

Theoretical study of cyameluric acid and related compounds

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Dedicated to Professor Enrique Meléndez on his 70th anniversary

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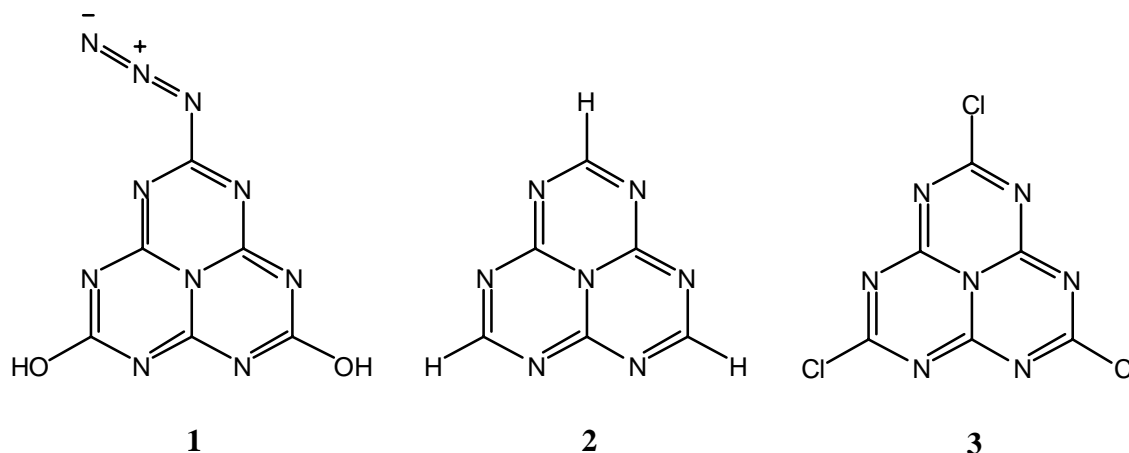
Abstract

DFT calculations (B3LYP/6-31G*) have been carried out on the seventeen tautomers of cyameluric acid. The C_{3h} trioxo tautomer **258** is the most stable. Some energies and absolute NMR shieldings (GIAO) were calculated for **258** and other tri-*s*-triazines, including cyamelurine and Pauling mystery molecule.

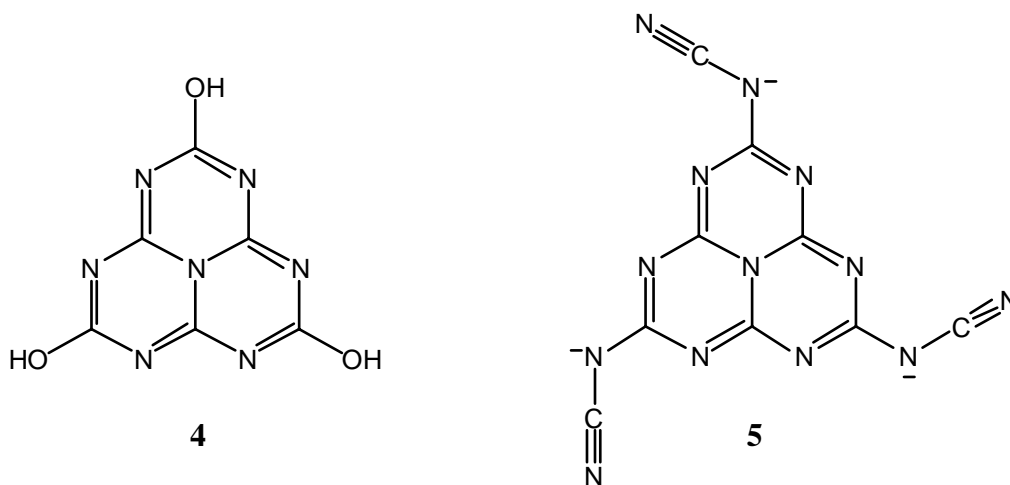
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Introduction

It is known that the last molecule represented on Pauling's chalkboard (1994, preserved to this day by his friends) was the azide derivative **1**^{1,2} of tri-*s*-triazine **2** (1,3,4,6,7,9,9*b*-heptaazaphenalene or cyamelurine):



Compound **2** was fully characterized by Leonard and coworkers in the eighties³ and more recently the X-ray structure of the trichloro derivative **3** was reported by Kroke *et al.*⁴. The interest of Pauling for compound **1** (called "the mystery molecule"¹), is related to some polymeric unidentified old compounds known as melon, melem, dimelemon and dates from very early in his career. For instance, in *The Nature of the Chemical Bond* (Second edition, 1945)⁵, pp. 224-226), Pauling discussed two related compounds: cyameluric acid **4** and hydromelonate ion **5**:

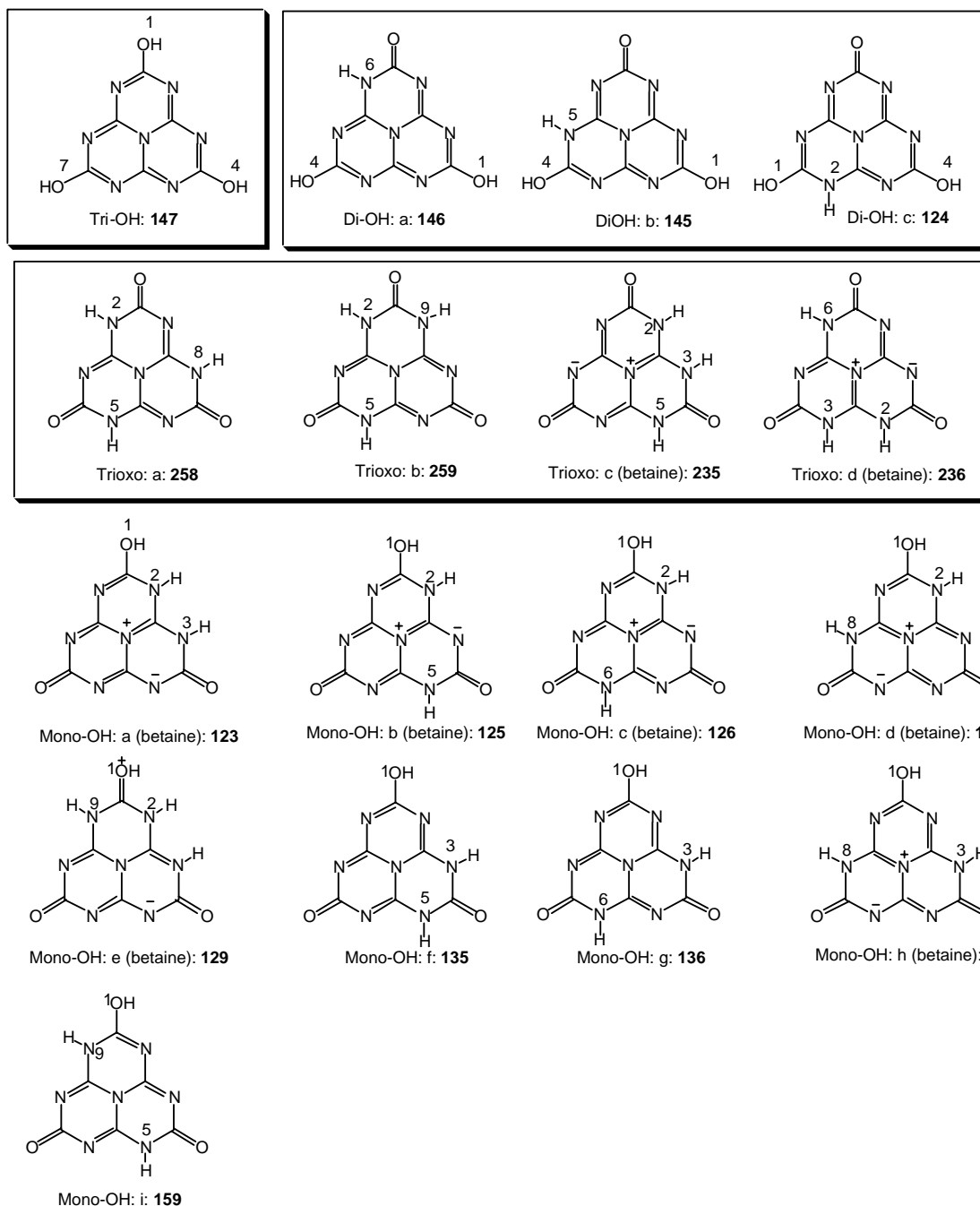


These molecules appeared in a publication by Pauling in 1937⁶. Therefore, it seems that he had been interested in these "resonant" structures for nearly sixty years!

Results and Discussion

We decided to theoretically study compound **4** (1,3,4,6,7,9,9*b*-heptaazaphenalene-2,5,8(1*H*,3*H*,6*H*)-trione) and its possible tautomeric structures. The synthesis and reactivity of this compound (CAS registry number: 1502-46-1, potassium salt: 1488-99-9) has been mainly studied by Russian authors⁷⁻¹² but no structural data were reported, probably due to its very high melting point and insoluble nature.

