Intrinsic Acidities of *meta*- and *para*-Substituted Phenols from Calculated Molecular Properties

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Intrinsic acidities of monosubstituted phenols have been calculated from a relationship obtained by comparing experimental data and energy differences between neutral molecules and the corresponding anions, calculated using the INDO method. Other calculated molecular properties (ionization potential of the anion, electric charge on the acidic hydrogen in the neutral molecule) have also been used, yielding values of the intrinsic acidity well within experimental errors. *Ab initio* calculations have been carried out on some systems which showed a difference between their predicted and experimental intrinsic acidities.

DIFFERENT techniques are now available [1-3] to measure the equilibrium constant for reactions such as (1) in the

$$AH + B^- = A^- + BH \qquad (1)$$

gas phase, where AH and BH are Brønsted acids. ΔG can be obtained from the equilibrium constant ' generally within ± 0.4 kcal mol^{-1} (ref. 4),' † and linear free energy relationships can be established since solvent effects that made ΔS a very important (often dominant) contribution to ΔG in experiments carried out in solution are now absent. More detailed discussions on this point, and on the adequacy of the assumptions in equations (2a) and (2b) have been reported.[4-10]

$$\Delta G^\circ(T) = \Delta G^\circ\ (298\ \mathrm{K}) = \Delta H^\circ \qquad (2a)$$

$$\Delta H^\circ = D(\mathrm{A{-}H}) - \mathrm{E.A.(A)} - D(\mathrm{B{-}H}) + \mathrm{E.A.(B)} \qquad (2b)$$

In equation (2b) D(A–H) and D(B–H) are the homolytic bond dissociation energies, and E.A.(A) and E.A.(B) are the electron affinities of the radicals A and B. If D(B–H) and E.A.(B) are known, equilibrium measurements of reaction (1) yield values of D(A–H) — E.A.(A), which can be taken as the intrinsic acidity of AH. We represent this difference by D — E.A. According to ref. 4, the error in the absolute value of D — E.A. is *ca.* 2—3 kcal mol^{-1}. Absolute values of the intrinsic acidity may be obtained by adding the ionization potential of hydrogen (313.6 kcal mol^{-1}) to the D — E.A. value.

We present here a theoretical study of the influence of substituents on the acidity of phenols.[4,9] This has already been done for some phenols, using isodesmic reactions [11] and changes in dipole moment.[12] We have obtained a relationship from comparison of experimental intrinsic acidities (D — E.A.) and calculated values of $\Delta E = E(\mathrm{AH}) - E(\mathrm{A}^-)$, which are directly related to ΔH°. We have used this relationship to predict intrinsic acidities (I.A.) of compounds that have not yet been studied, are unstable under experimental conditions, or contain more than one acidic proton. We are concerned with *meta*- and *para*-substituted phenols; we have not studied *ortho*-derivatives because intramolecular hydrogen bonding is often present,[13] with hydrogen-bond strengths of up to 8 kcal mol^{-1} (refs. 14 and 15), and unless one is sure that all these bonds are broken under the experimental conditions, a knowledge of the relative isomer populations is needed to estimate ΔE within the experimental precision.

We have tested our results by direct calculation of the homolytic bond dissociation energy (D_t) and the electron affinity of the radical A (E.A.$_t$). We have compared the difference D_t — E.A.$_t$ with the corresponding I.A. value. We have also calculated the charge on the acidic hydrogen and the 1*s* orbital energy of the phenolic oxygen from *ab initio* calculations on some *para*-substituted phenolates.

