Radical Cations in EI-MS Analysis of Drugs
I. Riboflavin, epinephrine, chloramphenicol, metronidazole and dipyridamole

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To better understand the behavior of riboflavin, epinephrine, chloramphenicol, metronidazole and dipyridamole under electron ionization mass spectrometric conditions, we have performed quantum chemical calculations on their radical cations, using both RM1 (Recife Model 1) and PM7 (Parameterized Model 7) semi-empirical methods. These attempts were generally aimed at explaining the shapes of their respective EI-MS spectra, especially regarding the high intensity of some fragmentation ions obtained in positive mode ionization.

Keywords: vicinal groups, radical cations, computational chemistry, RM1 and PM7 semi-empirical methods, electron ionization mass spectrometry

Vicinal groups are frequently encountered in the structure of both biomolecules and drugs. Carbohydrates, for example, have multiple hydroxyl groups positioned at neighboring carbon atoms, while some amino acids (and, implicitly, peptides and proteins) have vicinal amino and hydroxyl or thiol groups in their molecules [1].

In [2] was reported that the radical cations of compounds which contain vicinal groups, like ethylene glycol or ethylenediamine, could form long bonds (usually around 2 angstrom in length) between the vicinal carbon atoms. These bonds seem to be well stabilized by the vicinal electron donor groups, as shown by quantum chemical methods, so the radical cation, in this form, is itself more stable than in the absence of such a long bond [2-8].

In a recent paper [9] we have analyzed some sugar derivatives based on glucose, galactose and mannose and offered arguments for the formation of such long bonds, from both their mass spectrometry analysis and molecular modeling of their radical cations. In this paper we further investigate, from the same point of view, other compounds which contain vicinal groups. The five structures chosen for this study, namely riboflavin, epinephrine, chloramphenicol, metronidazole and dipyridamole, all have pharmacological properties (being found in both the Romanian Pharmacopoeia and the European Pharmacopoeia) and are all characterized by the presence of amino and hydroxyl groups placed in vicinal positions [10]. We have also selected three model compounds for additional study, namely 2-aminoethanol, 3-aminobutan-2-ol and 1-(methylamino)propan-2-ol [11].

Riboflavin (vitamin B_2) [12] is part of the vitamin B group, a class of water-soluble vitamins that play important roles in cell metabolism. It is the central component of the two cofactors found in flavoproteins, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). As part of oxidoreductases, these coenzymes act as electron carriers in many vital biological oxidoreduction systems, which include the mitochondrial respiratory chain, key enzymes in fatty acid and amino acid oxidation and the citric acid cycle. It is also a constituent of the cryptochromes, blue-light sensitive pigments in the eye that are important in the setting and maintenance of circadian rhythms [1, 13a, 14, 15].

Epinephrine (adrenaline) [16], together with the related compounds norepinephrine (noradrenaline) and dopamine, belongs to the catecholamines family. All of them behave as hormones (exerting endocrine effects) and also as neurotransmitters (chemical mediators for conveying the nerve impulses to effector organs). In common with other compounds containing the amino group, such as serotonin, they are also known as biogenic amines. Epinephrine contributes to activation of hepatic gluconeogenesis, providing an exogenous source of glucose for muscle. It suppresses the anabolic pathways (glycogen synthesis, lipogenesis) and it stimulates the catabolic pathways (glycogenolysis, lipolysis and proteolysis). Epinephrine remains a useful drug for several emergency indications, despite its non-specific action on adrenoceptor and the subsequent development of multiple selective medicines that target subtypes of adrenoceptors [1,13b,14,15,17].

Chloramphenicol is a broad-spectrum antibiotic, with antibacterial and antirickettsial properties. It is effective, for example, against gram-positive cocci (*Staphylococcus aureus*), gram-negative coccobacilli (*Brucella abortus*), *Klebsiella pneumoniae*, certain spirochetes, *Chlamydia*, *Anaplasma*, and the organisms of typhoid, typhus, and Rocky Mountain spotted fever. It is commonly used in solution 0.5% or ointment 1% to treat bacterial conjunctivitis or blepharitis [18a].

Metronidazole is a synthetic antimicrobial (antibacterial and antiprotozoal) drug effective against obligate anaerobes and used to treat bacterial, fungal and parasitic infections. It is prescribed in the treatment of anaerobic

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and antibiotic-induced infections, including trichomoniasis, amebiasis, giardiasis, balantidiasis, pseudomembranous colitis and bacterial vaginosis. It is the most effective agent for *Helicobacter pylori* infections. It is sold under the trade names *Flagyl*, *MetroGel*, *Metro IV* and *Protostat* [18b].

Dipyridamole is an antiplatelet agent (platelet aggregation inhibitor) and coronary vasodilator used to prevent thromboembolism (clotting) associated with mechanical heart valves, to treat transient ischemic attacks (TIA) and as an adjuvant in preventing myocardial reinfarction and in radionuclide myocardial perfusion imaging. It is prescribed as a vasodilator for coronary artery disease and peripheral arterial disease, in the long-term treatment of angina pectoris and in the prevention of coronary bypass graft occlusion. It is known by the brand names of *Apo-Dipyridamole FC*, *Apo-Dipyridamole SC*, *Persantin* or *Persantine* [15,18c,19].

