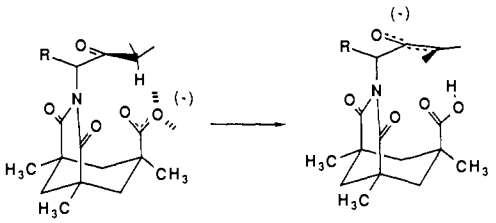


9a R = $CH_2C_6H_5$
9b R = $CH(CH_3)_2$

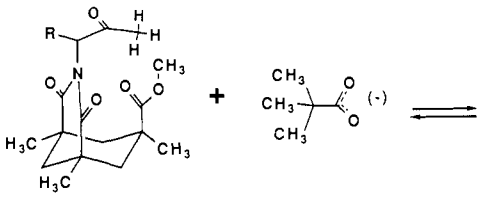
10a R = $CH_2C_6H_5$
10b R = $CH(CH_3)_2$

(4)

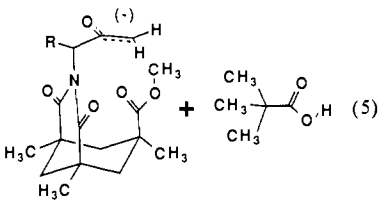
by Corey[9] for an optimal reaction rate.

The pD rate profile for enolization of this ketone is given in Figure 2. The rate of enolization was determined in 50:50 CD_3OD/D_2O at 60 °C using suitable buffers. The reaction was followed by NMR through the disappearance of the signal for the methyl ketone. The plateau region corresponds to the titrimetrically determined[10] pK_a (6.2). The kinetically determined pK_a of **8a** is 6.00 in the reaction medium. The rate is 6.6×10^{-6} s^{-1}. Parallel results were observed for **8b** (pK_a = 6.47 in this medium), although the rate constants for exchange of **8b** were ~3 times faster than those for **8a**. The rates observed in the plateau region were shown to be independent of concentration, as would be expected for an intramolecular process.

The calculation of an EM for the process requires an adequate bimolecular control. Accordingly, we have studied the enolization of the corresponding methyl esters **11** using pivalate[10] as the base under the same conditions, pD = 7.5, 60 °C (eq 5). The bi-



11a R = $CH_2C_6H_5$
11b R = $CH(CH_3)_2$



(5)

molecular rate measured for **11a** was 5.2×10^{-6} M^{-1} s^{-1}, and the EM involved in eq 4 is thus 7.17 M. For the valine derivative **11b** the corresponding values are $k_1 = 2.14 \times 10^{-5}$ s^{-1}, $k_2 = 3.1 \times 10^{-6}$ M^{-1} s^{-1}, and the EM is therefore 17 M.

These are the first cases of igbc in which the more basic lone pair of the carboxylate is involved, and the EM's are about an order of magnitude larger than most values reported[1] for the anti lone pairs. Yet, generalizations must be made with caution. It is possible that the rigidity of these structures does not permit facile intramolecular reaction. For example, proton transfer to the carboxylate would lead to a somewhat nonplanar carboxylic acid.[11] The energetic cost of such distortions has been explored with appropriate computations and is modest (2-4 kcal/mol) in the case at hand.[12] It appears that stereoelectronic effects at carboxylate oxygen do contribute to the low EM's involving igbc with these functional groups, but the full extent has yet to be determined. The current skeleton also appears suitable for the study of intramolecular nucleophile processes; such studies are in progress, and we shall report on them in due course.

Acknowledgment. We are grateful to the National Institutes of Health for support of this research and to R. Duff and Dr. W. Gordon for advice. We thank Professor K. N. Houk and Dr. Y. Li for sharing the results of their computations with us prior to publication.

