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Review

Mechanisms and pharmaceutical consequences of processes of stereoisomerisation — A didactic excursion

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ABSTRACT

This writing proposes an overview of chemical processes of isomerisation involving conformations and configurational isomers. Molecular structure is depicted as consisting in A) core features; and B) fluctuating properties. To avoid confusion and misuses in terminology, attention is paid to IUPAC recommendations and definitions, beginning with a focus on conformers versus conformations. Two sections consider rotations, the behaviour of exocyclic single bonds being kept separate from that of endocyclic single bonds. Processes of pyramidal inversions are discussed next, alone and combined with rotations. Given its sometimes unsuspected occurrence in some drug molecules, stereolability at tetracoordinated carbon centres receives particular attention. Stereolabile and stereostable nitrogen-containing groups come next, with a focus on the simultaneous contributions of inversion and rotation as occurring for example in the conformational reversal of saturated aza-heterocycles. The last type of isomerisation to be examined involves complex heterocyclic systems of medicinal relevance. The conclusion points to the mechanistic variety of stereoisomerisation processes, to a continuum in their energy barriers, to their relevance in all fields of stereochemistry, and to the need for junior medicinal chemists to be adequately trained in stereochemistry.

Contents

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1. Introduction: molecular structure and geometric properties

1.1. Scope

This review discusses and exemplifies a number of reactions of isomerisation, specifically reactions of stereoisomerisation. The first definition of the term that comes to mind is that of processes by which one chemical compound is transformed into a stereoisomer (by definition another chemical entity). Such a description, however, applies only to high-energy processes, namely reactions whose educts (reactants) and products are compounds endowed with chemically stability under normal conditions. In this sense, stereoisomerisation is defined as a change (often an inversion) in configuration.

A second type of process comes under the umbrella of stereoisomerisation, namely the fast interconversion of a flexible molecule between various 3D-geometries. In this sense, stereoisomerisation is defined as conformational change. As will be argued, the two definitions overlap when isomerisation processes involve barriers of interconversion having "intermediate" energy levels. In concrete terms, the energy barriers of the many documented reactions of stereoisomerisation are spread over a continuum of values.

Another point to note is the fact that stereoisomerisation processes can be chemical (e.g., spontaneous or catalysed by bases or acids) or biochemical (i.e., enzymatic) (Testa, 2015). This review, however, focusses exclusively on chemical processes, be they spontaneous (fluctuations) or abiotically catalysed.

Another necessary clarification is that this review is not intended as an exhaustive presentation of all processes of stereoisomerisation. Rather, priority has been given to significant processes such as full rotations at exocyclic single bonds, partial rotations at endocyclic single bonds, reversals in simple and complex rings systems, and pyramidal inversions.

Two types of examples will be shown, namely model compounds and drug molecules, the former being meant to simplify presentation and facilitate understanding, whereas the latter allow the pharmaceutical and/or pharmacological relevance of reactions of stereoisomerisation to be emphasised. Table 1 lists these model and medicinal compounds in their order of appearance in the text and offers readers a foretaste of what this review is about.

1.2. Overview

Molecular structure and properties are key concepts in all fields of the huge discipline of chemistry. However, these concepts may not mean the same to all chemists, nor are key concepts always understood unambiguously. In the didactic perspective adopted here (Testa et al., 2007; Testa et al., 2014a), the core properties of a chemical compound are the constant ones which distinguish a given chemical entity from any other chemical entity, and whose non-reversible alteration necessarily implies a transformation into another molecular entity. As shown in Fig. 1 (left panel), the constant features of a chemical compound are the number and nature of its atoms (its composition), the connectivity of its atoms (its constitution), and its configuration (given the presence of one or more stereogenic elements). And indeed, any change in composition, constitution or configuration yields another chemical entity, namely a derivative, an analog, a constitutional isomer or a stereoisomer.

As discussed below, these core properties are contrasted with fluctuating properties, namely those molecular features which fluctuate within ranges, thus defining property spaces.

1.3. Core properties

Before proceeding, a brief reminder at configurational properties may be useful. These properties are two, enantiomerism and diastereoisomerism, their difference being sharply defined (Testa et al., 2013a). Yet the possession of these two properties is not mutually exclusive, since a given chemical entity endowed with the property of stereoisomerism may display both enantiomerism (i.e., chirality, see Mislow and Bickart, 1977) and diastereoisomerism, or just one of the two. In fact, the difference is one in relationships. Each chiral compound by definition has one, and only one enantiomer with which it shares an enantiomeric relationship. In addition, a chiral compound possessing more than one stereogenic element may also share one or more diastereoisomeric relationship(s) with its non-enantiomeric stereoisomer(s). Similarly, stereoisomers sharing one or more diastereoisomeric relationship(s) may or may not be chiral, the latter case being exemplified by cases of *cis*- and *trans*-diastereoisomerism, or (*E*)- and (*Z*)-diastereoisomerism (Testa et al., 2014b).

Discriminating between enantiomeric and diastereoisomeric relationships is crucial when investigating processes of interconversion between stereoisomeric geometries. When two enantiomeric structures interconvert, the measurable end result of the reaction at equilibrium will be an equal proportions of the two in isotropic environments, a consequence of the fact that enantiomers have identical chemical reactivity and physicochemical properties. In contrast, interconversions between diastereoisomeric geometries will lead at equilibrium to non-equal mixtures, given that diastereoisomers have different reactivities and physicochemical properties, however small the differences.

1.4. Fluctuating properties

The three core properties presented in Fig. 1 are intangible ones which do not provide a complete description of the three-dimensional (3D) structure of a molecular entity. In an inspiring writing, Prigogine has underlined the major role of fluctuations, that is to say time- and energy-dependent features and properties (Prigogine, 1978). These may be designated as forming property spaces (Kirschner and Gerhart, 2005), namely the values and ranges of the measurable and computable properties of a chemical entity. They indeed are the observable expression of the core features of the compound, and as such are influenced by its environment. Important molecular properties and features (Fig. 1)