



Research article

Supramolecular architecture in 1:1 cocrystal of *N*-carbamothioylacetamide and *N,N'*-thiocarbonyldiacetamide from the attempted synthesis of 1,3-diacetyl-2-thioxoimidazolidine-4,5-dione (a thioparabanic acid derivative)Lateefah M. Durosinmi^a, Olatomide A. Fadare^a, Kayode Sanusi^{a,*}, Yusuf Yilmaz^b, Umit Ceylan^c, Craig A. Obafemi^a^a Department of Chemistry, Obafemi Awolowo University, Ile-Ife, Nigeria^b NT Vocational School, Gaziantep University, 27310, Gaziantep, Turkey^c Department of Medical Services and Techniques, Vocational High School Health Services, Giresun University, 28100, Giresun, Turkey

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ABSTRACT

An attempt to synthesize thioparabanic acid as precursor to other fused heterocyclic compounds, by a microwave assisted multistep one-pot reaction yielded a co-crystal of *N*-carbamothioylacetamide (NCTA) and *N,N'*-thiocarbonyldiacetamide (NNTCA) which is being reported in this paper. The structure of *N*-carbamothioylacetamide and *N,N'*-thiocarbonyldiacetamide from the attempted synthesis of 1,3-diacetyl-2-thioxoimidazolidine-4,5-dione, C₅H₈N₂O₂S.C₃H₆N₂OS, has triclinic (*P*-1) symmetry. It is of interest with respect to biological application. The structure displays inter- and intra-molecular hydrogen bonding through –C=O...H interactions. Similarly, –C=S...H hydrogen bonding interactions are present, providing additional intermolecular stability to the co-crystal. For application as a potential drug candidate, a density functional theory (DFT) simulation of the antioxidant activities of the co-crystal and its individual components (NCTA and NNTCA) has been performed. The computed redox potentials indicate that the study compounds show comparable antioxidant activities with ascorbic acid (AA) for a one electron transfer process. Meanwhile, for a two-electron process, AA showed significant antioxidant advantage over the titled compound.

1. Introduction

Co-crystals are interesting chemical species that have wide application in pharmaceuticals and electronics due to special improved properties that the co-crystals may possess as an advantage over the individual components. An attempt to synthesize thioparabanic acid, as precursor to other fused heterocyclic compounds, by a microwave-assisted multistep one-pot reaction yielded a co-crystal of *N*-carbamothioylacetamide (NCTA) and *N,N'*-thiocarbonyldiacetamide (NNTCA) (Scheme 1). Thioparabanic acid is a hydantoin derivative and hydantoins are useful precursors for organic synthesis of bioactive heterocyclic molecules [1, 2]. Hydantoin derivatives have been studied extensively for various pharmacological activities [3, 4, 5] and some have found use as drugs in the management of certain diseases, such as phenytoin and fosphenytoin as anticonvulsant; dantrolene as a muscle relaxant; ropitoin

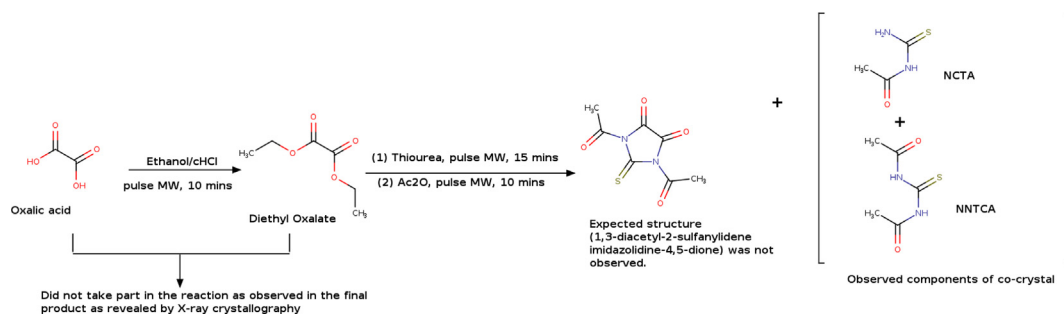
as an antiarrhythmic; and linezolid as an antibacterial, and so on. 2-thiohydantoins with close resemblance to the thioparabanic acid have also been documented to possess various pharmacological properties as well, and applied as hypolipidemic, anticarcinogenic, antiviral (e.g. herpes virus, HSV, HIV and tuberculosis), antimicrobial, anti-ulcer and anti-inflammatory agents [2, 6]. Thiourea and acylthiourea derivatives also have wide applications. They may serve as precursor for the synthesis of heterocyclic compounds that contain sulfur [7], as corrosion inhibitors [8], applied in the design of sensors and, as an organic catalysts [9, 10, 11, 12, 13]. For instance, thiourea have been used in palladium-catalyzed reactions as ligands, thiourea-based ligands are quite useful for the palladium-catalyzed bis(methoxycarbonylation) of terminal alkynes. A novel thiourea-based C₂-symmetric ligand has been used for an application in the palladium-catalyzed Heck and Suzuki coupling reactions of arenediazonium salts [14, 15, 16, 17, 18]. Some

