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Polar Substituent Effects in the Bicyclo[1.1.1]pentane Ring System: Acidities of 3-Substituted Bicyclo[1.1.1]pentane-1-carboxylic Acids

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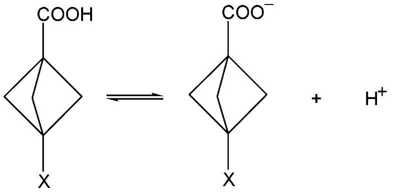
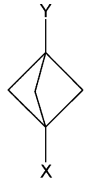


Experimental gas-phase acidities are reported for a series of 3-substituted (X) bicyclo [1.1.1]pent-1-yl carboxylic acids (**1**, Y = COOH). A comparison with available calculated data (MP2/6-311++G**// B3LYP/6-311+G**) reveals good agreement. The relative substituent effects are shown to be adequately described by a much lower level of theory (B3LYP/6-31+G*). Various correlations are presented which clearly point to polar field effects as being the origin of the relative acidities.

Introduction

Over the years, cage polycyclic alkanes have been deployed extensively as model substrates for the investigation of several important concepts in chemistry. In particular, their rigid molecular frameworks coupled with the absence of π-electrons provide ideal scaffolds for evaluating the nature and magnitude of remote polar substituent effects in saturated systems. Two of the most significant systems of this kind are 1,3-disubstituted bicyclo[1.1.1]pentanes (**1**) and 1,4-disubstituted bicyclo[2.2.2]octanes (**2**) in which the substituent (X) and probe (Y) located at termini bridgehead positions are both aligned along the major axis of the ring system. Hence, these cage systems allow accurate measurement of distances between substituent (X) and probe (Y) without uncertainty being created by an angle orientation factor.



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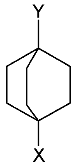

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Both chemical reactivity and NMR chemical shift probes (energy and charge density monitors, respectively) have been deployed (**1**, Y = COOH,[1-3] F,[4,5] $Sn(CH_3)_3$,[6] and **2**, Y = COOH,[3,7-9] NH_3^+[10], F,[5,11] $Sn(CH_3)_3$,[6,12] C≡CH,[13] C_6H_5,[11] CH_3,[14] p-FC_6H_4,[11] and FC_8H_{12}[11]), and the results of these studies have provided insightful complementary information on the modes of transmission ("through-bond" and "through-space") of polar substituent effects. Recently, Wiberg[3] reported calculated acidities of **1** and **2** (Y = COOH) at a high level of theory (MP2/6-311+ + G**//B3LYP/6-311+G**) for a number of substituents covering a reasonable range of polar effects. Whereas the results of the latter system were completely validated by comparison and correlation against appropriate available

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experimental data for several substituents,[8] the situation for the former remains less defined since only one measured gas-phase acidity result is available (**1**, X = H and Y = COOH)[3] to corroborate the calculations. Herein we report experimental gas-phase acidities of **1** (Y = COOH) for several substituents (X = H, NO_2, CN, CF_3, $COCH_3$, $COOCH_3$, F, Cl, Br, C_6H_5, CH_3, $C(CH_3)_3$, and $Si(CH_3)_3$) which permit substantiation of the aforementioned calculated acidities. In addition, we report dissociation constants (pK_a values) of several of the carboxylic acids (**1**, Y = COOH and X = H, NO_2, CN, CF_3, $COOCH_3$, F, and CH_3) determined in water by potentiometric titration. As we shall see below, the analysis of the new data strengthens the view[1−3] that the substituent-induced acidities of **1** (Y = COOH) appear to be best described in terms of an electrostatic field model.

Experimental Section

Synthesis of Compounds. Literature procedures were followed in the preparation of most of the carboxylic acids **1** (Y = COOH; X = H[2], CN,[15] CF_3[2], $COCH_3$,[15] $COOCH_3$,[16] F[2], Cl,[15] Br,[15] I,[15] C_6H_5,[17] CH_3,[18] and $C(CH_3)_3$[15]). The preparation of the others (**1**, Y = COOH; X = $Si(CH_3)_3$ and NO_2) are described below.

