

GAS-PHASE ACIDITY OF SOME α -KETO ALDOXIMES: EXPERIMENT AND THEORY

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Experimental gas-phase acidities of 2-oxopropanaloximes, $XCH_2COCH=NOH$ ($X = H, CH_3S, CH_3SO, CH_3SO_2$; compounds 1-4), were determined by Fourier transform ion cyclotron resonance (FT-ICR) spectrometry. The values are $\Delta G_{acid}^\circ = 1401, 1381, 1360$ and 1351 kJ mol^{-1} for 1, 2, 3, and 4, respectively. Molecular orbital calculations using the semi-empirical AM1 method provided information on the geometry and relative energy of neutrals species 1-4 and their conjugate bases, together with charge distributions and entropies of deprotonation. It is demonstrated that the proton abstraction occurs preferentially at the oxime function; the formation of an enolate as a conjugate base is unfavourable by $70-140 \text{ kJ mol}^{-1}$. The large variation of the gas-phase acidities for 1-4 is explained in terms of the field/inductive empirical substituent constant σ_f . The variation of solution acidities appears to be comparatively strongly attenuated. This attenuation is attributed mainly to charge delocalization in the anion, which was confirmed by charge density calculations.

INTRODUCTION

Oximes constitute an important class of chemical reagents, the usefulness in analytical chemistry for the identification of aldehydes or ketones having long been known. They are also useful in organic synthesis as precursors of amines, nitriles and amides. Some of them exhibit biological activities and are known as herbicidal, antifungal, anti-inflammatory, antibacterial, anticonvulsant and antiviral agents.¹⁻⁵

2-oxopropanaloxime **1** and its methylthio, methylsulphinyl and methylsulphonyl derivatives **2-4** studied here are of particular interest ($XCH_2COCH=NOH$: **1**, $X = H$; **2**, $X = MeS$; **3**, $X = MeSO$; **4**, $X = MeSO_2$). Compounds **1-4** have an antidotal effect against poisoning of the acetylcholinesterase by organophosphorus compounds.⁶⁻⁸ Their ability to reactivate the phosphorylated acetylcholinesterase by removing the phosphoryl residue from the active site has been related to the nucleophilic character (α -effect) of the corresponding oximate anion.^{8,9} However, the effect of solvation on the acidity of **1-4**, which may contribute to the interpretation of a quantitative estimate of the intrinsic acidity of **1-4** together with a reliable assignment of the acidic site, requires elucidation.

For this purpose, this paper describes the experimental determination of the gas-phase acidities of **1-4** obtained by Fourier transform ion cyclotron resonance (FT-ICR) spectrometry and structural information concerning neutrals species **1-4** and their conjugate bases given by molecular orbital calculations.

EXPERIMENTAL

FT-ICR measurements of gas-phase acidities. The methodology has been described previously.¹⁰ Briefly, measurements start by the introduction of the acid under study, AH, and the reference acid, RH, at known partial pressures in the range 10^{-5} Pa. A small amount (2.5×10^{-6} Pa) of *tert*-butyl nitrite (Aldrich) is added. A pulse of near thermal electrons (0.1 eV nominal energy) produces *t*-BuO⁻, which abstracts protons from AH and RH. We have also observed the formation of oximate anions even in the absence of negative ionization reagent. The proton exchange reaction is monitored for about 10 s. After 1-3 s a steady state is reached which corresponds to a constant R^-/A^- ratio. Partial pressures are read on a Bayard-Alpert gauge and corrected for the gauge sensitivity for each reactant.¹¹ The gauge sensitivities

relative to N_2 (S_r) were measured for the following compounds: **1** (3.40 ± 0.03), $HCOOH$ (1.61 ± 0.02), $MeCOCH_2COMe$ (4.64 ± 0.03), $CH_2(CN)_2$ (2.54 ± 0.02) and $CF_3COCH_2COCH_3$ (4.55 ± 0.15), for insufficiently volatile compounds S_r values were estimated from group increments based on experimental data: **2**, **3**, **4** (5.64), $PhCOOH$ (3.46), $4-CF_3PhOH$ (3.68) and $CF_3CONHPh$ (3.59). For the sake of homogeneity, group increments estimations were also used for $CH_2(CN)_2$ (2.78) and $CF_3COCH_2COCH_3$ (4.93).

