

E/Z Isomerism Without a Double Bond – an Unusual Type of Stereoisomerism, and an Unprecedented Isomerisation in a Bicyclobutane*

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Key words An unusual kind of stereoisomerism termed *E/Z* isomerism without a double bond or generalised *E/Z* isomerism is discussed for the first time. Examples are given of pairs of synthesized and separated compounds related by this kind of isomerism (**4a/5a** and **12a/15a**), which were obtained by an unusual rearrangement of substituents on a bicyclobutane ring system. Conditions for the occurrence of generalised *E/Z* isomerism are defined.

E/Z isomerism
stereoisomerism
substituted bicyclobutanes
isomerisation
rearrangement
substituted bicyclo[1.1.0]but-1(3)-ene
thia[1.1.1]propellane

INTRODUCTION

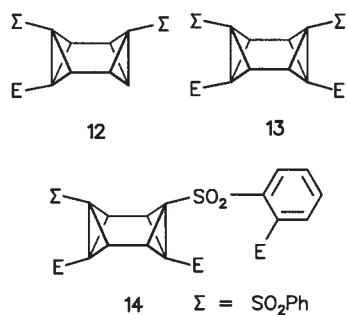
In a recent book on molecular structure the question is asked whether all causes of stereoisomerism are known, and the answer given is »probably no«. ¹ The purpose of the present article is to point to a type of stereoisomerism which (though known as a rare complication to a few specialists active in the synthesis of aliphatic polycycles)^{2–5} was widely overlooked. In particular, it is not mentioned in Eliel's book⁶ nor in any other stereochemistry text known to us. We here try to define the realm of this type of stereoisomerism, dubbed *E/Z iso-*

merism without a double bond or *generalised E/Z isomerism*, and for the first time present examples, pairs of synthesized and isolated *E/Z* isomeric compounds lacking a double bond.

Several years ago we aimed at and finally achieved the synthesis of the third and last possible saturated (CH)₈ compound, octabisvalene **1**,² the other two being cubane and cuneane.⁷ That work was motivated by the unusual and presumably highly strained nature of the octabisvalene ring system.⁸ The ring system was obtained from trisoxirane **2** by a stereocontrolled route (Scheme 1), a sequence of three epoxide opening steps and three

* This paper is dedicated to Professor Nenad Trinajstić on the occasion of his 65th birthday.

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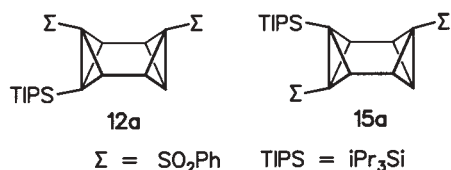
Scheme 4.

with products of type **13** and **14** two core-monosilylated bis(phenylsulfonyl)octabisvalenes are obtained, separable by HPLC on silica (20 % EtOAc in hexanes). Initially, these compounds were tentatively considered rotamers of **12a** (**12**, E = TIPS), based on their almost superimposable MS and NMR spectra.^{2c} However, on thermal activation (80 °C, 17 h) there was no sign of interconversion of these isomers, casting some doubt on their identities.¹³ Their true nature was revealed when they were treated with a solution of tetra-*n*-butylammonium fluoride in wet THF for desilylation, resulting in two silicon-free very similar compounds, separable by HPLC on silica (40 % EtOAc in hexanes). One of these proved to be the well-known **4a**, the other is assigned structure **5a** for the following evidence:

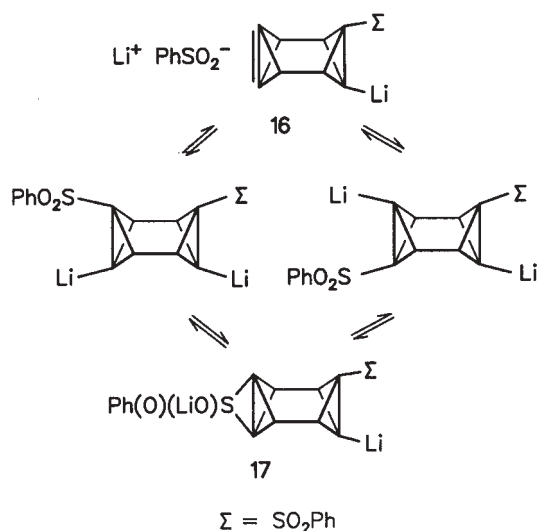
- (i) The mass spectrum is superimposable to that of **4a**;
- (ii) the ¹H NMR spectrum differs from that of **4a** only in a few small but reproducible chemical shift differences, the overall habitus and even the coupling fine structure of the core hydrogen signals being identical;¹⁴
- (iii) the ¹³C NMR spectrum differs from that of **4a** in a few small chemical shift differences only.^{14,15}

This structure assignment is corroborated by NOEs observed in the ¹H NMR spectra of the monosilylated precursors:¹⁶ In the *Z* isomer **12a** (Scheme 5), a weak NOE is observed between the TIPS hydrogen atoms and the *ortho* hydrogens of one phenylsulfonyl group. In the *E* isomer **15a**, precursor of **5a**, along with a weak NOE corresponding to the above another strong NOE is found between the TIPS hydrogen atoms and the *ortho* protons of the second phenyl ring. Further, in **12a** only another NOE between the TIPS H atoms and 8-H is observed.

