EXPERIMENTAL AND THEORETICAL STUDIES OF ROTATIONAL BARRIERS IN ACETO-, *N*-METHYLACETO- AND *N*-PHENYLACETOHYDROXAMIC ACID

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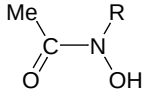
Experimental and theoretical calculations for the *E* and *Z* forms of aceto-, *N*-methylaceto- and *N*-phenylacetohydroxamic acid are reported. The experimental method was NMR spectroscopy, while the computational methods included Hartree–Fock, Møller–Plesset and density functional theory calculations, with and without solvation, using either the Onsager or Tomasi's PCM method. In all calculations zero point energy corrections were included. The computed results when compared with the experimental ones show that, irrespective of the method used, the differences in the rotational barriers, $\Delta(E–TS)$ and $\Delta(Z–TS)$, are slight and below the 3 kcal mol^{-1} limit of the theoretical methods. In general the results using the PCM method were worse than the ones obtained from gas phase calculations or using the Onsager method, even though the PCM method is computationally most expensive. The calculations show, using either the Hartree–Fock or the B3LYP approach, that considering solvation using the Onsager method improves agreement with the experiment results. The calculated barrier heights, excluding the PCM method, agree broadly with the experimental results. Thus using the Onsager approach or gas phase calculations adequate results for barrier heights, but not for relative differences, were obtained.

Keywords: Solvent effects; Hydroxamic acids; Rotational barriers; Hindered rotation; Atropisomerism; *Ab initio* calculations; NMR spectroscopy.

Hydroxamic acids (RCONHOH) are important bioligands[1] and are particularly important as sidereophores for iron[2].

Recently there has been great interest in their ability to inhibit enzyme activity[3]. In the case of hydrolases containing a dinuclear active site, *e.g.* urease, the inhibiting hydroxamic acid bonds to the dinuclear site through

the deprotonated OH group bridging the two metal centres and the carbonyl oxygen bonding to only one metal centre. This has been observed both in nature[4] and in model compounds[5,6]. In other cases, normal O,O



R = H, Me, Ph

chelation of a monomeric metal centre (*e.g.* Zn) is presumed[3]. For these types of bonding to metals to occur the hydroxamic acid must first attain the *Z*-conformation, so that both oxygen atoms are in the correct orientation either to chelate or bridge a dinuclear centre. Formation of the *Z*-isomer from the *E*-isomer requires rotation about the C–N bond, which has partial double bond character through the interaction of the nitrogen lone pair and the carbonyl double bond. Consequently determination of the rotational barriers and related solvent effects on the *E*/*Z* ratio are important.

A number of theoretical studies of hydroxamic acids have been reported[7–13]. The most recent high level gas phase calculations of both aceto- and *N*-methylacetohydroxamic acid showed that the Hartree–Fock method is inadequate and that relatively low level *ab initio* calculations which did not take into account electron correlation failed to discover the presence of the *Z*-iminol form[14]. However the DFT hybrid B3LYP, MP2 and CCSD(T) methods all showed the *Z*-keto, *E*-keto, *Z*-iminol and *E*-iminol to lie within the 3 kcal mol^{-1} accuracy of the methods. In particular the *Z*-keto and the *E*-keto forms lie very close in energy for both aceto- and *N*-methylacetohydroxamic acids (<2 kcal mol^{-1} differences). In view of these conclusions from high level gas phase calculations it was considered important to extend theoretical studies to a comparison of gas phase calculations with calculations with specific solvent environments and to compare these with the energy barriers obtained from variable temperature NMR studies in the same solvents.

EXPERIMENTAL

Solvents were purified by standard methods. Reagents were used directly without purification. The Microanalytical Section of the Chemical Services Unit of University College Dublin performed analyses. ^{1}H NMR spectra were obtained at 270 MHz on a Jeol-GX270 spectrometer with TMS as reference and in 5 mm tubes. Spectra were recorded over the temperature range 293–393 K with a spectral window in most cases of 0–15 ppm, a pulse angle of 30°, 32 K memory data points and a repetition time of 5.94 s. The assignment of peaks to the *Z*-keto and *E*-keto isomers was as described in previous studies[15].

Preparation of Hydroxamic Acids

Acetohydroxamic acid, *N*-methylhydroxamic acid and *N*-phenylhydroxamic acid were prepared as described previously[16].

