Substituent Effects on the Acidity of Weak Acids. 1. Bicyclo[2.2.2]octane-1-carboxylic Acids and Bicyclo[1.1.1]pentane-1-carboxylic Acids

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The acidities of 3- and 4-substituted bicyclooctane-1-carboxylic acids and 3-substituted bicyclo[1.1.1]pentane-1-carboxylic acids have been calculated at the MP2/6-311++G** theoretical level. There is good agreement between the calculated and observed gas-phase acidities. The acidities of the 4-substituted bicyclooctane acids were found to be linearly dependent on the C−X bond dipoles, as expected from a field effect. The substituents had a negligible effect on the electron density at C1. The difference in acidity between 4-chlorobicyclo[2.2.2]octane-1-carboxylic acid and the parent acid (6.2 kcal/mol) is reproduced by the Kirkwood−Westheimer treatment of substituent effects on acidity, but only if the bicyclooctane ring is given an effective dielectric constant of unity. The acidities of the 3-substituted bicyclooctane acids are linearly related to the corresponding 4-substituted acids with a slope of 0.9. The acidities of the 3-substituted bicyclo[1.1.1]pentane-1-carboxylic acids are linearly related to the C−X bond dipoles for this ring system (which are different than those for the bicyclooctanes), and they are also linearly related to the acidity of the 4-substituted bicyclo[2.2.2]octanecarboxylic acids with a slope of 1.34. The larger slope is due to the smaller bridgehead−bridgehead distance in the bicyclopentane ring than in bicyclo[2.2.2]octane.

The effect of substituents on the acidity of benzoic acids has received much study[1] and forms the basis of Hammett's σ/ρ linear free energy correlation.[2] It is generally recognized that these substituent effects have several components: a through-space field effect, a through-bond inductive effect, and a π-electron effect.[1] In an effort to separate these effects, Roberts and Moreland pointed out that the distance between the substituent and the carboxylate group for 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids is essentially the same as for the corresponding benzoic acids, but they eliminate the π-electron effect.[3] They prepared and measured the acidity of a number of these acids and proposed their use to determine σ_I, the inductive plus field effect. Subsequently, Stock measured the acidity of additional substituted acids.[4] The gas-phase acidities of a number of these acids also have been determined.[5]

As an initial part of a computational study of substituent effects on weak organic acids, we have examined the 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids. Despite the importance of these data, there have been relatively few computational studies of the substituent effects, and even fewer that make use of flexible basis sets and correction for electron correlation.[5] Therefore, we have carried out ab initio calculations of the acidity of a number of these acids in order to expand the available data. To complement these data, we have examined the corresponding 3-substituted bicyclo[2.2.2]octane-1-carboxylic acids, which are related to the *m*-substituted benzoic acids, and also the 3-substituted bicyclo[1.1.1]pentane-1-carboxylic acids in which the through-space effect should be larger than that for the bicyclooctane series because of the shorter bridgehead−bridgehead distance.

Calculations

The energies of the acids and their ions were obtained by geometry optimizations at the B3LYP/6-311+G* theoretical level, followed by the calculation of the vibrational frequencies at the same level. This allowed correction for zero-point energies and conversion of the calculated 0 K energies to 298 K. The B3LYP hybrid density functional model[6] that corrects for the effect of electron correlation has been found to usually give good relative energies in a wide range of systems.[7] The basis set is reasonably flexible and includes diffuse functions that are needed for anionic systems.[8]

The effect of basis set on the calculated energies was examined using the B3LYP/6-311+G* geometries. The use of 6-311++G** uniformly increased the calculated ΔH_{acid} by 3.6 kcal/mol, and 6-311++G(2df,2pd) gave a further small increase. The added diffuse and polarization functions at hydrogen presumably improve the description of the OH bond that is broken in the ionization process. The calculated acidities were still somewhat smaller than the observed values, and it was found that MP2/6-311++G** gave calculated acidities in better agreement with the experimental values.[9] In related

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(1) For a detailed analysis of the separation of the various components of the substituent effects, see: Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1.

(2) Hammett, L. P. *Chem. Rev.* **1935**, *11*, 125. Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: New York, 1940.

(3) Roberts, J. D.; Moreland, W. T. *J. Am. Chem. Soc.* **1953**, *75*, 2167.