3-Trimethylsilylbicyclo[1.1.1]pentane-1-carboxylic Acid 1 (X = Si(CH$_3$)$_3$, Y = COOH). A pentane solution (3.23 mL) of 1.7 M *tert*-butyllithium (5.51 mmol, 2 mol equiv) was added dropwise to a stirred solution of 1-bromo-3-(4,4-dimethyl-2-oxazolinyl)bicyclo[1.1.1]pentane **1** (X = Br, Y = Ox; 0.67 g, 2.75 mmol)[19] in anhydrous diethyl ether (25 mL) maintained at −70 °C under nitrogen. The resulting solution was allowed to warm to −50 °C for 15 min before the addition of Me_3SiCl (1 mL). The solution was maintained at this temperature with stirring for 5 min before being allowed to warm to room temperature. The reaction mixture was then quenched with water and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ before the solvents and volatiles were removed in vacuo. Kugelrohr distillation (50 °C/0.5 mmHg) of the residue gave the silyloxazoline **1** (X = $SiMe_3$, Y = Ox) as a colorless oil (400 mg, 61%): ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 2H), 1.90 (s, 6H), 1.26 (s, 6H), −0.043 (s, 9H); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 168.4, 78.5, 67.7, 51.1, 42.6, 30.7, 22.7, −3.6. By use of the procedure of Meyers et al.,[20] a solution of the silyloxazoline (400 mg) in THF (10 mL) was treated with 4.5 M HCl (50 mL) ,and the resulting solution was stirred at room temperature for ca. 20 h. The reaction mixture was then saturated with NaCl and extracted thoroughly with CH_2Cl_2. After the extracts were dried ($MgSO_4$), the solvent was removed in vacuo to afford the crude product which, after sublimation (80 °C/0.2 mmHg), gave the title compound **1** (X = $SiMe_3$, Y = COOH) as a white solid (270 mg, 87%): mp 155−156 °C (lit.[15] mp 165−166 °C); ^{1}H NMR ($CDCl_3$) δ 10.22 (bs, 1H), 1.97 (s, 6H), −0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 175.2, 50.9, 42.8, 30.5, −3.7.

3-Nitrobicyclo[1.1.1]pentane-1-carboxylic Acid 1 (X = NO$_2$, Y = COOH). Powdered sodium azide (284 mg) was added over 3×1 intervals in 1 h[21] to a stirred solution of 3-phenylbicyclo[1.1.1]pentane-1-carboxylic acid **1** (X = C_6H_5, Y = COOH; 410 mg, 2.18 mmol)[17] in $CHCl_3$ (5 mL) containing concentrated H_2SO_4 (0.76 mL) maintained at 35−40 °C. The reaction mixture was kept at this temperature for a further 1 h before being poured into water. The aqueous phase was extracted with $CHCl_3$ before being basified with a 20% NaOH solution and extracted thoroughly with diethyl ether. After the ether extract was dried ($MgSO_4$), the solvent was removed in vacuo to afford the free amine **1** (X = NH_2, Y = C_6H_5) as a yellow oil (300 mg, 87%): ^{1}H NMR ($CDCl_3$) δ 7.32−7.21 (m, 5H), 2.09 (s, 6H), 1.89 (bs, 2H); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 139.8, 128.0, 126.2, 126.17, 55.3, 48.3, 36.6.

A solution of the amine (300 mg) in acetone (5 mL) was added to a freshly prepared solution of dimethyldioxirane[22] in acetone (150 mL), and the mixture was stirred overnight at room temperature. Removal of the solvent in vacuo afforded the crude nitrophenyl derivative **1** (X = NO_2, Y = C_6H_5) as a solid (220 mg, 64%): mp 74−75 °C (lit.[1] mp 81.5−82 °C); ^{1}H NMR ($CDCl_3$) δ 7.40−7.24 (m, 5H), 2.64 (s, 6H); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 135.7, 128.5, 127.6, 126.4, 68.5, 55.2, 35.3. The crude nitrophenyl compound **1** (X = NO_2, Y = C_6H_5; 200 mg, 1.05 mmol) was oxidatively cleaved to the nitro acid **1** (X = NO_2, Y = COOH) by use of ruthenium tetraoxide[23] as recently described for the preparation of the fluoro acid **1** (X = F; Y = COOH) from the corresponding fluorophenyl compound **1** (X = F, Y = C_6H_5).[2] The reddish colored oxidation product was sublimed (80 °C/0.5 mmHg) to afford the desired acid **1** (X = NO_2, Y = COOH) as a light brown powder. A further sublimation followed by recrystallization from benzene gave the nitro acid as white colored rods (100 mg, 55%): mp 156−157 °C (lit.[1] mp 165−165.5 °C); ^{1}H NMR ($CDCl_3$) δ 7.87 (bs, 1H), 2.68 (s, 6H); ^{13}C NMR ($CDCl_3$, relative to Me_4Si) δ 173.2, 64.2, 55.0, 31.4.

