Computer Simulation of Collision Induced Dissociation and Isolobal Analogy: The Case of Biotin and its Analogues

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ABSTRACT

We have studied how collision induced dissociation (CID) products and associated mechanism are modified when a chemical group is modified by isolobal groups, and in particular S, O, NH and CH_2. At this end, we have considered protonated biotin (vitamin B_7) and corresponding oxybiotin, N-biotin and C-biotin, which have the same structures except for one chemical group (the S in biotin which is substituted with the aforementioned isolobal ones). Collisional simulations with Ar were performed to model CID fragmentations and to have directly access to related mechanisms. Simulations have shown that the CID fragmentation of the four compounds were similar and the resulting fragments involve in a similar way the isolobal groups. Details on the mechanisms as obtained from simulations are reported and discussed. This result shows that it is possible in principle to predict, with a reasonable confidence, mass spectra of unknown molecules based on mass spectrum of the known one when isolobal modifications are done.

Keywords: theoretical mass spectrometry; chemical dynamics simulations; isolobal analogy; biotin

1. INTRODUCTION

The concept of isolobal analogy was introduced years ago by Hoffmann as a practical tool to understand and easily predict organic and organometallic reactions.[1] In the original publication, discussing the properties of $M(CO)_3$ and $M(C_6H_6)$ (where M is a metal) they "mean to imply that the number, symmetry properties, extent in space and energy of the frontier orbitals of the fragments are similar – not identical, but similar".[2] Thus, two compounds where one chemical group is replaced by another with similar properties in the frontier orbitals is expected to behave similarly. In mass spectrometry, this concept could be used to predict fragmentation patterns of molecules which are derived from a known one where a group is replaced by an isolobal one.

Understanding and even better predicting fragmentation patterns in collision induced dissociation (CID) is crucial in both fundamental and practical applications of mass spectrometry. One class of approach consists in the use library searching, for example using the extended NIST library.[3] Of course, libraries need experiments on all the species of interest and mechanisms can be proposed only for data for which experiments are available. Another approach uses machine learning algorithms to guess fragmentation patterns, like in the competitive fragmentation model (CFM) by Allen et al. in which fragmentation patterns are obtained by using a probabilistic generative model.[4]

Another possibility to predict CID spectra independently from simulation is to use molecular simulations.[5] This approach, pioneered by Hase and co-workers,[6,7] was then extended in last 10 years to a variety of biological and organic molecules.[8] The same approach can be successfully used to model and predict surface induced dissociation and soft landing.[9,10] It is based on a physical representation of the activation, either by providing an excess energy equally distributed through the vibrational modes of the fragmenting molecule, either by direct simulating the collision with the inert gas.[11,12] Since it is based on the generation of an ensemble of reactive trajectories, the chemical dynamics approach provides at the same time the fragmentation products and the related mechanisms. The most relevant drawback is that it needs important computational effort, and thus for relatively large systems highly accurate quantum chemistry methods cannot be used. However, semi-empirical Hamiltonians have shown to be able to provide relatively good fragmentation patterns and mechanisms,[13,14,15,16] in particular for organic

and rigid molecules, like testosterone[17] or methyl-guanine.[18] In this last study, a comparison with CFM machine learning prediction was done, showing that the chemical trajectory approach is comparable with it, providing at the same time more information on reaction mechanisms and physically ground results.

Here, we have investigated the CID fragmentation in relation with the isolobal analogy. In particular we have considered protonated biotin (also called vitamin B_7 or H) and then substituted the S atom with O (oxybiotin), NH (N-biotin) and CH_2 (C-biotin), forming a set of compounds shown in **Figure 1**. These atoms and fragments fulfill the "isolobal analogy" prescription since their frontier orbitals have similar energy, shape and number of electrons.[1]

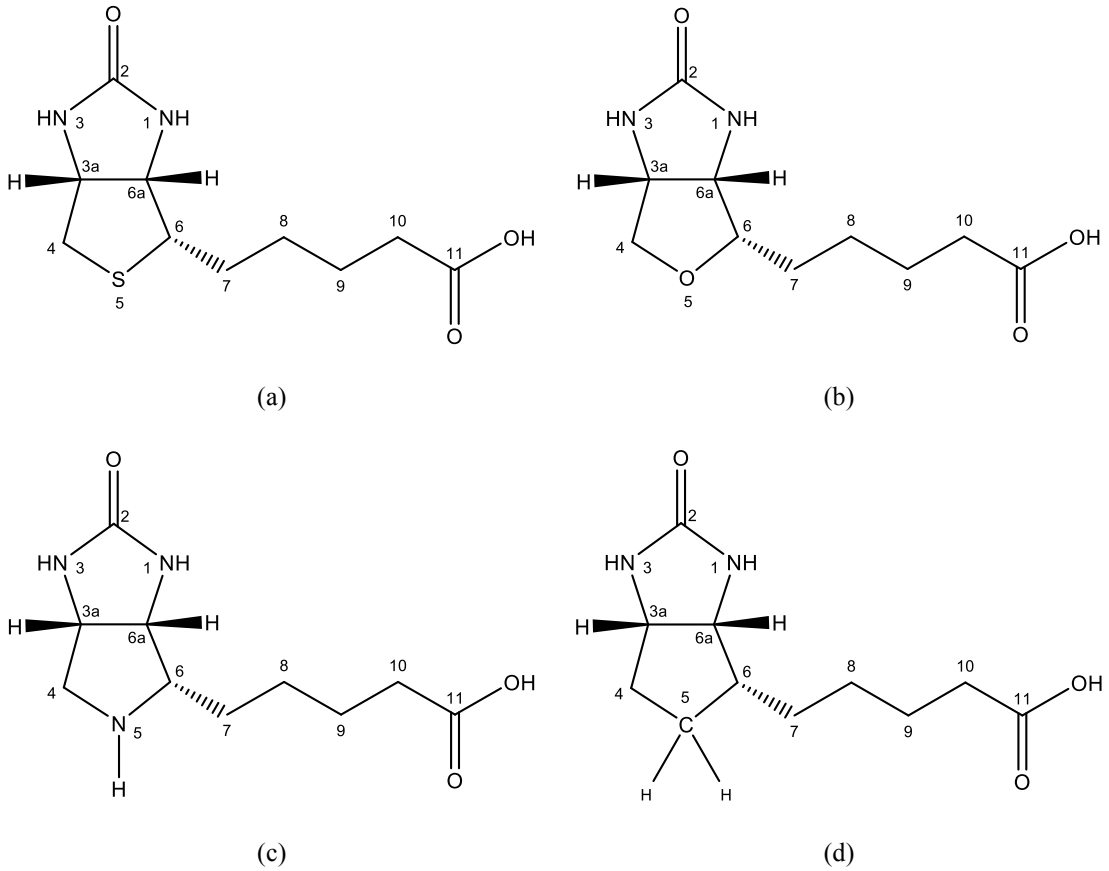


Figure 1. *Chemical structures of neutral (a) biotin, (b) oxybiotin, (c) N-biotin and (d) C-biotin.*