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Scheme 1. Synthetic route(s) to the formation of the co-crystal.

thioureas have also been observed to possess pharmacological properties such as antiepileptic [19], antidiabetic [20] and anticancer [21]. Acylthioureas, by virtue of their metal chelating ability have also been found to be potential inhibitors of zinc-dependent histone deacetylase enzymes [22]. There is a likely possibility that the accidentally synthesized co-crystal being reported here may possess some interesting pharmacological properties. We have also shown these pharmacological tendencies using the molecules' antioxidant properties, which were evaluated from the redox potentials obtained by density functional theory (DFT) calculations [23, 24, 25]. A review on the application of redox potentials to estimate the level of antioxidant activity of organic compounds is available in the literature [26].

2. Materials and methods

Oxalic acid (10.0 g, 0.11 mol) was added to a mixture of 50 ml of absolute ethanol and 10 ml of concentrated HCl in a 250 ml beaker. The reaction mixture was microwave (MW) pulse-irradiated for 10 min to give a clear colorless solution, with the characteristic fruity smell of ester. Thiourea (8.5 g, 0.11 mol) was added to the colorless solution and the MW irradiation continued for another 15 min to give a bright yellow solution which was heated continuously to reduce the ethanol to the barest minimum after which 30 ml of acetic anhydride (excess) was added. The MW pulse-irradiation continued for another 10 min and the reaction mixture was left to stand for few days under slow evaporation to give light-yellow rhomboids. The crystalline solid was submitted for X-ray crystallography which revealed the structure to be a mixture of *N*-carbamothioylacetamide and *N,N*-thiocarbonyldiacetamide (Figure 1) instead of the expected *N,N'*-diacetylparabanic acid (Scheme 1). The X-ray crystallographic analysis of the product revealed that the thiourea

was attacked by the acetic anhydride to form the mono and diacetylated thiourea which ended up as co-crystals of the crystalline solid reported here. The reaction was treated as a multicomponent, three-step, one-pot reaction. Large crystals good enough for X-ray crystallography (which elucidates structure absolutely) were obtained as the final product which revealed that the product consists of co-crystals of NCTA and NNTCA (Scheme 1). The final product must have been formed from the reaction between the acetic anhydride and the thiourea.

3. Results and discussion

A proposed reaction scheme may be described as follows according to Scheme 1. The reaction is a 4-component, one-pot synthesis that led to the reaction between only two of the components to form NCTA and NNTCA of the co-crystal. It is worthy of note that the X-ray crystallographic data shows that the oxalic acid is not part of the product. This may have happened because the intermediate di-ester must have existed in equilibrium with the oxalic acid, such that upon introduction of the thiourea, there was no reaction with the di-ester, but possibly with the oxalic acid, forming a "oxalate-thioureamidinium salt ($-\text{COO}^- \text{NH}_3\text{-CS}$). Consequently, upon addition of the acetic anhydride, a reaction between the acetic anhydride and the thiourea was triggered, leaving the very polar oxalate/oxalic acid unreacted and in solution.

