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Semi-empirical studies of substituent effects on the ionization of bicyclooctane carboxylic acids and quinuclidines

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ABSTRACT: Semiempirical AM1 calculations were performed for a representative series of 4-substituted bicyclooctane carboxylic acids and quinuclidines. It was found that the Hammett constant, σ_I, and the Swain and Lupton field constant, F, correlate linearly with the differences in the heat of formation of isodesmic reactions. These constants also correlate with the charges on the acid moiety of the bicyclooctane acids and their anions, and with the hydrogen net charge on the protonated quinuclidines. For all cases, the NO_2 was the poorest correlated substituent.

KEYWORDS: inductive effects; field effects; substituent effects; bicyclooctane carboxylic acids; quinuclidines

INTRODUCTION

One of the early postulates in the classical English school of organic chemistry was that electronic substituent effects are the product of two components: the inductive/field and the resonance components.[1] Following Hammett's success in the quantification of the total electronic substituent effect in terms of his constant σ, efforts were undertaken in order to express both the inductive/field and resonance components in terms of appropriate substituent constants (σ^*, σ_I, σ_F, σ_R, F, R).[2] For defining the inductive/field effects, it has been agreed that the ionization of bicyclooctane carboxylic acids and quinuclidines provides an unambiguous molecular probe since in these compounds there is little, if any, possibility of resonance effects. Thus, it is assumed that the only way in which the substituent X can influence the ionization at the reaction center is through space (the field component) and through bonds (the inductive component). Moreover, the substituent constants, obtained from the ionization of bicyclooctane carboxylic acids, σ_I (Stock), show a very good correlation with the constants derived from quinuclidines, σ_I (Grob):[2]

$$\sigma_I(\text{Stock}) = 0.191\sigma_I(\text{Grob}) - 0.037 \qquad (1)$$

$$n = 14, r = 0.989, s = 0.029$$

In this, and the following equations, n is the number of compounds used in the correlation test, s is the standard deviation and r is the correlation coefficient.

Despite the great efforts dedicated to finding a solid theoretical foundation for the Hammett equation (and the associated inductive/field-resonant separation), it still remains today as an empirical relationship, maybe the most famous and useful one in physical organic and medicinal chemistry. In general, the insights obtained from the Hammett relationship can only be rationalized by appealing to chemical intuition and empirical models, rather than to theoretical principles. The lack of a sound theoretical basis for the Hammett treatment of electronic substituent constants and, consequently, of an easy theoretical methodology for estimating new substituent constants, together with the rapid growth in computer power and quantum chemistry codes, has stimulated the use of molecular orbital-derived descriptors as an alternative to the more classical chemical ones,[3] and as a means to provide a deeper understanding of the process involved. In the case of the ionization of benzoic acids, which constitutes the classical Hammett molecular probe, there have been several attempts to assign theoretical significance to substituent constant values, employing to this end descriptors obtained from *ab initio* and semiempirical molecular orbital calculations.[3–12] Also,

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using the electronegativity equalization principle (EEP),[13–15] the hard and soft acid and base (HSAB) principle of Parr and Pearson,[16,17] the molecular electrostatic potential (MESP) topography[18,19] and the molecular surface local ionization energy,[20–23] recent studies in the context of density functional theory (DFT) have shown that Hammett-like linear relationships can be rationalized using local descriptors of reactivity. Additionally, Wiberg recently reported an *ab initio* study of the substituent effect on the acidity of 4-substituted bicyclooctane carboxylic acids.[24] The importance of and need for a common language between theoretical and empirical descriptors are highlighted in all these studies. In the spirit of these theoretical studies, in this work, for a set of 4-substituted bicyclooctane carboxylic acids and quinuclidines, we undertook a correlation analysis of AM1-calculated theoretical descriptors with the field/inductive substituent constants σ_I and F. From this analysis we aimed to establish some of the molecular parameters that show good correlations with σ_I and F. Thus, for cases where they are experimentally difficult to obtain, the computed parameter values may be used, together with the correlation expression, to obtain an estimate of those constants. Additionally, once the correlations have been clearly established, these parameters may constitute a potentially important set of descriptors in QSAR studies. Finally, from the numerical results presented here, we expect to acquire some insight regarding the transmission of electronic effects through space and through bonds.

