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Berberine alkaloid: Quantum chemical study of different forms by the DFT and MP2 methods

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Abstract

The stable structures and electronic properties for the berberine cation as well as possible ammonium, carbinol and amino-aldehyde forms of protoberberine salts in the presence of hydroxyl ions were investigated by the B3LYP/6-31G(d,p) and MP2/6-31++G(d,p) methods. The geometry optimizations by both methods lead to the nonplanar propeller-twisted and buckled structure for the all forms. The obtained bond lengths and bond angles agree with the experimental values. The comparison of total energies elucidates that the amino-aldehyde form is the most preferable tautomer in gas phase, while the carbinol form is less stable. The least stable tautomer is the ammonium form.

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1. Introduction

Natural alkaloid berberine is mainly contained in plants as hydrochloride or sulfate, and its structural formula is $C_{20}H_{19}NO_5$. Berberine hydrochloride is an isoquinoline alkaloid, and in aqueous solution it prevails as quaternary ammonium cation or quaternary ammonium base 9,10-dimethoxy-5,6-dihydro-[1,3]dioxolo[4,5-g]isoquino[3,2-a]isoquinoline-7-ium (by the IUAC nomenclature). Actually, it represents a tetra-substituted alkaloid with methylenedioxy group at C2 and C3 positions and two methoxy groups at C9 and C10 positions as shown in Fig. 1.

A structural formula of alkaloid berberine reported in most of publications and monographs is actually a structure of its cation $[C_{20}H_{18}NO_4]^+$. Berberine exhibits antimicrobial action against a great variety of organisms, including bacteria, viruses, fungi, protozoa and chlamydia [1,2].

One of the most important molecular targets for antitumor agents is DNA-topoisomerase that forms a covalent bond with both strands of helical DNA by breaking and releasing of sugar-phosphate bonds of DNA backbone. Berberine represents a structural class of organic cations that are important determinants of DNA-topoisomerase inhibition inducing a breakage of complex between this enzyme and DNA (so-called topoisomerase poisoning). The topoisomerase poisoning by certain protoberberine alkaloids is associated with their antitumor effect.

Moreover, berberine was found to possess antitumor properties and the O19 position in berberine analogues (see Fig. 1) is a key determinant of DNA-topoisomerase inhibition. Berberine antitumor activity is attributed to its ability to intercalate into DNA specifically binding to AT-rich regions. Like other intercalating agents, berberine complexation is stipulated by its planar structure that facilitates intercalation and subsequent π -stacking with base pairs. The binding of berberine to DNA untwists double helix of DNA by 11° [3], which is consistent with the intercalation mode of interaction between berberine and DNA.

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in solution as an equilibrium mixture of three tautomeric forms, its ammonium, carbinol and amino-aldehyde forms were studied by the MP2/6-31++G(d,p) method. Moreover these tautomeric forms were also studied by the DFT method with B3LYP/6-31G(d,p). The DFT calculations with PW91/6-311G(d,p) were performed using CACHE 5.04 package. At the same for the BLYP/6-311G(d,p), B3LYP/6-311G(d,p), PBEPW91/6-311G(d,p) and B3PW91/6-311G(d,p) calculations, we used PC GAMESS version 7.0 of the GAMESS US quantum chemistry package [8,9]. The main results of our calculations of the berberine cation by MP2/6-31G(d,p) and B3PW91/6-311G(d,p) methods are presented below. The results obtained by both methods are similar each other and moreover they accord with experimental data best of all.

3. Results and discussion

3.1. Stable structure and electronic properties of berberine cation

The bond lengths, propeller twist (PT) angles and dipole moments (μ) of berberine cationic form calculated by MP2/6-31G(d,p) and B3PW91/6-311G(d,p) methods are sum-

marized in Table 1. Table 1 also represents the experimental values for berberine dihydrate bromide [10], berberine azide and berberine thiocyanate [11] obtained by X-ray crystal analysis. It should be noted that the experimental values for some bonds in the berberine salts differ by 0.001–0.029 Å [10–12].

The comparison between the theoretical and experimental data on bond lengths in Table 1 shows a good agreement between them. In the experiments [10,11], the shortest bond in berberine salts was observed for N7–C8 bond in ring C, while the longest bonds are C4a–C5 (sp^2 – sp^3) and C5–C6 (sp^3 – sp^3). Our theoretical results obtained by the MP2 and B3PW91 methods confirm these experimental findings as shown in Table 1.