Reference acids were commercially available; samples of oximes **1–4** were provided by the authors of Ref. 7.

MO calculations. Molecular orbital calculations have proved to be useful for the interpretation of experimental data concerning gas-phase acidity or basicity.^{12–18} However, *ab initio* calculations of absolute acidity need the addition of diffuse functions to the basis set of atomic orbitals and the inclusion of electron correlation.^{12–15} Unfortunately, the large size of the investigated system does not allow such time-

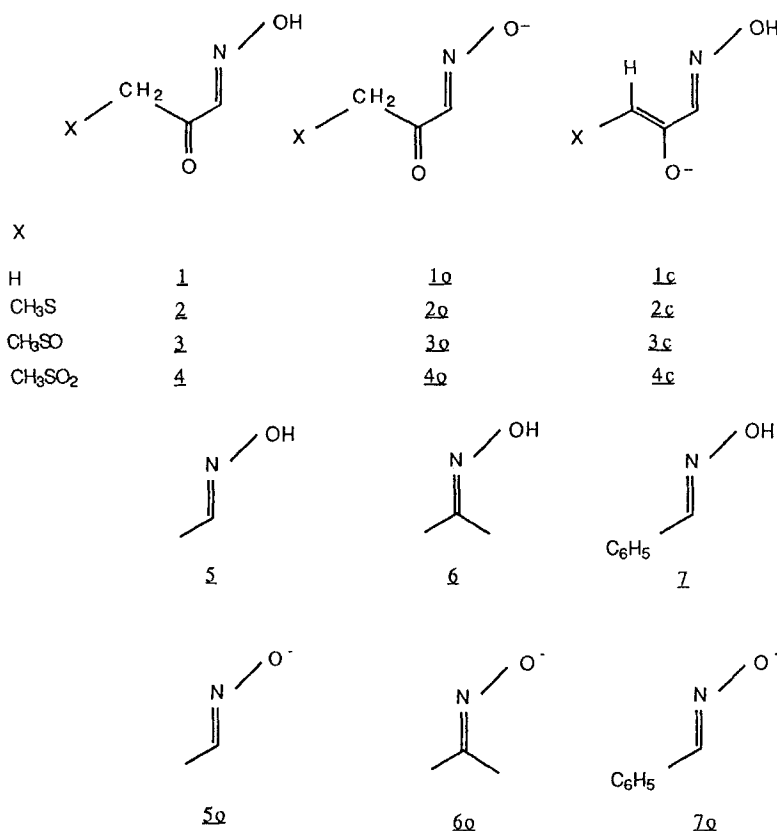
consuming calculations. Consequently, we chose the less expensive semi-empirical AM1 method,¹⁹ which is known to give reliable results if one considers only relative acidity estimates.^{16–18}

All computations were carried out by using the standard AM1 procedure as implemented in the AMPAC program (QCPE number 523). Neutral species **1–4** and their conjugate bases produced by deprotonation of either oxygen (**1o–4o**) or carbon (**1c–4c**) in the α -position with respect to the carbonyl were considered (Scheme 1).

For the purpose of comparison, simple oximes **5–7** and oximates **5o–7o** were also subjected to computation.

All geometries were optimized by minimizing the energy with respect to all internal coordinates and without any symmetry constraint. Detailed geometrical parameters are available from the authors on request.

In the α -ketoaldoxime series, the optimized geometries of the twelve species are characterized by an *s-trans* conformation, which minimizes the electronic repulsions between the negatively charged oxygen



Scheme 1

atoms. From an experimental point of view, information is only available for **1** and demonstrates that the *s-trans* conformation is indeed the most stable (gas-phase electron diffraction²⁰).

RESULTS AND DISCUSSION

Correlation of AM1 calculations and experimental gas-phase acidities

Calculations

Standard enthalpies of formation and absolute entropies as calculated by the AM1 method for neutral species AH = **1**–**7** and their conjugated bases are reported in Table 1.

The calculations indicate clearly that oximate anions **1o**–**4o** are more stable than the isomeric forms **1c**–**4c** by 140, 105, 95 and 70 kJ mol⁻¹, respectively. The

decrease in energy difference parallels the electron-withdrawing power of the substituent X.

