SYNTHESIS AND ANALYSIS OF COPPER(II) ION COORDINATION COMPOUND WITH KETOPROFEN AND CARBAMIDE

[1]Rustamov Temur Rustam ogli, [2]Azizjanov Khushnud Maxsudovich, [3]Khudoyberganov Oybek Ikromovich

[1]Doctoral Student, Khorezm Ma'mun Academy

[2]Urgench State University, department of Chemistry, candidate of chemical sciences, associate professor

[3]PhD., Senior Scientific Researcher, Khorezm Ma'mun Academy

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Abstract. *Nowadays, great amount of interest in the development of methods for the synthesis of metallocomplex compounds of biologically active compounds available in the world with 3d metals and in determining their physicochemical properties is steadily increasing. These compounds are actual for their use as antibiotics and painkillers in pharmaceutics, as biologically active substances in medicine, and as antibacterial active substances that inhibit the growth of bacteria for microorganism cells [1]. The synthesis of the complex combination of 2-(3-benzoylphenyl) propionic acid (Ketoprofen) with Cu^{2+} from saturated monocarboxylic acid derivatives was studied. Factors affecting the synthesis of $CuC_{34}H_{34}N_4O_8$ complex compound under room conditions were shown. In particular, the dependence of the yield of the reaction product on time, the effect of temperature, and the dependence on concentration were studied in practice. Physico-chemical research of the synthesized complex compound was studied using IR-Fourier-spectroscopy, elemental analysis, mass spectrometry, TG-DSK and X-ray structural analysis methods, its chemical structure was determined, and it was proved that this new complex compound is thermally and chemically stable. [2].*

Keywords: *ketoprofen, copper sulfate, carbamide, complex compound, metal complex, X-ray structural analysis, elemental analysis, antimicrobial, single crystals, Hirschfeld surface analysis.*

Introduction. The study of coordination compounds allows to explain their main chemical properties, to form complexes, to determine the nature of chemical bonds between ligands, to determine the mechanisms of processes involving coordination compounds and changes in the reactivity of coordinated ligands using modern physical and chemical research. The obtained information is important for purposefully finding and synthesizing new chemical substances with predetermined specific characteristics, composition and structure, as well as other important properties. This is especially necessary for substances with biologically active properties used in medicine [3]. A metal complex compound of bioactive ligand ketoprofen was synthesized together with laboratory staff. Ketoprofen has a pronounced analgesic effect, and is used as an anti-inflammatory and moderate antipyretic agent. Inflammation and fever appear due to the entry of various disease-causing bacteria into the human body from the external environment. Ketoprofen is one of the non-steroid substances used to eliminate this process, and in order to strengthen its effect, biometals such as Cu, Mn, Co, Zn, Mo, Fe were selected from 3d-metals and a metallocomplex compound was synthesized. When these new metallocomplex compounds are

poisoned by microbes, they bind to them and try to remove them from the body faster or completely lose their effect [4].

Aim of the research consists of developing a methodology for synthesizing a complex combination of Cu^{2+} ion with ketoprofen and studying the composition and structure of the synthesized complex using modern physico-chemical research methods.

Literature review. Synthesis of complex compounds of propionic acid, which is a representative of saturated carbonic acid, ketoprofen with biometals, their spatial structure, scientific research aimed at determining the relationship between "bioactivity-structure" and leading scientific centers and higher educational institutions of the world, including Delhi Institute of Pharmaceutical Sciences and Research (India), Institute of Inorganic Chemistry of Aachen University (Germany), Institute of General and Inorganic Chemistry, Moscow State University (Russia), University of Tokyo (Japan), Royal Institute of London (England), Institute of Engineering and Technology (China), Jagiellonian University (Poland), Institute of General and Inorganic Chemistry (Uzbekistan) [5]

