Correlations between the quantum-chemical parameters of amino acids and regioselectivity of isotope exchange with the spillover hydrogen

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The effective charges and the proton affinity of carbon atoms of α-amino acids were calculated by quantum-chemical methods. The relative reactivity of the C—H bonds of amino acids under conditions of high-temperature solid-state catalytic isotope exchange (HSCIE) was studied. Correlations between the electron structure of amino acids and the regioselectivity of the solid-state isotope exchange were established. The reactivity of the carbon atoms with high proton affinity increases under HSCIE conditions. An assumption was made that the interaction of a solid organic compound with the spillover hydrogen can be described as the electrophilic substitution at the saturated and aromatic carbon atoms.

Key words: quantum-chemical calculation, proton affinity, effective charge; isotope exchange; spillover-hydrogen.

In the case of interaction of gaseous hydrogen with supported catalysts (metals of the platinum group) the H atoms bound to the surface metal atoms migrate to the carrier. This effect is called the spillover hydrogen.[1] Fast reactions of hydrogenolysis proceed in the solid phase containing an organic or inorganic compound under the action of spillover hydrogen (SH). Among the solid-state processes, the reaction based on the application of high-temperature solid-state catalytic isotope exchange (HSCIE)[2,3] is efficient for synthesizing biologically active compounds labeled with hydrogen isotopes. In this case the isotope exchange proceeds to a large extent with retention of the configuration of carbon atoms to give tritium-labeled compounds with a high degree of substitution and without their racemization. It has been shown by performing HSCIE under conditions of spatial separation of the catalyst on which hydrogen is activated and the solid organic compound coated on the inorganic support that the reaction proceeds with participation of spillover-tritium.[4] A mechanism of the solid-state isotope exchange of hydrogen based on the synchronous transfer of two exchanging protons at one catalytic center has been suggested.[5] This approach was used for the quantum-chemical simulation of HSCIE in alanine. In the experimental study of the HSCIE reaction in L-alanine supported on carbon and calcium carbonate the activation energy of isotope exchange has been determined.[6] This work is dedicated to establishing correlations between the electronic structure of amino acids and the regioselectivity of the solid-state isotope exchange.

Experimental

The ^1H and ^3H NMR spectra of solutions of amino acids in D_2O were recorded on a Bruker AC 250 spectrometer at 250 and 266.8 MHz, respectively. Tritium-labeled amino acids (30—50 mCi) dissolved in 500 μL of D_2O were used in the measurements.[7]

Solid-state isotope exchange between L-amino acids and tritium. A solid mixture containing 0.5 mg of L-amino acid ("Sigma") and obtained by coating 0.5 mg of L-amino acid and 0.25 mg of $RhCl_3$ on 5 mg of the catalyst, 5% Pd/$CaCO_3$ ("Fluka"), was placed into an ampule of volume 10 mL. The ampule was evacuated and filled with gaseous tritium until a pressure of 250 Torr was reached. The reaction was carried out at 150 °C for 20—90 min. The ampule was cooled, evacuated, and blown with hydrogen. The amino acid was desorbed with 0.1 *N* aqueous ammonia containing 20% EtOH. The solution of tritium-labeled amino acid was evaporated to dryness, and then additionally evaporated twice with 20% aqueous ethanol to remove the labile tritium. The chromatographic purification of L-amino acids was performed by ligand exchange chromatography using chiral sorbents with L-Hyp groups.[8] The tritium distribution in the labeled amino acids was studied by the ^3H NMR spectroscopy.[7] The extent of tritium incorporation into amino acids was determined by liquid scintillation analysis.

Determination of relative reactivity of L-amino acids in the HSCIE with tritium. A solid mixture (10 mg) containing two amino acids under study was placed into an ampule of volume 10 mL. The amino acids were separately coated on the catalyst as described above and mixed. L-Valine was used as the reference. The ampule was evacuated and filled with a protium-tritium mixture (300 : 1) until a pressure of 250 Torr was reached. The reaction carried out at 150 °C for 20 min.

