The Role of Solvent in Tautomer Solvate Crystallization: A Case of 6-Amino-1,3-Dimethyl-5-Nitrosouracil

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Abstract
Tautomers are structural isomers that readily interconvert and may exhibit different properties. The effect of solvent on tautomeric equilibria in solution has been a subject of some research. Tautomer solvate is less common, and the role of solvent in the crystallization of tautomer solvate remains an interesting topic. In this work, we used 6-amino-1,3-dimethyl-5-nitrosouracil (NAU) as the tautomeric model material, which can present in nitrone–enamine form (Tautomer A) or oxime–imine form (Tautomer B). A solvate with NAU/DMSO ratio of 1:1 was discovered and characterized using single/powder X-ray diffraction and thermogravimetry. The crystal structure of NAU-DMSO was determined for the first time, where only Tautomer A was formed in the tautomeric crystal. Quantum chemical calculation and molecular dynamics simulation were conducted to determine the tautomer form in DMSO solution. Electrostatic potential analysis, radial distribution function analysis, and binding energy suggested possible DMSO–NAU interaction modes and stable tautomer complexes in solution. Tautomer A-containing complexes were found to dominate in solution, as verified by comparing predicted and experimental 1H NMR spectra. Findings reveal that the hydrogen bonding between DMSO and NAU is similar in solution and in NAU–DMSO solvate crystal, which helps preserve the form of Tautomer A during solvate crystallization.

Keywords Tautomerization · Solvate · Molecular dynamics simulation · Quantum chemical calculation

Introduction
Tautomerism describes the isomers of a compound with uncertainty of proton position [1]. Around 10% of the molecules in the Cambridge Structural Database (CSD) have the potential for tautomerism [2]. Tautomerism is complex, and the tautomeric compounds have two to dozens of tautomers; for example, warfarin can exist in 40 distinct tautomeric forms [3]. Tautomers may have very different physical
of solvent in crystal is an easy way to obtain tautomeric polymorphisms by forming solvate. For tautomeric solvate, the solvent effect on tautomerization in solution and in crystal may vary due to different arrangements and the local environments, which are seldom studied. Joseph et al. [19] studied tautomeric form preservation during crystallization. However, a comprehensive understanding remains absent on how the solvent molecules influence the tautomeric forms in solution and eventually in crystal.

6-Amino-1,3-dimethyl-5-nitrosouracil (NAU) is an intermediate of N-oxide organic photoredox catalysts [20] and caffeine [21]. A pair of NAU tautomeric forms (Fig. 1) has been reported [22, 23]. Tautomer A has amino and nitroso groups, while Tautomer B has imino and oximido groups, of which the fundamental difference is the position of H1 (or H1'). In this paper, we choose NAU and DMSO to analyze the role of solvent in the crystallization of tautomer. We first discovered the DMSO solvate of NAU and determined the tautomeric form in crystal. Then, the possible tautomeric forms in DMSO solution were studied in detail through experiments and theoretic computation, including molecular dynamics simulation and quantum chemical calculation. Furthermore, we compared the interactions between NAU and DMSO molecules in solution and crystal to discuss the role of solvent in the crystallization of solvate.

**Experimental**

**Materials**

NAU·H₂O (99.5% purity, CCDC number: 1198925) was purchased from Xinhua Pharmaceutical (Shouguang) Co., Ltd., China. NAU was obtained from the dehydration of NAU·H₂O. DMSO (99.5% purity) was purchased from Lian-long Bohua (Tianjin) Pharmaceutical Chemistry Co., Ltd., China. DMSO-d6 (99.9% purity) was purchased from Kmart (Tianjin) Chemical Technology Co., Ltd., China.

**Preparation of DMSO Solvate of NAU**

Anhydrous NAU was prepared by drying NAU·H₂O in a vacuum oven at 120 °C for 2 h. The as-prepared anhydrous NAU (about 300 mg) was dissolved in 5 mL DMSO at 50 °C for 3 h in a 10-mL screw-capped vial. The solution was filtered by an organic membrane (0.45 μm) and transferred into another screw-capped vial. Then, the vial was allowed to naturally cool to room temperature. Good-quality crystals that are suitable for single-crystal X-ray diffraction (SCXRD) can be obtained in 12 h.