Other than a chemical rationale in modifying the S atom of biotin, there is also a biological interest. In fact, biotin acts as coenzyme for carboxylase enzymes, involved in the synthesis of fatty acids, isoleucine, and valine, and in gluconeogenesis.[19,20] If there is

insufficient biotin, oxybiotin, is the only analogs capable of replacing biotin in the higher organisms.[21] More in general, single site substitution are common in biology and it can be useful to predict mass spectra of possible analogs independently from experiments. We have thus considered the four molecules, activated by modeling explicit collision with Ar atom and analyzed product ions and mechanisms. In particular, we focused on how the fragmentation spectra is eventually modified in the isolobal analogs and which are the related mechanism. This will provide a guide to possibly predict the CID of different isolobal species from the spectrum of a known one.

2. COMPUTATIONAL DETAILS

2.1 Reactant structures

The biotin has an imidazolidinone structure and thiolane ring (**Figure 1a**). The isolobal analogs considered here are: oxybiotin, N-biotin and C-biotin. They have the same structure as biotin but S is substituted by O, NH, CH_2 (also shown in **Figure 1**). Although N-biotin and C-biotin are hypothetical molecules, these two compounds provide optimal examples to study isolobal analogy on CID products and mechanisms.

Protonation can occur on different basic sites: six for biotin, oxybiotin and N-biotin and five for C-biotin. We define the different protonation sites as follows: (a) protonated on oxygen in the carbonyl group of the ring; (b) protonated on the nitrogen atom of amide group located in the opposite direction of the carboxylic group; (c) protonated on the other amide group; (d) protonated on S, O or N for biotin, oxybiotin and N-biotin, respectively (this site does not exist by definition in C-biotin); (e) protonated on the carbonyl of the carboxyl group and (f) protonated on the hydroxyl group. In **Figure 2** we show the resulting different tautomers for biotin, while in **Figures S1-S3** of the supporting material we report the same for oxybiotin, N-biotin and C-biotin.

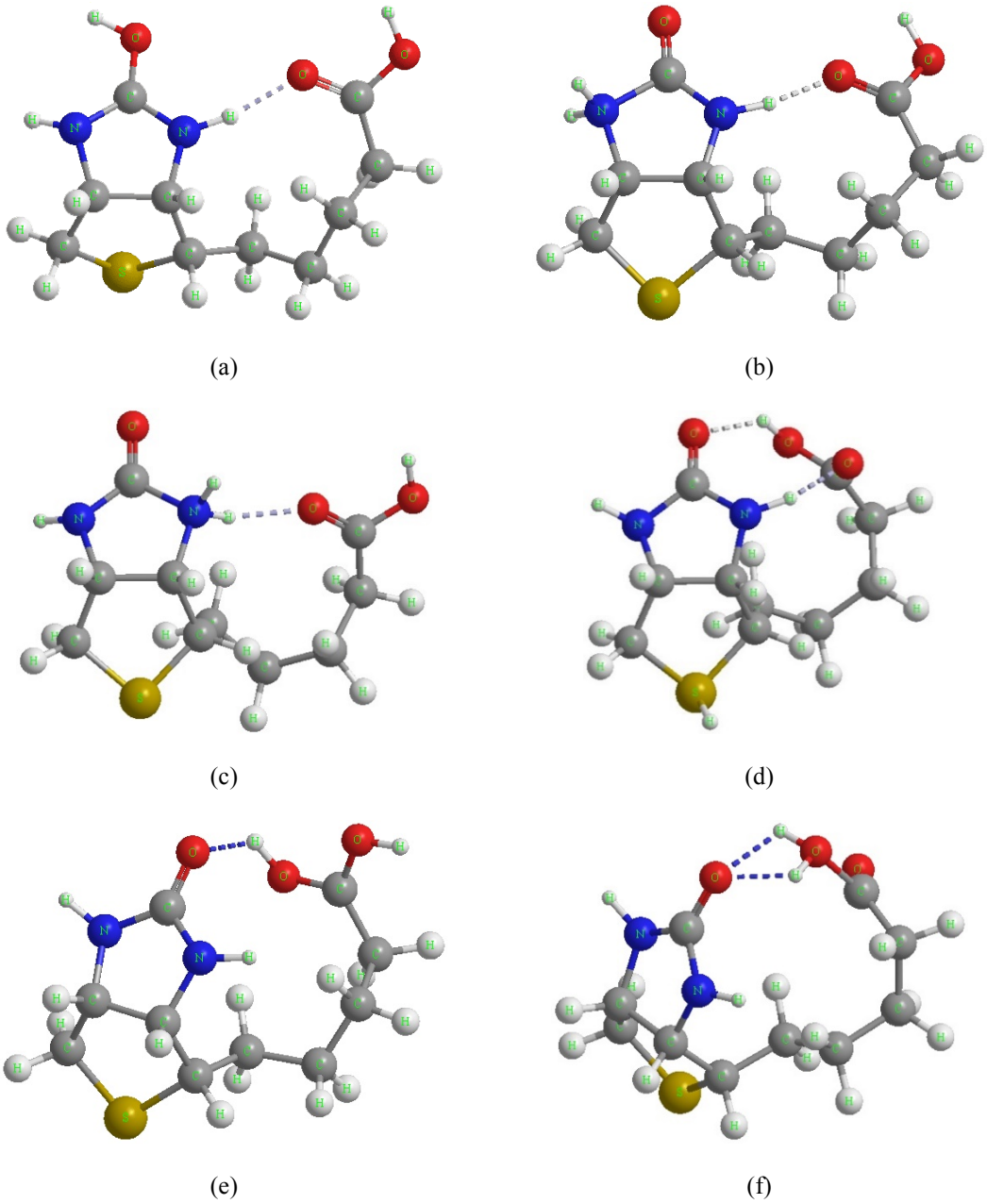


Figure 2. *Structures of the different tautomers of protonated biotin.*

The geometry of the neutrals and different protonated structures was optimized at Hartre-Fock (HF) and B3LYP [22, 23] levels of theory with the 6-31G(d,p) and 6-311++G(d,p) basis sets and with a number of semi-empirical Hamiltonians, namely: MNDO-d,[24,25] RM1,[26] PM3[27] and PM7.[28] The resulting optimized geometries of each tautomeric form are reported in **Figures 1** and **S1-S3**. From those calculations, it was possible to obtain the proton affinities of all considered structures at different levels of theory.