$\Delta H_{\text{acid}}^{\circ}$ is defined as the enthalpy of reaction for the deprotonation process $\text{AH} \rightarrow \text{A}^- + \text{H}^+$. The calculated $\Delta H_{\text{acid}}^{\circ}$ values were found by using $\Delta H_{\text{acid}}^{\circ} = \Delta H_{\text{f}}^{\circ}(\text{A}^-) + \Delta H_{\text{f}}^{\circ}(\text{H}^+) - \Delta H_{\text{f}}^{\circ}(\text{AH})$. Since AM1 gives a poor estimate of the heat of formation of the proton, the experimental value $\Delta H_{\text{f}}^{\circ}(\text{H}^+) = 1530 \text{ kJ mol}^{-1}$ (Ref. 21) (this value refers to the so-called stationary electron convention) was used in calculating $\Delta H_{\text{acid}}^{\circ}$.

Experimental gas-phase acidities

Experimentally, one reference acid RH allows the measurement of the proton transfer equilibrium constant:

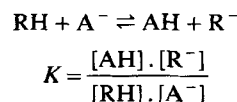


Table 1. Enthalpy of formation,^a entropy^b and thermodynamic acidity^a calculated by the AM1 method

AH	A ⁻	$\Delta H_{\text{f}}^{\circ}(\text{AH})$	$S^{\circ}(\text{AH})$	$\Delta H_{\text{f}}^{\circ}(\text{A}^-)$	$S^{\circ}(\text{A}^-)$	$\Delta H_{\text{acid}}^{\circ}$
1	1o	-150	343	-307	326	1373
	1c			-166		1514
2	2o	-138	420	-310	404	1358
	2c			-206		1462
3	3o	-1	443	-210	426	1321
	3c			-115		1416
4	4o	+312	481	+63	465	1281
	4c			+133		1351
5	5o	-33		-94		1469
6	6o	-61		-128		1463
7	7o	+102		-23		1405

^a kJ mol⁻¹.

^b S° at 298.15 K in J K⁻¹ mol⁻¹; standard state, ideal gas, 298 K and 0.1 MP.

Table 2. Experimental data^a relevant to the acidity of **1**–**4**

AH	RH	$-\Delta G_{\text{eq}}^{\circ}$	$\Delta G_{\text{acid}}^{\circ}(\text{RH})^{\text{b}}$	$\Delta G_{\text{acid}}^{\circ}(\text{AH})^{\text{c}}$	$\Delta H_{\text{acid}}^{\circ}(\text{AH})$
1	HCOOH	-9.7	1415.4	1403 ± 3	1430
	MeCOCH ₂ COMe	-7.5	1408.5		
	PhCOOH	+8.1	1393.3		
2	4-CF ₃ PhOH	-0.25	1381.1	1381 ± 2	1408
	CH ₂ (CN) ₂	+8.9	1373.0		
3	CH ₂ (CN) ₂	< -9.6	1373.0	1360 ± 6 ^d	1387
	4	> +5.9	1350.9		
4	CF ₃ CONHPh	≤ -11.1	1365.7	1353 ± 3	1379
	CF ₃ COCH ₂ COCH ₃	+3.4	1347.5		

^a kJ mol⁻¹; 298 K.

^b Ref. 22.

^c $\Delta G_{\text{acid}}^{\circ}(\text{AH}) = \Delta G_{\text{acid}}^{\circ}(\text{RH}) - \Delta G_{\text{eq}}^{\circ}$. Uncertainties due to the precision overlap of the various acidity standards and to the reproducibility of the experimental equilibrium constants (±1 kJ mol⁻¹).

^d Partial decomposition precluded more precise measurements.

In order to obtain accurate overlap with the most recent absolute acidity scale²² ($\Delta H_{\text{acid}}^{\circ}$ values are given in Ref. 21), at least two reference acids were used whenever possible. The resulting free energy changes $\Delta G_{\text{eq}}^{\circ} = -RT \ln K$, and the relevant $\Delta G_{\text{acid}}^{\circ}$ values are listed in Table 2.

