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| Item Type | Article |
| Authors | Abraham, R.J.;Cooper, M.A.;Aghamohammadi, Amin;Afarinkia, Kamyar;Liu, Xiangli |
| Citation | Abraham RJ, Cooper MA, Aghamohammadi A et al (2022) The use of MM/QM calculations of ¹³ C chemical shifts in the analysis of Edaravone tautomers. Journal of Solution Chemistry. 51: 1162-1167. |
| DOI | https://doi.org/10.1007/s10953-022-01186-8 |
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| Download date | 2026-03-05 23:06:27 |
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The Use of MM/QM Calculations of ^{13}C Chemical Shifts in the Analysis of Edaravone Tautomers

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Received: 6 July 2021 / Accepted: 24 June 2022 / Published online: 9 August 2022
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Abstract

The ^{13}C NMR chemical shifts of the three Edaravone tautomers (keto, enol, and amine) were calculated using a combined molecular mechanics (Pcmod 9.1/MMFF94) and ab initio (GIAO (B3LYP/DFT, 6–31 + G(d)) model. This method gave such good agreement with experiment that the assignment of the complex spectrum of Edaravone in solution, which is a mixture of the three tautomers could be made. This has been attempted previously by various methods with diverse results. In CDCl_3 solution, the observed spectra show only one form, the keto tautomer, and this is also the case with acetonitrile solvent. Acetone solvent reacts with Edaravone in the NMR tube. In the other solvents studied, methanol, pyridine, DMSO, trifluoroethanol (TFE), there is a mixture of the tautomers with populations which vary with the solvent. The application of the shift predictions allows the assignment of the ^{13}C spectra to the three tautomers and from this the proportions of the tautomers in the solution. The results at times differ significantly from previous studies, and this is discussed.

Keywords ^1H · ^{13}C · ^{13}C Chemical shifts · Edaravone tautomers · Conformations

1 Introduction

We are pleased to accept the invitation of professor Earle Waghorne to contribute to this special issue of the Journal of Solution Chemistry in honor of Michael Abraham. It is particularly relevant as the work described here is a direct consequence of our recent collaboration with Michael on descriptors for Edaravone [1].

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In recent years, we have developed a simple method of calculating ^{13}C chemical shifts by a combined molecular mechanics (Pcmodel 9.1/MMFF94) [2] and ab initio (GIAO (B3LYP/DFT, 6–31+G(d))) procedure [3, 4]. The molecular geometries are obtained from Pcmodel and the ^{13}C shifts from the GIAO magnetic isotropic shielding (C_{iso}) with separate references for sp^3 and sp^2 carbons ($\delta_{\text{c}} = \delta_{\text{ref}} - C_{\text{iso}}$) [5]. From these shieldings, the ^{13}C chemical shifts of a wide range of organic molecules in organic solvents such as CDCl_3 were compared with the observed shifts, which give excellent results (typical Mean Average Errors (MAE) 1–1.5 ppm) both in rigid molecules and cases where insight was provided on rotational isomers [5–7]. Most recently the method has been extended to various sugars in aqueous solution including sucrose, providing useful information on their conformations [8]. As previously, the present calculations do not include the solvent but the reference is TMS in solution. This implicitly assumes that the solvation effect on the ^{13}C chemical shifts is the same for TMS and the solutes. We have extended our method to study the solvent dependence of Edaravone and its tautomers (Fig. 1).

Edaravone is a free radical scavenger and antioxidant, used medicinally to help recovery after a stroke and to slow the progress amyotrophic lateral sclerosis. From a physico-chemical aspect, a number of studies have been made of Edaravone's tautomers and how their relative proportions vary according to the solvent, using energy calculations and NMR spectroscopy [9, 10]. Additionally, we have recently [1] used "Abraham descriptors" to study the proportions of tautomers in various solvents, including biological environments.

