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Strained Ring Systems. 16.[1a] Substituent Effects on the pK_a Values of *cis*- and *trans*-1,2-Dimethyl-2-X-cyclopropane-1-carboxylic Acids and Related Bicyclo[*n*.1.0]alkane-1-carboxylic Acids

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Abstract: The syntheses of certain 3-X-bicyclo[1.1.0]butane-1-carboxylic acids ([1.1.0] **1**; X = $CONH_2$, CO_2CH_3, CO_2H), *cis*- (cis **4**; X = H, CO_2CH_3, Br, CO_2H) and *trans*-1,2-dimethyl-2-X-cyclopropane-1-carboxylic acids (trans **5**; X = H, $CONH_2$, CO_2CH_3, Br, CN, CO_2H), are reported. The thermodynamic pK_a values in water at 25 °C were determined for these compounds as well as the related derivatives of 5-X-bicyclo[3.1.0]hexane-1-carboxylic acid ([3.1.0] **3**; X = H, $CONH_2$, CO_2CH_3, Br, CN, CO_2H) and 4-X-bicyclo[2.1.0]pentane-1-carboxylic acid ([2.1.0] **2**; X = H, $CONH_2$, CO_2CH_3, CN, CO_2H) previously syntheized, as were the pK_2 values for the dicarboxylic acids. Plots of pK_a values vs. σ_I substituent constants for these five series of acids, and of the substituent effects in the cis **4**, [3.1.0] **3**, [2.1.0] **2**, and [1.1.0] **1** series relative to that same substituent's effect in the trans **5** series where intramolecular hydrogen bonding is not possible are developed and discussed. In general, intramolecular hydrogen bonding in these four series of acids, **1**–**4**, was at a maximum in the [2.1.0] **2** series and minimal in the [1.1.0] **1** series. This is unusual since intramolecular hydrogen bonding was predicted to be the greatest in the [1.1.0] **1** series on the basis of the distance separating X and CO_2H at the bridgeheads. This anomaly was resolved by considering a strong ring C_1–C_3 bond interaction with CO_2H carbonyl carbon stabilizing the *perpendicular* conformer (**15**). This approach was supported by INDO MO calculations on bicyclo[1.1.0]butane-1-carboxylic acid and its carboxylate anion where the *perpendicular* conformations were preferred in both structures by 5.2 and 3.1 kcal/mol, respectively. A related but attenuated effect was presented to explain the lower than predicted acidity of cyclopropanecarboxylic acid which was used to discuss the substituent effects in the trans **5** and cis **4** series.

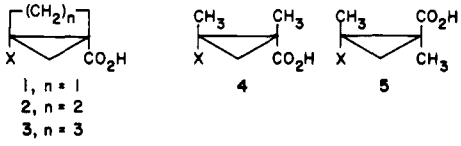
In the area of structure–property relationships of aliphatic compounds, the change in the acidities of carboxylic acids with structural variations continues to be a frequently used probe. The effects of remote, nonconjugated substituent groups on the reaction center have been examined by both the inductive and field effect models.[2] The results of various recently reported studies with several polycyclic systems[2,3] lead to the conclusion that the field model, not the inductive model, accurately describes the mechanism by which these substituent effects are transmitted. Correlations of such substituent effects with the empirical parameter σ_I have been successful, although the precise meaning of these correlations has been controversial.

From the above brief discussion we can conclude that the

roles of remote, nonconjugated substituent effects on reactivity of a reaction center are predictable and reasonably well understood. However, when we venture into the area of more proximate substituent effects we are immediately impressed with a wealth of controversial effects where qualitative arguments serve at best. Depending on the structure of the substrate carboxylic acid being considered, a number of factors may be considered in the total proximity effect by substituents: e.g., (1) electronic effect, (2) steric inhibition of resonance, (3) steric inhibition of solvation, and (4) intramolecular hydrogen bonding.

When considering proximity effects in carboxylic acid dissociation, one generally calls upon the ionization constant data determined in a variety of substrate types, ortho-substituted benzoic acids[4] (ortho effect), substituted acetic,supc4a,5 malonic,[4a] succinic,[4a,6] and glutaric acids,[4a] 3-substituted and 3,3-disubstituted cyclopropane-1,2-dicarboxylic acids,[4a,7] disubstituted maleic acids,[4a,8] and substituted acrylic acids.[4a,9]

Our general interests in the chemistry of strained ring systems led us to consider how substituent effects might manifest themselves in the series of acids **1-3** where *n* could be varied



from 1 to 3. Additional perturbations on these proximity effects would involve not only a changing distance of separation between CO_2H and X, but, likewise, a changing hybridization at C_1 bearing the acid function. Also, the structures of derivatives of **1-3** might be obtained in order to evaluate, at least qualitatively, observed intramolecular hydrogen bonding vs. other effects.

The *cis*- (**4**) and *trans*-1,2-dimethyl-2-X-cyclopropane-1-carboxylic acids (**5**) would be used as comparison standards. In the relatively unstrained cis **4** series, the X-substituent should be closer to the carboxylic acid group than in **1-3.** The trans **5** series was chosen because here the X and CO_2H groups were too far from each other to directly interact (e.g., hydrogen bonding), while the same basic structural unit, the cyclopropane ring, was retained for potential electronic interaction between X and CO_2H.

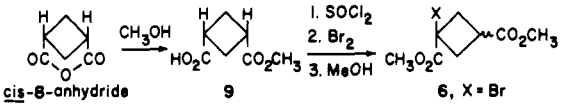
Substrate Syntheses

Following the results of previous investigations, the substituents X = H, $CONH_2$, CO_2CH_3, Br, CN, CO_2H, and CO_2^- are generally studied in projects of this nature, and standard synthetic routes to these derivatives are available.[10]

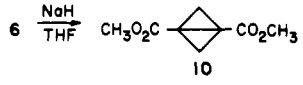
The syntheses of the derivatives of the [3.1.0] **3** (X = H, $CONH_2$, CO_2CH_3, Br, CN, and CO_2H)[11] and the [2.1.0] **2** series (X = H, $CONH_2$, CO_2CH_3, CN, and CO_2H)[12] have been reported.

In the [1.1.0] **1** series, the monocarboxylic acid (X = H) has been prepared and its acidity measured.[13] To obtain the remaining derivatives in this series it appeared most reasonable to approach this by way of a base-induced 1,3-elimination from a dimethyl 1-halocyclobutane-1,3-dicarboxylate (**6**). Dressel[14] had reported that reaction of tetraethyl propane-1,1,3,3-tetracarboxylate and methylene iodide with base yields tetraethyl cyclobutane-1,1,3,3-tetracarboxylate (**7**), a potential precursor to **6**. However, in our hands this reaction failed to produce any **7**.

We then carried through the reported synthesis of the tetraacid of **7**[15a] as described by Allinger.[15b] Double decarboxylation gave the *cis*- and *trans*-cyclobutane-1,3-dicarboxylic acids (**8**). Treatment of this cis-trans mixture of **8** with acetyl chloride converted *cis*-**8** to the anhydride; *trans*-**8**- and *cis*-**8**-anhydride were readily separated by distillation. Treatment of *cis*-**8**-anhydride with methanol gave the half-methyl ester **9** which was converted to **6** (X = Br) by the Hell-Volhard-elinskii reaction.[16]

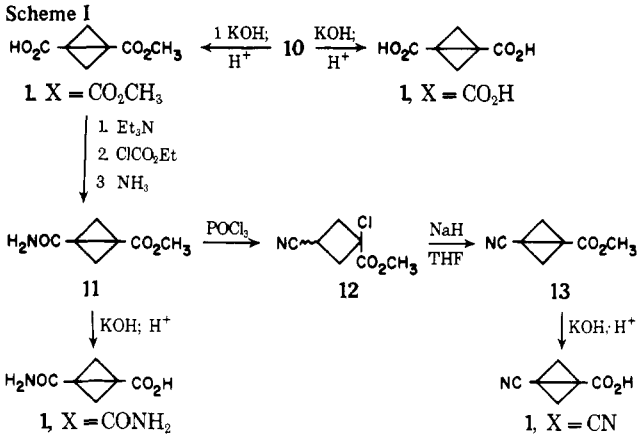


As this sequence was being completed, Drs. C. D. Smith and S. C. Cherkofsky[17] informed us of their alternate route to **6** (X = Cl)[18] and supplied us with a sample of this compound. In our hands, **6** (X = Cl) gave dimethyl bicyclo[1.1.0]butane-1,3-dicarboxylate (**10**) in 77-80% yield (61% reported)[18] when



allowed to react with sodium hydride in tetrahydrofuran at 45 °C. Similar reaction conditions with **6** (X = Br) gave **10** in 45% yield, and it was observed that this reaction proceeded surprisingly somewhat slower than that of the chloro analogue of **6** (X = Cl). The remaining derivatives in the [1.1.0] **1** series were prepared by the routes shown in Scheme I.

Scheme I

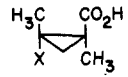
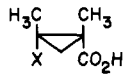
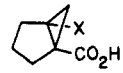
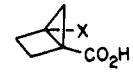
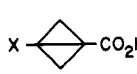


Since the Hunsdiecker reaction had failed to give methyl 4-bromobicyclo[2.1.0]pentane-1-carboxylate from **2** (X = CO_2CH_3)[12] probably due to reaction of the strained ring system with bromine, the analogous reaction with half-ester **1** (X = CO_2CH_3) was not attempted. When amide-ester **11** was treated with $POCl_3$ the product did not have the [1.1.0] structure based on the IR and NMR spectra and was assigned the cyclobutane structure **12,** the product of addition of hydrogen chlorine to the zero bridge. Reaction of a small amount of **12** with sodium hydride in tetrahydrofuran gave **13** in 45% yield. Hydrolysis of **13** gave impure cyano acid **1** (X = CN) which resisted purification by recrystallization. The impure **1** (X = CN) also appeared to decompose on standing; thus its preparation was not repeated since determination of "its pK_a" would most likely have been unreliable.

A mixture of the methyl esters of **4** and **5** (X = H) was obtained by photolysis of the mixed pyrazolines obtained from the reaction of diazoethane to methyl methacrylate.[19] The esters were separated by a combination of distillation and preparative GLPC giving the methyl ester of **4** in 94% purity and the methyl ester of **5** (X = H) in 96% purity; the major impurity in each was the other isomer. Hydrolysis of each gave the respective acids whose purity was assumed to be that of the starting ester.