Experimental part

All structures were initially modelled using the *HyperChem* software [20]. After the "Add H & Model Build" command, the starting neutral molecules were pre-optimized with the MM+ force field and then optimized with the RM1 semi-empirical method [21]. The radical cations (formal charge "+1", spin multiplicity "2") were obtained from these structures and were finally optimized with the RM1 semi-empirical method. Some additional work, like using molecular mechanics pre-optimization, was done in order to minimize the possibility of obtaining local energy minima instead of global energy minima for the radical cations. Force fields used for this purpose include MM+, AMBER99, BIO+ (CHARMM27) and OPLS, with their default parameters as implemented in the *HyperChem* software. As for "Spin Pairing", RHF operators were used for neutral molecules, while UHF operators were employed for radical cations. The SCF "Convergence limit" was set at 10^{-5}, without using the "Accelerate convergence" procedure. For geometry optimization and ΔH_f calculation [22-24], the "Polak-Ribičre (conjugate gradient)" algorithm was selected with a RMS gradient of 0.01 kcal/(A°mol), the molecules being considered in vacuum (conditions similar to those found in the EI-MS detectors).

The *MOPAC2012* software [25] was used for the PM7 semi-empirical method [26], with "CHARGE=+1" and "UHF" options for radical cations. The same *HyperChem* starting structures were used (the ones obtained after the "Add H & Model Build" command, with MM+ pre-optimization). The corresponding ".HIN" files were then converted to ".ZMT" (*MOPAC* Z-matrix) files and run through the MOPAC interface for geometry optimization and ΔH_f calculation. The line of parameters included "GNORM=0.01", "OPT", "BONDS", "AUX", "GRAPHF" and "PDBOUT", and also the keywords "SINGLET" (for neutral molecules) or "DOUBLET" (for radical cations). Two data sets were obtained, the first one by using the BFGS algorithm, while the second one by using the EF algorithm. The resulting structures were analyzed using the *Jmol* software [27].

The radical cation molecular graphs showing the spin density [28] were plotted in *HyperChem* using the "Wire mesh" rendering (carbon – cyan, hydrogen – white, chlorine – yellow, nitrogen – blue, oxygen – red, positive spin density – green wire mesh, negative spin density – violet wire mesh) [20].

Three different starting N-C-C-O dihedral angle values (-0.640°, -177.655° and 54.479°), borrowed from a recent paper [9], which were combined with different starting C-C bond lengths (1.6 – 2.1 A° domain using 0.1 A° steps), were used to optimize the radical cations of the simple model compounds (2-aminoethanol, 3-aminobutan-2-ol and 1-(methylamino)propan-2-ol).

The EI-MS spectral data for the analyzed compounds (2-aminoethanol, riboflavin, epinephrine, chloramphenicol, metronidazole and dipyridamole) were downloaded from the NIST Chemistry WebBook site [29], while the exact masses, the molecular weights and the *m/z* values given under the chemical formulas are those predicted by the *ChemBioDraw Ultra* (v. 12.0) program (*ChemBioOffice 2010* software package).

Results and discussions

The mass spectrum for 2-aminoethanol (ethanolamine or monoethanolamine) [29a], the simplest saturated compound that contains both the amino and the hydroxyl group in vicinal position, is presented in figure 1. The base peak at m/z = 30 comes from the C-C bond cleavage, the positive charge being retained by the methaniminium fragment:

The molecular modeling results for the 2-aminoethanol radical cation are given in table 1. As can be seen, the RM1 method and also the PM7 method with BFGS optimization algorithm do not offer any surprises, showing a standard 1.55-1.56 A° C-C bond length. This bond can also be easily broken if an initial length above 2.0 A° is chosen for some RM1 cases, this being an endotherm process (1.0 kcal/mol required). However, using the EF optimization algorithm for the PM7 method, a long bond structure was discovered, having a length of 1.849 A°, but being positioned on a higher energy state and thus less favored than the 1.56 A° variants (by 4.9 kcal/mol). The other geometric parameters for the found long bond structure are: N-C-C-O torsion angle (dihedral) 59.798°, N-C-C angle 107.183° and O-C-C angle 100.202°, together with a planar NH_2 group. To