Crystal data, data collection and structure refinement details are summarized in Table 1. The Uiso for H atoms were fixed at 1.5 times of all methyl groups. The rest of the data are redundant. The solved co-crystal structure is presented in Figure 1 as a 3D-image of the unit cell, and shows clearly the hydrogen bonding interactions, for e.g. N2–H2...O1 (intra), N3–H3A...S1 (inter), N3–H3B...O3 (intra), N3–H3A...O2 (inter) and N1–H1...O3 (inter). The classical hydrogen bonds where D—A distances generally range between 2.5 – 3.0 Å can be found between N2–H2...O1 (2.661 Å), N3–H3B...O3 (2.667 Å) and N3–H3A...O2 (2.794 Å). Whereas, others such as N1–H1...O3 (3.070 Å), N3–H3A...S1 (3.461 Å), N4–H4...O1 (3.132 Å), C5–H5C...S2 (3.455 Å) and C8–H8C...S1 (3.804 Å) have been identified as weak intermolecular hydrogen interactions with their D—H—A angles ranging between 125 – 170° (Table 2). Thus, the co-crystal exhibits both intermolecular (H3A...S1, H1...O3 etc.) and intramolecular (H2...O1, H3B...O3 etc.) hydrogen bonding interactions within and between its components, NCTA and NNTCA (Figure 1). The geometry of the intermolecular hydrogen bonding interactions within the co-crystal is also presented in Table 2 with the symmetry codes. The occurrence of these hydrogen bonding interactions results in the formation of a 1-dimensional tape along the [110] direction (Figure 2), similar to what has been reported previously in the literature [27]. Each unit of the NCTA and NNTCA forming the network are connected through the H4...O1, H5C...S2, H3A...S1, H8C...S1 and H1...O3 intermolecular hydrogen bonding (Figures 1 and 2).

The geometrical parameters of the co-crystal have been presented in Table 3. There are fragments within each component of the co-crystal with similar bond types and similar chemical environment. Some of these fragments were found to show similar bond lengths for the

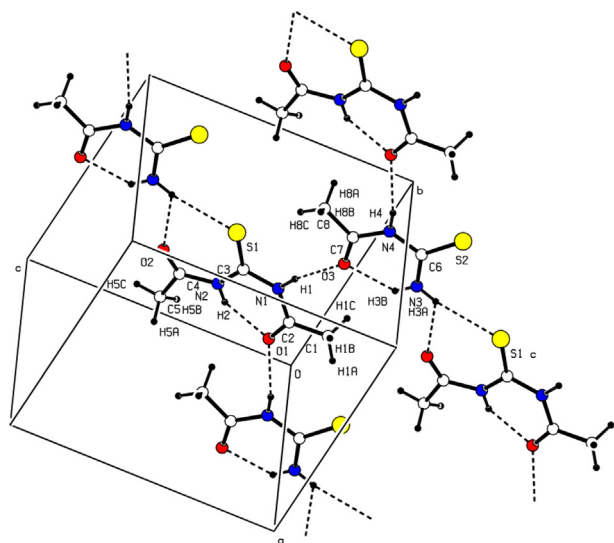


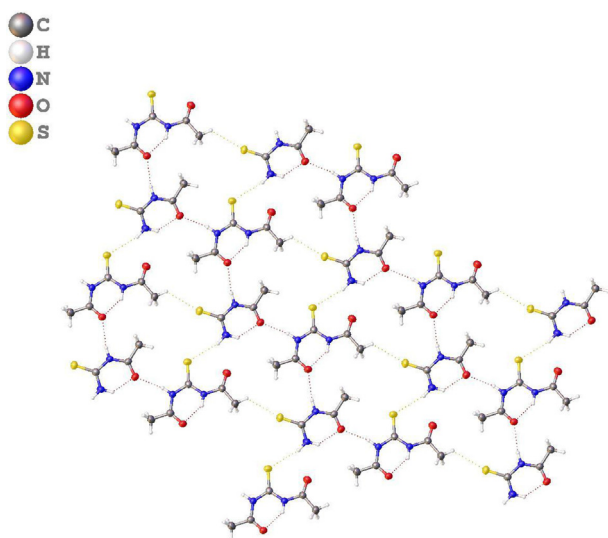
Figure 1. Unit cell of the co-crystallized NCTA and NNTCA.

Table 1. Selected Crystal data and structure refinement of the co-crystal (CCDC: 2002994).

