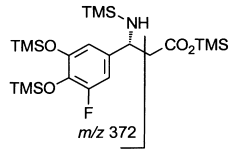
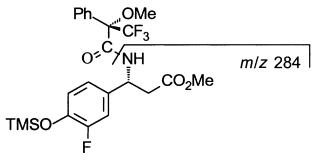
and the solvent completely removed in vacuo. The residue was dissolved in water (5 mL) and subjected to ion-exchange chromatography (Dowex 50W X8, eluent 4 N HCl) to remove the nonbasic components. The eluent was lyophilized and the residue dissolved in methanol (2 mL). In order to remove Fe^{III} ions, NaSCN (50 mg) was added. Chromatography on Sephadex LH-20 yielded 45 mg of the amino acids (0.09 % of fresh weight).

Determination of the incorporation of labeled precursors: The isolated amino acids were silylated with *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA) and subsequently analyzed by GC/MS. The incorporation of single fluoro-labeled precursors was determined by measuring the ion current of the base peak derived from **4** (*m*/*z* 372). In the case of double-labeled precursors the ion *m*/*z* 373 was used. If ^{13}C-labeled precursors were used the incorporation rates were determined by ^{13}C NMR measurements.



4

In order to determine the configuration of the derived 3-fluoro-β-tyrosine, the amino acid (0.5 mg) was esterified with methanol (0.5 mL) and Me_3SiCl (100 μL). After removal of the solvent, the residue was dissolved in pyridine (100 μL). (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid chloride (2 μL) and a catalytic amount of 4-dimethylaminopyridine (DMAP) were added, and the mixture was kept at room temperature for 12 h. The solvent was then removed and the residue treated with MSTFA (40 μL). The amino acid derivative **5** was identified by GC/MS monitoring of the ion *m*/*z* 284. Temperature program: 2 min isotherm at 50 °C, then 10 K min^{-1} to 300 °C, followed by 15 min isotherm at 300 °C. Column: fused-silica capillary column (DB-5 ms, J&W, 30 m × 0.25 mm × 0.25 μm). The Kováts indices were determined by coinjection with a mixture of straight chain saturated hydrocarbons (C_{10}–C_{36}). (2′*S*,3*R*)-**5**: GC: $R_i = 2622$; (2′*S*,3*S*)-**5:** GC: $R_i = 2649$.



(2′*S*,3*R*)-**5**

Received: March 7, 2000 [Z14815]

[1] F. von Nussbaum, P. Spiteller, M. Rüth, W. Steglich, G. Wanner, B. Gamblin, L. Stievano, F. E. Wagner, *Angew. Chem.* **1998**, *110*, 3483–3485; *Angew. Chem. Int. Ed.* **1998**, *37*, 3292–3295.

[2] The use of fluorine for labeling of biosynthetic precursors has many advantages. The label is tolerated by many enzymes, and the detection of the metabolites is very sensitive. Thus, one single fruit body of a mushroom is sufficient for determining the incorporation; see, for example: E. Leete, G. B. Bodem, M. F. Manuel, *Phytochemistry* **1971**, *10*, 2687–2692.

[3] R. J. Parry, Z. Kurylo-Borowska, *J. Am. Chem. Soc.* **1980**, *102*, 836–837.

[4] K. D. Walker, H. G. Floss, *J. Am. Chem. Soc.* **1998**, *120*, 5333–5334.

[5] D. J. Aberhart, S. J. Gould, H.-J. Lin, T. K. Thiruvengadam, B. H. Weiller, *J. Am. Chem. Soc.* **1983**, *105*, 5461–5470.

[6] P. A. Frey, *FASEB J.* **1993**, *7*, 662–670.

[7] P. C. Prabhakaran, N.-T. Woo, P. S. Yorgey, S. J. Gould, *J. Am. Chem. Soc.* **1988**, *110*, 5785–5791.

[8] I. Freer, G. Pedrocchi-Fantoni, D. J. Picken, K. H. Overton, *J. Chem. Soc. Chem. Commun.* **1981**, 80–82.

