Acidity of Hydroxamic Acids: An *ab Initio* and Semiempirical Study

Oscar N. Ventura,*,† José B. Rama,† László Turi,‡ and J. J. Dannenberg*,‡

Contribution from the Instituto de Química, Facultad de Ciencias y Cátedra de Química Cuántica, Facultad de Química, Universidad de la Republica, Avda. Gral. Flores 2124, C. C. 1157, 11800 Montevideo, Uruguay, and Department of Chemistry, Hunter College and the Graduate School, City University of New York, 695 Park Avenue, New York, New York 10025

Received May 19, 1992

Abstract: High-level *ab initio* calculations, using basis sets with several diffuse and polarization functions and including correlation energy through second-order Møller–Plesset (MP2) theory, were performed on the different possible structures of formo- and acetohydroxamate anions to determine their preferred conformations in the gas phase. We found that, in agreement with recent experimental determinations, both acids behave as NH acids rather than OH acids in the gas phase. AM1 semiempirical and *ab initio* calculations are in general agreement and agree with this particular conclusion. However, AM1 predicts one conformer, unstable at the MP2/6-311++G(2d,2p) level, to have a heat of formation very similar to that of the most stable structure. Comparison of the AM1 results with the experimental free energies of dissociation for several species in the gas phase supports the conclusion that acetohydroxamic acid is a NH acid. AM1 acidities are compared with the acidities of aceto- and benzohydroxamic acids in DMSO by correlating the (AM1) enthalpies of dissociation with the experimental pK_as. Acetohydroxamic acid is clearly predicted to be a NH acid in DMSO, but the behavior of benzohydroxamic acid seems less clear. The possibility that OH dissociation might occur is compatible with the data for benzohydroxamic acid. An analysis of the acidities of substituted anilines and benzoic acids in DMSO is presented to independently assess the ability of AM1 to represent NH and OH dissociations in simpler compounds. Finally, pK_as of several N-substituted and other hydroxamic acids in aqueous solution are compared with the calculated AM1 enthalpies of dissociation. The results indicate that in aqueous solution hydroxamic acids are OH (rather than NH) acids. An analysis of the calculated structures of hydroxamate anions solvated with four water or MeOH molecules explains the prevalence of OH over NH dissociation in protic solvents.

Introduction

Hydroxamic acids are chemical compounds first reported by Lossen more than a century ago.[1] In recent times they have attracted attention because of their properties as iron chelators (siderophores) with therapeutic potential,[2] because of their photochemical properties,[3] and because of their characteristics as specific enzyme inhibitors,[4] among other things. The structure of hydroxamic acids and their anions has been the subject of a long-standing controversy. In principle, several tautomeric structures of the acids are possible (Scheme I) which can produce the anions **4a–c**.

Older reviews indicate that the hydroxamic acids are O acids, with **4a** as the predominant structure.[5] Plapinger[6] reported an UV study of para-substituted benzohydroxamic acids. He found two absorption maxima, one bathochromic and the other hypsochromic to that of the corresponding hydroxamic acids. Comparing these with the absorption bands of O and N Me-substituted hydroxamic acids, he concluded the presence of both structures **4a** and **4b** (or **4c**) in acid and alkaline aqueous solution. Steinberg and Swidler[7] reached a similar conclusion, establishing that the benzohydroxamate anion exists as both **4a** and **4b** in approximately equal concentrations. The existence of **4c** could not be completely ruled out. However, its concentration must be much smaller than those of the other two forms to be in agreement with their findings. Gerstein and Jencks[8] discussed the structure of acetohydroxamic acid. They showed that N-methylacetohy-

droxamic acid is a *stronger* acid than the non-methylated analogue (pK_as of 8.8 and 9.4, respectively). For that reason, they concluded that acetohydroxamic acid must dissociate largely or entirely to structure **4a**. A similar situation occurred with N-phenylben-zohydroxamic acid.[9] More recently, Crumbliss and collaborators[10] showed that data for benzo- and acetohydroxamic acids fit a correlation for ΔH_a vs ΔS_a for several N-methyl- and N-arylhydroxamic acids in aqueous 2 M NaNO₃ solution. They concluded that the hydroxamic acids are acting as OH rather than NH acids in this medium.

On the other hand, Exner and associates[11] reported several studies of the IR and UV spectra, as well as pK_a values, of hydroxamic acids which challenge the conclusion that **4a** is the predominant structure. The extensive studies of Exner *et al.*, performed in dioxane and aqueous alcohol solvents, suggest that the hydroxamic acids are N acids. An ¹⁷O NMR study of the benzohydroxamate ion in MeOH[12] supported this same conclusion, as did an XPS study in the solid state.[13] Recently, Bordwell *et al.*[14] performed a comparison of the acidities of several types of oxygen, nitrogen, and carbon acids, including hydroxamic acids, in DMSO solution. They found that for both aceto- and benzohydroxamic acids, N-alkylation decreased the acidity more than did O-alkylation, indicating that the parents are NH rather than OH acids in DMSO. They observed that N-alkylhydroxamic acids exhibit strong homo-H-bonding, whereas the parent and

† Universidad de la Republica.
‡ City University of New York.
(1) Lossen, H. *Justus Liebigs Ann. Chem.* **1869**, *150*, 314–320.
(2) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563–1579.
(3) Lipczynska-Kochany, E. *Chem. Rev.* **1991**, *91*, 477–491.
(4) Stewart, A. O.; Martin, G. J. *J. Org. Chem.* **1989**, *54*, 1221–1223.
(5) Yale, H. L. *Chem. Rev.* **1943**, *33*, 209–256.
(6) Plapinger, R. E. *J. Org. Chem.* **1959**, *24*, 802–804.
(7) Steinberg, G. M.; Swidler, R. *J. Org. Chem.* **1965**, *30*, 2362–2365.
(8) Gerstein, J.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 4655–4663.