Identification code	smart_FAD4
Empirical formula	C ₈ H ₁₄ N ₄ O ₃ S ₂
Formula weight	278.35
Temperature/K	294(2)
Crystal system, space group	Triclinic, <i>P</i> -1
<i>a</i> , <i>b</i> , <i>c</i> /Å	7.3096(6), 9.8092(9), 10.0037(9),
α , β , γ /°	103.816(8), 107.431(8), 100.036(7)
<i>V</i> /Å ³	640.73(10)
<i>Z</i>	2
ρ_{calc} g/cm ³	1.443
μ /mm ⁻¹	0.418
F(000)	292.0
Crystal size/mm ³	0.595 × 0.452 × 0.352
Radiation	MoK α (λ = 0.71073)
2 θ range for data collection/°	6.492–51.362
Index ranges	-8 ≤ <i>h</i> ≤ 7, -10 ≤ <i>k</i> ≤ 11, -11 ≤ <i>l</i> ≤ 12
Reflections collected	3428
Independent reflections	2394 [R _{int} = 0.0184, R _{sigma} = 0.0490]
Data/restraints/parameters	2394/0/177
Goodness-of-fit on F ²	1.031
Final R indexes [I ≥ 2 σ (I)]	R ₁ = 0.0458, wR ₂ = 0.0974
Final R indexes [all data]	R ₁ = 0.0625, wR ₂ = 0.1094
Largest diff. peak/hole/e Å ⁻³	0.26/-0.25

Table 2. Hydrogen bond geometry of the co-crystals (Å, °).

D–H—A	D–H/Å	H–A/Å	D–A/Å	D–H—A/°
N1–H1—O3	0.86(3)	2.22(3)	3.070(3)	170(3)
N2–H2—O1	0.80(3)	2.00(3)	2.661(3)	140(3)
N3–H3A—S1 ⁱⁱⁱ	0.84(4)	2.63(4)	3.461(3)	167(4)
N3–H3A—O2 ⁱⁱⁱ	0.84(4)	2.30(4)	2.794(4)	118(3)
N3–H3B—O3	0.83(4)	2.01(4)	2.667(3)	135(4)
N4–H4—O1 ⁱⁱ	0.81(3)	2.34(3)	3.132(3)	167(3)
C5 – H5C – S2 ⁱ	0.96	2.81	3.455(3)	125
C8 – H8C – S1	0.96	2.86	3.804(3)	169

Symmetry codes: (i) +*x*, -1+*y*, 1 + *z* (ii) *x*+1 + *y* + *z*, (iii) *x* + *y*, -1+*z*.**Figure 2.** NCTA and NNTCA units in a network formed by the hydrogen bonding interactions holding the units together in the co-crystal.

corresponding bond-types in some cases, and a significantly different bond length in some other cases. For examples, S1–C3 (1.643 Å), O1–C2 (1.213 Å), N1–C3 (1.388 Å) and C1–C2 (1.490 Å) of the NNTCA are similar to S2–C6 (1.659 Å), O3–C7 (1.217 Å), N4–C6 (1.385 Å) and C7–C8 (1.492 Å) of the NCTA respectively and showed correspondingly similar bond lengths (Table 3). On the other hand, N1–C2 (1.385 Å) and N4–C7 (1.367 Å) have similar bond types and are in similar chemical environment but have different bond lengths. A similar trend was observed also for the bond angles with the affected fragment in each component matched accordingly (Table 3). The co-crystal crystallized in the triclinic space group *P*-1. The whole molecular structure of the NNTCA unit can be generated by an inversion centre that is located along the S1–C3 bond axis with a slight distortion resulting from the hydrogen bonding interaction between the carbonyl oxygen O1 and the 2° amine hydrogen H2. Meanwhile, the monomeric NCTA unit showed highly asymmetric ordering with no observable symmetry element other than the *E*. The ORTEP representation of the co-crystal is presented in Figure 3. The co-crystal was self-assembled as a trimer due to the hydrogen bonding interactions, Figure 2. The 3D image of the co-crystal lattice is presented in Figure 4.

A search through the Cambridge Structural Database [28, 29] gave only one match [30] and zero match when *N*-carbamothioylacetamide and *N,N*-thiocarbonyldiacetamide were used as the query words respectively. Both the co-crystal and the previously reported *N*-carbamothioylacetamide have the same space group of *P*-1 [30]. However, further literature search revealed that the crystal structure of the ring-substituted thiourea compounds are available [31, 32]. The structure reported in this reference (CDS refcode KECHIJ01 and deposition number 1009665) [30], was the only structure which shared very close identities with the titled co-crystal, besides the others with ring structures and thiourea moieties, whose properties have been well documented [31, 32]. It is worthy of note that the stabilization of the co-crystal was ensured by both intra- and inter-molecular C=O...H interactions, just as were observed in previous similar studies [31, 32, 33, 34]. The thiourea moiety of the co-crystal was observed to also perform a key function in stabilizing the components through the intermolecular C=S...H interaction, leading to the formation of the 1-dimensional tape [27, 31, 32, 33, 34].

