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Descriptors for Edaravone; Studies on its Structure, and Prediction of Properties.

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ABSTRACT

Literature solubilities and NMR and IR studies have been used to obtain properties or descriptors of edaravone. These show that edaravone has a significant hydrogen bond acidity so that it must exist in solution partly as the OH and NH forms, as found by Freyer et al. Descriptors have been assigned to the keto form which has a low hydrogen bond acidity, and which is the dominant form in nonpolar solvents. Physicochemical properties of the keto form can be calculated such as solubilities in nonpolar solvents, partition coefficients from water to nonpolar solvents, and partition coefficients from air to biological phases.

Keywords: Edaravone, Solubility, Keto-enol, Abraham descriptors, Hydrogen bond acidity, NMR, IR

1. Introduction

Edaravone is a free-radical scavenger and anti-oxidant, used to help recovery after a stroke and to slow the progress of amyotrophic lateral sclerosis (ALS). It has been used in Japan since 2001 to aid recovery after a stroke and was approved by the Food and Drug Administration (FDA) in 2017 to treat ALS. Although now widely used, there have only been

a few studies on the physicochemical properties of Edaravone. Solubilities have been recorded using mono solvents [1] and a number of aqueous-organic mixtures [2,3], and we can use these to obtain properties, or descriptors for Edaravone.

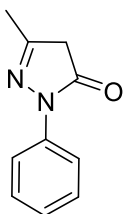


Figure 1a (keto, CH)

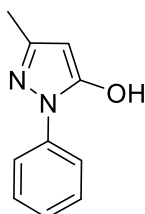


Figure 1b (enol, OH)

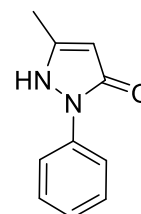


Figure 1c (amine, NH)

The structure of edaravone is normally given as shown in Figure 1a, but edaravone can also exist as the enol form, Figure 1b, or as the amine (NH) form, Figure 1c. Dardonville et al [4] have calculated that in the gas phase the order of stability of the three structures is CH > OH ~ NH. In trichloromethane solution they find that only the keto (CH) form exists but in DMSO the keto (CH) form is only a minor constituent. Freyer et al [5] have shown that the proportions of the three isomers is very solvent dependent and have listed a number of solvents for which they have determined the proportions of these isomers.

We have previously used data on water-solvent partition coefficients and solubilities of compounds in water and organic solvents to calculate properties or descriptors of compounds [6-9], and our methods have been reviewed several times [10-12]. The descriptors include the compound hydrogen bond acidity, **A**, and the compound hydrogen bond basicity, **B**. The keto form of edaravone is not expected to have any hydrogen bond acidity, but the -OH group in the enol form or the -NH group in the NH form would lead to substantial hydrogen bond acidity. Thus a calculation of descriptors for edaravone could lead to additional information about the edaravone equilibria.

2. Experimental work

Materials

The deuterated trichloromethane (CDCl_3) and propanone- d_6 used as the NMR solvents were purchased from Sigma Aldrich (UK), dimethyl sulfoxide (DMSO- d_6) from Cambridge Isotope Laboratories Inc, and 2,2,2-trifluoroethanol- d_3 from Alfa Aesar (UK).

Edaravone was purchased from Scientific Laboratory Supplies (UK).

NMR Studies

Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at 298K using Bruker Avance 400 spectrometer (BRUKER) operating at 400 MHz. Chemical shifts are reported in parts per million (δ , ppm). ^1H NMR chemical shifts are reported relative to an internal reference tetramethylsilane (TMS).

i.r. Studies

The Infrared spectra (IR) were obtained on Perkin Elmer Spectrum 100 FT-IR Spectrometer. The relative intensity of the signal is depicted by (s, m, and w for strong, medium, and weak). Broad peaks are labelled as br. Prior to sample runs the machine is calibrated to background transmittance.

