such as **12** should be formed in vivo in DNA upon metabolism of **1**.[17] Experiments designed to detect **12** or related adducts in vivo are currently in progress.

Acknowledgment. This study was supported by the National Cancer Institute (Grant CA-23901).

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[17] We have recently determined that glyoxal is a metabolite of **1**, which is in agreement with the present results.

Convergent Functional Groups Provide a Measure of Stereoelectronic Effects at Carboxyl Oxygen

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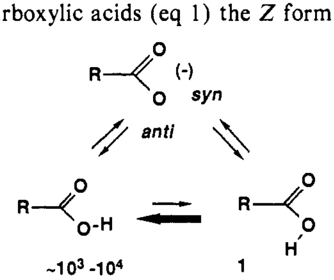
Acyl transfer reactions and aldol chemistry have provided a number of experimental methods by which stereoelectronic effects at carboxyl carbon may be assessed. By contrast, much less is known of these effects as they pertain to reactions at carboxyl *oxygen*. For carboxylic acids (eq 1) the *Z* form is regarded as some 5 kcal more stable than the *E* form.[1a-c] This difference has biochemical implications; Gandour[1d] has observed that carboxylates found at the active sites of enzymes generally employ the more basic syn lone pairs rather than the less basic anti lone pairs. Evaluating the importance of these effects through equilibrium measurements of lone pair basicity has not been possible because of the lack of suitable model systems, and even kinetic analyses[2] of intramolecular general base catalysis, A, involve only the less basic anti lone pairs.



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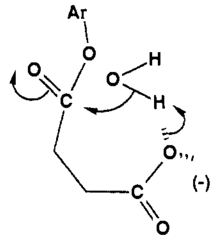


A

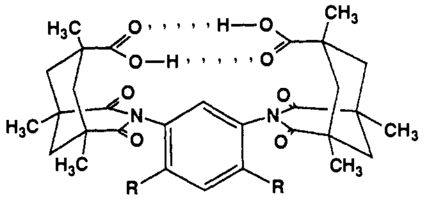
We recently introduced[3] the first molecular system having the appropriate structure to approach these issues. In these molecules, **1a**, **2**, and **3**, remote steric barriers *enforce the convergence of two carboxylic acids*, a feature which permits some control of the microenvironment of the syn lone pairs of a carboxylate. Here we report how these structural limitations affect ionization behavior.

Table I. Equilibrium Acidities of Carboxylic Acids (25 °C)

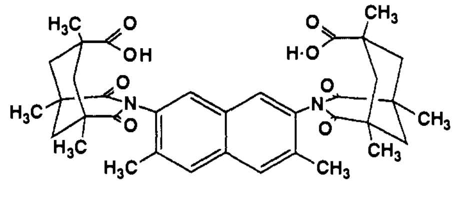
struct	pK_1	pK_{a2}	ΔpK_a	solvent	ref	dist,[a] Å
1a	4.8	11.1	6.3	$EtOH/H_2O$	this work[b]	3
1b	5.1	7.7	2.6			>8
2	5.5	7.5	2.0			5.8
3	6.5	7.8	1.2			8
4	4.7	7.6	2.9	$MeOH/H_2O$	4	3
5	6.0	6.9	0.9	$EtOH/H_2O$	5	4.5
6 (oxalic)	2.0	5.5	3.5	$EtOH/H_2O$[c]	6	3
7 (malonic)	3.4	7.1	3.7		6	3
8 (succinic)	5.0	6.8	1.8		6	6
9	6.3	8.0	1.7	Me_2SO/H_2O[d]	7	>8

[a] Approximate distance between oxygen atoms of the dicarboxylate as measured by CPK or Dreiding models. [b] Titration curves (30–50 points) were obtained in $EtOH/H_2O$ (1:1, w/w) at 0.01 M KCl, and regression analysis[8] was used to calculate pK_a's. Chemical shifts of the NMR of **3** in hydroxylic media indicate the dominance of the zwitterionic form shown.[9] [c] 40% EtOH by weight. [d] 65% Me_2SO by volume.

Dissociation constants of representative dicarboxylic acids in H_2O/alcohol mixtures are reported in Table I; all values have been corrected for statistical effects. While other diacids are available for evaluation, the selections below were intended to include structures in which the two $C_\alpha \rightarrow CO_2^-$ bonds are parallel (**4**, **5**), divergent (**1b**, **6**, **7**), and convergent (**1a**, **2**, **3**).