According to the experimental data, the conformations of cations of all berberine salts are very similar each other. First of all, quaternary cations of berberine consist of hexamers planar rings in the structure of frame. Deviation from planarity is observed only in the partly saturated ring B. The ring B adopts a twisted half-chair conformation with the atoms C5 and C6 significantly deviated from the best plane of the aromatic rings A and C. In all compounds, the dioxolane ring C2–O17–C14–O18–C3 slightly differs from the planar structure. The structure of berberine

Table 1

The bond lengths (Å), propeller twist (PT) angles and dipole moments (μ) of berberine cation form calculated by (1) MP2/6-31G(d,p) and (2) B3PW91/6-311G(d,p) methods are compared with their experimental values [10,11] for (3) berberine dihydrate bromide, (4) berberine azide, and (5) berberine thiocyanate

Bonds	1	2	3	4	5
C1–C2	1.379	1.369	1.358	–	–
C1–C13b	1.414	1.416	1.409	–	–
C2–C3	1.399	1.396	1.359	–	–
C2–O17	1.366	1.355	1.376	1.380	1.366
C3–C4	1.382	1.376	1.373	–	–
C3–O18	1.364	1.347	1.370	1.379	1.366
C4–C4a	1.403	1.400	1.397	–	–
C4a–C5	1.505	1.505	1.506	1.504	1.506
C4a–C13b	1.410	1.404	1.390	1.400	1.402
C5–C6	1.516	1.515	1.499	1.509	1.500
C6–N7	1.484	1.479	1.485	1.492	1.484
N7–C8	1.339	1.332	1.320	1.334	1.332
N7–C13a	1.388	1.389	1.393	1.391	1.390
C8–C8a	1.400	1.393	1.395	1.398	1.400
C8a–C9	1.416	1.423	1.417	–	–
C8a–C12a	1.436	1.430	1.424	1.423	1.410
C9–C10	1.404	1.397	1.375	–	–
C9–O19	1.360	1.342	1.358	1.376	1.364
C10–C11	1.419	1.414	1.408	–	–
C10–O20	1.349	1.346	1.349	1.358	1.350
C11–C12	1.381	1.375	1.358	–	–
C12–C12a	1.411	1.430	1.400	–	–
C12a–C13	1.404	1.406	1.398	1.404	1.406
C13–C13a	1.387	1.377	1.368	–	–
C13a–C13b	1.463	1.463	1.470	1.464	1.469
C14–O17	1.440	1.430	1.409	1.433	1.433
C14–O18	1.441	1.434	1.439	1.442	1.430
C15–O19	1.449	1.438	1.414	1.443	1.427
C16–O20	1.438	1.425	1.435	1.431	1.436
PT (°)	24	21	–	10–15	–
μ (D)	3.917	3.740	–	–	–

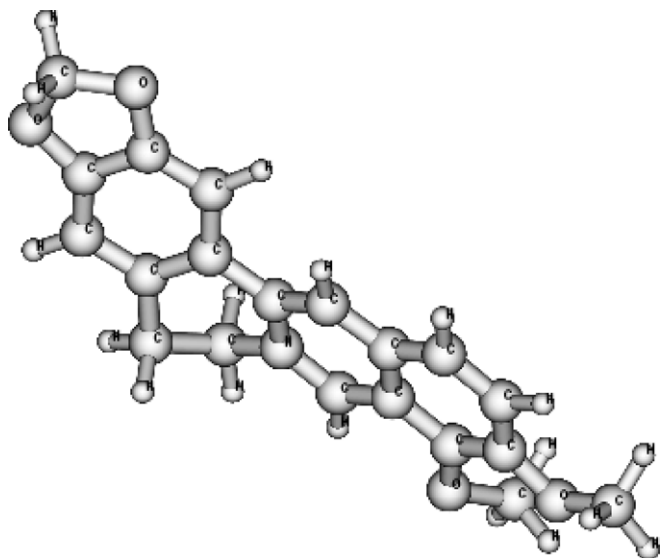


Fig. 2. The stable structure of berberine cationic form obtained by MP2/6-31G(d,p) method.

cation demonstrates that two methoxy groups are oppositely oriented, most likely due to steric constraint. The methoxy group at the position C10 (O20–C16) lies almost in the same plane as the ring D, while the methoxy group at the position C9 (O19–C15) is almost perpendicular to the plane. The calculated results also give evidence that the quaternary cation has relatively planar structure regardless of the theoretical method used. On the whole, the theoretical results obtained by the MP2 and B3PW91 methods are consistent with these experimental data, as shown in Fig. 2.

