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COCRYSTAL PREDICTION OF THE SALICYLIC ACID-NICOTINAMIDE

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ABSTRACT

Salicylic acid-nicotinamide was used as a prediction model in the hydrogen bond interactions dominating a cocrystal structure. The combined conformation of the two molecules was analyzed at the B3LYP-D3BJ and WB97M-D3BJ theoretical level. The existing hydrogen bond dimer conformations were compared with putative conformations to determine the bond energy and stability. Some parameters were assessed for predictive descriptors, such as geometric parameters, total energy, interaction energy, single hydrogen bond energy, HOMO-LUMO gap, Laplacian Bond Order, and Natural Bond Orbital. An existing conformation, SACNIC1, produced intermolecular hydrogen bond energy which was quite higher than the other conformations, including the pure homomolecular conformations of either salicylic acid or nicotinamide. The cocrystal packing formation seems to be initiated with **SACNIC1** as the basic structure conformation. Furthermore, the presence of the strongest intermolecular hydrogen bond energy in **SACNIC1** suggests its potential utility as a predictive descriptor.

Keywords: Cocrystal; Prediction; Salicylic Acid; Synthon; B3LYP-D3BJ; WB97M-D3BJ.

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INTRODUCTION

Cocrystal is a topic of interest in the pharmaceutical field. It involves the combination of two interacting molecules to form a new packing without changing the chemical structure of each molecule. Several cocrystal examples of approved dosage forms are valsartan-sacubitril and ipragliflozin-L-proline. Many other drugs currently being studied may also form cocrystal, such as furosemide-nicotinamide and theophylline-aspirin.[1,2] Cocrystal can play a role in increasing the stability and improving the compactibility of the active ingredients.[3] However, it can also reduce stability and affect dissolution.[4] The COVID-19 pandemic has changed several perspectives regarding non-essential experimental studies, making it difficult to perform laboratory work. Therefore, computational predictions are expected to bridge this gap. With computational prediction, the selection of cocrystal coformer screening can still be carried out despite the limitations of laboratory work.[5] This research aims to predict cocrystals by analyzing the conformations of two synthon-based molecules. Cocrystal screening is usually started based on synthon matching, which is a qualitative method developed to facilitate the manufacture of cocrystals. The synthon is formed in the conformation of two molecules, which can be either homo or heterodimer in cocrystals. Generally, this conformation is formed by at least one hydrogen bond. In the heterodimer case of CPHS, there are two intermolecular hydrogen bonds, namely O–H···N and C–H···O. There are a large number of geometrical dimer conformation alternatives, but only a few of them exist in the final crystal packing.[6] This research analyzes the salicylic acid-nicotinamide (SACNIC), an existing cocrystal-containing drug model, at the B3LYP-D3BJ and WB97M-D3BJ theoretical level with the 6-311G(d,p) basis set.[7] These theoretical levels and basis sets are reliable for a dimeric crystal conformational analysis.[8] The Fig.-1 illustrates that the analyzed cocrystal has three existing conformations, with one containing CPHS, namely SACNIC1. This

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study highlights the existence of these three conformations that survived in the final crystal packing formation, particularly those containing CPHS. Furthermore, it leads to assumptions about their distinctive features, which outperform other putative conformations. Further studies are expected to identify appropriate methods and parameters for predicting cocrystal formation, especially those with CPHS. Such predictions can accelerate and improve the accuracy of cocrystal screening in the pharmaceutical field.

EXPERIMENTAL

The SACNIC cocrystal reference was obtained from the Cambridge Crystallographic Data Center [CCDC Number: 678917].[7] A density functional theory (DFT) computation was performed at B3LYP-D3BJ and WB97M-D3BJ theoretical level with a 6-311G(d,p) basis set.[8] Geometry optimization and frequency calculation of existing and putative conformations were based on the combination of hydrogen bond donor and acceptor (Fig.-1). Avogadro 1.2.0 were used to prepare the initial conformational geometry.[9] The optimization was carried out in Orca 4.2.1[10,11] with the NBO7 add-on for NBO analysis.[12] GaussView 5.0.8 was used to visualize the geometry.[13] AIM parameters were calculated in MultiWFN 3.6[14], and electrostatic potential surface (EPS) visualization was performed at VMD 1.9.3.[15] This computation generated several descriptors such as geometric position, energy, HOMO-LUMO energy gap, and various other derived descriptors. The results of these optimizations were compared to each other, and logical relationships were sought to conclude what factors were dominant in influencing the formation of cocrystals.[16]

