COMMENTARY

Terminology Related to the Phenomenon 'Self-Disproportionation of Enantiomers' (SDE)

by **Vadim A. Soloshonok***[a])[b]) and **Karel D. Klika***[c])

[a]) Department of Organic Chemistry I, Faculty of Chemistry, University of the Basque Country UPV/EHU, ES-20018 San Sebastián
(phone: +34943-015177; fax: +34943-015270; e-mail: vadym.soloshonok@ehu.es)
[b]) IKERBASQUE, Basque Foundation for Science, ES-SP48011 Bilbao
[c]) Molecular Structure Analysis, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, DE-69009 Heidelberg (phone: +496221-424515; e-mail: klikakd@yahoo.co.uk)

Terms related to the phenomenon *self-disproportion of enantiomers* (SDE) are discussed, particularly with respect to recently suggested alternative terms. Of the numerous terms proffered to describe this phenomenon, it is recommended that the acronym SDE be retained based on its qualities and the fact that its perceived shortcomings are invalid. The term can be readily applied to any process that exhibits the phenomenon of transforming a scalemic sample into fractions containing different enantiomeric compositions in comparison to the enantiomeric composition of the starting sample, and is not restricted solely to chromatographic occurrences. Chromatographic observations, though, can be specifically described by the term *enantiomer self-disproportionation over achiral chromatography* (ESDAC). Use of the term *homochiral* in concert with its intended original meaning is also advocated.

1. Preamble. – The introduction of a new scientific terminology carries with it a deceptive amount of responsibility, as it affects the understanding, appreciation, development, and application of natural phenomena. On the other hand, there is not, and will never be, 'perfect' terminology as a result of subjectivity stemming from the multicultural and multilinguistic structure of the contemporary scientific community. What might make sense in one language may sound atrocious in another. Linguistically, the primary role of scientific terminology is to convey the concept in a short, concise, readily understandable, and efficient manner. Thus, the revision of established scientific terms is an inherently unappreciated endeavor, as it often only results in additional terms with consequent confusion and divisions between scientists supporting old *vs.* new terminology. Within the realm of stereochemistry, notorious examples of terminology include *asymmetric synthesis*, *chiral HPLC*, and *optical purification*, all of which are totally incorrect 'infelicitous nomenclature' according to the authoritative opinion of *Eliel* [1]. However, all these terms are in current use in organic chemistry and will continue to be so. Nevertheless, attempts to correct perceived deficiencies in terminology will persist due to cultural and language-biased preferences. This commentary was prompted by the recent review by *Martens* and *Bhushan* [2] in which they claimed shortcomings for the term *self-disproportionation of enantiomers* (SDE).

We feel compelled to express our opposition to the opinion of *Martens* and *Bhushan* [2] in that it is a misconception of the term and wish to take this opportunity to emphasize the rational linguistic design of the term and its true multidisciplinary nature which is not confined solely to 'achiral chromatography'. The area of SDE is currently undergoing tremendous growth, and we believe that misrepresentation can be detrimental to its development and, therefore, must be corrected.

2. Introduction to SDE. – The differences in the crystallographic structures adopted by mixtures of enantiomers or by single enantiomers result in different physicochemical properties such as melting point, density, and solubility that have been long known [3][4] and are enunciated as *Wallach*'s rule. Such differences are the quintessential basis for enantiomeric purification by fractional crystallization. In the minds of most chemists, fractional crystallization stands alone as a unique and extremely useful method for obtaining enantiomerically pure samples of a chiral compound from a scalemic mixture (scalemate [5]). The use of fractional crystallization for enantiomeric purification has been well reviewed [6].

