

A Priori Prediction of Substituent and Solvent Effects in the Basicity of Nitriles

Carles Colominas,^{†,‡} Modesto Orozco,[‡] Francisco J. Luque,[§] José I. Borrell,[†] and Jordi Teixidó^{*,†}

Departament de Química Orgànica, Institut Químic de Sarrià, Universitat Ramon Llull, Via Augusta 390, Barcelona 08017, Spain, Departament de Bioquímica, Facultat de Química, Universitat de Barcelona, Martí i Franquès 1, Barcelona 08028, Spain, and Departament de Farmàcia, Unitat de Físicoquímica, Facultat de Farmàcia, Universitat de Barcelona, Avda. Diagonal s/n, Barcelona 08028, Spain

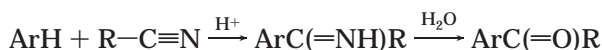
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The relative basicity of a series of nitriles in the gas phase, chloroform, and aqueous solution is studied using ab initio and state of the art SCRF methods. Theoretical results reproduce well the available experimental data for a large series of nitrile derivatives. The origin of basicity differences in solution within the series is analyzed. The impact of the results in the understanding of nitrile chemistry is discussed.

Introduction

Nitriles are frequently used in organic chemistry owing to the variety of synthetic routes leading to the preparation of chemical functional groups such as amides, carboxylic acids, or aldehydes. The chemistry of nitriles has also been exploited in the synthesis of nitrogen-containing heterocycles through the use of inter- or intramolecular cyclizations.¹ One of the fundamental aspects in the reactivity of nitriles is the ability to act as weak bases. Thus, protonation on the nitrogen atom seems to be the determining step in a number of reactions, since it enhances the susceptibility of the carbon atom to be attacked by nucleophilic reagents.² Two well-known examples are the Houben–Hoesch and the Gattermann reactions (acylation reactions where the nitrile is the acylating agent; see Scheme 1), where protonation promotes the formation of the reactive electrophilic species.³

Scheme 1



Another example of the importance of protonation in the chemistry of nitriles is the intramolecular cyclization of α,ω -dinitrile compounds in the presence of hydrogen halides. This reaction is very useful for the synthesis of substituted piridopyrimidines and naftyridines, among other nitrogenated heterocycles,^{4,5} yielding a new sub-

stituted pyridine (Z = C–R) or pyrimidine (Z = N) ring (see Scheme 2). The results obtained for a wide range of 1,5-dinitrile intramolecular cyclizations led us to postulate a reaction mechanism,^{6a} in which the position of the halogen atom in the final product is determined by the relative basicities of the nitrile groups. Accordingly, protonation occurs in the most basic nitrile group of compound I (Scheme 2), and the corresponding imidoyl halide acts as nucleophile against the other nitrile.

Analysis of the available experimental data^{1,6,7} in light of the proposed mechanism provided valuable information about the relative basicity of nitriles and, so, allowed the derivation of a few empirical rules.⁵ However, both the uncertainties arising from its *indirect* origin and the limited number of those empirical rules made their use difficult as predictive tools in nitrile chemistry. Owing to the relevance of protonation in the reactivity of nitriles, several studies were undertaken to gain insight into their basicity. Most of these studies were focused on the basicity in the gas phase,^{8–11} and much less attention was paid to the protonation of such weak bases in condensed phases.^{12–14} Since the solvent is known to greatly influence the acid/base properties,¹⁵ the scarcity of experi-

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* To whom correspondence should be addressed.

[†] Institut Químic de Sarrià, Universitat Ramon Llull.

[‡] Departament de Bioquímica, Universitat de Barcelona.

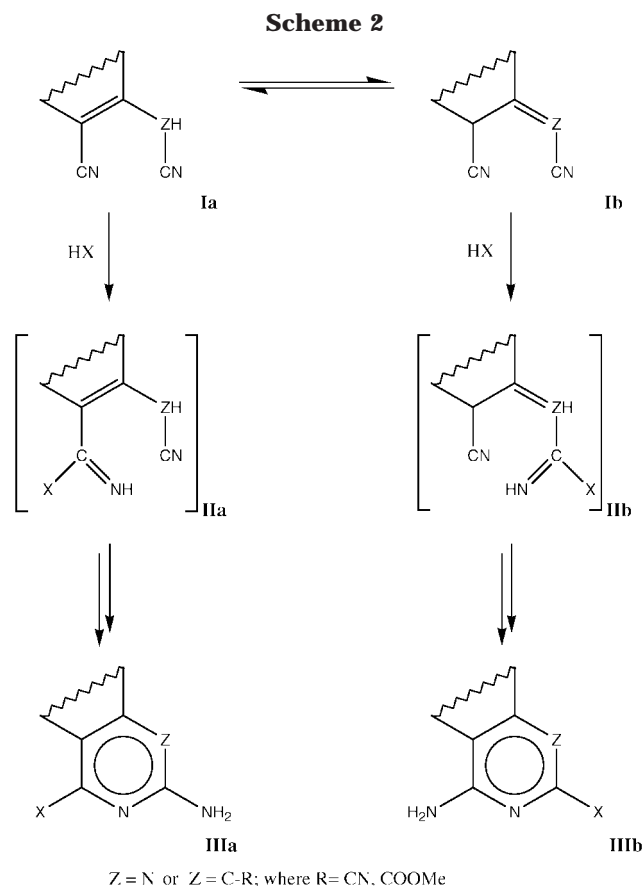
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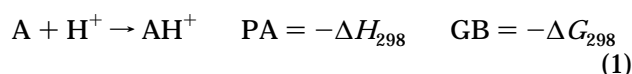


mental data in solution limits our understanding of the chemistry of nitriles.