**Characterizations**

**Power X-Ray Diffraction**

The samples were all analyzed by power X-ray diffraction (PXRD) using a D/MAX 2500 diffractometer (Cu-Kα radiation 1.5406 Å) at 40 kV and 100 mA. The scanning range was from 2° to 50° at a step of 8°/min. The collected data were analyzed by using commercial software Jade (version 6.0).

**Thermogravimetry**

Thermogravimetry (TG) analysis [24] was carried out on a Mettler Toledo TGA/DSC 1/SF. Samples (about 5–10 mg) were placed in a 70 μL standard alumina pan and heated from 30 to 300 °C at a heating rate of 10 °C/min under a nitrogen flow of 20 mL/min.

**Single-Crystal X-Ray Diffraction**

SCXRD data were collected on a Rigaku XtaLAB P200 diffractometer using graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). The structure was solved using SHELXS-97 [25] and refined using SHELXL-97 [26].

![Fig. 1 Tautomers of NAU](image-url)
**1H Nuclear Magnetic Resonance Spectra**

1H nuclear magnetic resonance spectra (1H NMR) experiment was performed at 500 MHz on a Varian INOVA spectrometer equipped with a positive phase probe. About 10 mg NAU was dissolved in 5 mL DMSO-d$_6$. Data were analyzed by MestReNova (version 6.1).

**Molecular Dynamics Simulation**

To evaluate the interaction between NAU and DMSO, radial distribution function (RDF) analysis was performed using molecular dynamics (MD) simulation in Materials Studio (version 17.1). The structures of NAU tautomers and DMSO were first generated manually. These structures were then used to build amorphous cells with periodic boundary conditions. The quantities of Tautomer A or B and DMSO were decided according to the concentration of solution in the 1H NMR experiment. Two dynamics experiments were conducted. One amorphous cell contained 8 Tautomer A and 1000 DMSO (8A-1000DMSO), and the other amorphous cell contained 8 Tautomer B and 1000 DMSO (8B-1000DMSO). The amorphous cells were subjected to geometry and dynamics simulation using Dreiding force field [27]. In dynamics simulation, an NVT (fixed number of particles, volume, and temperature) ensemble method was selected at a temperature of 298.15 K. The time step was 1.0 fs with a total simulation time of 500 ps, controlled by Andersen thermostat [28]. Then, the RDF was computed using the O atom of DMSO and the N atom of –NH$_2$ from Tautomer A or the N atom of =NH from Tautomer B. Finally, some hydrogen bonding complexes were obtained by setting the angle of X–H–A not less than 90° and the distance of H–A not more than 3.0 Å [29] in Materials Studio. DMSO molecules that have a van der Waals interaction with NAU as indicated by dynamics simulation results are eliminated to simplify the calculations.

**Quantum Chemical Calculation**

The geometries of NAU tautomers, hydrogen bonding complexes, and transition state were optimized at the B97D/6-31 + G(d,p) [30] level in vacuum or DMSO solvent using IEFPCM models [31] in GAUSSIAN 09. Hydrogen bonding complexes were generated from molecule dynamics experiments. To calculate the transition state (TS), we used the Berny method [32] in GAUSSIAN 09. To correct dispersion, the keyword “em = gd3” was used in all calculations [33]. Single-point energies were calculated for the optimized ground states and TS [2, 33] at the B97D/def2QZVPP level [30], in which the method was the same as the optimization calculation, but the basis was larger. The binding energy between NAU and DMSO in each complex is calculated by the following formula:

$$\Delta E_{\text{binding}} = E_{\text{complex}} - (E_{\text{NAU}} + nE_{\text{DMSO}})$$

where $E_{\text{complex}}$ is the energy of each complex; $E_{\text{NAU}}$ is the energy of Tautomer A or B (determined by the NAU tautomer form in each complex); $n$ is the number of DMSO in each complex; and $E_{\text{DMSO}}$ is the energy of DMSO molecule. 1H NMR chemical shifts (δ) were calculated relative to those of tetramethylsilane (TMS) by using the gauge-including atomic orbital (GIAO) method [30, 34]. The 1H NMR data for optimized structures and TMS were calculated at B97D/6-31 + G(d,p) [30] and B3LYP/6-311 + G(d,p) [35], respectively, in GAUSSIAN 09.