Dimethyl *cis*- and *trans*-1,2-dimethylcyclopropane-1,2-dicarboxylates (**14**) were prepared by the reaction of methyl methacrylate, methyl α-chloropropionate, and sodium hydride

Table I. Thermodynamic pK_a Values of Certain 2-Substituted Cyclopropane-1-carboxylic Acids in Water at 25.00 ± 0.01 °C[a]

X	 5	 4	 [3.1.0] 3	 [2.1.0] 2	 [1.1.0] 1
H	4.964 ± 0.003	5.171 ± 0.004	5.066 ± 0.003	4.696 ± 0.007	4.53 ± 0.1[c]
$CONH_2$	4.102 ± 0.005	*b*	4.778 ± 0.004	3.962 ± 0.010	3.727 ± 0.013
CO_2CH_3	3.932 ± 0.009	4.152 ± 0.006	4.154 ± 0.007	4.168 ± 0.007	3.316 ± 0.011
Br	3.777 ± 0.008	3.895 ± 0.007	4.215 ± 0.004	*b*	*b*
CN	3.430 ± 0.012	*b*	3.903 ± 0.006	3.581 ± 0.011	*b*
COOH[d]	3.631 ± 0.002	4.128 ± 0.006	3.306 ± 0.018	2.767 ± 0.035	3.176 ± 0.003
COO^-[d]	5.232 ± 0.003	6.531 ± 0.002	7.081 ± 0.005	7.294 ± 0.006	4.964 ± 0.022

[a] Concentrations used in potentiometric titrations: 3×10^{-3} M acid; 3×10^{-2} base. [b] These compounds not available synthetically. [c] Literature value.[13] [d] Not statistically corrected.

in dimethylformamide;[20] the *cis*-**14**/*trans*-**14** ratio was about 0.5. Fractional distillation separated these isomers, the lower boiling component being *trans*-**14**. These were the key compounds in the preparation of the desired derivatives of acids **4** and **5** which were prepared by conventional procedures.[10-12]

While all of the desired derivatives were available in the trans **5** series, several problems arose in the cis **4** series. Attempted purification of the half-methyl ester, 2-carbomethoxy-*cis*-1,2-dimethylcyclopropane-1-carboxylic acid (**4**, X = CO_2CH_3), by distillation or sublimation resulted in elimination of methanol and formation of the anhydride. The half-methyl ester **4** (X = CO_2CH_3) could be purified by recrystallization from a hydrocarbon solvent; however, the crystalline compound slowly formed anhydride on standing at room temperature.

Trans half-methyl ester **5** (X = CO_2CH_3) was converted to the amide-ester which was hydrolyzed to trans amide-acid **5** (X = $CONH_2$). Reaction of cis half-methyl ester **4** (X = CO_2CH_3) under the same conditions gave only the corresponding imide.

Using the method of McCoy[20b] the mixture of methyl 2-cyano-*cis*- and -*trans*-1,2-dimethylcyclopropane-1-carboxylates was obtained and separated by distillation. While hydrolysis of the trans cyano ester gave cyano acid **5** (X = CN), the cis cyano ester yielded an amorphous solid which we were unable to purify by recrystallization or sublimation. This impure cis cyano acid **4** (X = CN) decomposed on standing at room temperature giving the cis imide and the anhydride.

Each of these several observations led us to conclude that the X and CO_2H groups in **4** were in closer proximity to one another than that found in the [3.1.0] **3** series.

Identical Hunsdiecker reactions[21] with half-methyl esters **4** and **5** (X = CO_2CH_3) produced essentially the same mixture of the isomeric bromo esters, methyl 1-bromo-*cis*- and -*trans*-1,2-dimethylcyclopropane-1-carboxylates, in a 1:3 ratio. These were separated and hydrolyzed to their respective acids **4** and **5** (X = Br).

Acid Dissociation Constants and Discussion

The thermodynamic pK_a values and their standard deviations for the series **1**-**5** were determined in water at 25 °C and are listed in Table I. In general the standard deviations were less than 0.01; however, a trend in the standard deviation can be seen. As the pK_a's approach a value of 3 from larger values, the standard deviations increased. This was consistent with the statement of Albert and Sargeant that "accurate results cannot be expected if the pK_a is less than the negative logarithm of the concentration".[22] While standard deviation is a measure of precision, we believe that this increase in standard deviation is also indicative of some deterioration in accuracy as the measured pK_a approaches 3. Although some of the larger standard deviations might have been reduced by using more concentrated acid solutions, the corrections required for this change plus possible solubility problems would have placed additional uncertainties on the measurements.

Table II. ΔpK_a^H Values of Certain 2-Substituted Cyclopropane-1-carboxylic Acids in Water at 25.00 ± 0.01 °C

Substituent X	Acid series: Trans **5**	Cis **4**	[3.1.0] **3**	[2.1.0] **2**	[1.10] **1**
H	0.000	0.000	0.000	0.000	0.00
$CONH_2$	0.862	*c*	0.288	0.734	0.80
CO_2CH_3	1.032	1.019	0.912	0.528	1.21
Br	1.187	1.276	0.851	*c*	*c*
CN	1.534	*c*	1.163	1.115	*c*
CO_2H[a]	1.032	0.742	1.459	1.628	1.05
CO_2^-[b]	0.033	−1.059	−1.714	−2.297	−0.13

[a] Statistically corrected by subtraction of log 2 from the observed ΔpK_a. [b] Statistically corrected by addition of log 2 to the observed ΔpK_a. [c] Compounds not available.

The accuracy of the individual pK_a values in Table I was considered to be good (see Experimental Section for comparisons with known pK_a values). For our internal comparisons, ΔpK_a values are employed which should be more accurate than the pK_a values. The maximum expected error in the ΔpK_a values was calculated to be ±0.04 using the largest standard deviation, and ±0.015 using typical standard deviations. Likewise, our values for pK_1 and pK_2 for the diacids **4** and **5** (X = CO_2H) show good agreement with those reported by McCoy[7a] considering the difference in the method of measurement.

The ΔpK_a values [log (K_X/K_H)] for these five series of acids are listed in Table II. Since these values are internally referenced to the unsubstituted acid (X = H) within that series, we will denote these as ΔpK_a^H values to differentiate them from an externally compared set to be introduced later. Plots of these ΔpK_a^H values vs. σ_I constants are shown in Figure 1; the σ_I constants used were H (0.00), $CONH_2$ (0.27), CO_2H (0.33), CO_2CH_3 (0.34), Br (0.45), CN (0.58), and CO_2^- (−0.17).[23] Regression analysis of the data in Table II as plotted vs. σ_I constants in Figure 1 is given in Table III.

It is apparent in Table III that when all data points are used (correlation 1), three of the five series, trans **5**, cis **4**, and [1.1.0] **1**, yield reasonably good correlations with σ_I constants. However, the "absence" of intramolecular hydrogen bonding in the trans **5** and [1.1.0] **1** half-ionized diacids compared to cis **4** half-ionized diacid shows up in comparing the $\Delta\rho_I$ values of these three series between correlations 1 and 2: positive for the cis **4**, [3.1.0] **3**, and [2.1.0] **2** series, but slightly negative for both the trans **5** and [1.1.0] **1** series.

In correlation 2 of Table III, all of the pK_2 values of the five series of diacids (X = CO_2^-) and the pK_1 values of the [3.1.0]

Table III. Regression Analyses of ΔpK_a^H Values vs. σ_I Constants

Series	Correlation 1[a]			Correlation 2[b]			Correlation 3[c]		
	Slope, ρ_I	cc[d]	No.[e]	Slope, ρ_I	cc[d]	No.[e]	Slope, ρ_I	cc[d]	No.[e]
Trans **5**	2.2 ± 0.2	0.976	7	2.6 ± 0.2	0.988	6	2.2 ± 0.2	0.976	7
Cis **4**	3.5 ± 0.4	0.980	5	2.8 ± 0.4	0.980	4	2.8 ± 0.4	0.980	4
[3.1.0] **3**	3.6 ± 0.9	0.881	7	2.1 ± 0.5	0.934	5	2.1 ± 0.5	0.934	5
[2.1.0] **2**	4.4 ± 1.4	0.849	6	1.9 ± 0.4	0.953	4	1.9 ± 0.4	0.953	4
[1.1.0] **1**	2.6 ± 0.4	0.974	5	3.3 ± 0.3	0.990	4	2.6 ± 0.4	0.974	5

[a] All data points in Table II were used. [b] The CO_2^- points for all series and the CO_2H points in the [3.1.0] **3** and [2.1.0] **2** series were omitted. [c] The CO_2^- and the CO_2H points in [3.1.0] **3** and [2.1.0] series and the CO_2^- point in the cis **4** series were omitted. [d] Correlation coefficient. [e] Number of data points.

3 and [2.1.0] **2** series (X = CO_2H) were omitted for different reasons. The CO_2^- was the only charged substituent group investigated. It appeared reasonable that the full negative charge could significantly alter the properties of the solvent (e.g., structure) in the relatively small spatial region between the substituent and the CO_2H group in these molecules compared to that space (largely molecular skeleton of low dielectric constant) in the substrates used to define σ_I constants. The pK_1 values of the [3.1.0] **3** and [2.1.0] **2** series were omitted since intramolecular hydrogen bonding is the dominant effect in these diacids. For these reasons, we believe that correlation 2 is the best and most reasonable treatment of these data.

Correlation 3 in Table III reintroduces the CO_2^- substituent effect into the trans **5** and [1.1.0] **1** series over that found in correlation 2.

It is interesting to note that the CO_2^- group had essentially no effect (same as H) on the second ionization constant of the trans **5** and [1.1.0] **1** diacids when statistically corrected. Thus, in these two series the σ_I constant for the CO_2^- group would be better represented as 0.00. This was unusual even though the cyclopropane ring is known not to effectively transmit substituent group effects,[24] and gives further credence to the above suggestion concerning correlation 2 that the σ_I constant of the charged substituent CO_2^- is ill-defined for the proximity effects in the molecules.

Substituent Effects of X = H, Br, CN, and CO_2CH_3. We will first deal with the substituent effects in the five acid series where X = H, Br, CN, and CO_2CH_3. These substituent effects involve smaller changes in the pK_a values compared to those in the diacids' pK_1 and pK_2 values and the carboxamides. Since several factors are undoubtedly operating at the same time on each acid in the same or in different directions, the following discussion will be qualitative and somewhat biased by what we presently believe to be the specific factors which adequately explain the data.

We believe that four factors or effects may be involved in comparisons of the data sets for these five series of acid pK_a values: (1) field effects, (2) intramolecular hydrogen bonding, (3) hybridization changes in the ring C–CO_2H bond, and (4) steric effects. While effects 1–3 have considerable literature support, we believe that some comment is necessary about the possibility of factor 4, steric effects, in these cyclopropane systems.

Our concern about the possible involvement of steric effects in these acids arises from the known conformation preference (17.5 kcal/mol from ab initio calculations)[25] for the bisected form vs. the perpendicular conformer in the cyclopropylcarbinyl cation. Thus, the bisected conformer of cyclopropanecarboxylic acid should be acid weakening while, in the perpendicular rotamer, the full acid strengthening effect of the strained cyclopropane ring would be felt. That this may not be a neglible effect is seen in the pK_a data of Table IV. In the pK_a values of the cycloalkylamines we see the magnitude of the acid strengthening (base weakening) effect of the cyclopropyl group.[26] However, in the pK_a values of the cycloalkanecarboxylic acids, the net effect of changing from a four- to a three-membered ring is reversed and we see that cyclopropanecarboxylic acid is a *weaker* acid than is cyclobutanecarboxylic acid. Considering the ΔpK_a values of the amines and the observed ΔpK_a values of five- to four-ring carboxylic acids, we suggest that this bisected acid weakening interaction in the cyclopropanecarboxylic acid is ≥ 0.25 pK_a unit (see later discussion and ref 41).

