Scientific article
UDC 547.587.11:547.525.3
DOI: 10.52957/27821900_2022_03_87

QUANTUM-CHEMICAL STUDY OF THE CARBOXYLATION REACTION OF 4-AMINOPHENOL, 4-ACETYLAMINOPHENOL AND THEIR SALTS IN THE SYNTHESIS OF 5-AMINOSALICYLIC ACID

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Keywords: *carboxylation, 4-aminophenol, 4-acetylaminophenol, 5-aminosalicylic acid, mesalazine, thermodynamic functions, Gibbs free energy*

Abstract. *We studied the reaction mechanism of 5-aminosalicylic acid by carboxylation of 4-aminophenol, 4-acetylaminophenol and their sodium salts by interaction with carbon dioxide using the quantum density functional method. We calculated the changes in total electron energy and Gibbs free energy of the components as a result of the reaction and performed a multidimensional scan of the potential energy surface. The scan analyzed the change of total electron energy at different distances between the carbon atom in the carbon dioxide molecule and the carbon atom in the benzene ring to which the bonding takes place. We have shown that 4-aminophenol and 4-acetylaminophenol are not able to react as it is thermodynamically unfavourable. At the same time, the salts of 4-aminophenol and 4-acetylaminophenol are ready to reaction. The difference between using 4-aminophenol and 4-acetylaminophenol is not significant. This makes it possible to use 4-acetylaminophenol, which is more resistant to oxidation and less toxic, as a starting compound. We proposed a mechanism for the carboxylation of 4-acetylaminophenol salt based on a multidimensional scan of the potential energy surfaces of the reacting particles. In order to experimentally confirm the feasibility of this reaction we conducted a gas-phase catalytic carboxylation of sodium 4-acetylaminophenolate prepared in situ from 4-acetylaminophenol and sodium carbonate. We conducted the reaction at 190 °C for 2 hours at 3 MPa carbon dioxide pressure without using a solvent. The structure and purity of the 5-aminosalicylic acid obtained (47% yield) have been validated by various physico-chemical methods. This method for the synthesis of 5-aminosalicylic acid is prospective for industrial implementation.*

For citation:
Varvarkin, S.V., Soloviev, M.E. & Gerasimova, N.P. (2022) Quantum-chemical study of the carboxylation reaction of 4-aminophenol, 4-acetylaminophenol and their salts in the synthesis of 5-aminosalicylic acid, *From Chemistry Towards Technology Step-By-Step*, 3(3), pp. 87-92 [online]. Available at: http://chemintech.ru/index.php/tor/2022tom3no3

Introduction

5-Aminosalicylic acid (5-ASA) is the structural isomer of 4-aminosalicylic acid (*para*-aminosalicylic acid, PASA), differing by the position of the amino group. PASA was the first

synthetic drug to find widespread practical use in the treatment of tuberculosis. Although the first information on the synthesis of PASA was published in 1902 [1] and there were discovered more effective anti-tuberculosis drugs, PASA and its derivatives still retain their importance as components of combined tuberculosis chemotherapy up today.

Unlike PASA, 5-ASA does not have anti-tuberculosis activity. It has an anti-inflammatory effect, partly similar to that of non-steroidal anti-inflammatory drugs (salicylates), as well as an immunomodulatory effect. Original 5-ASA was part of the sulphosalazine molecule, but later it was used as a stand-alone drug, mesalazine [2]. Mesalazine is the basic treatment for inflammatory intestinal diseases, such as non-specific ulcerative colitis and Crohn's disease, in the mild to medium acute stage and for the prevention of relapse (3-5). Mesalazine is produced as gastric-resistant tablets, suppositories, modified-release pellets and enemas [6]. 5-ASA is included in the list of vital and essential medicines for medical use in the Russian Federation under code A07EC. 5-ASA is also used in industry in the production of azo dyes, for the creation of complex chromium dyes [7] and for the production of light-sensitive paper.

The main current methods of producing 5-aminosalicylic acid are the reduction of 5-phenylazosalicylic acid (5-PHASA) and the nitration of salicylic acid followed by the reduction of the nitro compound to an amine.

Aniline and salicylic acid are used to produce 5-PHASA, and its reduction produces 5-ASA and aniline. Although the initial compounds are readily available and cheap and the reaction conditions are relatively mild, the use of toxic aniline in the process creates hazardous working conditions and requires careful purification of the target product, which significantly increases its cost [8-10].