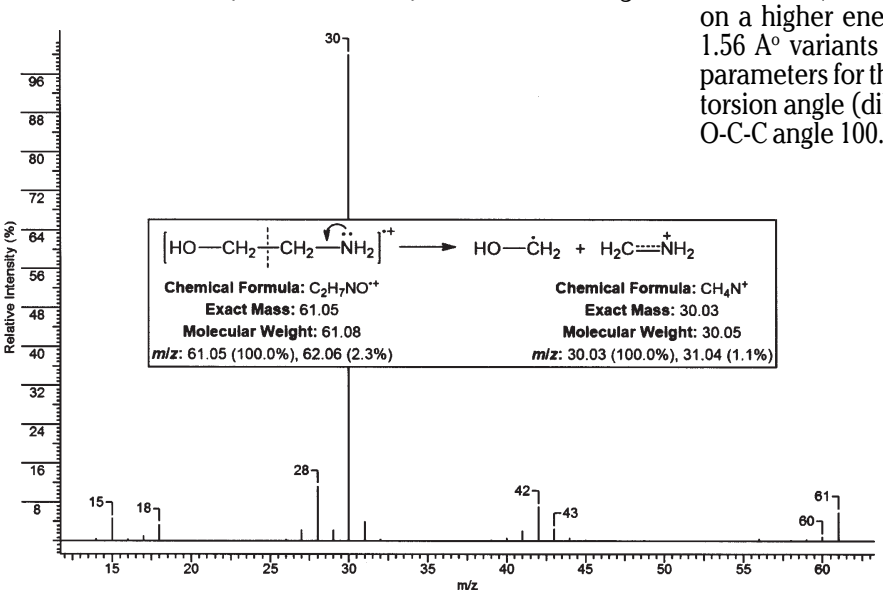

Fig. 1. EI-MS spectrum of 2-aminoethanol [29a]

Initial N-C-C-O dihedral	Initial C-C bond length	RM1		PM7 (BFGS)		PM7 (EF)	
		Final C-C bond length	ΔH_f	Final C-C bond length	ΔH_f	Final C-C bond length	ΔH_f
-0.640°	1.6	1.556	136.392	1.555	140.896	1.570	141.509
	1.7	1.556	136.392	1.550	140.905	1.587	142.966
	1.8	1.556	136.392	1.550	140.905	1.609	144.039
	1.9	1.556	136.392	1.550	140.885	1.657	146.048
	2.0	3.344*	137.604*	1.550	140.885	1.694	147.470
	2.1	3.251*	137.746*	1.550	140.886	1.849	145.754
-177.655°	1.6	1.554	141.053	1.550	140.905	1.550	140.905
	1.7	1.554	141.053	1.550	140.905	1.555#	140.896#
	1.8	1.554	141.053	1.550	140.905	1.572	147.339
	1.9	1.554	141.053	1.555	140.877	1.623	149.803
	2.0	1.554	141.053	1.550	140.885	1.550	140.885
	2.1	1.554	141.053	1.550	140.885	1.576	147.336
54.479°	1.6	1.556	136.392	1.556	140.896	1.555	140.896
	1.7	1.550	136.373	1.550	140.905	1.556	140.896
	1.8	1.556	136.392	1.555	140.896	1.555	140.896
	1.9	1.556	136.392	1.550	140.885	1.556	140.877
	2.0	3.757*	137.387*	1.550	140.885	1.556	140.877
	2.1	3.757*	137.387*	1.555	140.877	1.555	140.877

Table 1
C-C BOND LENGTH (A°) AND HEAT OF FORMATION (kcal/mol) VALUES FOR THE 2-AMINOETHANOL RADICAL CATION

* C-C bond breaking;
# without using the "OPT" parameter.

make a proper comparison, the geometry of the final structure from table 1, which has a 1.555 A° C-C bond length and the radical character localized at the nitrogen atom, is given: N-C-C-O torsion angle (dihedral) 38.373°, N-C-C angle 110.754° and O-C-C angle 104.933°, together with a planar NH_2 group.

It is interesting that, if we take the 1.849 A° PM7 long bond structure and we do a RM1 geometric re-optimization, a new 2.121 A° long bond structure is obtained, having the following geometric parameters: N-C-C-O torsion angle (dihedral) 56.034°, N-C-C angle 103.384° and O-C-C angle 101.052°, together with a planar NH_2 group. The radical character is mainly distributed in the C-O bond and at the nitrogen atom, as seen from the spin population values: 0.525 (C), 0.157 (O) and 0.407 (N). The heat of formation for this structure is 138.787 kcal/mol, and thus it is located 2.4 kcal/mol higher than the 1.550 A° RM1 radical cation structure.

Similar results were obtained for 3-aminobutan-2-ol radical cation (table 2), except that no "genuine" long bond structure was identified. Still, the C-C bond is generally somewhat longer (1.57, 1.59 or 1.61 A°) and it also breaks more often (the final C-C distance becoming longer than 3.26 A°), suggesting a less stable entity. This is also confirmed by the lower energy of the resulting two-component system relative to the initial radical cation, the breaking thus being an exothermic process (-8.5 kcal/mol for RM1, -7.1 kcal/mol for PM7).

