cis-trans Isomerization in Biochemistry

Edited by
Christophe Dugave

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The Editor

Christophe Dugave
CEA/Saclay
Department of Protein Engineering and Research
Bâtiment 152
91121 Gif-sur-Yvette
France

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Contents

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.

Althought 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*

List of Contributors

Alzir Azevedo Batista
Universidade Federal de São Carlos
Departamento de Química
Campus São Carlos, Rodovia
Washington Luís
São Carlos – SP 13565-905
Brazil

Chryssostomos Chatgilialoglu
I.S.O.F.
Consiglio Nazionale delle Ricerche
Via P. Gobetti 101
40129 Bologna
Italy

Christophe Dugave
CEA/Saclay
Department of Protein Engineering
and Studies
Building 152
91191 Gif-sur-Yvette
France

Carla Ferreri
I.S.O.F.
Consiglio Nazionale delle Ricerche
Via P. Gobetti 101
40129 Bologna
Italy

Gunter Fischer
Max Planck Research Unit for
Enzymology of Protein Folding
Weinbergweg 22
06120 Halle/Saale
Germany

Muriel Gondry
CEA/Saclay
Department of Protein Engineering
and Studies
Building 152
91191 Gif sur Yvette
France

Hideki Kandori
Nagoya Institute of Technology
Department of Materials Science
and Engineering
Showa-Ku
Nagoya 466-8555
Japan

Yoshinori Kakitani
Kwansei Gakuin University
Faculty of Science and Technology
2-1 Gakuen
Sanda 669-1337
Japan

Yasushi Koyama
Kwansei Gakuin University
Faculty of Science and Technology
2-1 Gakuen
Sanda 669-1337
Japan

John J. Lopez
Ecole Polytechnique Federale de Lausanne (EPFL)
Institute of Chemical Sciences and Engineering
1015 Lausanne
Switzerland

Luis Moroder
Max-Planck-Institut für Biochemie
Am Klopferspitz 18
82152 Martinsried
Germany

Manfred Mutter
Ecole Polytechnique Federale de Lausanne (EPFL)
Institute of Chemical Sciences and Engineering
1015 Lausanne
Switzerland

Hiroyoshi Nagae
Kobe City University of Foreign Studies
9-1 Gakuen-Higashimachi, Nishi-ku
Kobe 651-2187
Japan

Salete Linhares Queiroz
Universidade de São Paulo
Instituto de Química de São Carlos
Av. Dr. Carlos Botelho 1465
São Carlos – SP 13560-970
Brazil

Christian Renner
Nottingham Trent University
Nottingham NG11 8NS
UK

Ute F. Röhrig
Ecole polytechnique fédérale de Lausanne
Institut des sciences et ingénierie chimiques
BCH – LCBC
1015 Lausanne
Swizerland

Ursula Rothlisberger
Ecole polytechnique fédérale de Lausanne
Institut des sciences et ingénierie chimiques
BCH – LCBC
1015 Lausanne
Swizerland

Ivano Tavernelli
Ecole polytechnique fédérale de Lausanne
Institut des sciences et ingénierie chimiques
BCH – LCBC
1015 Lausanne
Swizerland

Gabriele Tuchscherer
Ecole Polytechnique Federale de Lausanne (EPFL)
Institute of Chemical Sciences and Engineering
1015 Lausanne
Switzerland

Stephan Wawra
Max Planck Research Unit for
Enzymology of Protein Folding
Weinbergweg 22
06120 Halle/Saale
Germany

Marc Zimmer
Connecticut College
Department of Chemistry
New London
Connecticut 06320
USA

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 $\Delta G°$ of each rotamer. They can interconvert provided the intrinsic rotational barrier $\Delta G‡$ 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).

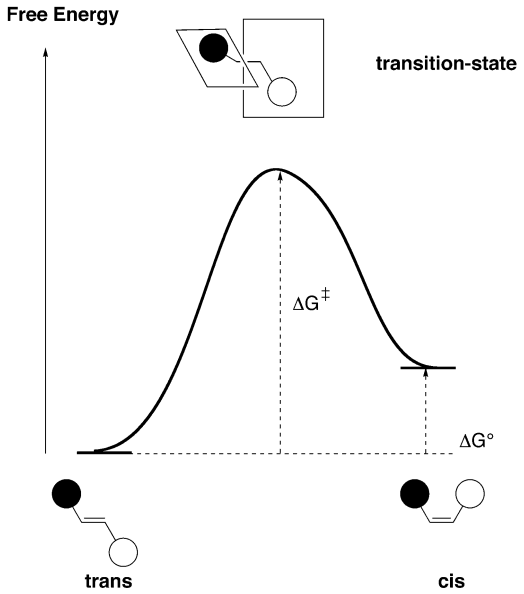

Fig. 1.1 Schematic representation of general *cis-trans* isomerism of a double bond.