In this paper, we present a theoretical study on the basicity of a series of nitrile compounds covering a wide range of prototypical substituents in the gas phase and in two different solvents, water and chloroform. The results were determined from *ab initio* quantum mechanical calculations in the gas phase, which were combined with self-consistent reaction field (SCRF) calculations to estimate the basicity in solution. Comparison of the theoretical results with the few available experimental values allows us to examine the reliability of computations to predict the susceptibility to protonation in solution. The influence of both the substituent and the solvent in modulating the basicity of nitriles is discussed.

Methods

The basicity in the gas phase of a given base, A, is described by its proton affinity (PA) and its gas phase basicity (GB), which are defined as the negative of the enthalpy and of the free energy for the protonation reaction, respectively (eq 1).



The PA can be determined from quantum mechanical calculations according to eq 2, where the symbol Δ denotes the difference between the values of the electronic energy at 0 K (E^{elec}) and the zero-point energy

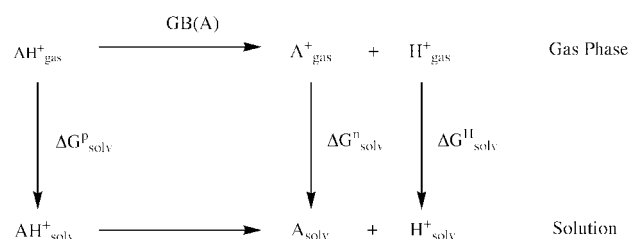


Figure 1. Schematic representation of the thermodynamic cycle used to compute free energy differences in solution (ΔG^{sol}).

(ZPE) of AH^+ and A. Indeed, $\Delta E_{298}^{\text{vib}}$, $\Delta E_{298}^{\text{rot}}$, and $\Delta E_{298}^{\text{trans}}$ are the changes in vibrational, rotational, and translational energy between 0 and 298 K, respectively, and the last term refers to the variation in the expansion work.

$$\begin{aligned} PA = & \Delta E^{\text{elec}}(A - AH^+) + \Delta ZPE(A - AH^+) + \\ & \Delta E_{298}^{\text{vib}}(A - AH^+) + \Delta E_{298}^{\text{rot}}(A - AH^+) + \\ & \Delta E_{298}^{\text{trans}}(A + H^+ - AH^+) + \Delta(PV) = \\ & \Delta E^{\text{elec}}(A - AH^+) + \Delta ZPE(A - AH^+) + \\ & \Delta E_{298}^{\text{vib}}(A - AH^+) + \frac{5}{2}RT \quad (2) \end{aligned}$$

The relative proton affinity (ΔPA) between two compounds, A and B, is calculated as follows:

$$\Delta PA = PA(A) - PA(B) \quad (3)$$

Although ΔPA is useful for comparative studies in the gas phase, the GB is necessary to determine the basicity in solution. ΔGB between compounds A and B can be derived from ΔPA using the following relation:

$$\begin{aligned} \Delta GB = GB(A) - GB(B) = \\ \Delta PA + T\Delta S(A - AH^+) - T\Delta S(B - BH^+) \quad (4) \end{aligned}$$

The difference in pK_a (ΔpK_a) between two species, AH^+ and BH^+ , can be estimated from the values of ΔGB and the free energies of solvation according to eq 5

$$\Delta pK_a(AH^+ - BH^+) = \frac{1}{2.303RT}(\Delta GB + \Delta\Delta G_{\text{solv}}^{\text{n-p}}) \quad (5)$$

where $\Delta\Delta G_{\text{solv}}^{\text{n-p}}$ denotes the difference in the free energies of solvation for the neutral ($\Delta G_{\text{solv}}^{\text{n}}$) and protonated ($\Delta G_{\text{solv}}^{\text{p}}$) forms (see Figure 1 and eq 6).¹⁶

$$\begin{aligned} \Delta\Delta G_{\text{solv}}^{\text{n-p}} = & (\Delta G_{\text{solv}}^{\text{n}}(A) - \Delta G_{\text{solv}}^{\text{p}}(AH^+)) - \\ & (\Delta G_{\text{solv}}^{\text{n}}(B) - \Delta G_{\text{solv}}^{\text{p}}(BH^+)) \quad (6) \end{aligned}$$

In the following, ΔG_{solv} will be denoted as ΔG_{hyd} for aqueous solution and ΔG_{chl} for chloroform solution.

