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Accurate location of hydrogen atoms in hydrogen bonds of Tizoxanide from the combination of experimental and theoretical models

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Supporting Information

Computational Details

The conversion of the calculated isotropic chemical shielding (σ_{iso}) into the corresponding chemical shift (δ_{iso}) was performed according to the following equation:

$$\delta_{exp} = \sigma_{ref} - \sigma_{iso} \qquad \text{SE1}$$

The shielding of reference, σ_{ref}, was obtained by applying two different procedures. For the solid-state model a linear regression between δ_{exp} and σ_{iso}, and the independent term is the σ_{ref} was performed. It should be noted that in the case of carbon's resonances the carbons bonded to heavy atoms were not considered in the linear regression. On the other side, for protons and nitrogen, all atoms were taken into account.

In the case of the molecular model, two different procedures were used. In the first one experimental results on TMS were considered as the reference for hydrogen and carbon atoms ($\delta^{TMS}(H) = 30{,}84ppm$ and $\delta^{TMS}(C) = 188{,}1ppm$). For nitrogen atoms, the value of reference was taken from nitromethane ($\delta^{NTM}(N) = -135{,}8ppm$). The second procedure consisted of taking σ_{ref} for all atoms from calculations using the same level of theory as that employed for calculations on the TIZ molecule. From theoretical calculations on TMS and nitromethane, we obtained $\sigma^{TMS}(H) = 35{,}51ppm$, $\sigma^{TMS}(C) = 206{,}16ppm$ and $\sigma^{NTM}(N) = -121{,}46ppm$, at PBE0/cc-pVTZ level of theory.

The experimental/theoretical chemical shifts were calculated from the following expressions:

$$\delta^{TMS}(H,C) = \sigma^{TMS}(H,C) - \sigma_{ref}(H,C) \qquad \text{SE2}$$

$$\delta^{NTM}(N) = \sigma^{NTM}(N) - \sigma_{ref}(N) \qquad \text{SE3}$$

Structural Data

TIZ crystallizes in a triclinic system, with spatial group P (-1) (No.2) with the following network parameters at 173 K: a=5.4110(3) Å, b=7.3315(6) Å, c=13.5293(9) Å, α=97.528(3)°, β=95.390(4)°, γ=97.316(5)°, V=524.41(6)Å^3, Z=2, Dc=1.680g/cm^3, R1=0.0482 and wR2=0.0911 for 2374 reflections[10]. The crystal structure data published in the CCDC (Cambridge Crystallographic Data Center) was used to create the input files for the calculations.