(4) Stock, L. M. *J. Chem. Educ.* **1972**, *49*, 400 and references therein.

(5) Koppell, I. A.; Mishima, M.; Stock, L. M.; Taft, R. W.; Topsom, R. D. *J. Phys. Org. Chem.* **1993**, *6*, 685.

(6) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. Stephens, P. J.; Devlin, F. J.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

(7) Koch, W.; Holthausen, M. C. *A Chemist's Guide to Density Functional Theory*; Wiley-VCH: Weinheim, 2000.

(8) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R *J. Comput. Chem.* **1983**, *4*, 294.

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studies we have found that the use of the larger basis set with MP2 gave a negligible further change in the calculated acidities.[10]

The distribution of atomic charges is of interest for the acids and their anions, particularly with regard to the mechanisms by which substituent effects are expressed. There are many ways in which the charges can be calculated.[11] The Mulliken population analysis[12] fails when extended basis sets and diffuse functions are used.[13] The Natural Population Analysis[14] is not subject to these problems but leads to exaggerated C−H bond dipoles[15] that are inconvenient in the present context. We have chosen to use the Hirshfeld charges[16] which should be ideal for calculating the changes caused by remote substituents. Here, a 3D grid is placed about the molecule in question, and the electron density is calculated at each point from the molecular wave function. A *promolecule* is constructed by placing *proatoms* (spherically symmetrical neutral atoms) at each of the nuclear positions for the real molecule. At each point on the grid, the contribution to the electron density from each of the *proatoms* is calculated, and the density of the real molecule is partitioned among its atoms in proportion to the contributions from the *proatoms*.

4-Substituted Bicyclo[2.2.2]octane-1-carboxylic Acids. In view of the wide use of the acidity of these acids, we have calculated the gas-phase acidities of the bicyclo[2.2.2]octane-1-carboxylic acids to supplement the available gas-phase experimental data.[6] The geometries were obtained at the B3LYP/6-311+G* level followed by energy calculations using MP2/6-311++G**. In the geometry optimizations for the acids, it was found that the lower energy conformer was the one with the C═O group eclipsed with one of the ring C−C bonds. The alternate structure in which the C−O−H group eclipses a ring C−C bond was found to be a transition state. This was also true for the substituted acids. The orientation of the substituent also was examined. The CH_3, CF_3, OH, NH_2, and SH groups were staggered with respect to the ring carbons. The NO_2 and CHO groups had one bond to oxygen eclipsed with a ring C−C bond.

The gas-phase acidities (ΔH_{acid}) are defined as the enthalpy change for $HA \rightarrow A^- + H^+$. The calculated acidities were obtained from the total energies of HA and A^-, corrected for the zero-point energies and the change in enthalpy on going to 298 K.[9] The electronic energy of the proton is zero, but at 298 K it has translational entropy and a $\Delta(pV)$ term. The sum of these terms is 1.5 kcal/mol.

Experimental proton affinities (ΔG_{acid}) were taken from the NIST Chemistry Webbook[17] and were converted to ΔH_{acid} using the average $T\Delta S$ contribution of 7.2 kcal/mol.[18] The relative uncertainties for the series of acids is about ±0.5 kcal/mol, and the absolute acidities have an estimated uncertainty of ±2.5−3.0 kcal/mol.[18] The calculated acidities (MP2/6-311++G**) are compared with the experimental values in Figure 1. The numerical data are available as Table S1 of the Supporting Information. The agreement is satisfactory, with a slope of 1.00 and a small intercept. The rms deviation between experiment and theory was 0.4 kcal/mol Thus, the calculations are quite satisfactory.

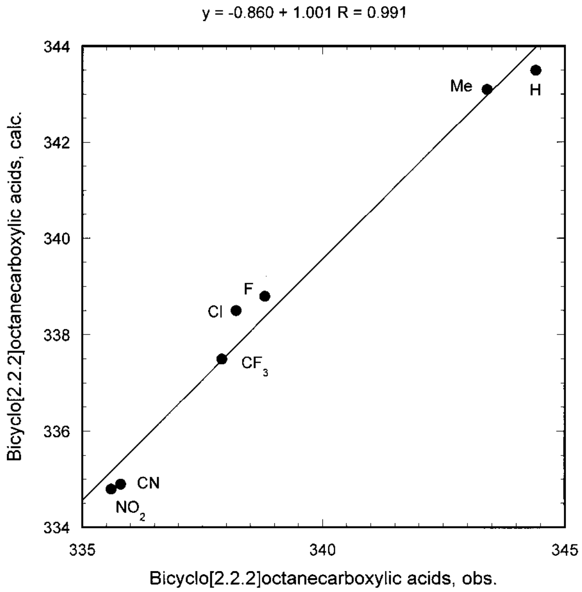

Figure 1. Relationship between the calculated and observed acidities of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids, kcal/mol.