3. Methods

Two general linear free energy relationships, Eq. (1) and Eq. (2), can be used for the transfer of neutral solutes from water to organic solvents and from the gas phase to organic solvents. The dependent variable in Eq. (1) is $\log P$, where P is the molar water to solvent partition coefficient for a series of solutes, and in Eq. (2) it is $\log K$ where K is the dimensionless gas phase to solvent partition coefficient for a series of solutes.

$$\text{Log } P = c + e \mathbf{E} + s \mathbf{S} + a \mathbf{A} + b \mathbf{B} + v \mathbf{V} \quad (1)$$

$$\text{Log } K = c + e \mathbf{E} + s \mathbf{S} + a \mathbf{A} + b \mathbf{B} + l \mathbf{L} \quad (2)$$

In Eq. (1) and Eq. (2) the independent variables, or descriptors, are properties of the neutral solutes as follows [6-12]. \mathbf{E} is the solute excess molar refraction in $\text{cm}^3 \text{mol}^{-1}/10$, \mathbf{S} is the solute dipolarity/polarizability, \mathbf{A} is the overall solute hydrogen bond acidity, \mathbf{B} is the overall solute hydrogen bond basicity, \mathbf{V} is McGowan's characteristic molecular volume in $\text{cm}^3 \text{mol}^{-1}/100$ and \mathbf{L} is the logarithm of the gas to hexadecane partition coefficient at 298 K. Coefficients in Eq (1) and Eq. (2) are shown in Table 1 for systems that we consider here.

For pure liquid compounds, E is obtained from the refractive index of the compound at 293 K [6] and for gases and solids the refractive index can be estimated or \mathbf{E} itself can be calculated quite easily [13,14]. For neutral molecules, the descriptors \mathbf{S} , \mathbf{A} and \mathbf{B} can be obtained from water to solvent partition measurements, and from solubilities in nonaqueous solvents, C_S [6-12]. The latter are transformed into water-solvent partition coefficients through Eq. (3), where C_W is the corresponding solubility in water [8-12].

$$P = C_S / C_W \quad \log P = \log C_S - \log C_W \quad (3)$$

Finally, P can be converted into the air-solvent partition coefficient K through Eq. (4)

$$\log K - \log K_W = \log P \quad (4)$$

where K_W is the dimensionless air to water partition coefficient defined through Eq. (5), where C_W and the corresponding gaseous concentration, C_G , are in units of mol dm⁻³. K_W is the reciprocal of the Henry's law constant in water, with due regard to units.

$$K_W = C_W / C_G \quad (5)$$

Table 1. Coefficients in Eq. (1) and in Eq. (2); calculated and observed values of $\log P$ and $\log K$ for transfer of edaravone from water and from the gas phase to solvents at 298 K, using the 'global' descriptors in Table 2.