METHODOLOGY

All computations were carried out with the AM1[25] Hamiltonian using the MOPAC 7.0 program.[26] This choice is based on the fact that recently the AM1 Hamiltonian was found to be the most accurate semiempirical method for determining orbital energy parameters, which is based on correlations with experiments and *ab initio* calculations.[27] Also, the calculated AM1 charges, dipoles and bond lengths are reported to be even more reliable than those obtained from low-level *ab initio* calculations.[28] Optimization was performed for all 4-substituted bicyclooctane carboxylic acids and quinuclidines without any failure. In order to tighten the convergence criteria, all conformations were fully optimized using the keywords PRECISE and GNORM = 0.05. The initial geometries were defined using standard bond lengths and angles. In all cases Mulliken atomic charges were used.

Representative substituent groups were selected based on the values of pK_a reported for 12 bicyclooctane carboxylic acids by Stock and co-workers[29,30] and the values for quinuclidines reported by Grob and Schlageter.[31] In addition to the more common σ_I values, here we also used the standard field parameter (F) of Swain and Lupton to explore the possible correlations.[2,32] The values of the substituent constants (σ_I and F) are given in Table 1. As was noted before, these constants correlate strongly among themselves.

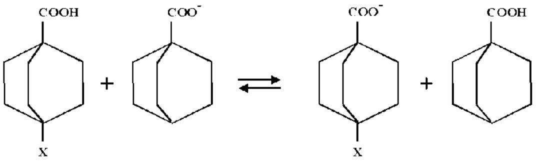
Table 1. Values of the field/inductive substituent constants used in this work, taken from Ref. 2[a]

Substituent, X	σ_I(Stock)	σ_I(Grob)	F
H	0.00	0.00	0.00
F	—	0.46	0.45
Cl	0.47	0.44	0.42
Br	0.45	0.47	0.45
I	—	0.41	0.42
CH_3	−0.02	−0.01	0.01
C_2H_5	−0.01	—	0.00
CH_2Cl	—	0.15	0.13
CH_2Br	—	0.16	0.14
CH_2I	—	0.16	0.12
CH_2OH	0.05	0.09	0.03
CN	0.54	0.55	0.51
NO_2	0.68	0.63	0.65
OH	0.26	—	0.33
OCH_3	0.30	0.31	0.29
SCH_3	—	0.28	0.23
NH_2	0.15	0.17	0.08
$COCH_3$	0.26	0.29	0.33

[a] For bicyclooctane carboxylic acids, we used the σ_I values, calculated by Stock *et al.*, σ_I(Stock),[19,20] and for quinuclidines we employed the Grob and Schlageter σ_I values.[21] The Swain and Lupton constant, F,[22] is also included.

IONIZATION OF BICYCLOOCTANE CARBOXYLIC ACIDS

Table 2 shows the calculated heat of reaction, $\Delta(\Delta H°)$ for the isodesmic reaction shown in Eqn. (2). $\Delta(\Delta H°)$ is defined as the difference between the ionization enthalpy of the X-substituted and the nunsubstituted bicyclooctane carboxylic acids, $\Delta(\Delta H°) = \Delta H_X - \Delta H_H$.



(2)

It is found that $\Delta(\Delta H°)$ displays a linear correlation with the 12 σ_I(Stock) and 18 F parameters of Table 1:

$$\sigma_I(\text{Stock}) = -0.070\ (\pm 0.007)\Delta(\Delta H°) + 0.043\ (\pm 0.029) \quad (3)$$

$$n = 12, r = 0.959, s = 0.071$$

$$F = -0.070\ (\pm 0.007)\Delta(\Delta H°) + 0.034\ (\pm 0.029) \quad (4)$$

$$n = 18, r = 0.926, s = 0.078$$

The figures in parentheses are the 95% confidence

Table 2. Calculated $\Delta(\Delta H°)$ and the associated energy partition for the ionization of bicyclooctane carboxylic acids [Eqn. (2)][a]

