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*Dear Editor,*

**Catiomers and aniomers: unique classes of isomeric ions**

In chemistry, isomers (from Greek ἰσομερής, isomerès; isos = "equal", méros = "part") are chemical species possessing the same formula (atomic composition) but different chemical structures.[1] Isomers are separated into two major categories: constitutional isomers and stereoisomers (Fig. 1). Constitutional isomers are those displaying different connectivities whereas stereoisomers display the same connectivity but different 2D or 3D spatial distributions of their atoms or groups of atoms. Constitutional isomers have been sub-divided in several types such as metamers and tautomers whereas stereoisomers are further sub-divided into two major classes: enantiomers and diastereomers. Enantiomers are non-superimposable mirror images, whereas all the others types of non-superimposable stereoisomers with multiple stereocenters are sub-classified as diastereomers. *cis/trans*- Isomers with fixed geometries as well as flexible conformers with different shapes, due to rotations along one or more bonds (rotamers), are sub-classes of diastereomers (Fig. 1).

A unique and also very common type of constitutional isomerism, which cannot be accommodated in any current definition of isomeric types summarized in Fig. 1, arises however for ions which are formed upon cationization or anionization of a molecule at different sites, as illustrated by the two isomeric ions of Scheme 1.[2] This 'terminology gap' showed up for the first time in mass spectrometry (MS) with the introduction of chemical ionization (CI) and fast desorption (FD)-MS but became crucial with the advent of electrospray ionization (ESI)-MS,[3] which has brought access to a variety of solution or gaseous ions that only differ in their coordination topology. Unfortunately, due to the lack of an appropriate term, these important and increasingly common isomeric ions have been termed in many unspecific, pleonastic or vague ways such as 'isomers',[4] 'ion isomers',[5] 'isomeric metal-cationized molecules',[6] 'isomeric adduct ions'[7] and 'cationic ions'.[8] These terms only inform that we are dealing with isomeric species, but the crucial information of the type of isomerism involved is not provided. More specifically but incorrectly, these isomers have also been termed either as tautomers[9–11] or, more frequently, as 'conformers'.[12,13]

'Tautomers' (from the Greek tautó meaning 'the same' and meros meaning 'parts') is an inappropriate term to describe such unique isomeric ions since the term is widely recognized in chemistry to describe a well-defined type of constitutional isomerism (Fig. 1). Tautomers exist *in equilibrium* and are involved in isomerism of the general form G-X-Y = Z ⇄ X = Y-Z-G; hence they are interconverted by the relocation of an electrofuge *G group plus a double bond*. The commonest case of tautomerism, when the G electrofuge is $H^+$, is termed 'prototropy', such as the equilibrium between the keto and enol forms of a carbonyl compound bearing an acidic Cα-H (Fig. 1). Conformers is also an inappropriate term since it describes a type of *stereoisomers* (Fig. 1) which are interconverted exclusively by *rotations* along one or more single bonds. As the pair of isomeric ions shown in

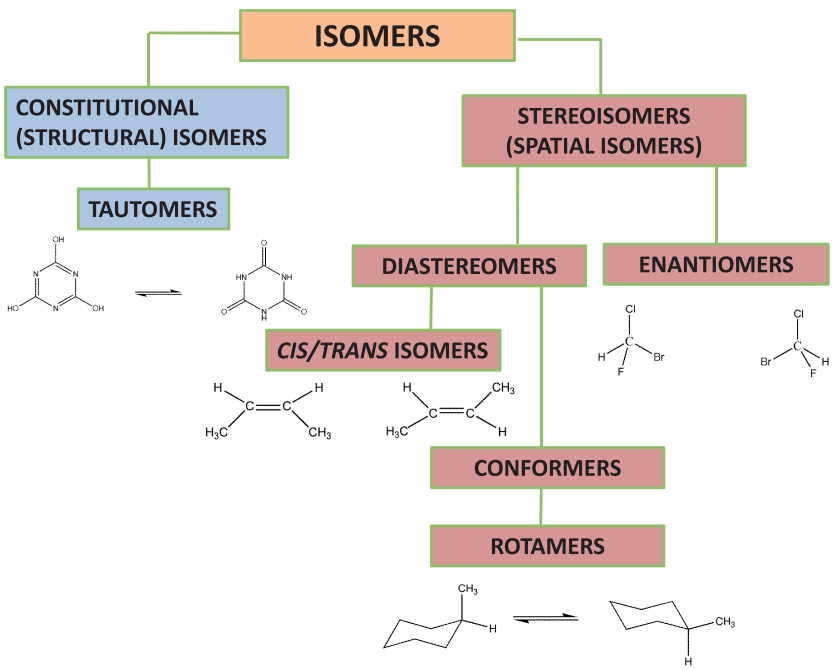
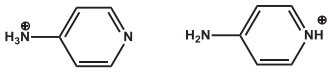