HF and B3LYP calculations were performed using Gaussin 09 Rev D.01 software,[29] while semi-empirical Hamiltonian calculations with MOPAC 2016.[30]

2.2 Ion-Ar interaction potential

The potential energy for the collision system, consisting of protonated molecule (the ion) and neutral Ar (the collision gas) is described by:

$$V = V_{ion} + V_{Ar-ion} \quad (1)$$

where V_{ion} is the intramolecular potential of the protonated molecules and V_{Ar-ion} is the intermolecular potential between Ar and the ion. This last term is as a sum of two-body interactions between Ar and the atoms of the ion. We used the expression proposed by Meroueh and Hase :[31]

$$V_{Ar-ion} = \sum_i a_{Ar-i}\exp(-b_{Ar-i}\times r_{Ar-i}) + \frac{c_{Ar-i}}{r_{Ar-i}^9} \quad (2)$$

where i runs over all atoms of protonated molecule and parameters a_{Ar-i}, b_{Ar-i} and c_{Ar-i} are always positive as reported in the original publication and found in sequent studies. This interaction potential was able to correctly simulate the CID of a series of systems, like protonated urea,[32] protonated *N*-formylalanylamide[13] and testosterone.[17] We used parameters of H, C, O, N as from the original works of Meroueh and Hase[31] and Ortiz et al.[33] Parameters for S were obtained previously for sulfate group,[33] but the electron density of sulfur in biotin is clearly different and thus we have re-parametrized the potential for this new atom type. We have used at this aim the interaction between Ar and thiolane molecule to obtain parameters for S atom. The thiolane molecule containing thioether group (R-S-R') is a good model to represent the short-range repulsive interaction between Ar and S of biotin. The interaction potential energy between Ar and S was calculated from the shortest possible distance up to 3.5 Å, and the parameters a, b and c of Eq. (2) were obtained by fitting *ab initio* interaction energy curves carried out on the QCISD(T)/6-31++G(d,p) level of theory, which is the same level of theory used in previous parametrizations.

2.3 Trajectory simulations

Direct dynamics simulations of the ion-Ar collision were performed for the most stable

precursor tautomer of each molecule (biotin, oxybiotin, N- and C-biotin). As we will show in the result sections, this will correspond to the tautomer (a) where the excess proton is on the oxygen of the carbonyl group of the imidazolidinone group.

Initial conditions for the ions were obtained from most stable structures, and initial positions and momenta obtained from vibrational normal mode Boltzmann sampling at 300 K.[34] Rotational energy was also added corresponding to the same temperature. The collisional system was set as follows: (1) the ion was randomly rotated about its Euler angles; (2) the Ar was placed at 13 Å distance (ensuring no ion-Ar interaction at the beginning); (3) an initial velocity of 30 eV was impressed to Ar atom in the direction of the center of mass of the ion (this corresponds to the collision energy in the center-of-mass framework); (4) the Ar atom was shifted by a randomly obtained impact parameter in the 0-5.0 Å range. This maximum value was estimated by the maximum length of the protonated systems which was about 9.2 Å. Simulations were then run and stopped when the Ar-ion distance exceeds 300 Å and in any case with a maximum simulation time of 40 ps. Equations of motions were integrated using velocity Verlet algorithm with a time step of 0.02 fs. For each system, we performed between 10,000 and 20,000 trajectories in order to have enough reactive events.

3. RESULTS AND DISCUSSIONS

3.1 Ar-S interaction potential parameters

The interaction potential between Ar and S bound to two carbon atoms (C-S-C) in thiolane was obtained by performing QCISD(T)/6-31++G(d,p) calculations along the Ar…S C_{2v} axis of thiolane. The resulting *ab initio* energy curve is plotted in **Figure 3** together with the result of fitted Equation 2. Corresponding parameters for Ar-S interaction are reported in **Table 1**.

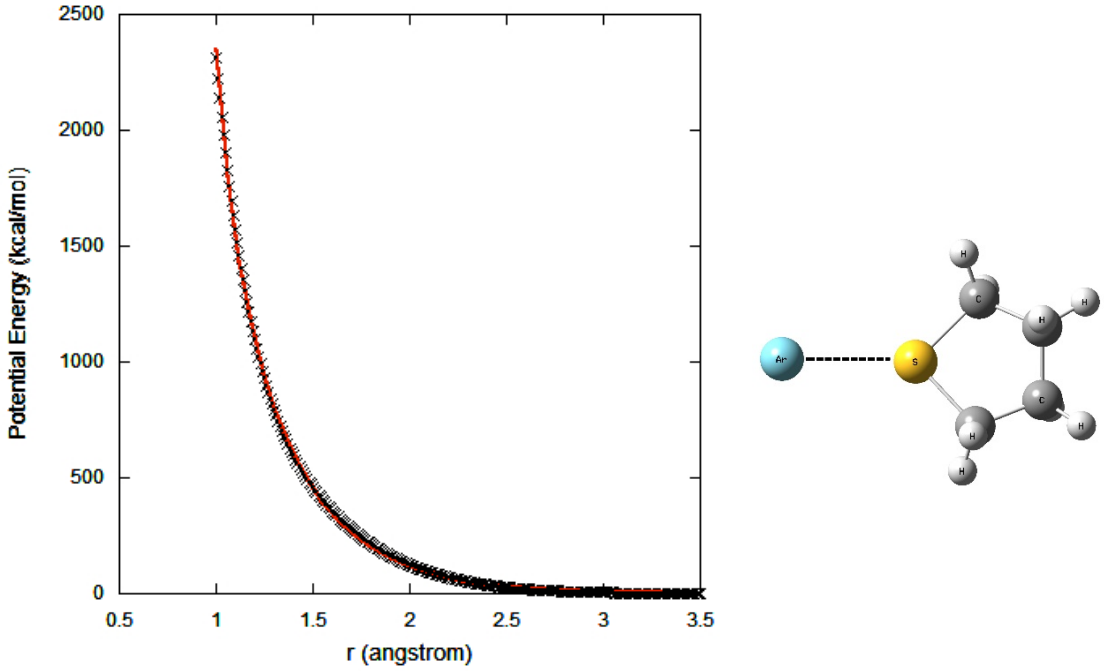


Figure 3. *Potential energy for Ar/S(CH2)4 as obtained from QCISD(T)/6-31++G(d,p) calculations (crosses) and fitted Equation 2.*

Table 1. Intermolecular potential parameters of sulfur atom

potential	a [(1)]	b [(2)]	c [(3)]
Ar/S$(CH_2)_4$(ArS)	21634.0	2.5991	739.11

[(1)] Units are in kcal/mol. [(2)] Units are in $Å^{-1}$. [(3)] Units are in $Å^9$ kcal/mol.