Molecular electrostatic potential (ESP) analysis was performed at B97D/def2QZVPP, which was the same as the level used in single-point energy analysis. ESP was projected onto the van der Waals surface. Multiwfn and visual molecular dynamics (VMD) were used for ESP analysis [36, 37].

**Results and Discussion**

**DMSO Solvate of NAU and Tautomer in Its Crystal**

The PXRD pattern of the crystals obtained from DMSO solution was compared with that of anhydrous NAU and NAU·H$_2$O in Fig. 2. The crystals obtained from DMSO have distinct characteristic peaks at 2θ = 7.69°, 9.09°, 15.07°, and 22.85°, which are different from the characteristic peaks of either NAU·H$_2$O (12.44°, 16.46°, 17.00°, and 18.68°) or NAU (9.34°, 12.38°, 13.96°, and 14.76°). This finding reveals that the crystal obtained from DMSO is a new crystalline phase of NAU.

![Fig. 2 PXRD patterns of NAU, NAU-H$_2$O, and the sample obtained from DMSO](image-url)
The new phases of NAU and the sample obtained from DMSO were then analyzed by using TG–DSC with NAU·H₂O as a reference. The TG–DSC plot of NAU·H₂O (Fig. 3a) indicates that NAU·H₂O dehydrated from 100 to 150 °C with a corresponding weight loss of 8.96%, which is consistent with the stoichiometric ratio of 1:1 for NAU·H₂O. According to Fig. 3b, no water trace remained after dehydration of NAU·H₂O. For the sample obtained from DMSO (Fig. 3c), the loss of weight and the corresponding endothermic peak below 120 °C imply that the sample is a DMSO solvate. The weight loss of DMSO solvate (31%) can give a NAU-to-DMSO stoichiometric ratio of about 1:1.

High-quality crystal of the DMSO solvate of NAU (NAU·DMSO) was cultivated, and the crystal structure was determined by SCXRD. The detailed crystallographic data are listed in Table 1. The NAU–DMSO crystallizes in the orthorhombic Pbc a space group. The 1:1 stoichiometric ratio of NAU to DMSO is consistent with the result of the TG experiment. All the NAU molecules are precisely recognized as Tautomer A. Crystal packing diagrams along three axes are shown in Fig. 4. Figure 4a, c shows that the crystal is stacked along the c-axis with a layer structure parallel to aob. The layer (Fig. 4a) is

| Table 1 | Crystallographic data of DMSO solvate |
|---------|--------------------------------------|
| Formula | C₈H₁₄N₄O₄S |
| Crystal system | Orthorhombic |
| Space group | Pbc a |
| Temperature (K) | 113.2(2) |
| a (Å) | 17.526 (4) |
| b (Å) | 5.6789 (11) |
| c (Å) | 23.439 (5) |
| α (°) | 90 |
| β (°) | 90 |
| γ (°) | 90 |
| Cell volume (Å³) | 2332.9 (8) |
| Calc density (g/cm³) | 1.494 |
| Z | 8 |
| R₁ (I > 2σ(I)) | 0.0674 |
| ωR₂ | 0.0524 |
| GOF(S) | 0.1656 |
| CCDC | 1946769 |

Fig. 3  TG–DSC plots of a NAU·H₂O, b NAU, and c the sample obtained from DMSO
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Identification of NAU Tautomeric Form in DMSO Solution

ESP Analysis

The tautomer state in solution may be influenced by solvent–solute interaction, which is important to possible tautomerization during crystallization. Compared with the solvent role of stabilizing Tautomer A in crystal, the effect of DMSO on the tautomer in a solution is more complex due to the irregular molecular arrangement and complex molecular vibration and movement. To identify NAU tautomeric form in solution, ESP of DMSO and two NAU tautomers were analyzed first to find the possible solvent–solute interaction sites [37]. In the ESP maps (Fig. 5), the blue and red indicate negatively and positively charged regions, respectively. The spots on the surface represent the extreme point of potential in the corresponding regions. The most negatively charged region for DMSO (Fig. 5a) locates at the O atom, while the positive charge disperses on the two methyl groups. The charge distributions for Tautomer A (Fig. 5b) and Tautomer B (Fig. 5c) are similar, where the positive charge focuses on the H2 in Tautomer A and the H2’ in Tautomer B. Therefore, the most possible interaction mode in solution should form between the O atom of DMSO and the H2 in Tautomer A or the H2’ in Tautomer B, which is the same as the DMSO–NAU interaction in crystal.