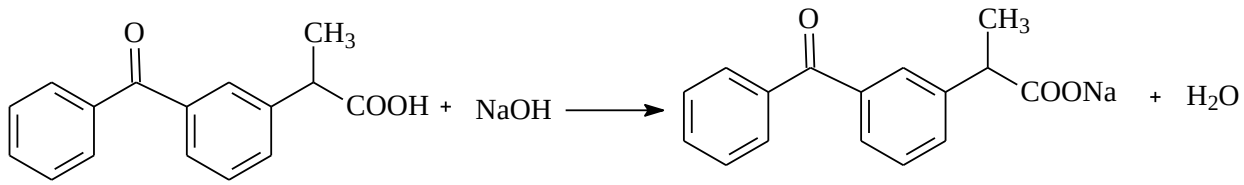
As a result of research conducted in the world on the structure of complexes of ketoprofen with biometals and their biological activities, a number of scientific results were obtained, including the following: synthesis of chelated complexes of metals was carried out, their spatial structure and charge density were determined (Institute of Inorganic Chemistry of Aachen University, Germany); mixed-ligand coordination compounds involving carboxylates were synthesized (Institute of General and Inorganic Chemistry, Moscow State University, Russia); complexes based on biometals were synthesized, molecular and crystalline structures, as well as bioactivity were determined (Royal Institute of London, Great Britain);

Scientific researches by Weiqing Mao Li, Xiang Yaofeng Chen, Dahale N.D., Chawla K.L., Venugopal V., Aubert T., Ledneva A., Grasset F., Kimoto K., Naumov N., Molard Y., Saito N., Haneda H., Cordier S., Amela-Cortes M., Circu V., Lang E.S., Stieler R., de Oliveira G.M., Mammino L., Kabanda M.M., Gier H., Roth W., Shumm S., Gerhards M. and others were devoted to the synthesis of complex compounds of 3d metals and ketorolac in solutions and the study of physico-chemical research methods in the world [6,7].

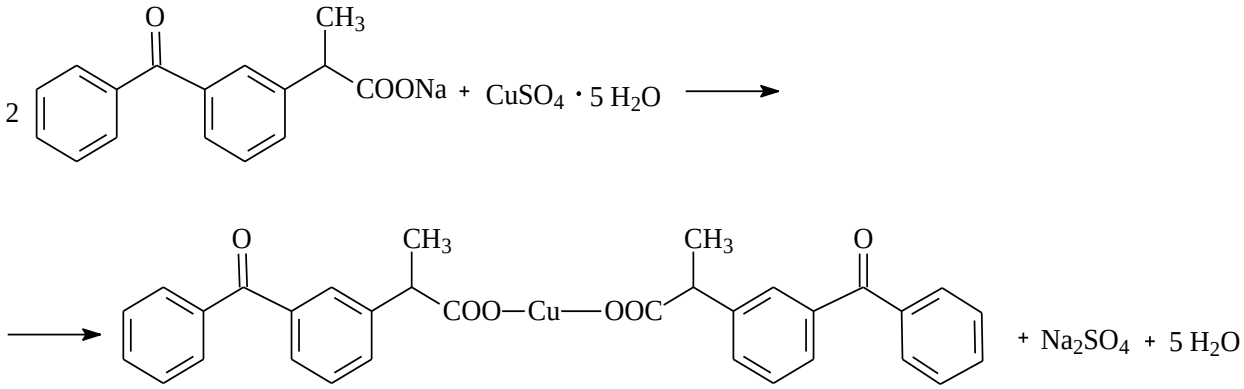
The technology of obtaining complex compounds of various salts of metals with bioactive organic ligands was developed, the processes of formation of coordination compounds in solutions and solid phases were studied. The physicochemical properties of the synthesized compounds were analyzed. Despite the fact that there are many experimental materials on the study of complexes of metal salts with substances containing the carboxyl group and amino group, the synthesis of metallocomplexes of Cu^{2+} mixed with ketoprofen from these 3d-metal salts in solution has not been studied. In addition, there is no information about the structure of the coordination knot of compounds of this class [8].