There is some controversy about the relative proportions of the Edaravone tautomers in various solvents. For example, in DMSO, Ref. [10] gives the proportions of keto:enol:amine as 22:50:28, but Ref. [11] gives them as 13:81:6. Also in DMSO, [12] finds only two tautomers assigned as keto and amine. In our ^{13}C spectrum, we also see only two tautomers, but we assign these as keto and enol. Another example is that Ref. [10] finds the tautomer proportions in trifluoroethanol (TFE) solution to be 17:0:83 whereas the result using descriptors (Ref. [1]) was 45% keto.

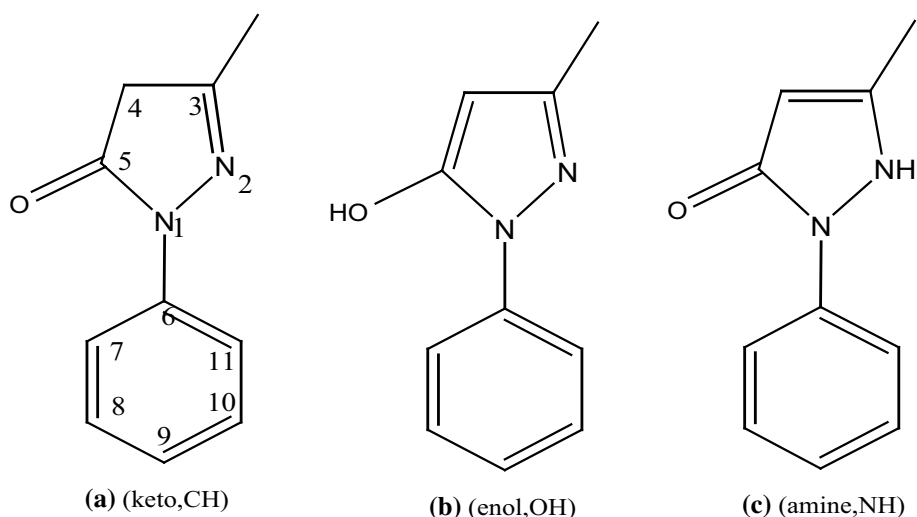


Fig. 1 a (keto,CH), b (enol,OH), c (amine,NH)

2 Experimental

The NMR spectra were recorded on a Bruker Avance 400 spectrometer at 298 K. with TMS reference.

3 Computational

We use, as previously [5–7] a combined MM (Pcmod 9.1/MMFF94) to provide geometries and ab initio (GIAO (B3LYP/DFT, 6–31 + G(d)) to calculate the isotropic magnetic shielding tensor C_{iso} . The chemical shifts relative to TMS were then calculated from the tensor using Eq. 1 for sp^3 carbons and Eq. 2 for sp^2 carbons as in our previous work [5–7].

$$C_{\text{shift}} = 189.2 - C_{\text{iso}}, \quad (1)$$

$$C_{\text{shift}} = 195.4 - C_{\text{iso}}. \quad (2)$$

This method gave poor agreement with observed values. We suspect that this is because Pcmodel may not be well parametrized for species like the isomers of the pyrazole ring such as we are dealing with here. We, therefore, took the PCM geometries and further optimized them using B3LYP/6–31 + G(d), before obtaining the isotropic shielding tensors at the same level of GIAO and calculating chemical shifts using Eqs. 1 and 2 as before. It was also observed that for the pyridines, the simple 6-31G(d) gave better results than the 6–31 + G(d), and this was used for these molecules. Geometry minimizations of Edaravone with Pcmodel were instantaneous but with B3LYP/6–31 + could take hours. The shielding calculations took several minutes.