The calculated free energies of solvation in water and in chloroform of neutral species were compared with the available experimental values in order to examine the estimated ΔpK_a . Indeed, the reliability of the free energies of solvation for neutral compounds was also examined from the comparison of calculated and experi-

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(16) To determine the influence of solvent in zero-point, thermal, and entropy corrections, Onsager's calculations were performed for the protonation reaction of CH_3CN . The variations were very small: 0.6 kcal/mol for the thermal and zero-point energy and 0.8 eu for the entropy. It is clear that such variations can be neglected in a qualitative study like that reported here.

mental values of water/chloroform partition coefficients (log P) (see eq 7).

$$\log P (\text{water/chloroform}) = -\frac{1}{2.303RT}(\Delta G_{\text{hyd}}^{\text{n}} - \Delta G_{\text{chl}}^{\text{n}}) \quad (7)$$

To rationalize the influence of substituents on the basicity of nitriles, the differences in ΔPA for the series of compounds were analyzed from the values of the molecular electrostatic potential (MEP; eq 8) and the generalized molecular interaction potential with polarization¹⁷ (GMIPp; eq 9)

$$V(r_1) = \sum_A \frac{Z_A}{|r_1 - R_A|} - \sum_{\mu} \sum_{\nu} P_{\mu\nu} \left\langle \phi_{\mu} \left| \frac{1}{|r_1 - r|} \right| \phi_{\nu} \right\rangle \quad (8)$$

where A stands for the nuclei, Z_A is the atomic number, $P_{\mu\nu}$ is the element $\mu\nu$ of the first-order density matrix, and $\{\phi\}$ denotes the basis set of atomic orbitals.

$$\text{GMIPp}(r_1) = V(r_1) + \sum_i \sum_j \frac{1}{\epsilon_i - \epsilon_j} \left\{ \sum_{\mu} \sum_{\nu} c_{\mu i} c_{\nu j} \left\langle \phi_{\mu} \left| \frac{1}{|r_1 - r|} \right| \phi_{\nu} \right\rangle \right\}^2 \quad (9)$$

where ϵ stands for the energy of occupied (i) and virtual (j) molecular orbitals. Since the GMIPp explicitly includes the polarization exerted by the positive unit charge on the molecular charge distribution, it provides complementary information for the description given by the MEP. To capture the "covalent" nature of the protonation, the van der Waals contribution to the GMIPp was omitted. Accordingly, the difference between the GMIPp as computed from eq 9 and the SCF interaction energy between the molecule and the unit positive charge is mainly due to charge transfer, which is expected to be important in protonation processes.

Computational Details

Gas-Phase Calculations. Geometries were fully optimized at the restricted Hartree–Fock level with the 6-31G(d) basis set¹⁸ using the GAMESS program.¹⁹ In all cases, the nature of minimum-energy structures of the optimized geometries was verified by frequency calculations. The HF/6-31G(d) frequencies were scaled by 0.8929²⁰ to determine the zero-point energies and the thermal and entropic corrections. Single-point energy calculations were performed at the MP2/6-311++G(d,p) level^{21,22} using the HF/6-31G(d)-optimized geometries. The selection of this level of theory adheres to previous studies and showed very good results with experimental PA.²³

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Calculations in Solution. The free energy of solvation in water and chloroform can be obtained with reasonable accuracy using SCRF methods.²⁴ Three versions of the polarizable continuum model (PCM) developed by the Pisa group²⁵ were used in this study: the MST-optimized version developed by Luque and Orozco,²⁶ the SCI-PCM method,²⁷ and a recent version of the PCM model parametrized for water by Cossi, Barone, and Tomasi (denoted as UAHF, united atoms for Hartree–Fock).²⁸ MST calculations were carried out with a modified version of Monstergauss,²⁹ SCI-PCM computations with the standard GAUSSIAN-94 quantum mechanical package,³⁰ and UAHF calculations were carried out with a modified version of Gaussian-94.³¹ The gas-phase HF/6-31G(d)-optimized geometries were used in HF/6-31G(d) SCRF calculations.³²

Calculations were performed on IBM and SGI workstations in our laboratories, as well as in the IBM-SP2 computer of the Centre de Supercomputació de Catalunya (CESCA).

Results and Discussion

Protonation in the Gas Phase. A set of 14 nitrile derivatives was selected to examine the influence of substituents on the gas-phase protonation. The compounds include a variety of substituents, which lead to a range of experimental proton affinities between 171 and 205 kcal/mol. The values are given in Table 1, which also shows the results obtained from theoretical calculations.

The theoretical PAs agree well with the experimental data, as noted in the statistical results given in Table 1. The HF values slightly overestimate the relative PAs, while the MP2 results slightly underestimate them. It is worth noting that electron correlation does not have a dramatic impact in the relative PAs, since both MP2 and

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(32) To determine the influence of geometry relaxation in solution, we recomputed the ΔE of protonation of CH_3CN in water using geometries optimized in solution using the SCI-PCM and UAHF models (HF/6-31G(d) level). The differences between the results with and without geometry optimization in solution were around 0.9 kcal/mol (more negative if geometry was reoptimized in solution). Negligible differences were found between the results obtained after geometry optimization with the SCI-PCM and UAHF algorithms.