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Theoretical Assessments of the Basicity and Nucleophilicity of Carboxylate Syn and Anti Lone Pairs

Yi Li and K. N. Houk*

Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, California 90024-1569

Received December 12, 1988
Revised Manuscript Received March 6, 1989

Carboxyl groups at active sites of enzymes may be involved in general acid-base or nucleophilic catalysis.[1] Intramolecular reactions of carboxyl groups sometimes approach the efficiency of enzymes when the carboxyl groups are involved in intramolecular nucleophilic catalysis, but intramolecular general base catalysis usually occurs with only moderate rate acceleration as compared to the intermolecular cases.[2] Gandour pointed out that the syn lone pair of a carboxylate is $>10^4$ more basic than the anti.[3] He attributed the inefficient general base catalysis observed in most intramolecular models to poor geometric design. An anti lone pair is the base in these chemical models, whereas nature's designer uses syn lone pairs in enzymatic catalysis.[1,3] There have been several recent reports of chemical models to measure the relative hydrogen bonding and basicity of syn and anti lone pairs.[4,5] The surprisingly small differences observed prompt us to report our theoretical assessments of the stereoelectronic effects of syn and anti lone pairs of carboxyl oxygen.

The syn conformations of simple carboxylic acids and esters are 6-8 kcal/mol more stable than the anti.[6] There is less electron repulsion between lone pair electrons on the two oxygens in the syn conformation.[6] The importance of this effect in transition states or in hydrogen bonding was evaluated theoretically using ab initio molecular orbital calculations. Geometry optimizations were performed with the 3-21G or 6-31G* basis sets, and single-point energy calculations were carried out on these geometries with the 6-31G* basis set or 6-31+G* basis set for anionic systems.[7] Such calculations are known to reproduce energetics of hydrogen bonding.[8,9]

Two complexes of formate with a planar ammonia, to mimic imidazole in Zimmerman's model,[4c] are shown in Figure 1. The syn lone pair of carboxylate forms a slightly stronger hydrogen

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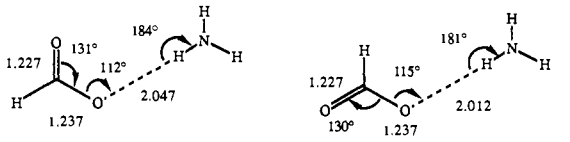
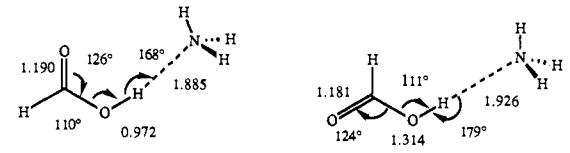
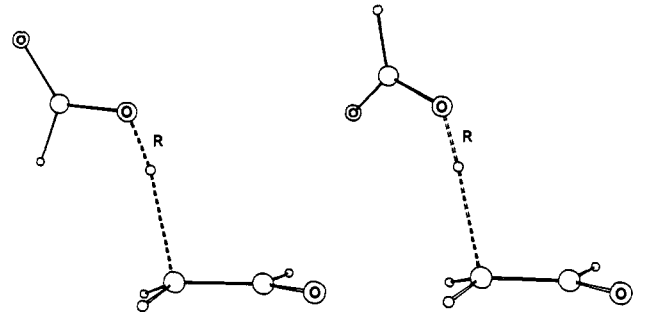


6-31G*//6-31G*	0.0	0.6 kcal/mol
6-31+G*//6-31G*	0.0	0.3 kcal/mol



6-31G*//6-31G*	0.0	6.0 kcal/mol

Figure 1. The 6-31G* optimized hydrogen bonding complexes of formate anion with planar ammonia and of formic acid with ammonia.



anti-deprotonation by formate syn-deprotonation by formate

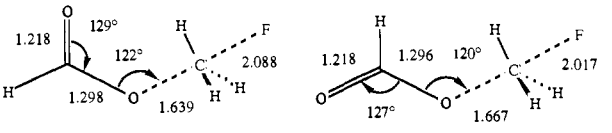
R	R(CH)		
1.0	1.8	0.0	+2.5 kcal/mol
1.1	1.6	0.0	+1.6
1.3	1.3	0.0	-0.3

Figure 2. Relative energies of deprotonation of acetaldehyde by formate anion (6-31+G*//3-21G).

bond than the anti. The syn acid hydrogen bonded to ammonia is about 6 kcal/mol more stable than the anti complex, a smaller difference than for the free acid. Thus, the syn conformational preference of carboxylic acids is diminished somewhat upon hydrogen bonding.