Calculations.—All systems studied are assumed to be planar.[12] Molecular geometries have been totally optimized using the INDO method [16] and the technique developed by Rinaldi *et al.*[17] Convergence is assumed to be reached when changes in bond lengths, angles, and total energy values are within $\pm 0.000\,7$ Å, $\pm$ 0.02°, and $\pm 10^{-7}$ a.u., respectively.‡

For neutral systems this criterion results in excellent agreement between calculated and experimental geometries.[12] To test the influence of molecular relaxation on the energies, anion geometries have been optimized starting with the neutral molecule geometry, and using the same criteria for convergence. Values of $\Delta E_{\mathrm{relax}} = E^-(\text{opt. geom.}) - E^-(\text{mol. geom.})$ are in Table 1. $\Delta E_{\mathrm{relax}}$ is almost constant for a family of compounds but there are some exceptions that may make optimization of anion geometries an important factor, particularly in the study of isodesmic reactions.

TABLE 1

Energy differences, $\Delta E_{\mathrm{relax}}$, between relaxed and unrelaxed monosubstituted (X) phenolic anions

	$-\Delta E_{\mathrm{relax}}$/kcal mol^{-1}	
X	*meta*	*para*
H	7.0	7.0
OH	7.4	6.7
F	7.3	7.0
Me	7.1	7.7
NH_2	7.6	7.0
CN	7.1	8.3
NO_2	7.2	9.5
CO_2H	7.8	10.0

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† 1 cal = 4.184 J.

‡ 1 atomic unit (a.u.) of energy — 4.3598×10^{-18} J.

RESULTS AND DISCUSSION

(a) *INDO Calculations.*—Acidities, estimated as the energy difference ΔE between the neutral molecule and the corresponding anion, in both cases calculated for optimized geometries, are plotted in Figure 1 against values (experimental) of D — E.A.,[4] for some substituted phenols. We find a good linear relationship for all compounds studied, except *m*- and *p*-cyano-, *p*-methyl-, and *m*-hydroxy-phenol.

Similar calculations have been carried out for *m*-hydroxybenzoic acid and some *para*-substituted derivatives in order to see whether the *p*-cyano-derivative shows a similar deviation, and to investigate whether *m*- and *p*-hydroxy-benzoic acid first loses the phenolic or the carboxylic proton in the gas phase.[4] The results are in Figure 2. *p*-Cyanobenzoic acid deviates from the straight line while the results for *m*-hydroxy- and *p*-methyl-benzoic acid seem to indicate that there would be problems in consideration of the corresponding phenols. Taking into account the possible isomeric forms of these molecules and their anions does not eliminate the discrepancies.

We postulate that the straight lines obtained by comparing D — E.A. and ΔE values in Figures 1 and 2 (disregarding the compounds just discussed) can be used to estimate intrinsic acidities from calculated ΔE values.

This postulate can be checked since intrinsic acidities can also be calculated as D_t — E.A.$_t$ values, where D_t is the energy term (E_{HO}) for the bond that loses the proton and can be calculated by partitioning the energy.[18] —E.A.$_t$ is taken to be the ionization potential of the corresponding anion, or the orbital energy of the highest occupied M.O.[19]