Research Methodology. The synthesis process of the metal complex compound ketoprofen was carried out as follows: aqueous solutions of 0.25 g (0.001 mol) of $CuSO_4 \cdot 5H_2O$ crystal hydrate salt and 0.508 g (0.002 mol) of ketoprofen were prepared. At the first stage, in order to increase the reactivity of ketoprofen, its sodium salt was obtained by reacting it with NaOH in a ratio of 1:1. At the second stage, ketoprofen sodium salt and $CuSO_4 \cdot 5H_2O$ crystalline hydrate salt were mixed in a ratio of 2:1. Then, at the last stage, 1ml of the 0.1N solution of carbamide solution obtained as an auxiliary ligand was added dropwise to the complex salt solution. Then it was thoroughly mixed in a MS-H280-Pro magnetic stirrer at a temperature of

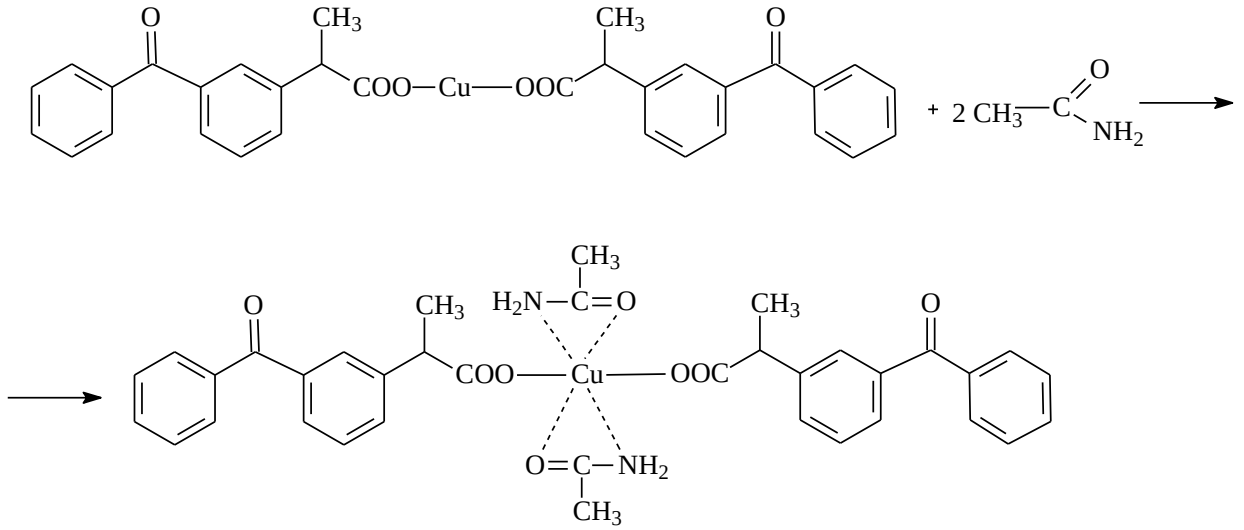
60°C for 40 minutes [9]. Then, the solution of the synthesized complex compound is left to slowly evaporate at room temperature. After five days, the obtained precipitates were filtered, washed with ethyl alcohol, then evaporated to a dry residue in a rotary evaporator at 60°C and dried. As a result, dark-green crystals of the complex compound were formed. The synthesis reaction can be expressed as follows:



Scheme 1: The reaction to obtain the sodium salt of ketoprofen



Scheme 2: The reaction to obtain the copper salt of ketoprofen



Scheme 3: Reaction of coordination compound of copper (II) ion with ketoprofen and carbamide

Analysis and results. The complex formed by ketoprofen with Cu(II) ion has a 6-coordinate, tetragonal (octahedral) geometric structure. The complex connection between Cu(II) ion and two molecules of ketoprofen was formed as a result of binding of metal ion to carboxyl-O and amide group, N,O-atoms of carbamide containing oxygen atoms. The carbonyl group of ketoprofen does not participate in complex formation, so the carbonyl group is still free in the ketoprofen complex [10]. Elemental analysis was conducted on the complex compound $[Cu(HL)_2(Kar)_2]$.