Solvent	<i>c</i>	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>l</i>	<i>v</i>		Calc	Obs
Dichloromethane	0.319	0.102	-0.187	-3.058	-4.090	0.000	4.324	log P	2.072	2.114
Toluene	0.125	0.431	-0.644	-3.002	-4.748	0.000	4.524	log P	1.460	1.388
Acetonitrile	0.413	0.077	0.326	1.536	-4.391	0.000	3.364	log P	1.633	1.567
Methanol	0.276	0.334	-0.714	0.243	-3.320	0.000	3.549	log P	1.936	1.975
Ethanol	0.222	0.471	-1.035	0.326	-3.596	0.000	3.857	log P	1.844	1.825
Propan-1-ol	0.139	0.405	-1.029	0.247	-3.767	0.000	3.986	log P	1.699	1.768
Butan-1-ol	0.165	0.401	-1.011	0.056	-3.958	0.000	4.044	log P	1.627	1.643
Pentan-1-ol	0.150	0.536	-1.229	0.141	-3.864	0.000	4.077	log P	1.637	1.591
Propan-2-ol	0.099	0.344	-1.049	0.406	-3.827	0.000	4.033	log P	1.599	1.565
Isobutanol	0.188	0.354	-1.127	0.016	-3.568	0.000	3.986	log P	1.652	1.536
Butan-2-ol	0.127	0.253	-0.976	0.158	-3.882	0.000	4.114	log P	1.613	1.545
Gas-water	-0.994	0.577	2.549	3.813	4.841	0.000	-0.869	logK _w	6.802	6.694
100% Ethanol	0.222	0.471	-1.035	0.326	-3.596	0.000	3.857	log P	1.844	1.729
96% Ethanol	0.238	0.353	-0.833	0.297	-3.533	0.000	3.724	log P	1.741	1.724
95% Ethanol	0.239	0.328	-0.795	0.294	-3.514	0.000	3.697	log P	1.789	1.727
90% Ethanol	0.243	0.213	-0.575	0.262	-3.450	0.000	3.545	log P	1.823	1.744
80% Ethanol	0.172	0.175	-0.465	0.260	-3.212	0.000	3.323	log P	1.741	1.720
70% Ethanol	0.063	0.085	-0.368	0.311	-2.936	0.000	3.102	log P	1.576	1.594
60% Ethanol	-0.040	0.138	-0.335	0.293	-2.675	0.000	2.812	log P	1.404	1.409
50% Ethanol	-0.142	0.124	-0.252	0.251	-2.275	0.000	2.415	log P	1.172	1.180
40% Ethanol	-0.221	0.131	-0.159	0.171	-1.809	0.000	1.918	log P	0.915	0.936
30% Ethanol	-0.269	0.107	-0.098	0.133	-1.316	0.000	1.414	log P	0.624	0.688
20% Ethanol	-0.252	0.042	-0.040	0.096	-0.823	0.000	0.916	log P	0.347	0.450
10% Ethanol	-0.173	-0.023	-0.001	0.065	-0.372	0.000	0.454	log P	0.122	0.219
0% Ethanol	0.000	0.000	0.000	0.000	0.000	0.000	0.000	log P	0.000	0.000
100% Methanol	0.276	0.334	-0.714	0.243	-3.320	0.000	3.549	log P	1.936	1.757
95% Methanol	0.270	0.278	-0.520	0.230	-3.368	0.000	3.365	log P	1.829	1.822
90% Methanol	0.258	0.250	-0.452	0.229	-3.206	0.000	3.175	log P	1.745	1.821