(9) Wise, W. M.; Brant, W. W. *J. Am. Chem. Soc.* **1955**, *77*, 1058–1059. Fields, A. R.; Daye, B. M.; Christian, R., Jr. *Talanta* **1966**, *13*, 929–937.
(10) Monzyk, B.; Crumbliss, A. L. *J. Org. Chem.* **1980**, *45*, 4670–4675. Brink, C. P.; Crumbliss, A. L. *J. Org. Chem.* **1982**, *47*, 1171–1176. Brink, C. P.; Fish, L. L.; Crumbliss, A. L. *J. Org. Chem.* **1985**, *50*, 2277–2281.
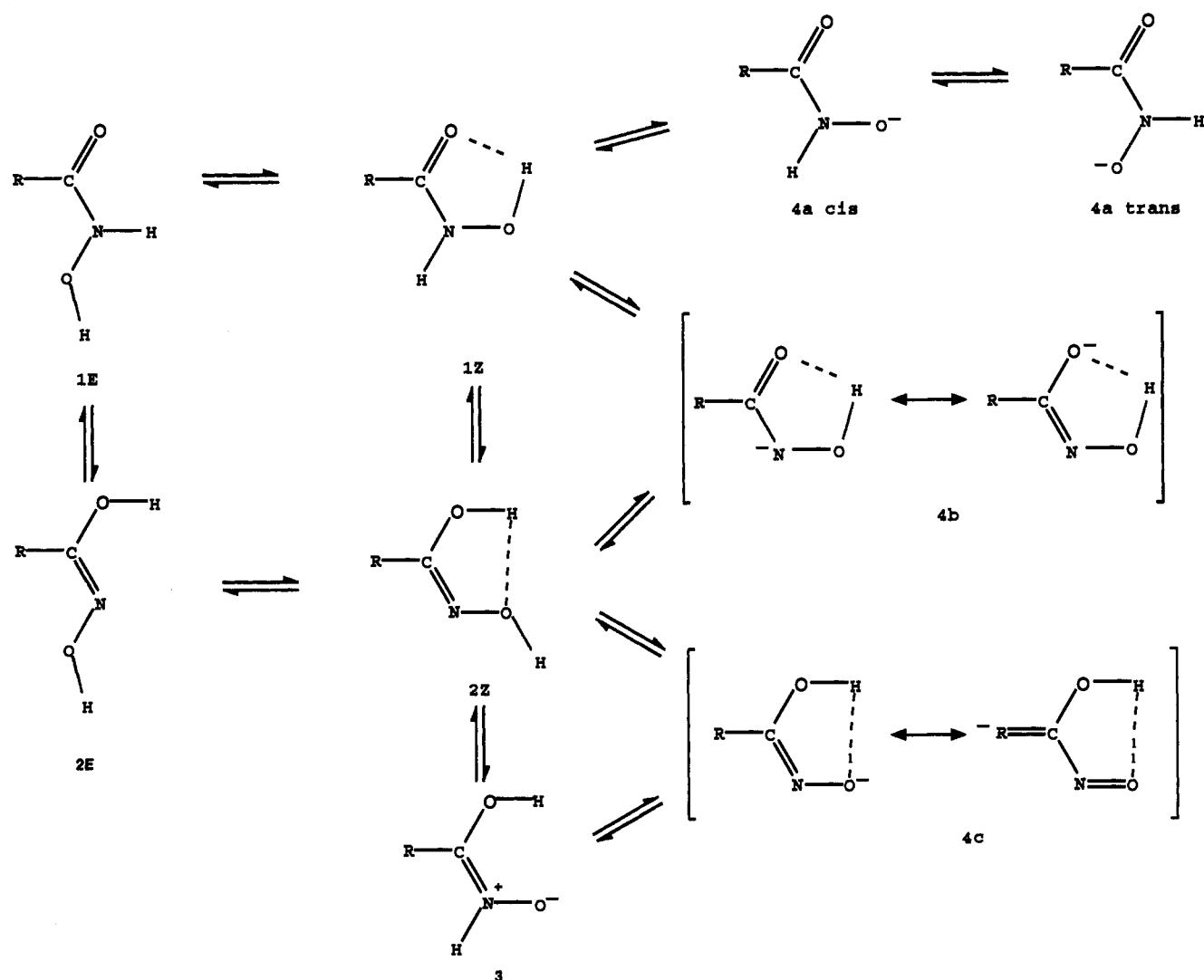(11) Bauer, L.; Exner, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 376–384.
(12) Lipczynska-Kochany, E.; Iwamura, H. *J. Org. Chem.* **1982**, *47*, 5277–5282.
(13) Lindberg, B.; Berndtsson, A.; Nilsson, R.; Nyholm, R.; Exner, O. *Acta Chem. Scand. A* **1978**, *32*, 353–359.
(14) Bordwell, F. G.; Fried, H. E.; Hughes, D. L.; Lynch, T.-Y.; Satish, A. V.; Whang, Y. E. *J. Org. Chem.* **1990**, *55*, 3330–3336.

Acidity of Hydroxamic Acids

J. Am. Chem. Soc., Vol. 115, No. 13, 1993 5755

Scheme I

3

O-alkylhydroxamic acids did not, supporting their behavior as NH acids. However, although the oxidation potentials of the hydroxamate anions in DMSO are consistent with NH ionization, oxidation potential measurements in MeOH admit OH ionization as well. In a recent work, Gal et al.[15] measured the gas-phase acidities of acetohydroxamic acid and its *O*-methyl and *N*-methyl derivatives. On the basis of these results, as well as the analysis of collision-induced dissociation spectra of the corresponding deprotonated species, they concluded that acetohydroxamic acid behaves essentially as a NH acid in the gas phase.

All the somewhat contradictory experimental results cited can be reconciled under the hypothesis that the structures of the anions heavily depend on substituents as well as the media in which the experiments are performed. Few theoretical studies of hydroxamic acids are present in recent literature. Fitzpatrick and Mageswaran[16] performed a self-consistent-field (SCF) *ab initio* study, using the small 3-21G basis set, of several tautomers of formo- and acetohydroxamic acids. More recently, we performed a more sophisticated *ab initio* study, with better basis sets and including correlation energy, of the four tautomers of formohydroxamic acids **1(E)** to **2(Z)** (R = H).[17] The semiempirical AM1 and MNDO-PM3 methods were also employed for the study. Moreover, several substituted hydroxamic acids were also

studied at the semiempirical and SCF levels, including both aceto- and benzohydroxamic acids.

Although simple theoretical studies suggest that hydroxamic acids exist preferentially as the keto form **1(E)** in the gas phase,[16,17a] this preference is reduced at better levels of theory. At the best level of calculation used, MP2/6-311G(d,p)//HF/6-311G(d,p), the three conformers **1(E)** **1(Z)**, and **2(Z)** of formohydroxamic acid are within 1.3 kcal/mol of each other.[17a] The relative importance of hydrogen-bonded structures such as **1(Z)** became evident *only* when correlation energy was included in the calculations of formohydroxamic acid.[17b] Moreover, substitution by methyl, cyano, or phenyl groups are predicted by all methods to stabilize the **1(Z)** and the **2(Z)** forms.[17a] The same effect is noted if supermolecule calculations with water molecules simulating the effect of the solvent are performed.[16]

We report here the results of a theoretical study of the acidity of hydroxamic acids and the structure of hydroxamate anions. The paper is organized as follows. First, we report reasonably accurate *ab initio* calculations on the structures of the anions of (a) formohydroxamic acid (to establish the preferences of the unsubstituted molecule in the gas phase) and (b) acetohydroxamic acid (for which good experimental data are available[15]). Semiempirical methods, which must be used for those acids substituted with large substituent groups, are reported and compared with the *ab initio* calculations. Second, the (gas-phase) experimental and semiempirical results for the ionizations of acetohydroxamic acids and related species,[15] as well as aceto- and benzohydroxamic acids and related compounds in DMSO,[14] are compared to

(15) Decouzon, M.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Org. Chem.* **1990**, *55*, 3980–3981.

(16) Fitzpatrick, N. J.; Mageswaran, R. *Polyhedron* **1989**, *8*, 2255–2263.

(17) (a) Turi, L.; Dannenberg, J. J.; Rama, J.; Ventura, O. N. *J. Phys. Chem.* **1992**, *96*, 3709–3712. (b) Ventura, O. N.; Rama, J. B.; Turi, L.; Dannenberg, J. J., unpublished.

ascertain the relative stabilities of **4a** and **4b** in vacuo and in nonaqueous solvents. Theoretical (gas-phase) ΔH°_0 are plotted against experimental values of ΔG° or pK_a for a series of acids that can be only O acids or N acids, and the identity of the form (**4a** or **4b**) is inferred by whether the data for one or the other best fit the linear regression line. Finally, we consider Crumbliss[10] pK_as of hydroxamic acids and their derivatives in aqueous solution. The effects of solvation by protic solvents are analyzed using supermolecule calculations on formo-, aceto-, and benzohydroxamic acid complexes with four water or methanol molecules.

