Ab initio calculations of methionines and their protonated forms

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Ab initio calculations of molecular and electronic structures of neutral molecules and protonated forms of methionine and its derivatives in the gaseous phase were carried out by the Hartree—Fock method using the 6-31G* basis set with full geometry optimization. Proton affinities of methionine (**1**), methionine sulfoxide (**2**), and methionine sulfone (**3**) were calculated for different modes of coordination of the proton. The results of calculations demonstrated that in protonated forms of **1** and **3**, bonding between the proton and the N atom is most favorable, while in protonated form of **2**, bonding between the proton and the O atom of the SO group is most favorable. The proton affinities of the amino acids are as follows: 223.2 (**1**), 241.2 (**2**), and 221.5 (**3**) kcal mol^{-1}, *i.e.*, methionine sulfoxide **2** exhibits the highest proton affinity in the series of the amino acids under consideration.

Key words: methionines, *ab initio* calculations, proton affinity.

Determination of thermodynamic and structural parameters of protonated forms of biologically active molecules is of importance in studies of proton transfer processes in biological systems. Experimentally, the basicity of organic compounds in the gaseous phase is studied by mass spectrometry.[1—3] *Ab initio* calculations are also very successfully used for determining the proton affinity.[4,5] For example, the G2 method[6] allows quantitative determination of proton affinities of small neutral molecules and enthalpies of proton transfer.[7] It was demonstrated[8] that the proton affinities of alanine, glycine, and related dipeptides, which were calculated by the Hartree—Fock method with the 6-31G* basis set taking into account entropy factors, differ from the corresponding experimental values by no more than 1.0 kcal mol^{-1}.

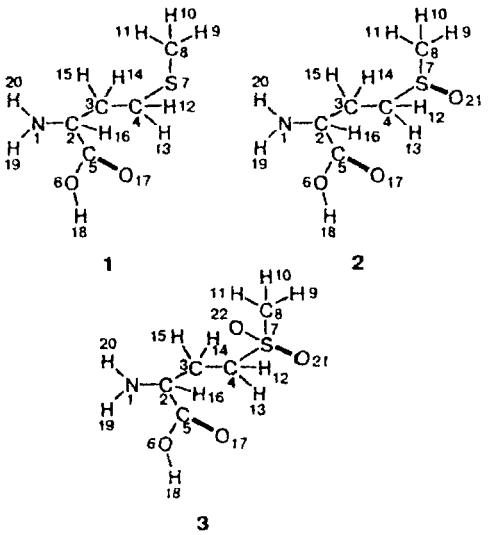
In this work, we calculated molecular and electronic structures of methionine (**1**), methionine sulfoxide (**2**), and methionine sulfone (**3**) in the gaseous phase as well as of the protonated forms of these molecules corresponding to different modes of coordination of the proton.

Calculation procedure

The electronic structures and geometries of neutral molecules **1**—**3** and their protonated forms were calculated by the unrestricted Hartree—Fock method using the GAUSSIAN 92,[9] GAUSSIAN 94,[10] and GAMESS[11] programs with the 6-31G* basis set. The geometries of the molecules were optimized with the 6-31G* basis set. Calculations were carried out on a CRAY C90 supercomputer (Supercomputer Center, Livermore, USA) and on a DEC AXP 3000-400 workstation (A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, Russian Federation).

Molecular and electronic structures of neutral molecules of methionines in the gaseous phase

Below are given the atomic numbering schemes for molecules **1**—**3** used in this work.



1 **2**

3

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Table 1. Optimized interatomic distances (d), bond angles (φ), total energies (E), and dipole moments (μ) of methionine (**1**), methionine sulfoxide (**2**), and methionine sulfone (**3**)

Parameter	1	2	3
Interatomic distance		d/Å	
N(1)—C(2)	1.449	1.450	1.447
C(2)—C(3)	1.539	1.537	1.539
C(3)—C(4)	1.529	1.529	1.528
C(4)—S(7)	1.816	1.807	1.785
S(7)—C(8)	1.810	1.796	1.775
C(2)—C(5)	1.522	1.522	1.523
C(5)—O(6)	1.332	1.333	1.329
C(5)—O(17)	1.188	1.187	1.188
S(7)—O(21)	—	1.486	1.439
S(7)—O(22)	—	—	1.437
Angle		φ/deg	
N(1)—C(2)—C(3)	109.2	109.0	108.8
N(1)—C(2)—C(5)	114.3	113.8	115.0
N(1)—C(2)—H(16)	108.3	108.3	108.4
C(2)—N(1)—H(19)	111.4	111.4	111.3
C(2)—N(1)—H(20)	110.9	111.1	111.0
C(2)—C(5)—O(6)	112.8	112.4	113.0
C(2)—C(5)—O(17)	125.0	125.1	124.4
C(2)—C(3)—C(4)	113.9	113.5	113.3
C(2)—C(3)—H(14)	109.5	109.0	109.7
C(2)—C(3)—H(15)	106.1	105.9	105.9
C(3)—C(4)—S(7)	114.2	113.7	114.0
C(3)—C(4)—H(12)	110.7	111.9	112.3
C(3)—C(4)—H(13)	111.1	112.3	112.3
C(4)—S(7)—C(8)	101.6	99.2	105.7
S(7)—C(8)—H(9)	106.9	109.7	109.8
S(7)—C(8)—H(10)	111.0	106.8	106.1
S(7)—C(8)—H(11)	112.1	111.0	110.3
C(5)—O(6)—H(18)	108.3	108.4	108.5
C(4)—S(7)—O(21)	—	105.9	108.1
C(4)—S(7)—O(22)	—	—	107.0
Total energy		E (au)	
	797.4399	872.2407	947.0967
Dipole moment		μ/D	
	2.1	5.5	5.4