The detailed mode of formation of **15a** from **4a**, ≥ 2 eq. *n*-BuLi, and TIPS-OTf awaits further study. We pro-



Scheme 5.

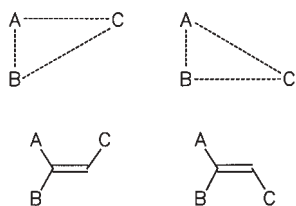


Scheme 6.

pose a »symmetrical« intermediate such as the bicyclobut-1(3)-ene **16** or the thia[1.1.1]propellane **17** (Scheme 6). Bicyclobut-1(3)-enes are known to result as short-lived intermediates from base-induced elimination of bridgehead-halosubstituted bicyclobutanes,⁴ elimination of LiO₂SPh to form cyclopropenes was observed.¹⁷ Heteroatom analogs of the well-known [1.1.1]propellanes were targets of calculations.¹⁸ The driving force for reversible formation of **16** or **17** from the 4,8-dilithio derivative of **4a** might be the cumulative effect of better separation of two negative charges and of better accommodation of a negative charge on oxygen than on carbon.

The isomerism discussed here is to be differentiated from the usual *cis/trans* isomerism observed with substituents on a ring system, e.g. *cis*- and *trans*-1,3-dichlorocyclobutane. In these isomers each chlorine atom is attached to its carbon atom in one out of two possible positions, whereas in **4** and **5** at each carbon atom there is but one possible position to be occupied by a substituent. In contrast to the 1,3-dichlorocyclobutane case, in fact the substituents in **4/5** are not even necessary for isomerism to occur, they simply label the respective C atom. Another kind of label is e.g. isotopic or heteroatomic replacement, so that 3,7-di-¹³C-octabisvalene or 3,7-diazaoctabisvalene or a 7-substituted 3-azaoctabisvalene likewise may come as two *E/Z*-isomers, though experimentally this has not yet been observed.⁵ Likewise, *E/Z* isomerism without a double bond is different from the *cis/trans* or *syn/anti* isomerism of nonaromatic ring systems, where the isomers differ in the relative steric arrangement of fused rings.

The present kind of stereoisomerism occurs in the following situation: Three geometrically well-defined positions (necessarily in one plane) are occupied by individual atoms A, B, C, such that C is not on the line perpendicular to and halfway dissecting line A-B. (C

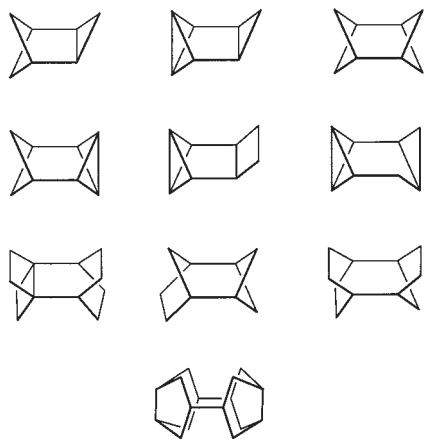


Scheme 7.

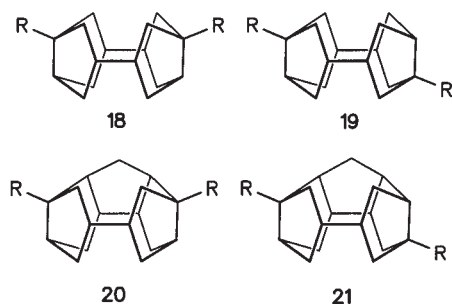
may be identical to A or B, and the triangle may be scalene.) Then there are two different rigid arrangements as shown in Scheme 7. The broken lines represent geometrical relations rather than chemical bonds. The simplest chemical framework supporting such an arrangement is a double bond, so that the common *E/Z* isomerism is a special case.

However, there are other molecular skeletons supporting such an arrangement, a few are given in Scheme 8, most taken from the hydrocarbon collection compiled by Shields,¹⁹ their similarity to the octabisvalene framework is obvious.

Two compounds derived from such a skeleton by appropriate substitution or other labeling as described above are general *E/Z* isomers unless there is another covalent linkage between the right and left molecular halves out of the plane defined by the two central bonds (which is perpendicular to the ABC plane). If there is such an addi-



Scheme 8.