As substituent groups (X) replace the hydrogen at C_2 of the ring cis to the CO_2H group in cyclopropanecarboxylic acid,

Table IV. Dissociation Constants of Certain Cycloalkane Acids and Bases[4a]

	pK_a		pK_a
Cyclopropanecarboxylic acid	4.83[a]	Cyclopropylamine	8.66[b]
Cyclobutanecarboxylic acid	4.79[a]	Cyclobutylamine	9.34[b]
Cyclopentanecarboxylic acid	4.99[a]	Cyclopentylamine	9.95[b]

[a] H_2O, 25 °C (M. Kilpatrick and J. G. Morse, *J. Am. Chem. Soc.*, 75, 1854 (1953)). [b] 50% EtOH (J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, 73, 5030 (1951)).

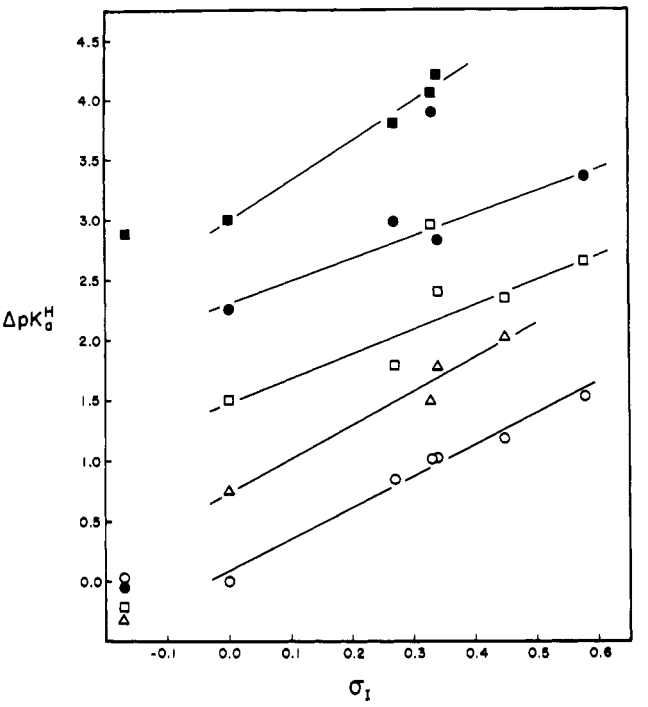


Figure 1. Linear free-energy relationships of ΔpK_a^H values of the five series of acids, **1–5**, vs. σ_I constants.[23] The legend is as follows: (○) trans **5**; (△) cis **4** (ΔpK_a^H + 0.75); (□) [3.1.0] **3** (ΔpK_a^H + 1.50); (●) [2.1.0] **2** (ΔpK_a^H + 2.25); (■) [1.1.0] **1** (ΔpK_a^H + 3.00). Slopes are those calculated in correlation 2, Table III.

steric repulsion between X and the CO_2H in the bisected conformation is expected. This is seen in Dreiding models of *cis*-2-methylcyclopropanecarboxylic acid where the methyl C to carboxyl C distance is 2.88 Å. This is the same C→C distance as measured in Dreiding models of *o*-toluic acid where steric inhibition of resonance was recently established as a major contributor to the ortho proximity effect.[27] Thus, a related steric effect in the two molecular systems should be observed although its magnitude will be attenuated in the *cis*-2-X-cyclopropanecarboxylic acids since the ring-to-CH_3 effects will be different for the cyclopropane and benzene systems; the poor transmission of electrical effects via the cyclopropane ring has been established.[24]

When we compare the trans **5** (X = H) and cis **4** (X = H) acid pK_a values, the cis **4** acid (H cis to CO_2H) is found to be weaker than the trans **5** acid (CH_3 cis to CO_2H) by 0.21 pK_a unit. Although it is tempting to ascribe this to the steric effect described above, we must remember that this could only be so *if* the methyl group field effects (and other effects) cancelled (were the same) in this comparison (the field effects will be discussed below). The remaining changes in the X = H pK_a values for the [3.1.0] **3**, [2.1.0] **2**, and [1.1.0] **1** acids compared to that of cis **4** (X = H) acid are considered to be due primarily to changes in the hybridization at ring C_1.

In the Kirkwood–Westheimer equation for the field effect,[2,3] comparison of the same substituent group in different geometric relationships to the ionizing CO_2H group involves the factor $(\cos\theta/R^2D_E)$. Changes in this factor would be expected to be most abrupt in the comparison of substituent effects between the trans **5** and cis **4** acid series. The angle θ is more acute and R is larger in the trans **5** ($X \neq H$) than the cis **4** acids ($X \neq H$); the opposite is true for X = H where we have a cis and trans C_2CH_3 effect, respectively, on 1-methylcyclopropanecarboxylic acid pK_a. While values for θ and R in both systems could be arrived at reasonably, values for the effective dielectric, D_E, would be speculative at this point, and it is probably the most significant part of the entire factor. In the trans **5** series ($X \neq H$), the field effect is probably partially transmitted through molecular structure ($D_E \simeq 4$) and partially through the medium $D_E = 80$ (H_2O, 25 °C). In the cis **4** series ($X \neq H$), D_E may be larger than that in the trans **5** series.

From the relationship:[28]

$$\log (K_X^5/K_X^4) = \frac{e\mu}{2.3kT}\left[\left(\frac{\cos\theta}{R^2D_E}\right)_5 - \left(\frac{\cos\theta}{R^2D_E}\right)_4\right] \quad (1)$$

we expect that:

$$\left(\frac{\cos\theta}{R^2D_E}\right)_5 > \left(\frac{\cos\theta}{R^2D_E}\right)_4 \text{ for } X \neq H \quad (2)$$

primarily due to the larger D_E in the cis **4** series ($X \neq H$).

Moving to the X = Br comparison offers somewhat of a simplification in that steric effects between trans **5** and cis **4** bromo acids are removed since the steric size of Br $\simeq$ CH_3. In the trans **5** (X = H to X = Br) acids the cis CH_3 steric effect is constant. The $\Delta pK_a^H = 1.187$ in trans **5** (X = Br) is therefore due to the field effect of Br in this geometric relationship to the CO_2H group. In the cis **5** acid series the change from X = H to X = Br involves two major changes: (1) the steric effect and (2) the field effect of cis Br and CO_2H contribute to this $\Delta pK_a^H = 1.276$.

Proceeding to the [3.1.0] **3** series where the cis CH_3's of cis **4** are constrained into a five-membered ring, we see that the substitution of Br for H at bridgehead C_5 has a considerably smaller acid strengthening effect (ΔpK_a^H values) than the same change in the cis **4** series: $[\Delta pK_a^H(\mathbf{3}) - \Delta pK_a^H(\mathbf{4})]^{X=Br} = -0.42$. The acid weakening effect observed in this structural change may be due to several factors: (1) relief of steric interaction between the Br and CO_2H groups, (2) a reduced field effect by Br since θ and R are larger in the [3.1.0] **3** series even assuming the D_E is constant, and (3) intramolecular hydrogen bonding from CO_2H to Br in the [3.1.0] **3** bromo acid.

At this point, a brief comment on the CN effect is worthwhile since intramolecular hydrogen bonding from CO_2H to the π orbitals of CN is not considered important (to be discussed later). The ΔpK_a^H values of the [3.1.0] **3** and [2.1.0] **2** (X = CN) cyano acids show only a minor change which we attribute to a minor change in the field effect (less in [2.1.0] **2** series). If this is correct the steric effect between CO_2H and CN in the [3.1.0] **3** cyano acid is no longer present. That a steric effect was a major factor in the cis **4** cyano acid was seen in its transformation to the imide on standing.

Thus, we argue that in the bromo acids the steric effect in the cis **4** is relieved (partially or totally) in the [3.1.0] **3** bromo acid and possibly accounts for the major amount of the 0.42 change observed. Some intramolecular hydrogen bonding in the [3.1.0] **3** bromo acid cannot be presently ruled out.

Although only three of the cyano acids (X = CN) are available for comparison, their substituent effects are of interest as a standard for the absence of intramolecular hydrogen bonding. Murray and Schneider[29] explained complex formation between nitriles and hydrogen chloride or chloroform as involving a linear, "end-on" attachment of the acid and the nitrogen of the cyano group, e.g. RC≡N···H—X. It would be impossible to form such an intramolecular hydrogen bond in any of the five acid series studied in this investigation without very large molecular distortions. Furthermore, hydrogen bonding to the cyano groups π cloud should be much weaker than with the nonbonded electron pair in nitrogen.[29] This led to the above conclusion that steric effects between CN and CO_2H in the [3.1.0] **3** cyano acid were absent. The approximately equal field effect of CN in the [3.1.0] **3** and [2.1.0] **2** cyano acids is graphically shown in Figure 2 where the slope of the line connecting these points is very similar to that for these bicyclic acids, X = H. Thus, the increased acidity of the [2.1.0] cyano acid compared to the [3.1.0] cyano acid is explained by the hybridization change at C_1.

In the ester acids ($X = CO_2CH_3$), the acid strengthening effect of replacing X = H by $X = CO_2CH_3$ is only slightly smaller (0.01 pK_a unit) in cis **4** compared to trans **5**. From eq 2 we would expect this difference to be larger based on the field effect alone. Although one would normally assign a smaller steric size to CO_2CH_3 compared to CH_3 (sp^2 vs. sp^3 carbon hybridization), we suggest that the *opposite* is true in the present examples. This could result from *both* carbonyl groups (CO_2H and CO_2CH_3) seeking the bisected conformation with respect to the cyclopropane ring, thus increasing the steric size of CO_2CH_3 in cis **4** over that of CH_3 in trans **5**. This acid strengthening effect felt in cis **4** ($X = CO_2CH_3$) then compensates for the reduced field effect in this ester acid (compared to the trans **5** ester acid) leading to the observed results.

The reduced CO_2CH_3 substituent effect in the [3.1.0] **3** ester acid (ΔpK_a^H of 0.1) compared to that of the cis **4** ester acid may be due to a smaller steric effect, a reduced field effect (θ and R increase assuming no change in D_E in this structural change), and/or some intramolecular hydrogen bonding. All three of these factors are acid weakening and can also be used to rationalize the greater change observed in the [2.1.0] **2** ester acid, $[\Delta pK_a^H(\mathbf{3}) - \Delta pK_a^H(\mathbf{2})]^{X=CO_2CH_3} = 0.4$. However, in the case of the [2.1.0] **2** ester acid we attribute most of this change to intramolecular hydrogen bonding since it is in this bicyclic structure where this effect is at a maximum in the diacids (to be discussed later).

Continuing to the ΔpK_a^H for the [1.1.0] **1** ester acid, the abrupt change from the trend of acid weakening seen in the previous examples to acid strengthening is observed, $[\Delta pK_a^H(\mathbf{2}) - \Delta pK_a^H(\mathbf{1})]^{X=CO_2CH_3} = -0.7$. This marked change also is found when the K_1/K_2 ratios for the diacids are

Table V. Calculated Intramolecular Hydrogen Bonding Distances, d_1, in Cis **4**, [2.1.0] **2**, and [1.1.0] **1** Diacids Monoanions

	Cis **4**[a]	[2.1.0] **2**[30]	[1.1.0] **1**[31a]
d_2, A	1.515	1.439	1.497
α, deg	118	122	128
d_1(calcd), A	1.56	1.82	2.37

[a] Structural parameters used were those of cyclopropyl chloride; R. H. Schwendeman, G. D. Jacobs, and T. M. Krigas, *J. Chem. Phys.*, **40**, 1022 (1964).