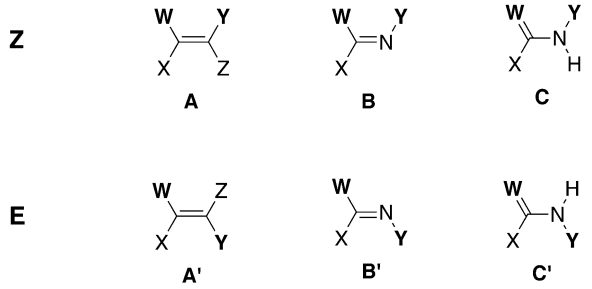

Fig. 1.2 General *Z*/*E* nomenclature for the description of geometrical isomers in π-systems.

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 ≠ X and Y ≠ 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*

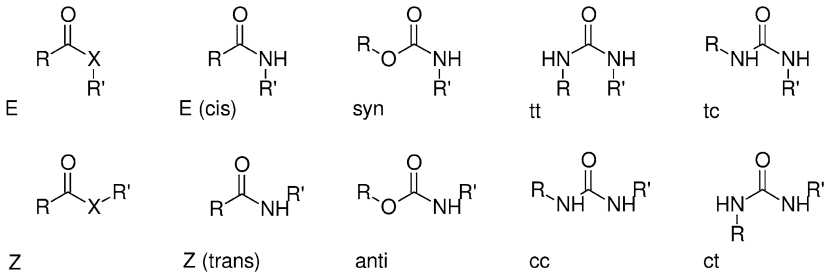

Fig. 1.3 Usual nomenclature for geometric isomers of esters, amides, carbamates, and ureas (*t*: *trans*, *c*: *cis*).

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 $\omega = 180°$ (anti) and $\pm 60°$ (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 Si_nX2n+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* ($\omega \approx 0°$) and *anti* ($\omega \approx 180°$) configurations [3].

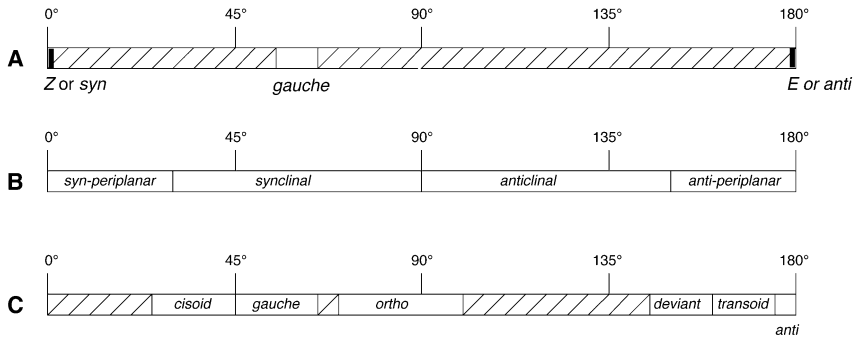

Fig. 1.4 Proposed labels for favored dihedral angles in the Cahn–Ingold–Prelog (A), Prelog–Klyne (B), and Michl–West (C) nomenclatures.

Metal complexes display a wide variety of coordination geometries that permit the existence of several geometric isomers. The situation is rather more complicated thanwith 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].

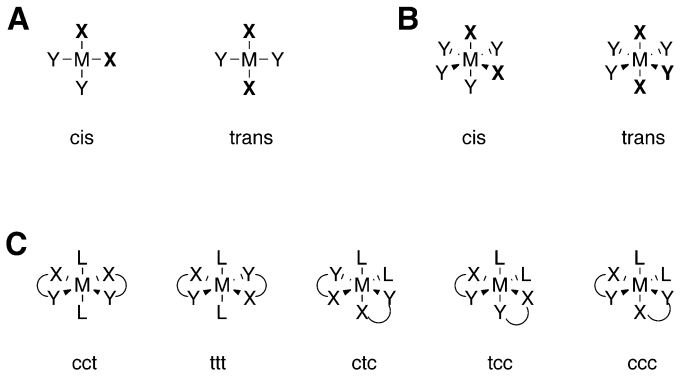

Fig. 1.5 Possible geometric isomerism around a metal core in a square planar (A) and two octahedral complexes (B, C).