It is worth noting that in berberine molecule the two aromatic fragments (ring A and fused rings C, D) may be distinguished. According to the experimental data [9–11], the planes of these two fragments are turned one to another by the angle within 10°–15° interval. Meanwhile, in accordance with the results obtained by the MP2/6-31G(d,p) and B3PW91/6-311G(d,p) methods, this angle is 24° and 21°, respectively. Therefore, the theoretically calculated values of the angle noticeably differ from the experimental values. This discrepancy is not surprising, since the calculations were performed for gas phase, while the experimental data were obtained in crystals. In experimentally studied structures, the cations are packed into centrosymmetrical pairs that in turn form the columns parallel to one axis. The space between the columns is filled by anions and water molecules that is evidence of the presence not only of electrostatic forces but also H-bonds in crystals. Therefore, in crystals there are significant packing forces, which affect greatly the spatial structure of berberine cation, resulting in the compact spatial packing.

Thus, the structure of berberine cation obtained by the quantum-chemical investigation gives evidence that rings C and D are most likely to intercalate into DNA helix. This is in agreement with the result of computer simulation [3] for the complexes of protoberberine and DNA.

3.2. Stable structures and electronic properties of berberine tautomers

The structures of three tautomeric forms of berberine (its ammonium, carbinol and amino-aldehyde forms) were optimized in gas phase by the MP2/6-31++G(d,p) method. These optimized structures are shown in Figs. 3–5, respectively. From the comparison of total energies calculated by the MP2/6-31++G(d,p) method, it is elucidated that the most energetically preferable tautomer in gas phase is the amino-aldehyde form shown in Fig. 3. The dipole moment of this amino-aldehyde form is 2.17 D.

The next stable tautomer is a carbinol (non-ionic, prototropic) form, so-called pseudo-base (Fig. 4). This tautomer is less preferable by 19.93 kcal/mol than the most stable one. As seen in Fig. 4, hydrogen bond is formed between the N–H group and the carbonyl oxygen. The pseudo-base has dipole moment of 3.33 D, indicating that this form is stabilized in aqueous solution to the larger degree than the amino-aldehyde one.

The least stable tautomer is an ammonium (ionic, ionotropic) form (Fig. 5), which is less stable by 5.21 kcal/mol than the carbinol one. This fact is not surprising, since the existence of neutral berberine hydroxide is extremely unfavourable in gas phase: one of its fragments is positively charged (ammonium form), while the other is negatively charged (hydroxide). In fact, the initial structure of berberine hydroxide in gas phase could be represented as $[\text{C}_{20}\text{H}_{18}\text{NO}_4]^+[\text{OH}^-]$, but its finally optimized structure appeared to be $[\text{C}_{20}\text{H}_{17}\text{NO}_4] \cdot [\text{H}_2\text{O}]$. In other words, in order that berberine hydroxide does not have localized charges on different fragments, its hydroxyl ion joins a proton of ammonium form and forms a water molecule tightly associated with fragment $[\text{C}_{20}\text{H}_{17}\text{NO}_4]$. This form pos-

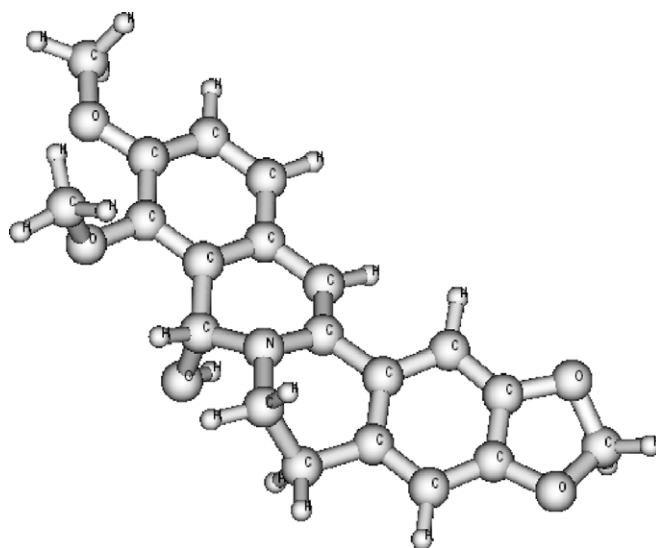


Fig. 3. The stable structure of berberine amino-aldehyde form obtained by MP2/6-31++G(d,p) method.