Scheme 9.

tional linkage, then the compounds are constitutional isomers, see hypothetical compounds **18–21** (Scheme 9): Isomers **18** and **19** are *Z/E* isomers without a double bond and thus stereoisomers. On the other hand, **20** and **21** are constitutional isomers.²⁰ This example demonstrates that the notions of constitution and configuration are not always so clearcut as one might expect.²¹

The stringent conditions for two compounds to be generalised *E/Z* isomers explain why this phenomenon is not well-known to chemists: In many planar ABC cases there is a central double bond, resulting in the common (special) *E/Z* isomerism, in many others (polycyclics) there is an additional linkage as in **20/21**, resulting in constitutional isomerism, e.g. in substituted dodecahedranes or in fullerene adducts.

The case of a general triangle ABC in a plane resulting in generalised *E/Z* isomerism without the need for a double bond is completely analogous to the case of a general tetrahedron ABCD in 3D space resulting in enantiomerism without the need for a chiral center. In both the 2D and the 3D case stereoisomerism is not caused by the presence of a particular structural feature such as a chiral center or a double bond, but by the lack of a certain symmetry.

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10. As is well-expressed by the identical IUPAC names, the difference between **4** and **5** is not a matter of constitution, nor is it a matter of rotation about single bonds. So **4** and **5** differ in configuration, they are diastereoisomers.
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13. TIPS compounds were recently found often to be contaminated with the diisopropyl-n-propylsilyl analogs (D. J. Barden and I. Fleming, *Chem. Commun.* (2001) 2366–2367). However, the two monosilylated bis(phenylsulfonyl)octabisvalenes are not related in this manner, as proven by their NMR spectra and by the desilylation reaction.
14. ^1H NMR (CDCl_3 , 250 MHz, δ/ppm):
4a: 7.8–7.3 (10 H, arom), 3.25 (m, 1,2,5,6–H), 2.77 (m, 4,8–H).
5a: 7.96–7.55 (10 H, arom), 3.15 (m, 1,2,5,6–H), 2.79 (m, 4,8–H).
 ^{13}C NMR (CDCl_3 , 100.6 MHz, δ/ppm):
4a: 140.87, 133.34, 129.26, 126.87, 43.07, 35.27, 21.39; $^1J_{\text{C-4,H}} = 214$ Hz.
5a: 141.11, 133.42, 129.31, 127.04, 42.31, 33.16, 24.32.
15. The possibility that the isomer of **4a** is a sulfonic acid ester rather than a disulfone is excluded by its ^1H NMR spectrum. We prepared several octabisvalenesulfonates, and their ^1H NMR spectra are much more complicated due to loss of symmetry (asymmetrically substituted S atom).
16. ^1H NMR (CDCl_3 , 400 MHz, δ/ppm):
12a: 7.88–7.35 (10 H, arom), 3.05 (m, 1,6–H), 2.86 (m, 2,5–H), 2.52 (t, 8–H), 1.28–1.03 (21 H, TIPS); $J_{1,8} = 3.5$ Hz.
15a: 8.00–7.48 (10 H, arom), 3.05 (m, 1,6–H), 2.75 (m, 2,5–H), 2.57 (t, 8–H), 1.00–0.76 (21 H, TIPS); $J_{1,8} = 3.5$ Hz.
 ^{13}C NMR (CDCl_3 , 100.6 MHz, δ/ppm):
12a: 141.94, 139.78, 133.41, 133.33, 129.30, 129.25, 127.41, 126.85, 45.65, 42.22, 41.29, 36.49, 23.29, 22.18, 18.82, 11.95; $^1J_{\text{C-1,H}} = ^1J_{\text{C-2,H}} = 170$ Hz, $^1J_{\text{C-8,H}} = 212$ Hz.
15a: 142.52, 141.18, 133.41, 133.29, 129.32, 129.30, 127.80, 127.14, 42.69, 42.57, 41.15, 33.14, 27.54, 25.18, 18.62, 11.94; $^1J_{\text{C-1,H}} = ^1J_{\text{C-2,H}} = 170$ Hz, $^1J_{\text{C-8,H}} = 212$ Hz.
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20. **18** and **19** both are 4,10-disubstituted pentacyclo[8.2.1.1^{2,5}–1^{4,7}.1^{8,11}]hexadecanes, while **20** and **21** are 12,16- and 3,12-disubstituted hexacyclo[8.7.0.0^{3,16}.0^{5,15}.0^{6,13}.0^{8,12}]heptadecanes, respectively.
21. Eliel in reference 6 discusses in detail that the distinction between configuration and conformation is not clearcut.

SAŽETAK

E/Z izomerija bez dvostruke veze – neobičan primjer stereoizomerije i dosada nezabilježena izomerizacija u biciklobutanu

Christoph Rücker i Gunter Haftstein

Prikazan je po prvi puta neobičan primjer stereoizomerije nazvan stereoizomerija bez dvostruke veze ili poopćena *E/Z* izomerija. Dani su primjeri parova spojeva koji posjeduju tu izomeriju, a koji su dobiveni neobičnom predgradnjom supstituenata na biciklobutanu. Određeni su uvjeti pod kojima dolazi do poopćene *E/Z* izomerizacije.