RDF Analysis

The possible DMSO–NAU interaction in solution may vary from that provided by ESP analysis because ESP was analyzed in vacuum without conformational variation. Hence, MD simulations with systems containing 1000 DMSO and 8 NAU molecules were performed to discover the DMSO–NAU interaction and the NAU tautomer form in solution more precisely. On the basis of the result of ESP analysis, the O atom of DMSO and the N atom of –NH2 from Tautomer A or the N atom of =NH from Tautomer B were chosen for RDF analysis (Fig. 6), which can be used to evaluate the interaction strength in solution [28]. In RDF results, chemical bonds or hydrogen bonds usually contribute to a sharp peak within 3.5 Å, while van der Waals interactions contribute to a peak between 3.5 and 5.0 Å [38]. A sharp peak at 3.03 Å can be observed in Fig. 6a, indicating that the H2 atom of –NH2 from Tautomer A formed a hydrogen bond with the O atom of DMSO in the experiment 8A-1000DMSO. Another sharp peak at 3.05 Å can be observed in Fig. 6b, indicating that the H atom of =NH from Tautomer B also formed a hydrogen bond with the O atom of DMSO in the experiment 8B-1000DMSO.

Binding Energies of Solute–Solvent Complexes in Solution

After MD simulations, 13 structures, including monomer and hydrogen bonding solute–solvent complexes, were found in amorphous cells (Fig. S1–S13). Complexes 1–6 and Complexes 7–13 were derived from experiment 8A-1000DMSO and experiment 8B-1000DMSO, respectively.

To evaluate the stabilities of the 13 complexes in solution, the binding energy between NAU and DMSO in each complex was calculated. The information and binding energies of Complexes 1–13 are listed in Table 2. For complexes that contain the same tautomer, complexes with multiple DMSO molecules exhibit higher binding energies and thus are more stable than those that combine one DMSO molecule. This finding indicates that interactions between DMSO and NAU are important to the stability of DMSO–NAU complexes in solution. For complexes with the same DMSO/NAU ratio, all the complexes of Tautomer A show higher binding energies and thus better stability than the corresponding complexes of Tautomer B. According to Table 3, Complexes 2, 3, and 8 express the highest binding energies and stabilities in solution.

Notably, tautomerization from Tautomer B to Tautomer A was discovered for some complexes of Tautomer B during the optimization calculation, whereas no TS was found from Tautomer B to Tautomer A. The tautomerization occurred for both 1:1 complex (Complex 13) and 2:1 complex (Complexes 8–10). A comparison of those complexes showed that the DMSO–NAU interaction site was critical for the
tautomerization from Tautomer B to Tautomer A. In case the O atom of DMSO locates between the H1’ and H2’ of Tautomer B in the complex, as illustrated in Fig. 7 (Complex 9 as an example), the O atom of DMSO (negative charge center of DMSO, Fig. 5a) preferred to move toward the N atom of NAU (positive charge center, Fig. 5c). Consequently, H1 of NAU transferred from the O atom of –N–O–H to the N atom of C= N–H and experienced tautomerization via attraction from both the O atom of the DMSO and the N atom of C=N–H from NAU.

Cases were also found in which the DMSO molecule located around H2 and formed a hydrogen bond with NAU. To further determine the role of this DMSO molecule in possible tautomerization, the energies of monostructure and 1:1 DMSO–tautomer complexes were calculated and the corresponding TS was searched. Vacuum was chosen for simulation experiments to eliminate the effects of all other molecules. Pure tautomers have similar energies; a TS with high energy barrier (Fig. 8a) indicates difficult mutual conversions between the two tautomers. The DMSO–Tautomer B complex exhibits higher energy than the DMSO–Tautomer A complex (Fig. 8b). Moreover, the location of the TS of these complexes is close to that of the DMSO–Tautomer B complex, which gives a low barrier for the conversion from Tautomer B to Tautomer A. This result implies that interactions between DMSO and NAU promote the transformation from Tautomer B to Tautomer A in both thermodynamics and kinetics.

Fig. 4 Crystal packing diagrams of NAU-DMSO solvate view along: a b-axis, b c-axis (DMSO molecules are removed for clarity), and c a-axis. Molecules shown in stick-ball model in a–c represent the same layer of molecules. d Diagram of packing unit. e Interaction between NAU in the layer. F Weak interactions between neighbored layers. Molecules in boxes with the same color have the same structure in different diagrams.

