**Vibrational features of dacarbazine and detecine revealed by Raman, SERS, THz-Raman and DFT methods**

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**Introduction**

Dacarbazine (DTIC, 5-(3,3-dimethyltriazeno)imidazo[4,5-b]pyridine), is one of the most used anti-neoplastic chemotherapy compound in treating metastasized malignant melanoma, advanced lymph node cancer ( Hodgkin’s disease) and advanced cancers of soft tissue (soft tissue sarcoma) [Eq. 64, Tag. 58]. The drug is administered through injection (commercially known as DTIC – DET), which is reconstructed from DTIC with citric acid and mannitol at a pH of 3.0-4.0. DTIC is extremely sensitive to light, its biological activity being also greatly affected by the pH of the medium in the biological range 7.0-8.8 [Saule]. Since the protonated and deprotonated nitrogens act as a proton donor or acceptor in hydrogen bonding, interactions of dacarbazine with proteins/nucleic acids may depend on a particular molecular form of dacarbazine. Thus, in order to get further insight into the structure/activity relationship, it is important to understand the precise molecular structure and structural behavior of the drug at different pH values.

**Materials and methods**

DTIC was purchased from Sigma Aldrich as crystalline powder. Detergents used in this study was a commercial drug supplied by the food industry. Bi-distilled water was used to prepare the aqueous solutions. The Raman spectra of DTIC and DET were recorded from solutions of 1 M and 0.02 M, respectively. To adjust the pH to the desired values, small amounts of HCl, NaOH or NaF were added.

Hydroxylamine reduced silver colloids was prepared according to the method published by Leopold and Lambl [Lesol]. The SERS spectra at different pH values were recorded by adding 30 ml 10 M of DTIC or Detcine aqueous solution to 500 ml silver colloids. Raman and SERS spectra of the solutions were recorded using a Raman monochromator Raman system using a 514 nm diode pumped solid state (Nd:YAG) laser with a maximum power of 200 mW and a grating with 1800 lines/mm. For the acquisition of the ultra-low frequency Raman spectra we used the near Excitation Tunable (NExT) laser from Renishaw plc.

As starting geometry for energy minimizations, we used the 3-21G (d, p) basis set from Hartree-Fock data reported by Freeman and D. Buchmeiser [Pre79]. The calculations were performed at B3LYP/6-31G(d, p) level of theory, using the Gaussian 99 package [Gaus99]. Solvent effects have been considered by using the Polarizable Continuum Model [Mod02].

**Results and Discussion**

**Dacarbazine’s conformers**

Fig. 1. Calculated conformers (Allley data – dark color) of the DTIC monomers calculated at B3LYP/6-31G(d,p) level of theory, in gas (gray) and water (blue)

Absorption spectrum of Dacarbazine

Fig. 2. Calculated absorption spectra of DBC

**Conclusions**

- Both, in gas-phase and water solution, the m2 tautomer is the most stable.
- Unlike the solid state, the spectroscopic response of DTIC in water solution must be exploited considering the contribution coming from both tautomers, m2cx and m1cx.
- Proper model and solvent effects must be considered for a reliable assignment of UV-Vis spectra
- Raman and SERS spectra of DTIC and DET doublet characteristic for DTIC and DET and the same absorption geometry is concluded.
- Similar species have been detected adsorbed on Ag colloids for DTIC and DET and the same absorption geometry is concluded.
- Detection limit of DTIC, Raman - 10^14 M, SERS - 9.09 10^-7 M
- Characteristic low frequency bands for DTIC 38, 48, 75 and 93 cm^-1

**References**


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