Rotational Barriers (VTNMR)

These were calculated by the method of Anet and Basus[17] employing as solvents DMSO-d_6 for acetohydroxamic acid, $CDCl_3$ for *N*-methylacetohydroxamic acid and CD_2Cl_2 for *N*-phenylacetohydroxamic acid, thus allowing for measurements of the variable temperature ^{1}H NMR spectra to be made over the temperature ranges 293–373, 293–323 and 308–338 K, respectively. This choice of solvents allowed comparison of peak coalescence behaviour for a number of peaks, *e.g.* for *N*-phenylacetohydroxamic acid the methyl signals coalesced at a higher temperature than the N-OH signals. In all cases the pair of peaks which collapsed at the highest temperature were selected to determine the coalescence temperature. In the region of slow exchange, precise integration gives an accurate measure of the percentage population of each rotamer at that temperature and hence ΔG^0. On the assumption that ΔG^0 for the rotamers is invariant over the experimental temperature range, supported by our relevant calculations, free energies of activation were calculated for the two conformers. We have carried out B3LYP(O) calculations of the changes in Gibbs free energy between the *E* and *Z* forms of acetohydroxamic acid over the temperature range at which NMR measurements were made. These calculations found that the change in Gibbs free energy difference for this system was not significant, being 0.01 kcal mol^{-1} over the temperature range considered. Values for *N*-phenylacetohydroxamic acid are less accurate than for the two other hydroxamic acids as the Anet and Basus method (applicable to unequal populations, >10 : 1) is less precise in this case. Results are given in Table I.

Calculational Methods

The energy differences in the Tables were based on energy calculations using optimised geometries. The optimised geometry computation, using the methods indicated, was followed by a single point calculation, using where appropriate a solvation model. Zero point energies using the indicated method were included in all calculations. Thus the notation HF(G)/MP2(O)/HF(G) refers to an energy calculation using the Hartree–Fock optimised gas phase geometry for a single point Møller–Plesset 2 calculation with the Onsager solvation approach and the Hartree–Fock gas-phase zero point energy correction was used. Similarly B3LYP(O)/B3LYP(PCM)/B3LYP(G) refers to a calculation using the B3LYP and the Onsager approaches to find the geometry used for a single point B3LYP(PCM) solvation calculation and the zero point correction derived from a B3LYP frequency calculation in the gas phase was used.

The calculations were performed using the Gaussian 94 and 98 suite of programs of Pople and coworkers[18]. Hartree–Fock[19], Møller–Plesset 2 (ref.[20]) and the hybrid B3LYP density functional method[21] were used in the calculations. The basis set used throughout was 6-311++G(D,P) (ref.[22]). The Onsager[23] and PCM (ref.[24]) treatments of solvation were used to study the effects of solvation and the validity of these methods for studying acetohydroxamic acids in solution was considered. Gas phase, *i.e.* non-solvated, calculations were also considered. In all cases zero point corrections obtained from frequency calculations were included.

The transition states were located initially by gas phase searches for first order saddle points on the potential energy surface. The geometries found at this stage were reoptimised using the appropriate model, Onsager or PCM, to account for solvent effects. The resulting geometries were characterised by frequency calculations using the same solvent model. In calculating energy barriers the contributions of the imaginary frequencies were not included.

RESULTS AND DISCUSSION

Tables II–IV show the rotational barrier heights for the *E*-keto and *Z*-keto forms of the hydroxamic acids considered using the approaches described above, $\Delta(E–TS)$ and $\Delta(Z–TS)$. The final column in the Tables gives the differences between the energies of the *E*- and *Z*-keto forms of the hydroxamic acids, $\Delta(E–Z)$.

The experimental values in the final rows of the tables compare well with those measured by Santos and co-workers for a number of secondary hydroxamic acids, which lie in the range 16–17 kcal mol^{-1} (ref.[25]).

From the Tables it is noteworthy that in all cases the calculations approximately agree with the experimental values, with the exception of the PCM

TABLE I
Experimental parameters obtained from the NMR rotational barrier studies, together with derived thermodynamic data. Estimated errors are ±2 K in T_c, ±0.10 kcal mol^{-1} in $\Delta G^{\ddagger}$ values and ±10% in rate constant values