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].

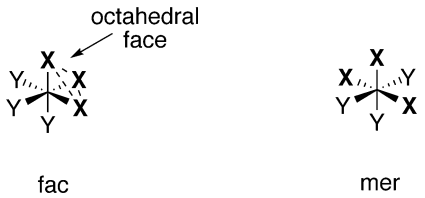

Fig. 1.6 *Fac* and *mer* isomers in octahedral metal complexes.

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).

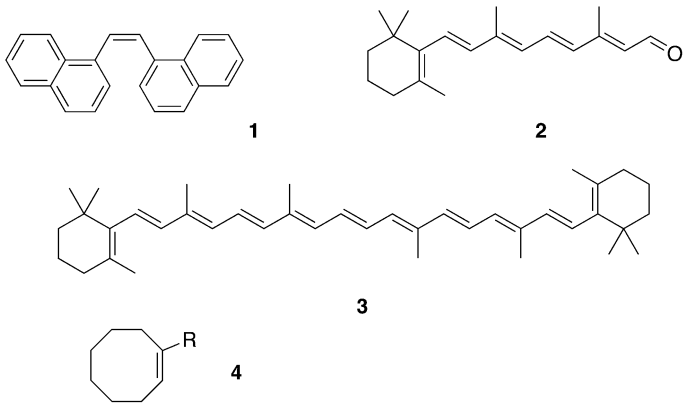

Fig. 2.1 Some model compounds used for studying photoisomerization processes: *Z*-1,2-bis-*α*-naphthylethylene **1**, retinal **2**, *β*-carotene **3**, cyclooctene **4**.

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).

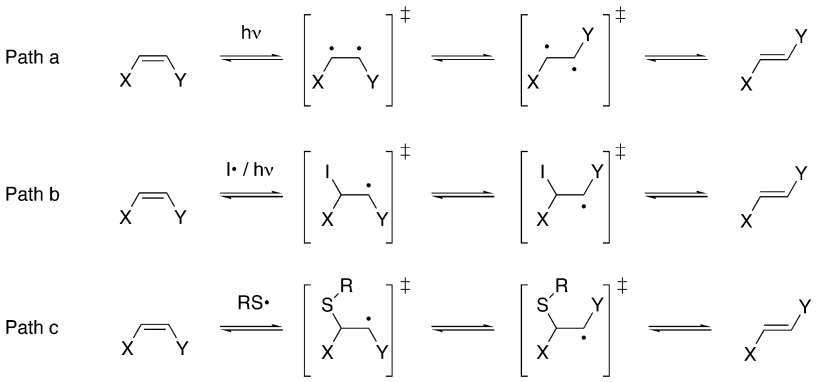

Fig. 2.2 Possible mechanisms of *cis-trans* (*Z-E*) isomerization of olefins and related compounds via heterolytic cleavage of the C=C bond: photoisomerization (path A).

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 λ_{max} = 319 nm for azobenzene and λ_{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

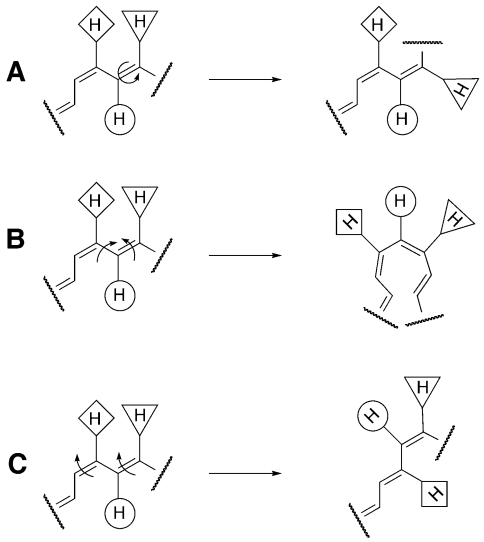

Fig. 2.3 Three possible pathways for the photo-CTI of polyenes: (A) one-bond flip (OBF); (B) hula twist (HT); (C) bicyclic pedal (BP).

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).