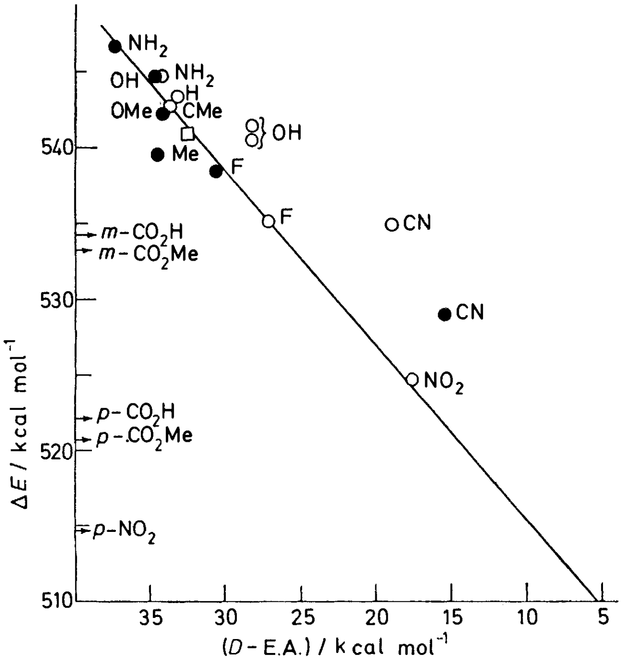


FIGURE 1 ΔE values *vs.* experimental (D — E.A.) intrinsic acidities for *meta*- (○) and *para*- (●) monosubstituted phenols. □ is the point for *o*-cresol. ΔE values for compounds not studied experimentally are indicated by arrows on the axis. The equation of the line is I.A. (ΔE) = 0.8694 × ΔE − 438.1 (r = 0.991)

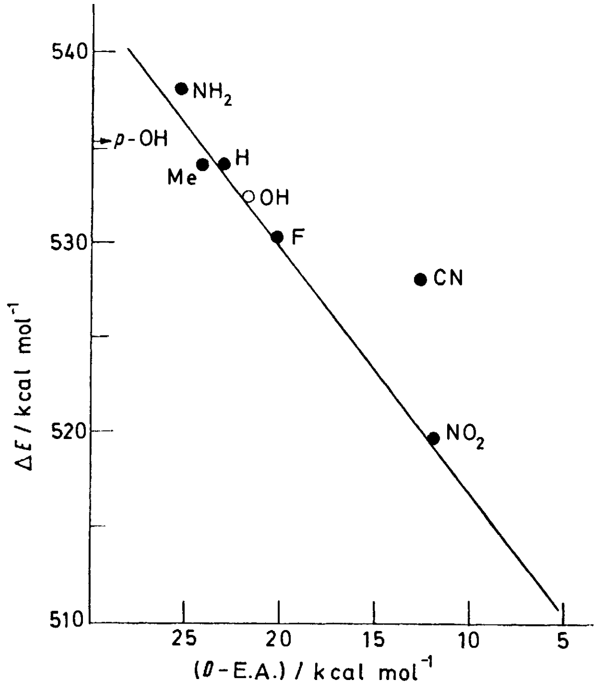


FIGURE 2 ΔE values *vs.* experimental (D — E.A.) intrinsic acidities for *meta*- (○) and *para*- (●) monosubstituted benzoic acids. The ΔE value for p-HOC$_6$H$_4$CO$_2$H, not studied experimentally, is indicated by an arrow on the axis. The equation of the line is I.A. (ΔE) = 0.7889 × ΔE − 397.8 (r = 0.996)

Figures 3 and 4 are plots of D_t — E.A.$_t$ *vs.* I.A. for substituted phenols and benzoic acids, respectively. Figures 3 and 4 include compounds whose D — E.A. values were not determined, but whose I.A. values were obtained from the corresponding value of ΔE and the linear relationship derived from data in Figures 1 and 2. Plots of D_t — E.A.$_t$ *vs.* D — E.A., which show similar deviations to those in Figures 1 and 2, are not included. It appears that either D_t — E.A.$_t$ or ΔE can be used to predict intrinsic acidities of compounds that are unstable under the experimental conditions (*p*-nitrophenol), contain more than one acidic proton (*m*- and *p*-hydroxybenzoic acid, and resorcinol), or have not been studied (*m*- and *p*-acetoxy-, and *m*- and *p*-formyl-phenol). Table 2 includes some I.A. values. Given the very carefully determined experimental data[4] that we have used to obtain the linear relationships we must conclude that the anomalous behaviour of *m*-hydroxy-, *p*-methyl-, *m*-cyano-, and *p*-cyano-phenol and *p*-cyanobenzoic acid indicates some, so far undetected, difficulty in the determination of D — E.A. for these compounds, which is not surprising given the extreme experimental conditions, or that INDO results for these compounds are not reliable. We shall return to this point later.