[9] J. A. Dale, L. Dull, H. S. Mosher, *J. Org. Chem.* **1969**, *34*, 2543–2549.

[10] W. Buckel, B. T. Golding, *FEMS Microbiol. Rev.* **1999**, *22*, 523–541.

[11] Review on aminomutases: P. A. Frey, C. H. Chang in *Chemistry and Biochemistry of B_{12}* (Ed.: R. Banerjee), Wiley, New York, **1999**, pp. 835–857.

[12] Review: P. A. Frey, G. H. Reed, M. L. Moss, R. M. Petrovich, M. D. Ballinger, K. W. Lieder, W. Wu, C. H. Chang, V. Banderian, F. J. Ruzicka, R. Lo Brutto, H. Beinert in *Vitamin B_{12} and B_{12} Proteins* (Eds.: B. Kräutler, D. Arigoni, B. T. Golding), Wiley-VCH, Weinheim, **1998**, pp. 435–446.

[13] J. R. Roth, J. G. Lawrence, T. A. Bobik, *Annu. Rev. Microbiol.* **1996**, *50*, 137–181.

[14] W. M. Rodionov, E. A. Postovskaja, *J. Am. Chem. Soc.* **1929**, *51*, 841–847.

[15] The feeding experiments were performed in Autumn 1998 and 1999 near Breitbrunn and Gilching in Bavaria, Germany.

Demonstration of Chiral Enantiomerization in a Four-Atom Molecule**

Paul von Ragué Schleyer* and Michael Mauksch

In 1997, we presented the first example of the enantiomerization of a chiral five-atom molecule, *cyclo*-SeSSOS, via a completely asymmetric reaction path in a single-step process.[1] Is it possible for a chiral molecule with only four atoms to enantiomerize via a chiral pathway? The answer is "no" if all four atoms are different. Oddly, the answer may be "yes" if two of the four atoms are the same.

In 1992 and 1993, Mislow et al. presented an elegant proof that fully chiral paths might be involved in the interconversion of mirror images of asymmetric (geometrically distorted) tetrahedra, *which are not fully labeled*.[2, 3] In contrast, Mislow demonstrated in 1995 that this is an exception: No path for interconverting mirror images can preserve chirality for fully labeled, three-dimensional, four-vertex simplexes.[4] These must pass through a two-dimensional boundary in order to reach the enantiomorphic forms.[5–7] Later in 1995, Mezey explained this conundrum, "Mislow's Labeling Paradox",[8, 9] by showing, in an abstract form (Figure 1), that chiral four-vertex simplexes, in which at least two identically labeled vertices can switch roles (for example, as a permutation of sites), may be transformed to their enantiomorphs on a fully asymmetric reaction path.[10] In tetraatomic molecules, such a "permutation of sites", which leads to an enantiomer, can occur only if two atoms of the same chemical element and isotope have distinguishable sites and exchange their chemical and spatial environments.

Weinberg and Mislow's 1996 dimensional analysis[11] showed that all submaximally labeled chiral simplexes are chirally connected (for example, asymmetric tetrahedrons with at least two identical atoms can be converted into their

[*] Prof. Dr. P. von R. Schleyer
Computational Chemistry Annex
University of Georgia
Athens, GA 30602-2525 (USA)
Fax: (+1) 706-542-7514
E-mail: schleyer@uga.ed

Dr. M. Mauksch
Computational Chemistry Center
Institute of Organic Chemistry
University of Erlangen-Nuremberg
91052 Erlangen (Germany)

[**] This work was supported at Erlangen by the Deutsche Forschungsgemeinschaft and the Fond der Chemischen Industrie. We thank Prof. K. Mislow (Princeton) and Prof. P. Mezey (Saskatoon, Saskatchewan) for helpful discussions.