Methods

Standard *ab initio* calculations were performed at the SCF level using the 3-21G, 6-31G(d), 6-31+G(d,p), 6-311+G(d,p), and 6-311++G(2d, 2p) basis sets developed by Pople and his group.[18] The largest basis set required the use of 175 basis functions for the acetohydroxamate anion. Correlation energy was included using full (*i.e.*, all electrons) second-order Møller–Plesset perturbation theory (MP2). All *ab initio* calculations were performed using the IBM RS/6000 version of the Gaussian 90 system of programs.[19] Semiempirical calculations were performed using the AM1 method[20] as coded in the AMPAC program.[21] Full geometry optimization was performed for each compound at each level of calculation cited in the tables, unless explicitly stated otherwise.

Discussion

The *ab initio* results reported in Table I for the geometries of the anions were obtained using larger basis sets than previously used for these systems. The calculations appear to be converged with respect to the basis set. Use of polarization and diffuse functions is crucial for good descriptions of the geometries, specifically for the NO bond (which is predicted to be too long by small basis set calculations). Inclusion of correlation energy also has a strong effect upon this bond. For instance, while the rest of the bonds in **4a** become longer upon optimization at the MP2 level, the NO bond is shortened. This observation indicates that geometric optimization of correlated wave functions using good basis sets is necessary for the proper description of the interaction between the two electronegative atoms which bear most of the negative charge in the anion. The partial double-bond character of the CN bond is apparent from Table I. The shortest CN bond length at the SCF level occurs in structure **4c**. Since the substituent in formohydroxamic acid (R = H) is unable to delocalize the charge as indicated in the resonance structure on the right in Scheme I, the structure is better described as the resonance structure on the left. This is consistent with the partial double-bond character of the CN bond. The single-bond character of the CO bond in **4c** is also evident from the Hartree–Fock (HF) calculations.

Optimization at the MP2 level (for all basis sets used) failed to locate a minimum corresponding to **4c**. All attempts collapsed to **4b**. **4c** is stable only at the HF level (with a calculated barrier for the transformation to **4b** of about 4 kcal/mol). Our inability to obtain a potential minimum corresponding to **4c** is consistent with its lack of experimental detection.

(18) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(19) Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A. *Gaussian 90*; Gaussian Inc.: Pittsburgh, PA, 1990.

(20) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. G.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.

(21) Dewar, M. J. S.; Stewart, J. J. P.; Eggar, M. AMPAC, Program No. 527, QCPE, Indiana University, Bloomington, IN.

(22) Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964–2968.

(23) Ritchie, C. D.; Uschold, R. E. *J. Am. Chem. Soc.* **1968**, *90*, 2821–2804.

(24) Fountain, K. R.; Fountain, D. P.; Michaels, B.; Myers, D. B.; Salmon, J. K.; Van Galen, D. A.; Yu, P. *Can. J. Chem.* **1991**, *69*, 798–810.

(25) Bartmess, J. *Gas Phase Acidity Scale*, personal communication.

(26) Splitter, J. S.; Calvin, M. *J. Org. Chem.* **1965**, *30*, 3427–3436.

Comparison of structures of *cis*- and *trans*-**4a** demonstrates that the CO and NO bonds are longer, while the NC bond is shorter in the *trans* conformer than in the *cis* form. This change in geometry is consistent with the contribution of a resonance structure such as **4a′**. At the MP2 level, *trans*-**4a** has a NC bond

4a'
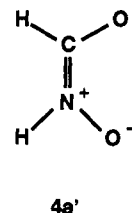
length almost equal to that of **4b**, implying similar participation of resonance structures with C=N double bonds in *trans*-**4a** and **4b**. Lipczynska-Kochany and Iwamura[12] suggested that the large bathochromic shift (from 270 to 310 nm) in the absorption spectra of *N*-phenylbenzohydroxamate anion could be explained by significant charge delocalization—as implied in **4a**—by analogy to that of *C,N*-diphenylnitrone.[27]

The substitution of R = H by R = Me does not produce major changes in the optimized geometries of the different structures. The largest change is for the NO bond length of *trans*-**4a**, which is shorter in formohydroxamic than in acetohydroxamic acid. In the SCF-optimized **4c** structure of formohydroxamic acid, the CN bond is shorter and the NO bond longer than in acetohydroxamic acid. Despite the fact that **4c** is unstable at the MP2 level, this change in geometry is an indication of the increased importance of the right-hand resonance structure upon Me substitution. A comparison of the relative stabilities of the **4a** and **4b** structures of formo- and acetohydroxamate anions shows that the *trans*-**4a** conformer is stabilized while *cis*-**4a** is destabilized with respect to **4b** after Me substitution. Even so, **4b** is more stable than *trans*-**4a** by more than 9 kcal/mol.

AM1 predicts bonds somewhat longer than the *ab initio* calculations predict, except for the NO bond which is noticeably shorter. One should note that AM1 is in much better agreement with the MP2 than with the SCF calculations, even for the NO bond. However, AM1 predicts **4c** to be stable, in agreement with the Hartree–Fock but not the MP2 results. Nonetheless, the general trends are completely in agreement with the best *ab initio* calculations. The NO bond length is shorter in *trans*-**4a** than in **4b**, but it is even shorter in **4c**. Also, the CO and NO bonds are longer and the NC bond shorter in *trans*-**4a** than in *cis*-**4a**, again indicating the importance of the resonance structure **4a′**. Finally, the largest changes in bond length upon methyl substitution occur in the NC bonds of *trans*-**4a** and **4b**. Thus, except for the anomaly of the stable **4c** structure, AM1 agrees quite well with the best *ab initio* predictions.

Semiempirical heats of formation at 298 K are collected in Table II, while *ab initio* relative energies are given in Table III. Both the semiempirical and *ab initio* methods predict the structure **4b** of formohydroxamic acid to be the most stable. Moreover, they also agree in predicting the *trans* conformer of **4a** to be more stable than the *cis*. The most important difference concerns **4c**, least stable at the SCF level, unstable at the MP2 level, but similar in stability to **4b** by AM1. Furthermore, AM1 predicts **4c** to be the most stable structure upon Me substitution. As it is unlikely that this marked difference between the semiempirical and *ab initio* methods is due to considering enthalpies at 25 °C in the first case and internal energies (0 K) in the second, these differences between the AM1 and *ab initio* results remain unexplained. Further work is in progress.

All methods clearly predict formo- and acetohydroxamic acids to be NH acids (rather than OH acids) in the gas phase, in agreement with the experimental findings of Gal et al.[15] Their

(27) Topsom, R. D. *Prog. Phys. Org. Chem.* **1990**, *17*, 107–120.