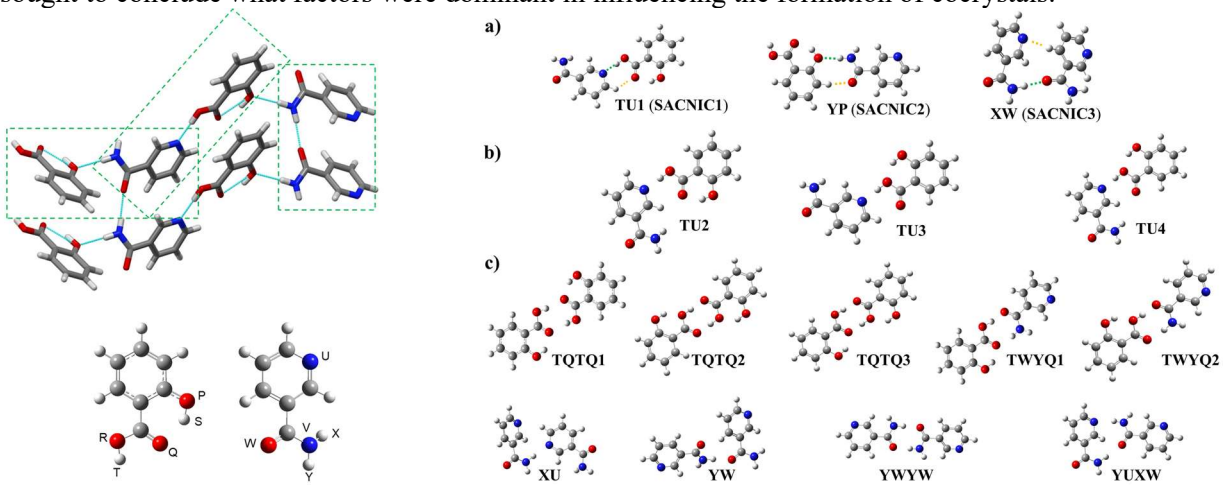

Fig.-1: Left. Cocrystal Packing of SACNIC and Hydrogen Bond Donor-Acceptor; Right. Dimer Conformations Optimized by B3LYP-D3BJ: a) existing; b) Variations of the Existing; c) Putative. The WB97M-D3BJ Was not Shown due to Simplicity and very Similar Geometry

RESULTS AND DISCUSSION

Geometry Optimization

The existing SACNIC1-3 conformations show comparable results to the crystallographic reference at the B3LYP-D3BJ and WB97M-D3BJ levels. Geometry optimization is also conducted on the putative conformations which may form hydrogen bonds but do not exist in the final packing of SACNIC (Fig.-1). Among the putative conformations, there are also existing pure homomolecular crystal conformations of SAC and NIC. They are TQTQ1 for SAC and YUXW for NIC.[17,18] There are also the polymorphs of NIC consisting of YWYW, YW, and XU conformations.[19] Among them, flip-flop conformations, such as TQTQ1 and YWYW, are almost always present in the pure crystal packing. This type of conformation is formed from a pair of strong hydrogen bonds (O–H···O and N–H···O), and the energy of these bonds likely contributes to its existence. However, the SACNIC does not exhibit this type of conformation, as the cocrystal generally favors the CPHS conformation. Therefore, factors other than the strength of the combined hydrogen bonds are likely to influence cocrystal formation.[20]

Total Energy

The DFT is a reliable computational method for chemical compounds.[21–23] The DFT optimization will result in a geometry corresponding to the lowest energy level in a molecule (local minima).[24] SACNIC1 comprises