Substituent	$\Delta(\Delta H°)$	$\Delta(\Delta E_{OC})$	$\Delta(\Delta E_R)$	$\Delta(\Delta E_X)$	$\Delta(\Delta E_{Coul})$
H	0.0000	0.0000	0.0000	0.0000	0.0000
F	−4.1527	−6.5075	4.1600	3.0209	−4.8288
Cl	−4.8346	−9.9319	7.6559	5.3568	−7.9165
Br	−4.9782	−9.6575	4.6904	4.5059	−4.5198
I	−4.5385	−7.9465	1.3813	2.3060	−0.2836
CH_3	−0.1492	−0.4428	0.1222	0.0300	0.1361
C_2H_5	−0.1920	−0.8970	0.7056	0.1753	−0.1799
CH_2Cl	−2.4134	−6.4245	4.2799	2.9517	−3.2215
CH_2Br	−2.6207	−6.8926	2.9609	2.5205	−1.2130
CH_2I	−2.5950	−6.1247	1.2614	1.3582	0.9086
CH_2OH	0.0543	−2.3360	1.2245	0.5996	0.5673
CN	−6.1785	−8.9012	3.4359	4.3284	−5.0409
NO_2	−10.7518	−15.4525	12.9205	9.0188	−17.1981
OH	−2.7303	−3.5974	3.1823	1.9647	−4.2822
OCH_3	−2.4364	−2.3613	1.6626	1.2522	−2.9932
SCH_3	−3.0988	−9.0718	3.0116	1.7226	1.2337
NH_2	−1.5172	−5.7120	5.0294	1.3167	−2.1492
$COCH_3$	−3.5546	−4.9902	3.9386	3.3529	−5.8572

[a] $\Delta(\Delta E_{OC})$ corresponds to the one-center energy component, $\Delta(\Delta E_R)$ to the two-center resonance component, $\Delta(\Delta E_X)$ to the two-center exchange component and $\Delta(\Delta E_{Coul})$ to the two-center electrostatic component. All energies are in kcal mol^{-1} (1 kcal = 4.184 kJ).

intervals of the regression coefficients and the intercepts. The compound for which the poorest correlation was found was the NO_2 derivative, for which considerably lower acidity was predicted. If this compound is not included, the correlation was improved:

$$\sigma_I(\text{Stock}) = -0.089\ (\pm 0.006)\Delta(\Delta H°) + 0.008\ (\pm 0.002) \quad (5)$$

$$n = 11, r = 0.982, s = 0.043$$

$$F = -0.090\ (\pm 0.008)\Delta(\Delta H°) + 0.011\ (\pm 0.026) \quad (6)$$

$$n = 17, r = 0.948, s = 0.061$$

Hence the statistical evidence indicates that the derived model equations give a good account of the experimental data. Moreover, on the basis of the regression model, it is clear that the predictions of the Swain–Lupton inductive/field parameter, F, are inferior to those obtained for the σ_I constant, derived from the Stock pK_a values. Additionally, our results contrast with those of Sotomatsu *et al.*,[7] who, also using the AM1 Hamiltonian, did not find a notable correlation between $\Delta(\Delta H°)$ and the Hammett σ substituent constant obtained from the analysis of the acidity of benzoic acids. The distinction between these results indicates the different, and even sometimes contrasting, behavior of the resonance and inductive/field contributions to σ. Thus, based on these correlations, we can conclude that, in the absence of a resonance component, as happens in the case studied here, the isodesmic reaction (2) is an isoentropic reaction, as has been assumed previously.[33]

Once the correlation between the substituent constants and the change in enthalpy had been established, next we explored the possible root for this correlation. Thus, $\Delta(\Delta H°)$ is divided into one-center, $\Delta(\Delta E_{OC})$, and two-center components. The latter can be partitioned into a resonance, $\Delta(\Delta E_R)$, a two-center exchange, $\Delta(\Delta E_X)$, and a two center-electrostatic contribution, $\Delta(\Delta E_{Coul})$:

$$\Delta(\Delta H°) = \Delta(\Delta E_{OC}) + \Delta(\Delta E_R) + \Delta(\Delta E_X) + \Delta(\Delta E_{Coul}) \quad (7)$$