Acidity of Hydroxamic Acids

J. Am. Chem. Soc., Vol. 115, No. 13, 1993 5757

Table I. Optimum Geometries for the Formo- and Acetohydroxamate Anions 4a–4c Using Different Methods of Calculation[a]

species	method	R	r_{XC}[b]	r_{OC}	r_{NC}	r_{ON}	r_{HO}	r_{HN}	θ_{OCX}[c]	θ_{NCO}	θ_{ONC}	θ_{HON}	θ_{HNC}	θ_{HOC}
cis-4a	AM1	H	1.124	1.266	1.350	1.263		1.011	119.4	128.6	128.8		114.8	
		Me	1.525	1.270	1.357	1.262		1.010	118.0	126.0	127.9		115.2	
	HF/3-21G	H	1.107	1.237	1.311	1.470		1.002	118.8	131.0	126.6		116.9	
		Me	1.557	1.238	1.313	1.471		1.002	118.3	129.0	125.7		118.1	
	MP2/3-21G	H	1.127	1.274	1.353	1.427		1.031	121.6	130.4	128.0		113.8	
		Me	1.580	1.276	1.349	1.433		1.029	119.8	128.6	126.6		115.7	
	HF/6-31G(d)	H	1.107	1.221	1.308	1.346		1.001	119.6	131.0	128.9		114.9	
		Me	1.542	1.224	1.311	1.352		1.000	118.5	128.4	128.3		116.2	
	MP2/6-31G(d)	H	1.122	1.254	1.339	1.330		1.029	121.8	130.1	130.1		112.7	
		Me	1.543	1.259	1.337	1.336		1.027	119.9	127.7	129.2		114.5	
	HF/6-31+G(d,p)	H	1.104	1.223	1.310	1.343		0.998	119.6	130.5	128.6		115.3	
		Me	1.538	1.226	1.312	1.350		0.997	118.6	127.9	128.0		116.6	
	MP2/6-31+G(d,p)	H	1.110	1.257	1.341	1.336		1.020	121.8	129.5	129.5		113.7	
		Me	1.538	1.262	1.338	1.346		1.017	120.1	127.0	128.9		114.8	
	HF/6-311+G(d,p)	H	1.105	1.217	1.310	1.338		0.998	119.8	130.6	128.7		115.0	
		Me	1.538	1.220	1.312	1.346		0.997	118.8	127.9	128.1		116.4	
	MP2/6-311+G(d,p)	H	1.117	1.246	1.343	1.323		1.022	122.3	129.5	129.7		112.9	
		Me	1.542	1.252	1.339	1.332		1.019	120.3	127.1	128.9		114.8	
	HF/6-311++G(2d,2p)	H	1.101	1.217	1.307	1.337		0.994	119.9	130.4	128.8		114.8	
		Me	1.535	1.220	1.309	1.344		0.993	118.8	127.7	128.2		116.1	
	MP2/6-311++G(2d,2p)	H	1.109	1.248	1.338	1.329		1.015	122.1	129.6	129.7		112.9	
		Me	1.537	1.253	1.335	1.337		1.013	120.1	127.0	129.1		114.5	
trans-4a	AM1	H	1.110	1.276	1.347	1.269		1.007	122.1	122.3	124.7		117.7	
		Me	1.506	1.280	1.355	1.267		1.006	120.6	120.0	125.4		116.5	
	HF/3-21G	H	1.088	1.250	1.306	1.475		1.002	121.8	128.6	122.2		118.4	
		Me	1.521	1.251	1.312	1.468		1.001	122.5	126.0	122.5		117.9	
	MP2/3-21G	H	1.106	1.285	1.344	1.444		1.027	124.2	128.0	124.6		115.7	
		Me	1.538	1.285	1.347	1.444		1.025	125.1	126.0	123.1		114.5	
	HF/6-31G(d)	H	1.093	1.234	1.302	1.359		1.001	121.7	127.3	125.7		116.2	
		Me	1.516	1.238	1.306	1.359		1.000	121.4	124.6	126.0		115.7	
	MP2/6-31G(d)	H	1.108	1.266	1.331	1.346		1.027	123.5	126.3	128.0		113.5	
		Me	1.515	1.269	1.332	1.349		1.025	123.6	124.3	127.0		114.1	
	HF/6-31+G(d,p)	H	1.091	1.237	1.301	1.360		0.998	121.4	126.8	125.1		117.3	
		Me	1.513	1.241	1.307	1.359		0.997	121.0	123.8	125.8		116.4	
	MP2/6-31+G(d,p)	H	1.098	1.273	1.328	1.359		1.017	122.6	125.7	127.0		115.7	
		Me	1.509	1.277	1.331	1.360		1.016	122.7	123.3	126.6		115.6	
	HF/6-311+G(d,p)	H	1.093	1.231	1.302	1.356		0.998	121.5	126.9	125.3		117.0	
		Me	1.513	1.236	1.307	1.356		0.997	121.1	124.0	126.0		116.3	
	MP2/6-311+G(d,p)	H	1.104	1.261	1.330	1.347		1.019	123.0	125.9	127.4		115.0	
		Me	1.512	1.266	1.332	1.348		1.019	122.9	123.7	127.0		114.9	
	HF/6-311++G(2d,2p)	H	1.090	1.231	1.298	1.356		0.995	121.4	126.8	125.4		116.9	
		Me	1.511	1.235	1.304	1.355		0.994	121.0	123.9	126.0		116.1	
	MP2/6-311++G(2d,2p)	H	1.097	1.263	1.325	1.353		1.013	122.7	126.0	127.3		115.0	
		Me	1.508	1.267	1.328	1.353		1.013	122.7	123.6	126.7		115.1	
4b	AM1	H	1.116	1.284	1.336	1.323	0.979		119.2	127.5	118.3	110.4		
		Me	1.514	1.288	1.346	1.322	0.979		117.8	124.7	117.2	110.7		
	HF/3-21G	H	1.094	1.272	1.301	1.492	0.977		119.9	128.9	107.7	102.1		
		Me	1.538	1.273	1.303	1.490	0.977		119.4	127.5	107.9	102.0		
	MP2/3-21G	H	1.090	1.311	1.347	1.544	1.022		120.7	127.7	105.0	96.8		
		Me	1.552	1.314	1.345	1.541	1.023		119.8	126.7	105.3	96.6		
	HF/6-31G(d)	H	1.099	1.250	1.292	1.424	0.954		119.3	129.6	109.7	103.6		
		Me	1.531	1.254	1.294	1.421	0.954		118.6	127.8	109.9	103.4		
	MP2/6-31G(d)	H	1.110	1.283	1.322	1.459	0.993		120.3	128.0	107.3	99.2		
		Me	1.527	1.288	1.322	1.456	0.995		119.3	126.5	107.6	98.9		
	HF/6-31G(d,p)	H	1.095	1.254	1.293	1.414	0.951		119.6	128.9	110.4	105.0		
		Me	1.526	1.258	1.295	1.413	0.951		118.7	127.0	110.5	104.7		
	MP2/6-31G(d,p)	H	1.099	1.289	1.324	1.454	0.987		120.7	127.2	107.8	100.5		
		Me	1.521	1.295	1.323	1.452	0.989		119.8	125.6	108.2	100.1		
	HF/6-311+G(d,p)	H	1.096	1.249	1.291	1.410	0.948		119.7	129.0	110.6	105.1		
		Me	1.527	1.253	1.293	1.408	0.948		118.8	127.1	110.7	104.8		
	MP2/6-311+G(d,p)	H	1.104	1.279	1.322	1.438	0.981		121.1	127.0	108.0	100.3		
		Me	1.525	1.285	1.321	1.436	0.983		120.1	125.4	108.3	100.0		
	HF/6-311++G(2d,2p)	H	1.093	1.249	1.289	1.413	0.946		119.7	129.0	110.4	104.6		
		Me	1.525	1.252	1.291	1.412	0.947		118.8	127.2	110.6	104.3		
	MP2/6-311++G(2d,2p)	H	1.098	1.281	1.318	1.449	0.981		121.0	127.1	107.9	100.0		
		Me	1.520	1.286	1.317	1.447	0.982		119.8	125.6	108.2	99.7		
4c[c]	AM1	H	1.092	1.407	1.328	1.223	0.965		109.9	127.9	121.2			106.1
		Me	1.480	1.416	1.341	1.219	0.966		110.6	124.9	120.2			105.8
	3-21G	H	1.073	1.387	1.261	1.462	1.021		115.8	119.7	108.4			94.9
		Me	1.508	1.383	1.262	1.465	1.037		116.2	118.6	108.0			94.0
	6-31G(d)	H	1.076	1.361	1.258	1.347	0.975		115.9	121.0	112.4			96.8
		Me	1.505	1.362	1.257	1.353	0.980		115.9	119.6	112.3			96.5