TU, which has four conformational variations, namely TU1-4. However, instead of TU2, which has the best energy level, it is apparent that the second lowest energy level (TU1) forms the crystal packing geometry. Moreover, the conformation with the strongest total energy (TWYQ) does not exists in SACNIC (Table-1). Therefore, the low total energy does not necessarily guarantee to be observed in the final crystal packing. In this regard, crystal packing seems to be a collective work, not a partial work of a particular fragment. One of the fragments may downgrade its position to obtain a better collective result, which in this case is the lower total energy in a crystal packing.[25]

Table-1: Energy Descriptors of SACNIC at B3LYP-D3BJ/6-311G(d,p)

Structure	E (kJ/mol)	Eint (kJ/mol)	EHB1 (kJ/mol)	EHB2 (kJ/mol)	LBO1	LBO2
SACNIC (Existing)						
SACNIC1(TU1)	-2396740.81	-56.22	-53.59	-2.63	0.00050119	0.00002459
TU2	-2396746.52	-61.40	-57.94	-3.47	0.00052803	0.00003162
TU3	-2396729.50	-59.74	-57.00	-2.73	0.00061383	0.00002944
TU4	-2396736.40	-66.09	-62.13	-3.96	0.00064043	0.00004087
SACNIC2(YP)	-2396712.39	-29.95	-22.58	-7.37	0.00010506	0.00003427
SACNIC3(XW)	-2189136.04	-41.56	-33.51	-5.79	0.00009508	0.00001642
SACNIC (Putative)						
TWYQ1	-2396757.24	-70.75	-54.35	-16.40	0.00078961	0.00023834
TWYQ2	-2396748.50	-76.86	-58.92	-17.94	0.00095573	0.00029099
YR	-2396704.34	-21.45	-16.97	-4.48	0.00005370	0.00001419
TQTQ1	-2604349.35	-72.60	-36.30	-36.30	0.00057664	0.00057658
TQTQ2	-2604331.74	-84.52	-42.42	-42.10	0.00089619	0.00088944
TQTQ3	-2604339.98	-78.01	-39.99	-38.02	0.00072616	0.00069037
XU	-2189129.35	-37.37	-35.75	-0.89	0.00006986	0.00000174
YUXW	-2189147.78	-52.51	-25.76	-21.05	0.00007220	0.00005901
YW	-2189135.21	-41.36	-34.78	-6.57	0.00020073	0.00003794
YWYW	-2189158.52	-62.86	-31.77	-31.09	0.00028387	0.00027774

QTAIM

Quantum Theory of Atoms in Molecules (QTAIM) is used to assess intra- and intermolecular bonds.[26,27] The QTAIM descriptors in Table-2 indicate that all intermolecular interactions in the existing and putative SACNIC conformations are mainly based on the formation of hydrogen bonds.[28,29] According to those descriptors, the strong hydrogen bond O–H···O at the non-existing putative conformations TWYQ2 and TQTQ2, outperform the existing O–H···N at TU conformation. Therefore, these QTAIM parameters do not clearly show the superiority of the SACNIC existing cocrystal conformations compared to its homomolecular putative conformations. Contrarily, a good predictor descriptor must be able to distinguish them clearly. It seems that these descriptors can only compare the hydrogen bond strengths in the same conformation rather than comparing it to another conformation.[27]

Table-2: QTAIM Descriptors of SACNIC at B3LYP-D3BJ/6-311G(d,p)

Structure	Bond 1							
	Bond	ρ_{BCP} (a.u)	$\nabla^2\rho_{BCP}$ (a.u)	G_{BCP} (a.u)	V_{BCP} (a.u)	H_{BCP} (a.u)	E (a.u)	E (kJ/mol)
SACNIC (Existing)								
SACNIC1(TU1)	O–H···N	0.0552	0.1029	0.0380	-0.0503	-0.0123	-0.0252	-66.0514
TU2	O–H···N	0.0559	0.1017	0.0383	-0.0511	-0.0129	-0.0256	-67.1223
TU3	O–H···N	0.0588	0.1011	0.0400	-0.0548	-0.0148	-0.0274	-71.9779
TU4	O–H···N	0.0594	0.0996	0.0402	-0.0554	-0.0152	-0.0277	-72.7220
SACNIC2(YP)	N–H···O	0.0217	0.0835	0.0181	-0.0154	0.0027	-0.0077	-20.2158
SACNIC3(XW)	N–H···O	0.0192	0.0834	0.0174	-0.0139	0.0035	-0.0070	-18.2768
SACNIC (Putative)								
TWYQ1	O–H···O	0.0565	0.1483	0.0469	-0.0568	-0.0098	-0.0284	-74.5164
TWYQ2	O–H···O	0.0604	0.1503	0.0499	-0.0621	-0.0123	-0.0311	-81.5602