4 Results and Discussion

Table 1 shows the calculated shifts for the three tautomers as well as the observed shifts in solvents $CDCl_3$, MeCN, MeOD, pyridine, DMSO, and TFE. The largest differences in the calculated ^{13}C chemical shifts occur at C4 (range 70 ppm) which are due to the change from a saturated CH_2 carbon to an unsaturated $=CH.OH$ carbon, while the ranges at C3 and C5 are smaller at approx. 10–15 ppm. In all other cases, the ranges are less than 5 ppm. We note also that the calculated shifts for the C3 Me are clearly distinct for the three tautomers with calculated values of 17.4, 14.8, and 13.2 ppm for the keto, enol, and amine res. This is supported by the observed values of 17.0 (± 0.2), 14.6 (± 0.4), and 11.5 (± 1.0), respectively. (Table 1). The agreement is good enough to provide an assignment in those cases where only these tautomers are present. For example, for acetone solvent, the value is 19.0 ppm which supports other data suggesting that the acetone solvent is reacting with Edaravone. When the assignment of the C3 methyl is clear, the intensities of the methyl peaks give immediately the ratio of the tautomers. In our experiments, the intensities are accurate to $\pm 5\%$.

Further examination of the spectra shows that in $CDCl_3$ and MeCN, only eight peaks are seen in the ^{13}C spectra consistent with a single tautomer. In pyridine and DMSO, further peaks are present at very similar positions to those seen in $CDCl_3$ and MeCN. If we consider the calculated results for keto, a striking feature is the excellent agreement

Table 1 Observed vs Calculated ^{13}C NMR Chemical Shifts (δ ppm) of Edaravone tautomers

| Tautomer | calc/obs Solvent ^a | C3 | C4 | C5 | C6 | C7,11 | C9 | C8,10 | Me |
|----------|-------------------------------|--------|--------|--------|--------|--------|--------|--------|-------|
| Keto | Calc | 155.77 | 41.65 | 168.92 | 140.20 | 117.22 | 122.96 | 128.51 | 17.43 |
| | Obs | | | | | | | | |
| | CDCl_3^c | 156.28 | 43.11 | 170.57 | 138.05 | 118.88 | 125.04 | 128.83 | 17.03 |
| | CH_3CN | 158.76 | 43.82 | 172.29 | 139.69 | 119.35 | 125.33 | 129.82 | 17.11 |
| | MeOD | 159.76 | b | 173.40 | 139.5 | 120.16 | 126..1 | 129.7 | 16.70 |
| | Pyridine | 158.33 | 43.62 | 171.81 | 140* | 119.20 | 125* | 129.64 | 17.14 |
| Enol | DMSO ^c | 158.37 | 42.91 | 171.14 | 138.08 | 117.87 | 124.30 | 128.60 | 17.11 |
| | Calc | 148.88 | 88.02 | 151.09 | 140.13 | 120.97 | 124.30 | 128.14 | 14.83 |
| | Obs | | | | | | | | |
| | Pyridine | 149.45 | 88.93 | 155.82 | 141.14 | 121.77 | 125.64 | 129.63 | 15.22 |
| | DMSO ^d | 147.96 | 88.06 | 153.85 | 138.70 | 120.17 | 124.77 | 128.60 | 13.93 |
| | TFE | 160.75 | 93.41 | 164.18 | 136.17 | 123.19 | 127.27 | 128.88 | 14.54 |
| Amine | Calc | 146.58 | 119.82 | 164.50 | 135.48 | 120.58 | 124.65 | 128.85 | 13.21 |
| | Obs | | | | | | | | |
| | MeOD | 150.8 | b | 173.4 | 138.3 | 122.8 | 127.4 | 130.0 | 12.85 |
| | TFE ^d | 149.57 | 121.91 | 172.93 | 134.51 | 123.19 | 127.98 | 129.15 | 10.04 |

*Broad peak

^aThe calculated shifts are independent of solvent

^bC4H exchanges with the OD in solvent

^cMAE (keto) 1.28 ppm (CDCl_3), 1.33 ppm (DMSO),

^dMAE(enol) 1.0 ppm (DMSO), MAE (amine) 3.0 ppm (TFE)

between the observed peaks at approx. 43 ppm in all four solvents due to the CH_2 group and the calculated C4 peak at 41.7 ppm. It is not difficult to assign the other signals from the keto tautomer, the mean average error (MAE) is in the range 1.3 ppm to 1.9 ppm across the solvents. The result for CDCl_3 confirms previous work [10] that the keto tautomer is dominant here. We also see only keto in MeCN whereas Ref. [9] records a few % each of enol and amine. We do, however, see extra signals apart from keto in pyridine and DMSO solvent, as follows.