Measurement of Gas-Phase Acidities. (i) Methodology. The gas-phase acidity (GPA) of an acid AH is defined as the Gibbs free energy change (ΔG) of the $AH \rightarrow A^- + H^+$ reaction usually defined at 298 K. The gas-phase acidities of the [1.1.1] acids (AH; **1**, Y = COOH) were measured by means of the kinetic method introduced by Cooks and co-workers.[24] This method is based upon the generation of cluster ions $[A{\cdot}H{\cdot}B]^-$, where BH is a suitable reference compound, in an electrospray

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(ESI) source of a FT-ICR spectrometer.[25] The mass-selected $[A{\cdot}H{\cdot}B]^-$ ion is activated by collision with a suitable gas (e.g., N_2), and the fragments ($[A]^-$ and $[B]^-$) arising from the collision-induced fragmentation (CID; eg 1) are mass analyzed.

$$[A]^- \xleftarrow{k_1} [A{\cdot}H{\cdot}B]^- \xrightarrow{k_2} [B]^- \qquad (1)$$

The standard form of the kinetic method allows quantitative determination of the gas-phase acidity of AH provided that certain requirements such as the absence of reverse activation barriers for the two dissociation channels of eq 1 are met. Within this framework the ΔGPA difference (GPA(BH) − GPA(AH)) is calculated from the relative abundances of the individual deprotonated fragments ($[A]^-/[B]^-$) through eq 2.

$$\ln\frac{k_1}{k_2} = \ln\frac{[A]^-}{[B]^-} = \frac{\Delta GPA}{RT_{eff}} \qquad (2)$$

Accordingly, the slope of the linear plot of $\ln([A]^-/[B]^-)$ versus the GPA of a series of reference acids (BH) provides an estimate of the effective temperature term ($T_{eff} = 300$ K), while the *y*-intercept gives the GPA(AH) value.The constraints for the measurement of GPA values by the standard kinetic method are likely met in the case of the [1.1.1] acids (AH; **1**, Y = COOH) since the loss of a proton from carboxylic acids hardly involves reverse activation barriers.

(ii) Procedure. The CID experiments were performed by using a commercial APEX 47e FT-ICR mass spectrometer equipped with an ESI source and a syringe pump. Operating conditions for the ESI source were as follows: spray voltage, 3.8 kV; capillary temperature, 298 K; sheath gas (N_2) flow rate, 30 units (roughly 0.75 L/min). The selected gas-phase complexes were generated by electrospraying at a flow rate of 10 mL/min an acetonitrile solution containing equimolar amounts (10 μM each) of the [1.1.1] acid (AH) and the reference acid (BH). The FT-ICR-CID experiments were carried out in the negative ion mode. The so-formed $[A{\cdot}H{\cdot}B]^-$ complexes were injected from the external source of the instrument into the analyzer, quenched by multiple collision with N_2, admitted into the analyzer via a pulsed valve assembly (the nominal peak pressure was ca. 5×10^{-6} mbar), and eventually isolated by broad-band ejection of the unwanted fragments. Sustained off-resonance irradiation CID experiments were carried out by accelerating the quenched ions with an activation frequency 0.30 kHz higher than the cyclotron frequency of the ion and by allowing them to collide for 1.5 s with N_2 present in the analyzer at the constant pressure of 2×10^{-8} mbar.

