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1,1′,1″-(2,4,6-Trihydroxybenzene-1,3,5-triyl)triethanone tautomerism revisited

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ABSTRACT

It has recently been suggested that 1,1′,1″-(2,4,6-trihydroxybenzene-1,3,5-triyl)triethanone may be tautomeric. Using ^{13}C NMR chemical shifts and deuterium isotope effects on ^{13}C chemical shifts, it is demonstrated that this is not the case. This compound occurs as a strongly hydrogen bonded benzene structure with hydrogen bonds between OH groups and the acetyl groups in both non-polar and hydrogen donating solvents. Quantum-chemical calculations using MP2 and M06-2X methods show substantial preference for the phenol structure in both the gas phase, and in cyclohexane and methanol. In addition, conventional UV–vis spectroscopy data suggest not tautomeric, but aggregation behaviour of the molecule in methanol and acetonitrile.

Prototropic tautomerism is a process of migration of a hydrogen atom within the same organic molecule, leading to changes in its structural skeleton, electronic density distribution and chemical properties. Being a special case of structural isomerism, dynamic as in nature and potentially reversible, tautomerism, especially when it exists as equilibrium, is problematic for both theoretical and experimental studies.[1]

On the one hand, in the general case, the individual tautomers cannot be experimentally isolated, which causes difficulties in the interpretation of their molecular spectra. On the other hand—the correct description of the small relative energies between tautomeric species and the specific solvent stabilization of a particular tautomer is still a difficult challenge for quantum chemical methods.[2] NMR, UV and theoretical calculations can be useful in such studies. In the case of NMR, deuterium isotope effects on chemical shifts are well suited in studies of intramolecularly hydrogen bonded systems, both non-tautomeric and tautomeric.[3–5] In non-tautomeric intramolecularly hydrogen bonded systems, the intrinsic isotope effects depend on differences in zero point energy,[4,5] but do not vary very much with temperature.[6]

Deuteration leads in non-symmetrical tautomeric systems to a change in the chemical equilibrium, and as a consequence to deuterium equilibrium isotope effects on chemical shifts. The equilibrium isotope effects vary with the position of the equilibrium[7] and depend on the chemical shift differences of the pairs of nuclei of the two tautomeric forms. Furthermore, they also vary with temperature.[3] The ^{13}C NMR chemical shifts as well as the OH chemical shifts will likewise vary with temperature.

In a very recent paper Serdiuk et al.[8] suggested that 1,1′,1″-(2,4,6-trihydroxybenzene-1,3,5-triyl)triethanone (also called 1,3,5-triacetyl-2,4,6-trihydroxybenzene, TTT) may exist as a tautomeric equilibrium in methanol as shown in Figure 1 based on MP2/cc-pVDZ calculations in the PCM approximation. This we would like to show is not the case neither in chloroform based on measurements over a wide temperature range and on previous findings[6,9], nor in methanol based on deuterium isotope effects on ^{13}C NMR chemical shifts in methanol.

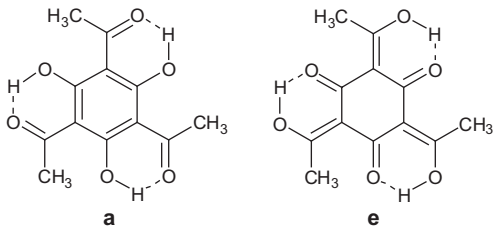

Figure 1. Most stable tautomers of TTT as suggested in Ref. 8.

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These measurements are supported by further theoretical calculations and UV measurements.

In the present Letter we present deuterium isotope effects on the ^{1}H and ^{13}C NMR chemical shifts in $CDCl_3$ (Fig. 2). Isotope effects on ^{13}C NMR chemical shifts are defined as: $^{n}\Delta C(OD) = \delta C(OH) - \delta C(OD)$; where n is the number of bonds between the isotope and the ^{13}C nuclei in question.

The isotope effects are found to be independent of temperature (300–170 K). As the three OH sites may be deuterated very easily and as deuterium exchange is slow in this solvent, isotope effects can be observed due to all three sites of deuteriation. An analysis has been presented earlier.[6,9] The very large isotope effects at C-2 show that the **a**-form is dominant (Fig. 1). The advantage of using deuterium isotope effects on ^{13}C NMR chemical shifts is that they are able to respond to even a very small occurrence of a tautomer.[7] The fact that the isotope effects do not vary with temperature, combined with the invariance of the ^{13}C NMR chemical shifts and OH chemical shifts excludes the possibility of a tautomeric equilibrium. Besides the invariance with temperature, other specific features can be mentioned. The fact that the deuterium isotope effects on the ^{13}C NMR chemical shifts show a progression from 2-hydroxyacetophenone to TTT[9] further indicates that all these isotope effects are intrinsic and not of equilibrium type. The finding that the OH stretching frequency of the **a**-form is predicted as 2434 cm^{-1} compared to the experimental value of 2440 cm^{-1} again supports the **a**-form.[10]