The amount of metal in the synthesized complex compounds was determined using the Novaa 300 apparatus of Analytik Jena (Germany), and the analysis of carbon, hydrogen, nitrogen and oxygen elements was determined using the EA 1108 apparatus of Carlo-Erba (Italy) (Table 1).

Table 1

The result of the elemental analysis of the complex formed by the Cu (II) ion with ketoprofen

The total formula of the synthesized complex compound	Cu, %		C, %		H, %		N, %	
	Obtained	Calculated	Obtained	Calculated	Obtained	Obtained	Calculated	Obtained
$CuC_{34}H_{34}N_4O_8$	9,27	9,34	59,13	59,24	4,92	4,96	8,14	8,24

In order to better study the coordination number of the Cu atom and the geometric knot structure in this synthesized complex compound, IR-analysis of the synthesized complex compound was also carried out. In order to determine the binding properties of the coordination centers of the ligands to the central atom, the IR spectrum of the synthesized complex of 3d-metal salts with the ketorolac ligand was obtained [11]. Valence vibrations of the carboxyl group were manifested in the 3310 cm^{-1} region, and for the CH-group, they were recorded in the 2980-3100 cm^{-1} region. When comparing the IR spectra of 3d metals, ketorolac and metal complexes with formate, acetate and carbamide, the absorption lines of the symmetric valence vibrations of the M-N bond and the =M-O= bond valence vibration in the ring undergo a sharp change, and the IR spectra of the complexes have a strong frequency compared to the ligand was observed to shift by ~20-40 cm^{-1} towards the field, and by ~30-40 cm^{-1} in the low-frequency field.

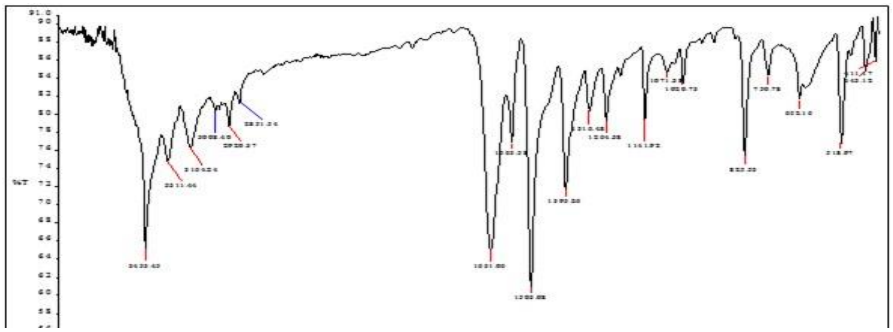


Figure 1. IR spectrum of ketoprofen

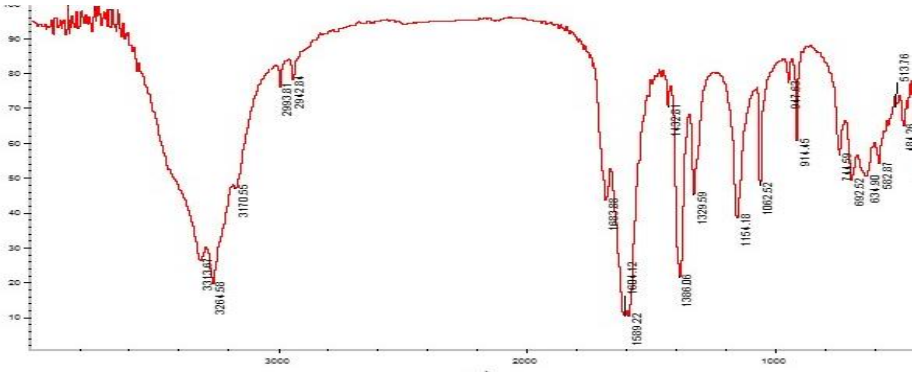


Figure 2. IR-spectrum of the coordination compound of Cu (II) with ketoprofen and carbamide