DFT calculations were carried out on the co-crystal and its oxidized form to obtain its two-electron redox potential (E^0) according to the described procedures [23, 24, 25]. Geometry and frequency calculations were performed at B3LYP/6-311g(d,p) level of theory for both the gas and aqueous phases. The optimized structures of the co-crystal and its oxidized form are presented in Figure 5. The computed co-crystal geometric parameters have also been presented (Table 4). The %relative error presented in Table 4 for the calculated bond lengths is lower (15.68%) than that of the method reported before (16.30%) for systems with similar atoms [24]. The %relative error was obtained by taking the crystallography data as the True value. The lower total %relative error compared to that of the previous method is an indication that the current method is also suitable for the description of the co-crystal.

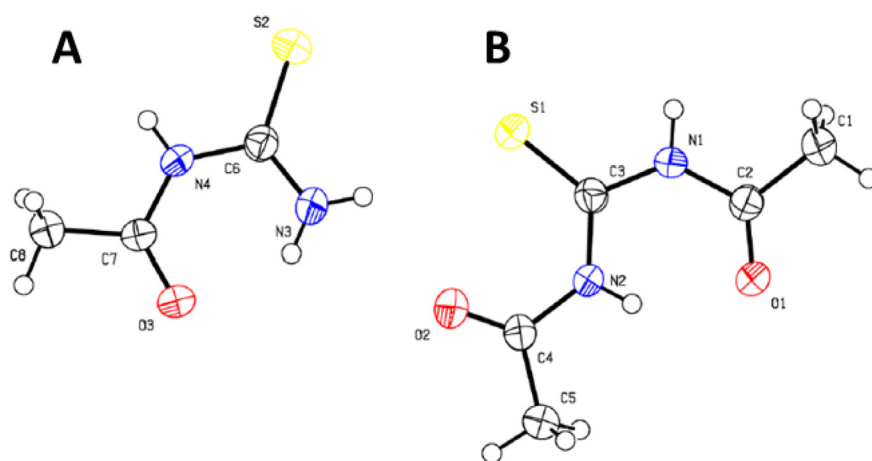
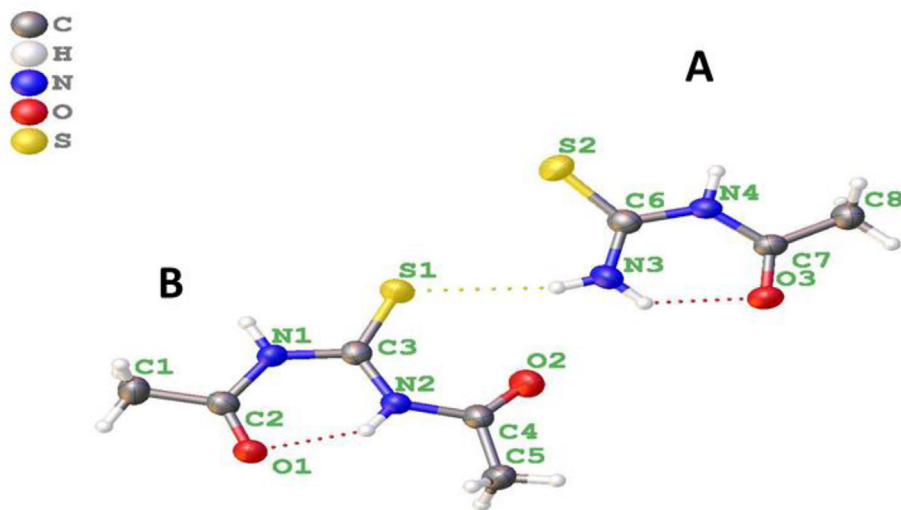
Gas and aqueous phase free-energy changes were obtained using the general isodesmic reaction scheme shown in Figure 6, with catechol (Cat) as the reference molecule. One-electron redox potential value of catechol (0.53 V) at pH 7 was employed as the reference electrode potential to derive the redox potentials of the studied compounds [35]. Integral equation formalism polarizable continuum model (IEF-PCM) was employed for the solvent-phase calculation at B3LYP/6-311g(d,p) level of theory. Table 5 summarizes the results obtained in this work. A close examination on the results reveals that the electron transfer processes that occurred in obtaining the one- and two-electron reduction potentials (E^0) for the studied molecules are all thermodynamically favourable as shown from their +ve E^0 values. The computed co-crystal two-electron redox potential (based on catechol) is 530.2 mV, showing that it possesses the highest reducing ability relative to the NCTA and NNTCA, whose one-electron redox potentials are 531.0 and 530.7 mV

Table 3. Geometric parameters of the co-crystals (\AA , $^\circ$).