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The amino acids were isolated as described above. The chromatographic analysis of L-amino acids was performed by ligand exchange HPLC.[9] Incorporation of tritium into amino acids was determined by liquid scintillation analysis.

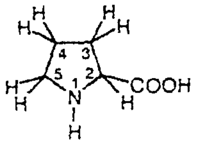
Procedure of Calculations

The systems containing a large number of atoms were calculated by the semiempirical AM1 method incorporated into the AMPAC program. More precise calculations were performed in the Hartree—Fock approximation[10] using various basis sets (STO-3G, 3-21G, 6-31G*, and 6-311G*) and at the second-order Møller-Plesset level of perturbation theory (MP2)[11] using the GAMESS and GAUSSIAN-94 programs. All the calculations of the molecular systems in the ground electronic state were carried out with the full optimization of the energy over geometric parameters including the interatomic distances, and bond and dihedral angles. The electron density distribution in the molecules was analyzed according to Mulliken on the basis of calculations of neutral molecules of amino acids. The proton affinities of amino acids were determined as the differences between the energies of the protonated and neutral molecules of amino acids at the equilibrium geometries.[12] The calculations were carried out on a DEC AXP 3000—400 workstation at the A. N. Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences.

Results and Discussion

Experimental study of the isotope exchange in L-amino acids. In the reaction of HSCIE, tritium activated on a heterogeneous catalyst interacts with the solid organic substance to give isotopically substituted compounds. To study the reaction of the solid-state isotope exchange, natural α-amino acids were selected. These compounds contain asymmetric carbon atoms, which makes it possible to observe the stereochemistry of the replacement of hydrogen by tritium, and remain solid at 200 °C and higher temperatures.

Previously,[4,6] it has been shown that the interaction between hydrogen activated on the catalyst and the solid organic compound occurs outside the metal surface of heterogeneous catalyst, *i.e.*, that this hydrogen is SH. To investigate the HSCIE, regioselectivity of the substitution in α-amino acids was determined under the same conditions, which allowed us to estimate the reactivity of their hydrogen atoms. The effect of the structure of amino acids on their reactivity with respect to the SH was estimated from the ratio of the molar radioactivities in a mixture of two amino acids synthesized in the HSCIE reaction at 150 °C. This temperature was chosen since the amount of tritium formed at lower temperatures and incorporated into the labeled amino acid is insufficient for recording the ^3H NMR spectrum. At higher temperatures, an increase in the overall content of tritium is accompanied by decreasing the regioselectivity of isotope exchange.[4] Determination of the relative reactivities of amino acids (A_{rel}) with respect to L-valine (Table 1) made it possible to reduce the effects of changes in the activity of the catalyst, in the composition of the solid and gas phases, as well as in other parameters of the reaction. The distribution of the isotopic label in aliphatic amino acids obtained in the HSCIE with tritium is also shown in Table 1. The A_{rel} values for L-valine, leucine, and isoleucine are close. Each of these amino acids contains two Me groups most reactive in the course of the HSCIE. The relative reactivity of the only Me group in the L-alanine molecule is also close to that of L-valine. The reactivities of the C—H bonds in the methyl groups of threonine and (*O*-methyl)serine and L-alanine are close. The most reactive are the C—H bonds at the primary carbon atoms. The presence of the oxygen atom at the β-C atom of serine, threonine,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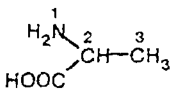
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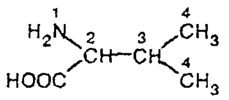
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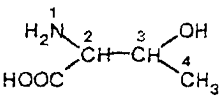
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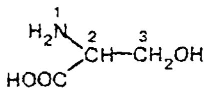
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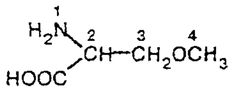
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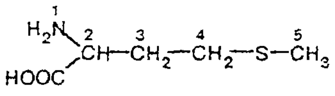
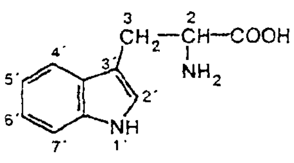