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Initial N-C-C-O dihedral	Initial C-C bond length	RM1		PM7 (BFGS)		PM7(EF)	
		Final C-C bond length	ΔH_f	Final C-C bond length	ΔH_f	Final C-C bond length	ΔH_f
-0.640°	1.6	1.568	117.405	1.609	119.069	1.608	119.068
	1.7	1.568	117.405	1.610	119.069	1.608	119.068
	1.8	1.568	117.405	4.353*	112.130*	1.609	119.068
	1.9	3.821*	108.323*	4.358*	111.972*	4.345*#	111.974*#
	2.0	3.847*	108.324*	4.357*	111.977*	4.353*#	111.973*#
	2.1	3.842*	108.323*	4.368*	111.975*	4.349*#	111.974*#
-177.655°	1.6	1.574	121.816	3.307*	114.625*	3.319*	114.687*
	1.7	1.574	121.816	3.261*	114.539*	3.338*	114.679*
	1.8	1.574	121.816	4.315*	112.135*	3.262*#	114.540*#
	1.9	1.574	121.816	3.268*	114.438*	4.366*	111.973*
	2.0	1.574	121.816	4.365*	112.014*	3.274*#	114.442*#
	2.1	3.837*	108.323*	4.350*	111.975*	3.269*#	114.439*#
54.479°	1.6	1.592	116.864	1.609	119.069	1.609	119.068
	1.7	1.592	116.864	1.609	119.069	1.609	119.068
	1.8	1.592	116.864	4.292*	112.222*	1.608	119.068
	1.9	3.844*	108.323*	4.354*	111.972*	4.362*	111.973*
	2.0	3.880*	108.324*	4.346*	111.974*	4.354*#	111.976*#
	2.1	3.838*	108.323*	4.206*	112.388*	4.354*	112.063*

Table 2
C(2)-C(3) BOND LENGTH (A°) AND HEAT OF FORMATION (kcal/mol) VALUES FOR THE 3-AMINOBUTAN-2-OL RADICAL CATION

* C(2)-C(3) bond breaking;
# without using the "OPT" parameter.

Initial N-C-C-O dihedral	Initial C-C bond length	RM1		PM7 (BFGS)		PM7 (EF)	
		Final C-C bond length	ΔH_f	Final C-C bond length	ΔH_f	Final C-C bond length	ΔH_f
-0.640° (*S*)	1.6	1.553	117.213	1.564	115.302	1.572	114.481
	1.7	1.553	117.213	1.564	115.300	1.572	114.481
	1.8	1.553	117.213	1.564	115.300	1.572	114.481
	1.9	1.553	117.213	1.578	116.809	1.572	114.438
	2.0	3.777*	123.794*	1.572	114.438	1.572	114.438
	2.1	3.898*	123.828*	1.564	115.256	1.572	114.438
-177.655° (*R*)	1.6	1.558	121.807	1.572	114.481	1.572	114.481
	1.7	1.558	121.807	1.572	114.481	1.574	114.806
	1.8	1.558	121.807	1.572	114.481	1.572	114.481
	1.9	1.558	121.807	1.572	114.438	1.572#	114.439#
	2.0	1.558	121.807	1.596	115.783	1.572	114.438
	2.1	2.043	127.450	1.572	114.438	1.572	114.438
54.479° (*S*)	1.6	1.564	116.968	1.572	114.481	1.572	114.481
	1.7	1.564	116.968	1.573	114.485	1.572	114.481
	1.8	1.564	116.968	1.572	114.481	1.572	114.481
	1.9	1.564	116.968	1.572	114.437	1.572	114.438
	2.0	2.036	127.027	1.572	114.438	1.572	114.438
	2.1	2.036	127.027	1.572	114.438	1.572	114.438

Table 3
C(1)-C(2) BOND LENGTH (IN A°) AND HEAT OF FORMATION (kcal/mol) VALUES FOR THE 1-(METHYLAMINO)PROPAN-2-OL RADICAL CATION (CHIRAL CONFIGURATION SHOWN IN PARENTHESES)

* C(1)-C(2) bond breaking;
# without using the "OPT" parameter.

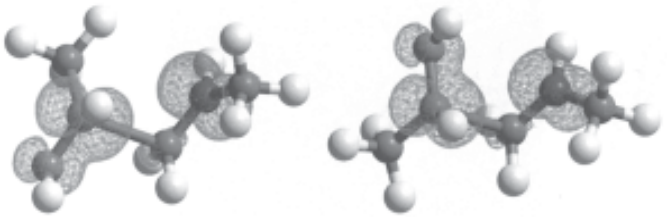

Fig. 2. The radical cation of 1-(methylamino)propan-2-ol, showing a C(1)-C(2) long bond; the radical character is mainly distributed in the C-O bond and at the nitrogen atom (starting N-C-C-O dihedral: left -177.655°, right 54.479°); spin density was plotted in *HyperChem*

breaking thus being an exothermic process (-8.5 kcal/mol for RM1, -7.1 kcal/mol for PM7).

For the 1-(methylamino)propan-2-ol radical cation (table 3), the RM1 method offered long bond structures (fig. 2) in three cases, all of them being located on a higher energy state than the 1.56 A° C-C bond length structure (by 5.6 kcal/mol for the *R* enantiomer and 10.1 kcal/mol for the *S* enantiomer). Only two cases of endothermic C-C bond breakings were registered, with an energy requirement of about 6.8 kcal/mol.