In the spectra of the complexes, absorption lines were observed in the region of 412-452 cm^{-1} corresponding to M-N valence vibrations in the short wavelength range. Vibrations related to the -CH group of the benzene ring remained unchanged and appeared in the region of 2980-3100 cm^{-1}. The carbonyl group in the complexes shifted to shorter wavelengths and was observed in the region of 3313-3264 cm^{-1}, which indicates that it is not involved in coordination. The X-ray structural analysis of the synthesized complex compound was also carried out and the parameters specific to the single crystal of the complex compound were determined.

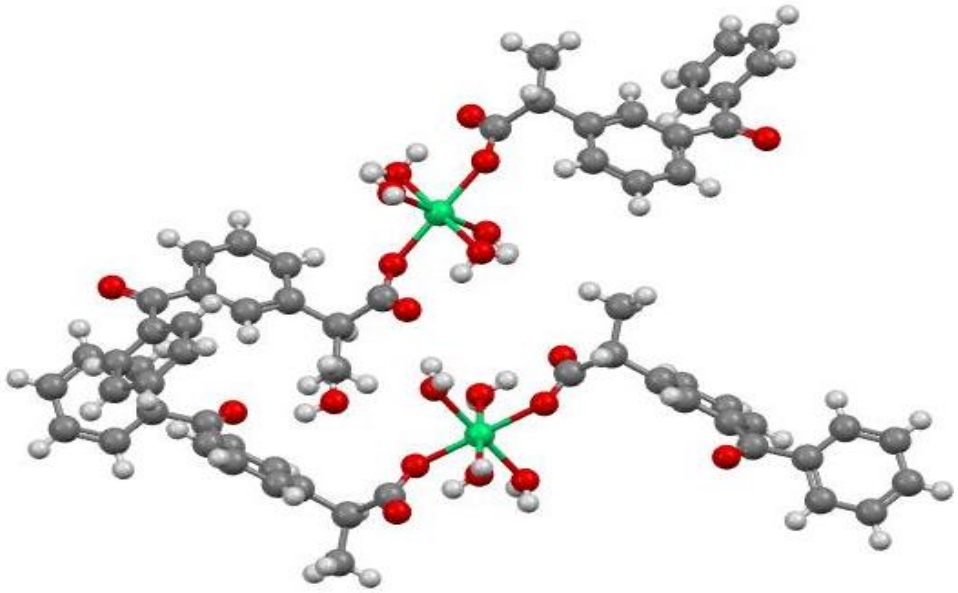


Figure 3. Illustration of Cu (II) coordination compound with ketoprofen and carbamide

Table 2

Crystallographic data and parameters clarifying the structure of the Cu-complex compound.

	Cu-complex compound		
Formula	$CuC_{34}H_{34}N_4O_8$	Crystal size, [mm]	0.18×0.15×0.12
Molecular mass	690	T, °K	312
Syngonia	monoclinic	θ,°grad.	2,6; 52,4
Spatial group	$P2_1/n$	Interval h,k,l	999;-99 ; 999:-99 ; 999:-99
a, Å	31.26 (9)	Reflex	10281
b, Å	32.36 (9)	Refractive index	7137
c, Å	32.54 (13)	R_{int}	1672
α, *β*, *γ*, deg	90(7);90(7);90(6)	$F^2 \geq 2\sigma (F^2)$ criterion	0.71073
V, $Å^3$	30549.523	Parameter	3682
Z	4	Eligibility Criteria (F^2)	322