The optimized values of the bond lengths and bond angles in derivatives **1**—**3** calculated by the Hartree—Fock method with the 6-31G* basis set are given in Table 1. In this work, we do not report the results of calculations for numerous conformers of these molecules and restrict our consideration to the most stable configurations. The calculated geometric parameters of the molecule of methionine **1** in the gaseous phase (see Table 1) agree well with the X-ray structural data on the α and β forms of DL-methionine.[12] Table 1 also lists the total energies and dipole moments. The effective Mulliken atomic charges of compounds **1**—**3** are given in Table 2. The N atoms carry the largest negative charges, and the O atoms of the SO and SO_2 groups in **2** and **3** carry rather large charges. The dipole moment of molecule **1** is 2.1 D. The dipole moments of compounds **2** and **3** are larger than 5 D.

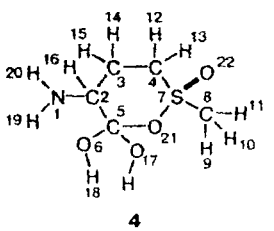
Table 2. Effective charges (au) on the atoms in methionines **1**—**3**

Atom	1	2	3
N(1)	−0.83	−0.84	−0.83
C(2)	−0.07	−0.07	−0.07
C(3)	−0.33	−0.36	−0.37
C(4)	−0.49	−0.57	−0.59
C(5)	0.74	0.74	0.74
O(6)	−0.71	−0.71	−0.70
S(7)	0.12	0.96	1.47
C(8)	−0.64	−0.71	−0.73
H(9)	0.20	0.22	0.25
H(10)	0.19	0.21	0.22
H(11)	0.19	0.19	0.22
H(12)	0.22	0.24	0.22
H(13)	0.20	0.22	0.27
H(14)	0.19	0.20	0.21
H(15)	0.20	0.21	0.23
H(16)	0.21	0.22	0.22
O(17)	−0.56	−0.55	−0.56
H(18)	0.47	0.47	0.47
H(19)	0.35	0.35	0.35
H(20)	0.36	0.36	0.36
O(21)	—	−0.79	−0.68
O(22)	—	—	−0.69

Molecular and electronic structures of protonated forms of methionines in the gaseous phase. Proton affinity

If one ignores temperature-dependent energy contributions and zero-point vibrations, the proton affinity is determined as the difference between the total energies of the neutral molecule and its protonated form.[13] Preliminary calculations demonstrated that the proton can be attached to the N, S, or O atoms of molecule **1**. In the cases of amino acids **2** and **3**, the attack of the proton occurs on the N atom of the amino group, the O atom of the SO (or SO_2) group, and the O atom of the carboxyl group.

The results of calculations of the geometric parameters of the most stable protonated forms of **1**—**3** are given in Table 3. Analysis of the structure of **4** that appears after the attachment of the proton to the O atom of the carboxyl group demonstrated that this positively charged ion has the cyclic structure, which is represented schematically.



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The calculated values of the proton affinities (PA) of the most active positions in molecules **1**—**3** are given in Table 4.

Table 3. Optimized interatomic distances (d) and bond angles (φ) in the protonated forms of amino acids **1**—**3**