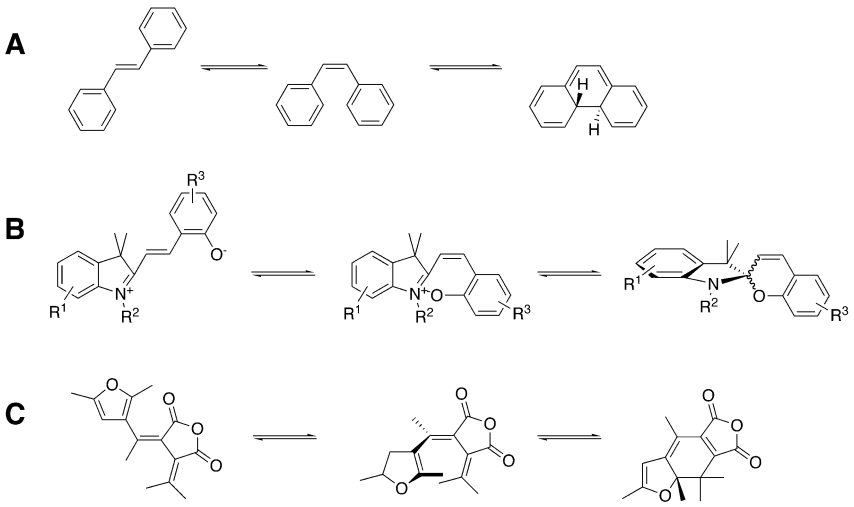

Fig. 2.4 Photoisomerization of *E*-stilbene gives a mixture of *Z*-stilbene and dihydrophenantrene (A), whereas merocyanines isomerize directly to the enantiomeric spiropyran forms (B) and *E*-fulgides transform into the corresponding cyclic adduct.

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 azosulfides 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].

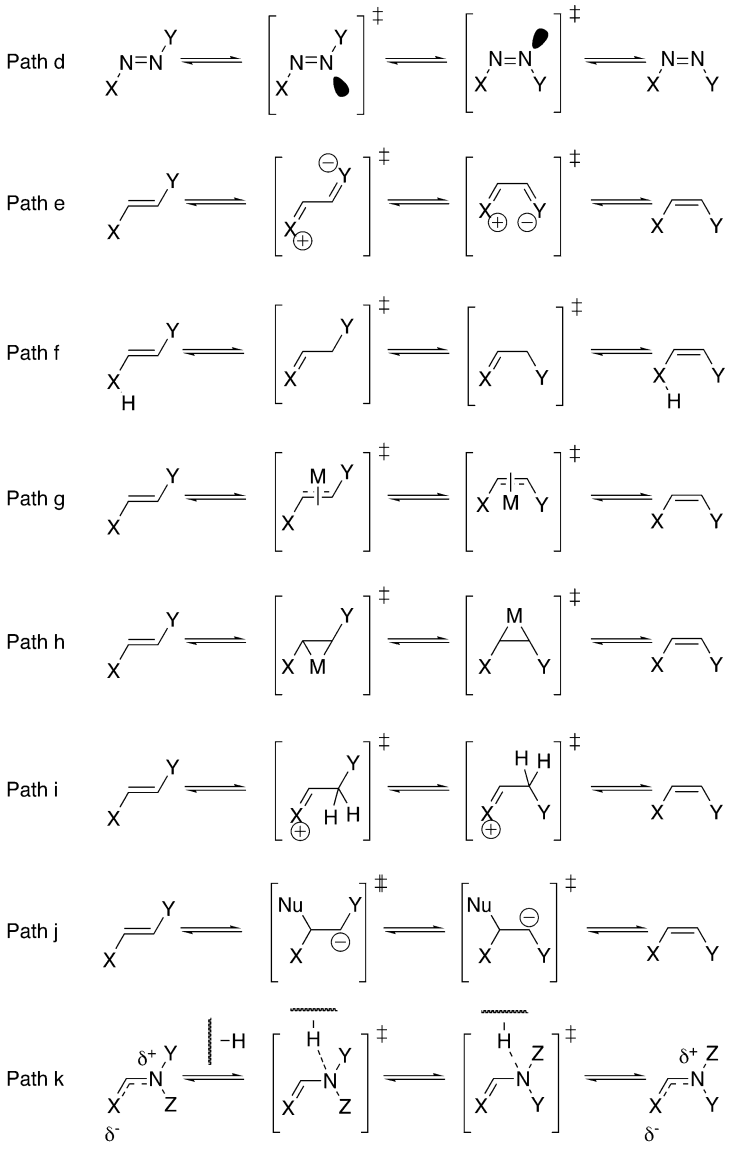

Fig. 2.5 Possible mechanisms for CTI via the heterolytic disruption of the conjugation of double bonds and pseudo double bonds (radical cleavage/recombination pathway was omitted there since it is not a true CTI process).

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]. Brønstedt 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 occurs 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 retrained 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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