Solid-State NMR spectra

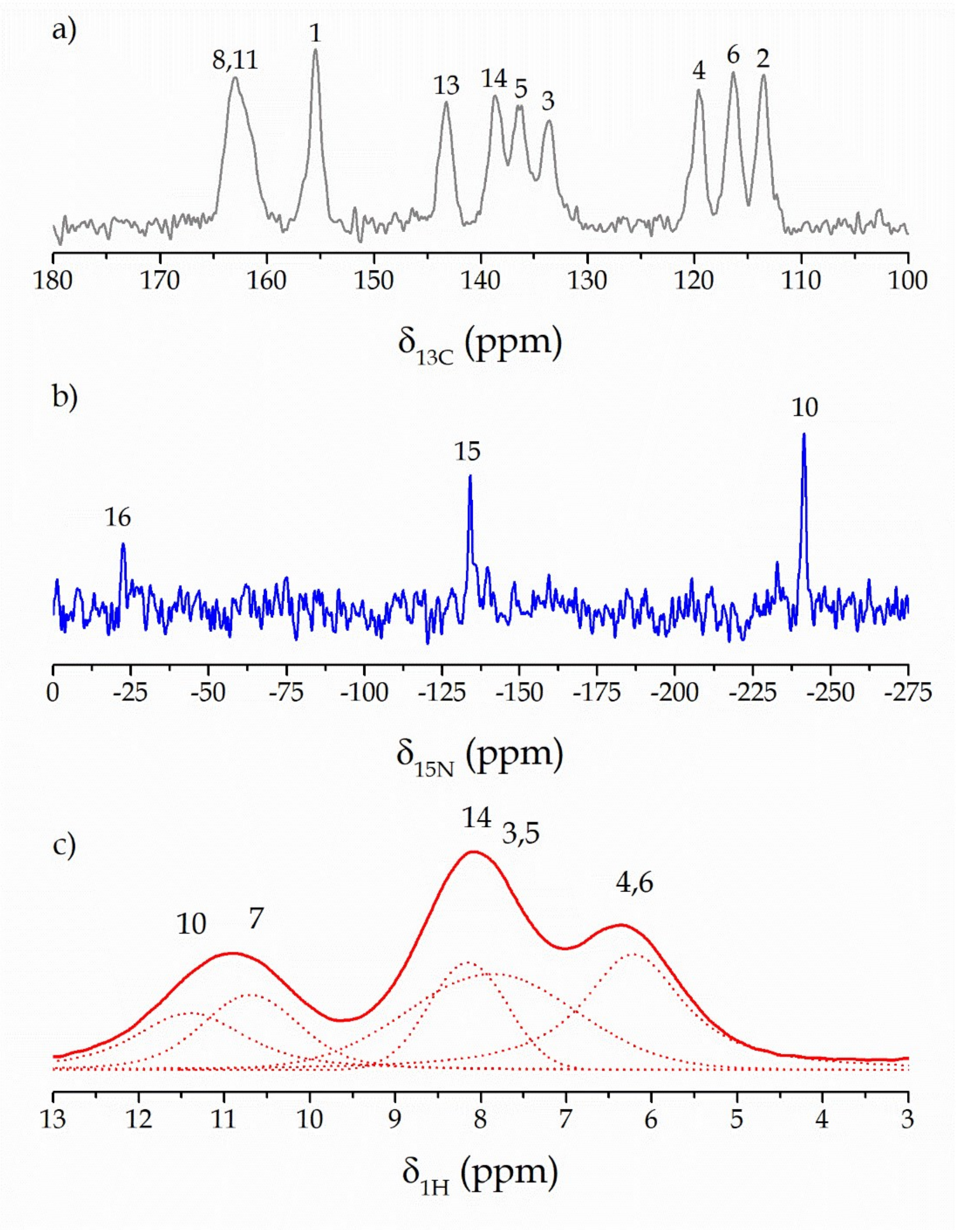

Figure S1: a) ^{13}C ,and b) ^{15}N TIZ CPMAS spectra respectively, and c) ^{1}H MAS TIZ experimental and simulated spectrum.

Table S1: Experimental chemical shifts for ^{13}C, ^{15}N, and ^{1}H

Nucleus	Chemical Shift [ppm]	Nucleus	Chemical Shift [ppm]
C_1	155.50	N_{10}	-241.50
C_2	113.60	N_{15}	-134.10
C_3	133.30	N_{16}	-22.60
C_4	119.60	H_3, H_5	6.30
C_5	136.30	H_4, H_6	7.70
C_6	116.40	H_7	10.60
C_8, C_{11}	163.10	H_{10}	11.40
C_{13}	143.30	H_{14}	8.10
C_{14}	138.60		

Variation of positions of H_{10}

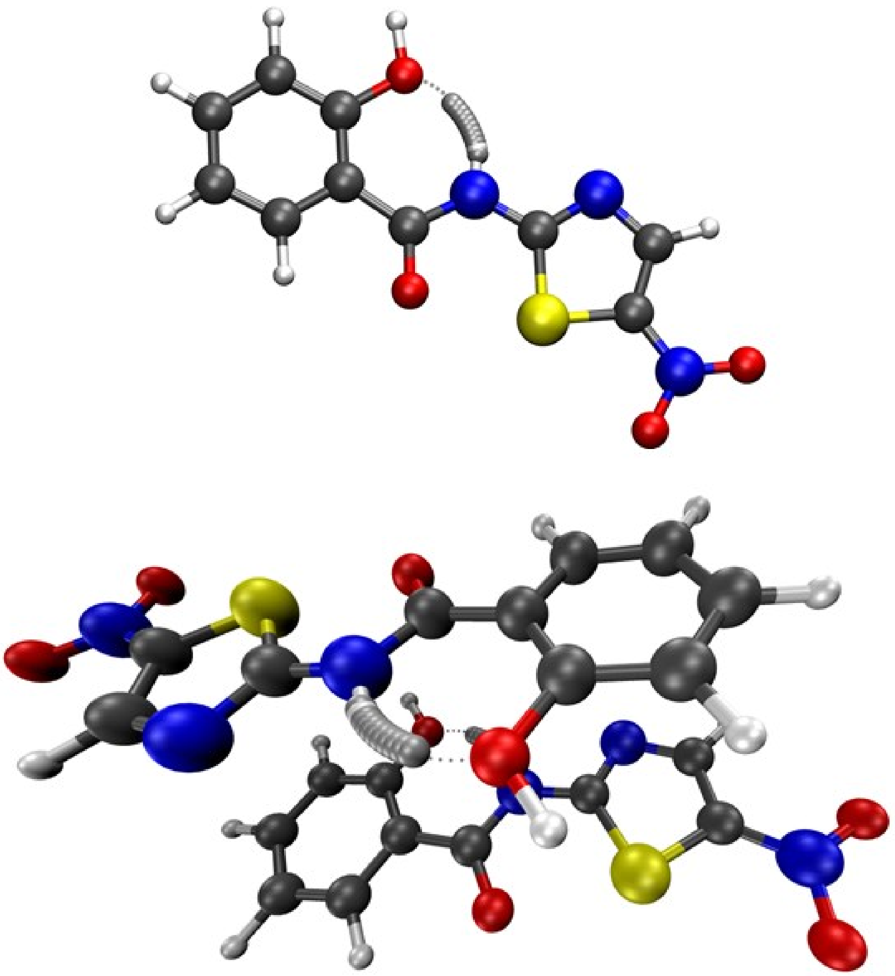

Figure S2: Calculated proton positions in the mean plane of the TIZ molecule.

