საქართველოს მეცნიერებათა ეროვნული აკადემიის მოამბე, ტ. 10, №4, 2016
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Physical Chemistry

Modeling of the Synthesis of Sulfanilamide Monoglucoside by Quantum-Chemical Method

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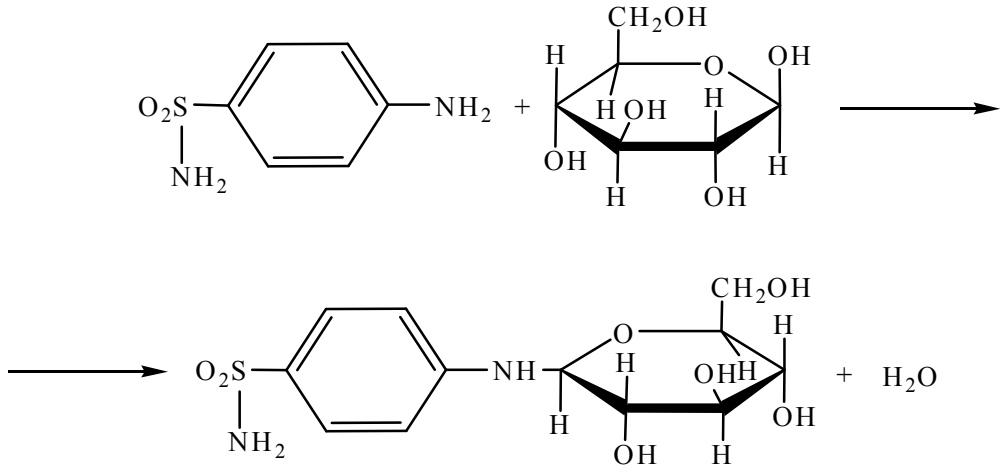
ABSTRACT. The transfer of sulfanilamide preparations into water-soluble forms (streptocide, sulfidinum, sulfazolum and others) gained great importance especially in medicine as bacteriostatic agents towards a number of pathogenic microorganisms. By binding of carbohydrate molecules the insoluble drugs are dissolved in water and easily absorbed into the body, their toxicity is significantly reduced, which significantly increases the effectiveness of treatment preparations. Such approach is now widely used for "ennobling" of anti-cancer drugs and other medicines. The quantum-chemical method AM1 calculations were applied during conducting sulfanilamide interaction with *D*-glucose molecule diluted in alcohol area by formation of sulfanilamide monoglucoside. Proceeding from the comparison of activation energies (ΔΔH # = 427.77 kJ/mol, ΔΔH # = 781.03 kJ/mol) and the reaction of thermal effects (ΔΔH = 109.02 kJ/mol, ΔΔH = 110.66 kJ/mol) the paper represents the interaction of sulfanilamide with two molecules of glucose diluted in alcohol area by formation of sulfanilamide diglucoside that is energetically favourable. It is possible to provide the formation of diglucoside by sequential reactions in more favorable conditions, which are the subject of further research. © *2016 Bull. Georg. Natl. Acad. Sci.*

Key words: sulfanilamide, glucose, monoglucoside, quantum-chemical method AM1

Traditional approach to the solution of efficiency of medical preparations problems is the search of new classes of defined biologically active compounds as well as creation of already known structural analogues of pharmacological preparations for the purpose of increasing of the therapeutic effect and reducing of the toxicity action.

The glycosylation principle of medicinal remedies based on the carbohydrate fragments of active transport in cell membranes is considered be a new approach to creation problem of targeted action of effective medical preparations[1-3]. The deficiency of the preparations being insoluble in water can be taken only by the internal way or external influence. This circumstance limits their usage in medical practice; in case of the possible usage it is necessary to take



Scheme. Synthesis sulfanilamide monoglucosides.

them in large doses. The transfer of insoluble drugs in water-soluble forms is extensively used in medical practice, as it is possible to inject them subcutaneously or intravenously, which in turn, change not only the speed of assimilation, but nature of validity. The transfer *of sulfanilamide* preparations in water-soluble forms gained great importance especially in medicine as bacteriostatic agents towards to a number of pathogenic microorganisms[4]. By „binding" of carbohydrate molecules the insoluble drugs are dissolved in water and easily absorbed into the body and their toxicity is significantly reduced, which significantly increases the effectiveness of treatment preparations. Such approach is now widely used for „ennobling" of anti-cancer drugs and other medicines.