In order to estimate $\Delta H_{\text{acid}}^{\circ}$, the entropy variation associated with the reaction $\text{AH} \rightarrow \text{A}^{-} + \text{H}^{+}$ has to be calculated.²³ In addition to the entropy of the proton ($S^{\circ} = 108.95 \text{ J K}^{-1} \text{ mol}^{-1}$ at 298.15 K and 0.1 MPa), a second contribution to the entropy variation is associated with the disappearance of an internal rotation in the anion (entropy variations due to internal rotations have been estimated using Benson's tables²⁴). Two limiting cases can be considered: (i) an OH free rotation ($S_{\text{rot}}^{\circ} = 19 \text{ J K}^{-1} \text{ mol}^{-1}$) or (ii) an OH hindered rotation for which an S_{rot}° term of *ca* $7 \text{ J K}^{-1} \text{ mol}^{-1}$ may be proposed by analogy with the case of the phenol molecule (this corresponds to a rotational barrier of 14 kJ mol^{-1} ; Ref. 25). This leads to $\Delta S_{\text{acid}}^{\circ} = 96 \pm 6 \text{ J K}^{-1} \text{ mol}^{-1}$. Note that an increase in the (CO)-(CH=NO) rotational barrier height is also expected during deprotonation (when passing from 20 to 40 kJ mol^{-1} a decrease in entropy of $4 \text{ J K}^{-1} \text{ mol}^{-1}$ is predicted). This suggests a $\Delta S_{\text{acid}}^{\circ}$ value closer to the lower limit.

The calculation of entropies by AM1 (Table 1) gives $\Delta S_{\text{acid}}^{\circ} = 92 \pm 1 \text{ J K}^{-1} \text{ mol}^{-1}$, in perfect agreement with the preceding estimations. This value was retained in the derivation of $\Delta H_{\text{acid}}^{\circ}$ from experimental data (Table 2).

Experiment versus theory.

From examination of Tables 1 and 2, it is clear that AM1 seriously underestimates the deprotonation enthalpy, $\Delta H_{\text{acid}}^{\circ}$, of the compounds under scrutiny. The same observation is also evident for the simple oximes 5-7, for which the experimental $\Delta H_{\text{acid}}^{\circ}$ values are equal to 1530, 1532 and 1477 kJ mol^{-1} , respectively.²² Hopefully, this systematic underestimation is nearly constant. Accordingly, a linear correlation between $\Delta H_{\text{acid}}^{\circ}(\text{AM1})$ and $\Delta H_{\text{acid}}^{\circ}(\text{exp})$ is observed:

$$\Delta H_{\text{acid}}^{\circ}(\text{AM1}) = (1.05 \pm 0.10)\Delta H_{\text{acid}}^{\circ}(\text{exp}) - 141.7$$

$$r = 0.9770, \quad n = 7$$

and is illustrated in Figure 1.

The good fit and a value close to unity for the slope of the line indicate that relative acidities may be deduced from AM1 calculation with some confidence; a relative precision of 20 kJ mol^{-1} is deduced from the data. Because the selected compounds include 'true' oximes such as 5-7, the correlation is believed to confirm the favoured deprotonation site on the hydroxyl group for 1-4.

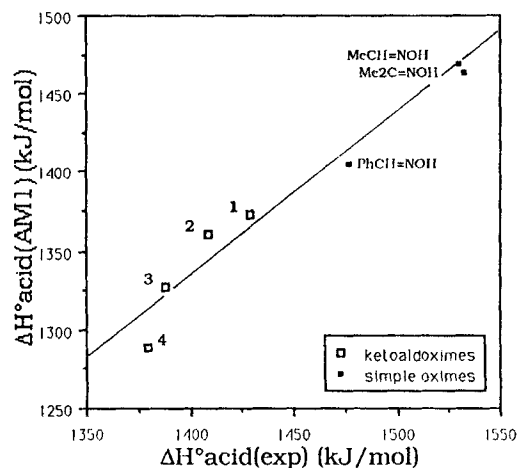


Figure 1. Relationship between the gas-phase acidities ($\Delta H_{\text{acid}}^{\circ}$) calculated by the AM1 method and the experimental values. The slope is 1.05