  1433-7851/00/3915-2756 $ 17.50+.50/0

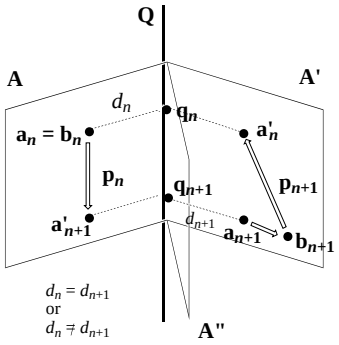
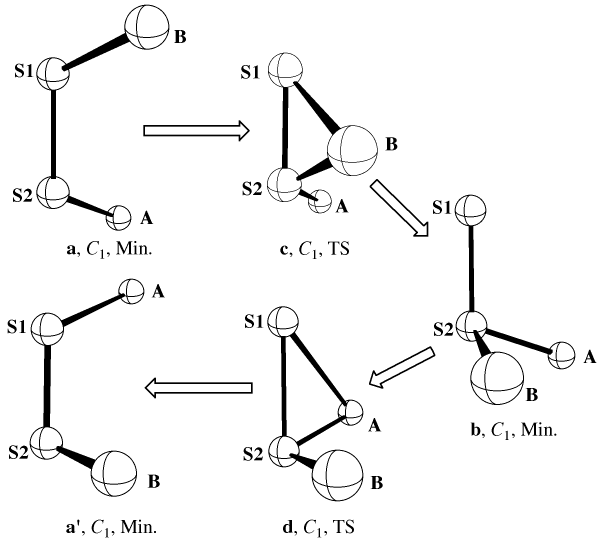


Figure 1. Illustration of the "Labeling Paradox" process, taken from ref. [8] (see therein for further details). Only if $\mathbf{a}_n = \mathbf{a}_{n+1}$ is a completely asymmetric transformation of the n-chiral $\mathbf{S} = \{\mathbf{a}_1,\mathbf{a}_2,\mathbf{a}_3,\ldots\mathbf{a}_{n-1},\mathbf{a}_n,\mathbf{a}_{n+1}\}$ into $\mathbf{S}'$ possible. The combination of $\mathbf{p}_n$ and $\mathbf{p}_{n+1}$ then constitutes the reaction coordinate for the enantiomerisation of a real molecule. The distances $\mathbf{d}_n$ and $\mathbf{d}_{n+1}$ will generally be different in actual chemical examples.

mirror image forms without encountering achiral configurations).[11] Can the abstract Mislow–Mezey solution be realized in tetraatomic molecules? Is it possible, in an intramolecular process and by purely chemical means, to exchange the sites of two atoms without transposing them? The theoretical proofs are general and do not specify the potential-energy surface (PES), that is, whether the process proceeds, for example, by one or by two steps. The independent internal motions in a two- or multistep enantiomerization should, in principle, permit the occurrence of an asymmetric path comprising different sequential steps. All instantaneous configurations on the enantiomerization path must be chiral—which includes transition states and minimum energy conformations. As discussed above, this rules out the enantiomerization of a fully labeled molecule with four different atoms (which must pass through a coplanar arrangement).

Exemplary molecular systems of the X_2AB type are easy to visualize: S_2ClF **1**, S_2BrF **2**, and S_2BrCl **3**, with branched S=SAB and linear ASSB isomers; all have the ability to enantiomerize in two steps via fully asymmetric paths (Scheme 1 and Table 1). The unimolecular chiral process can take place by two consecutive 1,2-halogen shifts through C_1 transition states (TS) **c** and **d** (Scheme 1).[12] The two asymmetric enantiomerization itineraries have different initial stages (enantiomers are denoted by primes; Scheme 2): **a** → **c** → **b** → **d** → **a′** and **a** → **d′** → **b′** → **c′** → **a′**.[13] Mezey's "role switch" of identical atoms takes place because the mono- and tricoordinate sulfur atoms S1 and S2 in **a** (Scheme 1) have exchanged their role in the enantiomers **a′**. These simple S_2AB systems illustrate that chiral enantiomerizations in tetraatomic molecules are possible.