3.2 Proton affinities

Proton affinities are calculated for biotin and isolobal analogs for each stable tautomer of the different systems. This will provide us the most stable pronation state which will be used as starting structure for the following chemical dynamics simulations. Results are reported in **Tables 2-5**. In all systems, the (a) protonation site (on the carboxyl oxygen of imidazolidinone ring) is the most favorable one. Values are very similar for the different structures, which is reasonable since the protonation site is relatively far from the modified group. Interestingly, for N-biotin the proton affinity of N-analog atom –site (d) – is much closer to site (a) than in biotin and oxybiotin, such that it becomes slightly higher when calculated at B3LYP/6-311++G(d,p), RM1 or PM7 levels of theory.

Table 2. Proton affinities for biotin [a]

	ion type (a)	ion type (b)	ion type (c)	ion type (d)	ion type (e)	ion type (f)
HF / 6-31G(d,p)	237.827	217.820	223.635	208.919	230.635	224.321
HF / 6-311++G(d,p)	235.860	217.365	223.029	209.893	212.692	222.274
B3LYP / 6-31G(d,p)	233.257	220.055	224.987	206.991	229.003	222.569
B3LYP / 6-311++G(d,p)	229.203	216.975	221.778	206.434	223.698	218.001
MNDO-d	168.318	145.957	148.263	161.202	157.071	137.742
RM1	182.809	177.649	181.017	158.401	181.173	176.824
PM3	202.598	191.167	190.578	182.970	182.814	172.221
PM7	152.531	149.646	151.436	142.566	151.382	149.319

[a] Units are in kcal/mol.

Table 3. Proton affinities for oxybiotin [a]

	ion type (a)	ion type (b)	ion type (c)	ion type (d)	ion type (e)	ion type (f)
HF / 6-31G(d,p)	240.516	218.196	224.224	214.428	231.060	228.388
HF / 6-311++G(d,p)	238.161	216.888	193.723	213.397	213.943	222.894
B3LYP / 6-31G(d,p)	235.175	226.335	225.271	204.091	229.577	223.728
B3LYP / 6-311++G(d,p)	230.962	216.836	221.573	185.463	227.396	218.707
MNDO-d	167.439	145.622	147.426	139.601	155.568	136.016
RM1	183.149	177.279	180.386	147.046	180.745	175.970
PM3	204.633	191.597	192.426	154.288	183.683	172.915
PM7	151.894	149.218	151.678	124.786	151.427	148.708

[a] Units are in kcal/mol.

Table 4. Proton affinities for N-biotin [a]

	ion type (a)	ion type (b)	ion type (c)	ion type (d)	ion type (e)	ion type (f)
HF / 6-31G(d,p)	240.469	224.928	227.665	240.371	234.100	229.235
HF / 6-311++G(d,p)	238.829	210.509	226.882	238.758	216.545	227.104
B3LYP / 6-31G(d,p)	235.884	227.754	228.457	235.132	232.183	226.714
B3LYP / 6-311++G(d,p)	231.122	224.040	224.890	232.102	226.507	221.886
MNDO-d	168.188	146.629	147.445	160.405	155.386	136.159
RM1	186.119	182.625	183.743	190.428	183.195	179.376
PM3	205.433	194.979	194.711	192.415	184.334	174.060
PM7	153.257	152.973	152.803	155.431	152.232	150.253

[a] Units are in kcal/mol.

Table 5. Proton affinities for C-biotin [a]

	ion type (a)	ion type (b)	ion type (c)	ion type (d)	ion type (e)	ion type (f)
HF / 6-31G(d,p)	242.297	227.125	229.229	-	235.556	230.259
HF / 6-311++G(d,p)	240.450	226.376	228.566	-	233.123	228.259
B3LYP / 6-31G(d,p)	237.473	229.051	229.942	-	233.574	227.890
B3LYP / 6-311++G(d,p)	233.422	225.434	226.586	-	228.130	223.305
MNDO-d	171.302	150.931	152.705	-	157.584	138.550
RM1	188.189	185.302	186.140	-	184.884	181.569
PM3	207.837	197.899	197.084	-	185.424	175.551
PM7	156.033	155.932	155.617	-	154.596	153.030

[a] Units are in kcal/mol.

The semi-empirical methods globally underestimate the proton affinity, but they show similar trend as from HF and B3LYP calculations. Between different methods tested, PM3 seems to better reproduce these values, we have thus used it in subsequent simulations. Note that the same semi-empirical Hamiltonian was successfully used to study CID of other molecules, like notably galactose sulfate.[33]

3.3 Fragmentation yields and products

Reactivity yield is about 10% for biotin, but then it decreases when moving to oxybiotin (7.8%), N-biotin (4.2%) and C-biotin (2.4%), which roughly reflects the increasing in C-X bond strength from S to C (where X = S, O, N and C). Details are reported in **Table S1** of the supporting material.

Fragmentation products of biotin are compared with what reported from experiments[35] in the MassBank database.[36] The two fragmentation spectra are shown in **Figure 4**. From simulations, the theoretical MS/MS spectrum is obtained simply by counting the product ions at the end of each trajectory and normalizing them, in the present case to the *m/z* 227.08 which is the same normalization reported in the database.

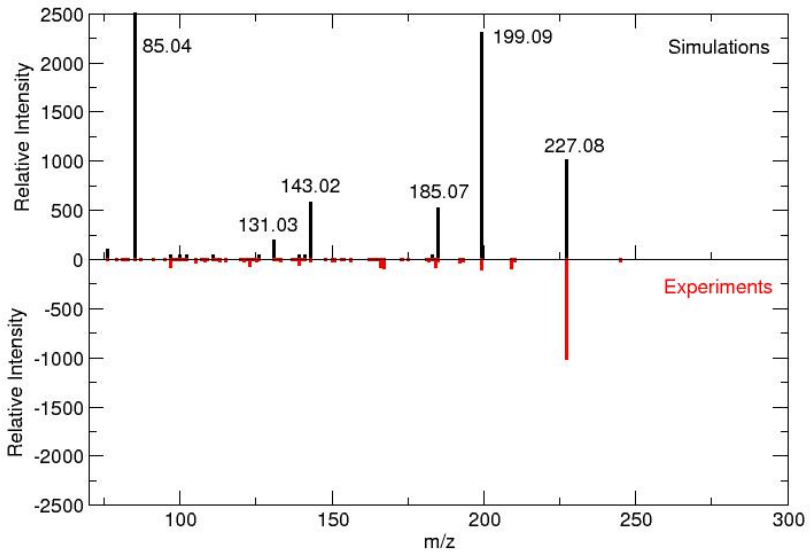


Figure 4. *CID spectra of biotin as obtained from simulations (upper panel, in black) and reported experimentally (lower panel, in red; the sign is inversed). Both spectra are normalized with respect to the first peak, m/z 227.08. Precursor ion is not reported.*