The following geometric parameters were obtained for the long bond structures (for comparison, the values for the *N*-localized radical cations are given in parentheses): N-C-C-O torsion angle 174.250° (-171.616°), N-C-C angle 105.803° (112.364°) and O-C-C angle 99.836° (101.869°) for the *R* enantiomer, and N-C-C-O torsion angle 55.909° (51.869°), N-C-C angle 105.308° (111.268°) and O-C-C angle 101.144° (107.264°) for the *S* enantiomer, together with a planar NH_2 group in all cases. The radical character is mainly distributed in the C-O bond and at the nitrogen atom, as seen from the spin population values: 0.389 (C), 0.121 (O) and 0.533 (N) for the *R* enantiomer, and 0.385 (C), 0.112 (O) and 0.524 (N) for the *S* enantiomer. These long bonds do not hold up after PM7 re-optimization, although both BFGS and EF algorithms were tested.

The heats of formation for the radical cations of the five drugs considered in this study, obtained using both the RM1 and the PM7 semi-empirical methods, are given in table 4.

Drug	RM1	AMBER99/ RM1	BIO+/ RM1	MM+/ RM1	OPLS/ RM1	PM7 (BFGS)	PM7 (EF)
Riboflavin	-40.802	-41.564	**-41.565**	-41.564	-40.801	-20.767	**-24.164**
Epinephrine	56.717	**56.708**	56.717	56.709	56.717	59.443	**59.405**
Chloramphenicol*	**57.530**	57.541	62.879	93.817	70.691	**63.101**	71.865
Metronidazole	180.118	180.118	180.118	**180.118**	202.213	183.438	**183.437#**
Dipyridamole	17.231	16.723	**12.794**	17.318	17.227	**-1.306**	5.992

Table 4
HEATS OF FORMATION (kcal/mol) FOR RADICAL CATIONS OF DRUGS (MINIMAL VALUES FOR BOTH RM1 AND PM7 SEMI-EMPIRICAL METHODS ARE MARKED IN BOLD)

* 0.02 kcal/(Å mol) RMS gradient for neutral molecule MM+ pre-optimization;
# without using the "OPT" parameter.

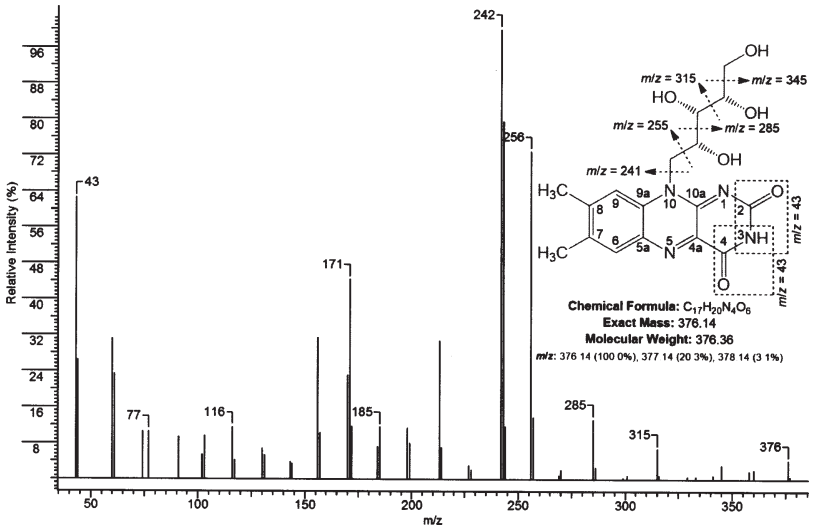

Fig. 3. EI-MS spectrum of riboflavin [29b]

Fig.4. The radical cation of riboflavin (BIO + / RM1 quantum chemical calculation); spin density was plotted in *HyperChem*

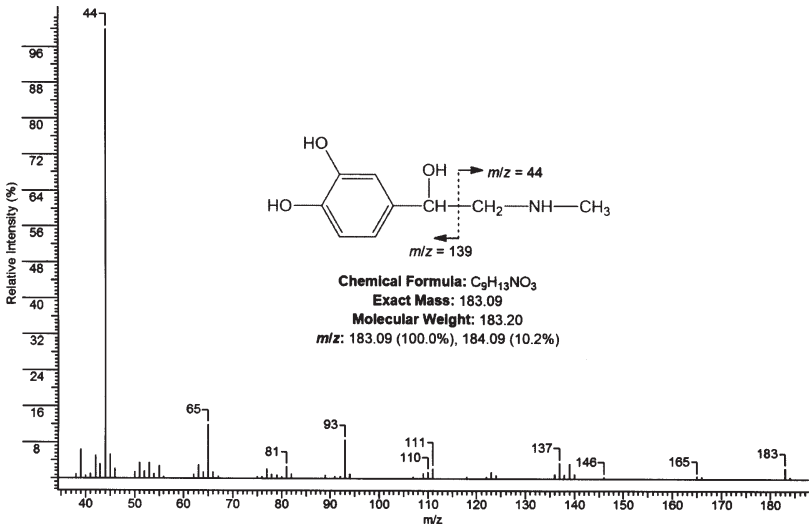

Fig. 5. EI-MS spectrum of epinephrine [29c]

The calculated riboflavin radical cation structures did not exhibit any long bonds that would explain the high intensity peaks (m/z = 242, 243 and 256, shown in figure 3 [29b]). The radical character seems to be distributed mainly in the isoalloxazine moiety, specifically in atoms 1, 4a, 5, 5a, 6, 7, 8, 9, 9a, 10 and 10a, with a minor amount in the C=O groups and the ribitol carbon atom connected with the nitrogen atom, as shown in figure 4.