Table VI. Experimental K_1/K_2 and K_1/K_E Ratios for the Diacids and Half-Methyl Esters in Series **1**–**5**[a]

Acid series	K_1/K_2	K_1/K_E
Trans **5**	40 (34)[7a]	2.0
Cis **4**	253 (312)[7a]	1.06
[3.1.0] **3**	5 960	7.05
[2.1.0] **2**	33 700	25.2
[1.1.0] **1**	61	1.38

[a] The ratios are not statistically corrected.

compared in Table VI (to be seen in the next section). That this change was not expected is seen in the calculated O-H···O distance (d_1) for the [2.1.0] **2** and [1.1.0] **1** diacids using McCoys equation:[8]

$$d_1 = d_2 + 2.96 \sin(\alpha - 90°) - 2.54 \cos(\alpha + 300°) \quad (3)$$

and the structural parameters for bicyclo[2.1.0]pentane[30] and bicyclo[1.1.0]butane[31a] and 1,3-dicyanobicyclo[1.1.0]butane (d_2 = 1.502 Å, α = 124.6°).[31b] Since d_1 for the [1.1.0] **1** system is less than 2.45 Å discussed by McCoy as the optimum hydrogen bonding distance for the monoanions of diacids,[8] we expected to find a continuation in the acid weakening of the ester acids. Either the modeling parameters used in calculating d_1 in Table V for the [1.1.0] system are in error leading to an underestimate of d_1[32] or a special type of bicyclic ring to bridgehead substituent effect may be operating here.[34] These points will be dealt with further in the next section on the diacids.

Dissociation Constants of Diacids. In comparing the dissociation constants, K_1 and K_2, of the diacids in these five series of structures, many of the effects or factors discussed in the above substituent effects are subordinate to intramolecular hydrogen bonding. The major importance of this single factor is believed to be responsible for the large K_1/K_2 ratios listed in Table VI. The general trends observed in these ratios are seen in the K_1/K_E ratios which are also listed in Table VI.

Since intramolecular hydrogen bonding is geometrically impossible in the trans **5** diacid or its monoanion, it appeared reasonable to compare the effects of pK_1 and pK_2 in series **1**–**4** to those observed in trans **5**. These are referred to as ΔpK_a^5 values and are listed in Table VII along with the related comparisons of the other substituent groups studied in this investigation.

It must be noted that the differences in substituent effects where X = H, Br, CN, and CO_2CH_3 have been discussed in the preceding section and substantial differences between the trans **5** and the remaining **1**–**4** series were pointed out. However, certain of the trends observed in the various substituent effects as the molecular skeleton was varied in these five acid series are also seen in the ΔpK_a^5 values and their plot in Figure 2.

Figure 2 graphically shows the striking changes in pK_1 (CO_2H) and pK_2 (CO_2^-) of the diacids. The pK_1 and pK_2 values had their largest separation in the [2.1.0] **2** series which rapidly decayed as we proceeded to the [1.1.0] **1** series. This indicates that intramolecular hydrogen bonding in the half-

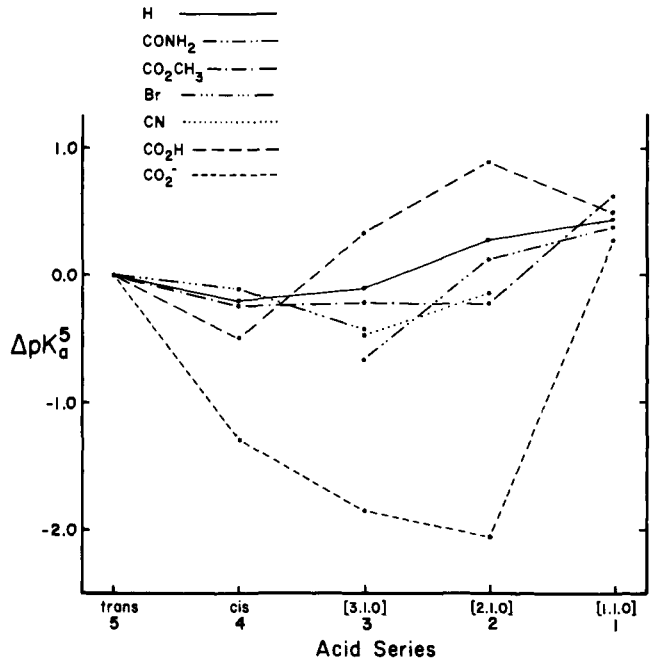


Figure 2. Plot of ΔpK_a^5 values of the four acid series, **1**–**4**, relative to that same substituent in trans **5**; the values are from Table VII. The order of these series was chosen so that the X to CO_2H distance increased from left to right for series **4**–**1** with the trans **5** series as a point of reference. The equal spacing between the acid series on the abscissa is arbitrary.

Table VII. ΔpK_a^5 Values of Certain 2-Substituted Cyclopropane-1-carboxylic Acids in Water at 25.00 ± 0.01 °C

Substituent X	Acid series: Trans **5**	Cis **4**	[3.1.0] **3**	[2.1.0] **2**	[1.1.0] **1**
H	0.000	−0.207	−0.102	0.268	0.43
$CONH_2$	0.000		−0.676	0.140	0.375
CO_2CH_3	0.000	−0.220	−0.222	−0.236	0.616
Br	0.000	−0.118	−0.438		
CN	0.000		−0.473	−0.151	
CO_2H	0.000	−0.497	0.325	0.864	0.455
CO_2^-	0.000	−1.299	−1.849	−2.062	0.268

ionized forms of the diacids reaches a maximum in the [2.1.0] **2** series (K_1/K_2 = 33 700) and that the distance separating CO_2H and CO_2^- in the [1.1.0] **1** series is now apparently too great for such stabilization through intramolecular hydrogen bonding, K_1/K_2 = 61.

This leads us back to our discussion of the effect of the CO_2CH_3 substituent in the previous section shown in the small K_1/K_E ratio in Table VI in the [1.1.0] **1** ester acid and the calculated hydrogen bonding distance in the [1.1.0] **1** diacid-monocarboxylate anion in Table V. We believe that the calculated intramolecular hydrogen bonding distance for the [1.1.0] **1** diacid-monocarboxylate anion given in Table V is approximately correct (based on the [1.1.0] hydrocarbon and its 1,3-dicyano derivatives geometries). This is about 0.1 Å less than that for optimum hydrogen bonding for monoanions of diacids (2.45 Å) suggested by McCoy.[8,35] On this basis, we are left with the grand incongruity of having a system where the largest K_1/K_2 ratio is predicted to be found, but the smallest is actually observed (similar for the K_1/K_E ratios, Table VI). We suggest that a potent conformational effect in this bicyclic system could account for this anomalous behavior.

To see if such an effect may be present in the [1.1.0] **1** acids, we have considered the change in hybridization of the ring C_1-CO_2H bond on the pK_a values for a series of carboxylic acids using the $J_{^{13}C-H}$ coupling constants of the hydrocarbons

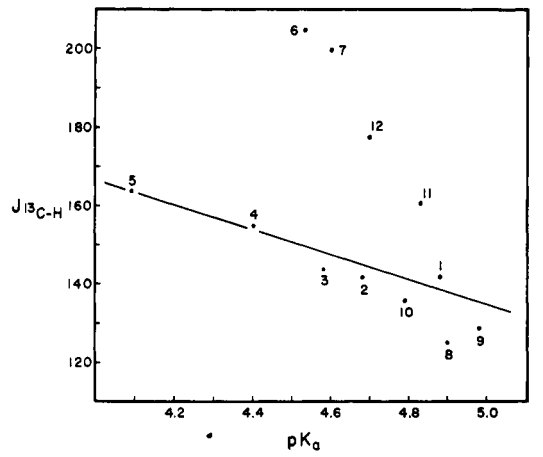


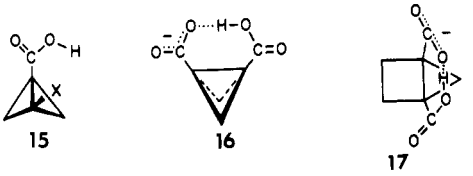
Figure 3. Plot of $J_{^{13}C-H}$ of certain hydrocarbons vs. the pK_a values of the corresponding carboxylic acids where CO_2H has replaced H on the hydrocarbon skeleton. The numbered points refer to the entries in Table VIII. The correlation line was determined from points (1)-(5).

(ring C-H) as a measure of this hybridization change (percent s character in the bond).[36] These data are listed in Table VIII and are plotted in Figure 3.

Acids (1)-(5) in Table VIII were chosen to depict the influence of percent s character in the C_1-CO_2H bond on acidity maintaining the same degree of substitution at bridgehead C_1. The observed correlation of pK_a vs. $J_{^{13}C-H}$ at these bridgehead centers for (1)-(5) shown in Figure 3 is reasonable. However, the marked deviation by both of the 1-bicyclo[1.1.0]butane acids (6) and (7) is obvious; both acids (6) and (7) are considerably weaker acids than expected by this relationship.

In Table VIII and Figure 3 the six- to three-membered cycloalkanecarboxylic acids (8)-(11) are included. While a meaningful correlation cannot be derived due to the close arrangement of (8)-(10) in Figure 3, it is reasonable to expect a similar correlation in these structures to that observed for (1)-(5). With this assumption cyclopropanecarboxylic acid is shown to be weaker than expected. We believe that this diagrammatically confirms our previously stated proposition of a ring C_1-CO_2H electronic interaction occurring in this three-membered ring acid which is acid weakening and is conformationally dependent (see previous section of Discussion).

Application of a similar argument to the further acid weakening in the [1.1.0] **1** acid (X = H) compared to that predicted in Figure 3 would suggest that alignment of the C p orbital of the CO_2H with the C_1-C_3 bond (large p character)[37] would be the preferred conformation.[38] This is shown in structure **15** and will be referred to as the *perpendicular*



conformer.[39] This conformation effectively rules out intramolecular hydrogen bonding between CO_2H and X and a "normal" substituent effect is exerted by X. This would explain the equally good σ_I correlations for all the data points in both the trans **5** and [1.1.0] **1** series (Figure 1 and correlation 1, Table III). The *perpendicular* conformation may also be preferred for various reasons in the carboxylate anion.

If we estimate that the K_1/K_2 ratio expected for the calculated (Table V) geometry of the [1.1.0] **1** diacid is 10^5, this requires that the above conformational effects must be equal to or greater than $\Delta G° = -RT \ln [(K_1/K_2)_{calcd}/(K_1/K_2)_{obsd}] = -4.4$ kcal/mol.