The results for this energy partition of the isodesmic reaction (2) are given in Table 2. We tested for possible correlations between $\Delta(\Delta H°)$ and each of its components, obtaining results worth mentioning only for $\Delta(\Delta E_X)$ ($r = 0.950$) and $\Delta(\Delta E_{OC})$ ($r = 0.911$). The test was repeated, but this time considering pairs of combinations, and only those corresponding to $\Delta(\Delta E_{OC}) + \Delta(\Delta E_{Coul})$ ($r = 0.955$) and $\Delta(\Delta E_R) + \Delta(\Delta E_X)$ ($r = 0.899$) display acceptable correlations. Finally, when considering groups of three contributions, good quality results were found only for $\Delta(\Delta E_{OC}) + \Delta(\Delta E_R) + \Delta(\Delta E_{Coul})$ ($r = 0.989$) and $\Delta(\Delta E_{OC}) + \Delta(\Delta E_X) + \Delta(\Delta E_{Coul})$ ($r = 0.950$).

The previous results show that the most important contributions to the enthalpy variations correspond to those reflecting charge interactions, or charge density redistribution throughout the system (or combinations of them). In addition, on inspecting Table 2, one notes that the values of $\Delta(\Delta E_{OC})$ for all the substituents are negative; thus, the one-center energy variations favor the formation of the ionized substituted carboxylic anion. In contrast, the two-center resonance, $\Delta(\Delta E_R)$, and exchange, $\Delta(\Delta E_X)$, components always favor the left direction of Eqn. (2). The remaining term is the electrostatic two-center contribution, $\Delta(\Delta E_{Coul})$, which, in contrast to the others, does not show any well defined

Table 3. Calculated net charges on carbonyl oxygen, $q(=\mathrm{O})$, hydroxy oxygen, $q(\text{—O—})$, hydroxy proton, $q(\mathrm{H})$, carbonyl carbon, $q(\mathrm{C})$, and the sum of the charges in the carboxylic acid group, $\Sigma q(\mathrm{COOH})$, of neutral acids, and the sum of the charge in carboxylate ions atoms, $\Sigma q(\mathrm{CO_2}^-)$

Substituent	$q(=\mathrm{O})$	$q(\text{—O—})$	$q(\mathrm{H})$	$q(\mathrm{C})$	$\Sigma q(\mathrm{COOH})$	$\Sigma q(\mathrm{CO_2}^-)$
H	−0.3622	−0.3170	0.2409	0.3124	−0.1259	−0.8164
F	−0.3573	−0.3164	0.2433	0.3126	−0.1178	−0.8057
Cl	−0.3570	−0.3164	0.2434	0.3129	−0.1171	−0.8022
Br	−0.3570	−0.3163	0.2434	0.3128	−0.1171	−0.8015
I	−0.3577	−0.3165	0.2431	0.3126	−0.1185	−0.8026
CH_3	−0.3618	−0.3174	0.2409	0.3123	−0.1260	−0.8157
C_2H_5	−0.3619	−0.3173	0.2409	0.3127	−0.1256	−0.8154
CH_2Cl	−0.3590	−0.3175	0.2421	0.3123	−0.1221	−0.8097
CH_2Br	−0.3588	−0.3174	0.2422	0.3123	−0.1217	−0.8090
CH_2I	−0.3590	−0.3173	0.2421	0.3123	−0.1219	−0.8088
CH_2OH	−0.3612	−0.3181	0.2408	0.3125	−0.1260	−0.8151
CN	−0.3559	−0.3162	0.2442	0.3123	−0.1156	−0.8010
NO_2	−0.3508	−0.3151	0.2467	0.3129	−0.1063	−0.7873
OH	−0.3594	−0.3165	0.2425	0.3126	−0.1208	−0.8091
OCH_3	−0.3587	−0.3177	0.2421	0.3126	−0.1217	−0.8090
SCH_3	−0.3587	−0.3174	0.2422	0.3124	−0.1215	−0.8066
NH_2	−0.3599	−0.3175	0.2417	0.3122	−0.1235	−0.8120
$COCH_3$	−0.3595	−0.3160	0.2426	0.3123	−0.1206	−0.8070

behavior. However, for several of the cases studied, the opposite tendencies mentioned above approximately cancel each other, leaving the electrostatic contribution as the determinant one. This contribution contains the electron–electron repulsion and the attraction of the electrons on one center to the core of the others, which depend on the atomic densities, and the nuclear–nuclear repulsion, which is relatively constant.