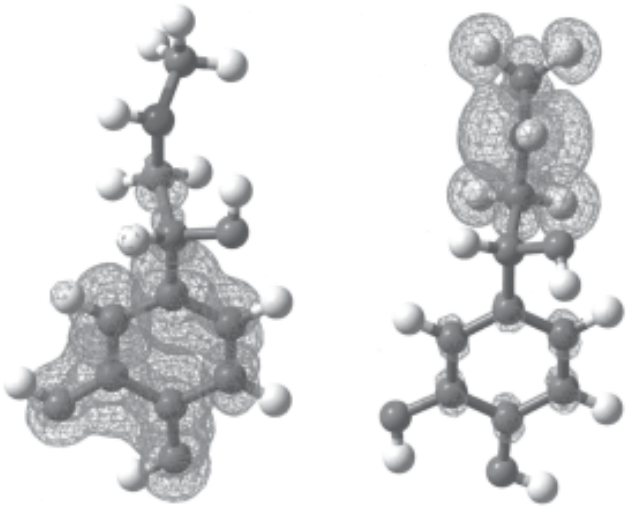

Fig. 6. Two radical cation variants for epinephrine; the higher energy structure is at left; spin density was plotted in *HyperChem*

None of the calculated epinephrine radical cation structures show any long bonds, although its EI-MS spectrum has the base peak at m/z = 44 (fig. 5) [29c]. For the absolute minimum energy structure (56.708 kcal/mol), the radical character is localized mainly at the nitrogen atom, which formerly had *S* configuration, before becoming planar. A second, less stable type of radical cation (65.390 kcal/mol) was also identified, in which the radical character is distributed between the carbon and oxygen atoms forming the catechol moiety; the nitrogen atom has *R* configuration in this case. Both variants, shown in figure 6, were obtained using the AMBER force field pre-optimization, followed by RM1 geometry optimization. The PM7 method offered only the first variant.

After RM1 optimization, chloramphenicol (EI-MS spectrum given in figure 7 [29d]) offered several different variants for its radical cation, as shown in figures 8 and 9, with spiranic structure A (radical character mainly distributed in five from the six aromatic carbon atoms) having the lowest heat of formation and thus being the most stable. The PM7 method with BFGS algorithm offered the seven member cyclic structure B, while using the EF algorithm a 1.975 A° long bond was discovered which connects the CH_2OH group with the rest of the molecule. It has the following geometric parameters: N-C-C-O torsion angle 93.134°, N-C-C angle 103.640° and O-C-C angle 99.905°. The heats of formation for all the obtained radical cations are given in table 4.

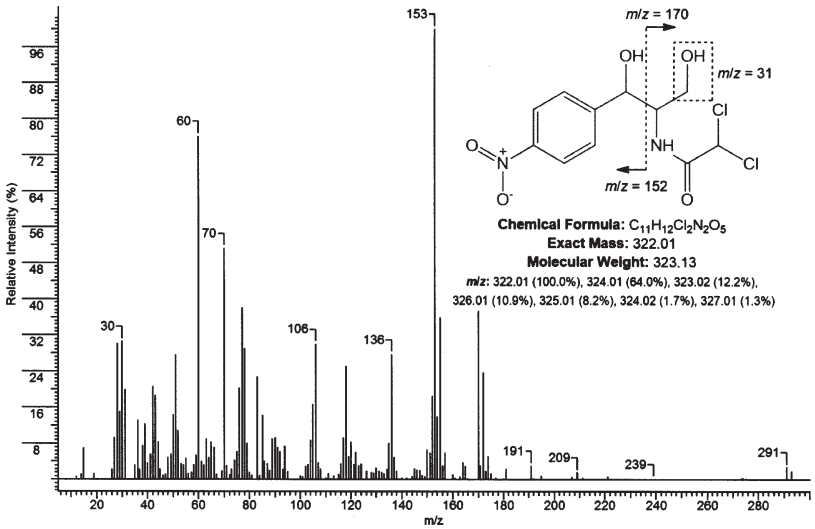

Fig. 7. EI-MS spectrum of chloramphenicol [29d]

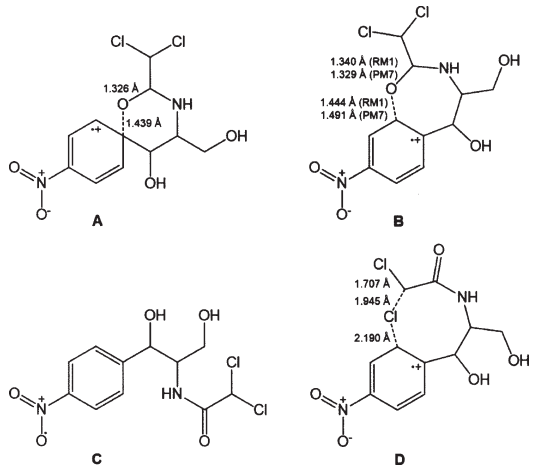

Fig. 8. Possible chloramphenicol radical cation configuration A – RM1 or AMBER99/RM1; B – BIO+/RM1 or PM7 (BFGS); C – MM+/RM1; D – OPLS/RM1