Parameter	1			2			3		
	N	O	S	N	O	SO	N	O	SO
Interatomic distance					d/Å				
N(1)—C(2)	1.516	1.449	1.444	1.516	1.424	1.439	1.514	1.433	1.438
C(2)—C(3)	1.540	1.530	1.534	1.539	1.548	1.545	1.534	1.532	1.540
C(3)—C(4)	1.535	1.532	1.541	1.531	1.527	1.536	1.533	1.532	1.542
C(4)—S(7)	1.812	1.813	1.830	1.819	1.821	1.814	1.794	1.778	1.804
S(7)—C(8)	1.812	1.812	1.813	1.796	1.794	1.790	1.769	1.769	1.766
C(2)—C(5)	1.522	1.515	1.525	1.524	1.527	1.526	1.524	1.532	1.524
C(5)—O(6)	1.326	1.266	1.310	1.325	1.260	1.303	1.325	1.337	1.301
C(5)—O(17)	1.175	1.267	1.198	1.174	1.267	1.204	1.177	1.353	1.204
S(7)—H[a]	—	—	1.328	1.476	1.478	1.595	1.437	1.418	1.545
O(21)—H	—	—	—	—	—	0.964	—	—	0.975
S(7)—O(22)	—	—	—	—	—		1.436	1.542	1.421
Angle					φ/deg				
N(1)—C(2)—C(3)	108.6	115.7	108.8	108.8	110.5	108.8	108.1	109.6	108.1
N(1)—C(2)—C(5)	108.8	99.1	113.9	108.7	113.4	115.8	109.5	112.6	115.7
N(1)—C(2)—H(16)	106.6	110.3	107.1	106.6	108.9	107.3	106.1	108.2	107.3
C(2)—N(1)—H(19)	112.4	113.5	112.0	112.1	115.7	112.0	112.2	112.7	112.3
C(2)—N(1)—H(20)	110.9	113.2	112.8	111.0	115.1	112.5	111.3	113.1	112.7
C(2)—C(5)—O(6)	111.5	118.5	112.4	111.3	118.4	114.6	112.0	111.0	114.3
C(2)—C(5)—O(17)	122.6	117.9	124.7	122.6	124.9	122.9	122.0	111.3	123.3
C(2)—C(3)—C(4)	113.4	113.4	115.4	112.4	114.4	118.6	113.7	113.0	117.8
C(2)—C(3)—H(14)	107.7	106.0	109.4	107.7	104.2	110.8	108.0	110.6	110.6
C(2)—C(3)—H(15)	109.5	109.8	106.0	109.2	108.9	104.9	110.0	107.7	105.0
C(3)—C(4)—S(7)	112.5	114.0	117.1	113.3	114.7	116.7	106.5	112.8	115.1
C(3)—C(4)—H(12)	110.8	110.8	112.7	112.0	112.3	112.9	111.6	112.1	114.2
C(3)—C(4)—H(13)	110.5	110.7	111.7	111.4	112.3	108.4	112.1	113.3	109.2
C(4)—S(7)—C(8)	101.7	101.6	105.2	99.2	99.1	101.4	105.1	109.8	107.8
S(7)—C(8)—H(9)	111.0	111.0	107.1	109.8	109.9	109.8	109.7	106.4	109.5
S(7)—C(8)—H(10)	106.5	106.4	107.4	106.8	106.8	107.1	109.7	107.2	106.6
S(7)—C(8)—H(11)	112.5	112.2	111.1	111.1	110.9	108.2	106.2	110.4	107.9
C(5)—O(6)—H(18)	110.5	118.5	110.4	110.5	114.9	110.4	110.5	113.3	110.6
C(2)—N(1)—H	111.0	—	—	111.3	—	—	110.9	—	—
C(5)—O(17)—H	—	118.5	—	—	114.9	—	—	111.9	—
C(4)—S(7)—H[b]	—	—	99.0	104.6	103.6	104.5	106.1	113.1	107.7
C(4)—S(7)—O(22)	—	—	—	—	—	—	106.2	113.9	112.4
S(7)—O(21)—H	—		—	—	—	108.0	—	—	110.6

Note. In the second row of the amino-acid name, the position of attachment of the proton (the N atom, the O atom of the carboxyl group, the S atom, or the SO group) is denoted. [a] For **1**, S(7)—O(21). [b] For **1**, C(4)—S(7)—O(21).

Results and Discussion

The calculations gave the following patterns of the changes in the proton affinity in going from methionine to methionine sulfoxide and methionine sulfone. Qualitative theories assume that the proton affinity of molecules correlates with the effective charge on the atom to which the proton is directly attached. However, for the compounds under consideration, this correlation is not observed, which can be seen by comparing the calculated values of the proton affinity and the effective charges on the corresponding atoms (see Tables 2 and 4). For methionine, the attachment of the proton occurs preferentially to the N atom. As can be seen from Table 2, the effective charges on the N and S atoms of methionine differ significantly, while the difference in the values of the proton affinity is not so large. On the other hand, the effective charges on the N and O atoms are similar, while the proton affinities differ by 25 kcal mol^{-1}. In going from derivative **1** to **2**, the attachment of the proton occurs preferentially to the oxygen atom of the SO group. The carboxyl group acts also as a weak proton acceptor. For compound **3**, the values of the proton affinity of the N atom and of the oxygen atom of the SO group are comparable (~5 kcal mol^{-1} higher for the N atom than for the O atom), while the cyclic protonated form of **4** is less favorable. For methionine sulfide **2**, protonation occurs predominantly at the O atom of the SO group. The difference in the energies of protonation at the oxygen

Table 4. Calculated proton affinities (kcal mol^{-1}) of the most favorable positions of methionines **1**—**3**

Compound	Protonation center	Proton affinity
1	N	223.2
	O	197.2
	S	211.4
2	N	217.1
	O	195.0
	SO	241.2
3	N	221.5
	O	200.6
	SO	216.8

and nitrogen atoms is 24 kcal mol^{-1}. The protonated form of **2**, in which the proton is attached to the O atom of the carboxyl group, is the least stable.

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