Fig. 5 ESP analysis of a DMSO, b Tautomer A, and c Tautomer B.
Table 2 Binding energies of possible dominant complexes

| Optimized complex | Initial tautomer form | Tautomer form | DMSO/NAU ratio | Binding energy (kJ/mol) |
|-------------------|-----------------------|---------------|----------------|------------------------|
| Complex 1         | A                     | A             | 0              | 0                      |
| Complex 2         | A                     | A             | 2              | -54.92                 |
| Complex 3         | A                     | A             | 2              | -53.27                 |
| Complex 4         | A                     | A             | 1              | -31.04                 |
| Complex 5         | A                     | A             | 1              | -30.75                 |
| Complex 6         | A                     | A             | 1              | -29.59                 |
| Complex 7         | B                     | B             | 0              | 0                      |
| Complex 8         | B                     | A             | 2              | -55.71                 |
| Complex 9         | B                     | A             | 1              | -28.53                 |
| Complex 10        | B                     | A             | 1              | -30.13                 |
| Complex 11        | B                     | B             | 1              | -19.60                 |
| Complex 12        | B                     | B             | 1              | -14.15                 |
| Complex 13        | B                     | A             | 1              | -28.32                 |

Table 3 Experimental and predicted chemical shifts for H in Complexes 1–13

| Complexes | H1(′) | H2(′) | H3(′) & H4(′) | Q       |
|-----------|-------|-------|---------------|---------|
|           | B97D  | B3LYP | B97D          | B3LYP   | B97D  | B3LYP |
| Complex 1 | 13.39 | 13.10 | 4.99          | 5.16    | 3.44  | 3.45  | 17.026 | 15.524 |
| Complex 2 | 12.84 | 12.63 | 9.21          | 9.57    | 3.43  | 3.46  | 0.210  | 0.605  |
| Complex 3 | 12.79 | 12.69 | 9.95          | 10.19   | 3.43  | 3.47  | 0.968  | 1.590  |
| Complex 4 | 13.03 | 12.74 | 10.23         | 10.53   | 3.44  | 3.49  | 1.561  | 2.496  |
| Complex 5 | 13.09 | 12.79 | 10.19         | 10.44   | 3.45  | 3.49  | 1.474  | 2.224  |
| Complex 6 | 12.85 | 12.58 | 10.42         | 10.73   | 3.44  | 3.47  | 2.013  | 3.169  |
| Complex 7 | 20.43 | 20.57 | 7.40          | 7.54    | 3.40  | 3.40  | 58.666 | 60.351 |
| Complex 8 | 12.77 | 12.52 | 10.49         | 10.77   | 3.41  | 3.46  | 2.188  | 3.297  |
| Complex 9 | 12.89 | 12.60 | 10.30         | 10.63   | 3.42  | 3.49  | 1.675  | 2.882  |
| Complex 10 | 13.07 | 12.76 | 10.19         | 10.44   | 3.46  | 3.51  | 1.507  | 2.292  |
| Complex 11 | 20.37 | 20.45 | 7.45          | 7.56    | 3.34  | 3.34  | 57.584 | 58.374 |
| Complex 12 | 20.57 | 20.71 | 7.50          | 7.61    | 3.34  | 3.36  | 60.436 | 62.212 |
| Complex 13 | 12.91 | 12.59 | 10.37         | 10.64   | 3.45  | 3.52  | 1.902  | 2.988  |
| Experimental | 12.96 | 9.07  | 3.26          |         |       |       |        |
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1H NMR Calculation and Verification

1H NMR has been widely used in many tautomer systems to determine the tautomer states, for example, Schiff base [4, 35], porphyrin [7], azo dyes [39], and other substances [40–43]. We also measured the 1H NMR spectra of the DMSO solution of NAU (Fig. 9) to determine the tautomeric form in solution. The peaks at 2.50 and 3.35 could be associated with impurities of DMSO without deuterium and water, respectively. The peaks at 3.20 and 3.33 belong to the two methyls in NAU. However, the peaks at 9.07 and 12.96 are difficult to assign due to the similar positions and environment of H1(′) and H2(′) in the two tautomer forms.