The effect of the second-row substituents on acidities is interesting. Silicon is less electronegative than carbon,[19] but the silyl-substituted acid is more acidic than the methyl-substituted acid (Figure 2). Sulfur is about as electronegative as carbon, but the SH-substituted acid is considerably more acidic than the parent acid. One might think that the increased acidity of the acids with second-row substituents is a polarization effect, as found in comparing methanol and *tert*-butyl alcohol[20] and other cases. However, we shall show below that it is due to the larger C−X bond dipoles in these acids.

Since π-electron interactions are eliminated, there can only be through-space and through-bond interactions. It is generally believed that the former is the more important factor in this case.[1] However, the calculations provide a means for examining these interactions. If through-bond interactions are important, there should be a change in the electron densities at the carbon adjacent to the carboxylate group. On the other hand, if the through-space interactions are important, there should be a linear relationship between the acidity and the bond dipole of the C−X bond.[21]

A calculation of the Hirshfeld charges found that the charge at C1 is essentially unchanged for the full range

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(9) The full data are available as Supporting Information.

(10) This was found in a study of substituted benzoic acids (to be published). The use of the larger basis set with the present compounds was not practical because of their size.

(11) Wiberg, K. B.; Rablen, P. R. *J. Comput. Chem.* **1993**, *14*, 1504.

(12) Mulliken, R. S. *J. Chem. Phys.* **1962**, *36*, 3428.

(13) As an example, with the 6-311+G* basis set the Mulliken population analysis gives a negative charge at the carbonyl carbon of benzoic acid (−0.110) even though it is connected to two electronegative oxygens. The NPA charge is +0.794 and the ChelpG (Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361) charge is +0.665.

(14) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735. Reed, A. E.; Weinhold, F.; Curtiss, L. A. *Chem. Rev.* **1988**, *88*, 899.

(15) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1986**, *84*, 2428.

(16) Hirshfeld, F. L. *Theoret. Chim. Acta* **1977**, *44*, 129.

(17) www.webbook.nist.gov. The original data are from ref 5.

(18) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Sup 1.

(19) Allred, A. L.; Rochow, E. G. *J. Inorg. Nucl. Chem.* **1958**, *5*, 264.

(20) Brauman, J. I.; Blair, L. K. *J. Am. Chem. Soc.* **1968**, *90*, 6561.

(21) Bjerrum, N. *Z. Phys. Chem.* **1923**, *106*, 219. The distance between the substituent and the carboxyl oxygens is essentially constant in this series.

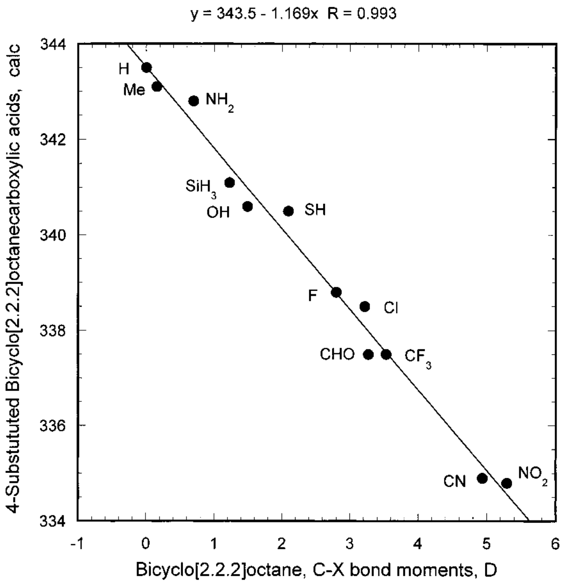

Figure 2. Relationship between the calculated acidities of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids and the C−X bond dipoles.

of substituents (Table S2, Supporting Information). Thus, there is no indication of a through-bond interaction. The C−X bond dipoles were obtained by taking the geometry of the carboxylate anions, replacing the carboxylate group by a hydrogen using a standard geometry, and calculating the dipole moments. This was done because the bicyclo[2.2.2]octane ring system is quite flexible, and a representative geometry for the anion was desired. The values are included in Table S1. The correlation between the acidities and the bond dipole is shown in Figure 2. The agreement is quite good, indicating that the through-space interaction is dominant in this case.