**Figure 1.** Classical types of isomers and typical examples.



**Scheme 1.**

Scheme 1 illustrates, tautomers and conformers are, therefore, misleading terms that should be avoided when describing isomerism arising from binding of an ion to different sites of a molecule.

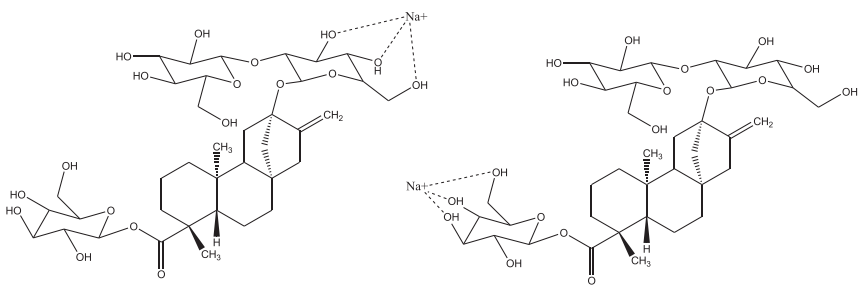
This mislabeling arises because a proper and specific term is unavailable, inducing authors to feel justified in proposing their own terms or making misleading use of an existing term created for other purposes. We have recently revisited the term 'protomer'[14] suggesting its use to describe isomers arising from protonation at different sites of a molecule. This term was not coined by us but has a long history in organic chemistry[15] and gas-phase ion chemistry.[16] In the 1950s, but as far as we could verify as early as 1947,[17] organic chemists started to use the term *protomers* to describe isomeric forms of a protonated molecule in rapid *equilibrium* in solution. These studies exemplify the role of the term *protomers* in the early development of quantitative concepts of bonding, and much of the current knowledge of structure-stability relationships is derived from these studies.[18] In the 1980s, with the introduction of mass spectrometry, studies of *protomerism*, i.e. equilibria involving *protomers*, were initiated in the gas phase mainly by Cacace and coworkers,[19] providing measurements of intrinsic acidity and basicity scales unperturbed by solvent and counter ion effects. In the 1990s, *protomers* were investigated by electron ionization or chemical ionization ion cyclotron resonance MS.[20–22] Although since 1986 it has also come into use in protein science to describe the structural unit of an oligomeric protein,[23] we are glad to note that the term *protomer* is gaining acceptance and has been increasingly used in MS studies to describe this important isomerism of protonated molecules, the purpose for which it was originally coined.[24–30]

However, the advent of the ESI-MS technique gave access not only to *protomers*[31] but also to many isomeric forms of molecules which are cationized, for instance, by $NH_4^+$, $Na^+$, $K^+$, $Rb^+$, $Cs^+$, $Ag^+$ and $Li^+$,[32] or anionized by deprotonation or $Cl^-$ binding,[33] forming both organic[34] and inorganic ions.[35] As for (de)protonation, the binding site has often deep effects on the tridimensional structure, reactivity and stability of a cationized or anionized molecule. Also, with the development of several commercially available instruments for ion mobility spectrometry coupled to mass spectrometry (IMS-MS), many cationized or anionized molecules have been separated and found to display contrasting chemistry, shapes and polarizabilities.[36] We have recently separated and characterized the 'isomeric ions' formed upon sodiation (Scheme 2) and potassiation of steviol glycosides stevioside (Stv) and Rebaudioside A (RebA) by traveling wave IMS-MS (TWIM-MS) and post-TWIM-MS/MS experiments sampled in the gas phase via ESI(+). In this study,[37] we have for the first time used the general term *cationers* to describe such isomeric ions which were found to considerably differ in shape and polarizability and hence could be properly resolved by TWIM-MS.