However, fractional crystallization is not the only process known to effect perturbation of the enantiomer distribution within a sample when applied to a scalemate. There are other physical processes which, when applied to a scalemate under conditions lacking any imposed chirality, *e.g.*, by the use of a chiral selector [5] (CS), chiral stationary phase (CSP), or chiral mobile phase (CMP), other than the intrinsic chirality of the sample itself arising from the uneven contents of the enantiomeric components, can also transform the sample into fractions containing different proportions of the enantiomers in comparison to the enantiomer composition (ec) [7] of the starting sample. Numerous accounts have reported this phenomenon to occur *via* ultracentrifugation [3][8], achiral chromatography [9][10], sublimation [11], and even by distillation [12], and the various reports have been well-reviewed [2][13]. These processes can be categorized as dependent on: *1*) the response to mechanical, gravitational, or other external forces; *2*) phase transition (crystallization, sublimation, and distillation); and *3*) the application of chromatographic processes. For each of these three categories, the underlying mechanisms responsible for the phenomenon are different. Furthermore, in the case of phase transition, each has its own unique mechanism distinct from the other two. Despite the physicochemical, physical, and mechanistic differences, all these phenomena lead to the same result, *viz.* the obtainment of enantiomerically enriched and enantiomerically depleted fractions compared with the starting sample.

3. Rational Design of the Term SDE. – Naturally, researchers, reporting their observations, have used a variety of terminologies to describe for what is essentially the same outcome. For example, a multitude of terms have been proposed [2][9] to refer to the occurrence of the phenomenon under chromatographic processes, and these include *enantiomeric enrichment on achiral-phase chromatography*, *self-amplification of optical activity*, *amplification of optical purity*, *enantiomer differentiation*, *auto-separation of enantiomers*, *separation of excess enantiomer*, *enantiomeric enrichment*, *optical purification*, *solute–solute interactions of enantiomers*, *chiral amplification*, *auto-resolution*, *enantiomer differentiation by enantiomeric enrichment*, *optical fractio-*

nation, *self-induced enrichment of enantiomers*, *enantiomeric modification*, *fractionalization of enantiomers*, and *self-segregation of enantiomeric associates.* It is almost as if anyone who has observed the phenomenon has come up with his (her) own terminology to describe the event. Some of these terms are quite unwieldy, and some are indeed inaccurate, and, most disconcertingly, misleading and unscientific implying 'chirogenic' properties, *i.e.* generation of chirality. Needless to say, the plethora of terms is obviously an unwelcome state and reflect clear misunderstanding of the observed phenomena. The commonality of the various processes, of course, is that they all lead to the same general result, that of obtaining enantiomerically enriched and enantiomerically depleted fractions in comparison to the starting sample in the absence of an external stereogenic influence. Rational consideration of this point from a standpoint of standard English suggests that the term *disproportionation* might be apt to describe this differentiation in enantiomer proportions between the initial and various final states. It also leads naturally to the phrase *disproportionation of enantiomers.* Moreover, considering the fact that such disproportionation can occur spontaneously, *e.g.*, in the case of open-air sublimation, and its rate cannot be controlled, the term *self* can also be pre-appended to emphasize the spontaneous feature of these phenomena. Consequently, the term *self-disproportionation of enantiomers* has been rationally designed for the description of these seemingly unrelated natural phenomena [9].

Disconcerting to some, however, the term *disproportionation* is already used in chemistry, *e.g.*, for a change in oxidation state, and, therefore, its appropriateness, and indeed meaning, has been questioned [2]. The first report [14] of disproportionation with respect to a change in oxidation state was for the reaction

$$2 \times \mathrm{Sn}^{2+} \rightarrow \mathrm{Sn}^{4+} + \mathrm{Sn}^{0}$$

by the Turkulainen chemist *Johan Gadolin*. The Old Swedish word used to describe the phenomenon, *söndring*, does not translate well into English; 'disruption' or 'breaking' are the best transliterations but do not convey the meaning aesthetically. Perhaps it is unsurprising that a new word was invented to describe the phenomenon in English. However, a reallocation of oxidation states is not the only chemical rearrangement for which the term *disproportionation* is used, it is also applied to changes in radical states [15], as well as for the acid-base disproportionation for amphiprotic substances [16]. Thus, its use is actually more general than might initially be considered.

4. Criticism. – In their fine and timely review, *Martens* and *Bhushan* [2] also succinctly highlighted the perennial problem of terminology related to the phenomenon under discussion. However, we take exception to two points raised by *Martens* and *Bhushan* [2], regarding the use of the established term *homochiral* with respect to its use generally, as well as in conjunction with other terms, and the invention of the term *self-disproportion of enantiomers* to describe the phenomenon, both in the original paper [9] and a number of subsequent papers [17][18].