All these qualitative tendencies discussed above lead us to think that changes in the atomic electron charge density may affect, in a crucial manner, the values of the substituent constants for bicyclooctane carboxylic acids. The results of this analysis would support the implicit assumption, incorporated in many theoretical treatments,[4–23] that energy changes depend on the movements of charges. It is for this reason that we studied the possible relation between the substituent constant values and the charges on the reaction center. Table 3 lists the calculated net charges on the carbonyl oxygen, $q(=\mathrm{O})$, hydroxy oxygen, $q(\text{—O—})$, carbonyl carbon, $q(\mathrm{C})$ and hydroxy proton, q(H), of neutral bicyclooctane carboxylic acids, and also the sum of these net charges on the acid group, $\Sigma q(\mathrm{COOH})$, and its equivalent for the carboxylate ion, $\Sigma q(\mathrm{CO_2}^-)$. A significant correlation was found with both of these sums:

$$\sigma_{\mathrm{I}}(\mathrm{Stock}) = 51.48\ (\pm 2.76)\Sigma q(\mathrm{COOH}) + 6.49\ (\pm 0.34) \tag{8}$$

$$n = 11, r = 0.975, s = 0.034$$

$$F = 51.82\ (\pm 2.81)\Sigma q(\mathrm{COOH}) + 6.52\ (\pm 0.35) \tag{9}$$

$$n = 17, r = 0.962, s = 0.051,$$

$$\sigma_{\mathrm{I}}(\mathrm{Stock}) = 33.92\ (\pm 1.93)\Sigma q(\mathrm{CO_2}^-) + 27.68\ (\pm 1.56) \tag{10}$$

$$n = 11, r = 0.986, s = 0.036,$$

$$F = 33.08\ (\pm 3.25)\Sigma q(\mathrm{CO_2}^-) + 26.98\ (\pm 2.63) \tag{11}$$

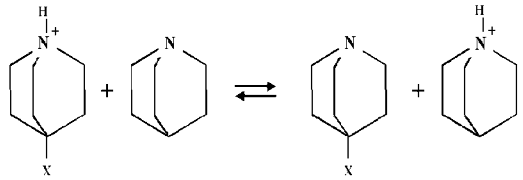
$$n = 17, r = 0.934, s = 0.066.$$

As in the case of $\Delta(\Delta H°)$, the NO_2 substituent was not included in these correlation tests. Additionally, when testing each of the net charges mentioned above, good correlations were also found. For the substituted benzoic acids Sotomatsu *et al.*[7] and Kim and Martin[8] found similar correlations with the total neutral acid charges, $\Sigma q(\mathrm{COOH})$, when 27 and 49 substituents were tested, respectively. There, the only outlier was *p*-CN. Let us emphasize that, from the statistical point of view, all these correlations are essentially equivalent; therefore, one may conclude that the substituents affect in a similar fashion the neutral acids and their anions.

Finally, we did not find any significant correlations between substituent constant values and E_{HOMO}, E_{LUMO}, the inverse of these energies and the total two-center energy contribution for the OH.

IONIZATION OF QUINUCLIDINES

Table 4 shows the calculated heat of formation, $\Delta(\Delta H°)$, for the isodesmic reaction of Eqn. (12).