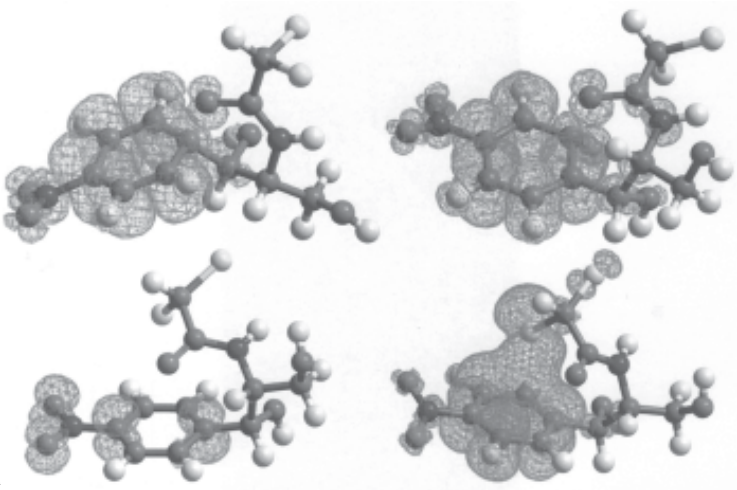

Fig. 9. The radical cations of chloramphenicol (corresponding structures are given in fig. 8); spin density was plotted in *HyperChem*

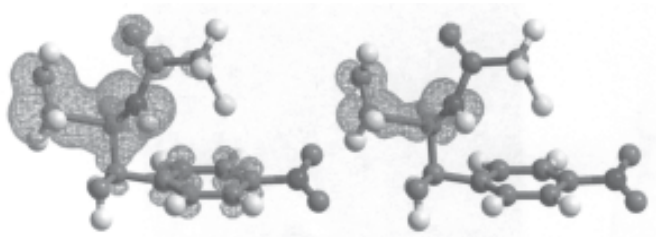

Fig. 10. The C-C long bond in chloramphenicol (PM7 with EF algorithm, followed by RM1); total spin density contour value: left 0.001, right 0.005 (spin density was plotted in *HyperChem*)

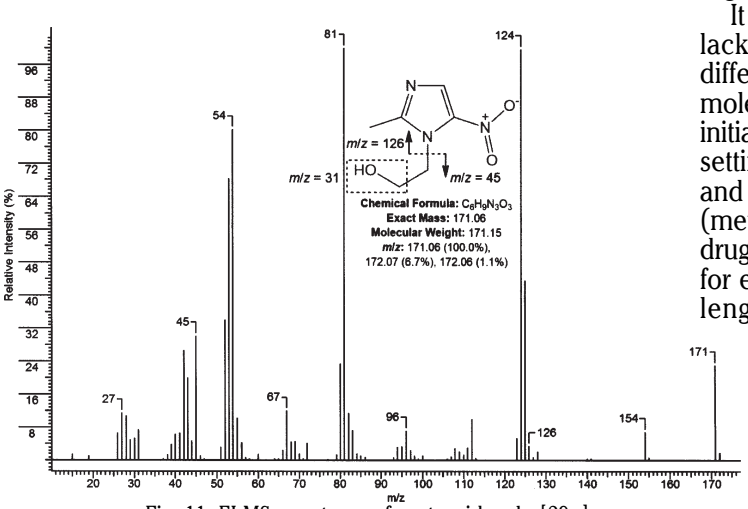

Fig. 11. EI-MS spectrum of metronidazole [29e]

The long bond structure also holds up if subjected to a RM1 geometric re-optimization, giving a new 2.058 A° long bond structure which has the following geometric parameters: N-C-C-O torsion angle (dihedral) 85.283°, N-C-C angle 102.387° and O-C-C angle 101.540°, together with a non-planar amide group (fig. 10). The spin density is distributed between the N-C-C-O atoms (0.373, 0.150, 0.311 and 0.154). The heat of formation for this structure is 72.150 kcal/mol, and thus it is located 14.6 kcal/mol higher than the minimal energy radical cation structure (obtained directly with the RM1 method).

The obtained long bond justifies the *m/z* 291 and 293 mass spectral peaks, which appear due to the cleavage of the CH_2OH radical (the positive charge remaining at the amide nitrogen).

The lowest energy state (MM+/RM1) for the radical cation of metronidazole (EI-MS spectrum in figure 11 [29e]) showed the radical character spread in the imidazole moiety. Another higher energy state (OPLS/RM1) has the radical character located in the nitro group, specifically in its oxygen atoms, with a minor amount in the imidazole moiety. Both variants are shown in figure 12.