80% Methanol	0.172	0.197	-0.319	0.241	-2.912	0.000	2.842 log P	1.558	1.700
70% Methanol	0.098	0.192	-0.260	0.266	-2.558	0.000	2.474 log P	1.351	1.534
60% Methanol	0.053	0.207	-0.238	0.272	-2.157	0.000	2.073 log P	1.138	1.314
50% Methanol	0.023	0.223	-0.222	0.264	-1.747	0.000	1.662 log P	0.924	1.082
40% Methanol	0.020	0.222	-0.205	0.218	-1.329	0.000	1.259 log P	0.724	0.849
30% Methanol	0.016	0.187	-0.172	0.165	-0.953	0.000	0.898 log P	0.520	0.622
20% Methanol	0.022	0.142	-0.138	0.088	-0.574	0.000	0.559 log P	0.341	0.408
10% Methanol	0.012	0.072	-0.081	0.026	-0.249	0.000	0.266 log P	0.164	0.206
Dichloromethane	0.192	-0.572	1.492	0.460	0.847	0.965	0.000 log K	8.800	8.808
Toluene	0.085	-0.400	1.063	0.501	0.154	1.011	0.000 log K	8.114	8.082
Acetonitrile	-0.007	-0.595	2.461	2.085	0.418	0.738	0.000 log K	8.363	8.261
Methanol	-0.039	-0.338	1.317	3.826	1.396	0.773	0.000 log K	8.530	8.669
Ethanol	0.017	-0.232	0.867	3.894	1.192	0.846	0.000 log K	8.467	8.519
Propan-1-ol	-0.042	-0.246	0.749	3.888	1.076	0.874	0.000 log K	8.326	8.462
Butan-1-ol	-0.004	-0.285	0.768	3.705	0.879	0.892	0.000 log K	8.248	8.337
Pentan-1-ol	-0.002	-0.161	0.535	3.778	0.960	0.900	0.000 log K	8.250	8.311
Propan-2-ol	-0.048	-0.324	0.713	4.036	1.055	0.884	0.000 log K	8.249	8.259
Isobutanol	-0.003	-0.357	0.699	3.595	1.277	0.881	0.000 log K	8.264	8.239
Butan-2-ol	-0.034	-0.387	0.719	3.736	1.082	0.905	0.000 log K	8.288	8.239
Gas-water	-1.271	0.822	2.743	3.904	4.814	-0.213	0.000 log K	6.836	6.694
100% Ethanol	0.017	-0.232	0.867	3.894	1.192	0.846	0.000 log K	8.467	8.392
96% Ethanol	-0.032	-0.181	0.980	3.920	1.379	0.802	0.000 log K	8.501	8.387
95% Ethanol	-0.040	-0.200	1.024	3.950	1.400	0.795	0.000 log K	8.498	8.390
90% Ethanol	-0.084	-0.280	1.180	3.959	1.474	0.757	0.000 log K	8.360	8.407
80% Ethanol	-0.253	-0.278	1.400	4.000	1.775	0.715	0.000 log K	8.456	8.383
70% Ethanol	-0.438	-0.255	1.558	4.040	2.074	0.659	0.000 log K	8.369	8.257
60% Ethanol	-0.631	-0.186	1.646	4.054	2.355	0.584	0.000 log K	8.119	8.072
50% Ethanol	-0.851	-0.063	1.806	4.050	2.745	0.479	0.000 log K	7.878	7.843
40% Ethanol	-1.074	0.075	2.076	4.020	3.196	0.347	0.000 log K	7.663	7.599
30% Ethanol	-1.258	0.194	2.300	4.000	3.713	0.206	0.000 log K	7.392	7.351
20% Ethanol	-1.364	0.323	2.385	3.950	4.280	0.065	0.000 log K	7.139	7.113
10% Ethanol	-1.447	0.446	2.536	3.905	4.750	-0.052	0.000 log K	6.914	6.882
0% Ethanol	-1.271	0.822	2.743	3.904	4.814	-0.213	0.000 log K	6.836	6.663
100% Methanol	-0.039	-0.338	1.317	3.826	1.396	0.773	0.000 log K	8.530	8.420
95% Methanol	0.013	-0.300	1.517	3.811	1.463	0.706	0.000 log K	8.499	8.485
90% Methanol	-0.050	-0.200	1.615	3.827	1.637	0.647	0.000 log K	8.445	8.484
80% Methanol	-0.238	-0.086	1.790	3.895	1.931	0.554	0.000 log K	8.266	8.363
70% Methanol	-0.378	0.040	1.941	3.943	2.365	0.440	0.000 log K	8.082	8.197
60% Methanol	-0.530	0.149	2.081	3.995	2.778	0.330	0.000 log K	7.860	7.977
50% Methanol	-0.694	0.236	2.228	4.051	3.157	0.224	0.000 log K	7.607	7.745
40% Methanol	-0.811	0.311	2.370	4.053	3.575	0.117	0.000 log K	7.389	7.512
30% Methanol	-0.927	0.338	2.431	4.047	3.869	0.053	0.000 log K	7.190	7.285
20% Methanol	-1.035	0.389	2.655	4.004	4.291	-0.064	0.000 log K	6.985	7.071
10% Methanol	-1.107	0.500	2.722	3.974	4.658	-0.151	0.000 log K	6.848	6.869
GLC-NIST	0.070	0.012	0.076	0.000	0.000	0.200	0.000 I/1000	1.553	1.603