An alternative, more economical, procedure would be to calculate D_t as already indicated and E.A.$_t$ from the ionization potential of the unrelaxed anion, since we have

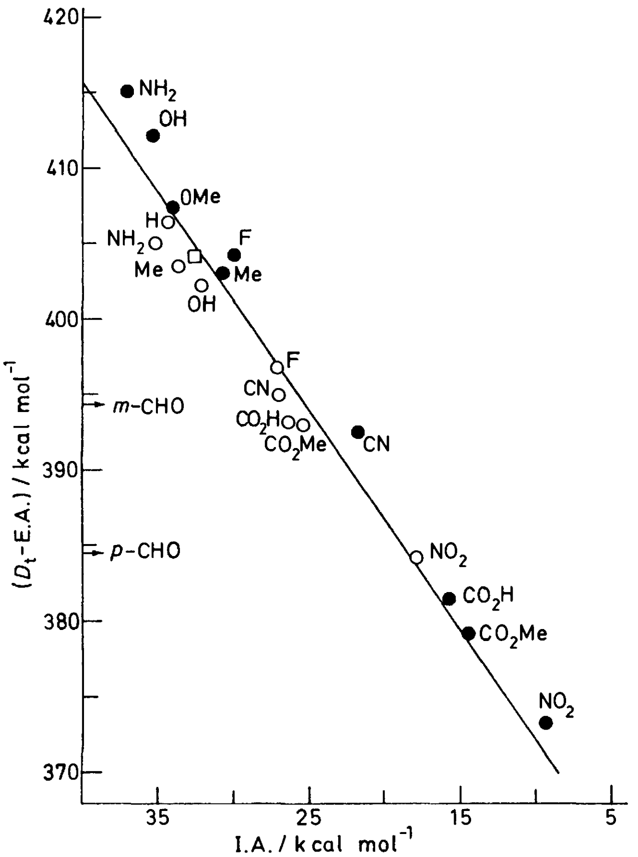


FIGURE 3 D_t — E.A.$_t$ values *vs.* I.A. (ΔE) for phenols (see caption to Figure 1). The equation of the line is I.A. = 0.6874 × (D_t — E.A.$_t$) — 245.7 (r = 0.981), for all points

found that the relationship (3) holds for the systems studied in this work.

$$\text{I.P.(relaxed) (in a.u.)} = \text{I.P.(unrelaxed)} \times 1.069 - 0.001\,4 \quad (3)$$
$$(r = 0.998)$$

We have observed that E.A.$_t$ values seem to confirm that the most important term in determining the acidity of a substituted phenol is the electron affinity of the phenoxyl radical.[4,20]

The data in Figures 1 and 3 can be separated into those for the *meta*- and the *para*-families, and an independent (better) linear relationship is then obtained for each of them. This has been done to predict intrinsic acidities (Table 2).

It has been pointed out that there is a relationship between acidity and the electric charge, q_H, on the protonic hydrogen (in the neutral molecule).[21-23] When the calculated values of q_H are plotted against D — E.A. and I.A. for phenols and acids, the results in Figure 5 are obtained. The agreement is significantly better for I.A. values which confirms our previous conclusions. Again, phenols can be grouped in *meta*- and *para*-families, yielding better linear relationships. The differences between our values of q_H and those of Kang and