Table I   (Continued)[a]

species	method	R	r_{XC}[b]	r_{OC}	r_{NC}	r_{ON}	r_{HO}	r_{HN}	θ_{OCX}[c]	θ_{NCO}	θ_{ONC}	θ_{HON}	θ_{HNC}	θ_{HOC}
6-31G(d,p)	H	1.074	1.359	1.260	1.340	0.963		115.8	121.5	113.3			99.9
	Me	1.504	1.360	1.257	1.350	0.968		115.5	120.0	118.1			99.2
6-311+G(d,p)	H	1.075	1.358	1.258	1.334	0.960		115.8	121.5	113.5			100.0
	Me	1.504	1.359	1.255	1.345	0.965		115.6	120.1	113.4			99.4
6-311++G(2d,2p)	H	1.072	1.356	1.255	1.338	0.961		116.1	121.4	113.3			99.5
	Me	1.502	1.356	1.252	1.349	0.965		115.8	120.0	113.2			98.7

[a] All structures are planar except for the methyl group, whose optimum geometries are not reported in this table for simplicity; bond lengths are in angstroms, bond angles in degrees. [b] X stands for H in formohydroxamates and CH_3 in acetohydroxamates. [c] **4c** is not stable at the MP2 level; it collapses to **4b** on optimization.

Table II.   AM1 Heats of Formation at 298 K for the Different Tautomers of Formo- and Acetohydroxamic Acids, in kcal/mol

species	R	ΔH_f°	relative ΔH_f°
cis-**4a**	H	−47.89	18.9
	Me	−52.52	19.9
trans-**4a**	H	−57.45	9.4
	Me	−61.72	10.7
4b	H	−66.81	0.0
	Me	−71.32	1.1
4c	H	−66.36	0.45
	Me	−72.44	0.0

Table III.   Relative Energies of the Different Tautomers of Formohydroxamic Acid, in kcal/mol

R	method	basis set	*cis*-**4a**	*trans*-**4a**	**4b**[a]	**4c**[b]
H	SCF	3-21G	21.4	11.3	0.0(−241.761 405)	18.5
		6-31G(d)	17.9	10.3	0.0(−243.134 751)	22.8
		6-31+G(d,p)	15.1	8.5	0.0(−243.168 429)	20.1
		6-311+G(d,p)	14.9	9.0	0.0(−243.228 090)	20.6
		6-311++G(2d,2p)	14.2	9.0	0.0(−243.236 513)	21.0
	MP2	3-21G	30.7	22.9	0.0(−242.215 634)	
		6-31G(d)	20.7	15.2	0.0(−243.806 263)	
		6-31+G(d,p)	16.1	11.9	0.0(−243.872 488)	
		6-311+G(d,p)	16.4	13.4	0.0(−244.036 476)	
		6-311++G(2d,2p)	15.3	12.8	0.0(−244.105 286)	
Me	SCF	3-21G	21.5	7.1	0.0(−280.587 736)	19.2
		6-31G(d)	19.0	7.8	0.0(−282.175 257)	23.3
		6-31+G(d,p)	16.5	6.3	0.0(−282.211 357)	21.0
		6-311+G(d,p)	16.4	6.7	0.0(−282.277 039)	21.5
		6-311++G(2d,2p)	15.6	6.8	0.0(−282.287 889)	21.9
	MP2	3-21G	31.4	17.5	0.0(−281.133 749)	
		6-31G(d)	22.5	11.8	0.0(−282.982 002)	
		6-31+G(d,p)	18.2	9.1	0.0(−283.065 636)	
		6-311+G(d,p)	18.7	10.5	0.0(−283.255 179)	
		6-311++G(2d,2p)	17.5	9.8	0.0(−283.336 474)	

[a] In parentheses are given the total energies of this isomer at the different levels of calculation. [b] **4c** is not stable at the MP2 level of calculation.

Table IV.   Comparison of Experimental and Theoretical Acidities of Acetohydroxamic Acid and Related Species[a]

species	exptl[b] ΔG°_{acid}	AM1 ΔH_f neutral	AM1 ΔH_f ion	enthalpy of dissociation[c]
MeCONHOH	339.1	−55.03	−71.29 (N-acid)	298.7
			−63.81 (O-acid)	306.1
MeCONHOMe	343.7	−47.75	−62.96	299.7
MeCONMeOH	346.9	−49.21	−57.08	307.1
MeCONH₂	355.0	−50.47	−48.21	317.2
MeCONHMe	354.5	−46.56	−50.07	311.4

[a] All enthalpies in kcal/mol. [b] Reference 15. [c] The theoretical acidity was calculated using the AM1 heat of formation of H^+, 314.92 kcal/mol.

experimental data for *N*-methyl- and *O*-methyl-substituted and unsubstituted acetohydroxamate anions (see Table IV) indicate the ΔG°_{acid} difference between NH and OH dissociations to be between 3.2 and 7.8 kcal/mol, in reasonable agreement with both the *ab initio* energy (9.8 kcal/mol) and AM1 enthalpy (7.5 kcal/mol) reported here. Both experimental and theoretical (AM1 results, Table IV) studies suggest that *N*-methyl and
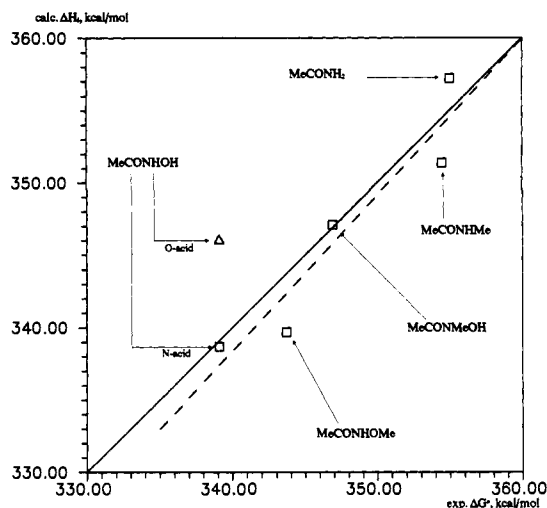

Figure 1. Correlation of the experimental free energies of dissociation[15] of acetohydroxamic acid, acetamide, and their methyl derivatives with the theoretical AM1 enthalpies of dissociation. The full line of slope = 1 would indicate exact equivalence between both sets of data; the dashed line is the best regression line obtained with the data excluding both points for acetohydroxamic acid. AM1 values were shifted 40 kcal/mol upwards to express them in the same scale as the experimental ΔG°_0. All values in kcal/mol.

O-methyl acetohydroxamic acids are weaker than the parent. Gal reported that N- and O-methylation weaken acetohydroxamic acid by 7.8 and 4.6 kcal/mol, respectively. The corresponding theoretical values for the ΔH° of dissociation are 8.4 and 1.0 kcal/mol. As we have used a semiempirical method that incorporates several approximations and are comparing theoretical enthalpies with experimental free energies, we find the agreement between theory and experiment quite encouraging. A more accurate *ab initio* investigation is in progress.