4. Results and Discussion

Solubilities of edaravone have been determined using a number of solvents [15] and water-solvent mixtures [16], and we can convert these into values of $\log P$ using the observed water solubility [15] of $\log C_w = -2.033$, through Eq. (3), or we can allow the value of $\log C_w$ to float. Finally, all the $\log P$ values yield air-solvent partition coefficients through Eq. (4). In the present case, the required values of $\log K_w$ are not available, but we can take $\log K_w$ as another unknown descriptor to be determined. We have two extra equations in $\log K_w$ (see Table 1) and an equation for the Kovats retention index, see also Table 1, giving a combined total of 81 equations. The data for solubilities in dioxane, ethyl acetate and propanone were well out of line and were not used in the analysis of the remaining 75 equations. A value of 1.35 for **E** was obtained from a calculated refractive index [17], and **E** was directly calculated as 1.36 [14] and 1.29 [13]. We took **E** as 1.36, and **V** can be calculated as 1.3427 trivially [6, 13, 14]. We are left with the descriptors **S**, **A**, **B**, **L**, $\log K_w$ and $\log C_w$ to obtain from a set of 73 simultaneous equations. The set was solved by trial-and-error using the ‘Solver’ add-on in Microsoft Excel to yield the descriptors in Table 2 with a standard deviation, *SD* between observed and calculated dependent variables of 0.090 log units. Our calculated solubility was $\log C_w = -2.124$ in good agreement with an observed solubility of -2.033 [15]. The observed and calculated dependent variables are in Table 1, and the obtained descriptors are in Table 2.

Table 2 Descriptors for edaravone obtained by solution of the sets of simultaneous equations

Species	E	S	A	B	V	L	Log Kw	N	SD
Global	1.360	1.361	0.223	0.797	1.3437	6.816	6.694	73	0.090
Keto 1a	1.360	1.525	0.070	0.753	1.3437	7.069	6.418	21	0.070

However, the descriptors for ‘global’ edaravone represent no more than an average over the three possible forms. The only significant value for any descriptor is that of **A** = 0.223. For the keto form, (CH, 1a), we expect **A** = 0, but for the OH or the NH form we would expect **A** to be around 0.4 to 0.45, so that our results indicate that edaravone can exist in solution as the keto (CH, 1a) the enol (OH, 1b) or the (NH, 1c) form. This is as found by Freyer et al [5] and through our own measurements, as shown in Table 3. Note that the possible error in the % species, Table 3, must be around 5-10%. In non-polar solvents and in solvents with little hydrogen bond acidity and little hydrogen bond basicity, the keto form, (CH, 1a), predominates. The Kamlet-Taft solvatochromic equation [18, 19] that is widely used to correlate and to predict properties of solvents has as independent variables the solvent hydrogen bond acidity, α , the solvent hydrogen bond basicity, β , and the solvent dipolarity,

π^* , Eq. (6), where XYZ is some property of a solute in a series of solvents, so it is an obvious choice to use in order to examine the data in Table 3.

$$XYZ = XYZ^0 + a'\alpha + b'\beta + s'\pi^* \quad (6)$$

Table 3 Determined percentages of edaravone species present in various solvents

Solvent	CH 1a	OH 1b	NH 1c	Ref
Tetrachloromethane	100	0	0	5
Trichloromethane	100	0	0	4, 5, This work
Dichloromethane	100	0	0	5
Benzene	100	0	0	5
Acetonitrile	93	4	3	5
Butyronitrile	91	3	6	5
Sulfolane	84	7	9	5
Propanone	86	6	8	5, This work
Dioxane	90	10	0	5
Tetrahydrofuran	63	31	6	5
Dimethylformamide	28	50	22	5
Pyridine	18	70	12	5
DMSO	22	50	28	4, 5, This work
HMPT	0	97	5	5
Methanol	16	25	59	5
Propan-1-ol	20	35	45	5
2,2,2-Trifluoroethanol	17	0	83	5
2,2,2-Trifluoroethanol	45			This work
Hexafluoroisopropanol	50	0	50	5