Methionine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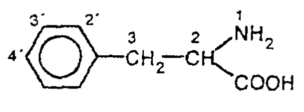

Phenylalanine

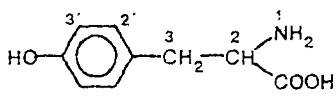

Tyrosine

Table 1. Relative reactivity of amino acids (A_{rel}) with respect to L-valine and distribution of tritium (*C*) in the HSCIE reaction with tritium at 150 °C

Amino acid	A_{rel}	*C* (%)				
		C(2)	C(3)	C(4)	C(5)	C(6)
Ala	0.52	4	96			
Asn	0.75	40	60			
Asp	0.25	40	60			
Arg	2.53	19	23	14	44	
Gly	0.23	100				
Hyp	0.58	6	7	5	83	
Pro	0.63	9	6	4	81	
Met	0.21	75	—	4	21	
Met(O)	0.41	14	—	25	61	
Met(O_2)	0.56	—	—	40	60	
Ser	0.58	70	30			
(OMe)Ser	0.85	29	7	64		
Thr	0.76	18	9	73		
Leu	1.04	4	5	5	86	
Ile	0.95	4	5	5	86	
Lys	2.04	31	10	12	18	29
Val	1.0	4	4	92		

Note. Ala is alanine, Asn is aspartic acid, Asp is asparagine, Arg is arginine, Gly is glutamic acid, Hyp is hydroxyproline, Pro is proline, Met is methionine, Met(O) is methioninesulfoxide, Met(O_2) is methioninesulfone, Ser is serine, (OMe)Ser is (*O*-methyl)serine, Thr is threonine, Leu is leucine, Ile is isoleucine, Lys is lysine, and Val is valine.

and (*O*-methyl)serine results in an appreciable increase in the reactivity of the C—H bond at the α-C atom. The A_{rel} value for aspartic acid is lower while those for basic amino acids, lysine and arginine, are higher than the relative reactivities of aliphatic amino acids containing no ionic groups. It can be noted that similar dependences of the reactivity on the structure of the amino acid residues were observed in the solid-state isotope exchange in the protein β-glycosidase.[4]

The distribution of the isotopic label in the molecules of aromatic amino acids and their relative reactivities are given in Table 2. Histidine is the most reactive compound under conditions of HSCIE; in this case more than 50% of the label is incorporated in position 2′ of the imidazolyl cycle. In the case of phenylalanine, tyrosine, and tryptophan, the β-C atoms in the side chain exhibit the highest ability to exchange. The H atoms in *meta*-position to the hydrocarbon substituent in the aromatic systems of phenylalanine and tyrosine are the most readily exchanged. The H atoms in position 2′ of the heteroaromatic groups of tryptophan were shown to be most reactive toward the SH.

The electron density distribution in neutral molecules of amino acids and its relation to the reactivity under conditions of HSCIE. No data on theoretical studies of HSCIE have been reported in the literature until this work, nor has the nature of the spillover hydrogen coated on an inorganic support been established. For this reason, to elucidate the mechanism of the solid-state catalytic isotope exchange with participation of SH, the correlation between the electronic structure of free molecules of amino acids and their reactivity under conditions of HSCIE was considered as a first approximation. Quantum-chemical calculations of the geometry and electronic structure of α-amino acids were performed.

The calculated charge distribution in the molecules of amino acids is given in Table 3. The relative reactivities of the H atoms of amino acids compared with those of the hydrogen atoms of the Me group of valine are also given in Table 3.

Experimental data on the distribution of tritium in labeled amino acids obtained in the reaction of HSCIE are presented in Table 1.

In the alanine and valine molecules, the largest negative charges are concentrated on the carbon atoms of methyl groups. The H atoms of these groups are exchanged for tritium to the greatest degree. The same regularity is observed for threonine. For these amino acids, the larger the negative charge on the carbon atom, the easier is the exchange of the H atom bonded to it. Such a correlation between the calculated charges of the C atoms and the reactivity of the H atoms bonded to the C atoms is evidence of the electrophilic character of SH in the course of the reaction of HSCIE.