The deprotonation of acetaldehyde with formate anion was studied as a prototype for carboxylate basicity. The reaction of formate anion with acetaldehyde is very endothermic, so no transition structure could be found for this reaction. Instead, geometry optimizations were performed with fixed OH distances (Figure 2). For OH distances ranging from 1.3 to 1.0 Å (optimized CH distances of 1.3–1.8 Å), the syn deprotonation is preferred only slightly over the anti deprotonation at the early stage but becomes disfavored when deprotonation is more advanced. This surprising result occurs as a consequence of the electrostatic repulsion between the negatively charged enolate and the carboxylic acid. When the acid is syn, there is more repulsion between the distal oxygen lone pairs and the enolate than when the acid is anti. This effect is expected to disappear when the enolate is protonated either before or during α-deprotonation, or when the enolate is solvated. Calculations of structures in which the forming enolate oxygen is solvated by one water molecule give a 5 kcal/mol preference for syn deprotonation, similar to the preference in hydrogen bonding.

The relative nucleophilicities of syn and anti lone pairs are expected to be parallel to the corresponding basicities.[10] We have located transition structures for the S_N2 alkylation of formate anion with methyl fluoride. Each transition structure was fully characterized by harmonic vibrational frequency calculations. The



3-21G//3-21G	0	+0.4 kcal/mol
6-31+G*//3-21G	0	+1.6 kcal/mol

Figure 3. The 3-21G optimized geometries of the transition structures for the reaction of formation anion with methyl fluoride.

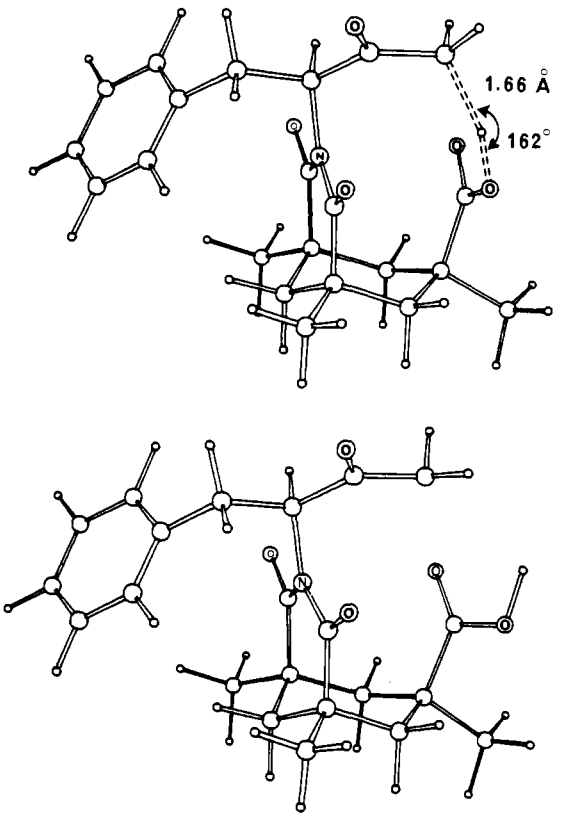


Figure 4.

optimized geometries of saddle points are shown in Figure 3, along with the calculated relative energies.