Substituent and solvation effects

Substituent effects on gas-phase acidities have been thoroughly analysed by Taft and Topsom,²⁶ using a set of empirical substituent constants: σ_{α} (polarizability), σ_{F} (field/inductive) and σ_{R} (resonance). In the case of compounds 1-4 the resonance effect of substituents X is expected to be nil. A dual substituent parameter correlation of $\Delta G_{\text{acid}}^{\circ}$ against σ_{α} and σ_{F} has shown that the polarizability effect is not statistically significant in this restricted series (the three sulphur-containing substituents have very close σ_{α} values). A fairly good correlation with σ_{F} alone is obtained:

$$\Delta G_{\text{acid}}^{\circ} = (-88.6 \pm 10.4)\sigma_{\text{F}} + 1400.7 \text{ kJ mol}^{-1}$$

$$r = 0.9865, \quad n = 4$$

The slope is slightly lower than that observed for the carboxylic acid series $\text{XCH}_2\text{CO}_2\text{H}$ ($-102.9 \pm 4.6 \text{ kJ mol}^{-1}$).²⁶ This is attributed to the delocalization of the negative charge on a larger framework (five atoms for the α -ketoaldoximate ion as compared with three atoms for the carboxylate ion). This delocalization also contributes to weakening the polarizability effect. Already weak in carboxylic acids, this effect almost vanishes in the α -ketoaldoxime series. The above reasoning confirms *a posteriori* the oxime function as the preferred site of deprotonation.

Valuable information on solvation effects can be obtained from plots of gas-phase acidities vs acidities in solution.^{27,28} As the $\text{p}K_{\text{a}}$ values in water of oximes 1-4 have been determined recently,^{7,9} a comparison can be made with the gas-phase acidities presented above. A plot of gas-phase versus aqueous solution Gibbs energy change of deprotonation reaction is presented in Figure 2 for a large variety of acids (gas-phase data