D_x, g cm^{-3}	0.165	R_1, $wR_2(I>2\sigma(I))$	1.04
μ(CuK_α), mm^{-1}	0.027		

Table 3

Bond lengths and bond angles of a complex compound

Bond	d, Å	Angle	ω, degree
Cu(1)-O(1)	2.2739	O(1)-Cu(1)-O(2)	91.20
Cu(1)-O(2)	2.2726	O(1)-Cu(1)-O(3)	178.34
Cu(1)-O(3)	2.2712	O(1)-Cu(1)-O(4)	89.26
Cu(1)-O(4)	2.2575	O(2)-Cu(1)-O(3)	89.91
O(2)-C(1)	1.3585	O(2)-Cu(1)-O(4)	176.52
O(3)-C(2)	1.2011	O(3)-Cu(1)-O(4)	89.70
O(4)-C(3)	1.3622	Cu(1)-O(2)-C(1)	124.36
O(5)-C(1)	1.2236	Cu(1)-O(3)-C(2)	123.39
O(6)-C(3)	1.2221	Cu(1)-O(4)-C(3)	116.88
N(1)-C(2)	1.3365	H(1)-O(1)-H(2)	105.00
O(1)-H(1)	0.9900	Cu(1)-O(1)-H(1)	105.00
O(1)-H(2)	0.9900	Cu(1)-O(1)-H(2)	106.00
N(2)-C(6)	1.4299	C(6)-N(2)-C(9)	121.61
N(2)-C(9)	1.2879	O(2)-C(1)-O(5)	118.67
N(1)-H(3)	1.0300	O(2)-C(1)-C(5)	122.12

Table 4

Hydrogen bonds in the crystal structure (A˚)

Bond D–H···A	Distance, Å			Angle D–H··A, grad.	Atomic coordinates, A
	D–H	H···A	D···A		
[$CuC_{34}H_{34}N_4O_8$]					
O(5)--H(5)…O(1)	1.11	2.34	3.241	138	1-x,-1/2+y,3/2-z
O(6)--H(6)…O(2)	1.12	2.39	3.444	159	1-x,1/2+y,3/2-z
O(2)--H(2B)...O(3)	0.78	1.83	2.664	142	1-x,-1/2+y,3/2-z
O(3)--H(3C)...O(4)	0.86	1.85	2.724	156	1-x,1/2+y,3/2-z
O(3)--H(3D)...O(1)	0.92	1.96	2.736	138	x,3/2-y,1/2+z

Also, differential thermal analysis was conducted in order to determine the thermal stability of the obtained complex compounds. In the derivatograms of the studied compounds, endo- and exo-effects corresponding to various processes were observed: evaporation of crystallization water, phase transition and thermal oxidation and decomposition processes were observed. The analysis of the derivatograms of the complexes showed that the thermal decomposition of the organic part in all compounds ends in the temperature range of 100^{o}C-700^{o}C. In DTGA curves, this process is explained by endo- and exo-effects, which indicate the breaking of previous chemical bonds and the formation of new ones [12].