Interaction of sulfanilamide with glucose by formation of mono- and diglucosides was studied experimentally by A.M. Gakhokidze. The purpose of our study was theoretical confirmation of results and the fixation of recommendations for improving experiments [5]. The calculations are carried out by means of semi-empirical quantum-chemical method – AM1, for full characterization of the reaction [6]. For all initial, intermediate and final products there were calculated formation heat (ΔH_f), a system of energy transfer (ΔH) on bond distance (R_{C-N}) alteration, as well as the meanings of charges on atoms (q_i), dipole moments (μ) and bond orders (P_{ij}). For the purpose of preservation of β anomerical structure of *D*-glucose, some valent and dihedral angles were preserved in a constant fixing regime maintained in a series of calculations.

Interaction of sulfanilamide in the area of one molecule of *D*-glucose diluted with alcohol ($C_{\omega\%}$ = 95, ε = 24.95) by monoglucoside of sulfanilamide formation was considered.

The distance between N_{13} amino group nitrogen atom and C_1 glucose carbon atom connected with C_{14} atom of carbon of sulfanilamide was taken more than 1.0 Å than bond distance in the final product. The alteration of R_{C-N} distance between N_{13} atom and C_1 atom, as well as R_{N-H} N_{13} atom and H_{37} atom, between R_{C-O} – O_8 atom and C_1 atom happened by 0.05 Å intervals. The dependency of energy system alteration (ΔH) between nitrogen and carbon atoms R_{C-N} distance is given in Fig. 1.

As Fig.1 shows, the system of energy increases at approaching of N_{13} atom to the C_1 atom to the distance of R_{C-N} = 1.84 Å. The bond order between N_{13} and C_1 atoms increases from 0.008 to 0.480. At the same time the bond order decreases between N_{13} and H_{37} atoms (P_{N-H} = 0.890-0.632) and O_8 and C_1 atoms (P_{O-C} = 0.964-0.333). It is noticeable a new bond formation (P_{O-H} = 0.012-0.233) by the possibility of forming a water molecule. The system energy decreases

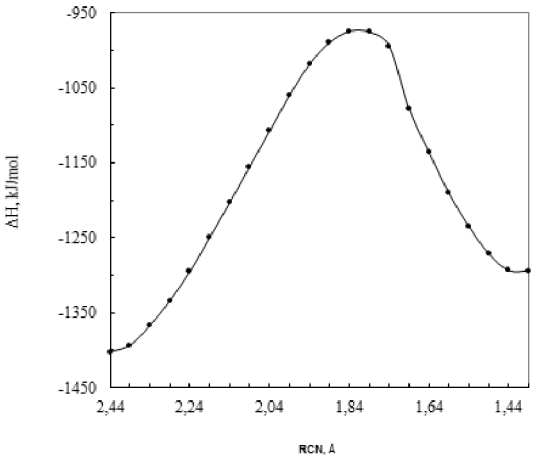


Fig. 1. The dependence of energy system change (ΔH) between nitrogen and carbon atoms $R_{C\text{-}N}$ distance during interaction of sulfanilamide glucose with a single molecule.

in the 1.44 Å distance between N_{13} and C_1 atoms. The bond order between N_{13} and C_1 atoms reaches to 0.973, between O_8 and H_{37} atoms gets to 0.932, but between N_{13} and H_{37} atoms reduces to 0.005. Thus, the hydrogen atom is entirely separating from the nitrogen atom and joins the oxygen atom by means of the water molecule formation. Sulfanilamide monoglucoside will be formed by making a single bond between N_{13} and C_1 atoms. The activation energy of the reaction is ΔΔH# = 427.77 kJ/mol, and the reaction heat effect is ΔΔH = 109.02 kJ/mol. Initial, intermediate and final conditions are given in Figs. 2,3.

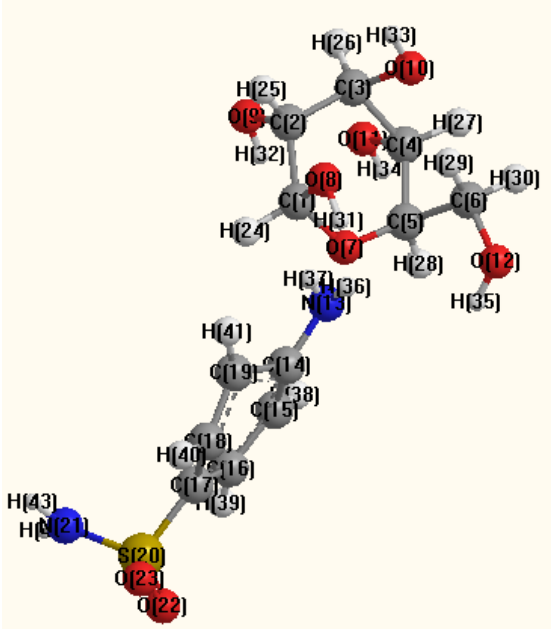


Fig. 2. Initial interaction condition of sulfanilamide glucose with a single molecule.