Table VIII. pK_a Values (H_2O, 25 °C) of Some Cyclic and Polycyclic Carboxylic Acids and $J_{^{13}C-H}$ Values of the Corresponding Hydrocarbons

Acids	pK_a	$J_{^{13}C-H}$, Hz[a,m]
(1) Bicyclo[2.2.1]heptane-1-carboxylic	4.88[b]	142
(2) Bicyclo[2.2.1]hept-2-ene-1-carboxylic	4.68[c,d]	142
(3) Benzobicyclo[2.2.1]hept-2-ene-1-carboxylic	4.58[c,d]	144
(4) Cubanecarboxylic	4.40[d,e]	155[f]
(5) Bicyclo[1.1.1]pentane-1-carboxylic	4.09[g]	164
(6) Bicyclo[1.1.0]butane-1-carboxylic	4.53[h]	205
(7) Tricyclo[4.1.0.0^{2,7}]-heptane-1-carboxylic	4.6[i]	200
(8) Cyclohexanecarboxylic	4.90[j]	125
(9) Cyclopentanecarboxylic	4.99[j]	128
(10) Cyclobutanecarboxylic	4.79[j]	136
(11) Cyclopropanecarboxylic	4.83[j]	161
(12) Bicyclo[2.1.0]pentane-1-carboxylic	4.70[k]	178[l]

[a] J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, N.Y., 1972, pp 333-334. [b] Reference 3b. [c] J. W. Wilt, H. F. Dabek, J. P. Berliner, and C. A. Schneider, *J. Org. Chem.*, **35**, 2402 (1970). [d] Determined in 50% EtOH; pK_a corrected by subtracting the difference between the pK_a of benzoic acid in that medium and 4.20 ($C_6H_5CO_2H$ pK_a in H_2O) from the observed pK_a. [e] T. W. Cole, C. J. Mayers, and L. M. Stock, *J. Am. Chem. Soc.*, **96**, 4555 (1974). [f] T.-Y. Luh and L. M. Stock, *J. Am. Chem. Soc.*, **96**, 3712 (1974). [g] K. B. Wiberg and V. Z. Williams, *J. Org. Chem.* **35**, 369 (1970). [h] Reference 13. [i] G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **85**, 2022 (1963). [j] Reference 4a. [k] This work. [l] Reference 36a. [m] For the hydrocarbon where H has replaced CO_2H of the acid.

We have approached this point using INDO calculations[40] of bicyclo[1.1.0]butane-1-carboxylic acid and its carboxylate anion in the *perpendicular* and *bisected* (CO_2H or CO_2^- and C_1-C_3 in the same plane) conformations using the geometry found for 1,3-dicyanobicyclo[1.1.0]butane for the [1.1.0] skeleton and the following bond angles and bond lengths for the CO_2H and CO_2^- groups: C_1—C—O bond angles, 120°; C—O—H angle, 104°; C_1—CO_2H length, 1.48 Å; C=O length, 1.23 Å; C—OH length, 1.31 Å; C—O length in CO_2^-, 1.26 Å; and O—H length, 0.97 Å. The results show that the *perpendicular* conformation is *preferred* in *both* the acid and carboxylate anion forms by 5.2 and 3.1 kcal/mol, respectively. Since coplanar, *bisected* arrangement of the CO_2H and CO_2^- groups must occur for intramolecular hydrogen bonding (**16**), the sum of these energies (8.3 kcal/mol) must be overcome. Thus, this quantum mechanical modelling of the system is at least in agreement with the observed results, and sufficient energy appears to be present in the above conformational arguments to overcome that for intramolecular hydrogen bonding.[41]

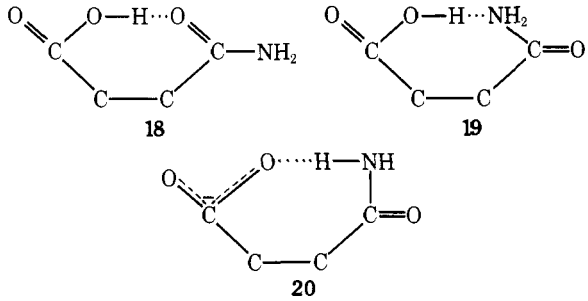
The [2.1.0] **2** acid (X = H) was included in Table III and Figure 3 as acid (12). In the case of the [2.1.0] **2** diacid (X = CO_2H) and half-methyl ester (X = CO_2CH_3), the maximum K_1/K_2 and K_1/K_E ratios are observed in this study (Table VI). We believe that in this structure the most important interaction of the bicyclic skeleton is that with the three-membered ring rather than with the C_1-C_4 zero bridge. Since the distance d_1 (Table V) is quite short in the half-ionized diacid assuming the CO_2^- and CO_2H groups lie in the same plane, intramolecular hydrogen bonding can be maximized in this structure by rotation of the carboxyl-ring C-C bonds so that these groups project out over the three-membered ring as in projection **17**. This rotation would involve reduced steric interactions of the carboxyl groups with neighboring C-H bonds than the opposite

rotation projecting the carboxyl groups over the four-membered ring. Such a rotation will not only benefit the intramolecular hydrogen bonding by increasing the O-H···O distance (d_1),[8] but will also lock the CO_2H group in the bisected conformation relative to the three-membered ring, thus increasing its stability and decreasing K_2. Intramolecular hydrogen bonding in the half-ionized [1.1.0] diacid while spatially allowed as in structure **16** (see Table V) must overcome what we suggest is a significant CO_2H and C_1-C_3 zero bridge interaction. The result is that related ring to CO_2H interactions benefit intramolecular hydrogen bonding in the [2.1.0] system while reducing it to an unimportant factor in the [1.1.0] system.

Substituent Effects of X = $CONH_2$. In the set of amide acids (X = $CONH_2$) only the one for the cis **4** series is missing. Ready formation of the imide in the attempted conversion of cis **4** ester acid (X = CO_2CH_3) to the amide acid (X = $CONH_2$) again demonstrated the close proximity of X and CO_2H in the cis **4** series.

Referring to the ΔpK_a^H values listed in Table II the maximum acid strengthening effects by the electronegative $CONH_2$ group are felt in the trans **5** and [1.1.0] **1** series where intramolecular hydrogen bondings either in the acid or the carboxylate anions are argued to be absent (similar reasoning to that used in the previous section). This acid strengthening effect by X = $CONH_2$ is most strongly attenuated in the [3.1.0] **3** amide acid with that in the [2.1.0] **2** amide acid being intermediate. These changes are graphically approximated in Figure 2 using the ΔpK_a^5 values.

Intramolecular hydrogen bonding should be the most important factor in considering the proximity effects in these amide acid series.[35] Hydrogen bonding in the un-ionized amide acids will be principally of two types, either to carbonyl O (**18**) or to amide N (**19**), both being acid weakening effects. In the ionized carboxylate anion, the major acid strengthening effect will be N-H···^-O_2C hydrogen bonding (**20**).



18 **19** **20**

Most regrettably in the comparison of these amide acids we lack the data for the cis **4** amide acid. However, the structurally related CO_2CH_3 effects in the ester acids of the available amide acids may serve as a reference point for the present discussion.

In the discussion of the [3.1.0] **3** ester acid relative to the trans **5** we attributed part of the small acid weakening effect (0.1 pK_a unit) to intramolecular hydrogen bonding. However, in this same comparison of the amide acids this acid weakening is more pronounced, 0.6 pK_a unit. From the structure of the [3.1.0] system we do not believe that hydrogen bonding of the types shown in **19** or **20** can be considered since it is known that the O···H-N is longer than the O-H···O distance.[35] Thus, we relate the increased acid weakening effect of $CONH_2$ vs. CO_2CH_3 in the [3.1.0] acids to the increased basicity of the carbonyl O in the amide group.[42]

In the [2.1.0] system where intramolecular hydrogen bonding was maximum in these five series of diacids (K_1/K_2) and ester acids (K_1/K_E), a return to the acid strengthening effect by the $CONH_2$ seen in the trans **5** and [1.1.0] **1** amide acids was observed. The interpretation here is that the increased distance separating $CONH_2$ and CO_2H (or CO_2^-) in changing from the [3.1.0] to the [2.1.0] skeleton now allows both acid weakening (as in **18** and/or **19**) and acid strengthening (as in **20**) to balance each other.

Epilogue

In some respects, the above discussion sections deal with the data presented in a "state of the art" manner in that considerable literature precedence has been laid for the conclusions reached. On the other hand, various portions of this discussion represent speculative interpretations based on "related" data obtained by others. It is the ardent hope of the authors that more structural information on these and other strained ring systems will soon be forthcoming so that conclusions which are in error can be pointed out and then ignored, and those that are correct can be used and "thrust home".

Experimental Section[43]

***cis*-Cyclobutane-1,3-dicarboxylic Anhydride.** The title compound was prepared by the synthetic scheme described by Allinger and Tushaus.[15b] The same quantities and yields were obtained in the stepwise procedure down to the step for the preparation of 1,1,3,3-cyclobutanetetracarboxylic acid. The procedure called for destroying traces of nitric acid by addition of formic acid. A fairly violent reaction ensued with addition of the formic acid with much evolution of nitrogen oxides. The isolated yield was then about half of that reported.[15b]

A slight modification of the procedure allowed preparation of a larger yield of material. After removal of nitric acid under reduced pressure by heating on a steam bath, the tetraacid product was extracted into ether without the addition of formic acid. Starting with 50.0 g of 7-phenyl-6,8-dioxaspiro[3.5]nonane-2,2-dicarboxylic acid, 31 g (75%) of 1,1,3,3-cyclobutanetetracarboxylic acid was produced.

Decarboxylation and formation of *cis*-cyclobutane-1,3-dicarboxylic anhydride proceeded as described[15b] giving 11.76 g (46%) of the anhydride. The trans diacid (8.65 g, 24%) was converted to dimethyl cyclobutane-1,3-dicarboxylate (7.96 g, 77%) as described.[15b]

Dimethyl 1-Bromocyclobutane-1,3-dicarboxylate. *cis*-Cyclobutane-1,3-dicarboxylic anhydride (11.47 g, 81.3 mmol) was heated under reflux in CH_3OH (50 ml) for 1 h and the methanol was removed at reduced pressure. Thionyl chloride (25 ml) was added, along with 4 drops of dimethylformamide (DMF), and the solution was warmed to 50 °C for 0.5 h. Excess thionyl chloride was removed at reduced pressure. Bromine (16 g, 0.1 mol) was added to the acid chloride-ester kept at 70-80 °C until evolution of hydrogen bromide had ceased. Excess bromine was removed at reduced pressure and the crude product was added slowly to 75 ml of chilled CH_3OH. After standing 24 h, the solvent was removed and the product was short-path distilled [85 °C (0.1 mm)] giving 20.88 g (91%) of crude product which showed impurities by NMR spectroscopy. Fractionation using an 8-in. Vigreux column gave two fractions: bp 60-70 °C (0.1 mm) (4 g) and 75-79 °C (0.1 mm) (14.91 g). The second fraction was the desired bromo diester and was obtained in 65% yield: IR (thin film) 1740 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.18 and 6.21 (s, OCH_3 geminal to Br, 3), 6.33 and 6.35 (s, OCH_3, 3), and 6.6-7.7 (m, ring protons, 5). The product was indicated to be a cis/trans mixture from the two sets of methyl esters. Anal. Calcd for $C_8H_{11}O_4Br$: C, 38.27; H, 4.42. Found: C, 38.45; H, 4.36.

Dimethyl Bicyclo[1.1.0]butane-1,3-dicarboxylate. (1) From Dimethyl 1-Chlorocyclobutane-1,3-dicarboxylate. The method described by Hall and co-workers was employed.[18] Dimethyl 1-chlorocyclobutane-1,3-carboxylate[17] (2.00 g, 9.70 mmol) in 20 ml of dry THF and 0.63 g (15 mmol) of sodium hydride (57% in oil) were stirred at 45 °C under nitrogen for 3 h. The mixture was diluted with 100 ml of ether, filtered, and then washed with 200 ml of water. The organic layer was dried ($MgSO_4$) and concentrated giving a liquid which crystallized upon standing. The product was recrystallized from hexane at −70 °C and sublimed [50 °C (0.1 mm)] giving 1.332 g (80%) of the desired product (lit.[18] yield 61%): mp 57.5-58.0 °C; IR (thin film, CCl_4) 1730 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.30 (s, OCH_3, 6), 7.09 (m, exo ring protons, 2), and 8.55 (m, endo ring protons, 2).