However, these examples have practical drawbacks in experimental realization. Our computations (Table 1) confirm expectations based on earlier results[14] on related systems, that achiral pathways may be more favorable. Indeed, planar transition states with *cis*- (**1e**–**3e**) and with *trans*-configurations (**1f**–**3f**), as well as those that involve inversion at one sulfur center (TS **g**), are prefered energetically over the asymmetric paths involving **c** and **d** (Scheme 2). The energies of **c** and **d** are not lowered below those of **e**–**g** with the heavier halogens (Table 1).

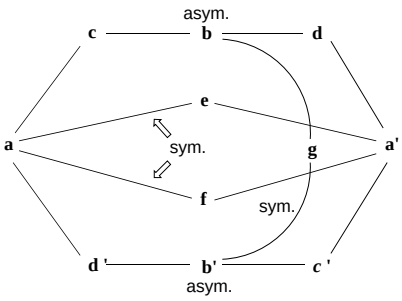


Scheme 1. Schematic representation of the S_2AB structures **a**–**d** involved in the enantiomerization of **1a**,**b**–**3a**,**b** (**1**: A = Cl, B = F; **2**: A = Br, B = F; **3**: A = Br, B = Cl). The S–S bonds are always in the paper plane. For relative energies, see Table 1.

Table 1. Zero-point energy (ZPE) corrected relative energies E_{rel} of S_2AB species at the B3LYP/6-31G* level. The stationary points of S_2F_2 at the same level of theory are included for comparison.

Structure, point group	Nature of the stationary point[a]	E_{rel}[b] [kcal mol^{-1}] S_2ClF **1**	S_2BrF **2**	S_2BrCl **3**	S_2F_2 **4**
a, C_1	Min.	0.0	0.0	0.0	0.0 (C_2)[c]
b, C_1	Min.	9.8	8.8	14.6	0.1 (C_s)
c, C_1	TS	45.3 (Cl)[d]	54.4 (F)	39.4 (Cl)	49.6 (C_1)
d, C_1	TS	36.6 (F)	36.4 (Br)	40.1 (Br)	–
e, C_s	TS	24.9	21.7	18.8	25.7 (C_{2h})
f, C_s	TS	21.6	19.3	15.7	–
g, C_s	TS	36.5	37.5	36.5	33.7 (C_{2v})

[a] Based on vibrational analysis at the B3LYP/6-31G* level. [b] With respect to the (most stable) 1,2-isomers **1a**–**3a**. [c] The point groups in parenthesis refer to S_2F_2 alone. [d] Migrating atom.



Scheme 2. Possible reaction paths in the intramolecular enantiomerization of **1a**,**b**–**3a**,**b**. Two asymmetric (asym.) and three symmetric (sym.) alternatives exist. For relative energies, see Table 1.

The ClSSCl[15] and BrSSBr[16, 17] forms are well known experimentally.[18] The thio-thionyl isomers S=SCl_2 and S=SBr_2 are much less stable (Table 1) but there is at least experimental evidence for S=SCl_2.[19] In contrast, S=SF_2 is -2.7 ± 0.4 kcal mol^{-1} [20a] more stable than the corresponding FSSF isomer.[20] Experimentally, FSSF isomerizes slowly to S=SF_2 above $-100\,^{\circ}C$,[21] which indicates a much lower

activation barrier than the 40 – 60 kcal mol^{-1} computed for the TS of the intramolecular isomerization at various levels (such as 46.1 kcal mol^{-1} at the B3LYP/6-311 + + G(3df) level[22a]).[22, 23] However, according to Seel, Budenz, and Werner,[21] a bimolecular complex [FSSF · S=SF_2]$_{(g)}$ forms at temperatures below − 80 °C; this suggests that the actual isomerisation mechanism may not be unimolecular. Possible associative or dissociative mechanisms[14, 21] would complicate experimental studies of these systems further.