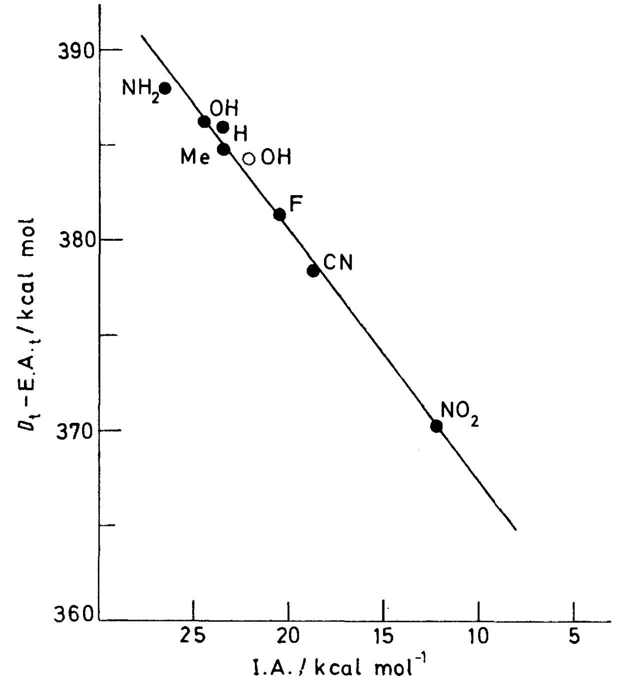


FIGURE 4 D_t — E.A.$_t$ values *vs.* I.A. (ΔE) for benzoic acids (see caption to Figure 2). The equation of the line is I.A. = 0.7627 × (D_t — E.A.$_t$) — 270.2 (r = 0.993)

TABLE 2

Experimental and calculated intrinsic acidities (I.A.) of monosubstituted phenols

	Exptl.		I.A. (ΔE)[b]		I.A. (D_t — E.A.$_t$)[c,d]		I.A. (q_H)[e,f]	
X	*meta*	*para*	*meta*	*para*	*meta*	*para*	*meta*	*para*
H	33.3	33.3	34.3	34.3	35.3	35.5	33.6	33.6
OH	28.2	34.5[a]	32.2	35.4	32.7	35.9	31.8	35.0
F	27.5	30.7	27.2	30.0	28.1	30.6	25.7	27.2
Me	33.7	34.6	33.7	30.9	33.3	29.8	34.2	30.9
NH$_2$	34.2	37.5	35.4	37.1	34.4	37.8	35.6	38.5
CN	18.9	15.6	27.0	21.8	26.7	22.6	28.1	22.3
NO$_2$	17.6		18.0	9.4	18.5	10.0	18.3	8.7
CO$_2$H			26.4	15.8	25.4	16.4	27.1	17.0
OMe		34.1		33.2		32.7		33.9
CO$_2$Me			25.5	14.6	25.3	14.0	25.1	15.4
CHO					26.4	17.6	27.3	17.2

[a] P. Kebarle, in ' Environmental Effects on Molecular Structures and Properties,' ed. B. Pullman, Reidel, Dordrecht, 1976, p. 85. [b] I.A. (ΔE) = 0.8694 × ΔE — 438.1 (r = 0.991). [c] I.A. (D_t — E.A.$_t$)$_m$ = 0.7579 × (D_t — E.A.$_t$)$_m$ — 272.5 (r = 0.990). [d] I.A. (D_t — E.A.$_t$)$_p$ = 0.6624 × (D_t — E.A.$_t$)q — 237.1 (r = 0.996). [e] I.A. (q_H)$_m$ = 1 631.86 × q_H — 1 354.19 (r = 0.989). [f] I.A. (q_H)$_p$ = 1 953.65 × q_H — 1 630.46 (r = 0.992).

TABLE 3

Calculated intrinsic acidities (from ΔE values) for dissociation of the phenolic [I.A. (OH)] or carboxylic acid [I.A. (CO_2H)] group of *m*- and *p*-hydroxybenzoic acid

	I.A. (OH)	I.A. (CO_2H)	Exptl.
meta	26.4	22.2	21.8
para	15.8	24.5	19.1

Beveridge[21] are due to their use of standard geometries in their calculations. Since calculated dipole moments improve with geometry optimization,[12] it is reasonable to assume that charge distributions would also improve.