S1–C3	1.643(3)	C4–C5	1.484(4)
O1–C2	1.213(3)	S2–C6	1.659(3)
O2–C4	1.197(3)	O3–C7	1.217(3)
N1–C2	1.385(3)	N3–C6	1.310(3)
N1–C3	1.388(3)	N4–C6	1.385(3)
N2–C3	1.354(3)	N4–C7	1.367(3)
N2–C4	1.395(3)	C7–C8	1.492(3)
C1–C2	1.490(4)		
C2 – N1 – C3	129.5(2) ^a	O2 – C4 – C5	123.0(2)
O1 – C2 – N1	122.8(2) ^b	C7 – N4 – C6	128.8(2) ^a
O1 – C2 – C1	122.9(2) ^c	N3 – C6 – S2	123.9(2)
N1 – C2 – C1	114.3(2) ^d	N3 – C6 – N4	116.8(2)
N1 – C3 – S1	118.6(19) ^e	N4 – C6 – S2	119.32(19) ^e
N2 – C3 – S1	126.9(2)	O3 – C7 – N4	122.7(2) ^b
N2 – C3 – N1	114.5(2)	O3 – C7 – C8	123.0(2) ^c
O2 – C4 – N2	123.6(3)	N4 – C7 – C8	114.3(2) ^d

^{a-d} showed bond angles in the fragments of each component of the co-crystal that are similar.

^e for bond angles that are not similar in the fragments of each component of the co-crystal.

**Figure 3.** (A) NCTA and (B) NNTCA ORTEP.**Figure 4.** The two components of the co-crystal (A) NCTA and (B) NNTCA, with the inter- and intra-molecular hydrogen bonding interactions holding the components being shown.

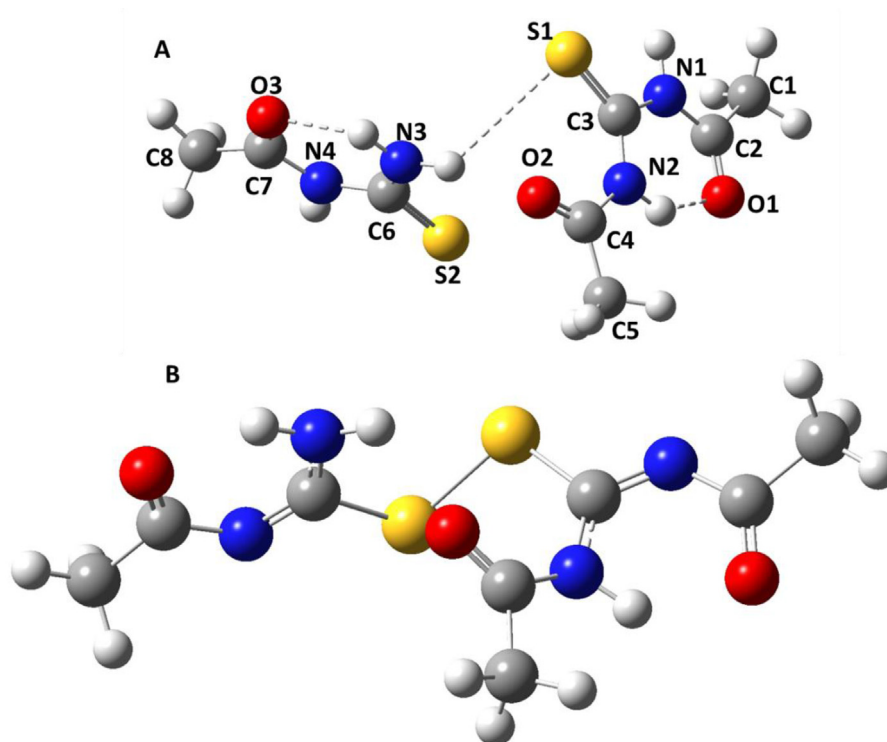


Figure 5. (A) The optimized geometry of the co-crystal in its reduced form – the inter- and intra-molecular hydrogen bonds are shown in dashes. (B) The optimized oxidized form (loss of two hydrogen atoms to afford a two-electron transfer process – the optimization of the hydrogen-deficient co-crystal yielded the optimized disulphide, the oxidized form).