Table IV collects the experimental acidities reported by Gal *et al.*[15] and the AM1 enthalpies for the reaction HA → A⁻ + H⁺. Both **4a** and **4b** were considered for acetohydroxamic acid. None of the other species can undergo more than one type of dissociation. Figure 1 displays correlation between these data. The theoretical results have been uniformly increased by 40 kcal/mol to make them fit the same scale as the experimental data. This does not affect the slope of the line. One should notice that the experimental data are Gibbs free energies, while the theoretical results are enthalpies. Nevertheless, Crumbliss et al.[10] showed that there is a linear relation between ΔH°_{acid} and ΔS. This fact implies, in turn, that the isokinetic relationship—a linear relation between ΔH°_{acid} and ΔG°_{acid}—holds, at least in aqueous solution. The linear relation may not be applicable in the gas phase, however.[26,28] The full line in the graph of Figure 1 represents exact correspondence (slope = 1) between the two sets of data. The dashed line represents the best linear fit. Note that the agreement improves upon inclusion of the data for acetamide and methylacetamide. The regression line is almost of unit slope. Moreover, the point corresponding to structure **4b** (R = Me)

(28) Gal, J.-F.; Maria, P.-C. *Prog. Phys. Org. Chem.* **1990**, *17*, 159–238.

Table V. Comparison of Experimental pK_{HA} and Theoretical Acidities of Hydroxamic Acids and Related Species[a]

species	exptl[b] pK_{HA}	AM1 ΔH_f neutral	AM1 ΔH_f ion	enthalpy of dissociation[c]
MeCONH$_2$	25.5	−50.47	−48.21	317.5
MeCONHOH	16.03	−55.03	−71.29 (N-acid)	298.7
			−63.81 (O-acid)	306.1
MeCONHOMe	17.1	−47.75	−62.96	299.7
MeCONMeOH	19.6	−49.21	−57.08	307.1
PhCONH$_2$	23.5	−15.61	−19.71	310.9
PhCONHOH	13.65	−16.05	−42.17 (N-acid)	288.8
			−33.46 (O-acid)	297.5
PhCONMeOH	18.2	−12.85	−25.81	302.0

[a] All enthalpies in kcal/mol. [b] Reference 14. [c] The theoretical acidity was calculated using the AM1 heat of formation of H$^+$, 314.92 kcal/mol.
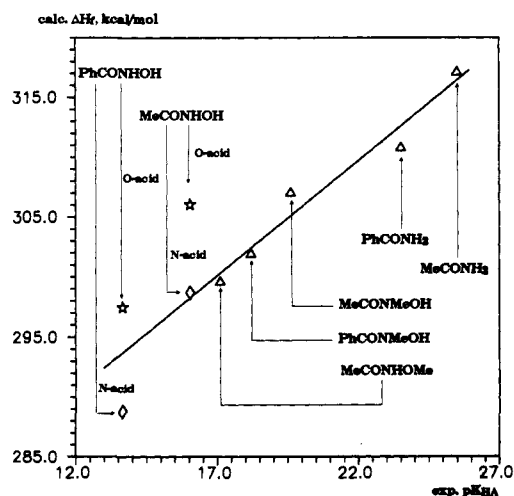
Figure 2. Correlation of the experimental pK_as in DMSO of aceto- and benzohydroxamic acids, their *N*- and *O*-methyl derivatives,[14] and the corresponding amides with the theoretical AM1 enthalpies of dissociation (in kcal/mol). The line is the best regression line obtained excluding the points for the hydroxamic acids, for which values corresponding to NH and OH dissociation are both shown in the figure.

is clearly nearer the regression line than that for **4a** (R = Me), confirming the NH nature of the acid.

Table V collects Bordwell's experimental pK_{HA} values in DMSO,[14] together with the corresponding AM1 enthalpies of deprotonation. The values calculated for both forms of the anions, **4a** and **4b**, are included for aceto- and benzohydroxamic acids but are not used for the correlation. Figure 2 illustrates the correlation of the experimental pK_{HA} values in DMSO with the AM1 enthalpies of deprotonation. The correlation is similar to that for the gas-phase data. As the point corresponding to **4b** (R = Me) in Figure 2 is much nearer the regression line than that for **4a** (R = Me), the AM1 calculations indicate that acetohydroxamic acids is an NH acid in DMSO solution. The situation is less clear for benzohydroxamic acid. The point corresponding to **4b** (R = Ph) is as far from the regression line as that corresponding to **4a** (R = Ph). Either the calculations fail here or there is a significant change in substituent effect in DMSO when Me is replaced by Ph. To ascertain the ability of AM1 to describe NH and OH dissociations in DMSO, we used this method to study the dissociations of substituted anilines[22] (Table VI and Figure 3) and benzoic acids[23] (Table VII and Figure 4). A linear relation between the experimental and theoretical results holds quite well for the NH dissociations of anilines over a large range of pK_a units. The agreement for benzoic acids is less good, with an especially large deviation in the case of 4-nitrobenzoic acid. The relatively good agreement of the experimental and theoretical results for the other benzoic acids and the fact that 4-nitroaniline behaves similarly to the other anilines tend to illustrate an unexpected problem. (Actually, the $\Delta H^{\circ}{}_a$ difference in the gas-

Table VI. Comparison of Experimental pK_as[22] in DMSO and AM1 Enthalpies of Dissociation of Several Substituted Anilines

substituent	pK_a(DMSO)	ΔH_f neutral[a]	ΔH_f anion[a]	enthalpy of dissociation[a,b]
2,4-(NO$_2$)$_2$	15.9	25.6	−21.1	268.2
4-NO$_2$-2,5-Cl$_2$	17.4	15.2	−20.9	278.8
4-NO$_2$	20.9	21.7	−7.1	286.1
4-CN	25.3	50.9	33.3	297.3
3-CN	27.5	52.7	40.9	302.6
2-Cl	27.6	14.0	4.7	305.6
3-Cl	28.5	13.5	5.4	306.7
4-Cl	29.4	13.3	4.6	306.2
H	30.7	20.7	19.4	313.6
3-Me	31.0	13.0	12.1	314.0

[a] In kcal/mol. [b] Using the AM1 heat of formation of H$^+$, 314.92 kcal/mol.
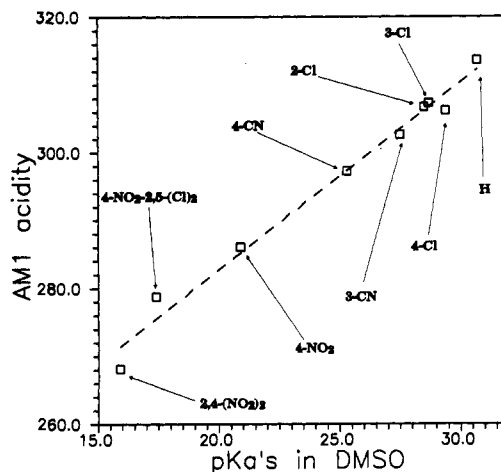
Figure 3. Correlation of the experimental pK_as in DMSO of several substituted anilines[22] with their theoretical AM1 enthalpies of dissociation (in kcal/mol). The best regression line is shown on the dashed line in the figure.