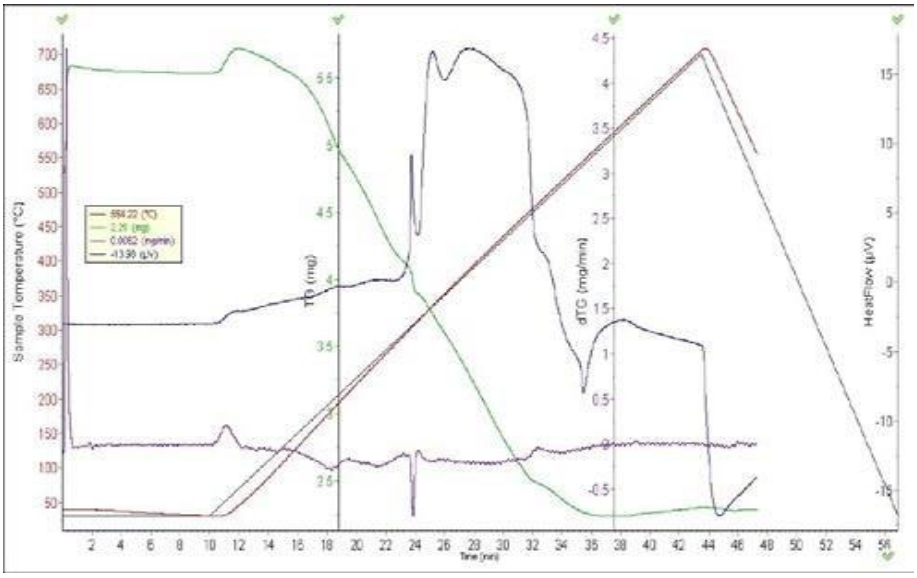


Figure 4. Derivatogram of a similar complex compound

A number of endothermic and exothermic effects were observed in the DTA curve of the $[Cu(HL)_2 (Kar)_2]$ complex. Above 100^0C, the endothermic effect refers to the decomposition of water of crystallization. As a result of the increase in temperature, the decomposition of the complex compound increases intensively. As a result, hydrazine begins to break down into components such as nitrogen oxides and carbon dioxide. Copper (II) oxide is formed as a thermolysis product. Based on the analysis of the research results, the thermal stability of the synthesized complex compounds is expressed by the nature of the central ion and the acid residue, as well as the absence of water molecules in the complex compounds. It was concluded that the complex compound synthesized on the basis of ketoprofen is $[Cu(HL)_2(Kar)_2]$ [13].

Conclusion. The complex $[Cu(HL)_2(Kar)_2]$ is a mixed-ligand complex of Cu(II), ketoprofen, and carbamide with a 2:1 composition. The complex molecule contains O(5)--H(5)...O(1) and O(6)--H(6)...O(2) groups that can participate as donors in hydrogen bonds. The fact that the synthesized ketoprofen complex is important for temporary pain relief and anti-inflammatory use in all living organisms was shown by studying using physico-chemical research methods [14]. The solubility of the newly synthesized ketoprofen complex is 25 times higher than that of ketoprofen itself. It was determined by analyzing the Hirshfeld surface using the Crystall Explorer 17.5 program. According to it, the percentage of O···H/H···O interactions in the structure is higher than 36% on average and the share of H···H interactions was less than 26% [8]. Therefore, this result increased the solubility of the obtained compound [15].

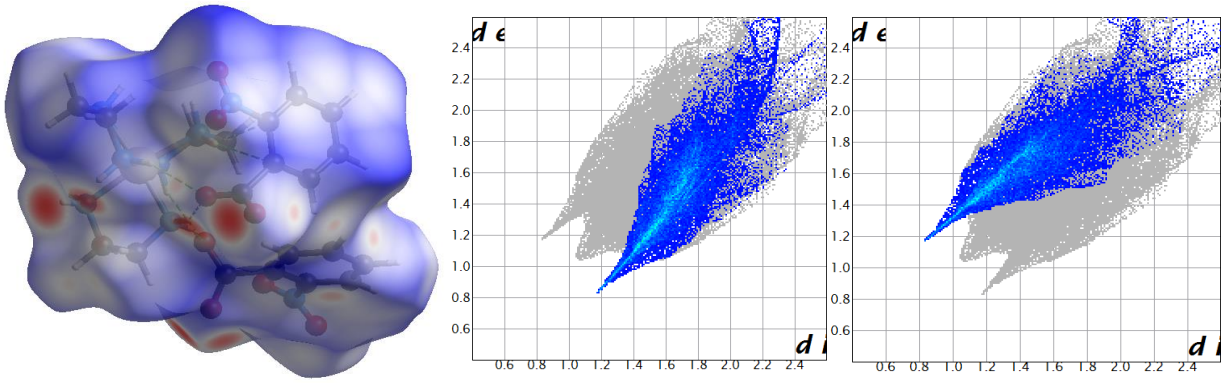


Figure 5. Hirschfeld surface analysis.

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