 °C. In the same way, diarylazo compounds require less energy to isomerize from *trans* to *cis* than stilbene derivatives, reflecting the optimal wavelength needed to induce CTI, for example $\lambda_{\text{max}} = 319$ nm for azobenzene and $\lambda_{\text{max}} = 294$ nm for stilbene.

Z-E isomerization via simple geometric inversion (one-bond flip, OBF, Fig. 2.3A) involves the torsional relaxation of the perpendicular excited state via an adiabatic mechanism which implies a non-volume-conserving process. This is not compatible with the ultrafast CTI in polyenes, in particular retinyl chromophores, and two other possible ways of photo-CTI have been proposed over the past 15 years [11].

The hula twist mechanism (HT, Fig. 2.3B), first validated with carotenoids, is not consistent with the time-scale of photoisomerization of chromoproteins since CTI of the retinal chromophore, which is inserted deep inside the protein, necessitates a major reorganization of the peptide molecular framework. Therefore, a new volume-conserving mechanism, called bicyclic pedal (BP, Fig. 2.3C), was proposed. In fact, all these mechanisms are still a topic of discussion since chromoprotein photo-intermediates highlighted by recent studies do not confirm this hypothesis. In particular, several photo-products of the retinal Schiff base in the

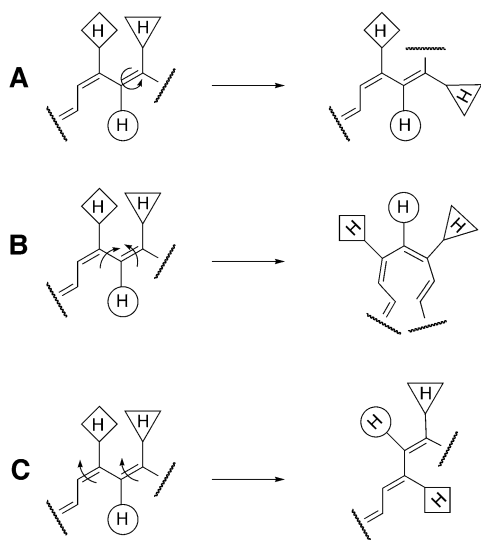


Fig. 2.3 Three possible pathways for the photo-CTI of polyenes: (A) one-bond flip (OBF); (B) hula twist (HT); (C) bicyclic pedal (BP).

rhodopsin protein family display a slightly constrained structure which is not taken into account by such theories.

In many cases, the CTI process competes with rearrangements and cyclizations that occur during the radiationless transition. *Z*-Stilbene is well known to give dihydrophenanthrene as a photoproduct along with *E*-stilbene (Fig. 2.4A). Reversible photocyclization is even the dominant reaction in fulgide [12] and merocyanine [13] systems [3] (Fig. 2.4B,C).

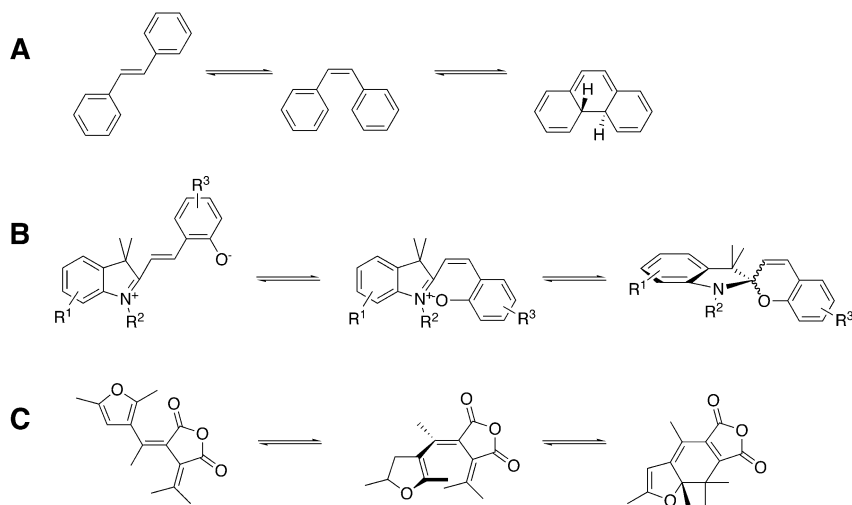


Fig. 2.4 Photoisomerization of *E*-stilbene gives a mixture of *Z*-stilbene and dihydrophenanthrene (A), whereas merocyanines isomerize directly to the enantiomeric spiropyran forms (B) and *E*-fulgides transform into the corresponding cyclic adduct.

2.3 Heterolytic *Cis-Trans* Isomerization

Although diazene compounds undergo photoisomerization in a similar way to alkenes [14,15], they also interconvert from *Z* to *E* and *E* to *Z* via simple doublet inversion (Fig. 2.5 path d), as also observed with other nitrogen-containing compounds such as nitroso derivatives. Moreover, the ultrafast isomerization of azo-sulfides implies a cleavage/recombination mechanism though radical anion cleavage seems to operate in the *Z* isomer exclusively, preventing isomerization from *Z* to *E* [16].