Table 1. Differences^a in Gas-Phase Proton Affinities (Δ PA) for Nitriles (in kcal mol⁻¹)

no.	nitrile	method ^b			expt	ref
		HF/6-31G(d)	HF/6-311++G(d,p)	MP2/6-311++G(d,p)		
1	CH ₃ CN	(188.8) 0.0	(189.9) 0.0	(184.8) 0.0	(188.4) 0.0	8
2	CH ₃ CH ₂ CN	3.2	3.1	2.7	4.2	8
3	CH ₂ =CHCN	3.3	2.3	0.9	1.3	8
4	HC≡CCN	-7.7	-8.7	-6.8	-8.3	33
5	(CH ₃) ₂ CHCN	5.7	5.5	4.7	5.9	8
6	(CH ₃) ₃ CCN	7.9	7.6	6.5	7.1	8
7	H ₂ NCN	6.7	5.5	6.4	6.1	10
8	(CH ₃)HNCN	12.4	11.6	11.6	<i>c</i>	
9	(CH ₃) ₂ NCN	17.5	17.1	18.2	16.9	34
10	NCCH ₂ CN	-14.5	-14.9	-13.7	-12.8	8
11	ClCH ₂ CN	-8.9	-8.5	-7.6	-8.9	8
12	PhCN	9.3	8.0	7.1	7.5	8
13	PhCH ₂ CN	7.1	6.2	5.4	6.5	11
14	HCN	-16.3	-16.6	-15.9	-17.0	8
	corr coeff ^d	0.996	0.997	0.994		
	slope ^d	1.03	1.02	0.97		
	intercept ^d	0.37	-0.18	-0.03		
	rms error ^e	1.1	0.8	1.0		

^a Relative to CH₃CN, for which the absolute values are shown in parentheses. ^b Thermal corrections determined from HF/6-31G(d) frequency calculations. The frequencies were scaled by the standard value of 0.8929. ^c No available data. ^d Linear regression equation $\Delta PA_{\text{calc}} = a\Delta PA_{\text{exp}} + b$. ^e Root-mean-square error (in kcal/mol) between experimental and calculated values.

HF results deviate around 1 kcal·mol⁻¹ from the experimental data. The agreement between theoretical and experimental PAs gives confidence in these results to derive further thermodynamic quantities in this study.

Nitriles with PA's lower than that of acetonitrile (HCN, NCCH₂CN, and HCCCN) correspond to compounds with a well-known acid character. In nitriles with the cyano group bound to a saturated alkyl chain, methylation at the α -carbon increases the PA, which reflects the electron-donating nature of the methyl group. Such an increase is even larger when an amino group is attached to the cyano moiety. Within the cyanamide series (RNH-CN), alkylation at the nitrogen also favors the protonation. On the contrary, electron-withdrawing substituents, like chlorine in ClCH₂CN, reduce the PA. The presence of π -electrons increases the PA, as stated in the values of CH₂=CHCN and especially PhCN. In summary, the differences in PA for the set of compounds can be qualitatively understood from simple reasoning based on the chemical nature of substituents.

To gain a more quantitative insight into the basicity of nitriles, the relationship between the experimental PA and molecular descriptors of reactivity, particularly the depth of the MEP minimum on the nitrile nitrogen, was examined. The results (see Table 2) show that the MEP minima explain around 83% (r^2) of the variance in experimental PAs. However, since the MEP only accounts for a fraction (~30%) of the total energy, other components might contribute significantly to the proton affinity. The results in Table 2 show that the polarization and the electrostatic terms are similar in magnitude. As expected from the large magnitude of the charge transfer occurring upon protonation, GMIPp values still underestimate experimental (or SCF) values. Nevertheless, the addition of polarization effects to the MEP not only brings the theoretical estimate nearer to the experimental values but improves drastically the ability to predict relative PAs. Thus, the GMIPp explains around 94% of the variance of experimental PAs (compared to 83% when the MEP was used). Moreover, details of the PAs along the series are explained. For instance, the greater basicity of PhCN relative to that of CH₃CN or the large difference in basicity between HCN and HC≡

Table 2. MEP Minima, Polarization Energy,^a and GMIPp^b Values for the Series of Nitriles (in kcal mol⁻¹) Determined at the HF/6-31G(d) Level

no.	nitrile	MEP	POL(PT)	POL(SCF)	GMIPp ^b	PA exp
1	CH ₃ CN	-57.8	-51.4	-52.8	-109.2	188.4
2	CH ₃ CH ₂ CN	-58.9	-52.0	-54.2	-110.9	192.6
3	CH ₂ =CHCN	-56.5	-52.9	-55.5	-109.3	189.7
4	HC≡CCN	-47.0	-53.6	-54.9	-100.6	180.1
5	(CH ₃) ₂ CHCN	-59.8	-52.6	-55.3	-112.4	194.3
6	(CH ₃) ₃ CCN	-60.5	-53.2	-56.3	-113.7	195.5
7	H ₂ NCN	-63.3	-53.1	-53.8	-116.4	194.5
8	(CH ₃)HNCN	-63.1	-53.6	-55.4	-116.7	
9	(CH ₃) ₂ NCN	-64.5	-54.9	-57.5	-119.4	204.6
10	NCCH ₂ CN	-44.4	-48.5	-51.1	-93.0	175.6
11	ClCH ₂ CN	-48.5	-49.6	-52.0	-98.1	179.5
12	PhCN	-57.7	-55.3	-59.3	-113.0	195.9
13	PhCH ₂ CN	-58.6	-53.1	-55.9	-111.7	194.9
14	HCN	-49.7	-46.8	-47.3	-96.5	171.4
	corr coeff ^c	0.91			0.97	

^a Determined from perturbation (PT) and SCF calculations. ^b See eq 9. ^c Correlation coefficient with respect to experimental PAs.