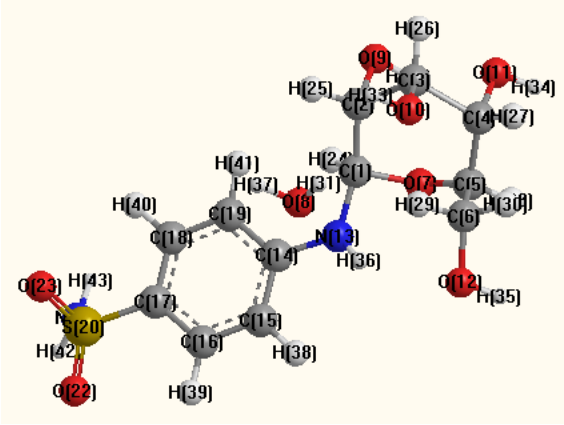


Fig. 3. Final interaction condition of sulfanilamide glucose with a single molecule.

ფიზიკური ქიმია

კვანტურ-ქიმიური მეთოდით სულფანილამიდის მონოგლუკოზიდის სინთეზის მოდელირება

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*** ზუსტ და საბუნებისმეტყველო მეცნიერებათა ფაკულტეტი. ფანე ჯ.ჯაჯიშვილის სახელობის თბილისის სახელმწიფო უნივერსიტეტი, თბილისი, საქართველო*

(წარმოდგენილია აკადემიის წევრის გ. ცინცაძის მიერ)

ნახშირწყლების მოლეკულათა გამობმით უხსნადი პრეპარატები წყალში იხსნება და ადვილად იწოვება ორგანიზმში, რაც მნიშვნელოვნად ზრდის სამკურნალო პრეპარატების ეფექტიანობას, ამიტომ უხსნადი პრეპარატების გადაყვანა წყალში ხსნად ფორმებში დიდ გამოყენებას პოვებს სამედიცინო პრაქტიკაში. ნახევრადემპირიული კვანტურ-ქიმიური მეთოდით AM1 ჩატარებულ იქნა სულფანილამიდის ერთ მოლეკულა D-გლუკოზასთან განზავებული სპირტის არეში ურთიერთქმედების გათვლები, სულფანილამიდის მონოგლუკოზიდის წარმოქმნით. N_{13} ატომის მიახლოებისას C_1 ატომთან, R_{C-N} = 1,84 Å მანძილამდე სისტემის ენერგია იზრდება. ბმის რიგი N_{13} და C_1 ატომებს შორის იზრდება 0,008-დან 0,480-მდე. ამავე დროს მცირდება ბმის რიგი N_{13} ატომსა და H_{37} ატომს შორის (P_{N-H} = 0,890-0,632) და O_8 და C_1 ატომს შორის (P_{O-C} = 0,964-0,333). შეიმჩნევა ახალი ბმის წარმოქმნა (P_{O-H} = 0,012-0,233) წყლის მოლეკულის წარმოქმნის შესაძლებლობით. N_{13} ატომსა და C_1 ატომს შორის 1,44 Å მანძილზე სისტემის ენერგია მკვეთრად მცირდება. ბმის რიგი N_{13} ატომსა და C_1 ატომს შორის აღწევს 0,973-ს, O_8 ატომსა და H_{37} ატომს შორის 0,932-ს, ხოლო N_{13} ატომსა და H_{37} ატომს შორის მცირდება 0,005-მდე. წყალბადის ატომი სრულად წყდება აზოტის ატომს და უერთდება ჟანგბადის ატომს წყლის მოლეკულის წარმოქმნით. N_{13} ატომსა და C_1 ატომს შორის ერთმაგი ბმის დამყარებით წარმოიქმნება სულფანილამიდის მონოგლუკოზიდი. რეაქციის აქტივაციის ენერგია ΔΔH# = 427,77 კჯ/მოლი, ხოლო რეაქციის სითბური ეფექტი ΔΔH = 109,02 კჯ/მოლი.

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