Globally, the match between experiments and simulations is quite good: the main experimental peaks are found also in simulations with some differences in relative intensity. In particular, experimentally, the most intense peak is *m/z* 227.08 which is found less intense in simulations. Simulations report ion *m/z* 199.09 more abundant, while it is found less in experiments. The difference is likely due to the fact that in experiments when *m/z* 199.09 is formed as primary fragment, it can further react providing smaller fragment. The largest difference concerns peak *m/z* 85.04 which is very abundant in simulations while very small in experiments. This is one of the lightest peak observed and thus the difference in abundance can be due to several reasons. One possibility is that the energy in simulations is higher than in experiments (a direct comparison on energetics cannot be done since experiments were not done in a triple-quad or QQTof instrument), thus smallest fragments are more probable. Furthermore, we do not have information on how the detection range is set in experiments, which can impact the observed number of ions in the low mass range of the instrument if it was optimized for higher *m/z* peaks. In any case, this low mass peak is not a characteristic peak. Details on most important mechanisms will be reported in section 3.4, here we mostly remark that the characteristic peak is obtained (*m/z* 227.08) and the global pattern is in reasonable agreement with experiments. Note that collisional conditions are also different, so we do not expect a perfect match, in particular concerning intensities.

In **Figure 5** we show the theoretical MS/MS spectrum obtained as results of all collisional simulations. Details and corresponding formula are listed in **Table S2** where the isolobal corresponding products are reported in the same raw. Globally, the fragmentation patterns are very similar, in particular concerning the characteristic peaks of biotin. The intensities show some differences. In particular, moving from biotin to C-biotin, the relative intensity of ion *m/z* 109.09 (which is *m/z* 183.11, 182.13 and 181.13 in oxybiotin, N- and C-biotin, respectively) becomes more intense, and also other peaks that are less intense in biotin become more relevant. As we have discussed previously, simulations of biotin report the low *m/z* ion 85.04 with high intensity. This same *m/z* ion was found in other isolobal analogs, showing that the modified groups are in the neutral fragments. Details on the mechanism are reported in next section.

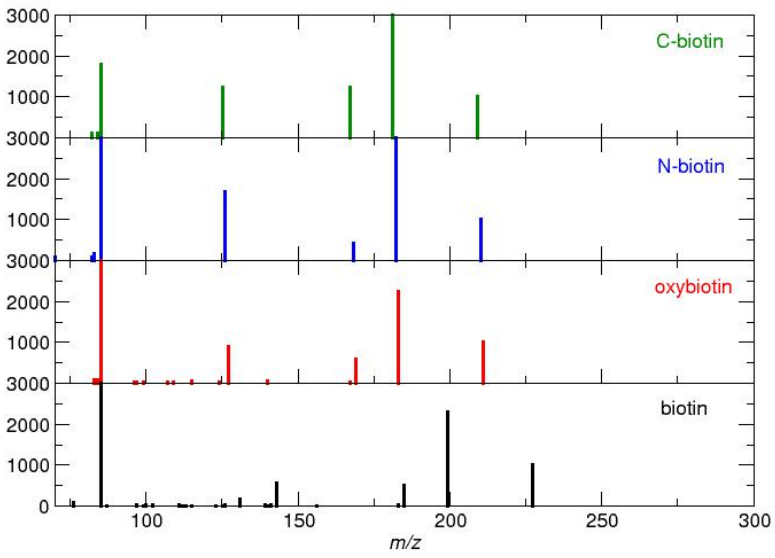


Figure 5. *Comparison of fragmentation products obtained from CID simulations of biotin, oxybiotin, N-biotin and C-biotin. In y-axis relative intensity, where the normalization was set on the first fragmentation peak of each species. Precursor ions are not reported.*