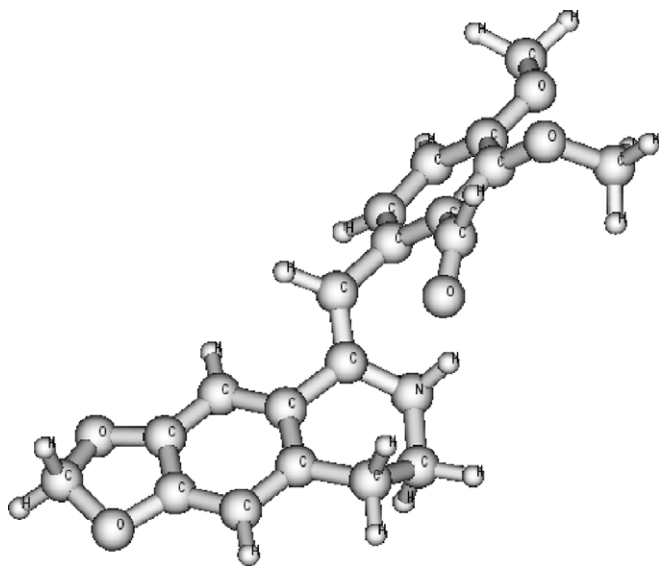


Fig. 4. The stable structure of berberine carbinol form (pseudo-base) obtained by MP2/6-31++G(d,p) method.

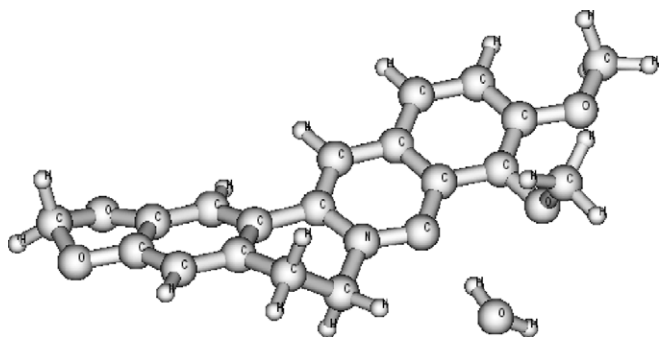


Fig. 5. The stable structure of berberine ammonium form obtained by MP2/6-31++G(d,p) method.

sesses a large dipole moment of 6.22 D, which stabilizes considerably the form in solution.

Although the structure of berberine cation is well known from X-ray crystal analyses [10–12], the structure of the free base of quaternary isoquinoline alkaloid is poorly investigated so far. Some experimental data on the structure of the berberine free base were reported in [13]. The comparison of the calculated values of bond lengths and angles in berberine pseudo-base (8-hydroxydihydroberberine) and the experimental values reveals a good agreement. All bond lengths and angles of 8-hydroxydihydroberberine are within usual values. The calculated length of C8–OH bond is 1.436 Å, while the experimental value is 1.440 Å. The theoretical magnitude of the sum of three valence angles around nitrogen atom is 359.99°, while the experimental value equals to 353.98°. This implies that the hybridisation around nitrogen atom is close to sp^2 hybridisation. Partly hydrogenated hetero-ring B adopts a conformation of twisted half-chair, while the ring C has a conformation of shallow half-chair. The C8 atom is devi-

ated by 0.373 Å from the plane made by the rings C and D. The hemiaminoacetal hydroxyl group C8–OH is located at the axial position as to the ring C conformation as shown in Fig. 4. The methoxy group attached to C9 atom is almost perpendicular to the D plane, while the other methoxy group attached to C10 atom is almost in the plane. The calculated torsion angles are 117.0° [C8a–C9–O19–C15], –66.7° [C10–C9–O19–C15], –176.7° [C9–C10–O20–C16] and 1.8° [C11–C10–O20–C16], respectively. The corresponding experimental values are 117.7°, 71.3°, 175.7° and –3.6°. Therefore, the theoretical data fully agree with the experimental ones [13]. Similar to quaternary berberine salts, this is a general feature of berberine quaternary 8-adducts. Within a reasonable accuracy, the dioxolane ring C2–C3–O18–C14–O17 is planar with the average deviation from the plane of 0.0511 Å. The angle between two aromatic rings A and D is equal to 148.5°. There is a good agreement between this angle and its experimental magnitude.

4. Conclusions

The present quantum-chemical investigations based on MP2 and DFT methods for the tautomeric forms of berberine alkaloid as well as its cationic form proved to obtain a comparable structural parameters to the experimentally observed ones. In spite of the nonplanar propeller-twisted and buckled structures for all berberine alkaloid forms, two rings C and D in the cation remain coplanar structure that is favored for the intercalation into DNA helix.

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