(2) **From Dimethyl 1-Bromocyclobutane-1,3-dicarboxylate.** The same procedure described above using the chloro diester as starting material was followed.[18] The reaction appeared much slower than with the chloro diester; thus, 2 drops of *tert*-butyl alcohol was added to help speed the reaction. Heating of a mixture of 2.00 g (7.95 mmol) of dimethyl 1-bromocyclobutane-1,3-dicarboxylate and 0.7 g (20 mmol) of sodium hydride (57% in oil) in 20 ml of THF for 15 h at 45 °C gave, after work-up, 0.605 g (45%) of the desired diester as identified by NMR spectroscopy.

3-Carbomethoxybicyclo[1.1.0]butane-1-carboxylic Acid. To 9.79 g (57.6 mol) of dimethyl bicyclo[1.1.0]butane-1,3-dicarboxylate in 40 ml of CH_3OH was added dropwise over a 2-h period at room temperature 3.80 g (57.6 mmol) of KOH in 50 ml of CH_3OH. After stirring an additional 2 h, the methanol was removed by flash evaporation and the salt was dissolved in 25 ml of water. The aqueous solution was extracted with ether to remove unreacted starting material (0.30 g, 3%), acidified to pH 3, and extracted with three 100-ml portions of ether. The extract was dried ($MgSO_4$) and the ether was removed leaving a white solid which was recrystallized from CH_2Cl_2–hexane giving 8.175 g (90%) of the product. An analytical sample was sublimed [90 °C (0.01 mm)]: mp 120.5–121.5 °C; IR (Fluorolube mull) 2400–3200 (acid OH), 1720 (ester C=O), and 1685 cm^{-1} (acid C=O); NMR ($CDCl_3$, internal Me_4Si) τ 0.3 (s, CO_2H, 1), 6.25 (s, OCH_3, 3), 7.05 (m, exo ring protons, 2), and 8.42 (m, endo ring protons, 2). Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.80; H, 5.17.

Bicyclo[1.1.0]butane-1,3-dicarboxylic Acid. Dimethyl bicyclo[1.1.0]butane-1,3-dicarboxylate (1.00 g, 5.88 mmol) and 1.0 g (18 mmol) of potassium hydroxide were stirred in 30 ml of methanol at 50 °C for 2 h. The CH_3OH was removed by flash evaporation. The salt was diluted with 25 ml of water, saturated with NaCl, acidified to pH 3, and extracted with four 50-ml portions of ether. The extract was dried ($MgSO_4$) and concentrated leaving a white solid which was recrystallized from ether–hexane giving 0.622 g (79%) of the desired diacid: mp 150–170 °C dec; IR (Fluorolube mull) 2400–3200 (acid OH) and 1700 cm^{-1} (br C=O); NMR (Me_2SO-d_6, internal Me_4Si) τ −1.1 (s, CO_2H, 2), 7.30 (m, exo ring protons, 2), and 8.48 (m, endo ring protons, 2). Anal. Calcd for $C_6H_6O_4$: C, 50.71; H, 4.26. Found: C, 50.50; H, 4.04.

Methyl 3-Carbamoylbicyclo[1.1.0]butane-1-carboxylate. 3-Carbomethoxybicyclo[1.1.0]butane-1-carboxylic acid (5.00 g, 32 mmol) and 4.50 ml (32 mmol) of triethylamine were stirred together at 25 °C in 50 ml of $CHCl_3$. This mixture was cooled to ice-bath temperature before addition of 2.65 ml (33 mmol) of ethyl chloroformate. After stirring for 20 min anhydrous ammonia was bubbled through the solution for 30 min; the precipitate was filtered and washed with $CHCl_3$. Only a small amount of compound was isolated from the filtrate. Water was added to the precipitate and this mixture was extracted with ether. Some material, neither ether nor water soluble, was isolated by filtration. This insoluble material proved to be the desired compound. Product isolated from the $CHCl_3$ and from the ether extraction was combined with the insoluble precipitate to give 1.48 g (30%) of the crude carbamoyl ester. An analytical sample was sublimed [90 °C (0.01 mm)]; mp 135–145 °C dec; IR (Fluorolube mull) 3300 and 3260 (N—H), 1725 (C=O), 1660 (C=O), and 1640 cm^{-1}; NMR (Me_2SO-d_6, internal Me_4Si) τ 2.2–3.0 (m, NH_2, 2), 6.35 (s, OCH_3, 3), 7.17 (m, exo ring protons, 2), and 8.53 (m, endo ring protons, 2). Anal. Calcd for $C_7H_9O_3N$: C, 54.19; H, 5.85. Found: C, 53.85; H, 5.92.

3-Carbamoylbicyclo[1.1.0]butane-1-carboxylic Acid. To 0.50 g (3.2 mmol) of methyl 3-carbamoylbicyclo[1.1.0]butane-1-carboxylate in 20 ml of CH_3OH was added 0.3 g (5.3 mmol) of KOH in 15 ml of CH_3OH. The mixture was allowed to stand at 25 °C for 3 h after which it was concentrated, diluted with water, washed with ether, and acidified to pH 4 at which point a precipitate formed which was not soluble in ether or water. This precipitate was isolated by filtration and dried. Attempted recrystallizations from ethanol, CH_2Cl_2, and water were not successful in dissolving all the material. Hot DMF proved to be the best solvent for recrystallization giving 0.28 g (62%) of the carbamoyl acid: mp 200–205 °C dec; IR (Fluorolube mull) 3320 and 3150 (N—H), 2400–3000 (acid OH), 1700 (C=O), and 1660 (C=O). Anal. Calcd for $C_6H_7O_3N$: C, 51.07; H, 5.00. Found: C, 51.20; H, 5.10.

Reaction of Methyl 3-Carbamoylbicyclo[1.1.0]butane-1-carboxylate with Phosphorus Oxychloride. Methyl 3-carbamoylbicyclo[1.1.0]butane-1-carboxylate (0.78 g, 5.0 mmol) and 1.1 ml (12 mmol) of $POCl_3$ in 20 ml of $ClCH_2CH_2Cl$ were stirred at 70–75 °C for 40 min. At that time, evolution of gas had ceased and the starting material, initially insoluble, had all dissolved. The reaction mixture was eluted rapidly with $CHCl_3$ over 100 g of alumina (neutral, activity 3). Heat was given off as the solution passed down the column. The residue remaining after concentration of the eluate was short-path distilled [60–70 °C (0.01 mm)] giving 0.44 g of colorless liquid. NMR spectroscopy showed this material not to be the desired product. From the IR and NMR spectra, this compound was assigned the structure methyl 1-chloro-3-cyanocyclobutanecarboxylate (50%) which could arise from addition of hydrogen chloride across the zero-bridge bond in the desired bicyclobutane:[13,44] IR (thin film) 2220 (C≡N) and 1740 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.18 (s, OCH_3, 3) and 6.5–7.4 (m, ring protons, 5).

Methyl 3-Cyanobicyclo[1.1.0]butane-1-carboxylate. Methyl 1-chloro-3-cyanocyclobutanecarboxylate (0.42 g, 2.43 mmol) was stirred with sodium hydride (57% in oil) (0.22 g, 5 mmol) in 15 ml of THF at 45 °C for 3 h. The usual work-up after short-path distillation [40–50 °C (0.001 mm)] gave 0.150 g (45%) of colorless liquid. The IR and NMR spectra agreed with those of the desired structure. The NMR spectrum showed the presence of approximately 18–20% impurity, probably starting material. The data for this compound are as follows: IR (thin film) 2050 (C≡N) and 1740 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.12 (s, OCH_3, 3), 7.17 (m, exo ring protons, 2), and 8.35 (m, endo ring protons, 2). An analytical sample was not obtained due to the small amount of material.

3-Cyanobicyclo[1.1.0]butane-1-carboxylic Acid. Methyl 3-cyanobicyclo[1.1.0]butane-1-carboxylate (150 mg, 1.1 mmol, 80% pure) was stirred with 0.25 g (4 mmol) of KOH in 20 ml of 80% CH_3OH at 25 °C for 2 h. After concentration, dilution with 20 ml of water, acidification to pH 3, and extraction with ether, 100 mg of crude product was isolated from the ether extract. Recrystallization from ether–hexane at −20 °C did not help with the purification. Sublimation [75–80 °C (0.01 mm)] gave 55 mg of solid with about half of the original material remaining behind as a polymeric brown solid. The material that did sublime showed two C≡N's and two C=O's in its IR spectrum. This material also turned brown on standing 2 days at room temperature. Thus, the cyano acid was not isolated in pure form.

***trans*-1,2-Dimethylcyclopropanecarboxylic Acid.** Methyl *trans*-1,2-dimethylcyclopropanecarboxylate[19] (1.70 g, 13.3 mmol; contaminated with 6% of its cis isomer) was stirred with 2.0 g (28 mmol) of KOH in 25 ml of 80% CH_3OH for 24 h at 25 °C and for 1 h at 50 °C. The mixture was concentrated, diluted with water, acidified to pH 2, and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated, and the remaining liquid was short-path distilled [50 °C (0.01 mm)] giving 1.24 g (82%) of the liquid trans acid (probably contaminated with 6% cis acid): IR (thin film) 2400–3300 (acid OH) and 1685 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ −1.2 (s, CO_2H, 1), 8.70 (s, CH_3, 3), 8.4–9.3 [m (characteristic peaks at τ 8.74 and 8.78), 6]. The NMR spectrum was quite similar to its trans ester.[19] Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.32; H, 8.90.

***cis*-1,2-Dimethylcyclopropanecarboxylic Acid.** Methyl *cis*-1,2-dimethylcyclopropanecarboxylate[19] (400 mg, 3.1 mmol; contaminated with 4% of its trans isomer) was stirred with 0.5 g (90 mmol) of KOH in 35 ml of 80% CH_3OH for 24 h at 25 °C. Product work-up was the same as described above for the trans isomer. The cis acid was short-path distilled [50 °C (0.01 mm)] giving 160 mg (45%) of the liquid cis acid (probably contaminated with 4% of its trans isomer). Further purification of this material was not attempted: IR (thin film) 2400–3300 (acid OH) and 1685 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ −1.2 (s, CO_2H, 1), 8.74 (s, CH_3, 3), 8.4–8.6 [m (characteristic peaks at τ 8.47 and 8.53), 1], 8.75–8.95 [m (characteristic peaks at τ 8.80 and 8.90), 4], and 9.55–9.75 (m, 1). The NMR spectrum was quite similar to its cis ester.[19] Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.26; H, 8.91.