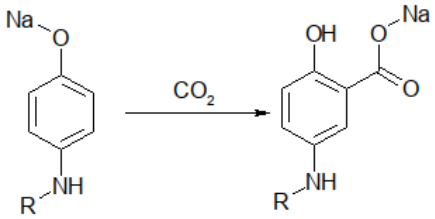
Nitration followed by reduction of the nitro compound has replaced the previous method in some industries. The total absence of toxic products and the relatively mild conditions have made this method attractive for the producers. However, nitric acid, which is a strong nitrating agent, makes the process, although fast, insufficiently selective: in addition to 5-ASA, 3-aminosalicylic acid is also obtained. It can be as much as 20% of the mass of the final product. Because of the similar physical properties of the isomers it is difficult to separate them, which increases production costs [11-14].

The carboxylation of 4-aminophenol with carbon dioxide is a prospective method for the production of 5-ASA. This method is based on the Kolbe-Schmidt reaction, which is used in industry to produce salicylic acid from phenol, PASA from 3-aminophenol [15], etc. The process takes place at increased pressure and temperature [16] in the presence of potassium or sodium carbonate or hydrocarbonate as additional carbon dioxide sources and catalysts [17]. In order to lower the reaction temperature, studies have been conducted on the use of enzymes during the process [18].

Obtaining 5-ASA by carboxylation requires very high pressure level. A pressure of 6 to 9 MPa is required for good diffusion of carbon dioxide into an aqueous solution of 5-ASA [19]. However, such conditions require very expensive equipment. Due to the development of Green Chemistry and in order to improve the carbon dioxide contact with 4-aminophenol, it is advisable to conduct the process without solvent. The carboxylation reaction itself of a dry starting compound is quite long, but if silicon or aluminium oxides are used as a catalyst, the process is relatively fast and does not require very high pressure.

However, 4-aminophenol is known to be toxic and easily oxidized. In order to solve this problem, 4-acetylaminophenol can be used as a starting compound. It is much less toxic and its amino group is protected from oxidation by an easily removable acetyl group.

In this way, we see new possibilities for the production of 5-aminosalicylic acid, potentially providing lower process costs and better environmental performance. Therefore the aim of the present paper was to quantum-chemically investigate the carboxylation reactions of sodium 4-acetylaminophenolate with carbon dioxide in comparison with sodium 4-aminophenolate (see scheme below).



R = H, $COCH_3$

Main body

We calculated the total electron energies and thermodynamic functions of the compounds involved in the reactions using the quantum-chemical density functional method with the hybrid DFT B3LYP/6-311G**, which provides a sufficiently high accuracy of geometry determination at relatively low computer requirements, using the ORCA software package [20-22]. By the calculation the initial compounds and reaction products were optimized and the conformations with the lowest potential energy were found as a result. In these conformations the total electronic energy of the compound and the Gibbs free energy [23] in the ideal gas state at 293.15 K were calculated. The results of the thermodynamic function calculations in the paper are given in kJ/mol.

Table 1 shows the calculated values of changes in total electron energy and Gibbs free energy in the carbon dioxide carboxylation reactions of 4-aminophenol and 4-acetylaminophenol as well as their sodium salts. According to the results obtained, both 4-aminophenol and 4-acetylaminophenol are unable to react with carbon dioxide in the carboxylation reaction. However, when their sodium salts are used the reactions become thermodynamically favourable. In this case the difference in the changes of the thermodynamic functions for both reagents is insignificant.

Table 1. Changes in thermodynamic functions for carboxylation reactions under gaseous conditions

Reaction	Δ*E*, kJ/mol	Δ*G*, kJ/mol
Carboxylation of 4-aminophenol	106.6	102.6
Carboxylation of 4-acetylaminophenol	92.18	90.29
Carboxylation of sodium 4-aminophenolate	-33.84	-36.04
Carboxylation of sodium 4-acetylaminophenolate	-33.75	-34.12

In order to study the reaction mechanism a multidimensional scanning of the potential energy surfaces of the reacting particles was conducted using the reaction of carboxylation of

sodium 4-acetylaminophenolate as an example. We have calculated various fixed distances between the CO_2 carbon atom and the carbon atom in the benzene ring where the bonding takes place by the conditional optimization method. Fig. 1 shows the dependence of the total electron energy of the reaction complex on the considered reaction coordinate, as well as the conformation of the reacting particles at different stages of the reaction.