(12)

Table 4. Calculated $\Delta(\Delta H^\circ)$ and the corresponding energy partition for the ionization of quinuclidines [Eqn. (12)][a]

Substituent	$\Delta(\Delta H^\circ)$	$\Delta(\Delta E_{OC})$	$\Delta(\Delta E_R)$	$\Delta(\Delta E_X)$	$\Delta(\Delta E_{Coul})$
H	0.0000	0.0000	0.0000	0.0000	0.0000
F	−6.1052	−7.4415	3.3852	3.5743	−5.6243
Cl	−5.4011	−10.7667	6.5283	4.7457	−5.9080
Br	−5.1652	−9.6875	2.4905	2.9033	−0.8717
I	−4.1836	−7.3538	−0.5996	0.0138	3.7565
CH_3	0.4355	0.7195	−0.5327	−0.5903	0.8348
C_2H_5	0.7977	0.9777	−0.6987	−1.0285	1.5427
CH_2Cl	−2.3764	−5.9933	3.6204	2.3475	−2.3498
CH_2Br	−2.4909	−6.4822	1.6027	1.4182	0.9893
CH_2I	−2.2738	−5.4883	−0.5327	−0.2929	4.0401
CH_2OH	1.1454	−1.1046	−0.1176	−0.3298	2.7026
CN	−7.6688	−10.5523	1.5450	3.7865	−2.4490
NO_2	−13.7919	−14.7653	12.3947	9.1594	−20.5834
OH	−3.5017	−3.4175	2.4213	2.0938	−4.6005
OCH_3	−2.2385	−0.6388	−0.1038	0.3413	−1.8356
SCH_3	−2.0969	−8.3247	1.3121	−0.6895	5.6059
NH_2	−1.5739	−8.5114	7.1924	1.4758	−1.7318
$COCH_3$	−3.4938	−3.2907	2.7095	2.4075	−5.3176

[a] The meaning of the columns is the same as in Table 2.

As in the case of bicyclooctane carboxylic acids, the $\Delta(\Delta H^\circ)$ values for quinuclidines show linear correlations with the 16 σ_I(Grob) and 18 F parameters of Table 1. Excluding the NO_2 substituent, the following results are obtained:

$$\sigma_I(\text{Grob}) = -0.0667\ (\pm 0.007)\Delta(\Delta H^\circ) + 0.069\ (\pm 0.026) \tag{13}$$

$$n = 15, r = 0.936, s = 0.065$$

$$F = -0.079\ (\pm 0.006)\Delta(\Delta H^\circ) + 0.047\ (\pm 0.023) \tag{14}$$

$$n = 17, r = 0.942, s = 0.062$$

Table 4 also shows the decomposition of $\Delta(\Delta H^\circ)$ into one-center and two-center terms. As in the previous section, we performed a numerical analysis to establish the possible correlations between $\Delta(\Delta H^\circ)$ and each of its components. Here, the only acceptable result was found for $\Delta(\Delta E_X)$ ($r = 0.917$). When the test was repeated for all possible pairs of contributions, only that corresponding to $\Delta(\Delta E_{OC}) + \Delta(\Delta E_{Coul})$ showed any significant correlation ($r = 0.936$). Finally, when groups of three contributions were considered, good quality results were found for $\Delta(\Delta E_{OC}) + \Delta(\Delta E_R) + \Delta(\Delta E_{Coul})$ ($r = 0.986$); for $\Delta(\Delta E_{OC}) + \Delta(\Delta E_X) + \Delta(\Delta E_{Coul})$ the correlation coefficient obtained was $r = 0.933$.

Again, these results lead us to think that the contributions that involve redistribution or concentration of charge density are the most important ones. In spite of this, on inspecting Table 4, no definite behavior is observed for each of the one- or two-body terms. However, if we take into account the fact that for quinuclidines the reaction center, which acts as a Lewis base, is part of the ring, we can expect that it may interact strongly with electron attractor substituents. Thus, when F, Cl, Br, I, CN, OH, OCH_3 and $COCH_3$ are employed, the correlation between $\Delta(\Delta H^\circ)$ and F improves ($r = 0.967$) and so does that between $\Delta(\Delta H^\circ)$ and $\Delta(\Delta E_{OC}) + \Delta(\Delta E_R) + \Delta(\Delta E_{Coul})$, where $r = 0.994$. Moreover, if for those substituents we now inspect Table 4, we find a behavior that qualitatively resembles that observed for bicyclooctane carboxylic acids. As a consequence of these results, we explored the possible dependence of the substituent constants with the charges on the reaction center generated by these changes in the electronic density. Table 5 lists the calculated net charge on the nitrogen, q(N), on the proton, q(H), and the sum of