pK_a Measurements. Potentiometric titrations were carried out in a water-jacketed vessel maintained at 298.2 K under a stream of argon. Data were obtained from 10 mL aliquots of solution containing 5.0×10^{-3} M HCl, 10^{-1} M KCl, and 1.0×10^{-3} M [1.1.1]-acid titrated with standardized 0.1 M KOH. The latter carbonate-free solution was titrated against oven-dried potassium hydrogen phthalate which was used as the primary standard. An autoburet equipped with a 5 mL buret was used to deliver the titrant, and the potential was measured by a Sure Flow 8165 BN combination electrode connected to a pH meter. The autoburet and pH meter were interfaced to an IBM-compatible personal computer which controlled the addition of titrant using a program AUTOTIT (written by Dr. A. P. Arnold and Dr. P. A. Duckworth) so that successive addition of titrant caused a decrease of ~4 mV in potential. The electrode was calibrated by a titration in the absence of organic acid and fitting the resulting data from this strong acid−base titration to the Nernst equation to find the correct values for $E°$ and pK_w. The pK_a values were determined using the program SUPERQUAD.[26] Three titrations were performed for each [1.1.1]-acid. In addition, the pK_a value of benzoic acid was similarly measured for comparison with literature values. The new value (4.11 ± 0.01) is about 0.10 units less than the best literature values.[27]

Computational Methods

All calculations reported below were carried out at the B3LYP/6-31+G* level of theory utilizing the GAUSSIAN 94 and 98 program packages.[28] Frequency calculations were performed on most of the density functional theory (DFT) optimized geometries to determine zero-point vibrational energies (ZPVE) and, as well, to ensure that there were no imaginary frequencies at the stationary point.

Results and Discussion

Gas-Phase Measurements. The gas-phase acidities (ΔG_{300}; kcal mol^{-1}) of the [1.1.1]-acids (**1**, Y = COOH) are displayed (in red) in Figure 1 together with the values for the various reference acids (in black). The relevant $\Delta\Delta G_{300}$ values are given in blue. It should be noted that no value is reported for the iodo acid (**1**, Y = COOH; X = I) because the corresponding carboxylate ion proved to be fragile under the conditions of measurement (see above). A noteworthy feature is that the methodology of measurement does not provide a reliable determination of the $\Delta\Delta S$ values associated with the competitive collision-induced fragmentation of the adduct (eq 1) between the [1.1.1]-carboxylates (**1**, Y = COO$^-$) and the reference carboxylate ions. However, since both competitors are carboxylic acids, it is assumed that the $\Delta\Delta S$ values are close to zero. It follows that the $\Delta\Delta G$ values coincide with the corresponding $\Delta\Delta H$ parameters. Anchoring the measured $\Delta\Delta G$ values to the reference gas-phase acidities produces the absolute acidity scale for **1** (Y = COOH) shown in red in Figure 1. The relevant absolute ΔH scale (Table 1) is obtained from this by adding to the ΔG_{300} values the $T\Delta S$ term calculated for a free proton with the Sackur−Tetrode equation (7.75 kcal/mol). It can be seen (Table 1) that there is fairly good agreement between the observed and available calculated ΔH values given the respective uncertainties in the numbers. This is exemplified by the very good linear correlation between them (Table 2, entry 1). Thus, the calculated acidities reported by Wiberg[3] at the MP2/6-311++G** theoretical level adequately account for the experimental absolute

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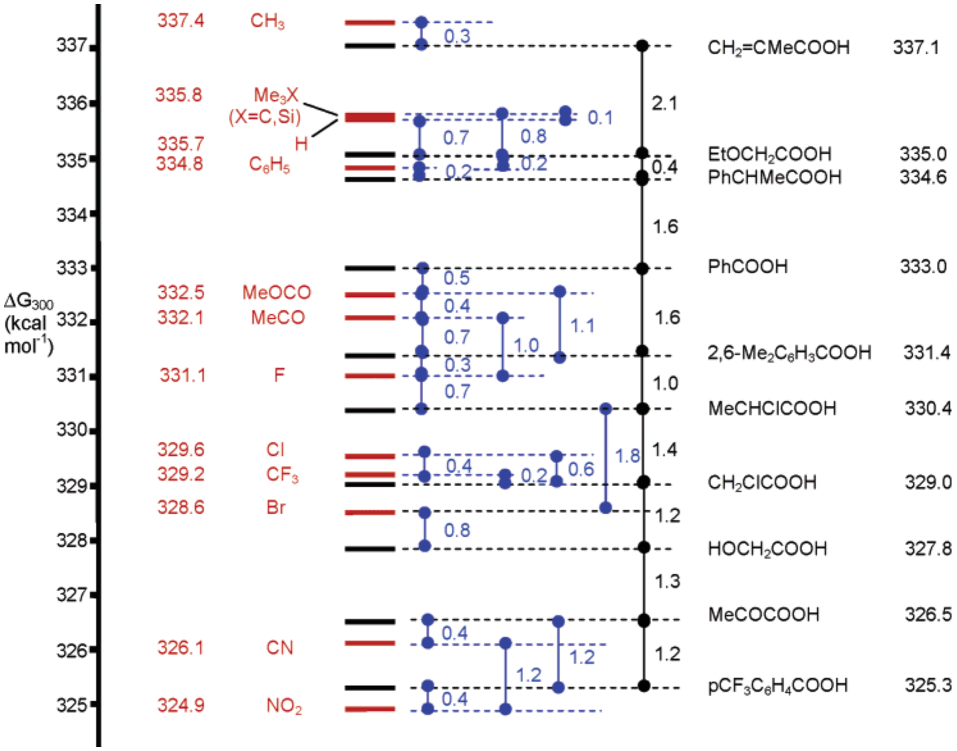