YR	N–H···O	0.0177	0.0657	0.0141	-0.0117	0.0023	-0.0059	-15.4163
TQTQ1	O–H···O	0.0503	0.1450	0.0426	-0.0490	-0.0064	-0.0245	-64.3709
TQTQ2	O–H···O	0.0591	0.1517	0.0493	-0.0607	-0.0114	-0.0304	-79.7189
TQTQ3	O–H···O	0.0548	0.1494	0.0462	-0.0550	-0.0088	-0.0275	-72.2519
XU	N–H···N	0.0250	0.0752	0.0174	-0.0160	0.0014	-0.0080	-20.9839
YUXW	N–H···N	0.0230	0.0724	0.0162	-0.0144	0.0019	-0.0072	-18.8543
YW	N–H···O	0.0274	0.1052	0.0239	-0.0215	0.0024	-0.0108	-28.2837
YWYW	N–H···O	0.0335	0.1124	0.0276	-0.0271	0.0005	-0.0136	-35.6196

Chemical Reactivity

The HOMO-LUMO energy gap is directly proportional to the global hardness[16,30] and inversely proportional to the global softness (Fig.-2).[16] The conformational stability of two molecules (the highest global hardness and the lowest global softness) is achieved by the conformation with the widest energy gap, such as the putative conformation YWYW for SACNIC. It consists of NIC-NIC with two N–H···O hydrogen bonds opposite each other. Although YWYW does not exist in the SACNIC crystal packing, the conformation does exist in a pure NIC polymorph. Furthermore, the large energy gap TQTQ conformation also exists in the pure SAC crystal.[19,31] Therefore, the energy gap becomes an important descriptor for homomolecular crystal packing but is less applicable for heteromolecular cocrystals.[25]

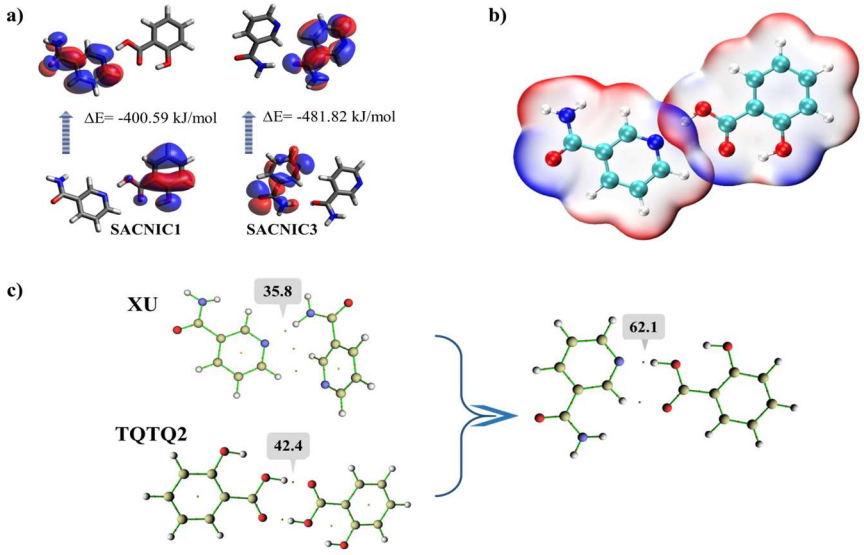

Fig.-2: a) Wider Energy Gap of SACNIC3 Compared to Main CPHS Conformations of SACNIC1; b) EPS of SACNIC; c) QTAIM-Based Interaction Profile of SACNIC. The Bond Energy Of Cocrystals are Stronger than that of their Homomolecular Form. The Values are Written in kJ/mol