We use the independent variables as listed by Marcus [20], see Table 4, and obtain Eq. (7). The % keto for 2,2,2-trifluoroethanol was out of line (17 % and 45 % obs and 74% calc on Eq. 7) and was omitted. The remaining 17 data points gave Eq. 7. The solvent dipolarity was not significant and was left out. The % keto (CH, 1a) form depends very largely on the solvent hydrogen bond basicity. Eq. (7) is probably good enough to estimate the % keto form in other solvents such as ethanol and sec-butanol (Table 4). Since $\alpha = \beta = 0$ for the gas phase, we can deduce that the % keto form will be present to 100 %.

$$\% \text{ Keto} = 118 - 29\alpha - 107\beta \quad (7)$$

$$N = 17, SD = 16, R^2 = 0.839, F = 36.5$$

Table 4 Kamlet-Taft solvent solvatochromic parameters.

Solvent	% (CH, 1a)	α	β	π^*
Tetrachloromethane	100	0.00	0.10	0.28
Trichloromethane	100	0.20	0.10	0.58
Dichloromethane	100	0.13	0.10	0.82
Benzene	100	0.00	0.10	0.59
Acetonitrile	93	0.19	0.40	0.79
Butyronitrile	91	0.00	0.40	0.71
Sulfolane	84	0.00	0.39	0.98
Propanone	86	0.08	0.43	0.71
Dioxane	90	0.00	0.37	0.55
Tetrahydrofuran	63	0.00	0.55	0.58
Dimethylformamide	28	0.00	0.69	0.88
Pyridine	18	0.00	0.64	0.87
DMSO	22	0.00	0.76	1.00
HMPT	0	0.00	1.05	0.87
Methanol	16	0.98	0.66	0.60
Propan-1-ol	20	0.84	0.90	0.52
2,2,2-Trifluoroethanol	17	1.51	0.90	0.73
Hexafluoroisopropanol	50	1.96	0.90	0.65
Ethanol	(13) ^a	0.60	0.80	0.54
sec-Butanol	(13) ^a	0.76	0.84	0.40

^a Predicted values, using Eq. (7)

We can take the solubilities of edaravone in nonpolar solvents as solubilities of the (CH, 1a) keto form. In addition, we can use the known % of the keto form to correct the overall solubility (as the partition coefficient) into the solubility (partition coefficient) of the keto form itself. In the case of ethanol and sec-butanol, we used the calculated % keto as obtained from Eq. (7). We were then able to analyze the solubilities (as partition coefficients) of the keto form in enough solvents to obtain a reliable set of descriptors for the keto form itself, Table 2. The A-descriptor is very nearly zero, as expected for the keto form. We point out that these descriptors for the keto (CH, 1a) form refer to a single specified form of edaravone and so can be used to estimate various properties of that particular form.

Now that we have descriptors for the (CH, 1a) form we can calculate further physicochemical properties for this form. One of the most useful is the water-(wet) octanol partition coefficient, as $\log P_{oct}$, usually taken as a measure of the compound hydrophobicity. We give in Table 5 our predicted value, and values for the keto form calculated by a number of common methods [14, 17, 21-23]. Note that the experimental value (23) is not for the keto form but for the global mixture. There are considerable disagreements

between the various calculations. Our value of 1.76 lies near the middle. The calculated aqueous solubility of the keto form, as $\log C_w$, is -2.70, and using this value we can estimate solubilities of the keto form in other nonpolar solvents, and then partition coefficients of the keto form (CH, 1a) from water to nonpolar solvents.