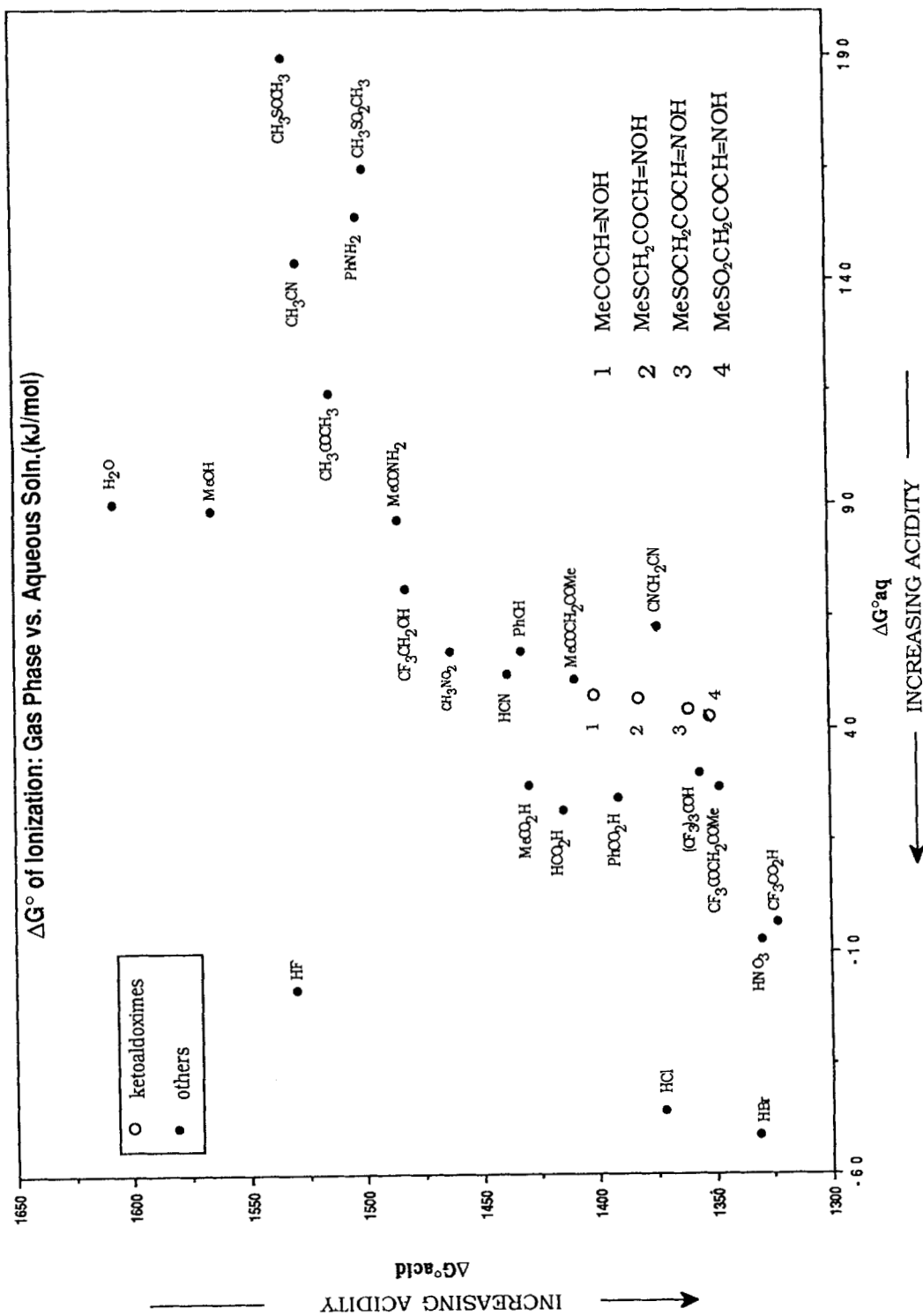
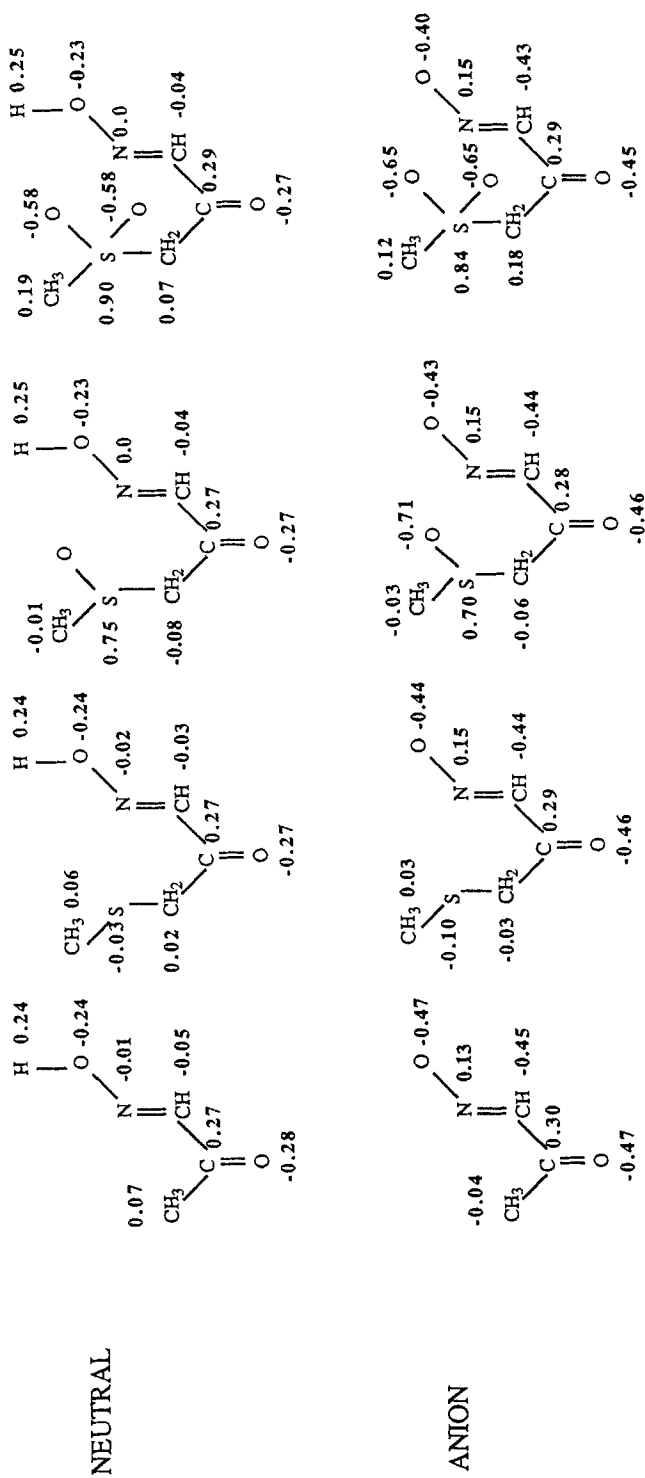


