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Modelling of Bonding Energy in the Glycosides of Quercetin and Anomers of *D*-Glucopyranose and *L*-Rhamnopyranose

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Abstract

The structures of glycosides formed in the interaction of polyphenolic compound quercetin as a model aglycon with a carbohydrate anomer, by the examples of *D*-glucopyranose and *L*-rhamnopyranose, were considered by means of computer modelling. The probability for the simulated structures to exist was estimated relying on bonding energy (as a change in the system energy) for different versions of aglycon binding to carbohydrate. A preferable type of the formed structures is binding between 3,5,7-hydroxyl group of quercetin with 1,4,6-hydroxyl groups of *D*-glucopyranose or 1,2,4-hydroxyl groups of *L*-rhamnopyranose.

Keywords: quercetin, *D*-glucopyranose, *L*-rhamnopyranose, glycosides, system energy

INTRODUCTION

Biologically active systems are to meet a number of mutually exclusive requirements. In particular, they need to ensure transport in living organisms, the solubility of biologically active substances (BAS) and systems in water. On the other hand, BAS are often insoluble. For example, most natural flavonoids, one of the main classes of plant compounds, are water-insoluble [1] and thus biologically unavailable.

There are some methods to provide the solubility of flavonoids including quercetin, which is required in various branches of industry. The formation of glycosides composed of two parts, namely poorly soluble aglycone and a soluble carbohydrate, allows one to enhance the solubility in water and provide biological availability of the preparations. The formation of glycosides from insoluble bioflavonoids derived from plant-based raw materials during the processes accompanying mechanical activation substantially broadens the range of the application of flavonoids, improves the environmental safety of the resulting preparations and the technological advantages of their manufacturing [2, 3].

Glycosylation is the interaction of a carbohydrate with a counteragent through an oxygen atom in hydroxy groups. Biological activity of the glycosides of a definite aglycone depends on the type of carbohydrate incorporated into the structure and on the glycoside structure. Since both flavonoids and carbohydrates have complex structures, the types of interaction can vary, and different structures can be formed. Questions arise: a) what is a numerical measure of the reactivity of hydroxy groups in the carbohydrate and in the aglycone; b) is it possible to obtain glycosides through all hydroxy groups of the carbohydrate without additional action (protective methylation *etc.*) and through all hydroxy groups of quercetin *via* direct interaction?

These questions can be solved by modeling the bonding energies in the formed structures. This approach allows one to assess the feasibility and direction of glycosylation during mechanochemical treatment. Potential energy of the system is one of the parameters characterizing sta-

bility of the compounds formed during the model study.

The goal of this study was to carry out a model investigation of changes in the potential energy of the system composed of quercetin and a *D*-glucopyranose or *L*-rhamnopyranose anomer and to determine the preferential resulting structure.

MODEL EXPERIMENT

Computer modeling of glycoside structures was carried out using the molecular mechanics method in the Ghemical software [4]. Optimization of the geometry and calculation of the potential energy were carried out using the GhFF potential (Ghemical). The more probable state had lower potential energy.

In the model, we varied the type of carbohydrate (*D*-glucopyranose or *L*-rhamnopyranose) added to quercetin molecule. Carbohydrate molecules were considered only in the cyclic pyranose form, while the effect of the open (linear) and furanose forms was not taken into account. Glucose and rhamnose in the pyranose form were considered in α- and β-anomeric modifications.

RESULTS AND DISCUSSION

The main complex component of glycoside is quercetin (general formula $C_{15}H_{16}O_7$, molecular weight M = 302 g/mol). The 2D structural formula of quercetin is shown in Fig. 1. The systematic name of quercetin is 3,3′,4′,5,7-pentahydroxyflavon. Cycles A, C and the attached cycle B are distinguished in quercetin molecule. Quercetin acts as an aglycone in the interaction with a carbohydrate. The interaction of carbohydrate molecule is possible at hydroxyl groups with the formation of an ether (including glycoside) bond.