Unlike methionine, the H atoms bonded to the C(4) and C(5) atoms are most reactive in methioninesulfoxide and methioninesulfone. In this case the negative charges concentrated on the above carbon atoms of methioninesulfoxide and methioninesulfone are much larger than those on the corresponding atoms of methionine, whereas the charges on the C(2) and C(3) atoms little differ. Correlations between the value of the negative charge on

Table 2. Relative reactivity of aromatic and heteroaromatic amino acids with respect to L-valine (A_{rel}) and distribution of tritium (*C*) in the HSCIE reaction with tritium at 150 °C

Amino acid	A_{rel}	*C* (%)							
		C(2)	C(3)	C(2′)	C(3′)	C(4′)	C(5′)	C(6′)	C(7′)
His	1.10	20	4	55	—	—	21		
Phe	0.77	13	40	4.5	16	6	16	4.5	
Tyr	0.72	11	35	6	21	—	21	6	
Trp	0.96	11	24	25	—	5	10	10	6

Note. His is histidine, Phe is phenylalanine, Tyr is tyrosine, and Trp is tryptophan.

Table 3. Relative reactivity of the C—H bonds in amino acids with respect to the C—H bond in the Me group of L-valine (R_{rel}) in the HSCIE reaction and distribution of effective charges (q) on the atoms of these amino acids (according to Mulliken) obtained from the AM1 calculations

Amino acid	C(2)		C(3)		C(4)		C(5)	
	R_{rel}	q/e	R_{rel}	q/e	R_{rel}	q/e	R_{rel}	q/e
Ala	0.14	−0.06	1.09	−0.23				
Val	0.26	−0.01	0.26	−0.10	1.00	−0.22		
Ser	2.65	−0.05	0.57	−0.01				
Thr	0.89	0.07	0.44	0.01	1.21	−0.26		
Pro	0.37	−0.07	0.12	−0.17	0.08	−0.17	1.67	−0.08
Met	1.03	0.08	—	−0.02	0.03	−0.08	0.10	0.05
Met(O)	0.38	0.09	—	−0.02	0.34	−0.24	0.55	−0.21
Met(O_2)	—	0.09	—	−0.04	0.72	−0.19	0.73	−0.16

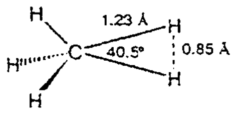
the carbon atom and the reactivity of the H atoms bonded to it is not necessarily observed if the carbon atom is directly bonded to the electronegative N or O atom. As can be seen by the example of proline, methionine, and several other amino acids, the preferable substitution of hydrogen by tritium occurs at the C atoms which have no large negative charge. To understand the reasons for the inconsistency between the charges on the C atoms and the reactivity in the course of HSCIE, it is necessary to consider the nature of the SH and the character of its interaction with the amino acid. Despite the fact that the processes with participation of the spillover hydrogen have long been known, the nature of SH has not been established unambiguously up to the present. According to existing hypotheses, it is a solvated proton,[13] a proton-electron pair,[14] or an atomized hydrogen.[15]

The reaction of isotope exchange of hydrogen based on the use of thermal atomization of gaseous tritium[16] has been studied in more detail. Thermally atomized tritium reacts as a radical particle in the two-stage reaction of isotope exchange. Since in this case an organic radical is obtained as an intermediate, the reactivity of the C—H bonds in amino acids should be dictated by the stability of corresponding radicals. This mechanism is consistent with other experimental data obtained when studying this reaction. The content of isotopic label in the methyl groups of labeled alanine in the case of thermal atomization of tritium is only 12%.[17] If the label is introduced into the α-position of L-alanine, the degree of racemization exceeds 60%.[18] The exchange in L-valine proceeds analogously. A preferable substitution of hydrogen at the tertiary β-C atom is observed for L-valine, L-isoleucine, and L-alloisoleucine.[19] This distribution of the label is in agreement with the assumed two-stage reaction mechanism, since the radicals at the tertiary C atom of amino acids exhibit the highest stability.[20]