Dimethyl *cis*- and *trans*-1,2-Dimethylcyclopropane-1,2-dicarboxylate. The procedure described by McCoy was followed.[20a,45] A mixture of 5.0 g (41 mmol) of methyl α-chloropropionate, 8.0 g (80 mmol) of methyl methacrylate, and 2.5 g (59 mmol) of sodium hydride (57% in oil) in 60 ml of DMF was stirred in a water bath at room temperature for 5 h until hydrogen evolution had ceased. The mixture was then filtered and concentrated by flash evaporation, and the product was short-path distilled [90 °C (0.1 mm)] giving 4.65 g (60%) of colorless liquid. The NMR spectrum showed this liquid to be a 2:1

mixture of trans and cis isomers, respectively. Separation of the isomers was accomplished on a larger scale by fractional distillation using an annular spinning band column. The lower boiling [65 °C (3 mm)] trans diester solidified at room temperature. When the head temperature increased by about 2 °C, the cis diester began distilling. A check of the remaining pot liquid at this point showed only the cis diester which was further purified by a short-path distillation. The NMR spectra of the cis and trans diesters agreed with those reported.[46] The data for dimethyl *trans*-1,2-dimethylcyclopropane-1,2-dicarboxylate are as follows: IR (thin film) 1730 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.33 (s, OCH_3, 6), 8.60 (s, CH_2, 2), and 8.74 (s, CH_3, 6); mass spectrum (70 eV, heated inlet) M^+ at *m/e* 186. The data for dimethyl *cis*-1,2-dimethylcyclopropane-1,2-dicarboxylate are as follows: IR (thin film) 1730 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.35 (s, OCH_3, 6), 8.10 (d, J = 4.5 Hz, methylene proton cis to CO_2CH_3's, 1), 8.66 (s, CH_3, 6), 9.37 [d, J = 4.5 Hz, methylene proton trans to CO_2CH_3's, 1); mass spectrum (70 eV, heated inlet) M^+ at *m/e* 186.

***trans*-1,2-Dimethylcyclopropane-1,2-dicarboxylic Acid.** Dimethyl *trans*-1,2-dimethylcyclopropane-1,2-dicarboxylate (2.88 g, 16.7 mmol) was stirred with 3.8 g (68 mmol) of KOH in 80% CH_3OH for 3 days. After concentration, dilution with water, acidification, and continuous extraction with ether for 24 h, 2.10 g (86%) of crystalline acid was obtained. It was recrystallized from ether–hexane and sublimed [100 °C (0.01 mm)]: mp 228–229 °C (lit.[45] 229–231 °C); ir (Fluorolube mull) 2400–3300 (acid OH) and 1690 cm^{-1} (C=O).

***cis*-1,2-Dimethylcyclopropane-1,2-dicarboxylic Acid.** Dimethyl *cis*-1,2-dimethylcyclopropane-1,2-dicarboxylate (2.10 g, 12.2 mmol) was stirred with 3.5 g (62 mmol) of KOH in 80% CH_3OH for 24 h. After concentration, dilution with water, acidification, and continuous extraction with ether, the crude product was treated with 10 ml of acetyl chloride at 50 °C for 2 h. Distillation [60 °C (0.01 mm)] gave 1.0 g of the cis anhydride as white needles: mp 55–56 ° (lit.[45] 55–57 °C); IR (thin film) 1825 and 1760 cm^{-1} (C=O); NMR (CCl_4, external Me_4Si) τ 8.28 (d, J = 5.0 Hz, 1), 8.55 (s, CH_3, 6), and 8.85 [d, J = 5.0 Hz, 1). The NMR spectrum agreed with that reported.[46]

The cis anhydride was then hydrolyzed with water at 70–80 °C for 30 min. Ether extraction after acidification to pH 3 and saturating the solution with sodium chloride produced 1.04 g (59%) of crystalline acid which was recrystallized from ether–hexane: mp 115–117 °C (lit.[45] 115–117 °C).

2-Carbomethoxy-*trans*-1,2-dimethylcyclopropanecarboxylic Acid. To 12.96 g (69.5 mmol) of dimethyl *trans*-1,2-dimethylcyclopropane-1,2-dicarboxylate in 30 ml of CH_3OH was added dropwise 38.3 ml of 1.86 N (71.5 mmol) KOH in CH_3OH. The mixture was then allowed to stand for 48 h before concentration by flash evaporation and dilution with water. Unreacted starting material (2.88 g, 22%) was extracted with ether. The solution was then acidified to pH 2, saturated with sodium chloride, and continuously extracted with ether for 16 h. The extract was dried ($MgSO_4$) and concentrated, and the product was short-path distilled [120 °C (0.01 mm)] yielding 6.25 g (52%) of the trans half-ester which solidified upon standing. The product was recrystallized from ether–hexane and sublimed [50 °C (0.01 mm): mp 55.5–56.5 °C IR (Fluorolube mull) 2400–3300 (acid OH), 1725 (ester C=O), and 1690 cm^{-1} (acid C=O); NMR (CCl_4, internal Me_4Si) τ −1.2 (s, CO_2H, 1), 6.31 (s, OCH_3, 3), 8.53 (s, CH_2, 2), 8.59 (s, CH_3, 3), and 8.68 (s, CH_3, 3); mass spectrum (70 eV, heated inlet) M^+ at *m/e* 172. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.77; H, 7.10.

2-Carbomethoxy-*cis*-1,2-dimethylcyclopropanecarboxylic Acid. To 19.65 g (106 mmol) of dimethyl *cis*-1,2-dimethylcyclopropane-1,2-dicarboxylate in 70 ml of CH_3OH was added 58 ml of 1.86 N (106 mmol) KOH in CH_3OH dropwise over a 1-h period. The mixture was then allowed to stand at room temperature for 48 h. After concentration by flash evaporation and dilution with water, unreacted diester (2.17 g, 11%) was removed by extraction with ether. The mixture was then acidified to pH 3 and continuously extracted with ether for 5 h. The extract was dried ($MgSO_4$) and concentrated, and the residue was short-path distilled 120–130 °C (0.01 mm)] giving 13.86 g of viscous liquid. The distillate was shown to be a mixture of the cis half-ester and cis anhydride from its IR spectrum. This crude mixture was heated under reflux in CH_3OH until the IR spectrum showed no remaining anhydride absorptions. CH_3OH was removed under reduced pressure and the residue was recrystallized from cyclohexane–hexane to give 13.50 g (74%) of the desired product. An analytical sample was obtained after additional recrystallizations: mp 56.5–57.5 °C; IR (Fluorolube mull) 2600–3300 (acid OH), 1725 (ester C=O), and 1685 cm^{-1} (acid C=O); NMR (CCl_4, internal Me_4Si) τ −1.2 (s, CO_2H, 1), 6.41 (s, OCH_3, 3), 8.04 (d, J = 4.5 Hz, methylene proton cis to CO_2CH_3's, 1), 8.62 (s, CH_3, 6), and 9.32 (d, J = 4.5 Hz, methylene proton trans to CO_2CH_3's, 1); mass spectrum (70 eV, heated inlet) M^+ at *m/e* 172. Anal. Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.92; H, 7.09.

Methyl 2-Bromo-*cis*- and -*trans*-1,2-dimethylcyclopropanecarboxylate. To 2.00 g (9.2 mmol) of red mercuric oxide in 20 ml of $BrCCl_3$ at 30–40 °C was added dropwise for a 6-h period 2.00 g (11.6 mmol) of 2-carbomethoxy-*cis*-1,2-dimethylcyclopropanecarboxylic acid and 1 ml (19 mmol) of bromine in 20 ml of $BrCCl_3$.[47] After 6 h 0.5 g of additional mercuric oxide was added and the mixture was warmed to 50 °C until the bromine color had disappeared. The mixture was filtered, concentrated, diluted with hexane, and filtered again. The product was short-path distilled [70 °C (0.01 mm)] yielding 1.15 g (47%) of the colorless, liquid bromo ester.

A second reaction was carried out using 2.00 g (11.6 mmol) of the isomeric trans half-ester using the same conditions and amounts of reactants as used above. Short-path distillation yielded 1.13 g (47%) of the bromo ester.

NMR spectra of the two reaction products showed them to both be a mixture of two components. GLPC analysis on a 10% Carbowax on Chromosorb W 8 ft × 0.25 in. column showed two components. Integration of the products from the first reaction showed a ratio of 72:28 and integration of the products from the second reaction showed a ratio of 75:25.

The two components were collected by GLPC on a 12 ft × 0.25 in. 10% Carbowax on Chromosorb W column. From the product derived from the two above reactions of 2-carbomethoxy-*cis*- and -*trans*-1,2-dimethylcyclopropanecarboxylic acid, there was 1.05 g of the first component and 0.425 g of the second component collected.

The first component was assigned the structure methyl 2-bromo-*trans*-1,2-dimethylcyclopropanecarboxylate: IR (thin film) 1725 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.30 (s, OCH_3, 3), 8.18 [s, CH_3 (geminal to Br), 3], 8.44 [s, CH_3 (geminal to CO_2CH_3), 3] 8.29 (d, J = 6.5 Hz, ring proton cis to Br, 1), and 8.42 (d, J = 6.5 Hz, ring proton cis to CO_2CH_3, 1); mass spectrum (70 eV, heated inlet) M^+ at *m/e* 206 and 208.

The second component was assigned the structure methyl 2-bromo-*cis*-1,2-dimethylcyclopropanecarboxylate: IR (thin film) 1725 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.32 (s, OCH_3, 3), 8.17 [s, CH_3 (geminal to Br), 3], 8.64 [s, CH_3 (geminal to CO_2CH_3), 3], 8.05 (d, J = 6.5 Hz, ring proton cis to Br, 1), and 9.25 (d, J = 6.5 Hz, ring proton trans to Br, 1); mass spectrum (70 eV, heated inlet) M^+ at *m/e* 206 and 208.

An analytical sample of the cis/trans mixture of isomers was collected by GLPC and short-path distilled for purification.

Anal. Calcd for $C_7H_{11}O_2Br$: C, 40.60; H, 5.35. Found: C, 40.63; H, 5.42.

2-Bromo-*trans*-1,2-dimethylcyclopropanecarboxylic Acid. Methyl 2-bromo-*trans*-1,2-dimethylcyclopropanecarboxylate (1.05 g, 5.08 mmol) was stirred with 0.5 g (10 mmol) of KOH in 80% CH_3OH for 25 h at room temperature. The mixture was concentrated, diluted with water, acidified to pH 2, and extracted with four 50-ml portions of ether. The extract was dried ($MgSO_4$) and the ether was evaporated. The residue was recrystallized from hexane at dry ice temperatures giving 0.805 g (82%) of the trans bromo acid. The acid was further purified by sublimation [50 °C (0.01 mm)]: mp 62.5–63.5 °C; IR (thin film) 2400–3300 (acid OH) and 1690 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ −1.2 (s, CO_2H, 1), 8.05 [s, CH_3 (geminal to Br), 3], 8.40 [s, CH_3 (geminal to CO_2H), 3], 8.24 (d, J = 6.5 Hz, ring proton cis to Br, 1), and 8.83 (d, J = 6.5 Hz, ring proton trans to Br, 1). Anal. Calcd for $C_6H_9O_2Br$: C, 37.33; H, 4.70. Found: C, 37.27; H, 4.75.