FIGURE 1. Interlocking ladder scale (kcal/mol) of gas-phase acidities of [1.1.1]-acids (**1**, Y = COOH) (in red) and reference acids (in black). $\Delta\Delta G_{300}$ values are given in blue.

TABLE 1. Enthalpies (ΔH, kcal/mol) of Dissociation of [1.1.1]-acids (1, Y = COOH)

X	ΔH_{exp}[a]	ΔH_{calcd}[b]
CH_3	345.15	343.5
$C(CH_3)_3$	343.55	
$Si(CH_3)_3$	343.55	
H	343.45 (342.9)[b]	343.0
C_6H_5	342.55	
$COOCH_3$	340.25	
$COCH_3$	339.85	
F	338.85	336.9
Cl	337.35	336.1
CF_3	336.95	334.8
Br	336.35	
CN	333.85	332.6
NO_2	332.65	330.9

[a] Calculated from the ΔG_{300} values (Figure 1) using the $T\Delta S$ contribution of 7.75 kcal/mol (calculated for a free proton by the Sackur–Tetrode equation). [b] Taken from ref 3.

values. However, it is worth noting that a much lower level of theory (B3LYP/6-31+G*) is equally adequate to describe the relative substituent effects on the acidities. Indeed, as shown in entry 2 of Table 2, an excellent correlation exists between the measured ΔH values (Table 1) and the B3LYP/6-31+G*-calculated energy changes (ΔE_3, kcal/mol) for the isodesmic reaction (eq 3; Table 3).[29]

$$\text{X-[1.1.1]-COOH} + \text{H-[1.1.1]-COO}^- \rightarrow \text{H-[1.1.1]-COOH} + \text{X-[1.1.1]-COO}^- \quad (3)$$

Note also (Table 2, entry 3) that the observed ΔH values correlate very well against polar field constants (σ_F) determined from the ^{19}F substituent chemical shifts (SCS) in c-C_6H_{12} of 1-substituted (X) 4-(p-fluorophenyl)-bicyclo[2.2.2]octanes (**2**, Y = p-FC_6H_4).[11] The fact that these σ_F values in nonpolar solvents mirror the gas-phase environment is clearly underlined by a correlation of very high precision (r = 0.997, n = 12) between them and recently published available energies (ΔE_4, kcal/mol) calculated at the B3LYP/6-311+G** level of theory of the isodesmic reaction (eq 4) for system **2** (Y = COOH). This result is particularly significant since the solution acidity data of **2** (Y = COOH)

$$\text{X-[2.2.2]-COOH} + \text{H-[2.2.2]-COO}^- \rightarrow \text{H-[2.2.2]-COOH} + \text{X-[2.2.2]-COO}^- \quad (4)$$

together with those of 4-substituted (X) quinuclidinium ions, underpin the empirical parameters ($\sigma_I \equiv \sigma_F$) which are believed to characterize polar field effects of substituents.[30] Thus, an obvious corollary from the very good correlation (Table 2, entry 3) between ΔH of **1** (Y = COOH) and σ_F is that the gas-phase acidities of **1** (Y = COOH) and **2** (Y = COOH) should parallel one another. This is clearly the case as revealed by the good correlation between them (Table 2, entry 4). The regression coefficient (1.295), which indicates an enhancement of polar substituent effects in **1** (Y = COOH), is in good agreement with the value (1.33) obtained by Wiberg[3] from a plot between the respective calculated ΔH parameters. The

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[29] The isodesmic energies listed in Table 3 are uncorrected (0.98 ZVPE corrections effect only minor perturbations).