First, the basis for their objection is that the term *disproportionation* '*refers to the situation or a reaction in which the molecules formed as a result of disproportionation are* *chemically different from the starting molecules. Thus, the term* 'self-disproportionation of enantiomers' *does not accord to the* language of chemistry *practiced and followed, as mentioned above, particularly because, at no stage, chemical disproportionation occurs in the proposed phenomenon of SDE; the chemical nature and composition of the starting molecules and the* products *(the enantiomers after separation) remain the same*' *[2]*. *Martens* and *Bhushan* [2] recommended that the term *self-segregation of enantiomeric associates* be applied instead, though they did not indicate if this term is for the phenomenon under any circumstances, *e.g.*, gravitational or other external forces or phase transition, or is to be restricted solely to processes involving chromatography.

5. Rebuttal. – It is worth noting that the term *disproportionation* is simply the noun formed from the adjective *disproportionate*, a word in standard English, and is used to describe a state or situation that is 'out of proportion'. Since fractions obtained after an SDE event are 'out of proportion' to their original composition, they could thus be described as disproportionate in any case, and the occurrence of such an event could, therefore, be described as a disproportionation. Which, although not synonymous with the act of separating something (segregating), the two concepts are nearly synonymous, the former referring to the result alone, while the latter refers to the process, together with the ensuing result being implicit.

While it is welcome that *Martens* and *Bhushan* [2] present within their review a compendium of terminology to highlight the problem of multiple terms, and even consider alternatives if they feel the current ones on offer are inadequate, we view their criticism digressive mainly due to a problem of language, since the terms *segregate* and *proportionate* have similar meanings. We fail to see why reservation should be given to the term *disproportionation*, because it has been used elsewhere in chemistry as there can be no source of confusion. Indeed, as used in this context, its meaning is effectively congruent – though there is no change in the chemistry for each molecule, the sample composition certainly has changed. However, in this case, there is an already established term, *self-disproportion of enantiomers*, so why unnecessarily complicate the issue with an additional term? What exactly does the new term offer? We also wish to point out that the phrase '*incompatible with the language of chemistry*' can only be used when in direct contravention of defined terms or the concepts of chemistry. The term SDE does neither. There is no officially accepted definition for the phenomenon (*IUPAC* does not have any recommendations on SDE), but what is widely used and recognized should be accepted, unless there are genuine problems; there are no such problems, and, as a consequence, we recommend to retain the term SDE.

As an aside, the term *enantiomer self-disproportionation over achiral chromatography* (ESDAC) is sometimes used in place of SDE explicitly for chromatography [17–19]. Bizarrely, the acronym ESDAC has been attributed independently by two authors [17][19] to *Soloshonok* [9], though he never actually coined the term and preferred the general phrase *self-disproportionation of enantiomers* (hence, SDE as it is now commonly referred to, though *Soloshonok* [9] himself did not use the acronym in his seminal article) or *enantiomer self-disproportionation* (hence, the 'ESD' in ESDAC). *Soloshonok* did compound, however, the former with the phrase *on achiral-phase* *chromatography* as his description of the SDE phenomenon by chromatography. SDE is a general term and can refer to any process exhibiting the phenomenon, while ESDAC is obviously explicit for chromatography. Though the term ESDAC is not really required, it does nevertheless seem to be in common use.

With respect to the use of the term *homochiral* and its use by *Soloshonok* [9] in phrases such as *homochiral species* and *homochiral associations*, it is used precisely in accordance with its originally conceived meaning [20] [21] as introduced by *Lord Kelvin* [22]. At no time was it used to refer to the enantiomer composition of the sample or of any subsequent fraction which would be in contravention of the intended meaning [20] [21] as claimed by *Martens* and *Bhushan* [2]. The use of the term *homochiral* should be reserved [20] for '*… the stereochemical relationship between molecules (or between substituents, moieties,* etc.*, within a molecule) that have the same sense of chirality*'. *Soloshonok* [9] is fully compliant with this notion by describing dimeric or higher-order associates as homochiral species, when the constituent molecules have the same sense of chirality, and, conversely, as heterochiral species, when they have different senses of chirality. *Martens* and *Bhushan* [2] suggested instead the terms *homoenantiomeric associates* and *heteroenantiomeric associates*, respectively, in place of *homochiral species* and *heterochiral species*. Again, we fail to see not only the problem with the terms *homochiral species*, *etc.*, but also any advantage that the proposed new terms offer. We, therefore, duly recommend retaining the terms *homochiral*, and *heterochiral,* and any compounded phrases of which they are a part, when used in concert with the originally intended meanings.