Table VII. Comparison of Experimental pK_as[23] in DMSO and AM1 Enthalpies of Dissociation of Several Substituted Benzoic Acids

substituent	pK_a(DMSO)	ΔH_f acid[a]	ΔH_f anion[a]	enthalpy of dissociation[a,b]
4-NO$_2$	8.9	−62.00	−94.82	282.1
4-Cl	10.1	−74.61	−97.60	291.9
H	11.0	−67.95	−86.92	296.0
3-Me	11.0	−75.38	−94.33	296.2
3-OH	11.1	−111.1	−131.4	294.5
4-EtO	11.5	−112.4	−130.8	296.5
3-NH$_2$	11.6	−69.13	−87.97	296.1
4-OH	11.8	−112.9	−132.4	295.5
4-NH$_2$	12.7	−71.05	−87.82	298.2

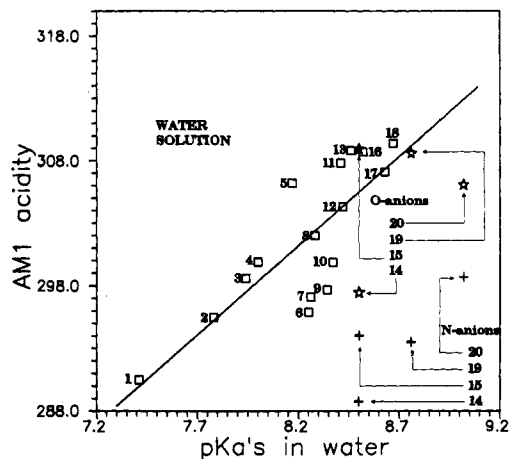[a] In kcal/mol. [b] Using the AM1 heat of formation of H$^+$, 314.92 kcal/mol.

phase between *p*-NO$_2$- and *p*-Cl-benzoic acids is 6.7 kcal/mol,[25] while the theoretical value is 9.8 kcal/mol, in better agreement than implied by the figure.) The problem possibly results from the different entropic contributions to ΔG° for 4-nitrobenzoic acid and 4-nitrobenzoate due to the probable increased rotational barrier for the nitro and carboxyl groups in the anion. We believe the data for the anilines and benzoic acids generally support the ability of the AM1 $\Delta H^{\circ}{}_a$ to discriminate between NH and OH acids. Thus, we conclude that benzohydroxamic acids, although mainly NH acids in DMSO, are more prone to OH dissociation than acetohydroxamic acid. Experimental studies by Lindberg et al.,[13] who found that benzohydroxamic acid dissociates to **4a** (R = Ph) in the crystal, and by Bordwell et al.,[14] who suggested that OH dissociation of benzohydroxamic acid might occur in MeOH solution, support this conclusion.
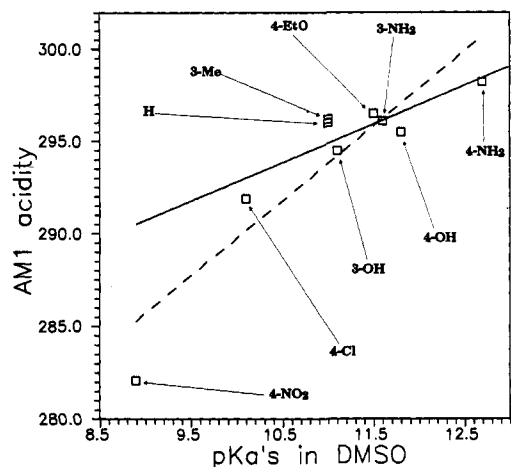
Figure 4. Correlation of the experimental pK_as in DMSO of several substituted benzoic acids[23] with their theoretical AM1 enthalpies of dissociation (in kcal/mol). The best regression line including all the points is shown as the dashed line in the first; the one discarding the point for 4-nitrobenzoic acid is shown as a full line.

Figure 5. Correlation of the experimental pK_as in water of several hydroxamic acids and N-substituted hydroxamic acids[10,24] with their theoretical AM1 enthalpies of dissociation (in kcal/mol). The best regression line obtained excluding the points for the unsubstituted acids is shown in the figure. Numbers refer to Table VIII.

The data for the dissociation of hydroxamic acids in aqueous solution reported by Crumbliss et al.[10] and more recently by Fountain et al.[24] are plotted against the AM1 enthalpies of dissociation in Figure 5 (numerical values given in Table VIII). The data are somewhat more scattered than those for the anilines in DMSO. However, the correlation is similar to that for benzoic acids, which is reasonable since all the species included in the comparison are OH acids.

The points for the **4b** structures of the four nonsubstituted hydroxamic acids deviate significantly from the regression line, while those for the *trans*-**4a** structures do not. This suggests that these acids behave as OH acids in aqueous solution. The change from NH to OH acidity is probably caused by interactions with the protic solvent. A limited study on the effect of solvent was performed to illustrate this point. Supermolecule calculations (AM1) using four water or MeOH molecules to simulate the first solvation shell of **4a** and **4b** for formo-, aceto-, and benzohydroxamic acids were performed. The minimum energy structures of the formohydroxamate/water and benzohydrox-amate/methanol supersystems are depicted in Figure 6. The results of these calculations (Tables IX and X) indicate the importance of two principal effects. First, the *cis*-**4a** structure

of formohydroxamate is now more stable than the *trans*-**4a**, in contrast to the gas-phase results. Second, despite the fact that four water molecules are clearly insufficient to model the full effect of solvation, **4a** becomes noticeably stabilized with respect to **4b** in aqueous solution in comparison with the gas phase. Therefore, we conclude that water strongly influences the structure of hydroxamate anions in aqueous solution. That methanol produces a similar effect suggests that the primary effect of protic solvents is due to hydrogen-bonding between the solute and solvent molecules. Nevertheless, the sizes of both the substituent and the solvent are also important. While the enthalpic differences between the **4a** and **4b** structures of formo- and acetohydroxamate are approximately the same in water and methanol, this is not the case for benzohydroxamate. This observation accords with the different behaviors of aceto- and benzohydroxamic acids in DMSO, as illustrated in Figure 2.

Conclusions

High-level *ab initio* methods were used to assess the structure of formo- and acetohydroxamate anions in the gas phase. Both SCF and MP2 geometry optimizations with extended basis sets including several sets of polarization functions allow us to conclude

Table VIII. Comparison of Experimental pK_as[10,24] in Water and Methanol Solutions and AM1 Enthalpies of Dissociation of Several Hydroxamic Acids and Its Derivatives

N	substituent	pK_a water	pK_a methanol	ΔH_f acid[a]	ΔH_f anion[a] OH	ΔH_f anion[a] NH	enthalpy of dissociation[a,b] OH	enthalpy of dissociation[a,b] NH
1	3,5-(NO₂)₂PhCON(Me)OH	7.41	10.80	3.36	−21.10		290.5	
2	4-Cl-3-NO₂PhCON(Me)OH	7.78		−5.91	−25.37		295.5	
3	O₂NPhCON(Me)OH	7.94	11.58	−6.59	−22.94		298.6	
4	PhCON(Ph)OH	8.00		24.79	9.72		299.9	
5	4-ClPhCON(Me)OH	8.17	12.04	−18.28	−27.02		306.2	
6	MeCON(4-CNPh)OH	8.25		19.22	0.23		295.9	
7	MeCON(3-CNPh)OH	8.26		19.55	1.77		297.1	
8	PhCON(Me)OH	8.28	12.38	−12.85	−25.81		302.0	
9	MeCON(4-MeCOPh)OH	8.34		−49.60	−66.72		297.1	
10	MeCON(4-ClPh)OH	8.37		−19.35	−34.37		299.9	
11	4-Me-3-MeOPhCON(Me)OH	8.41	12.32	−55.89	−63.06		307.8	
12	MeCON(Ph)OH	8.42		−12.81	−23.41		304.3	
13	4-MePhCON(Me)OH	8.46	12.45	−19.36	−25.46		308.8	
14	PhCONHOH	8.50		−16.05	−33.44	−42.17	297.5	288.8
15	4-MePhCONHOH	8.50		−28.50	−34.45	−49.41	309.0	294.0
16	3-MePhCON(Me)OH	8.52	12.30	−19.24	−25.47		308.7	
17	MeCON(Me)OH	8.63		−49.21	−57.08		307.1	
18	4-MeOPhCON(Me)OH	8.67	12.80	−50.22	−55.74		309.4	
19	4-MeOPhCONHOH	8.76		−58.89	−65.16	−80.29	308.7	293.5
20	MeCONHOH	9.02		−55.03	−63.81	−71.29	306.1	298.7