CCN are not correctly reproduced without the polarization contribution. Therefore, even for predicting relative PAs, the polarization effects cannot be ignored, especially in molecules with large polarizable, neutral groups. As a final remark, inspection of Table 2 demonstrates that the perturbative strategy used to compute the GMIPp (eq 9) is able to reproduce very accurately SCF estimates of polarization energy.

Solvation of Neutral Nitriles. The relative free energies of solvation in water and in chloroform for neutral nitriles are given in Table 3, which also shows the scarce experimental data available for comparison. It is worth noting that SCI-PCM results only include the electrostatic component of the free energy of solvation, while MST and UAHF values also incorporate the non-electrostatic terms. This fact probably explains the larger magnitude of SCI-PCM values relative to both MST and UAHF results in water, since the nonelectrostatic term makes a positive contribution to the free energy of hydration. However, irrespective of numerical uncertainties, all the methods behave similarly in regard to the relative variation in the free energies of solvation.

According to the results in Table 3, the best solvated molecules in water are NH₂CN, (CH₃)HNCN, and

Table 3. Differences^a in Free Energies of Solvation in Water ($\Delta G_{\text{hyd}}^{\text{n}}$) and in Chloroform ($\Delta G_{\text{chl}}^{\text{n}}$) for Neutral Nitriles (in kcal mol⁻¹)

no.	nitrile	rel $\Delta G_{\text{hyd}}^{\text{n}}$, method ^b				rel $\Delta G_{\text{chl}}^{\text{n}}$, method ^b		
		MST	SCI-PCM	UAHF	expt	MST	SCI-PCM	expt ^f
1	CH ₃ CN	(-4.4) 0.0	(-5.6) 0.0	(-3.7) 0.0	(-3.9) 0.0 ^c	(-5.6) 0.0	(-4.0) 0.0	(-4.5) 0.0
2	CH ₃ CH ₂ CN	-0.1	0.2	-0.7	0.0 ^c	-0.5	0.1	
3	CH ₂ =CHCN	-0.2	0.2	0.6		-1.0	0.2	
4	HC≡CCN	0.8	1.0	2.4		-1.2	0.8	
5	(CH ₃) ₂ CHCN	0.1	0.5	-0.6		-0.5	0.4	
6	(CH ₃) ₃ CCN	0.4	0.7	-0.2		-0.1	0.5	
7	H ₂ NCN	-5.2	-4.4	-7.4		-2.0	-3.1	
8	(CH ₃)HNCN	-3.3	-2.5	-6.3		-1.8	-1.7	
9	(CH ₃) ₂ NCN	-1.0	-0.8	-3.2		-1.6	-0.6	
10	NCCH ₂ CN	-2.8	-3.9	-4.4		-2.9	-2.6	
11	ClCH ₂ CN	0.5	-0.3	-3.0		-0.2	-0.1	
12	PhCN	-1.7	0.0	-1.3	-0.2 ^d	-3.5	0.0	-3.3
13	PhCH ₂ CN	-2.1	-0.9	-3.3		-4.3	-0.5	
14	HCN	1.0	-0.2	0.5	0.8 ^e	0.8	0.0	2.3

^a Relative to CH₃CN, for which absolute values are shown in parentheses. ^b Computations performed at the HF/6-31G(d) level in all cases. ^c Reference 35. ^d Reference 36. ^e Reference 37. ^f Derived from experimental $\Delta G_{\text{chl}}^{\text{n}}$ and log *P* (water/chloroform) in Table 4.

NCCH₂CN, which can be realized from their large dipole moment and small size, whereas the alkyl derivatives and HC≡CCN are the less well-hydrated compounds. As expected, the hydration of cyanamides decreases upon methylation at the nitrogen. Finally, replacement of the methyl group in acetonitrile by a phenyl ring favors the solvation in water according to both MST and UAHF results. Even though such a theoretical result might appear counterintuitive, it agrees with the available experimental data (Table 3). The results suggest that the phenyl ring leads to a certain increase in the strength of solute-solvent electrostatic interactions, which accounts for the better hydration of phenyl derivatives.

Since the nonelectrostatic term is expected to be extremely relevant for solvation in chloroform, the accuracy of SCI-PCM values may be limited. For instance, the SCI-PCM method does not predict the large solvation free energy of aromatic nitriles or the unfavorable solvation of HCN relative to that of acetonitrile. These trends are reproduced when the nonelectrostatic component is considered, as noted in the MST results. According to the MST results, solvation in chloroform is favored for aromatic and amine derivatives (see Table 3).

