

The Structure and Tautomerism of Cyameluric Acid*

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Z. Naturforsch. **61b**, 975–978 (2006); received February 27, 2006

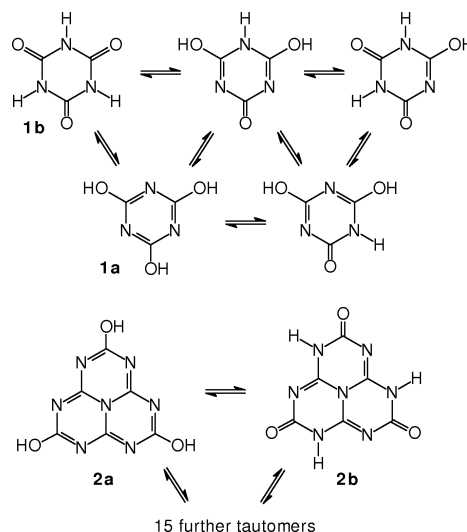
Dedicated to Prof. Dr.-Ing. Dr. h. c. Hartmut Fuess (Darmstadt), on the occasion of his 65th birthday

The single crystal X-ray structure of the DMSO solvate of cyameluric acid $C_6N_7O_3H_3 \cdot 3DMSO$, **2b'** has been determined. The results show that the most stable tautomer of solid cyameluric acid is the tri-keto form **2b** with C_{3h} symmetry. 1H and ^{13}C NMR data indicate that this isomer is also present in solution, with slow interchange of the N-H protons. This confirms previous theoretical results although almost all derivatives reported in the literature are derivatives of the tri-hydroxy tautomer **2a**.

Key words: Heptazine, Crystal Structure, Cyanuric Acid, Isomerism, Heterocycles

Introduction

Heterocycles with N=C-OH groups frequently show keto-enol or more precisely aminoketo-iminoalcohol tautomerism. A prominent example is the isomerism between cyanuric acid **1a** and isocyanuric acid **1b**. The related heterocyclic compound cyameluric acid $C_6N_7O_3H_3$, **2**, may exist in several different tautomeric forms (Scheme 1) [1]. Recently, theoretical studies were published on this subject and on the stability of heptazine derivatives $C_6N_7R_3$ in general [2–5]. Cyameluric acid as well as other derivatives of the class of sym-heptazine compounds $C_6N_7R_3$ have first been prepared as early as 1834 [6]. However, a first crystal structure was published 1982, when the parent compound sym-heptazine $C_6N_7H_3$ was investigated [7]. It took another 20 years until the first crystal structure of a heptazine derivative, namely cyameluric chloride $C_6N_7Cl_3$, was reported [8]. In the past two years several groups started to characterize further heptazine derivatives, all of which are derived from the tri-hydroxy tautomer of **2a**, namely the tri-amine melem $C_6N_7(NH_2)_3$ [9], the tri-azide $C_6N_7(N_3)_3$ [10], the tri-amide $C_6N_7(N(C_2H_5)_2)_3$ [11], another form of the above mentioned tri-chloride $C_6N_7Cl_3$ [12], and potassium melonate $K_3[C_6N_7(NCN)_3]$ [13]. Here we report the first crystal structure of cyameluric acid in



Scheme 1.

the form of the DMSO solvate $C_6N_7O_3H_3 \cdot 3DMSO$, **2b'**, which shows that at least in the crystal and with N-H...O(DMSO) hydrogen bonds the most stable tautomer is the tri-oxo form of **2**.

Results and Discussion

Cyameluric acid **2** has seventeen tautomeric forms: one tri-hydroxy, three di-hydroxy, four tri-oxo and nine mono-hydroxy isomers. It is an open question which tautomers are stable in the solid state and in solution,

* Tri-s-triazine derivatives. Part 4. For part 3 see ref. [13].