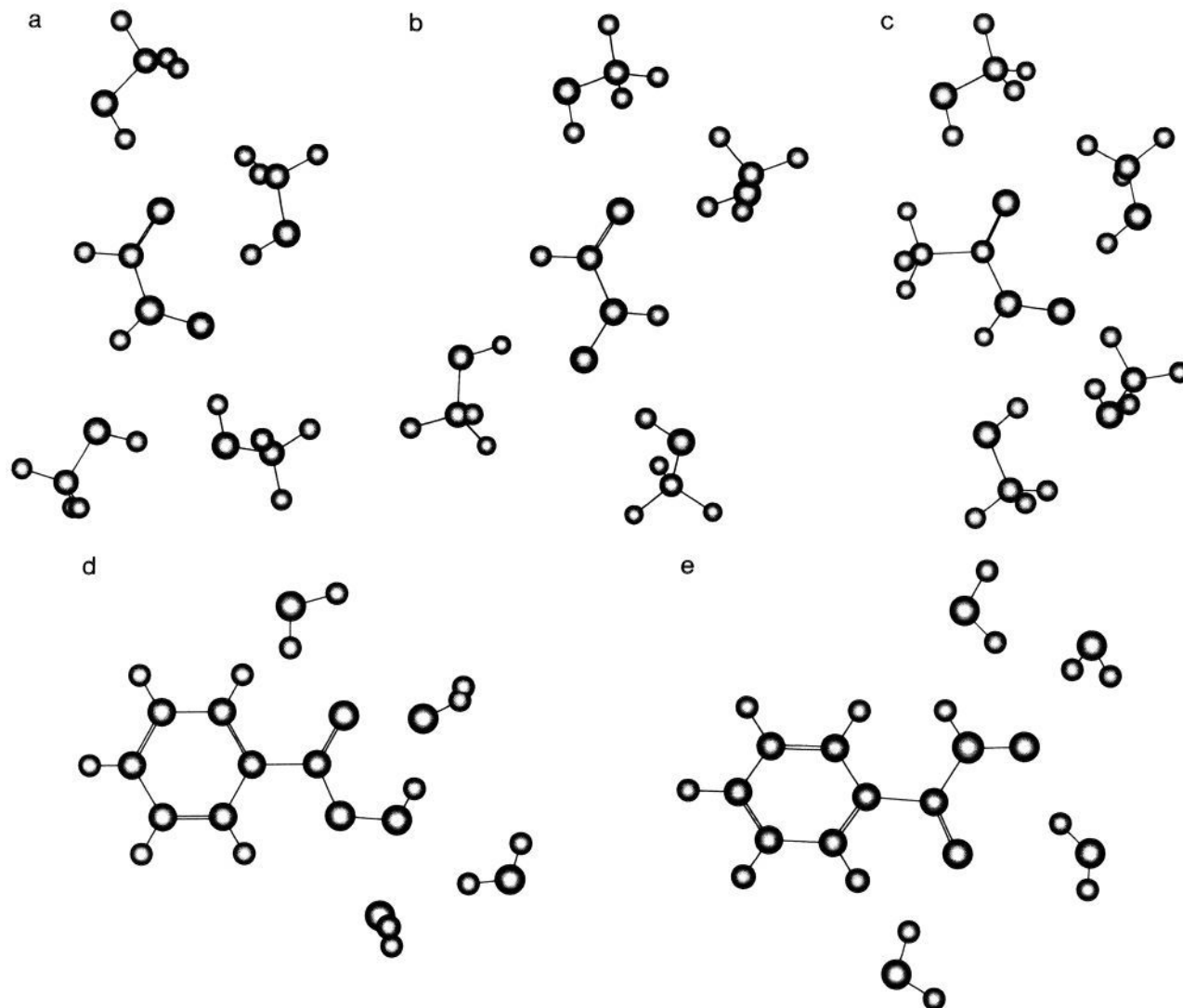[a] In kcal/mol. [b] Using the AM1 heat of formation of H⁺, 314.92 kcal/mol.

Figure 6. AM1 structures of the complexes of formohydroxamate structures **4a** (a) and **4a′** (b) with methanol, acetohydroxamate structure **4a** with methanol (c), and benzohydroxamate structures **4a** (d) and **4b** (e) with water.

Table IX. AM1 Enthalpies of the Different Structures of Formo-, Aceto-, and Benzohydroxamate Anions Complexed with Four H_2O or MeOH Molecules

	R = H	R = Me	R = Ph
Gas phase			
cis-**4a**	−47.9	−52.5	−26.3
trans-**4a**	−57.5	−61.7	−33.4
4b	−66.8	−71.3	−42.2
Water			
cis-**4a**	−337.9	−342.7	−310.9
trans-**4a**	−324.6	−347.4	−315.1
4b	−348.9	−353.7	−323.0
Methanol			
cis-**4a**	−314.0	−320.3	−287.7
trans-**4a**	−318.1	−326.3	−289.4
4b	−328.1	−332.9	−301.0

Table X. Differences in the Stability of *cis*- and *trans*-**4a** with Respect to **4b** in the Gas Phase and in Solution as a Function of the Substituent

	gas phase		water		methanol	
substituent	*cis*	*trans*	*cis*	*trans*	*cis*	*trans*
H	18.9	9.3	11.0	24.3	13.9	10.0
Me	18.8	9.6	11.0	6.3	12.6	6.6
Ph	15.9	8.8	12.1	7.9	13.3	11.6

that both formo- and acetohydroxamic acids behave as NH acids in the gas phase. This conclusion is also supported by semiempirical AM1 calculations. AM1 gives reasonable results when compared with *ab initio* calculations except for structure **4c**, which is not an energy minimum according to MP2 calculations. The dissociations in DMSO, studied by correlating the experimental data with AM1 enthalpies of dissociation, clearly indicate acetohydroxamic acid to be a NH acid. However, the same results indicate that OH dissociation may occur for benzohydroxamic

acids and some of their derivatives in DMSO. In contrast, correlation of theoretical and experimental data suggests that hydroxamic acids undergo OH rather than NH dissociation in aqueous solution, due to a large selective stabilization of **4a** with respect to **4b** by water. Although the evidence is not conclusive, this observation supports the possibility that **4a** and **4b** may both be present at equilibrium conditions in aqueous solution. The present study illustrates the utility of the AM1 semiempirical method for modeling the dissociations of hydroxamic acids, both in the gas phase and in solution.