A further test of this hypothesis can be found in the dipole moments of the acids. If the two groups (i.e., C−X and $C-CO_2H$) were independent, the dipole moments of the substituted acids should be the vector sum of the dipole moments of the substituted hydrocarbons and that of the parent bicyclic acid. One would not expect exact agreement since there are some changes in geometry, and the effects of the substituents are somewhat felt in the methylene groups ortho to them. The predicted dipole moments are compared with the observed values in Table S3. In most cases the agreement is quite good with differences between calculated and observed moments being less than 0.2 D out of a range of 5 D. In two cases, SiH_3 and CHO, the difference was somewhat greater (0.34 and 0.37 D).

It has been suggested that electrostatic interactions would be moderated by the part of the molecule that lies between the two centers,[22] and this has been made explicit in the Kirkwood−Westheimer treatment of the effect of substituents on acidity.[23] The part of the molecule through which the interaction between the substituent's dipole and the charged center (carboxylate anion) occurs is given a dielectric constant of 2, corresponding to cyclohexane, and the part of the interaction that passes through the solvent is given the dielectric constant of the solvent.

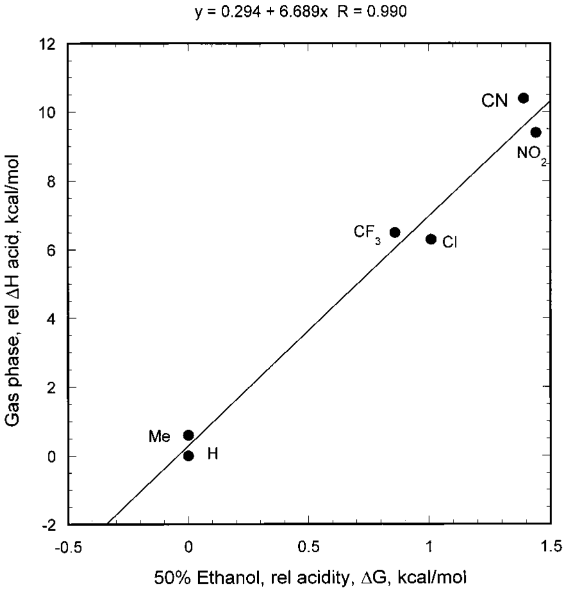

Figure 3. Relationship between the gas-phase and solution (50% ethanol) acidities of 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids, kcal/mol.

The data for the bicyclo[2.2.2]octanecarboxylic acids may be used to test this idea. Here, the interpretation of the results is simplified since the external medium has a dielectric constant of 1. We may use the Kirkwood−Westheimer equation:

$$\Delta\Delta H \sim \Delta\Delta G = e\mu \cos \alpha/r^2 D_E = 69.13\mu \cos \alpha/r^2 D_E \quad \text{kcal/mol}$$

where e is the charge of an electron, μ is the bond dipole of the C−X bond, r is the distance between the center of the C−X bond and the carboxylate oxygens, α is the angle between the C−X bond and the line to the anionic site (essentially 0 in the present case), and D_E is the effective dielectric constant. In the latter expression, μ is given in D and r in Å.

With 4-chlorobicyclo[2.2.2]octane-1-carboxylate, the distance between the center of the C−Cl bond and the carboxylate oxygens is 5.77 Å and the bond dipole is 2.959 D. Using $D_E = 1$, the calculated $\Delta\Delta G = 6.2$ kcal/mol, which is in exact agreement with the experimental change in acidity on going from the unsubstituted acid to the 4-chloro acid. Although the exact agreement must be fortuitous, these results clearly show that, at least for this system, the effective dielectric constant is essentially the same as that for the gas phase. Thus, the apparent dielectric constant of the bicyclooctane ring appears to be close to 1.