Further insight into the solvation properties of nitriles can be gained from the water/chloroform partition coefficients shown in Table 4. As expected, the SCI-PCM method does not lead to reliable values. This can be explained by the neglect of the nonelectrostatic contribution to the free energy of solvation and by the use of a common cavity definition for the two solvents. The MST results agree better with the experimental values. Nevertheless, even the accuracy of this parametrized method is limited in cases where the partition coefficient is small. According to the MST results, primary or secondary amines increase the population in the aqueous phase, while substituents with π -electron distributions enlarge the relative population in the organic phase. As noted above, it is worth noting that the enhanced hydrophobic-

Table 4. Log *P* (Water/Chloroform) Values

no.	nitrile	method ^a		
		MST	SCI-PCM	expt ^b
1	CH ₃ CN	-0.9	1.1	-0.4
2	CH ₃ CH ₂ CN	-1.1	1.1	
3	CH ₂ =CHCN	-1.5	1.1	
4	HC≡CCN	-2.3	1.0	
5	(CH ₃) ₂ CHCN	-1.3	1.0	
6	(CH ₃) ₃ CCN	-1.2	1.0	
7	H ₂ NCN	1.5	2.1	
8	(CH ₃)HNCN	0.2	1.7	
9	(CH ₃) ₂ NCN	-1.3	1.3	
10	NCCH ₂ CN	-0.9	2.1	0.5
11	ClCH ₂ CN	-1.3	1.3	
12	PhCN	-2.2	1.1	-2.7
13	PhCH ₂ CN	-2.5	1.4	-2.2
14	HCN	-1.0	1.3	0.7

^a Calculated from absolute free energies of solvation in water and chloroform in Table 3 (see text for details). ^b Reference 38.

ity of compounds with aromatic substituents does not stem from a lower stability in water but from the preferential solvation in chloroform. This finding makes evident the relative nature of the hydrophilicity/hydrophobicity concept, since very hydrophobic molecules can still have favorable solvation in water.

Solvation of Protonated Nitriles. The free energies of solvation in water and chloroform of protonated compounds are shown in Table 5. The three PCM methods provide similar results in water, which is remarkable considering the large magnitude of the free energy of solvation for protonated species and the fact that protonated CN groups were not typically considered in the parametrization of the methods. The largest discrepancies are found for the biggest molecules (*tert*-butyl and phenyl derivatives), for which the cavity definition used for charged species in MST calculations is probably not accurate enough. Alkylation makes the hydration of cations less favored, while polar (-NH₂; -CN) groups enlarge the solvent-induced stabilization. In contrast to the results obtained for neutral compounds, the hydration of phenyl derivatives is less favored than solvation of the protonated acetonitrile, reflecting that the relative solvation of cations is dominated by the size of the ion.

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Table 5. Differences^a in Free Energies of Solvation in Water ($\Delta G_{\text{hyd}}^{\text{p}}$) and in Chloroform ($\Delta G_{\text{chl}}^{\text{p}}$) for Protonated Nitriles (in kcal mol⁻¹)

no.	protonated nitrile	rel $\Delta G_{\text{hyd}}^{\text{p}}$, method ^b			rel $\Delta G_{\text{chl}}^{\text{p}}$, method ^b	
		MST	SCI-PCM	UAHF	MST	SCI-PCM
1	CH ₃ CNH ⁺	(-70.3) 0.0	(-67.3) 0.0	(-64.5) 0.0	(-46.4) 0.0	(-53.3) 0.0
2	CH ₃ CH ₂ CNH ⁺	4.7	3.2	1.3	1.9	2.8
3	CH ₂ =CHCNH ⁺	4.9	2.4	3.4	1.5	1.5
4	HC≡CCNH ⁺	2.5	1.5	2.4	0.0	1.4
5	(CH ₃) ₂ CHCNH ⁺	8.6	6.2	4.1	3.9	5.3
6	(CH ₃) ₃ CCNH ⁺	12.1	8.5	6.4	5.8	7.2
7	H ₂ NCNH ⁺	-8.4	-4.0	-8.3	-2.6	-3.0
8	(CH ₃)HNCNH ⁺	1.5	3.0	-2.4	1.1	2.6
9	(CH ₃) ₂ NCNH ⁺	7.8	8.0	5.0	4.0	6.5
10	NCCH ₂ CNH ⁺	-15.1	-10.9	-12.0	-5.0	-7.4
11	ClCH ₂ CNH ⁺	-4.9	-3.1	-5.7	-0.1	-1.8
12	PhCNH ⁺	14.3	8.0	7.9	3.9	7.1
13	PhCH ₂ CNH ⁺	14.1	5.6	2.2	2.2	5.2
14	HCNH ⁺	-10.4	-10.5	-8.2	-4.8	-8.4

^a Relative to CH₃CNH⁺, for which absolute values are shown in parentheses. ^b Computations performed at the HF/6-31G(d) level in all cases.