Table 4. DFT computed geometric parameters of the co-crystal.

Å		%Rel. error	Å		%Rel. error
S1–C3	1.654	0.670	C4–C5	1.512	1.887
O1–C2	1.221	0.660	S2–C6	1.687	1.688
O2–C4	1.209	1.003	O3–C7	1.218	0.082
N1–C2	1.386	0.072	N3–C6	1.326	1.221
N1–C3	1.406	1.297	N4–C6	1.402	1.227
N2–C3	1.368	1.034	N4–C7	1.385	1.317
N2–C4	1.402	0.502	C7–C8	1.515	1.542
C1–C2	1.512	1.477	Total %Rel. error (bond lengths)		15.68
Degree		%Rel. error	Degree		%Rel. error
C2 – N1 – C3	130.3	0.618	O2 – C4 – C5	123.1	0.081
O1 – C2 – N1	123.3	0.407	C7 – N4 – C6	129.0	0.155
O1 – C2 – C1	122.4	0.407	N3 – C6 – S2	125.9	1.614
N1 – C2 – C1	114.2	0.087	N3 – C6 – N4	116.4	0.342
N1 – C3 – S1	118.2	0.337	N4 – C6 – S2	117.7	1.358
N2 – C3 – S1	128.8	1.497	O3 – C7 – N4	123.4	0.570
N2 – C3 – N1	113.0	1.310	O3 – C7 – C8	122.7	0.244
O2 – C4 – N2	124.3	0.566	N4 – C7 – C8	114.0	0.262
Total %Rel. error (bond angles)					9.858

respectively. It can in addition be inferred from the results that the co-crystal has a significantly lower reducing ability when compared to AA, a known antioxidant with a reported two-electron redox potential of 265.0 mV [25]. The results also indicate that NNTCA with a lower one-electron E^0 value shows stronger reducing ability than NCTA. The one-electron redox potential obtained for AA suggests it still has the

highest reducing property amongst the molecules considered in this work, and the results may be summarized in increasing reducing property as NCTA (one-electron) < NNTCA (one-electron) < co-crystal (two-electron) < AA (one-electron) < AA (two-electron). This trend is a function of the stability of the radical-ion produced during the electron transfer process.