Also via TWIM-MS, we have separated and properly characterized a classical and much studied pair of *protomers*, the N- and ring-protonated forms of aniline,[14] and studied the aniomers of *ortho*-, *meta*-, and *para*-hydroxybenzoic acids.[26] The two *aniomers* of deprotonated hydroxybenzoic acid have also been separated and characterized via TWIM-MS by Schröder *et al*.[38] A recent combination of IR-vibrational spectroscopy with IMS-MS allowed for an unambiguous characterization of the two *protomers* of benzocaine: the N- and O-protonated forms.[25] For peptides, especially those bearing two or more basic amino acids, many peaks are commonly separated by IMS-MS and all of them have been frequently assigned simply to different 'conformers',[39] but we suspect that several 'protomers' may also be involved. The term *protomers* could likewise be helpful to further address the isomerism observed for 'curious' cases such as the two isomers of the protonated molecule of 4-aminobenzoic acid which have been recently separated and characterized by IMS-MS.[40]

We note many other cases of isomeric ions that are common in organic and inorganic chemistry which could benefit if this 'terminology gap' is resolved. Isomeric crown ester complexes that differ in the site of the $K^+$ coordination, for instance, also lack a proper description but could be properly termed as *cationers*. Phenolate ion isomers and the carboxylate forms of the *ortho*, *meta* and *para* isomers of hydroxybenzoic acid could also be considered pairs of *aniomers*.[32] In inorganic chemistry, or when sampled by ESI(–)-MS, the description of the pair of two possible 'isomeric anions' of peroxomonosulfuric acid, i.e. $[O–SO_2–OOH]^-$ and $[HO–SO_2–OO]^-$, or the disulfurous acid, $[O–SO_2–SOH]^-$ and $[HO–SO_2–SO]^-$, could also benefit from the term *aniomers*.

Note that pairs or large groups of *cationers* or *aniomers* could be formed from any type of molecules including those already involved in all types of isomerism. This would be the case, for instance, for the different *enantiomeric protomers* formed from (*S*)-(–)-nicotine (Scheme 3(a)), which could be



**Scheme 2.**

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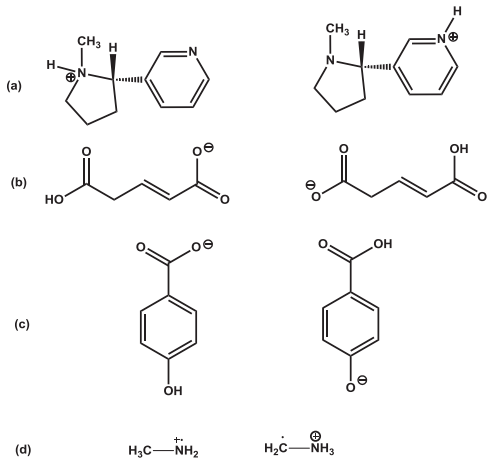

**Scheme 3.**

protonated either at the pyrrolidyl or pyridyl group, the *trans-aniomers* of the *trans*-glutaconic acid (Scheme 3(b)) and the *para-aniomers* of 4-hydroxybenzoic acid (Scheme 3(c)).

Note that a pair of isomeric distonic ions[41] such as $CH_3NH_2^+$ and $^{\cdot}CH_2NH_3^+$ and all their homologs and analogs could also be classified as a *distonic protomer* since their precursor molecules $CH_3NH_2$ and $^{-}CH_2NH_3^+$ formally differ in their protonation sites.

Due to this 'terminology gap' and their increasing importance, particularly in IMS-MS studies in which such species are actually separated and characterized, we would like therefore to suggest the use of the terms *cationers* or *aniomers* to properly describe such unique isomers formed upon cationization (e.g. by $H^+$, $Na^+$, $NH_4^+$, $K^+$, $Ag^+$, etc.) or anionization (eg. by deprotonation or $Cl^-$ clustering) at different sites of a molecule. Due to its overwhelming importance, *protomers* would then be used specifically for the sub-class of *cationers* formed upon protonation whereas deprotonated molecules would be more properly termed by the more general description as *aniomers*.

We fully recognize that the introduction of new terms should always be received with great reluctance by the scientific community since we ought to avoid unnecessary 'buzz words' that could contribute to form an uncontrolled 'terminology zoo' as much as possible. The introduction of new terms to describe the unique class of isomers described herein seems however inevitable and urgent in order not to create confusion but to remove a confusion that has already been installed in the scientific literature. Indeed the indiscriminate use of unspecific terms such as 'ion isomers', or misleading terms such as tautomers, conformers and 'isobars', only exacerbates the problem, and the terms cationers and aniomers seem to offer a solution.

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