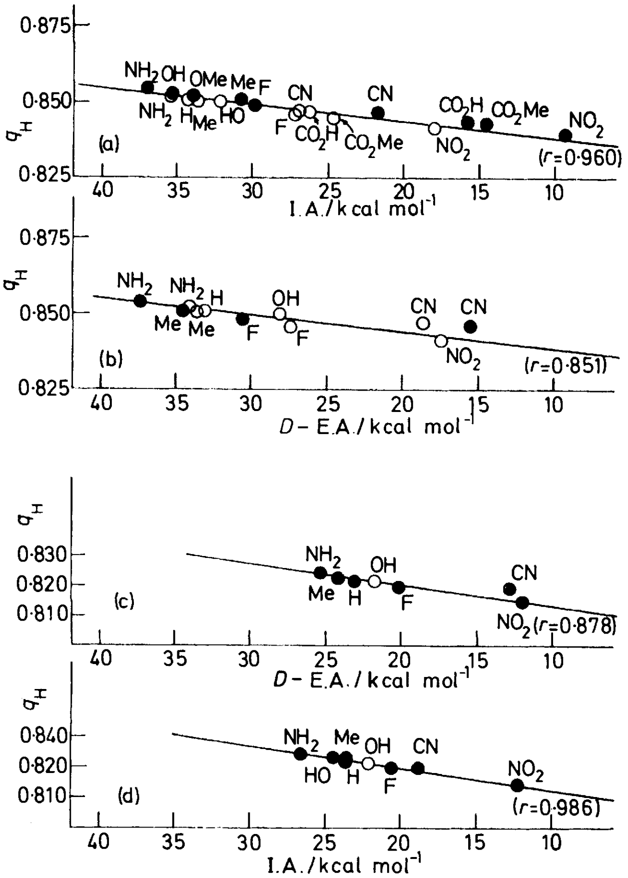
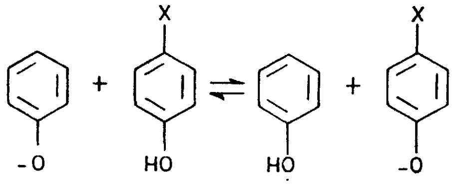


FIGURE 5 Electronic charge densities on the proton *vs.* calculated (I.A.) and experimental (D − E.A.) intrinsic acidities; (a) and (b), phenols; (c) and (d), benzoic acids

McMahon *et al.*[4] indicated that the most acidic hydrogen in *p*-hydroxybenzoic acid is the phenolic one, while the opposite is true for the *meta*-isomer. Table 3 shows I.A. values for these compounds dissociating either as an acid or a phenol. Comparison with values of D − E.A., also in Table 3, indicates that *m*-hydroxybenzoic acid is a *carboxylic* acid, while *p*-hydroxybenzoic acid dissociates both as a carboxylic acid and a phenol, the phenolic character being dominant.

(b) ab initio *Calculations*.—To study the influence of the method used on the final results, we have performed *ab initio* calculations using a STO-3G minimal basis set[24] to obtain the isodesmic reaction energies (see Scheme) for X = NH_2, Me, OH, CN, and NO_2 and the results are in Table 4. We attribute the difference between our result for *p*-cresol and that of Radom[11] to the fact that we used optimized (INDO) geometries in all calculations. As an example, the optimized C–O length varies from 1.323 Å (*p*-hydroxyphenolate) to 1.308 Å (*p*-nitrophenolate).



Isodesmic reactions

TABLE 4

Energies for the isodesmic reactions in the Scheme

	ΔE/kcal mol⁻¹	
X	Calc.	Exptl.[a]
NH_2	−2.5	−4.2
OH	−0.9	−1.2[b]
Me	1.0 (−1.0)[c]	−1.3
CN	24.1	17.7
NO_2	31.1	

[a] Ref. 4. [b] See footnote *a*, Table 2. [c] Ref. 11.

The HOMO energy calculated with this basis is positive for all these phenolate anions, which means that the basis set is not large enough for these orbitals to become stable.[25] The validity of energy values calculated for systems which present this problem is questionable.[26] For this reason, we do not draw any conclusions from the intrinsic acidity predicted from these ΔE values, even if the agreement with our former results is quite good.