Parameter	Acetohydroxamic acid	*N*-methylaceto-hydroxamic acid	*N*-phenylaceto-hydroxamic acid
P_Z, %	89.4	9.32	64.4
P_E, %	10.26	90.68	35.6
$K = P_Z/P_E$	8.747	0.103	1.809
ΔG^0, kcal mol^{-1}	1.284	–1.330	0.251
T_c, K	353	315	287
k_E, s^{-1}	1333.4	71.21	212.34
k_Z, s^{-1}	213.72	597.19	136.75
$K_c = k_E/k_Z$	6.239	0.119	1.553
$\Delta G_E^{\ddagger}$, kcal mol^{-1}	15.73	15.78	13.72
$\Delta G_Z^{\ddagger}$, kcal mol^{-1}	17.02	14.45	13.97
$\Delta G_{ZE}^{\ddagger}$, kcal mol^{-1}	1.29	–1.33	0.25

calculations, where it appears that the energy of the transition state is under-estimated leading to artificially high rotational barriers. Thus for the *E*-keto form of acetohydroxamic acid the range in calculated values, excluding the PCM calculations, is 14.45–16.50 kcal mol^{-1}, while the experimental value is 15.78 kcal mol^{-1}. For the *Z*-keto form the corresponding range is from 14.76–18.31 kcal mol^{-1}, while the experimental value is 16.96 kcal mol^{-1}. For *N*-methylacetohydroxamic acid the ranges for the *E*- and *Z*-isomers, excluding the PCM calculations, are 13.90–15.53 and 11.53–17.02 kcal mol^{-1} and the experimental values are 15.80 and 14.47 kcal mol^{-1}. For *N*-phenylacetohydroxamic acid the corresponding ranges are 12.10–14.31 and 12.32–16.67 kcal mol^{-1} and the experimental values are 13.72 and 13.97 kcal mol^{-1}.

However the most striking conclusion from Tables II–IV is that, whatever calculational method is used, the *E*-keto and *Z*-keto energies are very close

TABLE II
Rotational barriers for *E*-keto and *Z*-keto forms of acetohydroxamic acid and the energy difference between them (in kcal mol^{-1}). An explanation of column 1 is given in the text

Calculation	Δ(*E*–TS)	Δ(*Z*–TS)	Δ(*E*–*Z*)
HF(G)/HF(G)/HF(G)	14.45	14.76	0.31
HF(G)/HF(O)/HF(G)	16.50	17.08	0.58
HF(O)/HF(O)/HF(O)	16.49	16.39	–0.10
HF(G)/MP2(O)/HF(G)	15.58	16.08	0.50
HF(G)MP2(O)/B3LYP(G)	15.41	14.81	–0.60
B3LYP(G)/B3LYP(G)/HF(G)	15.69	18.31	2.62
B3LYP(G)/B3LYP(G)/HF(O)	15.68	17.62	1.94
B3LYP(G)/B3LYP(G)/B3LYP(G)	15.51	17.04	1.52
B3LYP(O)/B3LYP(O)/B3LYP(G)	15.74	17.18	1.43
B3LYP(O)/B3LYP(O)/B3LYP(O)	15.62	17.10	1.48
B3LYP(O)/B3LYP(PCM)/B3LYP(G)	15.48	16.18	0.70
B3LYP(O)/B3LYP(PCM)/B3LYP(O)	15.35	16.10	0.75
B3LYP(PCM)/B3LYP(PCM)/B3LYP(G)	19.68	20.57	0.89
B3LYP(PCM)/B3LYP(PCM)/B3LYP(O)	19.55	20.49	0.93
B3LYP(PCM)/B3LYP(PCM)/B3LYP(PCM)	19.55	20.63	1.08
Experimental	15.78	16.96	1.28

and lie in all cases below the 3 kcal mol^{-1} limit of these theoretical methods. This conclusion applies to both gaseous and solution model calculations. In most cases the *Z*-keto isomer is predicted to be more stable but only by very small amounts and less than the above limit so it would be very unwise to conclude from these calculations that it is the more stable.

The calculated rotational barriers being much larger (approximately 12–23 kcal mol^{-1}) than the energy differences Δ(*E*–*Z*), which range from –1.49 to 2.81 kcal mol^{-1}, may be compared with experiment and provide useful comments on the validity of the theoretical methods. For the acetohydroxamic acids considered the PCM method is clearly unsatisfactory for the calculation of rotational barriers, even though it is more expensive. There is no advantage in using this method within the series considered. However using both the Hartree–Fock and the B3LYP approach, the inclusion of solvation within the Onsager method improves, in general, the agreement with experiment.