d/Å		∠°	
C1-O1 / C3-O2 / C5-O3	1.18 / 1.22 / 1.18	N2-C1-O1 / O2-C3-N4 / O3-C5-N6	122.9 / 123.0 / 122.6
C1-N2 / C3-N4 / C5-N6	1.36 / 1.40 / 1.40	N1-C1-O1 / O2-C3-N3 / O3-C5-N5	119.0 / 118.4 / 119.0
C1-N1 / C3-N3 / C5-N5	1.40 / 1.40 / 1.36	N1-C1-N2 / N4-C3-N3 / N6-C5-N5	118.1 / 118.6 / 118.5
C2-N2 / C4-N4 / C6-N6	1.31 / 1.27 / 1.31	N2-C2-N3 / N4-C4-N5 / N6-C6-N1	120.7 / 120.9 / 120.8
C2-N3 / C6-N1 / C4-N5	1.36 / 1.35 / 1.36	N2-C2-N7 / N4-C4-N7 / N6-C6-N7	124.2 / 124.0 / 124.1
C2-N7 / C6-N7 / C4-N7	1.35 / 1.36 / 1.40	N3-C2-N7 / N5-C4-N7 / N1-C6-N7	115.1 / 115.0 / 115.0
N1-H1 / N3-H3 / N5-H5	0.84 / 0.84 / 0.87	C1-N2-C2 / C3-N4-C4 / C5-N6-C6	118.1 / 117.9 / 117.8
O5-H1 / O6-H3 / O4-H5	1.88 / 1.83 / 1.80	C2-N3-C3 / C4-N5-C5 / C1-N1-C6	124.2 / 124.6 / 124.5
		C2-N7-C4 / C4-N7-C6 / C6-N7-C2	120.0 / 120.0 / 120.0
		N1-H1-O5 / N5-H5-O4 / N3-H3-O6	175.6 / 175.5 / 175.4
		H5-O4-S1 / H1-O5-S2 / H3-O6-S3	119.5 / 112.6 / 112.4

Table 1. Selected bond lengths and bond angles of the cyameluric acid solvate $C_6N_7O_3H_3 \cdot 3DMSO$ **2b'** (compare Fig. 1). The standard deviation of the bond length values is relatively small, *i.e.* below 0.001 Å, which is due to the high quality of the crystal used for the diffraction experiment.

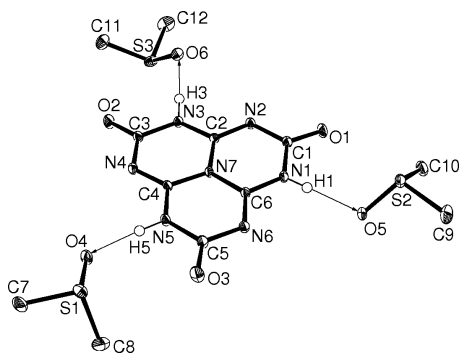


Fig. 1. Molecular structure of the cyameluric acid solvate $C_6N_7O_3H_3 \cdot 3DMSO$ **2b'** (ORTEP plot with 50% probability ellipsoids). The hydrogen atoms of the methyl groups have been omitted for clarity. N-H...OSMe₂ hydrogen bonds are indicated by thin arrows (compare Table 1 for bond lengths and angles).

where equilibria between these forms may be present. Considering the acidity of a potential hydroxyl group of **2** and the basicity of the peripheral nitrogen atoms of the tricyclic C_6N_7 unit it may be assumed that the tri-oxo tautomer **2b** with C_{3h} symmetry is the most stable form. This assumption was supported by three *ab initio* theoretical studies which were focused on the relative stability of all these cyameluric acid tautomers in the gas phase and in solution [2d, 2f, 3]. On the other hand, with only two exceptions, namely a stannyl [14] and a germyl [15] derivative, all compounds known so far are derived from the tri-hydroxy form of **2**. In order to get clear evidence for the molecular structure of cyameluric acid **2**, we tried to crystallize this compound from different solvents such as methanol, THF, water, ethanol, and DMSO as well as mixtures of these solvents. Single crystals suitable for an X-ray structural analysis were obtained from a hot DMSO solution upon addition of ethanol.

The molecular structure of the DMSO solvate **2b'** is shown in Fig. 1, selected and rounded values of

bond lengths and angles are summarized in Table 1. Although the $C_6N_7O_3H_3$ unit is slightly distorted, it is completely planar, as indicated by the sum of bond angles around the C and N atoms of 360° . As expected, the protonation of the peripheral N atoms N1, N3 and N5 does not significantly disturb the conjugated system of 20 π -electrons over the tricyclic heptazine core. Complete planarity of the $C_6N_7X_3$ unit was predicted theoretically [2, 3] and observed for alkali cyamelurates $M_3[C_6N_7O_3]$ [16] as well as for all other heptazine derivatives investigated so far [7–13].

The C-N bond lengths of the heptazine C_6N_7 unit in derivatives of the cyameluric acid tautomer **2a** are typically in the range of 1.30–1.42 Å [17], which is in between the length of C(sp³)-N single (1.47 Å) and C(sp²)=N double (1.28 Å) bonds [18]. For **2b'**, the three (H)N-C(O) distances are almost equal to the three N-C(O) distances as well as the C-N bond length to the central nitrogen atom N7, all of which are in the range of 1.36–1.40 Å. Only slightly shorter are the (H)N-C distances with 1.35–1.36 Å. The remaining C-N distances in **2b'** are 1.27–1.31 Å, which is close to pure C=N double bonds. Therefore, the Lewis formula **2b** in Scheme 1 describes the true structure of cyameluric acid with respect to bond lengths quite well. The latter conclusion is supported by the relatively short C-O bond lengths of 1.18–1.20 Å observed for **2b'** which is equal to or even shorter than typical C(sp²)=O distances [18].