CTI driven by conjugation transfer (including deconjugation and tautomeric effects) gives rise to a wide range of mechanisms that may explain isomerization of many molecular motifs such as push-pull olefins, acrylates, imines and enamines, amides, and related compounds. Push-pull olefins, which are substituted by electron-donating and electron-withdrawing groups simultaneously, can isomer-

ize spontaneously by simple transfer of conjugation which decreases the double bond character of C=C (Fig. 2.5 path e). The tautomeric effect in the enol/ketone and enamine/imine equilibria plays a similar role, since electron delocalization is disrupted by a change in polarity (Fig. 2.5 path f) [3].

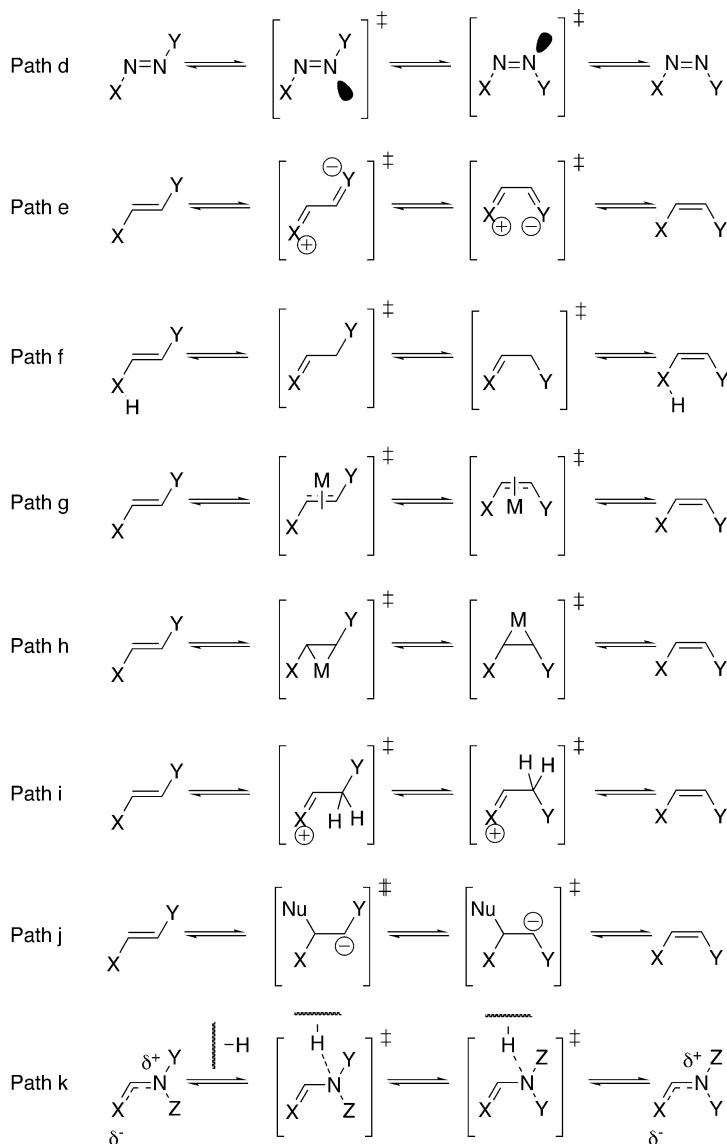


Fig. 2.5 Possible mechanisms for CTI via the heterolytic disruption of the conjugation of double bonds and pseudo double bonds (radical cleavage/recombination pathway was omitted there since it is not a true CTI process).

Several exogenous entities may also facilitate a *cis-trans* interconversion. Lewis acids and transition metals may disrupt conjugation by simply “hijacking” the π -electrons (Fig. 2.3 path g). Transition metal π -bases also operate via an insertion inside a triangular intermediate (path h) [17]. Brønsted acids (path i) and nucleophiles (path j) can also facilitate CTI via the formation of a tetrahedral intermediate. Amide and analogous compounds are undoubtedly the most versatile compounds in terms of possible mechanisms of CTI since most of the proposed pathways, including radical mechanisms, may account for the experimental results. This probably reflects the very low energy barrier (typically 5–30 kcal mol⁻¹) to CTI. In peptides and proteins, amide CTI seems to occur via a simple disruption of the double-bond character (path k) putatively through the creation of either intra- or intermolecular H-bonds [3,18]. The geometric deviation from double-bond planarity helps to lower the energy barrier to isomerization and also plays an important role in energy storage, as observed with photointermediates of chromoproteins.

Rotation around hindered or restrained single bonds usually implies that the molecule reaches the energy barrier that restricts interconversion from one conformer to another. In general terms, steric hindrance is the main limitation and heating is then sufficient to cross the barrier, although additional interactions such as H-bonds, stereoelectronic effects and ionic interactions may either hamper or facilitate the rotation.

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