If the field effect is the only important contributor to changes in acidity with the changes in substituents, the ratio of the gas-phase energy changes to those observed in solution should be a good approximation to the effective dielectric constant for these acids in the solution. A plot of the gas-phase data against that for 50% ethanol[3,4] is shown in Figure 3. Although the available data set is small, the correlation is fairly good, leading to an effective dielectric constant of 6.6 for these acids in 50% ethanol. It appears that the solvent effect on the acidity of these acids may provide a useful measure of effective dielectric constants. Although some data are available for acidities in methanol and in DMSO,[24] they

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[22] Eucken, A. *Angew. Chem.* **1932**, *45*, 203.

[23] Kirkwood, J. G.; Westheimer, F. H. *J. Chem. Phys.* **1938**, *6*, 506. Westheimer, F. H.; Kirkwood, J. G. *J. Chem. Phys.* **1938**, *6*, 513.

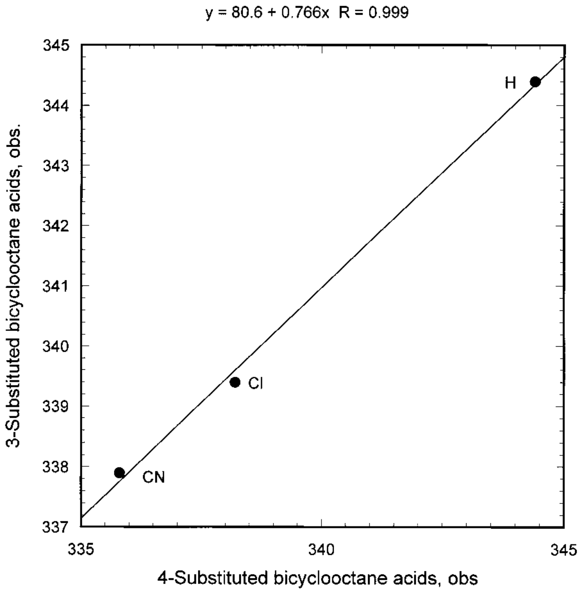

Figure 4. Relationship between the observed acidities of 3- and 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids, kcal/mol.

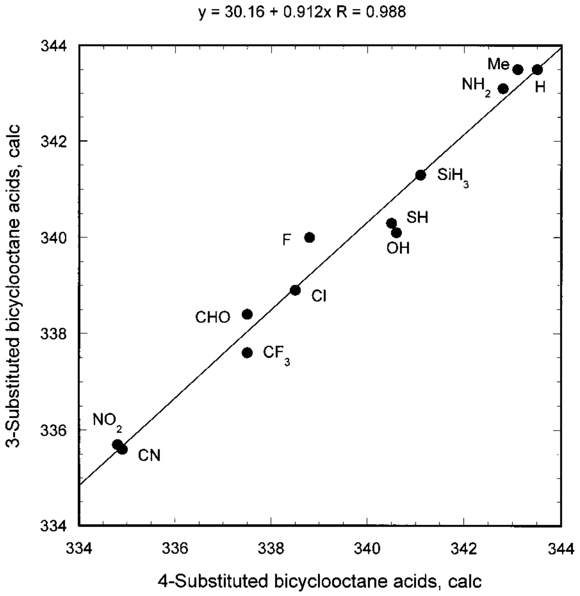

Figure 5. Relationship between the calculated acidities of 3-substituted and 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids.

are not sufficient for estimating the effective dielectric constants for these solvents.

3-Substituted Bicyclo[2.2.2]octane-1-carboxylic Acids. The 3-substituted acids are geometrically related to the *m*-substituted benzoic acids. The substituent is brought somewhat closer to the carboxylate group as compared to the 4-substituted acids, but the angle between the vector from the center of the substituent group and the carboxylate group would lead to a smaller effect. Figure 4 shows the relationship between the observed gas-phase acidities of the 3- and 4-substituted acids. Although there are limited data, there is a good linear relationship with a slope of 0.8. This indicates that the angle is the dominant factor.

To examine a wider range of substituents, the energies of the 3-substituted acids and their anions were obtained by geometry optimization at the B3LYP/6-311+G* level, including a calculation of the vibrational frequencies. When attached to a bridge that is not coupled with the acid's carbonyl group, the substituent can be oriented either toward the C=O group or the C−OH group of the acid. Both orientations were examined, and the full data are available as Supporting Information. The MP2/6-311++G** energies were obtained for the lower energy conformers using the B3LYP geometries. The calculated ΔH_{acid} are summarized in Table S4 of the Supporting Information.