Were the spillover tritium to participate in the HSCIE reaction as a radical particle, one would expect that the C—H bonds in the Me groups of alanine and valine would be less reactive than other C—H bonds. In the HSCIE reactions of alanine and valine, the hydrogen of the Me groups is the most readily exchanged. In this case the isotope exchange at the asymmetric α-C atoms proceeds with retention of the configuration. These data suggest that the SH participates in the HSCIE reaction as a proton-like particle rather than a radical particle.

The proton affinity of amino acids and their reactivity under conditions of HSCIE. We performed quantum-chemical calculations of the interaction between the proton and amino acids and determined the energies of the formation of amino acid complexes with proton. In these complexes, the proton is bonded to the saturated carbon atom, thus generating a structure with the pentacoordinated carbon. The structure of the methonium ion, CH_5^+ (Scheme 1), which exists in the gas phase,[16] was taken as a basis for calculations.

Scheme 1



As should be expected, the electronegative N and O atoms of the NH_2, COOH, and OH groups have the highest proton affinity. This is in agreement with the fact that the labile hydrogen in these positions is readily exchanged by tritium in the HSCIE reaction even at room temperature. The isotope exchange at the C—H bonds proceeds at an appreciable rate only at temperatures above 100 °C. Subsequent interaction of the solid phase with the solvent to isolate the labeled amino acid makes it possible to remove the isotopic label from the labile positions with ease. Therefore, only the bonding of the protons to the C atoms was considered in the search for correlations between the regioselectivity of isotope exchange and the proton affinity.

Let us consider the structure of the complexes of amino acids with proton in more detail. All these complexes have a specific fragment at the saturated C atoms; this fragment contains a pentacoordinated carbon atom and an H—H bond similar to that in the methonium ion, CH_5^+. As a rule, the complexes, in which the bonded proton can be additionally coordinated to the O, N, or S atoms of the amino acid with the formation of corresponding cycles, appear to be the most stable. The alanine complex with proton in β-position (Scheme 2, **B**; Table 4) is an example of this type of structure. The existence of similar structures is confirmed by *ab initio* calculations. The structure obtained by *ab initio* method differs from that obtained by the AM1 method only in the additional coordination of the H(12) atom to the N atom. Similar structures were also found for other amino acids. No additional stabili-

Table 4. Geometric parameters (*r* are interatomic distances, ω are bond angles, and φ are dihedral angles) of alanine complexes with proton in the α-position (**A**, see Scheme 2) and β-position (**B**, see Scheme 2)

