Isotopomers and Isotopologues: The History behind the Confusion

Stefan Stoll

Physical Chemistry Laboratory, ETH Zurich, 8093 Zurich, Switzerland, stefan.stoll@phys.chem.ethz.ch

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Abstract: The definitions, the history and the usage of the two terms *isotopologues* and *isotopomers* are discussed and didactical examples are presented.

What's in a name?

William Shakespeare, *Romeo and Juliet*, II-2

Introduction

How would one define the relationship between H_2O and D_2O? What is the relationship between CH_2DOH and CH_3OD? Both pairs consist of molecules with the same number of atoms of each element, but they clearly differ in isotopic substitution [1]. Students often use the terms *isotopes*, *labeled molecules*, or *isomers* indiscriminately to speak about such molecules. Rarely do they use their knowledge of organic stereochemical concepts to find more appropriate names. However, they usually immediately agree that the molecules in the two pairs have different relationships. The molecules in the first pair differ in molecular mass, and it is evident that they can have different physical and chemical properties; for example, they would give rise to two separate molecular peaks in a mass spectrum. The density of D_2O is about 10% larger than the density of H_2O, and the melting points at one atmosphere differ by almost 4 K [2]. The species in the second pair have identical molecular mass, but they are constitutionally different and can exhibit slightly different chemical behavior.

Definitions

Nowadays, the two relationships are given two different names, although these still have to find their way into all textbooks on mass spectrometry and stereochemistry. H_2O and D_2O are called *isotopologues* of each other, and the other two are *isotopomers*. Here are the current IUPAC definitions [3]:

Isotopologue: A molecular entity that differs only in isotopic composition (number of isotopic substitutions), for example, CH_4, CH_3D, CH_2D_2.

Isotopomer: Isomers having the same number of each isotopic atom but differing in their positions. The term is a contraction of "isotopic isomer." Isotopomers can be either constitutional isomers (e.g., $CH_2DCH{=}O$ and $CH_3CD{=}O$) or isotopic stereoisomers (e.g., (*R*)- and (*S*)-CH_3CHDOH or (*Z*)- and (*E*)-$CH_3CH{=}CHD$).

Isotopomers have the same molecular mass, whereas isotopologues do not. In a mass spectrum, isotopologues form separate peaks, each possibly containing several isotopomers [4].

History

It is instructive to follow the constituents of the two terms back to their first appearance in the chemical literature. Their originators all made it explicit that these are indeed new terms.

Two atomic nuclei are isotopes if they have the same number of protons, but different number of neutrons. This word seems to have been created by Frederic Soddy in 1913 [5] as reported in his 1921 Chemistry Nobel Lecture on "The origins of the conceptions of isotopes" [6]:

The same algebraic sum of the positive and negative charges in the nucleus, when the arithmetic sum is different, gives what I call "isotopes" or "isotopic elements", because they occupy the same place in the periodic table. They are chemically identical, and save only as regards the relatively few physical properties which depend upon atomic mass directly, physically identical also.

It is noteworthy that this definition is from a time when the neutron was not yet known and nuclei were assumed to be collections of positive and negative charges. So the term was created before the details of phenomenon were fully understood.

The term isomers is of much older vintage. It was coined by the great Swedish chemist Jöns Jacob Berzelius in 1830 [7]:

> Unter *isomerischen Körpern* verstehe ich also solche, welche, bei gleicher chemischen Zusammensetzung und gleichem Atomengewicht, ungleiche Eigenschaften besitzen. (Under *isomeric bodies* I therefore understand those that, with identical chemical composition and identical atomic [molecular] weight, have different chemical properties.)

His definition, which is still valid today, was a reaction to the perplexing discovery that substances with the same chemical composition can be chemically different, like fulminic acid and cyanic acid, both with the formula CHNO [8]. Again, the term was introduced without the knowledge of what was happening on the molecular level. Although Berzelius did not know about isotopes, his original definition already excludes pairs of molecules with different isotopic compositions like H_2O and D_2O, as he requires that isomers must have identical molecular masses.