The calculated shifts for the enol agree closely (MAE 1–1.4 ppm) with the observed values of peaks not already assigned to keto in the cases of pyridine and DMSO solution. The latter result strongly confirms the presence of enol and not amine as the second component, in contrast to Ref. [12].

The agreement for TFE solution is much poorer (MAE 5 ppm). This may be due to the intensely polar as well as H-bonding TFE forming a complex with the Edaravone which our methodology does not address. The proportions of the tautomers are for pyridine: the ratio of enol:keto is ca. 10:1, in DMSO ca. 3:1, and in TFE, the ratio of amine:enol is 1.7:1.

In TFE, the agreement of observed vs calculated values for the amine is poor (MAE 3 ppm) and as discussed for the enol, this may be due to complexation with the solvent. The evidence to support the identification of keto and enol in other solvents is good but the evidence for amine is weak. In the spectrum of Ref. [10], all three tautomers are recorded in DMSO solution in contrast to Ref. [12] and our work which only see two. We have, therefore, looked closely at the spectrum of Ref. [11]. It is our view that a

Table 2 Reassignment of the spectrum of Edaravone in DMSO [10] showing all three tautomers

| Tautomer | Obs | C3 | C4 | C5 | C6 | C7,11 | C9 | C8,10 | Me | MAE |
|----------|------------------------|-------|-------|-------|-------|-------|-------|-------|------|------|
| Keto | Obs/obs-calc (abs) | 159.0 | 43.4 | 171.6 | 138.7 | 118.4 | 124.8 | 129.3 | 17.1 | |
| | | 3.23 | 1.75 | 2.68 | 1.5 | 1.18 | 1.84 | 0.79 | 0.33 | 1.66 |
| Enol | Obs/obs-calc (abs) | 148.8 | 89.0 | 155.0 | 139.2 | 120.7 | 125.3 | 129.2 | 14.4 | |
| | | 0.08 | 0.98 | 3.91 | 0.93 | 0.27 | 1.00 | 1.06 | 0.43 | 1.08 |
| Amine | Calc/obs-calc (abs) | 146.0 | 120.0 | 168.9 | 138.0 | 120.0 | 124.0 | 129.0 | 15.0 | |
| | | 0.58 | 0.18 | 4.40 | 2.52 | 0.58 | 0.65 | 0.15 | 1.79 | 1.36 |

When the shift is an integer, no frequency is given in Ref. [11] and this has been interpolated by the current authors

number of the signals are misassigned, but with the guidance of the calculated values, a reassignment is possible (see Table 2) giving MAE values of 1.7 ppm, 1.1 ppm, and 1.4 ppm for keto, enol, and amine, respectively. The amine is observed in this spectrum and also in that of Ref. [9] (not shown in that paper and no table of shifts given) but not in the case of Ref. [12] and the current work. This may be due to traces of impurity in the TFE solvent or possibly reaction of Edaravone with the TFE. The reaction of Edaravone with water solvent has been investigated by Tanaka et al. [13]. When an aqueous solution was kept at 60 °C for 4 weeks, edavarone trimer and hydrogen peroxide were formed. This supports the suggestion that any water impurity in the DMSO or TFE solvent may react with the edavarone in solution.

5 Conclusion and Summary

The method of calculating ^{13}C chemical shifts given here which has been previously applied to a range of organic molecules in both organic solvents and water has proved to be capable of predicting the shifts in the Edaravone tautomers. In this case, geometries from Pmodel gave poor results while those from G03 at the B3LYP/6–31 + G(d) level were much better. The results enable the identification of the individual tautomers with less ambiguity than previously. There remains some controversy, for example, the case of DMSO solvent where Ref. [12] and this investigation see only the keto and enol tautomers in the spectra, but Ref. [11] observes the amine tautomer as well. The reason for this may be impurities in the solvent, in particular, water may be present. It may also be that the tautomer proportions are very sensitive to minor levels of contaminants but we have not seen any detailed work in this area.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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