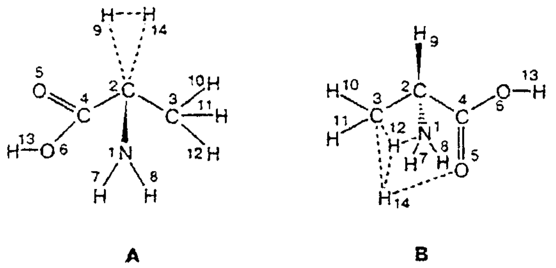
Parameter	Complex **A**, AM1	Parameter	Complex **B**	
			AM1	HF/3-21 G
Distance	*r*/Å	*Distance*	*r*/Å	
N(1)—C(2)	1.37	N(1)—C(2)	1.44	1.47
C(2)—C(3)	1.54	C(2)—C(3)	1.53	1.52
C(2)—C(4)	1.55	C(2)—C(4)	1.53	1.52
C(4)—O(5)	1.22	C(4)—O(5)	1.24	1.20
C(4)—O(6)	1.34	C(4)—O(6)	1.34	1.32
N(1)—(7)	1.00	N(1)—H(7)	1.00	1.01
N(1)—H(8)	1.00	N(1)—H(8)	1.00	1.01
C(2)—H(9)	1.37	C(2)—H(9)	1.14	1.08
C(2)—H(14)	1.37	C(3)—H(10)	1.12	1.08
C(3)—H(10)	1.12	C(3)—H(11)	1.12	1.08
C(3)—H(11)	1.12	C(3)—H(12)	1.36	1.29
C(3)—H(12)	1.12	C(3)—H(14)	1.48	1.27
O(6)—H(13)	0.98	O(6)—H(13)	0.98	0.97
O(5)—H(9)	2.30	O(5)—H(14)	2.02	2.19
O(6)—H(9)	3.27	O(6)—H(14)	3.79	3.76
N(1)—H(9)	2.18	N(1)—H(14)	3.10	2.70
O(5)—H(14)	2.78	O(5)—H(12)	2.69	2.72
O(6)—H(14)	3.60	O(6)—H(12)	4.17	3.84
N(1)—H(14)	2.25	N(1)—H(12)	2.79	2.12
H(9)—H(14)	0.76	H(12)—H(14)	0.82	0.85
Angle	ω/deg	*Angle*	ω/deg	
N(1)—C(2)—C(3)	116.9	N(1)—C(2)—C(3)	110.8	104.5
N(1)—C(2)—C(4)	116.7	N(1)—C(2)—C(4)	113.3	106.1
C(2)—C(4)—O(5)	124.5	C(2)—C(4)—O(5)	123.4	121.6
C(2)—C(4)—O(6)	112.3	C(2)—C(4)—O(6)	115.3	111.5
H(7)—N(1)—C(2)	120.7	H(7)—N(1)—C(2)	112.2	114.1
H(8)—N(1)—C(2)	120.1	H(8)—N(1)—C(2)	113.4	113.4
H(9)—C(2)—N(1)	105.5	H(9)—C(2)—N(1)	112.7	116.6
H(14)—C(2)—N(1)	110.7	H(10)—C(3)—C(2)	113.7	115.7
H(10)—C(3)—C(2)	107.8	H(11)—C(3)—C(2)	113.1	117.0
H(11)—C(3)—C(2)	112.0	H(12)—C(3)—C(2)	109.6	93.7
H(12)—C(3)—C(2)	110.3	H(14)—C(3)—C(2)	103.3	105.4
H(13)—O(6)—C(4)	110.0	H(13)—O(6)—C(4)	110.7	115.6
C(4)—O(5)—H(9)	62.6	C(4)—O(5)—H(14)	94.6	89.3
Angle	φ/deg	*Angle*	φ/deg	
N(1)—C(2)—C(4)—O(5)	−131.1	N(1)—C(2)—C(4)—O(5)	107.1	105.6
N(1)—C(2)—C(4)—O(6)	50.7	N(1)—C(2)—C(4)—O(6)	−71.9	−70.3
N(1)—C(4)—C(3)—H(10)	−68.3	N(1)—C(2)—C(3)—H(14)	−90.3	−70.3
N(1)—C(2)—C(3)—H(11)	51.2	C(2)—C(4)—O(5)—H(14)	−6.1	−16.5
N(1)—C(2)—C(3)—H(12)	173.2	C(2)—C(4)—O(6)—H(13)	−179.8	178.4
C(2)—C(4)—O(6)—H(13)	176.4	C(4)—C(2)—C(3)—H(10)	168.4	173.4
C(2)—C(4)—O(5)—H(9)	15.9	C(4)—C(2)—C(3)—H(11)	−63.2	−52.8
C(2)—C(4)—O(5)—H(14)	0.9	C(4)—C(2)—C(3)—H(12)	67.3	79.5
N(1)—C(2)—H(9)—H(14)	−104.3	C(4)—C(2)—C(3)—H(14)	33.2	41.8
		N(1)—C(2)—C(3)—H(12)	−56.3	−32.6

Table 5. The proton affinities (*PA*) of the C—H bonds of aliphatic amino acids (according to the AM1 calculations)

Amino	*PA*/kcal mol^{-1}			
acid	C(2)	C(3)	C(4)	C(5)
Ala	83.0	88.5	—	—
Val	87.9	90.9	99.9	—
Ser	74.5	80.0	—	—
Thr	80.8	82.2	93.5	—
Pro	78.1	85.5	77.7	88.6

zation is observed for the alanine complex with proton in α-position (Scheme 2, **A**).