6. Conclusions. – It is clear that a number of the previously suggested terms for the SDE phenomenon are unwieldy, but the SDE description is catchy, relatively short (as complete words rather than the acronym), meaningful, readily understandable, and in common use. It is also probably the most widespread of all the terms on offer. It seems, therefore, unnecessary to recommend the introduction of a replacement term, both because it is not apparent what the replacement term has to offer more than SDE, and because there is no valid identifiable deficiency in the term SDE. The term can readily be applied to any process, *e.g.*, gravitational or other external forces, phase transition, or chromatography, that exhibits the phenomenon of transforming a scalemic sample into fractions with different enantiomer compositions in comparison to the ec of the starting sample and is not restricted solely to chromatographic occurrences. Chromatographic events, though, can be specifically described by the term ESDAC if desired; similarly, we suggest the use of SDE-crystallization, SDE-sublimation, and so on, to convey the particular physical process giving rise to manifestation of the SDE phenomenon.

Similar sentiments are held for terms such as *homochiral species*, *etc.* In summary, the argument is not that we should make all terminology 'accurate', certainly it should be precise and clear in meaning, but unnecessary amendments otherwise are neither beneficial nor required. Though inaccurate terms are best avoided, once entrenched, if they are not problematic, then the effort to replace them may outweigh any benefit of doing so if their perceived transgressions are inconsequential. However, regarding the introduction of additional superfluous or redundant terms, certainly this is unwelcome and is best avoided.

V.A.S. is grateful to Prof. *Dennis P. Curran*, Distinguished Service and Bayer Professor (University of Pittsburgh, Pittsburgh, Pennsylvania) for inspiring discussions and suggestions in developing the term *self-disproportionation of enantiomers*.

REFERENCES

[1] E. L. Eliel, *Chirality* **1997**, *9*, 428.

[2] J. Martens, R. Bhushan, *Helv. Chim. Acta* **2014**, *97*, 161.

[3] C. Pratt Brock, W. B. Schweizer, J. D. Dunitz, *J. Am. Chem. Soc.* **1991**, *113*, 9811.

[4] O. Wallach, *Liebigs Ann. Chem.* **1895**, *286*, 90.

[5] K. D. Klika, *Int. J. Org. Chem.* **2012**, *2*, 224.

[6] F. Faigl, E. Fogassy, M. Nógrádi, E. Pálovics, J. Schindler, *Org. Biomol. Chem.* **2010**, *8*, 947.

[7] R. E. Gawley, *J. Org. Chem.* **2006**, *71*, 2411; H. B. Kagan, *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 203.

[8] Y. Mastai, A. Völkel, H. Cölfen, *J. Am. Chem. Soc.* **2008**, *130*, 2426.

[9] V. A. Soloshonok, *Angew. Chem., Int. Ed.* **2006**, *45*, 766.

[10] R. M. Carman, K. D. Klika, *Aust. J. Chem.* **1991**, *44*, 895; K. Tateishi, S. Tsukagoshi, T. Nakamura, S. Watanabe, V. A. Soloshonok, O. Kitagawa, *Tetrahedron Lett.* **2013**, *54*, 5220; A. E. Sorochinsky, T. Katagiri, T. Ono, A. Wzorek, J. L. Aceña, V. A. Soloshonok, *Chirality* **2013**, *25*, 365; J. L. Aceña, A. E. Sorochinsky, T. Katagiri, V. A. Soloshonok, *Chem. Commun.* **2013**, *49*, 373; T. Nakamura, K. Tateishi, S. Tsukagoshi, S. Hashimoto, S. Watanabe, V. A. Soloshonok, J. L. Aceña, O. Kitagawa, *Tetrahedron* **2012**, *68*, 4013; V. A. Soloshonok, D. O. Berbasov, *Chim. Oggi/Chem. Today* **2006**, *24*, 44; V. A. Soloshonok, D. O. Berbasov, *J. Fluor. Chem.* **2006**, *127*, 597.