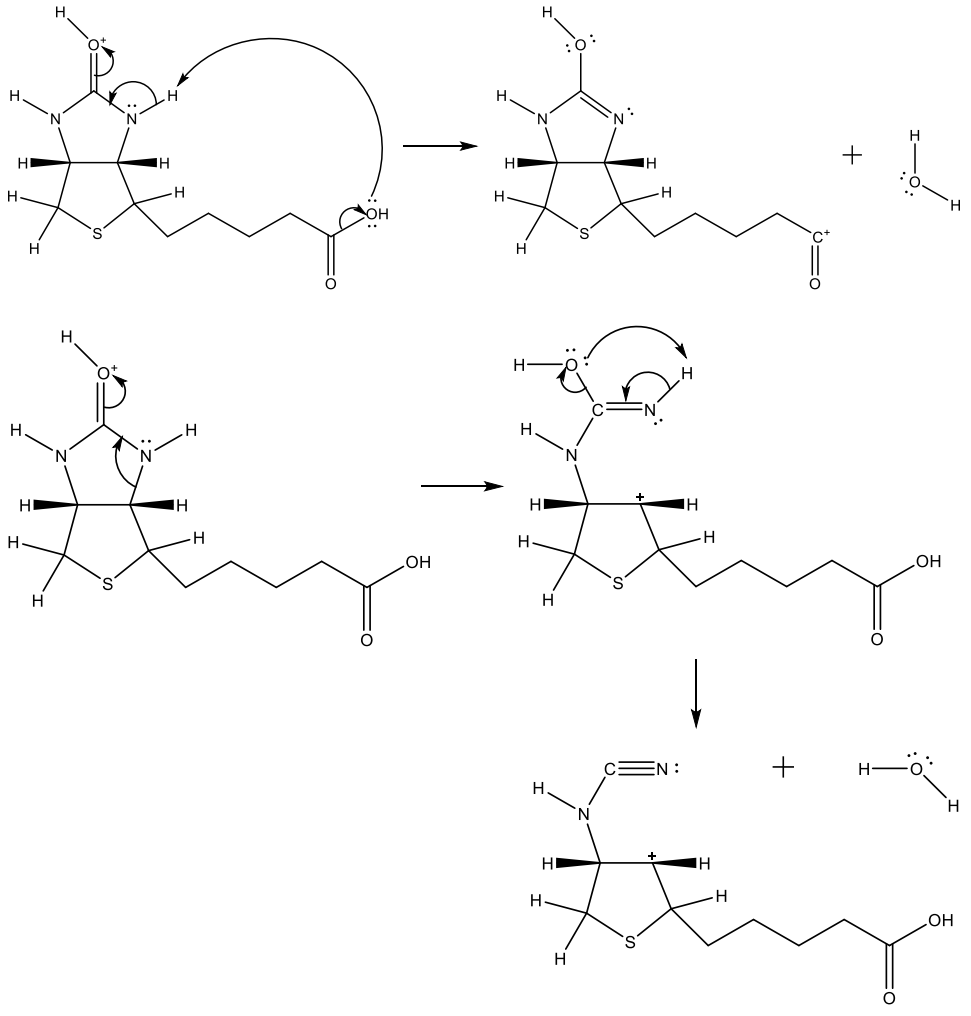
3.4 Fragmentation mechanisms

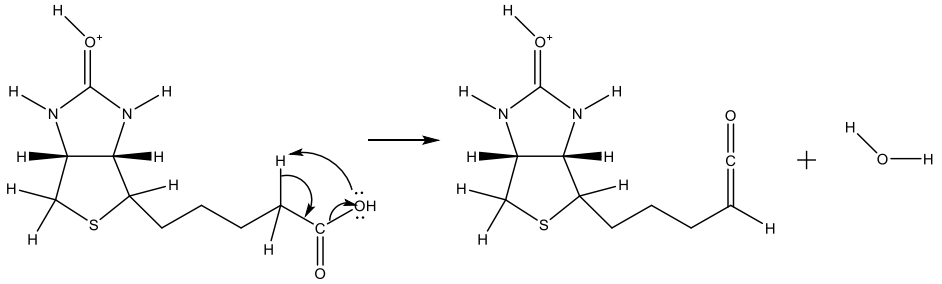
We now analyze in details reaction mechanisms for the formation of the most relevant reaction products. We discuss the mechanisms observed in biotin together with the equivalent ones for the other systems, leading to isolobal analog fragments.

$C_{10}H_{15}N_2O_2S^+$ (m/z=227.08) and isolobal analog ions. Fragment *m/z* 227.08 is the most abundant peak in experiments and, as discussed previously, obtained also in simulations, but with less relative abundance. Analog fragments *m/z* 211.11, 210.12 and 209.13 are obtained in simulations of oxybiotin, N-biotin and C-biotin, respectively. The product ion corresponds to water loss with three possible mechanisms, shown in **Scheme 1**, where for simplicity we report only what observed in biotin, the others being similar given the isolobal substitution. The water loss can be obtained from the two oxygen atoms, from carbonyl in the imidazolidinone ring or the carboxylic tail. In the first case the mechanism is rather complex, while for the latter the OH can pick and hydrogen from either the N-H group of imidazolidinone or a vicinal CH. The last mechanism is the most abundant

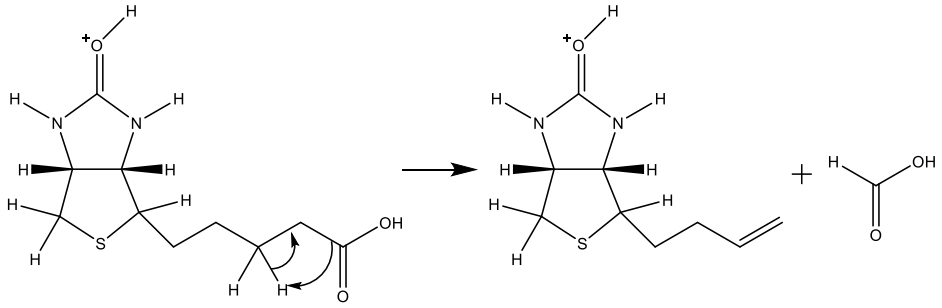
(about 67%) while the first two have lower abundance (12 and 21%, respectively). We should note that the product ion *m/z* 209.07, observed experimentally in biotin but not in simulations, corresponds to the subsequent water loss from the product ion *m/z* 227.08. Another ion, *m/z* 192.05 observed experimentally, but not in simulations, is likely coming from further ammonia loss from *m/z* 209.07. Collisional simulations are limited in time-length and this is clearly at the origin of the missing of these secondary and tertiary product ions in simulations.

$C_9H_{15}N_2OS^+$ (m/z=199.09) and isolobal analog ions. The peak *m/z* 199.09 corresponds to HCOOH lost and is observed in both simulations and experiments as an intense peak. The mechanisms are the same for the different species, leading to ions *m/z* 183.11, 182.13 and 181.13 for oxybiotin, N-biotin and C-biotin, respectively. For simplicity, we report in **Scheme 2** only the mechanism observed in biotin simulations.



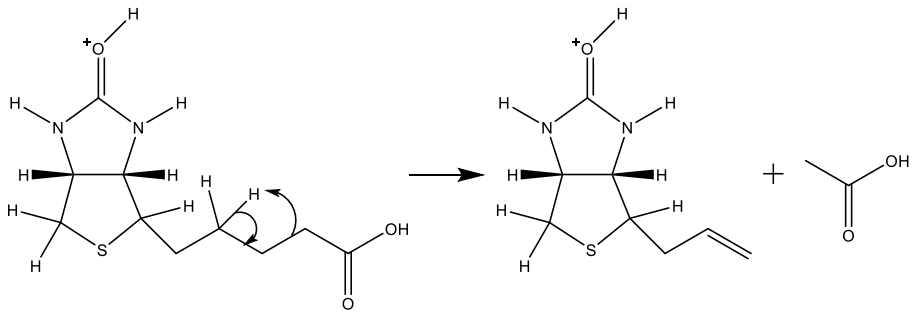


Scheme 1. *Mechanisms observed for the formation of m/z 277.08 as from CID simulations of biotin.*



Scheme 2. *Mechanism observed for the formation of m/z 199 as from CID simulations of biotin.*