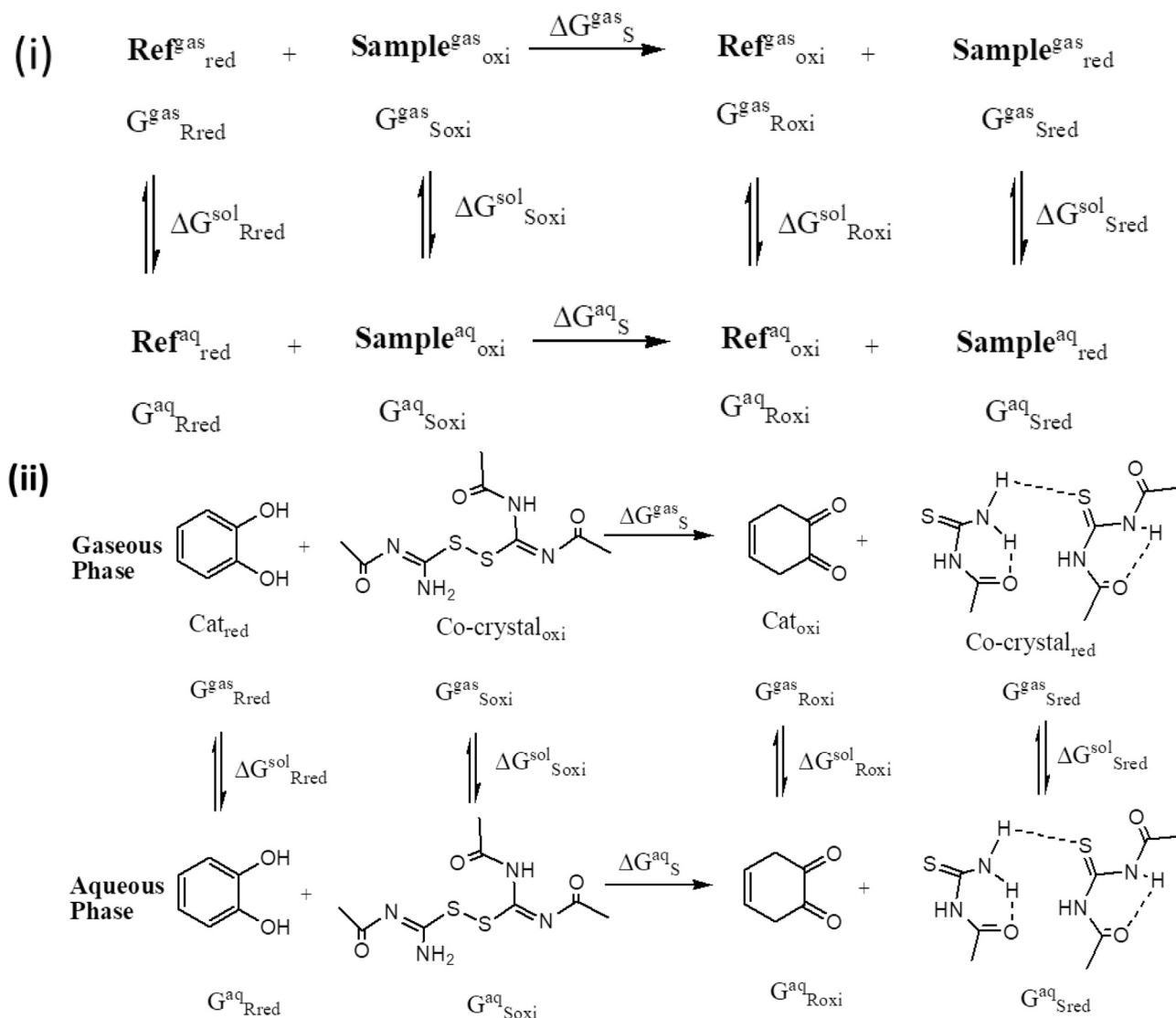


Figure 6. (i) The general isodesmic reaction cycle employed in the calculation of the solution and gas phase free-energy changes. G^x_{R} = free-energy of the reference molecule and G^x_{S} = free-energy of the sample (x = gas or aqueous). Oxi = oxidized form, red = reduced form (ii) An example of how the cycle was employed in the calculation of two-electron redox potential of the co-crystal (in which two-electrons are transferred).

Table 5. DFT computed redox potentials of the co-crystal, its components and ascorbic acid (AA).

	Co-crystal ^a	NCTA ^b	NNTCA ^b	AA ^c	AA ^b
E (mV)	530.2	531.0	530.7	265.0	530.0

^a Two-electron redox potentials in water.

^b One-electron redox potentials in water.

^c Two-electron redox potential obtained previously for AA [25].

4. Conclusion

In conclusion, a serendipitously formed co-crystal of NCTA and NNTCA from an attempted synthesis of 1,3-diacetyl-2-thioxoimidazolidine-4,5-dione has been studied using X-ray crystallography. The co-crystal has a space group of $P-1$ and exhibits both intermolecular and intramolecular hydrogen bonding interactions. The stabilization of the co-crystal was brought about by these intra- and inter-molecular interactions which lead to the formation of a 1-dimensional tape along the [110] direction. DFT calculations have been carried out on the co-crystal and its components to obtain their corresponding two- and one-electron redox potentials (E^0). The computed co-crystal two-electron redox

potential (based on catechol) showed that it possesses the highest reducing ability when compared to the individual NCTA and NNTCA components. It was observed from the study that the lower the redox potential, the higher the stability of the electron-transfer process radicalion, and the higher the reducing ability of the molecule.

Declarations

Author contribution statement

Kayode Sanusi: Analyzed and interpreted the data; Wrote the paper.
Lateefah M Durosinmi: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Olatomide A Fadare: Performed the experiments; Wrote the paper.
Yusuf Yilmaz, Ümit Ceylan: Analyzed and interpreted the data.

Craig A Obafemi: Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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