2-Bromo-*cis*-1,2-dimethylcyclopropanecarboxylic Acid. Hydrolysis of 0.425 g (2.05 mmol) of the cis bromo ester as above for the trans bromo ester yielded approximately 0.2 g (50%) of crystalline product. Hydrolysis of the cis ester appeared to be slower than the trans ester because a considerable amount of starting ester was recovered for the cis compound under the same hydrolysis conditions. The cis bromo acid was recrystallized from hexane at dry ice temperatures and sublimed several times [50 °C (0.01 mm)]: mp 86–88 °C; IR (thin film before it solidified) 2400–3400 (acid OH) and 1690 cm^{-1} (C=O). Anal. Calcd for $C_6H_9O_2Br$: C, 37.33; 4.70. Found: 37.48, H, 4.74.

Methyl 2-Carbamoyl-*trans*-1,2-dimethylcyclopropanecarboxylate. To 2.00 g (11.6 mmol) of 2-carbomethoxy-*trans*-1,2-dimethylcyclopropanecarboxylic acid dissolved in 50 ml of $CHCl_3$ was added 1.77 ml (13 mmol) of triethylamine. After stirring 5 min and cooling to ice bath temperature, 0.97 ml (13 mmol) of ethyl chloroformate was added rapidly. After stirring for 15 min, anhydrous ammonia was bubbled through the solution for 0.5 h. A white precipitate formed immediately. After standing for 3 h the mixture was filtered and concentrated. The solid residue was recrystallized twice from benzene–hexane giving 0.925 g (46%) of trans carbamoyl ester: mp 134.0–135.5 °C; IR (Fluorolube mull) 3230 and 3400 (N—H), 1735 (ester C=O), 1675 (carbamoyl C=O), and 1650 cm^{-1} (carbamoyl); NMR ($CDCl_3$, internal Me_4Si) τ 4.0–4.4 (br s, NH_2, 2), 6.29 (s, OCH_3, 3), 8.58 (s, CH_2, 2), 8.61 (s, CH_3, 3), and 8.65 (s, CH_3, 3); mass spectrum (70 eV, direct insert) M^+ at *m/e* 171. Anal. Calcd for $C_8H_{13}O_3N$: C, 56.13; H, 7.65. Found: C, 56.29; H, 7.79.

2-Carbamoyl-*trans*-1,2-dimethylcyclopropanecarboxylic Acid. Methyl 2-carbamoyl-*trans*-1,2-dimethylcyclopropanecarboxylate (0.825 g, 4.82 mmol) was hydrolyzed with excess KOH in 80% CH_3OH. After concentration, dilution with water, and acidification to pH 3, the solution was continuously extracted with ether for 24 h. The trans carbamoyl acid was isolated and recrystallized from ethyl acetate (0.305 g, 68%): mp 195–196 °C; IR (Fluorolube mull) 3320 and 3140 (N—H), 1700 (acid C=O), and 1670 cm^{-1} (carbamoyl C=O). Anal. Calcd for $C_7H_{13}O_3N$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.62; H, 7.12; N, 8.90.

Attempted Preparation of Methyl 2-Carbamoyl-*cis*-1,2-dimethylcyclopropanecarboxylate. The same quantities and reaction conditions were employed as used in the preparation of methyl 2-carbamoyl-*trans*-1,2-dimethylcyclopropanecarboxylate except that the starting material was the isomeric cis half-ester. The isolated product was recrystallized from benzene–hexane giving 0.43 g of white crystals. The IR and NMR spectra indicated that this product was *cis*-1,2-dimethylcyclopropane-1,2-dicarboximide (45%): mp 149.5–150.5 °C; IR (Fluorolube mull) 3200 (N—H), 1755 and 1700 cm^{-1} (C=O); NMR ($CDCl_3$, internal Me_4Si) τ 8.70 (s, CH_3, 6), 8.30 (d, J = 4.5 Hz, ring proton cis to imide, 1), and 8.96 (d, J = 4.5 Hz, ring proton trans to imide, 1). Anal. Calcd for $C_7H_9O_2N$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.65; H, 6.69; N, 10.12.

Methyl 2-Cyano-*cis*- and -*trans*-1,2-dimethylcyclopropanecarboxylate.[20b] Methacrylonitrile (6.70 g, 0.10 mmol), methyl α-chloropropionate (12.3 g, 0.10 mol), and sodium hydride (4.7 g, 0.10 mol) (mineral oil dispersion, 57%) in 50 ml of DMF were allowed to react at 20–30 °C. Evolution of hydrogen had ceased after 3 h at which time the mixture was filtered, diluted with ether, and washed with water. The ether layer was dried ($MgSO_4$) and concentrated. The product was short-path distilled [100 °C (0.1 mm)] giving 10.00 g (65%) of colorless liquid. NMR spectral analysis showed the product to be approximately a 1:1 mixture of the cis and trans isomers, plus a small amount of impurities. Fractional distillation (9 mm) using a semimicro platinum spinning band column successfully separated the two isomers. The trans isomer was collected from 80 to 82 °C (3.62 g, 23%) and only the cis isomer remained in the distillation pot after the head temperature reached 104 °C. Short-path distillation of the pot residue yielded 3.01 g (20%) of the cis isomer.

The data for methyl 2-cyano-*trans*-1,2-dimethylcyclopropanecarboxylate are as follows: IR (thin film) 2230 (C≡N) and 1730 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.30 (s, OCH_3, 3), 8.44 (s, CH_3, 3), 8.59 (s, CH_3, 3), 8.42 (d, J = 5.5 Hz, ring proton cis to CN, 1), and 8.80 (d, J = 5.5 Hz, ring proton trans to CN, 1); mass spectrum (70 eV, heated inlet) M^+ at *m/e* 153.

The data for methyl 2-cyano-*cis*-1,2-dimethylcyclopropanecarboxylate are as follows: ir (thin film) 2230 (C≡N) and 1735 cm^{-1} (C=O); NMR (CCl_4, internal Me_4Si) τ 6.26 (s, OCH_3, 3), 7.97 (d, J = 5.0 Hz, ring proton cis to CN, 1), 8.53 (s, CH_3, 3), 8.64 (s, CH_3, 3), and 9.17 (d, J = 5.0 Hz, ring proton trans to CN, 1); mass spectrum (70 eV, heated inlet) M^+ at *m/e* 153.

2-Cyano-*trans*-1,2-dimethylcyclopropanecarboxylic Acid. Methyl 2-cyano-*trans*-1,2-dimethylcyclopropanecarboxylate (3.63 g, 23.6 mmol) was stirred with 0.25 g (40 mmol) of KOH in 90% CH_3OH at room temperature for 24 h and then heated under reflux for 0.5 h. The mixture was concentrated by flash evaporation, diluted with water, acidified to pH 3, and extracted with ether. The ether extract was dried ($MgSO_4$) and the ether evaporated giving 2.65 g (80.6%) of trans cyano acid after recrystallization from ether–hexane and sublimed [100 °C (0.01 mm)]: mp 96–97 °C; IR (Fluorolube mull) 2300–3300 (acid OH), 2240 (C≡N), and 1690 cm^{-1} (C=O). Anal. Calcd for $C_7H_9O_2N$: C, 60.41; H, 6.52. Found: C, 60.53; H, 6.68.

2-Cyano-*cis*-1,2-dimethylcyclopropanecarboxylic Acid. Methyl 2-cyano-*cis*-1,2-dimethylcyclopropanecarboxylate (3.01 g, 19.7 mmol) was stirred with 0.25 g (40 mmol) of KOH in 90% CH_3OH at room temperature for 24 h. Concentration, dilution with water, acidification, and extraction with ether gave a viscous oil after removal of ether. The IR spectrum of the crude product showed impure cis cyano acid (nitrile absorption at 2240 cm^{-1}) and large amounts of impurities. The IR spectrum also showed the presence of *cis*-1,2-dimethylcyclopropane-1,2-dicarboxylic anhydride. Recrystallization from ether–hexane did not decrease the amounts of impurities. The impure crystalline material obtained appeared to decompose upon standing by changing to an amorphous mass. Sublimation did not increase purity either. *cis*-Dicarboxylic imide was also evident in the IR spectrum as one of the main decomposition products.

Determination of Dissociation Constants. The methods used for solvent handling, standardization, acid dissociation constants measurement, and data treatment were those previously described.[48]

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Synthesis and Reactions of the Tautomeric Complexes η-2,3,4,5-Cyclooctatrienoneiron Tricarbonyl and Bicyclo[4.2.0]octa-2,4-dien-7-oneiron Tricarbonyl. Generation of Bicyclo[4.2.0]octa-2,4-dien-7-one[1]

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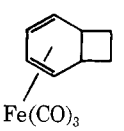
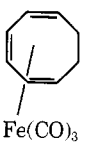
Abstract: Photolytic reaction of 2,4,6-cyclooctatrienone with iron pentacarbonyl in benzene yields η-2,3,4,5-cyclooctatrienoneiron tricarbonyl (XI), whereas thermal reaction of the ketone with benzylideneacetoneiron tricarbonyl or 3-penten-2-oneiron tricarbonyl in benzene at 60 °C results in trapping of the bicyclic diene tautomer of cyclooctatrienone as bicyclo[4.2.0]octa-2,4-dien-7-oneiron tricarbonyl (IX). Detailed ^1H and ^{13}C NMR studies have been carried out to elucidate the structures of these complexes. Low temperature (−30 °C) oxidative cleavage of IX gives bicyclo[4.2.0]octa-2,4-dien-7-one which at 0 °C undergoes ring opening to cyclooctatrienone with a first-order rate constant of 5.7×10^{-4} s^{-1}, $\Delta G^{\ddagger} = 20.0$ kcal/mol. The equilibrium ratio of 2,4,6-cyclooctatrienone to bicyclo[4.2.0]octadienone was estimated from ^1H FT-NMR studies to be ca. 135. This value agrees with one estimated from the ratio of rate constants for the ring opening and ring closing reactions of the two tautomers. When treated with sodium methoxide–methanol, the bicyclic ketone complex IX undergoes ring opening to yield the monocyclic ((carbomethoxymethyl)cyclohexadiene)iron tricarbonyl XIV; protonation of the intermediate anion was observed to occur stereospecifically exo. Upon treatment with methyllithium the bicyclic ketone complex IX is converted to the tertiary alcohol. This alcohol undergoes base-induced ring cleavage to yield the monocyclic ketone, ((2-oxopropyl)cyclohexadiene)iron tricarbonyl (XVI), again with stereospecific exo protonation of the intermediate anion.

Introduction

The reactions of cyclooctatriene and its derivatives with iron carbonyl reagents can lead to a variety of mononuclear cyclic polyolefin iron carbonyl complexes, the nature of which depends upon the triene derivative and the iron carbonyl reagent used as well as the reaction conditions. Early work by Stone showed that reaction of 1,3,5-cyclooctatriene with $Fe(CO)_5$ at 140 °C leads only to the complex of the bicyclic tautomer, bicyclo[4.2.0]octa-2,4-dieneiron tricarbonyl (I),[2] while reaction with $Fe_3(CO)_{12}$ at lower temperatures (80–100 °C) leads to mixtures of I plus cyclooctatrieneiron tricarbonyl



I



II

(II).[3] Pure samples of II can be generated photolytically at room temperature employing cyclooctatriene and $Fe(CO)_5$.[4] In the equilibrium between the uncomplexed cyclooctatriene and bicyclooctadiene tautomers, the triene is favored over the diene by a ratio of 85:15 at 100 °C;[5] however, in contrast for