[30] Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165 and references therein.

TABLE 2. Regression Statistics of Correlative Analyses[a]

entry	y^b	x^c	m^d	c^e	r^f	F^g	p^h	n^i
1	ΔH_{obs}[1.1.1]	ΔH_{calcd}[1.1.1]	0.950	18.322	0.994	398.896	<0.0001	7
2	ΔH_{obs}[1.1.1]	ΔE_{calcd}[1.1.1]	0.857	344.197	0.992	586.726	<0.0001	12
3.	ΔH_{obs}[1.1.1]	$\sigma_F{}^k$	−16.977	344.319	0.983	315.759	<0.0001	13
4.	ΔG_{obs}[1.1.1]	ΔG_{obs}[2.2.2]^j	1.295	−108.480	0.974	109.528	<0.0001	8
5.	ΔE_{calcd}[1.1.1][1.1.1]	ΔE_{calcd}[1.1.1]	0.495	0.095	0.996	1129.848	<0.0001	10
6	ΔpK_a	ΔG_{obs}[1.1.1]	0.081	−23.316	0.945	41.739	0.0013	7
7.	ΔpK_a	$\sigma_F{}^l$	−1.623	4.023	0.974	91.690	0.0002	7

[a] Simple linear regression, $y = mx + c$. [b] Dependent, variable. [c] Independent variable. [d] Regression coefficient. [e] Intercept. [f] Correlation coefficient. [g] F-test of variance for overall correlation. [h] Probability value. [i] Number of data points in correlation. [j] Taken from ref 8. [k] c-C_6H_{12}, taken from ref 11. [l] CH_3OH, taken from ref 11.

TABLE 3. Energies (ΔE, kcal/mol) of Isodesmic Reactions (eqs 3 and 5, Respectively)[a]

X	ΔE_3(eq 3)	ΔE_5(eq 5)
CH_3	0.57	0.32
$C(CH_3)_3$	−0.04	
$Si(CH_3)_3$	−0.79	
H	0.00	0.00
NH_2	−0.34	−0.12
C_6H_5	−2.29	
OH	−2.70	−1.18
$COOCH_3$	−4.63	−1.96
$COCH_3$	−5.67	
F	−6.55	−3.09
Cl	−8.92	−3.94
CF_3	−8.53	−4.50
CN	−11.09	−5.48
NO_2	−13.16	−6.47

[a] See the Supporting Information for B3LYP/6-31+G*-calculated energies and zero-point energies (ZPE) of the various structures.

TABLE 4. Acidities of [1.1.1]-Acids (1, Y = COOH) in H_2O at 298.2 K

X	$pK_a{}^a$
CH_3	4.12 ± 0.03
H	3.95 ± 0.00
$COOCH_3$	3.51 ± 0.10
F	3.29 ± 0.05
CF_3	3.25 ± 0.05
CN	3.21 ± 0.01
NO_2	3.08 ± 0.03

[a] Determined by potentiometric titration. Given as the mean of 3 × 1 titrations.

origin of the enhancement was ascribed to an increase in the field effect as the distance decreases and, moreover, is in agreement with the ratio (1.32) based on a distance dependency of $1/r^2$ from simple electrostatic theory (Kirkwood−Westheimer (K−W) equation).[31] However, it is highly probable that the latter accord is fortuitous given that one of the key approximations in the derivation of the K−W equation, namely, that the length of the substituent dipole is very small compared to the distance between the substituent and reaction center, is questionable on the molecular scale. Recently, a modified field effect model has been proposed with a “falloff” with distance considerably less than that expected from simple electrostatics.[32] Interestingly, a comparison of the gas-phase acidities of 4-substituted (X) quinuclidinium and bicyclo[2.2.2]octylammonium ions appears to support this proposition.[10] In view of the uncertainty in the actual dependence of the field effect on distance we decided to perform a stringent test by comparing the energetics of reaction 3 with those of reaction 5 in which the corresponding bis-bicyclopentyl compounds ([2]staffanes)[33] are deployed. These rod-shaped cage-structure compounds appear to be ideal molecular spacers for this purpose for three reasons: (i) the distance between the two systems being compared

$$\text{X-[1.1.1]-[1.1.1]-COOH} + \text{H-[1.1.1]-[1.1.1]-COO}^- \rightarrow \text{H-[1.1.1]-[1.1.1]-COOH} + \text{X-[1.1.1]-[1.1.1]-COO}^- \tag{5}$$

is now markedly different; (ii) no problem is created by an angle orientation factor; (iii) the B3LYP/6-31+G* level of theory, which was shown above to be adequate for describing relative substituent effects on acidities, can be economically and conveniently applied to these relatively large systems.