All three hydrogen atoms of the cyameluric acid molecule form hydrogen bridges to the oxygen atoms of the DMSO molecules. These bonds are almost linear as indicated by the N-H-O angles of $\sim 175^\circ$. They are comparatively short with (N)H-O distances of 1.80–1.88 Å.

Interestingly, no typical π -stacking of the cyameluric acid molecules is detectable as it was reported for cyamelurate $[C_6N_7O_3]^{3-}$ and melonate

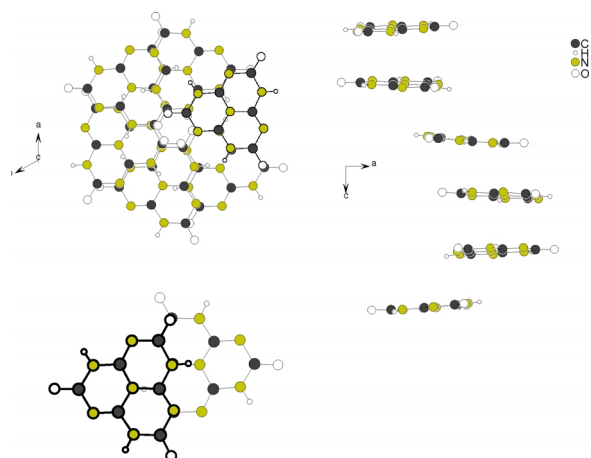


Fig. 2. Representation of the crystal structure of $C_6N_7O_3H_3 \cdot 3DMSO$ **2b'** showing the six-fold screw axis (view along the *c*-axis left, and view along the *b*-axis right). The lower part of the figure shows the relative orientation of two molecules, indicating π - π -interactions and/or Coulomb attraction between the partially positively and negatively charged atoms.

$[C_6N_7(NCN)_3]^{3-}$ anions, respectively [13, 16], or melem $C_6N_7(NH_2)_3$ [9]. However, the shortest intermolecular C–N and C–O distance between the coplanar molecules is 3.1 Å, indicating π - π -interactions or at least Coulomb attraction between partially positively and negatively charged C- and N/O-atoms. Fig. 2 shows the arrangement of the $C_6N_7O_3H_3$ species in the crystal, forming helices in the direction of the six-fold screw axis along the *c*-direction. A comparable stacking was reported for the tri-azide $C_6N_7(N_3)_3$ [10].

It is an interesting question whether the molecular structure and most stable tautomeric form of cyameluric acid found in the crystal is also present in solution. The 1H NMR spectrum of a solution of **2** in d_6 -DMSO shows a sharp singlet at 12.5 ppm, indicating that the proton exchange is relatively slow. Much faster proton exchange is to be expected in aqueous solution. As expected, the ^{13}C NMR spectrum shows two signals for the two different sets of three carbon atoms at 149.3 and 151.5 ppm. The intensity of both lines is comparable, but the latter signal is significantly broadened. According to theoretical estimations the chemical shift values should be 137.6 (CN₂O) and 139.7 ppm (CN₃) respectively [3]. Therefore, and due to the line broadening it can be suggested, that the ^{13}C resonance at 149.3 is caused by the carbonyl carbon atom, while the remaining C atoms bound to three N atoms is responsible for the other signal at lower

field. The number of ^{15}N or ^{14}N NMR signals, three – for the N(central), N(-N=) and N(NH) – versus two, might give additional information about the exchange of protons between the peripheral nitrogen atoms in the DMSO solution. Unfortunately, we were not able to record any of the nitrogen resonances.

In addition to cyameluric acid we prepared different derivatives, which are derived from the different tautomeric forms of **2**. These results underline the analogy between cyameluric acid **2** and cyanuric acid **1**, at least with respect to the occurrence of isomers. The latter data will be published elsewhere.

Conclusions

The single crystal X-ray structure of the cyameluric acid DMSO solvate **2b'** proves that in the crystal the most stable of the possible seventeen tautomeric forms of **2** is the tri-oxo form with C_{3h} symmetry. Its molecular structure is well described by the Lewis formula **2b**, with sp^2 -hybridization of all C-, N- and O-atoms, resulting in a completely planar molecule. NMR-investigations indicate that the same tautomer is also present in DMSO solution with slow exchange of the protons.