The 1H NMR spectra of possible complexes (Complexes 1–13) in the DMSO solution were then predicted at B97D/6-31 + G(d,p) and B3LYP/6-311 + G(d,p) levels, whose accuracy had been proven [30.35]. The experimental and predicted chemical shifts are shown in Table 3. The residual sum of square \((Q)\) of each complex was calculated by the following formula:

\[
Q = \sum_{i=1}^{4} (y_i - \hat{y}_i)^2 \times n_i
\]

where \(y_i\) is the experimental chemical shift of \(H_i\) \((i = 1–4)\); \(\hat{y}_i\) is the predicted chemical shift of \(H_i\); and \(n_i\) is the number of \(H\) in each functional group. The chemical shifts of 6 H atoms from the two methyls are close enough to be calculated as one kind of hydrogen.

According to Table 3, the residual sums of square of Complexes 2 and 3 are small enough to be acceptable at both B97D/6-31 + G(d,p) and B3LYP/6-311 + G(d,p) levels. This finding demonstrates that the peaks at 9.07 and 12.96 in experimental 1H NMR spectra could be assigned to Tautomer A-containing complexes. The difference between experimental and predicted chemical shifts for H may be attributed to the van der Waals interactions being ignored for simplicity. By comparing the discussion results of complex stability and 1H NMR spectra, one can conclude that Tautomer A would dominate in the DMSO solution via the interaction with DMSO molecules.
Tautomeric Form Preservation During Solvate Crystallization

The optimization results for the dominating Complexes 2 and 3 in solution are illustrated in Fig. 10. The findings indicate that only one DMSO molecule can form a stable hydrogen bond with Tautomer A at H2, which helps stabilize Tautomer A in solution. In NAU-DMSO crystal, Tautomer A is preserved, and DMSO and Tautomer A have hydrogen bonding with the same type of interaction. Although other DMSO molecules in the first solvent layer have weak van der Waals force with Tautomer A in solution, they have no chance to enter the crystal. A comparison of the interaction between DMSO and Tautomer A in solution and in crystal indicates that such hydrogen bonding from the O atom of DMSO and H2 of Tautomer A plays an important role in preserving Tautomer A during solvate crystallization.

Conclusions

A solvate with NAU/DMSO ratio of 1:1 was discovered, and its crystal structure was determined. Only Tautomer A exists in NAU–DMSO solvate crystal. The packing unit of the crystal is composed of 2 Tautomer A connecting via a $R_2^2(12)$ motif and 2 DMSO molecules hydrogen bonding to Tautomer A via N–H–O (1.966 Å, 162.88°). Tautomer A also exhibits an intramolecular N–H–O (1.911 Å, 134.61°) hydrogen bond. The crystal is stacked along the c-axis with layers that are parallel to the ab plane. Inside the layer, the packing units form a herringbone motif. The herringbone motifs in the neighbored layers are not parallel but interlaced. ESP analysis shows that the negative charge of DMSO focuses on the O atom. The positive charge center locates near H2(′) for both Tautomer A and Tautomer B, with Tautomer A having a higher positive charge density. RDF analysis indicates a strong hydrogen bond interaction within the first solvent layer of NAU. MD simulations of the systems that contain 1000 DMSO and 8 NAU molecules were conducted, and 13 complexes in solution were obtained, with Complexes 2, 3, and 8 showing the highest binding energies and stability. Stable Tautomer B-containing complexes have higher energy than corresponding complexes of Tautomer A. Two effects of DMSO were found in this case. Transition from Tautomer B to Tautomer A was discovered during structure optimization when the O atom of DMSO locates between the H1′ and H2′ atoms of Tautomer B in complexes. The TS search result implies that the hydrogen bond between the O atom of DMSO and the H2′ atom of Tautomer B could promote the transition from Tautomer B to Tautomer A. A comparison of predicted and experimental $^1$H NMR spectra verified that Tautomer A-containing complexes (Complexes 2 and 3) dominate in the DMSO solution. The hydrogen bonding between DMSO and NAU is similar in solution and in NAU-DMSO solvate crystal, which helps preserve the form of Tautomer A during solvate crystallization. A variety of solid-state NMR spectra may be useful for determining tautomeric form in solid states. Thus, further research and efforts can be expected and will be crucial.

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Accession Codes  CCDC 1946769 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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