Density functional theory seems to overestimate somewhat the relative stability of the C_2 (FSSF) over the C_s (S=SF_2) conformer (Table 1).[23] In contrast, the C_s form is preferred over the C_2 form by 3.0 kcal mol^{-1} at the MP4(SDTQ)/6-311G(2d)//MP2/6-311G(2d) level (including zero-point energy corrections at the MP2/6-31G* level),[23] which agrees well with the experimental value.[20a] At the same (MP4(SDTQ)) level of theory, the FSSF → S=SF_2 isomerization barrier is 46.6 kcal mol^{-1}, which is close to the value calculated at the B3LYP/6-311 + + G(3df) level.[22a] Hence, we believe that the use of density functional theory in this paper is justified.

Measurements of the He-I photoelectron spectra of a S=SF_2 sample at two different temperatures gave a first-order rate law with an activation barrier of 24.1 kcal mol^{-1} for an alleged S=SF_2 → FSSF isomerization (with reversed order of stability!).[24] However, our computation of the vertical ionization potentials for S=SF_2, FSSF, and SF_4 suggested the occurrence of a disproportionation 2 S=SF_2 → ⅜ S_8 + SF_4 rather than the purported isomerization.[25]

To conclude, we have shown the feasibility of "Mislow's Labeling Paradox" in molecular systems. However, other achiral paths are lower in energy for the illustrative cases reported here. A remaining challenge is in the identification of tetraatomic systems comprised of a different set of elements, which enantiomerize preferentially via unimolecular asymmetric rather than achiral paths, as well as the demonstration of a single step example. Other enantiomerizations might involve a similar "role switch".

Received: December 10, 1999
Revised: March 6, 2000 [Z12767]