Experimental Section

All reagents were commercially available. Dry DMSO and dry ethanol were used. NMR spectra were recorded on a BRUKER DPX 400 instrument at room temperature (d_6 -DMSO solutions with TMS as internal standard). Elemental analyses were carried out on a "Foss Heraeus CHN-O-Rapid" analyzer.

2: Cyameluric acid was synthesized according to an optimized literature synthesis [16]. A suspension of 25 g melon powder in 250 ml of a 2.5 molar aqueous KOH solution was refluxed for 45 min. The hot reaction mixture was filtered and slowly cooled to r. t. Tri-potassium cyamelurate was separated, washed with EtOH and dried at 100 °C under vacuum. The acid was obtained by precipitation with an excess of aqueous HCl (37%). The white precipitate was immediately filtered off, washed with distilled water and dried at 100 °C under vacuum.

2b': The DMSO solvate $C_6H_3N_7O_3 \cdot 3C_2H_6SO$ (colorless crystals) was obtained by re-crystallization from DMSO/ethanol. – 1H NMR (400 MHz, d_6 -DMSO): δ = 12.53 (s, 3H, NH). – ^{13}C NMR (101 MHz, d_6 -DMSO): δ = 149.3, 151.5 (broad). – $C_{12}H_{21}N_7O_6S_3$ (455.54): calcd. C 31.62, H 4.65, N 21.52; found C 31.59, H 5.01, N 21.26.

X-ray analysis

X-ray data of the cyameluric acid DMSO solvate **2b'** were recorded on a BRUKER-NONIUS-X8 APEXII-CCD-diffractometer with Mo-K α -radiation. The structure was solved with direct methods, refined with full-matrix least-squares methods. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms of the DMSO molecules were placed in idealized positions and refined isotropically. The acidic hydrogen atoms of the cyameluric acid were detected by analysis of the residual electron density and isotropically refined without bond length restraints. Structure solution and refinement of F² against all reflections were performed with SHELXS-97 and SHELXL-97 (G. M. Sheldrick, Universität Göttingen, 1986–1997).

Cyameluric acid · 3 DMSO **2b'**: C₁₂H₂₁N₇O₆S₃, $M_r = 455.54$, colourless crystal, $0.45 \times 0.30 \times 0.17$ mm, enantiomorphous hexagonal space groups $P6_1$ and $P6_5$ (see below), $a = b = 12.9184(2)$, $c = 20.7772(7)$ Å, $\alpha = \beta = 90^\circ$, $\gamma = 120^\circ$, $V = 3002.86(12)$ Å³, $Z = 6$, $\rho_{\text{calcd.}} = 1.511$ g·cm⁻³, $2\theta_{\text{max}} = 80^\circ$, $F(000) = 1428$, $\mu = 0.415$ mm⁻¹, absorption correction: multi-scan (SADABS), $\lambda = 0.71073$ Å, $T = 90(2)$ K, 69421 recorded reflections ($-23 \leq h \leq 23$, $-23 \leq k \leq 18$, $-37 \leq l \leq 32$), 11980 unique and 10729 observed reflections with $F_o > 2\sigma(F_o)$, 269 parameters, $R_1 = 0.0297$, $wR_2 = 0.0710$ [$I > 2\sigma(I)$], $R^1 = 0.0366$, $wR_2 = 0.0736$ (all data), residual electron den-

sity (highest peak and deepest hole) 0.570 and -0.264 eÅ⁻³. The Flack parameter was refined to 0.00(11) with a racemic twinning model (ratio 61 : 39 for $P6_1$: $P6_5$). In this case, it is not possible to distinguish between $P6_5$ and its enantiomorphous space group $P6_1$. Refinement without the twinning model in $P6_5$ only and $P6_1$ only, respectively, afforded structure models of similar quality, *i. e.* with neglectable differences in R_1 , wR_2 , Goodness-of-Fit and residual electron density. Only the Flack parameter value significantly deviates from zero in the latter cases. Due to the presence of sulphur atoms in the structure and the high quality of the reflection data, the racemic twinning, which was indicated by the Flack parameter, was accounted for in the structure refinement.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication no. CCDC-299068. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We gratefully acknowledge the German Research Foundation (DFG project-# KR 1739/9-1) and the A. v. Humboldt foundation (postdoctoral fellowship for N.E.A. E.-G.) for financial support.

- [1] Synonyms for cyameluric acid according to the Chemical Abstracts Registry file are 1,3,4,6,7,9b-heptaazaphenalene-2,5,8-triol and 2,5,8-trihydroxy-1,3,4,6,7,9b-heptaazaphenalene.
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