The term *homologues* for chemical species with different chemical composition, but similar properties dates back to the French chemist Charles Gerhardt. He devised the concept of homologues in his 1844 textbook on organic chemistry [9] as part of his effort to classify all known organic compounds:

Table 1. Ozone Molecules Differing in Isotopic Substitution

Isotopologues	$^{16}O_3$	$^{16}O_2{}^{18}O$	$^{16}O^{18}O_2$	$^{18}O_3$
Isotopomers	$^{16}O^{16}O^{16}O$	$^{16}O^{16}O^{18}O$ $^{16}O^{18}O^{16}O$	$^{16}O^{18}O^{18}O$ $^{18}O^{16}O^{18}O$	$^{18}O^{18}O^{18}O$

> Nous appelons substances homologues celles qui jouissent des mêmes propriétés chimiques et dont la composition offre certaines analogies dans les proportions relatives des éléments. (We call homologue species those that exhibit the same chemical properties and whose compositions have certain similarities in the relative proportions of the elements.)

or, in more quantitative terms, in his 1856 treatise [10]:

> Les corps semblables sont dits “homologues” lorsqu'il ne diffèrent, dans leur composition, que par C_nH_{2n}. (Similar species are called “homologues” if they do not differ in composition except by C_nH_{2n}.)

The combination *isotopic isomer* was first used in almost its modern sense in an educational paper in 1957 [11]. *Isotopomer* seems to have appeared first in 1966 explicitly as a contraction of isotopic isomer [12]:

> We have accordingly synthesized the isotopic isomers (for which we have coined the word “isotopomers”) *N*-trimethylsilylaniline-^{14}N and -^{15}N, ….

However, as the term is applied to two molecules with different isotopic composition and molecular mass, it is evident that the usage contrasts with the one recommended by IUPAC and with Berzelius' original definition of isomers.

The word *isotopologue* and the distinction between isotopomers and isotopologues is quite new and can be traced back to 1991 [13–15], where they were defined as [15]

Isotopologues (isotopic homologues) are species that have identical elemental composition but differ in isotopic content.

Isotopomers (isotopic isomers) are species that are compositionally identical but are constitutionally and/or stereochemically isomeric because of isotopic substitution.

Although these terms have been endorsed by IUPAC already in 1994 [16], it is interesting that the more recent revised IUPAC definitions [1] cited in the Introduction are apparently less concise than the original ones.

Current usage

As with language in general, it is neither history nor academic prescriptions alone which shape scientific terminology, but first and foremost everyday usage. For a long time, most authors did not linguistically distinguish between the two concepts and used the term isotopomers for both of them. The pair *positional isotopomers* and *mass isotopomers* seems to have been in use as well, although the latter is an obvious *contradictio in se*. A literature search reveals 10 times more published articles containing isotopomer than isotopologue in title or abstract; however, if the search is limited to articles published in the last couple of years, it is apparent that isotopologue is quickly gaining popularity, indicating that many scientists deem it appropriate to make the distinction.

Examples

Possibly the simplest chemical species that can be used to illustrate both terms simultaneously is ozone O_3. If we only take into account the two most abundant oxygen isotopes, ^{16}O and ^{18}O, there are a total of six molecules differing in isotopic substitution. There are four groups of isotopologues, two of which contain a pair of isotopomers, as listed in Table 1.

From the table it becomes clear that the two terms are sufficient to describe any pair of molecules with identical elemental but different isotopic composition: They are either isotopologues or isotopomers.

For students, the distinction between isotopologues and isotopomers can easily be explained and illustrated by referring to the concepts of homologues and isomers, already known from elementary organic chemistry classes. Take the pair $CH_3CH_2CH_2D$ and CH_3CHDCH_3. If, instead of D, a methyl group is imagined, it is immediately clear that the two species are isomers. The same recipe works for the pair CH_4 and CH_3D. Again, if a methyl group is substituted for the D, students instantly realize that the two molecules are homologues.

A more complex example is fullerene, C_{60}. Each of the 60 carbons can be replaced with ^{13}C. So there exist 61 different chemical compositions, $^{12}C_{60}$, $^{12}C_{59}{}^{13}C_1$, ..., $^{12}C_1{}^{13}C_{59}$, $^{13}C_{60}$, that is, there are 61 isotopologue groups. Counting the number of isotopomers of each isotopologue group is a more challenging problem, solvable by using Pólya's isomer enumeration method [17, 18].

Conclusion

For students, it is rewarding to be aware of the development of chemical terminology, which rarely follows a straight path. Often, the same terms are used differently in different fields or different schools of thought. Some terms are created at a time where all the underlying physical or chemical principles are fully understood, but more linguistic differentiation is needed. Others evolve together with the concepts behind them and become clearer with time, as more of the background is elucidated. It is fascinating that scientists try to define and use precise names even if the phenomena they label are not entirely understood. Conscious and careful use of language should be encouraged as much as possible in science education, as it helps to think more accurately about nature. As we work on our language, we work on our thoughts.

References and Notes

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