Electron density difference.

The electron density difference, Δρ, between the TIZ (ρ_{TIZ}) structure and those separated TIZ structure without the hydrogen H_{10} ($\rho_{TIZ\ H}$) and the isolated hydrogen H_{10} (ρ_H), at the optimized position. Thus, is given by:

$$\Delta\rho = \rho_{TIZ} - \rho_{TIZH} - \rho_H \qquad \text{SE4}$$

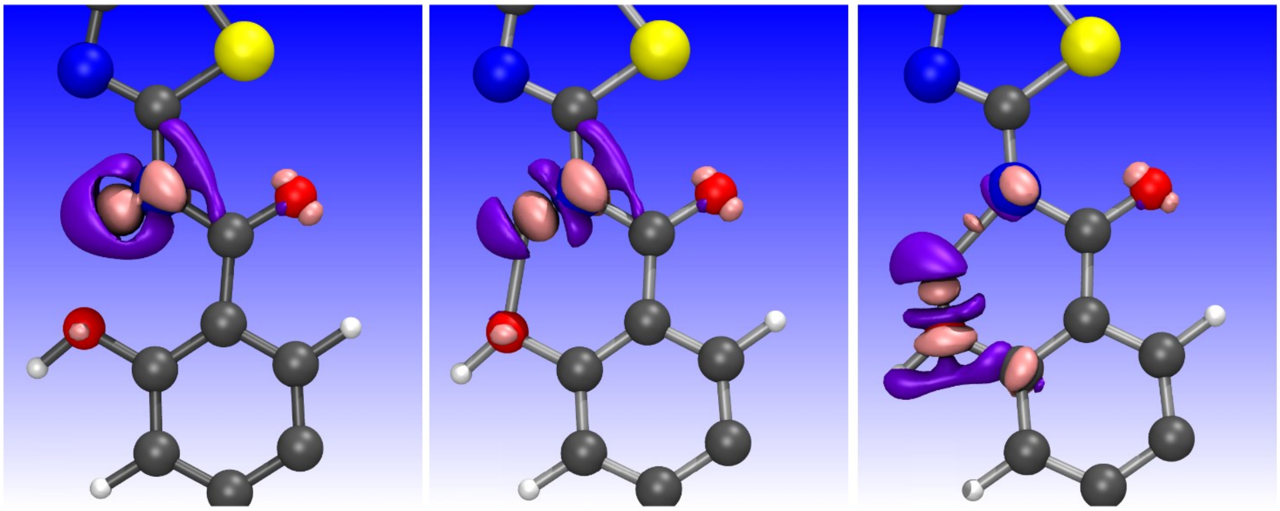

Figure S3: Electron redistribution in TIZ molecule for different N_{10}-H_{10} distance. a) 0.88 Å, b) 1.03 Å and c) 1.78 Å

The total energy of TIZ

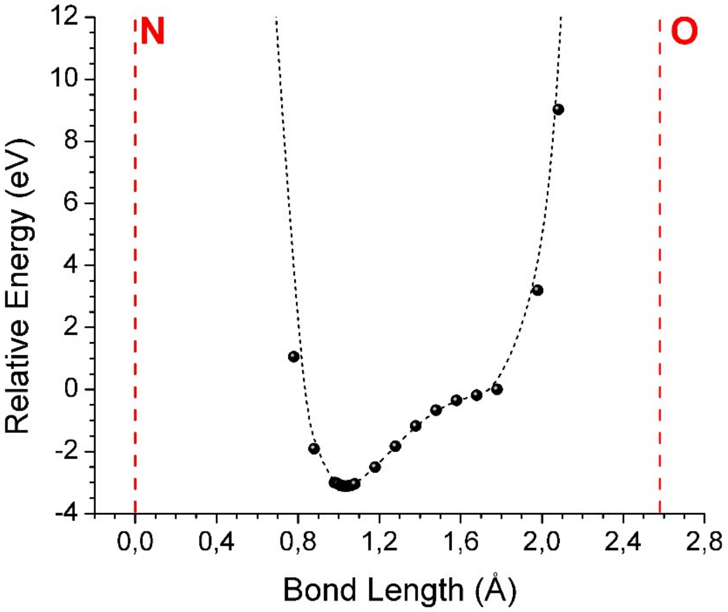

Figure S4: Total energy of the system as a function of the bond distance.