It was of interest to compare the calculated acidities of the 3- and 4-substituted acids, and this is shown in Figure 5. There is a good agreement with a slope of 0.9.

3-Substituted Bicyclo[1.1.1]pentane-1-carboxylic Acids. The bicyclo[1.1.1]pentane-1-carboxylic acids provide an interesting complement to the 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids. The main difference is the shorter bridgehead−bridgehead distance in the bicyclo[1.1.1]pentane series. This should lead to larger changes in acidity with changes in substituents.

Another factor may be significant in the bicyclopentane series. In bicyclo[1.1.1]pentane the NMR coupling constant between the bridgehead hydrogens is 18 Hz,[25] presumably due to the coupling of the bridgehead C−H bond orbitals. This will be much less important for the bicyclo[2.2.2]octane derivatives because of the greater bridgehead−bridgehead distance.[26] Will this coupling mechanism have any effect on the substituent effect in the bicyclopentane series?

The acids and their anions were studied by geometry optimization at the B3LYP/6-311+G* level, including the calculation of the vibrational frequencies. MP2/6-311++G** energies were calculated using the B3LYP geometries. The calculated acidities are given in Table S5 (Supporting Information), along with the calculated C−X bond dipoles that were obtained by geometry optimizations for substituted bicyclopentanes. There is only one measured gas-phase acidity, and there is good agreement between the calculated and observed values. The atomic charges were calculated and are given in Table S6.

Whereas the charge at C1 (the ipso carbon) is not affected by substituents in the bicyclooctane series, there is a small effect with the bicyclopentanes. However, the charges for the carboxylate ions are essentially the same as for the acids, and the change in charge on ionization is negligible. Thus, it appears that the substituent effects also result from the field effect in this case.

This is confirmed by the linear relationship between the acidity and the C−X bond dipoles (Figure 6). The relationship between the acidities of the bicyclopentane and bicyclooctane acids is explored in Figure 7, giving a slope of 1.33. The increased sensitivity toward substituents for the bicyclopentane acids results from the shorter bridgehead−bridgehead distance as compared to that of the bicyclooctanes. With bicyclo[2.2.2]octane-1-carboxylate, the distance between the hydrogen at C4 and the carboxylate oxygens is 6.01 Å whereas with the

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(24) Koppel, I.; Koppel, J.; Korgesaar, A.; Pihl, V. *Org. React. (Tartu)* **1988**, *25*, 272.

(25) Wiberg, K. B.; Connor, D. S. *J. Am. Chem. Soc.* **1966**, *88*, 4473.

(26) The bridgehead−bridgehead H−H NMR coupling is 1.5 Hz in bicyclo[2.2.1]hexane (King, R. W.; Butler, P. E. *Book of Abstracts*; 142nd National Meeting of the American Chemical Society, Atlantic City, Sept 1962; American Chemical Society: Washington, DC, 1962; Abstract p 84Q), and will surely be smaller in bicyclo[2.2.2]octane.

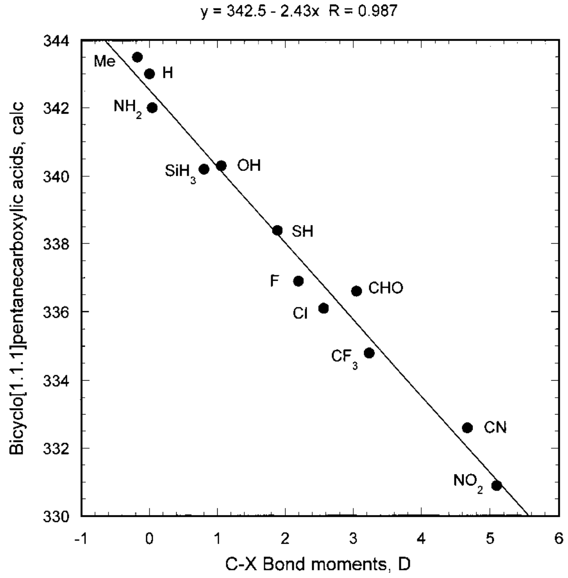

Figure 6. Relationship between the calculated acidities of 3-substituted bicyclo[1.1.1]octane-1-carboxylic acids and the C−X bond dipoles.