Not considering the orientation of the OH group, cyameluric acid (**4**) can exist in seventeen tautomeric forms: one mono-hydroxy, three di-hydroxy, four tri-oxo and nine mono-hydroxy (Scheme 1).



Scheme 1

All the possible tautomers (not considering the OH orientation) of the cyameluric acid have been calculated at the B3LYP/6-31G* level (see Computational details). The total and relative energies are gathered in Table 1. These results indicate that the most stable tautomer corresponds to the tri-oxo a (**258**). The tri-hydroxy tautomer **147** is 20 kcal/mol above the global minima in the gas phase.

Table 1. Total and relative energy of the different tautomers of the cyameluric acid

Tautomer (see Scheme 1)	E_T (hartree)	E_{rel} (kcal/mol)
147	-839.415259	19.84
147b	-839.414724	20.18
146	-839.418641	17.72
145	-839.380743	41.50
124	-839.375822	44.59
258	-839.446877	0.00
259	-839.437936	5.61
235	-839.416736	18.91
236	-839.41286	21.35
123	-839.344214	64.42
125	-839.395333	32.34
126	-839.397773	30.81
128	-839.373954	45.76
129	-839.323853	77.20
135	-839.416736	18.91
136	-839.429586	10.85
138	-839.419387	17.25
159	-839.412965	21.28

The difference between **147** and **147b** lies in the orientation of the OH groups: in **147** all point in the same direction (C_{3h}) while in **147b** (0.34 kcal mol⁻¹ less stable) one of them points in an opposite direction (C_s).

The structural information on the parent compound **2** can be summarized as follows. Leonard *et al.* reported its ¹H, ¹³C and ¹⁵N NMR chemical shifts^{3b,13}. Semiempirical calculations of the Dewar and Pariser-Parr-Pople type were carried out¹⁴ and resonance energies calculated¹⁵. Besides energy and density were estimated by Politzer *et al.*¹⁶ as well as aromaticity by Cyranski and Krygowski¹⁷ and heteroaromaticity by Bird¹⁸.

The σ absolute shieldings calculated for compound **2** by means of the GIAO method (Table 2) can be transformed into δ values by means of equations previously reported¹⁹: $\delta^1\text{H} = 0.97(32.5 - \sigma^1\text{H})$; $\delta^{13}\text{C} = 0.905(204.3 - \sigma^{13}\text{C})$; $\delta^{15}\text{N} = -130 - 0.75\sigma^{15}\text{N}$.

Table 2. NMR shieldings of compounds **2** and **258**

Compd/Atom	Absolute σ (ppm)	Exp. δ (ppm)	Estimated δ (ppm)
2 /H	24.08	8.3	8.16
2 /CH	22.85	171.6	164.2
2 /C(junction)	34.70	159.7	153.5
2 /N(central)	69.65	-194.3	-182.2
2 /N(peripheric)	13.52	-143.5	-140.1
258 /H	26.26	---	--- (NH)
258 /C(junction)	49.96	---	139.7
258 /C(C=O)	52.29	---	137.6
258 /N(central)	117.04	---	-217.8
258 /N(-N=)	122.49	---	-221.9
258 /N(NH)	65.05	---	-178.8
258 /O	-61.23	---	---

Actually, the values corresponding to compound **2** fit better with $\delta^{13}\text{C} = 194.6 - \sigma^{13}\text{C}$ and $\delta^{15}\text{N} = -131.3 - 0.905\sigma^{15}\text{N}$, equations very similar to those reported previously¹⁹ for a slightly different basis set.

According to the calculations reported for **4**, it is expected that Pauling compound **1** should not exist as a dihydroxy tautomer but in the dioxo form. Calculations at the same level affords -927.77591 and -927.79299 hartrees respectively, that is, the dioxo tautomer should be 10.72 kcal mol⁻¹ more stable than the dihydroxy one. It has been reported that Pauling's error to represent uracil in the hydroxy form prevented him to reach the structure of the double helix before Watson and Crick^{20,21}.

Computational Details

All the calculations have been carried out with the Gaussian-98 package²² using the 6-31G* basis²³ set at the B3LYP computational level^{24,25}. The geometry of all the molecules has been optimized maintaining an almost C_s symmetry in all the cases. For some selected cases, the minimum nature of the structure has been confirmed by frequency calculations. The absolute isotropic chemical shieldings have been calculated for some of the most representative structures with the GIAO method²⁶ at the same computational level mentioned before.

Acknowledgments

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