[11] R. Tonner, V. A. Soloshonok, P. Schwerdtfeger, *Phys. Chem. Chem. Phys.* **2011**, *13*, 4161; R. Tonner, V. A. Soloshonok, P. Schwerdtfeger, *Phys. Chem. Chem. Phys.* **2011**, *13*, 811; H. Ueki, M. Yasumoto, V. A. Soloshonok, *Tetrahedron: Asymmetry* **2010**, *21*, 1396; M. Yasumoto, H. Ueki, V. A. Soloshonok, *J. Fluor. Chem.* **2010**, *131*, 540; M. Yasumoto, H. Ueki, T. Ono, T. Katagiri, V. A. Soloshonok, *J. Fluor. Chem.* **2010**, *131*, 535; M. Albrecht, V. A. Soloshonok, L. Schrader, M. Yasumoto, M. A. Suhm, *J. Fluor. Chem.* **2010**, *131*, 495; S. Tsuzuki, H. Orita, H. Ueki, V. A. Soloshonok, *J. Fluor. Chem.* **2010**, *131*, 461; M. Yasumoto, H. Ueki, V. A. Soloshonok, *J. Fluor. Chem.* **2010**, *131*, 266; V. A. Soloshonok, H. Ueki, M. Yasumoto, S. Mekala, J. S. Hirschi, D. A. Singleton, *J. Am. Chem. Soc.* **2007**, *129*, 12112; V. A. Basiuk, T. Y. Gromovoy, A. A. Chuiko, V. A. Soloshonok, V. P. Kukhar, *Synthesis* **1992**, 449.

[12] B. Koppenhoefer, U. Trettin, *Fresenius Z. Anal. Chem.* **1989**, *333*, 750; T. Katagiri, C. Yoda, K. Furuhashi, K. Ueki, T. Kubota, *Chem. Lett.* **1996**, *25*, 115.

[13] J. Han, D. J. Nelson, A. E. Sorochinsky, V. A. Soloshonok, *Curr. Org. Synth.* **2011**, *8*, 310; V. A. Soloshonok, C. Roussel, O. Kitagawa, A. E. Sorochinsky, *Chem. Soc. Rev.* **2012**, *41*, 4180; A. E. Sorochinsky, J. L. Aceña, V. A. Soloshonok, *Synthesis* **2013**, *45*, 141.

[14] J. Gadolin, *K. Sv. Vet. Acad. Handl.* **1788**, 186; J. Gadolin, *Crells Chem. Annalen* **1790**, *I*, 260; P. Pyykkö, O. Orama, *Nouveau J. Chimie/New J. Chem.* **1988**, *12*, 881.

[15] M. J. Gibian, R. C. Corley, *Chem. Rev.* **1973**, *73*, 441; H. Fischer, *Chem. Rev.* **2001**, *101*, 3581; K. Matyjaszewski, J. Xia, *Chem. Rev.* **2001**, *101*, 2921.

[16] J. B. Clarke, J. W. Hastie, L. H. E. Kihlborg, R. Metselaar, M. M. Thackeray, *Pure Appl. Chem.* **1994**, *66*, 577; P. Muller, *Pure Appl. Chem.* **1994**, *66*, 1077.

[17] V. Nieminen, D. Y. Murzin, K. D. Klika, *Org. Biomol. Chem.* **2009**, *7*, 537.

[18] K. D. Klika, M. Budovská, P. Kutschy, *J. Fluor. Chem.* **2010**, *131*, 467; K. D. Klika, M. Budovská, P. Kutschy, *Tetrahedron: Asymmetry* **2010**, *21*, 647.

[19] V. Schurig, *J. Chromatogr. A* **2009**, *1216*, 1723.

[20] J. Gal, *J. Chromatogr. A* **1998**, *829*, 417.

[21] J. Gal, *Enantiomer* **1998**, *3*, 263; E. L. Eliel, S. H. Wilen, L. N. Mander, 'Stereochemistry of Organic Compounds', Wiley-Interscience, New York, 1994, pp. 1191–1210.

[22] Lord Kelvin (W. Thomson), 'Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light', C. J. Clay and Sons, London, 1904, p. 619 (The lectures were presented in 1884 and 1893 at Johns Hopkins University, Baltimore, MD, USA).

Received April 6, 2014