Carbohydrates under consideration are: *D*-glucopyranose (general formula $C_6H_{12}O_6$, M = 180 g/mol); *L*-rhamnopyranose (general formula $C_6H_{12}O_5$, M = 164 g/mol). *D*-glucose is the most thermodynamically stable hexose [5]. Six-membered cycles of both carbohydrates occur in nature in comparable amounts in the form of two α- and β-anomers which are in equilibrium with each other due to mutarotation. For *D*-glucopyranose, α-anomer is more widespread.

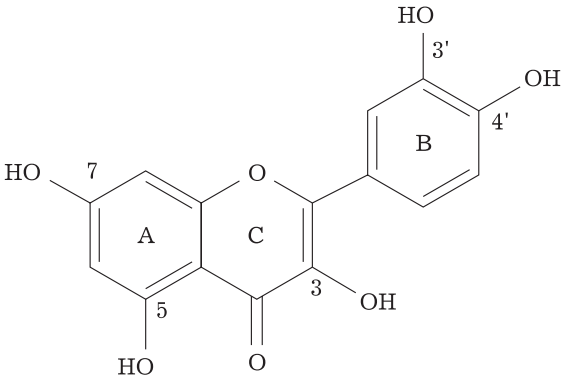

Fig. 1. Quercetin.

Further detailed elaboration of the six-membered carbohydrate cycle indicates that there are various conformational isomers. The pyranose cycle has a chair conformation. To consider the configuration, we may draw a plane through C2, C3, C5 and O atoms. It is generally accepted that a more stable conformation of *D*-glucopyranose is $^4C_1$, with C4 atom located above the plane, and C1 atom below it. In *L*-rhamnopyranose, $^1C_4$ conformation is more stable [5].

The obtained models of the structures of α- and β-*D*-glucopyranose and *L*-rhamnopyranose are presented in Fig. 2. They differ only by the position of the glycoside hydroxyl at the C1 atom: in the α-anomer it is perpendicular to the plane of the cycle (the axial position), while lying almost in the cycle plane in the β-anomer; therefore, all the substituents in β-*D*-glycopyranose are equatorial.

The following designations will be accepted: q3′H = $C_{15}H_{15}O_6$–O(3′)H – quercetin molecule in which the active hydroxyl group is attached to the 3′ carbon atom; a(b)-g1 = α(β)-1-*D*-$C_6H_{11}O_5$–OH is α(β)-O-glucopyranose molecule with active hydroxyl at C1 atom. The resulting glycoside of

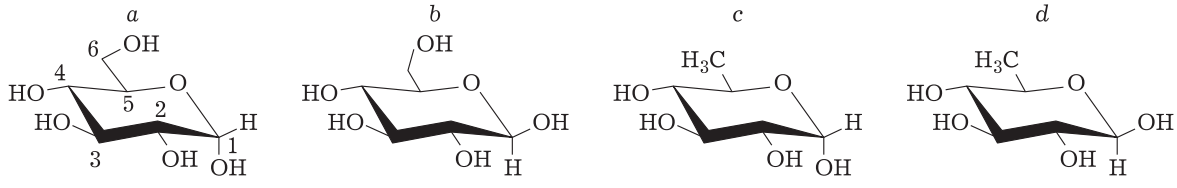

Fig. 2. Structural formulas of anomers: α-*D*-glucopyranose (*a*), β-*D*-glucopyranose (*b*), α-*L*-rhamnopyranose (*c*), β-*L*-rhamnopyranose (*d*).

the α-anomer may be written as q3′−a-g1. Thus, the formal reaction of glycoside formation is written as

$C_{15}H_{15}O_6$−O(3′)H + α-1-*D*-$C_6H_{11}O_5$−O(1)H →
$C_{15}H_{15}O_6$−O(3′) − α-1-*D*-$C_6H_{11}O_5$ + H_2O
or

q3′H + a-g1OH → q3′−a-g1 + H_2O

$\Delta E = E$(q3′−a-g1) + $E(H_2O)$ − E(q3′H) − E(a-g1OH), where E is the potential energy of reagents or products; ΔE is the change in the potential energy of the system (bonding energy).