TABLE III
Rotational barriers for *E*-keto and *Z*-keto forms of *N*-methylacetohydroxamic acid and the energy difference between them (in kcal mol^{-1}). An explanation of column 1 is given in the text

Calculation	Δ(*E*–TS)	Δ(*Z*–TS)	Δ(*E*–*Z*)
HF(G)/HF(G)/HF(G)	14.34	11.53	2.81
HF(O)/HF(O)/HF(O)	14.32	13.01	1.31
HF(G)/MP2(O)/HF(G)	13.90	13.95	–0.04
B3LYP(G)B3LYP(G)/HF(G)	14.63	15.78	–1.15
B3LYP(G)/B3LYP(G)/B3LYP(G)	14.48	15.45	–0.97
B3LYP(O)/B3LYP(O)/HF(G)	15.53	17.02	–1.49
B3LYP(O)/B3LYP(O)/B3LYP(G)	15.38	16.69	–1.31
B3LYP(O)/B3LYP(O)/B3LYP(O)	15.34	16.68	–1.35
B3LYP(O)/B3LYP(PCM)/B3LYP(G)	15.77	15.85	–0.07
B3LYP(O)/B3LYP(PCM)/B3LYP(O)	15.73	15.84	–0.11
B3LYP(PCM)/B3LYP(PCM)/B3LYP(G)	19.48	19.74	–0.26
B3LYP(PCM)/B3LYP(PCM)/B3LYP(O)	19.44	19.73	–0.30
B3LYP(PCM)/B3LYP(PCM)/B3LYP(PCM)	19.45	19.66	–0.21
Experimental	15.80	14.47	1.33

TABLE IV

Rotational barriers for *E*-keto and *Z*-keto forms of *N*-phenylacetohydroxamic acid and the energy difference between them (in kcal mol^{-1}). An explanation of column 1 is given in the text

Calculation	Δ(*E*–TS)	Δ(*Z*–TS)	Δ(*E*–*Z*)
HF(G)/HF(G)/HF(G)	12.62	12.32	–0.29
HF(G)/MP2(O)/HF(G)	12.30	14.53	2.23
HF(G)/MP2(O)/B3LYP(G)	12.10	13.82	1.72
B3LYP(G)/B3LYP(G)/HF(G)	14.31	16.67	2.36
B3LYP(G)/B3LYP(G)/B3LYP(G)	14.10	15.96	1.86
B3LYP(O)/B3LYP(O)/B3LYP(G)	14.26	16.58	2.32
B3LYP(O)/B3LYP(O)/B3LYP(O)	14.21	16.64	2.43
B3LYP(O)/B3LYP(PCM)/B3LYP(G)	14.71	15.08	0.37
B3LYP(O)/B3LYP(PCM)/B3LYP(O)	22.24	22.72	0.48
Experimental	13.72	13.97	0.25

TABLE V

Energy differences between the forms of aceto- and *N*-methylacetohydroxamic acids and their corresponding transition states and the energy differences between the *E* and *Z* forms of these acids. Energies in kcal mol^{-1}

Acids	Δ(*E*–TS)	Δ(*Z*–TS)	Δ(*E*–*Z*)
	Acetohydroxamic acid		
B3LYP(G)	0.27	–0.08	0.24
B3LYP(O)	0.16	–0.14	–0.20
B3LYP(PCM)	–3.77	–3.67	0.20
	N-methylacetohydroxamic acid		
B3LYP(G)	–1.32	0.98	–2.30
B3LYP(O)	0.46	2.21	–2.68
B3LYP(PCM)	3.65	5.19	–1.54

It is of interest to note that the Onsager model, the PCM model and the gas phase calculations give good results for the *E–Z* energy differences. However the PCM method gives anomalous values for *E–TS* and *Z–TS* energy differences, indicating an inadequate procedure for obtaining the energies of transition states within the PCM framework. This conclusion, based on the B3LYP calculations, is valid with or without the inclusion of zero point energies.

A detailed study of the PCM results show that the source of the error in calculating transition states using the PCM formalism is probably due to the solvent–solute electrostatic interaction term. Table V illustrates the relative accuracy of the results and clarifies the source of the difficulty within the PCM method. The table shows the difference in energy between the *E* form of acetohydroxamic and the transition state, the difference between the *Z* form and the transition state and the energy difference between the *E* and *Z* forms of acetohydroxamic acid. Corresponding results for *N*-methylacetohydroxamic acid are also given. In every case the differences between the optimised structures and the transition states are anomalous using the PCM method.

Therefore this study has shown that, with the exception of the PCM method, the range of theoretical methods engaged in this paper gives good agreement with the experimental values of the rotational barriers and shows clearly that the energy differences between the *E*-keto and *Z*-keto isomers are very small. In view of this it is not surprising that the measured *E*/*Z* ratio is solvent dependent as revealed by earlier NMR studies[15].

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