Scheme 2



As can be seen from a comparison of the data in Tables 1 and 5, in the case of alanine, valine, serine, and threonine molecules, tritium is preferably incorporated into the positions with highest calculated proton affinity and almost never incorporated into the positions characterized by the lowest proton affinity. Based on a comparison between the regioselectivity of the hydrogen substitution in the HSCIE reaction and quantum-chemical calculations of the stability of the complexes with proton, one can assume that the SH interacts with the aliphatic C—H bonds with the reversible formation of transition states with nonclassical pentacoordinated carbonium ions. The higher the total energy of the formation of protonated amino acids, the more readily such type ions can be generated. The possibility of additional interaction with the heteroatoms increases the stability of complexes with proton, thus making the isotope exchange easier. The fact that the configuration of the asymmetric C atoms is retained in the course of HSCIE also shows that this reaction proceeds *via* intermediate formation of ions with the pentacoordinated carbon atoms.

Calculations of the proton affinities for different atoms of aromatic and heteroaromatic groups of amino acids also confirms this regularity. The experimental data and the corresponding results of calculations are presented in Tables 2 and 6, respectively. The character of interaction of the proton with the aromatic C atom differs from the bonding with the aliphatic CH group. In this case a rather stable σ-complex is formed. This is likely the reason for the fact that the carbon atoms of aromatic groups have an appreciably higher proton affinity than the aliphatic C atoms in the same compounds. The degrees of hydrogen substitution at aromatic and aliphatic carbon atoms are close under conditions of HSCIE. This can be associated with close activation energies of the reactions of isotope exchange at aromatic and aliphatic carbon atoms. The reactivity of the aromatic C—H bonds of amino acids can change fundamentally with change in the mechanism of isotope exchange. In the case of thermal atomization of tritium the substitution of hydrogen in aromatic amino acids proceeds only in the side chain,[22] whereas in the case of acid homogeneous catalysis almost all substitution proceeds in the aromatic nucleus.[23] In the case of isotope exchange between phenylalanine and gaseous tritium on heterogeneous platinum catalysts in solution the isotope substitution affects the β-C atom of amino acid with high regioselectivity.[24] Data on the tritium distribution in the labeled phenylalanine suggest that the mechanism of HSCIE with participation of SH differs from the mechanism of the known reactions of isotope exchange of hydrogen.

In the temperature interval under study, the protons in the solid phase exist as complexes with electron-donor heteroatoms. The proton transfer from such a center to the C atom of a solid organic compound most likely corresponds more closely to the facts. The *ab initio* calculations for L-alanine have shown that the results of the quantum-chemical simulation are in satisfactory agreement with the experimental dependences.[6] The geometry of the pentacoordinated carbonium ion in the transition state appears to be close to that of the corresponding alanine complex with proton.

Thus, the spillover-hydrogen is of electrophilic nature, and the negative charge on the carbon atom favors the interaction of spillover-hydrogen with organic com-

Table 6. The proton affinities (*PA*) of the C—H bonds of aromatic amino acids (according to the AM1 calculations)

Amino	*PA*/kcal mol^{-1}							
acid	C(2)	C(3)	C(2′)	C(3′)	C(4′)	C(5′)	C(6′)	C(7′)
Phe	90.3	90.3	129.0	133.4	130.3			
Tyr	79.8	91.4	129.2	136.5				
Trp	92.3	99.6	154.2	—	152.1	152.6	150.9	152.1

pounds. The high-temperature solid-state catalytic isotope exchange can be considered as reversible electrophilic interaction between the SH in the form of a proton and the saturated carbon atom of the solid organic compound. In this case the formation of positively charged complexes with the pentacoordinated C atom is possible. The higher reactivity of the C—H bonds corresponds to the higher proton affinity.

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