A similar abridged notation of glycoside formation from quercetin (q3′H) and α-anomer of *L*-rhamnopyranose with active hydroxyl at C1 (a-r1OH) looks like

q3′H + a-r1OH → q3′−a-r1 + H_2O

$\Delta E = E$(q3′−a-r1) + $E(H_2O)$ − E(q3′H) − E(a-r1OH)

Reactions of the formation of other glycosides can be written in a similar manner.

The values of reaction energies ΔE determined by modeling (bonding energies) are presented in Fig. 3, 4. The most advantageous structure for the complex of quercetin with α-*D*-glucopyranose was determined by modeling (see Fig. 3, *a*). Among the twenty-five possible variants of positions, addition at the following positions is energetically favorable: q3g1, q3g6, q5g6 and q7g6. For these variants $\Delta E < 0$, which points to a substantial probability of the reaction (glycosylation) to proceed. The variants of glycoside formation at the positions 3′ and 4′ of cycle B in quercetin are the least probable ones because they are accompanied by a substantial increase in the energy of the system. This determinancy may lead to the formation of long polysaccharide chains with the clearly expressed repeating structural unit [5]. For the complex of quercetin with β-*D*-glucopyranose (see Fig. 3, *b*), q4′g6′ is also allowed in addition to the aforementioned combinations; however, all of them possess lower absolute energies of the reaction and are less sterically distinguishable. The latter factor is important for the formation of oligo- and polyglycosides and leads to obtaining branched structures. All other positions are characterized by $\Delta E > 0$.

Modeling of formation of a complex between quercetin and rhamnose showed that among twenty possible positions (Fig. 4) the energetically favorable variants ($\Delta E < 0$) are as follows: q3r1, q3r4, and q5r4 for α-anomers and q3r1, q3r2 for β-anomers.

With comparable ΔE values, reactions proceed *via* parallel routes with the formation of different products. Because of this, to obtain the target compound, it will be necessary both to purify the product and to apply various precautions during the synthesis, in particular, protective methylation of hydroxyl groups. In our case, the simultaneous formation of glycoside products with $\Delta E < 0$ will take place.

The results demonstrate that the reactivity of the reagents changes: the activity of flavonoid quercetin decreases in the sequence of carbon atom positions 3 > 5 > 7 > 3′, 4′; for glycopyranose − in the sequence 1, 6 > 4 > 2, 3; this activity also depends on the type of carbohydrate anomer (α- or β-).

The predicted leaders in the reactivity are quercetin through the hydroxy group at carbon atom 3 and *D*-glucopyranose through the hydroxy group at carbon atom 1 (α-anomer) and 6