The information we need can be obtained in a different way, from the same calculations, as follows: the heterolytic bond dissociation energy, $D(A^-{-}H^+)$, which measures the intrinsic acidity of a compound, AH, is equal to the proton affinity of the corresponding anion, A^-.[4] For a given family of compounds there exists a relationship between the proton affinity and the 1*s* orbital energy of the atom which is protonated.[27] The orbital energy in question, which corresponds to one of the lowest eigen-energies, is always negative; therefore, it is stable with respect to small variations of the basis set.[25] We have tested the influence of the basis set on that energy [$\varepsilon(O1_s)$] and we have found the ratio of $\varepsilon(O1_s)$ obtained with extended and with minimal basis sets to be almost constant for the singly negative charged systems that we have studied.

A plot of $\varepsilon(O1_s)$ for the phenolic oxygen *vs.* I.A. values is in Figure 6. Again, the value for *p*-cyanophenolate deviates from the straight line, but the value predicted with the equation (4) obtained from that line, without

$$\text{I.A. (A.P.)} = 244.92\,\varepsilon(O1_s) + 4\,886.26 \qquad (4)$$
$$(r = -0.998\,4)$$

considering the point for *p*-cyanophenolate, is the *experimental value*. On the other hand, using this equation and $\varepsilon(O_{1s})$ for *m*-hydroxyphenolate, we obtain a value of I.A. = 32.6 for that phenol, in good agreement with the INDO result.

For all compounds studied, the results agree with those obtained from INDO calculations, except for *p*-cyanophenol. Both INDO and *ab initio* calculations indicate that *p*-cresol is more acidic than phenol, contrary to experimental results.[4,9]

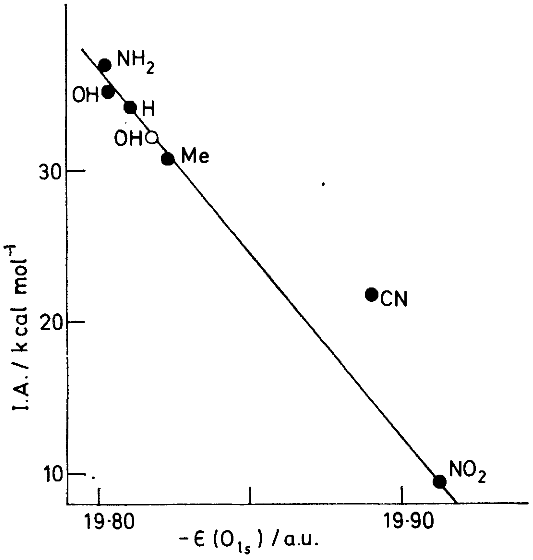


FIGURE 6 I.A. values *vs.* 1*s* orbital energies of the phenolic oxygen, calculated for the anion

CONCLUSIONS

We have found a correlation between calculated and experimental data for intrinsic acidities of monosubstituted phenols and monosubstituted benzoic acids, which can be used to predict acidities of similar compounds that have not been experimentally determined, contain more than one acidic proton, or are unstable under experimental conditions. These calculations require geometry optimizations for all molecules and anions. We have obtained, using three different (INDO) properties, the same results within experimental error.

As predicted by McMahon and Kebarle,[4] we found *p*-nitrophenol to be the strongest acid of all the phenols studied. Also, *m*-hydroxybenzoic acid dissociates as a carboxylic acid while the *para*-isomer dissociates mainly as a phenol.

Another linear relationship, which requires *ab initio* calculations, can be established between the intrinsic acidity and the calculated 1*s* orbital energy of the phenolic oxygen in the corresponding anion. The results confirm, in general, those obtained with the INDO method. However, in the case of *p*-cyanophenol there is no longer any discrepancy between experimental and calculated intrinsic acidities.

All calculations were carried out on the I.B.M. 360 computer at the I.B.M.–U.A.M. centre (Madrid).

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