1a R = CH_3
1b R = H



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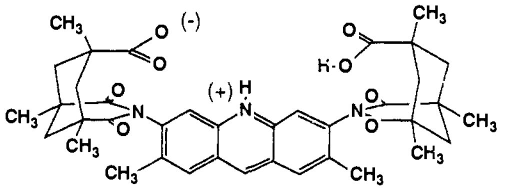

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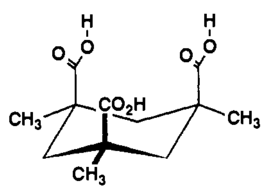

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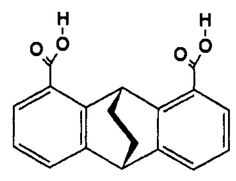

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The specific issue concerns the effect of orientation (rather than distance) on ΔpK_a. When about 3 Å separates the carboxylate oxygens (**4**, **6**, **7**), a ΔpK_a of 3 units is generally observed. In **6** and **7** the carboxyl groups diverge and, at worst, only the anti lone pairs can be directed toward each other in the dianion. In **4** the planes of the carboxyl groups are roughly parallel and only the π electrons of each may come into contact; intramolecular hydrogen bonds are not likely.[3] With **1a** the corresponding distance

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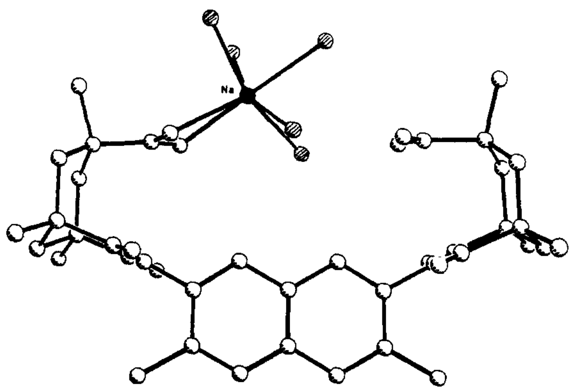
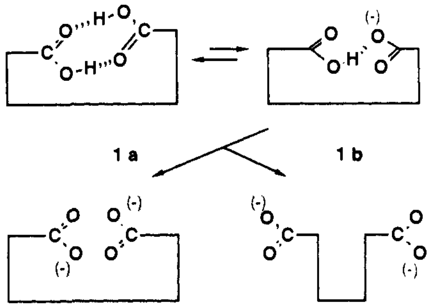

10

Figure 1. Crystal structure of the monosodium salt of **2**. The oxygens of the water molecules indicated by shaded circles; all hydrogens have been omitted for clarity.

is also about 3 Å, but the conformation forces the convergence of the syn lone pairs in the dianion. The result of such high electron density in a limited volume is seen in the extraordinary ΔpK_a of 6.3 units.

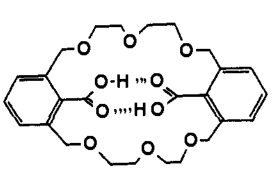
At first glance, the poor access of solvent to the syn lone pairs in the dianion of **1a** could be due to its instability. But even when hydroxylic solvents have access to the carboxyl groups an orientation effect of the lone pairs is observed. Specifically, the diacid **2** binds alcohols tenaciously,[10] and the crystal structure[11] of the monosodium salt, reproduced in **10** (Figure 1), shows extensive solvation by water. The distance that separates the carboxyl oxygens in **2** is seen to be 5.8 Å, or about 1 Å *larger* than that involved in **5**. *Yet the dianion of **2** is less stable.* The enforced convergence of the syn lone pairs in **2** vs. **5** accommodates this result quite nicely.

The effects of intramolecular hydrogen bonding are, admittedly, difficult to quantify in these systems. For example, **1a** may be unique in this group of acids in that its first ionization destroys one intramolecular hydrogen bond but improves[12] the remaining one. The loss of the latter upon the second ionization doubtless contributes to the very large ΔpK_a observed (eq 2).