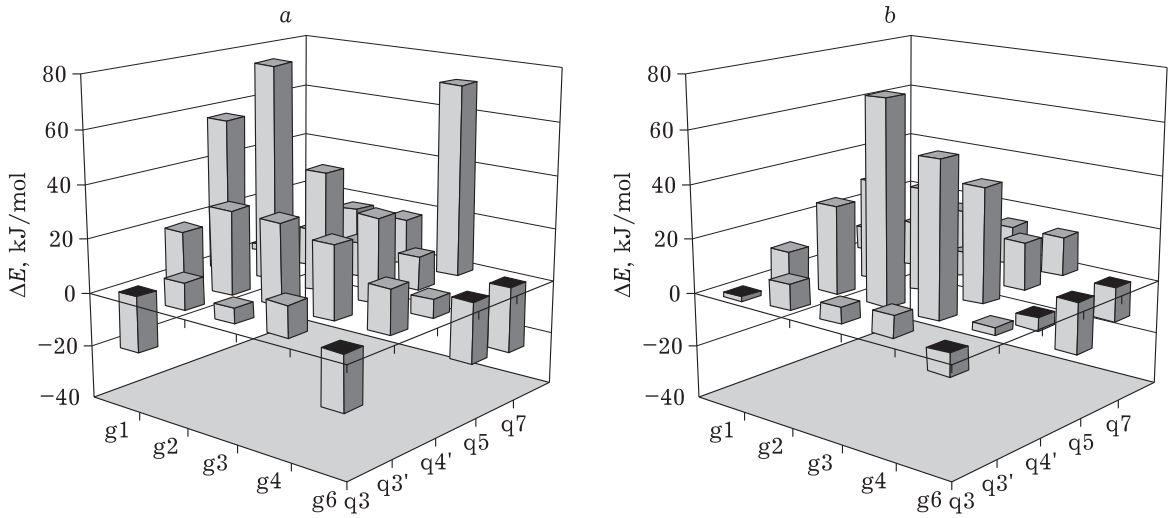

Fig. 3. Bonding energy for quercetin and *D*-glucopyranose: α- (*a*) and β-anomers (*b*); figures mean the positions of carbohydrate (g) addition to aglycone (q).

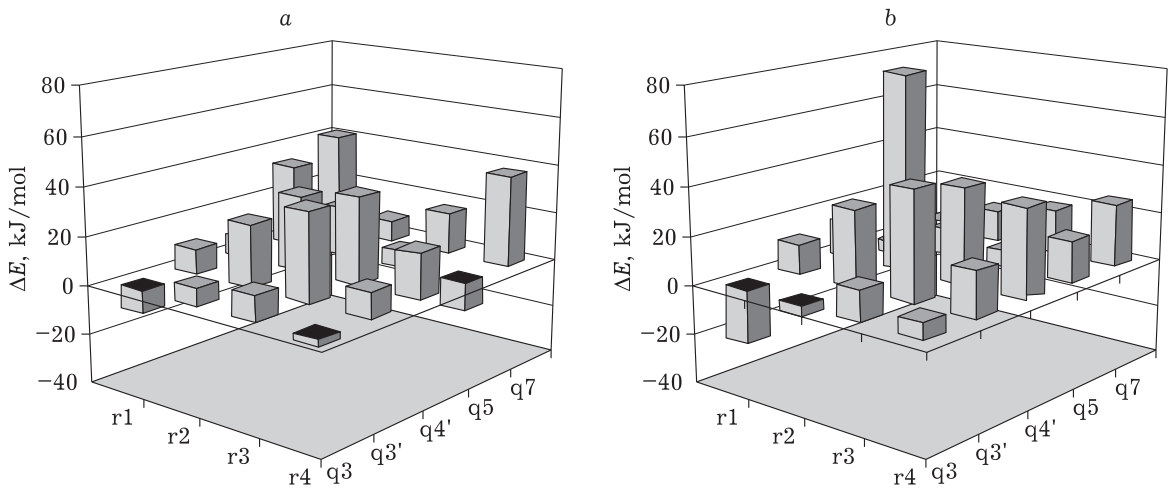

Fig. 4. Bonding energy for quercetin and *L*-rhamnopyranose: α- (*a*) and β-anomers (*b*); figures mean the positions of carbohydrate (g) addition to aglycone (q).

(β-anomer), their interaction proceeds with a substantial lowering of the system energy. In the calculated version (modeling) the reaction is accompanied by the formation of a stable product. An important reason in favor of comparison between modeling and experiment is the idea that calculation results explain the existence of the natural compounds of the considered isomers, for example, isoquercetin.

On the other hand, one may expect that the formation of isomers accompanied by positive changes in energy of the system will be prohibited in the reaction of direct interaction (*e.g.*, during mechanochemical synthesis).

The presented result differs from the data obtained previously for the interaction between quercetin and silica. Whereas in the quercetin–silica system, the reaction through hydroxy groups of quercetin at C3' and C4' atoms of cycle B is an appreciably energetically favorable interaction [6], the most reactive hydroxyl groups in the reactions with carbohydrates are those at C3, C5, and C7 atoms of the C ring.

CONCLUSIONS

1. Modeling of glycoside structures formed by flavonoid quercetin and carbohydrate glucose or rhamnose was carried out by means of molecular mechanics.

2. The most probable structures that can be formed *via* direct interaction between the reagents were determined for the potential energy parameter.

3. Comparative estimations of the reactivity of hydroxy groups in different positions in flavonoid quercetin and in carbohydrates glucose and rhamnose are presented.

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