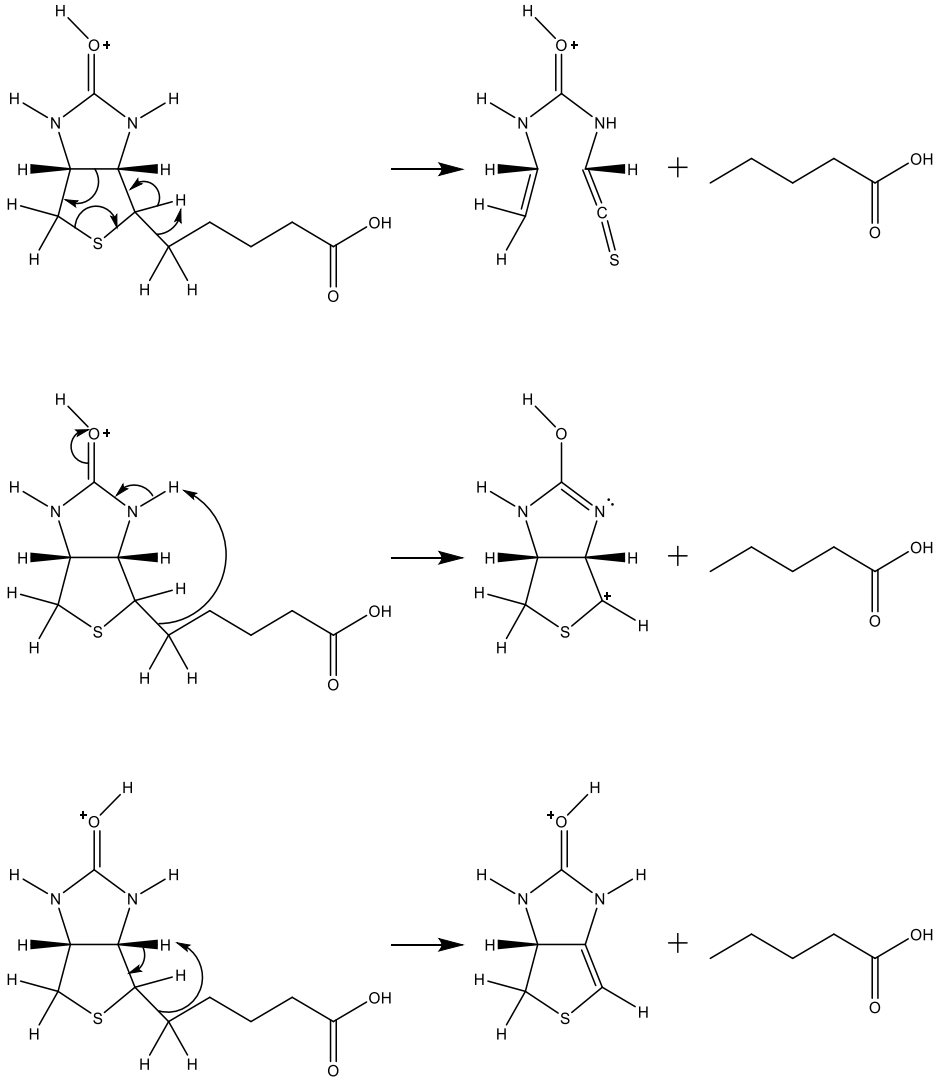
$C_8H_{13}N_2OS^+$ (m/z=185.07) and isolobal analog ions. Ion *m/z* 185.07 observed in biotin corresponds to CH_3COOH neutral loss and the same mechanism is reported for the other systems. As previously, the mechanism does not involve the S, O, NH or CH isolobal modified groups and thus they are the same (in **Scheme 3** we report for simplicity only the case of biotin).



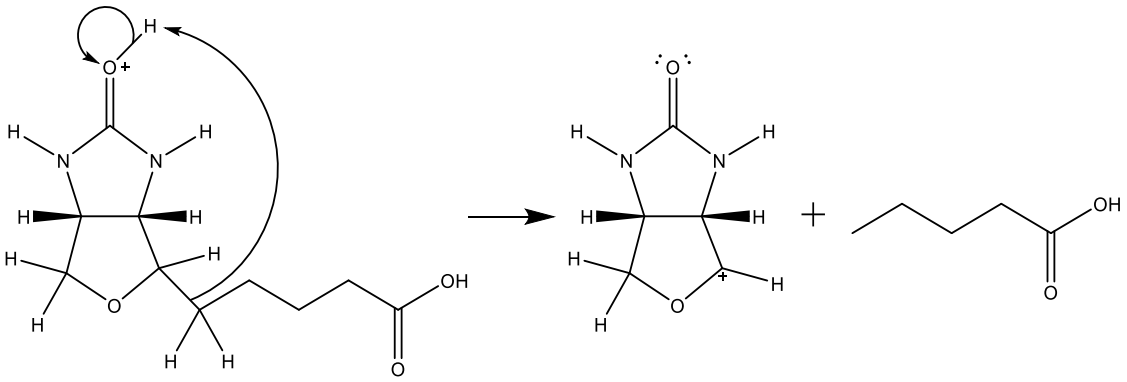
Scheme 3. *Mechanism observed for the formation of m/z 185.07 as from CID simulations of biotin.*

$C_5H_7N_2OS^+$ (m/z 143.02) and isolobal analog ions. The mechanism responsible for the

formation of these ions involve the isolobal moieties. They have in common the cleavage of C-C bond, but then the hydrogen atom is taken from a different site. The mechanisms observed in the case of biotin are reported in **Scheme 4**: hydrogen is released from one C atom of the broken C-C bond, from the N in the imidazolidinone ring or from the C-H in common between the two rings. Similar mechanisms are obtained for the oxybiotin (product ion $C_5H_7N_2O_2^+$, *m/z* 127.05), except for this last mechanism which is not observed, while a new one is observed. This corresponds to a proton transfer from the protonated carbonyl and it is reported in **Scheme 5**. For both biotin and oxybiotin the different mechanisms are observed with about the same occurrence.

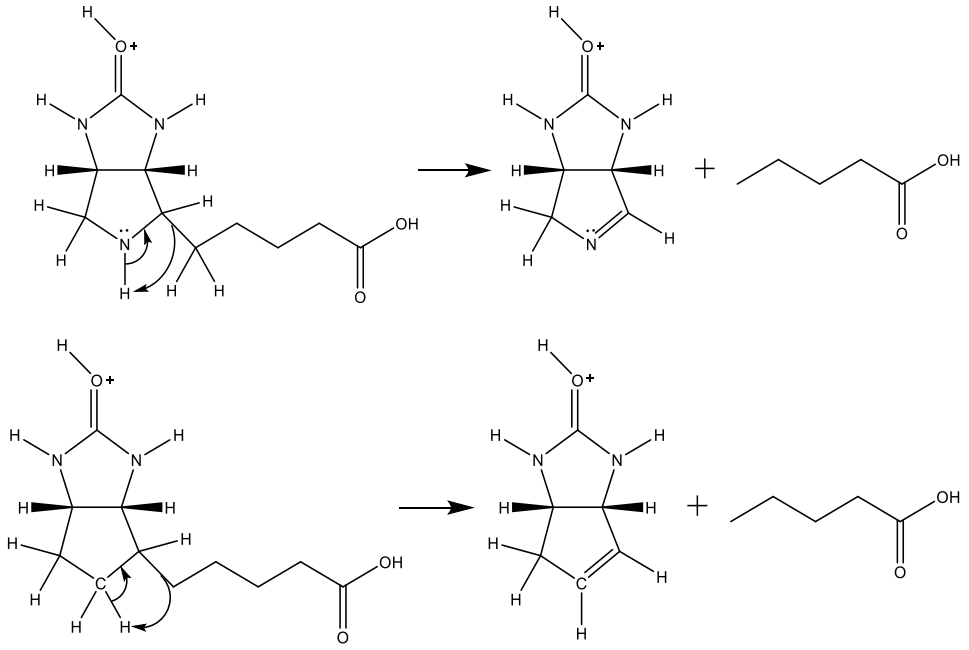


Scheme 4. *Mechanism observed for the formation of m/z 143.02 as from CID simulations of biotin.*