(2)

Perhaps a measure of this contribution is provided by **1b**. Here, the dianion surely assumes a divergent conformation, since rotations about the C_{aryl}–N bond are rapid at room temperature.[3] If the monoanion of **1b** enjoys an intramolecular hydrogen bond similar to that of **2a**, then a large part of the $\Delta pK_a = 2.6$ represents the cost of breaking it[13] (eq 2). Otherwise, a very small ΔpK_a could be expected. In the monoanions of **6–8** such bonding is also possible but structural limitations force the anti lone pair to interact with the anti acid as in **11**. What effect this has on ΔpK_a is not easily assessed.[14] The $\Delta pK_a = 1.7$ observed for **9**, for example, has been interpreted as inconsistent with an intramolecular hydrogen bond in the monoanion.[7]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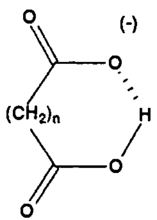
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In comparison of molecules which differ in more than one respect, the data generally admit to alternative interpretations. The present case is no exception, and the series **1a**, **2**, and **3** are merely readily accessible points in a continuum of structures. When intermediate distances and orientations become available, some finer tuning of the interpretations is also likely to follow. In the meantime, the orientation effects described here support the contention[1d] that the modest efficiency of processes such as A is a result of stereoelectronic effects at carboxyl oxygen.

Acknowledgment. We thank the National Science Foundation for support and Dr. Jaime Abola for his assistance in the crystallographic study.

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[11] General methods for the X-ray studies may be found in ref 3; details will be reported elsewhere.

[12] Hadzi, D.; Detoni, S. In *The Chemistry of Carboxylic Acid Derivatives*; Patai, S., Ed.; Wiley: New York, 1979; Suppl. B, Part 1, pp 214-241. For a recent, relevant discussion of hydrogen bonding, see: Fersht, A. R.; Shi, J.-P.; Knill-Jones, J.; Lowe, D. M.; Wilkinson, A. J.; Blow, D. M.; Brick, P.; Carter, P.; Waye, M. M. Y.; Winter, G. *Nature (London)* **1985**, *314*, 235-238.

[13] For an alternative measure of hydrogen bond strenghts, see: Kreevoy, M. M.; Liang, T.; Chan, K.-C. *J. Am. Chem. Soc.* **1977**, *99*, 5207-5209.

[14] See, for example: Eberson, L. *Acta Chem. Scand.* **1959**, *13*, 211-223.

Heterobimetallic $\mu(\eta^1\text{-C}:\eta^2\text{-O,O}')$ Carbon Dioxide and $\mu(\eta^1\text{-C,O})$ Formaldehyde Complexes $Cp(NO)(CO)Re\text{-}C(O)O\text{-}Zr(Cl)Cp_2$ and $Cp(NO)(CO)Re\text{-}CH_2O\text{-}Zr(Cl)Cp_2$

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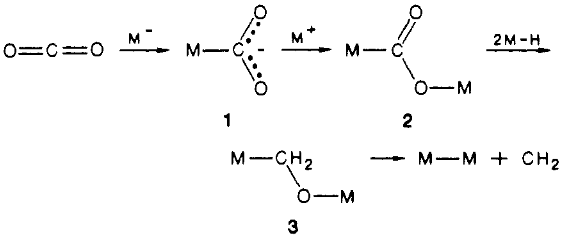
Reducing carbon dioxide[1] to formaldehyde with transition organometallic complexes has as one approach the bimetallic coordination–activation of C_1 fragments. For example (eq 1), an



(1)

η^1-C CO_2 complex (or metallocarboxylate) **1** could form a bimetallic $\mu(\eta^1\text{-C,O})$ carboxylate derivative **2**, which upon treating with a metal hydride gives a $\mu(\eta^1\text{-C,O})$ formaldehyde compound **3**. A few metallocarboxylates **1** have been characterized as a result of either coordinating CO_2 to an electron-rich transition-metal center,[2] or by adding excess hydroxide to a ligated carbonyl (eq

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[1] (a) Sneeden, R. P. A. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Ebel, E. W., Eds.; Pergamon Press: New York, 1982, Vol. 8, Chapter 50.4. (b) Ito, T.; Yamamoto, A. In *Organic and Bio-Organic Chemistry of Carbon Dioxide*; Inoue, S., Yamazaki, N., Eds.; Wiley: New York, 1982; Chapter 3. (c) Darensbourg, D. J.; Kudaroski, R. A. *Adv. Organomet. Chem.* **1983**, *22*, 129. (d) Behr, A. In *Catalysis in C_1 Chemistry*; Keim, W., Ed.; D. Reidel: Boston, 1983; pp 169-219. (g) Floriani, C. *Pure Appl. Chem.* **1983**, *55*, 1; **1982**, *54*, 59.

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