Table 5. Calculated net charges on nitrogen, q(N), proton, $q(H^+)$ and the sum of the charges in protonic amine, $\Sigma q(NH^+)$, of protonated quinuclidine, and the nitrogen charge in neutral quinuclidine, $q(N^\circ)$

Substituent	q(N)	$q(H^+)$	$\Sigma q(NH^+)$	$q(N^\circ)$
H	−0.0106	0.2524	0.2418	−0.1870
F	−0.0139	0.2569	0.2430	−0.1883
Cl	−0.0115	0.2559	0.2444	−0.1867
Br	−0.0096	0.2555	0.2459	−0.1855
I	−0.0083	0.2545	0.2462	−0.1846
CH_3	−0.0096	0.2516	0.2420	−0.1871
C_2H_5	−0.0094	0.2513	0.2419	−0.1870
CH_2Cl	−0.0103	0.2536	0.2433	−0.1862
CH_2Br	−0.0100	0.2536	0.2436	−0.1860
CH_2I	−0.0098	0.2534	0.2436	−0.1859
CH_2OH	−0.0109	0.2514	0.2405	−0.1879
CN	−0.0117	0.2573	0.2456	−0.1854
NO_2	−0.0146	0.2619	0.2473	−0.1855
OH	−0.0137	0.2547	0.2410	−0.1886
OCH_3	−0.0134	0.2534	0.2400	−0.1889
SCH_3	−0.0087	0.2529	0.2442	−0.1853
NH_2	−0.0096	0.2529	0.2433	−0.1878
$COCH_3$	−0.0103	0.2541	0.2438	−0.1864

them for the protonated quinuclidines, and on the nitrogen of neutral quinuclidines, $q(\mathrm{N}°)$. From this set of charge descriptors the only acceptable correlation obtained was that with $q(\mathrm{H})$, yielding the expression given in Eqns (15) and (16), which are of similar quality to those obtained for $\Delta(\Delta H°)$:

$$\sigma_\mathrm{I}(\mathrm{Grob}) = 90.3\ (\pm 11.7)q(\mathrm{H}) - 22.7\ (\pm 2.9) \tag{15}$$

$$n = 15, r = 0.906, s = 0.077$$

$$F = 90.3\ (\pm 10.2)q(\mathrm{H}) - 23.2\ (\pm 2.6) \tag{16}$$

$$n = 17, r = 0.919, s = 0.073$$

As in the bicyclooctane carboxylic acids, the tested energy descriptors (E_HOMO and E_LUMO) did not show any significant correlations with the quinuclidine substituent constants.

DISCUSSION

The inductive effect, one of the most important concepts in organic chemistry, is usually discussed in terms of its transmission forms, the so-called 'through-space', and 'through-bond' mechanisms.[34] They are often quantified in terms of various substituent constants, notably σ_I and F.[2] In this work, it has been found numerically that, with the exception of NO_2, inductive/field substituent constants correlate well with theoretical descriptors, particularly with formation enthalpies of 4-substituted bicyclooctane carboxylic acids and quinuclidines, and net charges obtained from AM1 semiempirical calculations. Unlike the other substituents, NO_2 has two resonant structures where the electronic density is delocalized on both oxygens and some deficiency of electronic density appears on the nitrogen. We think that owing to this high degree of electronic density separation, the NO_2 field/inductive effect on the reaction center is not as important for the kind of aliphatic framework studied in this work and, therefore, deviations would appear when correlations exploring these effects are tested. From an energy partition analysis it is possible to attribute the root of these correlations to an electron density redistribution, which may be quantified by the calculation of the net charges in the reaction center.