[1] M. Mauksch, P. von R. Schleyer, *Angew. Chem.* **1997**, *108*, 1976; *Angew. Chem. Int. Ed. Engl.* **1997**, *108*, 1856.
[2] K. Mislow, P. Poggi-Corradini, *J. Math. Chem.* **1993**, *13*, 209.
[3] A. B. Buda, K. Mislow, *J. Am. Chem. Soc.* **1992**, *114*, 6006.
[4] K. Mislow, *Proceedings of the 6th International Conference on Mathematical Chemistry* (Pitlochry, Scotland), **1995**.
[5] P. G. Mezey, *J. Math. Chem.* **1995**, *17*, 185.
[6] K. Mislow in *Fuzzy Logic in Chemistry* (Ed.: D. H. Rouvray), Academic Press, New York, **1996**.
[7] The two-dimensional boundary thus splits the three-dimensional space into two subsets containing the enantiomorphs. Maximally labeled simplexes (for dimensions greater than two) can therefore be partitioned into heterochiral subsets, identified as *R* and *L*.[6]
[8] a) P. G. Mezey, *J. Math. Chem.* **1995**, *18*, 133; b) P. G. Mezey, *Chirality* **1998**, *10*, 173.
[9] P. Mezey, *Proceedings of the 6th International Conference on Mathematical Chemistry* (Pitlochry, Scotland), **1995**.
[10] Mezey stated: "By allowing an exchange of roles between points of equivalent labels, an abandoning of the unique labeling … provides additional chances for a deformed point set to become the mirror image of its original *n*-chiral arrangement."[8a]
[11] N. Weinberg, K. Mislow, *Theor. Chim. Acta* **1997**, *95*, 63.
[12] Simultaneous 1,2-migrations of both halogens are much higher in energy (93.1 (**1**), 92.6 (**2**), and 78.7 kcal mol^{-1} (**3**)); the pertinent stationary points have two imaginary frequencies.
[13] In a private communication, Mezey remarked: "These two enantiomeric paths constitute a closed chiral loop on the potential surface. Such circular processes allows one to make predictions on the presence of critical points of both ground and excited state potential energy surfaces." See also: P. G. Mezey, *J. Am. Chem. Soc.* **1990**, *112*, 3791.
[14] a) R. S. Steudel, Y. Drozdova, K. Miaskiewicz, R. H. Hertwig, W. Koch, *J. Am. Chem. Soc.* **1997**, *110*, 1980; b) Y. Drozdova, K. Miaskiewicz, R. S. Steudel, *Z. Naturforsch. B* **1995**, *50*, 889.
[15] a) R. D. Brown, F. R. Burden, G. P. Pez, *J. Chem. Soc. Chem. Commun.* **1965**, 277; b) E. Hiruta, *Bull. Chem. Soc. Jpn.* **1958**, *31*, 130.
[16] a) R. D. Brown, G. P. Pez, *Aust. J. Chem.* **1967**, *20*, 2305; b) R. D. Brown, G. P. Pez, M. F. O'Dwyer, *Aust. J. Chem.* **1965**, *18*, 627.
[17] F. Seel, *Chimia* **1968**, *22*, 79.
[18] R. Kniep, L. Koorte, D. Z. Mootz, *Z. Naturforsch. B* **1983**, *38*, 1.
[19] a) M. Feuerhahn, G. Vahl, *Chem. Phys. Lett.* **1979**, *65*, 322; b) G. Holzmann, M. Feuerhahn, R. Minkwitz, G. Vahl, *J. Chem. Res. Synop.* **1980**, 71; c) B. M. Chadwick, J. M. Crzybowski, D. A. Long, *J. Mol. Struct. (THEOCHEM)* **1978**, *48*, 139.
[20] a) O. Lösking, H. Willner, H. Baumgaertel, H. W. Jochim, Z. Rühl, *Z. Anorg. Allg. Chem.* **1985**, *530*, 169; b) C. J. Marsden, H. Oberhammer, O. Lösking, H. Willner, *J. Mol. Struct. (THEOCHEM)* **1989**, *193*, 233; c) A. Haas, H. Willner, *Spectrochim. Acta A* **1979**, *35*, 953.
[21] F. Seel, R. Budenz, D. Werner, *Chem. Ber.* **1964**, *97*, 1369.
[22] a) B. S. Jursic, *J. Comput. Chem.* **1996**, *17*, 835; b) M. Torrant, M. Duran, M. Sola, *J. Mol. Struct. (THEOCHEM)* **1996**, *362*, 163.
[23] F. M. Bickelhaupt, M. Sola, P. von R. Schleyer, *J. Comput. Chem.* **1995**, *16*, 445, and references therein.
[24] Ionization peaks characteristic of the alleged product FSSF could not be found in the reported PES spectrum; SF_4 peaks appear instead. Hence, we regard this work as highly questionable: X. Y. Cao, X. M. Qian, C. H. Qiao, D. X. Wang, *Chem. Phys. Lett.* **1999**, *299*, 322.
[25] SSF_2 disproportionates rapidly in the presence of acid catalysts (for example, HF or BF_3), see: M. V. Carlowitz, H. Oberhammer, H. Willner, J. E. Boggs, *J. Mol. Struct. (THEOCHEM)* **1983**, *100*, 161.

1,3-Stereoinduction in Radical Reactions

Ahlke Hayen, Rainer Koch, and Jürgen O. Metzger*

Dedicated to Professor Gerhard Zimmermann on the occasion of his 70th birthday

The possibility of steering the stereoselectivity of the trapping reactions of acyclic radicals possessing a stereogenic center in the 3-position is of great importance, both with respect to the synthesis of natural products bearing stereogenic centers in the 1,3-position and to the free radical polymerization of vinyl monomers. However, most radical polymerizations are more or less unselective,[1a] with the exception of a few sterically highly demanding methacrylates.[2] On the other hand it has been shown during the last few years that acyclic radicals can react with high stereoselectivity;[1, 3] the addition of Lewis acids has proved to be

[*] Prof. Dr. J. O. Metzger, Dipl.-Chem. A. Hayen, Dr. R. Koch
Fachbereich Chemie der Carl-von-Ossietzky Universität Oldenburg
Carl-von-Ossietzky-Strasse 9 – 11, 26129 Oldenburg (Germany)
Fax: (+49) 441-798-33-29
E-mail: juergen.metzger@uni-oldenburg.de

  1433-7851/00/3915-2758 $ 17.50+.50/0