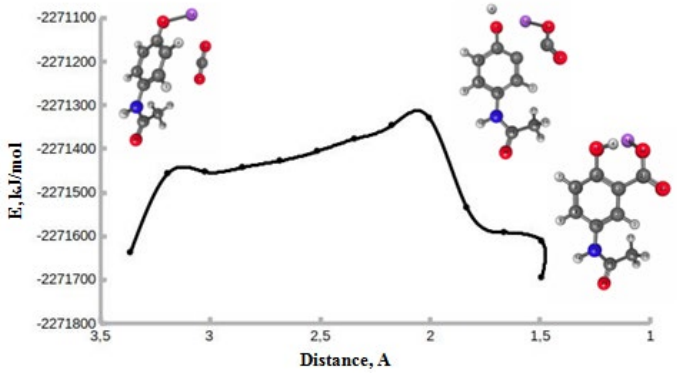
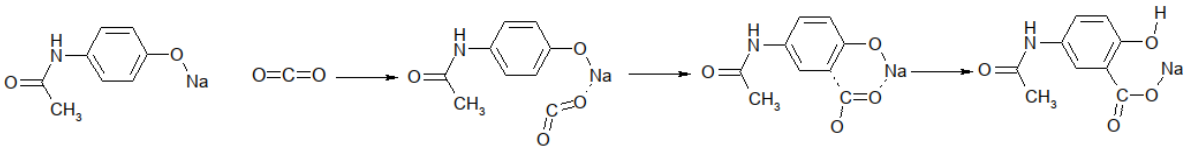


Fig. 1. Diagram of the energy variation of the complex of sodium 4-acetylaminophenolate and carbon dioxide molecules as a function of the distance between the carbon atoms of CO_2 and the benzene ring

As the analysis shows, when carbon from a carbon dioxide molecule is bonded to a carbon atom from the benzene ring, the sodium 4-acetylaminophenolate molecule changes its structure at the energy maximum, after which the structure is reduced, a carboxyl group is formed as a sodium salt and the hydrogen atom from the carbon from the benzene ring is bonded to the hydroxyl group oxygen.

Based on this calculation we can present the following possible mechanism for the carboxylation reactions of the sodium salts of 4-aminophenol and 4-acetylaminophenol with carbon dioxide on the example of the sodium salt of 4-acetylaminophenol:



In order to experimentally check the feasibility of this reaction, a trial synthesis of 5-ASA was conducted according to the proposed scheme. The yield of the desired product was 47% and its structure and purity were confirmed by various physical and chemical methods. This method of 5-ASA synthesis is notable for its environmental friendliness and relatively low cost of the process.

Methodology of the experiment

We conducted thin layer chromatography (TLC) on Silufol UV 254 plates in a solvent system ethyl acetate-methanol-25% ammonia solution (80:25:3), using an iodine camera and a UV light to observe the results. The 1H NMR spectra were recorded on a Varian UNITY plus spectrometer with an operating frequency of 400 MHz. IR spectra were obtained with a PerkinElmer UATR Two IR spectrometer. We measured the melting point on an Electrothermal 1102D Mel-Temp melting point tester.

Methodology for the synthesis of 5-aminosalicylic acid

In a 50 ml autoclave we added 1.5 g (0.01 mol) of 4-acetylaminophenol, 1.7 g (0.016 mol) of sodium carbonate, 0.78 g (0.013 mol) of silicon dioxide and then injected carbon dioxide to perform the carboxylation reaction at 3 MPa. We conducted the reaction at 190 °C for 2 hours, after which we cooled the reaction mass to 80 °C and added 150 ml of distilled water to dissolve the sodium salt of 5-ASA. We purified the solution with activated carbon, the filtrate was acidified with 20-30% hydrochloric acid solution to pH = 4. After cooling down we filtered off the precipitate of 5-ASA, washed with water and dried. The yield: 0,7 g (47%). T.melt. 280–282 °C [13]. Spectrum ^{1}H NMR (DMSO-d_6), δ, ppm: 6,70 d (J=8,8, 1H, H_{arom}), 6,92 dd (J=8,8, J=2,9, 1H, H_{arom}), 7.24d (J=2,9, 1H, H_{arom}). IR-spectrum, ν, cm^{-1}: 950 sl (OH_{def}), 1135, 1192 sl (C_{arom}-OH), 1244, 1267 s (-OH_{val}), 1315 s (C-N), 1450, 1489, 1580 s (C-C_{val}), 1620 s (NH_{2def}), 1650 s (C=O_{val}), 2555, 2785 (-OH_{val}), 3240 (OH_{val}), 3438 (NH_{val}).

Results and Discussion

As a result of the quantum-chemical calculations the possibility of carboxylation of sodium salts of 4-aminophenol and 4-acetylaminophenol by carbon dioxide by the Kolbe-Schmidt method in the synthesis of 5-aminosalicylic acid has been substantiated and a probable reaction mechanism has been described. We demonstrated that the reaction is only possible with phenol salts, the phenols themselves are not able to enter into reaction. Experimental confirmation of the possibility of the reaction under study was obtained – the synthesis of 5-aminosalicylic acid from sodium 4-acetylaminophenolate and carbon dioxide was successfully performed.

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Received 04.07.2022
Approved 12.09.2022
Accepted 12.09.2022