Scheme 5. *Mechanism observed for the formation of m/z 127.05 specific of oxybiotin as from CID simulations.*

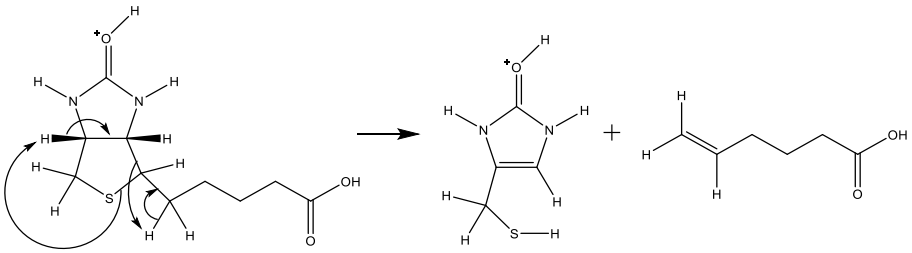
In the case of N-biotin the corresponding product ion $C_5H_8N_3O^+$(*m/z* 126.07) is formed with a different mechanism, where the hydrogen atom on the N-H isolobal group is abstracted, as reported in **Scheme 6**. Other two mechanisms common with biotin and oxybiotin (abstraction of H from the breaking C-C bond and from the other N-H group) are also observed. For C-biotin the product ion $C_6H_9N_2O^+$ (*m/z* 125.07) is also formed with a mechanism in which the hydrogen is taken from the isolobal modified group (see **Scheme 6**). These new mechanisms typical of N- and C-biotin cannot be observed by definition in biotin and oxybiotin, but, since the proton can be abstracted also from other sites, finally we do not observe any difference in product ions.



Scheme 6. *Mechanism observed for the formation of m/z 126.07 and 125.07 specific*

of N-biotin (upper) and C-biotin (lower), respectively, as from CID simulations.

$C_4H_7N_2OS^+$ (m/z 131.03) and isolobal analog ions. The formation of *m/z* 131.03 in biotin involves the breaking of S-C bond, as reported in **Scheme 7**. The analog mechanism is found also in oxybiotin (ion $C_4H_7N_2O_2^+$, *m/z* 115.05), but not in N-biotin and C-biotin. The final product for biotin and oxybiotin contains S-H and O-H group, respectively. Together with the difference in C-X bond (X = S, O, N, C) this can be at the origin of the absence of this product ion in simulations of N- and C-biotin.

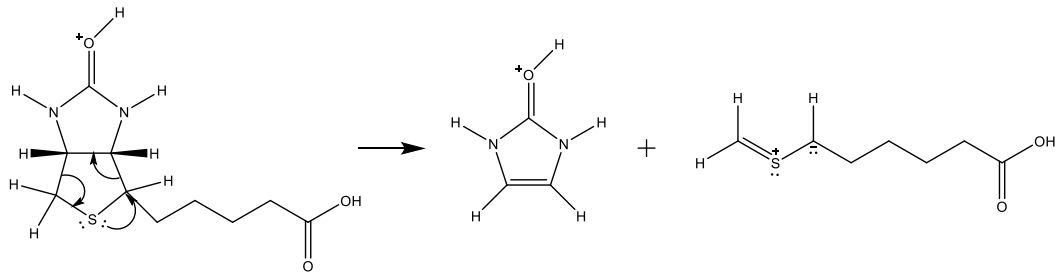


Scheme 7. *Mechanism observed for the formation of m/z 131.03 as from CID simulations of biotin.*

Differences in the reactivity of isolobal analogs for this and other products are minor since they concern ions for which we obtained only few reactive trajectories, so any conclusion is not statistically ground. They are reported for completeness in the supporting information. Moreover, they are in a region of the spectrum which shows experimentally very low signals.

$C_3H_5N_2O^+$ (m/z 85.04) product ion. This product was observed in all systems and with a very high intensity. It is the most abundant product in biotin, oxybiotin and N-biotin, while it is not reported in experiments. The mechanism is reported in **Scheme 8**. In some cases, the neutral further breaks in two molecules ($CH_2X + C_6H_{10}O_2$, where X = S or O). This occurs only in biotin and oxybiotin. The product ions are the same in all the systems, since the isolobal analog groups are in the neutral molecule after fragmentation. The abundance of this ion in simulations and discrepancy with respect to experiment can have at least three origins: (i) simulations are performed at relatively high energy and the direct collision of the Ar on the linear chain can enhance this pathway; (ii) the product ion can

further react and we do not observe these secondary reactions due to limitations in simulation time-length; (iii) an artefact due to the semi-empirical Hamiltonian; (iv) the experimental detector can be optimized for ions of higher *m/z* values and the low side of the experimental range can be underestimated.



Scheme 8. *Mechanism observed for the formation of m/z 85.04 as from CID simulations of biotin.*

4. CONCLUSIONS

In this work, we have studied how protonated biotin and isolobal analogs oxybiotin, C-biotin and N-biotin fragments in CID simulations. Experiments are available only for biotin and simulations shown a good agreement, being able to elucidate the different fragmentation mechanisms. The isolobal analogs seem to react in a similar way, in particular for characteristic peaks. Even when the mechanisms involve the isolobal analog part, often the final result is the same, because of the variety of possible mechanisms. The few differences in reactivity which are reflected in a difference in fragmentation ion products (and thus in MS/MS signal) concern reaction pathways with low abundance and which are not fingerprint peaks.

Concluding, this work shows that it is possible to use the isolobal analogy to guess with a certain confidence the presence many fragmentation products, but for this the detailed mechanisms should be known for at least one system. This result paves the way of using in the future chemical dynamics simulations on one species and use simple mechanistic considerations to propose fragments of isolobal analogs. In the future, it will be thus possible to predict mass spectrum of unknown molecules based on mass spectrum of the known ones with the help of computer simulations also with the aim of building a theoretical MS/MS database which can support experiments and complement existent databases.

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