Figure 2. Plot of the Gibbs free energies of deprotonation: gas-phase vs aqueous solution, for a few typical acids (●) and for the series of oximes studied in this work (○). Note that these oximes are relatively strong acids in the gas phase, but are in the medium range in water (pK_a values: 1, 8.30; 2, 8.16; 3, 7.74; 4, 7.46)

Figure 3. Charge densities for the α -ketoaldoximes and their *O*-deprotonated conjugate bases, calculated by the AM1 method

from Ref. 22; aqueous acidities from Refs 28 and 29); the points corresponding to α -ketoaldoximes 1–4 are represented by open circles. Figure 2 shows that, for all the compounds, the acidity is relatively increased in solution as compared with the gas phase. This behaviour is due to the fact that ions are generally better solvated than their neutral counterparts.

A linear relationship is found between the two thermodynamic quantities for 1–4. The slope, which is greater than unity, demonstrates strong damping of the global substituent effect on acidity on going from the gas phase to solution. Part of the attenuation is attributed to the (non-specific) weakening of the electric field effect of the substituent by the solvent permittivity (dielectric constant). The remaining part of the attenuation is due to specific solvation. Hydrogen bonding acidity of the oxime toward the solvent is increased by electron-withdrawing substituents, thus stabilizing the neutral species. On the other hand, anion solvation by a hydrogen bond donor solvent is decreased by electron-withdrawing substituents. Therefore, the substituent effect on the solvation of the acidic side decreases the variation in intrinsic acidity. When the differential solvation between the neutral species and the anion decreases, the corresponding point on the plot approaches a line of unit slope. This is the case, for example, for the carboxylic acid series, acetic, formic benzoic and trifluoroacetic acid. This trend is observed for the series of oximes 1–4 for which the most acidic compound falls on the reference line. For this compound, a very weak differential solvation, analogous to that of $\text{CH}_2(\text{CN})_2$, is expected.

In the gas phase, the acidities of α -ketoaldoximes and carboxylic acids are in the same range. In water, α -ketoaldoximes are weaker acids. This can be attributed to the weaker solvation of the α -ketoaldoximate anions due to a more dispersed charge (on five atoms) as compared with the carboxylate anions (three atoms). It is remarkable that acetylacetone, giving an anion for which the charge is also delocalized on five atoms, lies close to 1.

We have assumed above that solvation is due to non-specific electrostatic interactions, in addition to specific hydrogen bonding of recognized electrostatic character.³⁰ In this regard it is interesting to consider the charge distributions in the neutral species and in the anions.

The group charges (condensed to heavy atoms) as calculated by AM1 for oximes 1–4 and oximates 10–40 are displayed in Figure 3. For the neutral species, the polar groups are CO, OH and, increasingly from 1 to 4, the substituent X. Thus a strong solvation by the water molecules is expected. However, this solvation is expected to be weakly dependent on substitution, as indicated by variation of the charges on the functional moiety. For the oximate anions the negative charge on the COCHNO^- function decreases linearly with σ_F and

is shared between the two oxygen atoms and one carbon atom of the ketoaldoxime moiety. The delocalization of the negative charge is therefore confirmed in addition to the decreasing ion solvation on going from 1–4.

CONCLUSION

AM1 calculations show that in 1–4 the oxime function is the favoured site of deprotonation in the gas phase. The experimental values, being linearly related to the σ_F constants of the substituents, corroborate this finding.

α -Ketoaldoximes appear to be strong acids in the gas phase, comparable to HCl and carboxylic acids. This behaviour departs significantly from what is observed in solution where α -ketoaldoximes are weaker acids. The strong attenuation of the substituent effect in solution is attributed mainly to charge delocalization in the anion.

These anions belong to the class of α -nucleophiles,^{8,9} as does the acetoxyhydroxamate ion.³¹ The origin of the enhanced nucleophilicity of this class of anions as regards their basicity in water ($\text{p}K_a$) (the so-called α -effect) is still a subject of controversy. This point was discussed very recently by Terrier³² and Herschlag and Jencks.³¹ We believe that the results presented here, together with those concerning the gas-phase acidities of acetoxyhydroxamic acids,³³ will shed new light on the special behaviour of this class of compounds.

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