The calculated dipyridamole radical cation structures did not present any long bonds that would explain the high intensity peaks at *m/z* 473 and 429 (fig. 13) [29f]. For the minimum energy structure, the radical character seems to be distributed mainly in the nuclei and the nitrogen atoms (fig. 14).

It is also worth mentioning that, because of the general lack of expected long bond radical cation structures, different approaches were also tested for the five drug molecules in their radical cation states. These include the initial setting of the N-C-C-O dihedral to 0° or 180°, the initial setting of the vicinal C-C bond length to the value of 2 A°, and even using the long bond geometries found for 1-(methylamino)propan-2-ol around which the rest of the drug molecule was constructed. In the case of riboflavin, for example, we have also tried setting all the C-C bond lengths in the ribitol moiety at 2 A°, one at a time.

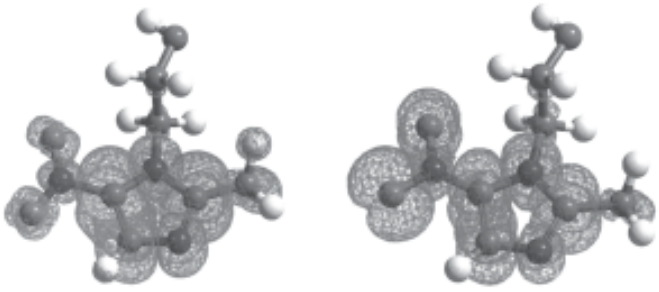

Fig. 12. Two radical cation variants for metronidazole (left, MM+/ / RM1; right, OPLS/RM1); spin density was plotted in *HyperChem*

Unfortunately, even after all these attempts, no significant different results have been found. However, this does not necessarily mean that other long bond variants cannot form in excited states, as intermediary stages in the C-C bond fragmentations for the analyzed radical cations.

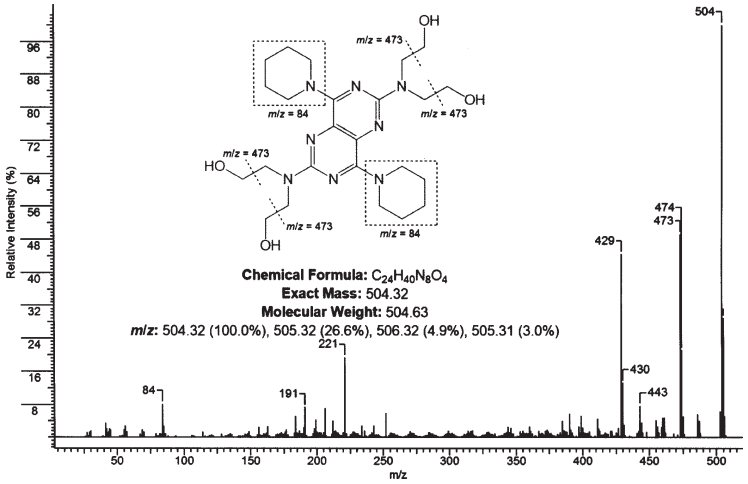

Fig. 13. EI-MS spectrum of dipyridamole [29f]

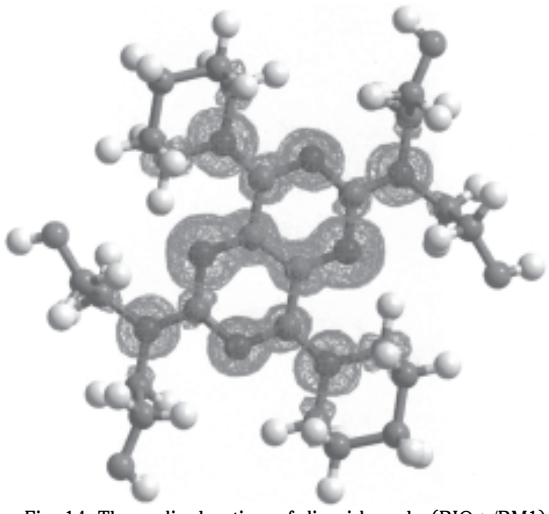

Fig. 14. The radical cation of dipyridamole (BIO+/RM1); spin density was plotted in *HyperChem*

Conclusions

Although two of the three considered model compounds, namely 2-aminoethanol and 1-(methylamino) propan-2-ol, offered examples of long bond structures in their radical cation states, the more complex drug molecules considered in this study do not seem to favor this phenomena, even when starting the geometry optimization from a well-established N-C-C-O long bond geometry. The only exception is chloramphenicol, who presents a long bond in direct relation with the observed pseudomolecular ions at *m/z* 291 and 293 (M-31). All drug radical cations show instead a preference for the localization of the radical character at the nitrogen atom or a delocalization in the aromatic nucleus/nuclei. It is thus difficult to predict the observed EI-MS preferred cleavages for these compounds. The long bond structures in the simpler model compounds, together with the one in chloramphenicol, have higher energies when compared with other forms of radical cations and thus do not represent the fundamental states.

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