Table 6. Differences^a in pK_a (ΔpK_a) in Aqueous Solution Calculated from the Relative Gas-Phase Basicities (ΔGB) and the Differences in $\Delta\Delta G_{\text{hyd}}^{\text{n-p}}$ for Nitriles

no.	nitrile	ΔGB^b	rel $\Delta\Delta G_{\text{hyd}}^{\text{n-p}}$, method			$\Delta pK_a,^c$ method			expt
			MST	SCI-PCM	UAHF	MST	SCI-PCM	UAHF	
1	CH ₃ CN	0.0	(65.9) 0.0	(61.8) 0.0	(60.8) 0.0	0.0	0.0	0.0	0.0 ^d
2	CH ₃ CH ₂ CN	2.8	-4.8	-3.1	-2.0	-1.5	-0.2	0.6	-1.7 ^e
3	CH ₂ =CHCN	0.9	-5.1	-2.2	-2.8	-3.0	-0.9	-1.4	
4	HC≡CCN	-6.7	-1.7	-0.6	0.0	-6.2	-5.4	-4.9	
5	(CH ₃) ₂ CHCN	4.8	-8.5	-5.7	-4.7	-2.7	-0.6	0.1	
6	(CH ₃) ₃ CCN	6.7	-11.7	-7.9	-6.6	-3.7	-0.8	0.1	
7	H ₂ NCN	7.0	3.2	-0.4	0.9	7.5	4.8	5.8	
8	(CH ₃)HNCN	13.3	-4.7	-5.5	-3.9	6.3	5.7	6.9	
9	(CH ₃) ₂ NCN	18.8	-8.8	-8.8	-8.2	7.3	7.3	7.8	
10	NCCH ₂ CN	-13.6	12.3	7.0	7.6	-1.0	-4.9	-4.4	
11	ClCH ₂ CN	-7.6	5.5	2.8	2.8	-1.6	-3.5	-3.5	-2.7 ^d
12	PhCN	7.3	-16.0	-8.0	-9.2	-6.4	-0.5	-1.4	-0.4 ^d
13	PhCH ₂ CN	4.7	-16.4	-6.5	-5.5	-8.6	-1.3	-0.6	
14	HCN	-15.9	11.4	10.4	8.7	-3.3	-4.1	-5.3	

^a Relative to CH₃CN, for which absolute values are shown in parentheses. ^b At the MP2/6-311++G(d,p) level. ^c $\Delta pK_a = (\Delta\text{GB} + \Delta\Delta G_{\text{hyd}}^{\text{n-p}})/1.363$. ^d Reference 13. ^e Derived from data in ref 13 and Hammett H_0 values in ref 39.

All the ions are more soluble in water than in chloroform, owing to the larger strength of electrostatic interactions in aqueous solution. The free energy of solvation in chloroform depends on the nature of the substituents, following the trends found in water, and indicates that electrostatics are the leading term for the solvation of ions even in chloroform. Thus, the introduction of bulky or even aromatic substituents makes less favored the solvation of ions, since the gain in nonelectrostatic interactions cannot compensate for the loss of electrostatic interactions as the size of the solute increases. These results strongly warn against the use of "transferable" parameters to represent the intrinsic solvation properties of substituents in molecules with very different "cores".

Protonation of Nitriles in Solution. Combination of the ab initio gas-phase results with the solvation free energies of neutral and protonated species allows the calculation of the relative pK_a in water and in chloroform (Tables 6 and 7). The results in Table 6 suggest that the PCM methods perform reasonably well in predicting the ΔpK_a of nitriles. The largest discrepancy occurs in the MST value for the phenyl derivatives, which is too negative, whereas the UAHF and SCI-PCM results agree with the scarce experimental data. The poor performance of MST at this point probably arises from the oversimplified method of cavity definition for large cations.

Table 7. Differences^a in pK_a (ΔpK_a) in Chloroform Solution Calculated from the Relative Gas-Phase Basicities (ΔGB) and the Differences in $\Delta\Delta G_{\text{chl}}^{\text{n-p}}$ for Nitriles

no.	nitrile	ΔGB^b	rel $\Delta\Delta G_{\text{chl}}^{\text{n-p}}$, method		$\Delta pK_a,^c$ method	
			MST	SCI-PCM	MST	SCI-PCM
1	CH ₃ CN	0.0	(40.8) 0.0	(49.2) 0.0	0.0	0.0
2	CH ₃ CH ₂ CN	2.8	-2.3	-2.7	0.3	0.1
3	CH ₂ =CHCN	0.9	-2.6	-1.4	-1.2	-0.3
4	HC≡CCN	-6.7	-1.2	-0.6	-5.8	-5.4
5	(CH ₃) ₂ CHCN	4.8	-4.4	-4.9	0.3	-0.1
6	(CH ₃) ₃ CCN	6.7	-5.9	-6.7	0.6	0.0
7	H ₂ NCN	7.0	0.5	0.0	5.5	5.1
8	(CH ₃)HNCN	13.3	-2.9	-4.3	7.6	6.6
9	(CH ₃) ₂ NCN	18.8	-5.5	-7.1	9.7	8.5
10	NCCH ₂ CN	-13.6	2.1	4.8	-8.5	-6.5
11	ClCH ₂ CN	-7.6	-0.1	1.7	-5.6	-4.3
12	PhCN	7.3	-7.4	-7.1	-0.1	0.2
13	PhCH ₂ CN	4.7	-6.6	-5.8	-1.4	-0.8
14	HCN	-15.9	5.6	8.4	-7.6	-5.6

^a Relative to CH₃CN, for which absolute values are shown in parentheses. ^b At the MP2/6-311++G(d,p) level. ^c $\Delta pK_a = (\Delta\text{GB} + \Delta\Delta G_{\text{chl}}^{\text{n-p}})/1.363$.