Table 5 Calculated values for the water-octanol partition coefficient, as $\log P_{oct}$, for the keto (CH, 1a) form of edaravone

Calc $\log P_{oct}$	Ref
1.76	This work
0.44	17
1.23	14
1.33	21
2.56	22
1.20 (Expt) ^a	23

^a see text

We have equations on the line of Eq. 1 for diffusion coefficients in a number of solvents [24], including acetonitrile and propanone where the keto form is the major species. The relevant equations are in Table 6, together with our calculated values of $\log D^o$, where D^o is the diffusion coefficient at 298 K in units of $10^{-5} \text{ cm}^2 \text{ s}^{-1}$

Table 6 Calculation of diffusion coefficients of the keto form of edaravone at 298 K

Solvent	<i>c</i>	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>v</i>	$\log D^o$
Propanone	0.6593	-0.0221	-0.0162	-0.1718	-0.0031	-0.1102	0.442
Acetonitrile	0.6612	-0.0283	-0.0126	-0.2311	-0.0511	-0.1399	0.361

In the gas phase, the keto form of edaravone is the predominant species [4], see also Eq. (7), and since it is also the main form in relatively nonpolar solvents, air to nonpolar phase partitions will refer specifically to the keto form. Thus equations for air to relatively nonpolar medium [25, 26] on the lines of Equation 2 can be used to calculate values for the keto (CH, 1a) form of edaravone, as shown in Table 7 for a number of biological systems.

Processes of environmental importance can also be studied. For example we have obtained an equation for the sorption of gases onto polydimethyl siloxane (PDMS) microextraction surfaces [27], as $\log K$. The coefficients are in Table 6, together with the predicted value of $\log K$. Endo and Goss [28] have reviewed the application of Eq. 1 and Eq. 2 to systems of

environmental importance. A very large compilation of coefficients in Eq. 2 for these systems is available [13] and can be used to predict values for the keto (CH, 1a) form of edaravone.

Table 7 Equations [25, 26] for partition from the gas phase to condensed phase systems, as $\log K$ at 310 K, and calculated values for the keto (CH, 1a) form of edaravone

System	<i>c</i>	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>l</i>	Calc
Air-brain	-0.987	0.263	0.411	3.358	2.025	0.591	5.94
Air-muscle	-1.039	0.207	0.723	3.242	2.469	0.463	5.71
Air-liver	-0.943	0.000	0.836	2.836	2.081	0.564	6.08
Air-lung	-1.250	0.639	1.038	3.661	3.043	0.420	6.72
Air-kidney	-1.005	0.489	0.774	3.000	2.710	0.497	6.61
Air-heart	-1.199	0.185	0.596	2.951	2.450	0.589	6.18
Air-fat	-0.052	0.051	0.728	1.783	0.332	0.743	6.76
Air-olive oil	-0.188	-0.095	0.851	1.468	0.000	0.873	7.26
Air-skin	-0.254	0.311	2.230	3.700	2.925	0.243	7.75
Air-PDMS ^a	-0.045	-0.197	0.490	1.271	0.347	0.856	1.94

^a At 298 K

Conclusions

We show that solubility data confirm that edaravone can exist in solution as a keto form (CH, 1a), an enol form (OH, 1b) or as an amine NH form (NH, 1c) in agreement with previous work [4, 5]. In the gas phase and in nonpolar solvents or solvents with very small hydrogen bond basicity, edaravone exists almost entirely as the keto form. The Kamlet-Taft equation can be used to correlate and to predict the % keto form over a wide range of solvents. We have been able to obtain descriptors for the keto form itself, and these can be used to predict numerous properties of the keto form (CH, 1a) in nonpolar or poorly polar solvents.

Conflicts of Interest

There are no conflicts of interest to declare

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Highlights

- Solubilities and NMR and IR studies used to obtain descriptors of edaravone
- Edaravone has a significant hydrogen bond acidity
- In solution partly as the OH and NH form
- Descriptors assigned to the keto form
- Physicochemical properties of the keto form calculated