Interaction Energy

The energy of the intermolecular interaction (Eint) is obtained from the difference between the energy of a two-molecule system and that of each constituent molecule {EAB-(EA+EB)}.[32] A counterpoise correction should also be performed to overcome the basis set superposition error (BSSE) in the dimeric conformation due to overlapping basis sets.[33] The interaction energy consists of one or several bond energies. The homomolecular SAC conformation of TQTQ2 produces the largest interaction energy (Table-1). However, the TQTQ variants do not appear in the existing SACNIC crystal packing. Another strong Eint conformation, TWYQ, does not exist in the SACNIC. Apparently, a strong Eint conformation does not necessarily exist in the crystal packing structure. Consequently, Eint cannot be used as a reliable descriptor to predict a cocrystal formation.[34]

LoED and LBO

The next descriptor is the Laplacian Bond Order (LBO), which is used to assess the bond strength within a system. It is based on the Laplacian of the electron density ($\nabla^2\rho_{BCP}$) at the BCP. According to the LBO, the strongest intermolecular bond is O–H···O at TWYQ and TQTQ variants, outperforming the existing

cocrystal conformation. However, the superior variants do not appear in the packing of SACNIC. This result indicates that while LBO can directly evaluate some particular bonds in a structure, it cannot sequence them with other structures that have different conformations, even if they have the same composition.[14]

Bond Energy

The single hydrogen bond energy (EHB) was based on Eint/LBO. It combines two previously-mentioned descriptors, namely Eint and LBO. The interaction of dimer conformation, Eint, is dominated by several intermolecular hydrogen bonds. It can range from an identical bond structure such as O–H···O in SAC dimer TQTQ1, to a non-identical bond structure such as O–H···O and N–H···O in TWYQ1. A rough estimate of the energy of each identical bond in such conformation is obtained simply by halving the Eint. However, this is not the case in a non-identical bond conformation since it requires an additional descriptor that can proportionally compare the two bond energies. One such descriptor is LBO which can compare the strength between bonds in the same conformation.[6] The magnitude of each bond energy, calculated from Eint/LBO, is shown in Table-1. The descriptor shows that in TWYQ1, the O–H···O bond is three times stronger than the N–H···O. Another fact reveals that O–H···N in SACNIC1 is superior to other single bonds in all of the conformations (Fig.-2). However, this is not the case for other existing cocrystal conformations SACNIC2 and SACNIC3, where several other stronger conformation bonds exist, such as TW1, XU, and TQTQ1. Apparently, due to the strength of the single hydrogen bond, the SACNIC1 can survive in the midst of competition with other surrounding molecules and become the basic structure for subsequent conformations in the crystal packing. However, the strongest Eint conformation, TQTQ, does not emerge in SACNIC crystal packing. As a result, EHB apparently plays a more important role than the total Eint, which is mainly composed of two or more EHBs as a determining factor for conformation existence. Therefore, predictions of the conformation existence can only be made for the basic crystal structure instead of all conformations that are likely to form.[25]

Natural Bond Orbital (NBO) Analysis

NBO analysis can determine the dominant electron orbitals in an atomic or whole molecular interaction (Table-3). It can also display the second-order perturbation theory which can assess the stabilization interaction energy due to overlapping orbitals, leading to the emergence of donor and acceptor orbitals. The stabilization interaction energy is equivalent to the single hydrogen bond energy based on NBO (ENBO). The greater the energy, the stronger the system.[35] At the B3LYP-D3BJ level, the strongest ENBO is produced by all conformation variants of TU in the 56.07-65.23 kJ/mol range. This ENBO trend is similar to the bond energy trend based on Eint/LBO (EHB). It seems that conformations with strong bond energies will tend to exist in crystal packing. The such tendency becomes stronger as the energy margin increases. The margin is obtained by comparing the energy of the cocrystal conformation with the homomolecular SAC and NIC conformations.[36]

Table-3: NBO Descriptor of SACNIC at B3LYP-D3BJ/6-311G(d,p)