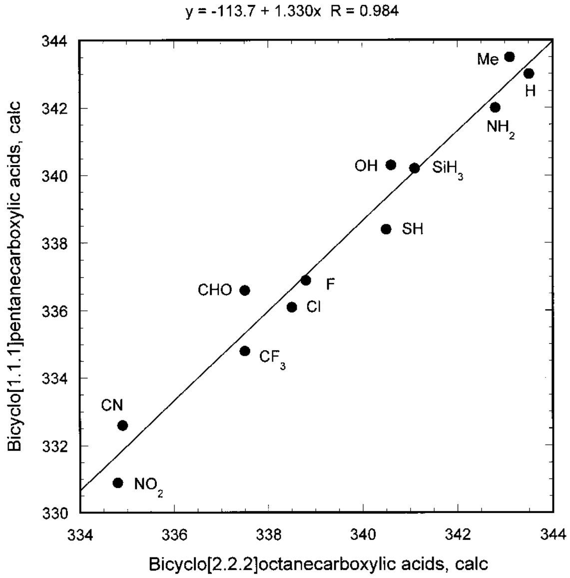

Figure 7. Relationship between the calculated acidities of 3-substituted bicyclo[1.1.1]pentane-1-carboxylic acids and 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids..

corresponding bicyclopentane carboxylate the distance is 5.23 Å. The square of the ratio of these distances is 1.32, in good agreement with the slope in Figure 7.

The relationship between the acidities shown in Figure 7 suggests that there should also be a relationship between the C−X bond dipoles for the two series. This is examined in Figure 8, and there is a linear relationship with a slope near unity. However, there is a constant difference of 0.5 D, reflecting the higher s-character in the C−X bonds for the bicyclopentanes as compared to the bicyclooctanes.[27]

Summary. The effect of substituents on the acidities of the bicyclic carboxylic acids results from a field effect,

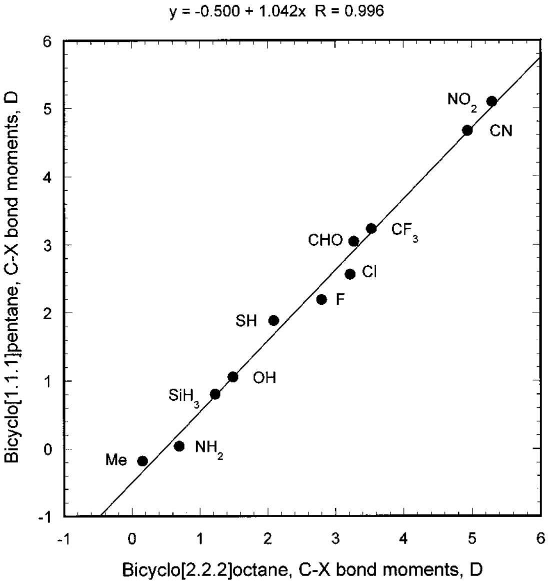

Figure 8. Relationship between the C−X bond dipoles for the bicyclooctanes and bicyclopentanes.

as shown by the linear dependence of the acidity on the C−X bond dipoles. Substituents have essentially no effect on the electron density at the carbon attached to the carboxylic acid group. A comparison of 3- and 4-substituted bicyclo[2.2.2]octanecarboxylic acids found the former to be less affected by substituents than the latter. The 3-substituted bicyclo[1.1.1]pentanecarboxylic acids are more sensitive to substituents than the 4-substituted bicyclo[2.2.2]octanecarboxylic acids because of the shorter bridgehead−bridgehead distance.

Experimental Calculations

The ab initio calculations were carried out using Gaussian-99.[28] The Hirshfeld charges were calculated using a program written by Paul Rablen.[29]

Acknowledgment. This investigation was supported by a grant from the National Science Foundation. I thank Prof. John Bartmess for helpful suggestions.

Supporting Information Available: Tables of calculated gas-phase acidities, charge distributions, dipole moments, and MP2/6-311+G* optimized geometries. This information is available free of charge via the Internet at http://pubs.acs.org.

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(28) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortis, J. V.; Baboul, A. G.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.;. Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T. A.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian 99, Development Version (Rev. B), Gaussian, Inc., Pittsburgh, PA, 1998.

(29) Paul Rablen, Ph.D. Thesis, Yale, 1994.