Despite the numerical uncertainties, the results show that the pK_a of nitriles in water stems from the delicate balance between the intrinsic gas-phase acidity and the relative solvation of neutral and cationic forms. Thus, CH₃CN(H⁺) is less acidic than HC≡CCN(H⁺) and HCN-

(H⁺) due mainly to the larger gas-phase basicity of its neutral form. When the methyl group of CH₃CN is replaced by bigger alkyl or phenyl groups, the protonated form is more stable in the gas phase due mainly to polarization effects (see Table 2), but this effect is reversed in solution owing to the relatively worse solvation of the protonated species. In fact, this finding is supported by the experimental values in the gas phase and in water for the phenyl derivatives. In the case of amine derivatives, the corresponding nitriles protonate more easily than CH₃CN in the gas phase, this effect being not counterbalanced upon solvation, leading to a net increase in the pK_a values of these compounds with regard to acetonitrile. In summary, the results indicate that substitution of the methyl group of CH₃CN by unsaturated hydrocarbons, chlorine, or phenyl groups leads to smaller pK_a's for the corresponding protonated species in water, while larger pK_a's are obtained upon replacement by an amino group. It is noteworthy that the experimental study of chemical mechanisms of dinitrile cyclizations in polar solutions supports the larger basicity of *N*-cyano compounds⁶. This is noted by the fact that the main product of the cyclization reaction (for these compounds) bears the halogen atom (X in Scheme 2) attached to the carbon corresponding to the *N*-cyano group. Note that the empirical suggestion⁶ that cyano groups bound to sp² carbons are more basic than those bound to sp³ carbons is not supported by our calculations in water, in good agreement with experimental pK_a measures of acetonitrile and benzonitrile.¹³

The results in Table 7 show that chloroform plays a modest, but still relevant, role in determining the acidity of nitriles. In general, the relative basicity in the gas phase is largely maintained in chloroform. However, in some cases, the solvent influence on the pK_a is far from being negligible, as noted in the nitriles with alkyl substituents and in the phenyl derivatives. This behavior can be realized from the fact that the relative solvation between neutral and protonated species in chloroform is not large enough to compensate for the gas-phase intrinsic acidity. These results suggest that structure–activity relationships made using descriptors of gas-phase reactivity can be used with reasonable confidence to represent the protonation characteristics of nitrile compounds in apolar solvents.

Comparison of the results in Tables 6 and 7 allowed us to analyze the relevance of the solvent nature in cyano group protonation and, accordingly, in all the cyano chemistry. For instance, both Tables 6 and 7 show that cyano groups bound to heteroatoms are more basic than any other cyano group. However, the poorer basicity of cyano groups bound to unsaturated carbons compared to those bound to sp³ carbons, which was found in water (see Table 6), is not so clear in apolar solvents such as chloroform (see Table 7). These results warn against the use of empirical rules derived from the study of reaction mechanism in one solvent to all possible solvents.

Conclusions

The results reported in this study show that the a priori prediction of the acid/base properties of compounds is difficult, even when high-level computational methods

are used. This is due to the large magnitude of the free-energy terms involved in the process of protonation/deprotonation, particularly in the description of free energy of solvation of protonated species.

The analysis of the relative acid/base properties in the gas phase shows that an accurate description of the influence played by substituents requires in some cases the explicit consideration of polarization effects. At this point, the use of the GMIPp as a molecular descriptor can be very useful as a predictive tool in areas such as chemical reactivity or quantitative structure–activity relationships (QSAR).

The results also show that the acid/base properties are determined by the subtle balance between two contributions: (i) the intrinsic acidity/basicity in the gas phase and (ii) the differential solvent-induced stabilization of the corresponding neutral and protonated species. The weight of the two contributions in determining the pK_a in solution depends on the solvent. Thus, the results indicate that the intrinsic gas phase basicity is the main factor in modulating the pK_a of nitriles in apolar or low polar solvents, like chloroform. Our results demonstrate that not only the electrostatic, but also the polarization effects are necessary to describe proton affinities. Thus, we found that electron-donating and highly polarizable groups increase proton affinity in the gas phase, leading to an increase in the intrinsic pK_a of the protonated species.

The role played by the solvation can be sensibly more important than the intrinsic gas-phase properties in polar solvents such as water. In this case, the magnitude of the solvent influence on the change in pK_a of nitriles is modulated by the size and polarity of the substituent: small, polar groups attached to the cyano moiety make more favorable the solvent contribution to protonation, while large, apolar groups reduces such an effect.

Overall, our results demonstrate that a proper selection of substituents and solvent effects can afford new perspectives into the use of the chemistry of nitriles. Moreover, the relative basicity trends found can introduce new insights in the interpretation of nitrile reactions in acidic media. All methods agree with the fact that nitriles attached to nitrogen atoms are more basic than any other nitriles considered here, both in water and in chloroform. However, in other cases not only the nature of the α position but also other structural features must be taken into account if a relative basicity order of nitriles is intended.

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