Structure	Bond 1			Bond 2		
	ENBO (kJ/mol)	Donor	Acceptor	ENBO (kJ/mol)	Donor	Acceptor
SACNIC (Existing)						
SACNIC1(TU1)	56.07	LP(1)N23	BD*(1) O1-H2	2.09	LP(1) O3	RY(1)H29
TU2	57.74	LP(1)N23	BD*(1) O1-H2	4.35	LP(1) O3	RY(1)H26
TU3	63.76	LP(1)N23	BD*(1) O2-H3	2.51	LP(2) O1	RY(1)H29
TU4	65.23	LP(1)N23	BD*(1) O2-H3	4.85	LP(2)O1	RY(1)H26
SACNIC2(YP)	7.99	LP(1)O4	RY(1) H31	5.94	LP(2)O25	RY(1)H10
SACNIC3(XW)	6.11	LP(1)O24	RY(1) H14	2.76	LP(2)O24	RY(1)H10
SACNIC (Putative)						
TWYQ1	38.37	LP(2)O25	BD*(1) O1-H2	9.62	LP(1)O3	BD*(1)N24-H31
TWYQ2	45.27	LP(2)O9	BD*(1)O17-H18	10.17	LP(2)O16	BD*(1)N8-H15
YR	4.39	LP(1)O1	RY(1) H31	3.35	LP(2)O25	RY(1)H16
TQTQ1	21.17	LP(2)O3	BD*(1)O17-H18	21.13	LP(2)O19	BD*(1)O1-H2
TQTQ2	19.25	LP(1)O1	BD*(1)O18-H19	19.16	LP(1)O17	BD*(1)O2-H3
TQTQ3	33.14	LP(2)O17	BD*(1) O1-H2	26.90	LP(2)O3	BD*(1)O18-H19

XU	11.55	LP(1)N22	BD*(1) N8-H14	0.25	LP(1)N7	BD*(1)C20-H28
YUXW	8.62	LP(1)N7	BD*(1)N23-H30	4.18	LP(1)O24	BD*(1)N8-H14
YW	8.08	LP(1)O24	BD*(1) N8-H15	6.74	LP(2)O9	RY(1)H26
YWYW	11.84	LP(2)O24	BD*(1) N8-H15	11.76	LP(2)O9	BD*(1)N23-H30

Table-4: Margin of Energies Between Cocrystals and their Homomolecular Constituents

Level	Conformation	EHB	Margin (%)	Conformation	ENBO	Margin (%)
B3LYP-D3BJ	TU4	-62.13	46.46	TU4	65.23	96.83
	TQTQ2	-42.42		TQTQ3	33.14	
WB97M-D3BJ	TU4	-56.96	43.34	TU3	86.40	60.56
	TQTQ2	-39.74		TQTQ2	53.81	

Unit of EHB and ENBO = kJ/mol

Therefore, the stronger the bond, the higher the likelihood of such a conformation.[36] The strongest SAC conformation (TQTQ variants) is used as a comparator since the bond energy is greater than that of NIC. The strongest SACNIC1 outperform TQTQ by more than 35% based on the EHB margin and even by more than 55% based on the ENBO margin (Table-4). Since the cocrystal's EHB is much larger than its homomolecular constituents, cocrystals are more likely to form when the two compounds are mixed. Apparently, the conformation would be unbreakable if the hydrogen bond is very strong, even if there is an alternative packing with better total energy and density. Therefore, it is more likely to reserve its place as a basic structure conformation in the packing to be built.[20]

CONCLUSION

The single intermolecular hydrogen bond energy descriptors, based on Eint/LBO and NBO, calculated at the B3LYP-D3BJ and WB97M-D3BJ levels, could help determine the conformational preference in the SACNIC cocrystal packing. Those two descriptors can be used as initial predictors of the basic structure conformation (SACNIC1), which can become the foundation for the next structure in the crystal packing. The results of the two descriptors indicate that the existence probability of the SACNIC conformations is in line with the strength of the single intermolecular hydrogen bond energy. Therefore, the prediction of cocrystal forming, either in pharmaceutical or non-pharmaceutical molecule can also be made based on the margin of EHB.[20]

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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