It can be seen (Table 2, entry 5) that the linearity between ΔE_5 and ΔE_3 (listed in Table 3) is excellent with a regression coefficient of 0.495. This measure of the “falloff” with distance is clearly not in agreement with either the square of the ratio of the distances between the bridgehead hydrogens and the carboxylate oxygens in the respective systems ($(5.184/8.507)^2 = 0.371$) or simply the ratio of the distances ($5.184/8.507 = 0.609$). In fact, it lies somewhere between $1/r$ and $1/r^2$ and, hence, gives credence to the proposal that the field effect model requires modification.[32]

pK_a Measurements. The pK_a values for some of the [1.1.1]-acids (**1**, Y = COOH) were determined in water and are given in Table 4. Values for the chloro and bromo acids could not be determined due to their rapid solvolyses. In several cases (X = $C(CH_3)_3$, $Si(CH_3)_3$, C_6H_5, and $COCH_3$), solubility was an intractable problem. The correlation between these pK_a values (Table 4) and the corresponding gas-phase acidities (Figure 1) is not of high precision (Table 2, entry 6), but a strong linear trend is indicated. Hence, the solution acidity trends can clearly be predominantly attributed to intrinsic structural factors. The significantly improved fit of the correlation between the pK_a values and the σ_F values for methanol

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(31) (a) Westheimer, F. H.; Kirkwood, J. G. *Trans. Faraday Soc.* **1947**, *43*, 77 and references therein. (b) Bowden, K.; Grubbs, E. J. *Chem. Soc. Rev.* **1996**, *25*, 171 and references therein.

(32) (a) Charton, M. *J. Phys. Org. Chem.* **1999**, *12*, 275. (b) Charton, M.; Charton, B. I. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2203.

(33) Kaszynski, P.; McMurdie, N. D.; Michl, J. *J. Am. Chem. Soc.* **1991**, *56*, 307.

(Table 2, entry 7) attests to specific substituent−solvent interactions having a minor bearing on the trends.

Conclusions

The experimental gas-phase acidity data of the [1.1.1]-acids (**1**, Y = COOH) presented in this paper corroborate calculated values determined at a high level of theory (MP2/6-311++G**//B3LYP/6-311+G**) recently reported by Wiberg.[3] The relative substituent effects on the acidities, however, are accurately described by a much lower level of theory (B3LYP/6-31+G*). The origin of these effects can be ascribed exclusively to an electrostatic effect of the substituent dipole acting directly through space. Cross-cage interactions due to the proximity of the bridgehead positions (ca. 1.85 Å) appear to be negligible. This picture corroborates an earlier deduction of Applequist et al.[1] that some solution acidities of such acids could be described satisfactorily in terms of an electrostatic field model. Further, it is in agreement with recent evidence presented by Wiberg[3] for the operation of polar field effects rather than inductive transmission through bonds. By contrast, it is worth noting that the use of charge density probes in the [1.1.1]-system (**1**, Y = F and $Sn(CH_3)_3$) reveals the importance of electron delocalization effects rather than polar field effects.[4−6]

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Supporting Information Available: Electronic energies (*E*) and zero-point vibrational energies (ZPVE) obtained from DFT calculations (B3LYP/6-31+G*) for 3-substituted (X) bicyclo[1.1.1]pentane-1-carboxylic acids, 3′-substituted (X) 1′,3-bibicyclo[1.1.1]pentane-1-carboxylic acids, and their corresponding anions (Tables S1 and S2); Cartesian coordinates of bicyclo[1.1.1]pentane-1-carboxylic acids and their corresponding anions; ^1H and ^{13}C NMR spectra of 3-nitro- and 3-trimethylsilylbicyclo[1.1.1]pentane-1-carboxylic acids **1** (Y = COOH; X = NO_2 and $Si(CH_3)_3$, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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