Before continuing, some comments are in order. The charge on an atom in a molecule is not a physical observable, and several methods have been proposed to compute it, each of them based on different assumptions on the manner of partitioning the electron density, and in general, each of them renders different quantitative results. However, it is important to emphasize that, in spite of this fact, usually the qualitative tendencies found from these methods agree well with each other. Therefore, the correlations obtained by means of one of them should remain valid if another one is employed (although different numerical values would characterize each correlation). Additionally, since we have chosen AM1, one may wonder how reliable the results given by this method are. As was mentioned earlier, this question has been addressed by several authors,[27,28] indicating, for the kind of systems studied here, that the AM1 results reproduce well those rendered by high-level calculations with small basis sets.

Table 6. Enthalpy variation, $\Delta(\Delta H°)_1$, for the ionization of carboxylic acids [Eqn. (1)] and quinuclidines [Eqn. (12)] calculated employing the isolated molecule techniques[a]

	Carboxylic acids		Quinuclidines	
Substituent	$\Delta(\Delta H°)$	$\Delta(\Delta H°)_1$	$\Delta(\Delta H°)$	$\Delta(\Delta H°)_1$
H	0.0000	0.0000	0.0000	0.0000
F	−4.1527	−3.5002	−6.1052	−5.3700
Cl	−4.8346	−3.2292	−5.4011	−5.3299
Br	−4.9782	−3.5008	−5.1652	−4.3176
I	−4.5385	−2.8174	−4.1836	−3.4679
CH_3	−0.1492	−0.1157	0.4355	0.1147
C_2H_5	−0.1920	−0.1430	0.7977	0.5661
CH_2Cl	−2.4134	−2.1649	−2.3764	−1.2560
CH_2Br	−2.6207	−1.9915	−2.4909	−1.6131
CH_2I	−2.5950	−1.5675	−2.2738	−1.6513
CH_2OH	0.0543	0.1141	1.1454	2.9484
CN	−6.1785	−4.8901	−7.6688	−6.8146
NO_2	−10.7518	−8.1425	−13.7919	−11.8834
OH	−2.7303	−2.3092	−3.5017	−3.1559
OCH_3	−2.4364	−1.9534	−2.2385	−2.1347
SCH_3	−3.0988	−1.9534	−2.0969	−2.0063
NH_2	−1.5172	−3.3471	−1.5739	−0.3359
$COCH_3$	−3.5546	−1.9239	−3.4938	−2.5222

[a] For comparison, the results corresponding the full molecular framework reaction are also included, $\Delta(\Delta H°)$.

Since the importance of the charge redistribution to $\Delta(\Delta H°)$ has been determined, it is desirable to access the relative contribution of the field and inductive effects. Aiming for this goal, we employed the isolated molecule technique.[35] Thus, for Eqns (2) and (12), the pairs constituted by the substituent and the reaction center are kept at the same geometry as in the bicyclooctane carboxylic acid and the quinuclidines, and the molecular skeleton between them is removed, then for those pairs the enthalpy variation, $\Delta(\Delta H°)_1$, is calculated. These results, together with those corresponding to Eqns (2) and (12), $\Delta(\Delta H°)_0$, are displayed in Table 6. From there one sees that, for most of the substituents the removal of the framework does not change the enthalpy variation appreciably. To support this point, for each system we explored the correlation between both sets of results, obtaining for the acids

$$\Delta(\Delta H°)_1 = 0.717\Delta(\Delta H°)_0 - 0.154 \tag{17}$$

$$n = 18, r = 0.951, s = 0.075$$

and for the quinuclidines

$$\Delta(\Delta H^\circ)_1 = 0.919\Delta(\Delta H^\circ)_0 - 0.383 \qquad (18)$$

$$n = 18, r = 0.987, s = 0.067$$

These results show that, in general, the inductive effects are not of particular significance compared with field effects. Nevertheless, for the first set, NH_2 shows a clear deviation from this correlation and, when it is not considered, the results improve ($r = 0.987$). We think that this may be attributed to the fact that in this case the reaction center and the substituent form an acid–base pair, for which the inductive effect may have some relevance. Finally, the results suggest that the theoretical parameters calculated here (or other similar ones) may constitute a robust set of indicators which can be used in QSAR analysis. However, we recognize that more analysis in this direction is required.

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