To evaluate the deuterium isotope effects on the ^{13}C NMR chemical shifts in methanol the measurements were performed in a mixture of $CDCl_3$ and methanol or CD_3OD (400 μl $CDCl_3$ and 350 μl methanol/CD_3OD) as TTT is poorly soluble in methanol. The measurements were recorded with the percentage of CD_3OD as 50%. One would expect fast exchange of deuterium. However, the exchange turned out to be slow enough to observe large isotope effects at C-1. The magnitude of the isotope effects was large enough not to be influenced by exchange. This is confirmed as the isotope effects on the methanol carbon of the solvent were observed as being 0.105 ppm. This value compares well with published values for alcohols.[11] The obtained values for TTT are given in Figure 2. In order to obtain smaller isotope effects measurements were recorded with 0% and 97% of CD_3OD as described in reference[12] previously. To obtain the isotope effects extrapolation to 100% D was carried out. The obtained values are given in Figure 3. The observed deuterium isotope effects are sums as all the OH groups are exchanged due to the large excess of methanol/CD_3OD. The sums represent for C-1 $^{3}\Delta$C-1(OD-2) + $^{3}\Delta$C-1(OD-6) + $^{5}\Delta$C-1(OD-4), for C-2 $^{2}\Delta$C-2(OD-2) + $^{4}\Delta$C-2(OD-4) + $^{4}\Delta$C-2(OD-6), for C=O $^{4}\Delta$C=O(OD-2) + $^{4}\Delta$C=O(OD-6) + $^{6}\Delta$C=O(OD-4) and for CH_3 $^{5}\Delta$CH3(OD-2) + $^{5}\Delta$CH3(OD-6) + $^{7}\Delta$CH3(OD-4). It is seen that there is a very good agreement between the sums obtained in a mixture of $CDCl_3$ and methanol or CD_3OD (400 μl $CDCl_3$ and 350 μl methanolOH/methanolOD) and those obtained from $CDCl_3$ (values given in parentheses) in (Fig. 3).

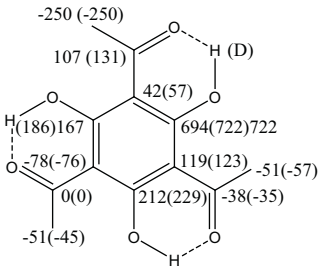

Figure 2. Deuterium isotope effects on ^{13}C NMR chemical shifts measured in $CDCl_3$ at 213 K in ppb. Values in parentheses at ambient temperature taken from Ref. 9. The value in square brackets is that obtained from a mixture of $CDCl_3$ and CH_3OH/D.

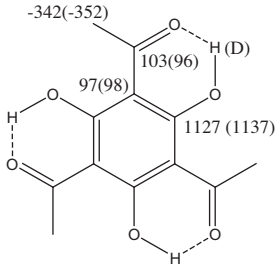

Figure 3. Deuterium isotope effects on ^{13}C NMR chemical shifts in ppb obtained in a mixture of $CDCl_3$ and methanol/CD_3OD (see text). The sums (in parentheses) are taken from $CDCl_3$.

It can be seen from a comparison of the values in Figure 2 that the isotope effects for C-1 are very similar. However, can one be sure that the small differences are not due to a tautomeric equilibrium? The difference between that seen in $CDCl_3$ and in methanol is very small indeed. If a tautomeric equilibrium is taking place in methanol this would influence the isotope effect of C-1 rather much, as the difference in chemical shifts of a C=O and a COH carbon is around 20 ppm[7] and the changes in the chemical equilibrium upon deuteration for β-diketones are usually rather large.[7] Assuming a mole fraction of 0.96, an equilibrium contribution of 0.25 ppm can roughly be estimated from Figure 5 of Ref. 7. As no such change is seen between $CDCl_3$ and CD_3OD, no tautomeric equilibrium takes place in methanol and as a consequence not in ethanol. Furthermore, this conclusion is supported by the comparison made in Figure 3 in which the values of $CDCl_3$/methanol/CD_3OD are shown to be very similar. The ^{1}H and ^{13}C NMR chemical shifts clearly point to a symmetrical structure.[6,9] The lack of a temperature effect both on the deuterium isotope effects on the chemical shifts (see discussion earlier) and also on the chemical shifts excludes a tautomeric equilibrium in non-polar solvent. The measurement of deuterium isotope effects in a mixture of chloroform and methanol excludes also a tautomeric equilibrium in more polar and proton-donating solvents showing that the **a**-form (Fig. 1) is the only actual structure of TTT.

These results are strongly supported by quantum-chemical calculations.[13] These were performed by using MP2 (to be comparable with Ref. 8) and M06-2X methods.[14] The latter is a fitted hybrid meta-GGA functional with 54% HF exchange specially developed to describe main-group thermochemistry and the non-covalent interactions, showing very good results in predicting the position of tautomeric equilibria in azo-naphthols possessing intramolecular hydrogen bonding.[15] In addition, we found two asymmetric structures (**e′** and **e″**, Fig. 4) that are energetically comparable to the symmetric **a** and **e** forms, but that are not discussed in Ref. 8. These four structures are the most stable and their relative stabilities are summarized in Table 1.

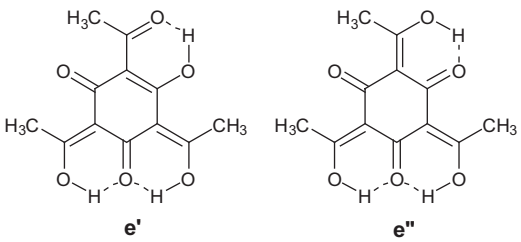

Figure 4. Asymmetric tautomers of TTT.