The gas-phase S_N2 reaction of formate anion with methyl fluoride is highly endothermic, and the OC bond is almost fully formed in these transition structures. Nevertheless, the transition structure leading to the syn ester is only 1.6 kcal/mol more stable than that leading to the anti ester. While there is no transition structure in which the methyl group attacks perpendicularly to the formate plane, a rigid rotation of the forming OC bond around the C–O⁻ bond from the most stable transition structure raises the energy by 0.8 kcal/mol for a 20° rotation and 8.7 kcal/mol for a 90° rotation. The stereoelectronic effects observed here are consistent with the results of our earlier calculations on the O alkylation of the enolate anion.[11]

The large stereoelectronic preference for syn carboxylic acids (6–8 kcal/mol) may be significantly altered in hydrogen bonding or in reaction transition states because of electrostatic interaction between the carboxylate oxygen and the reaction partner. For the cases studied here, the magnitude of syn stereoelectronic preference of the carboxylate group is around 1–2 kcal/mol, but the gas-phase deprotonation example shows that cases may be found where the anti lone pair is more basic kinetically than the syn!

Why was no intramolecular rate enhancement observed in the deprotonation in Rebek's model which uses a syn lone pair for deprotonation?[5] Our molecular mechanics calculations using a

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modified MM2 force field designed to model the transition structure[12] indicate that the O=C—O—H torsional angle is 17° and the O=C—C---H torsional angle is 118°, whereas these are 0° and 90° in the preferred deprotonation. These deviations from ideality (Figure 4) are predicted to raise the activation energy by 2-4 kcal/mol, reducing the rate by one to two orders of magnitude versus an unstrained model.

Acknowledgment. We are grateful to the National Institutes of Health for financial support, to the San Diego Supercomputer Center and the Office of Academic Computing of U.C.L.A. for computer time, and to Professors Julius Rebek, Jr., and Richard D. Gandour for helpful discussions.

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$[Li(Me_2NCH_2CH_2NMe_2)_2][Li_2(Me_2NCH_2CH_2NMe_2)_2(\mu\text{-}\eta^5,\eta^5\text{-}MeC_5H_4)][(\eta^5\text{-}MeC_5H_4)_6U_2(\mu\text{-}Me)]_2$: A Compound with Symmetrically Bridging MeC_5H_4 and Me Groups

Stephen D. Stults, Richard A. Andersen,* and Allan Zalkin

Chemistry Department and Materials and Chemical Sciences Division of Lawrence Berkeley Laboratory University of California, Berkeley, California 94720

Received October 24, 1988

Organometallic compounds of the alkali metals which contain symmetrical bridging cyclopentadienyl groups, i.e., those in which two metal centers are located at equal distance on either side of and on the pseudo C_5-axis of the cyclopentadienyl group, are rare; the only example is the linear zigzag polymeric structure of $[Na(Me_2NCH_2CH_2NMe_2)Cp]$.[1] Symmetrically bridging methyl groups, i.e., those in which the metal-carbon-metal angle is 180° and the carbon atom is an equal distance from the metals, are unknown, though four recent structures have revealed bridging methyl groups in which the angle at carbon is near-linear and the metal-carbon distances are slightly asymmetric[2a] or linear and highly asymmetric.[2b-d] In this communication we describe the synthesis and X-ray crystal structure of $[Li(Me_2NCH_2CH_2NMe_2)_2]\cdot[Li(Me_2NCH_2CH_2NMe_2)]_2[\mu\text{-}MeC_5H_4]\cdot[(MeC_5H_4)_3U]_2[\mu\text{-}Me]$, a compound that contains a MeC_5H_4 group sandwiched between two $Li(Me_2NCH_2CH_2NMe_2)$ fragments and a methyl group that is symmetrically bridging between two $(MeC_5H_4)_3U$ groups.

Jonas has shown that d-transition-metal metallocenes react with lithium alkyls to give compounds in which the alkyl group replaces the cyclopentadienyl group and that this elegant synthetic method leads to many unusual compounds.[3] In the f-transition-metal series, substitution (eq 1 and 2)[4] and addition (eq 3)[4b,c,5] reactions

$$Cp_3M + LiR \rightarrow Cp_2MR + LiCp \quad (1)$$

$$Cp_3UR' + LiR \rightarrow Cp_3UR + LiR' \quad (2)$$

$$Cp_3M + LiR \rightarrow LiCp_3MR \quad (3)$$

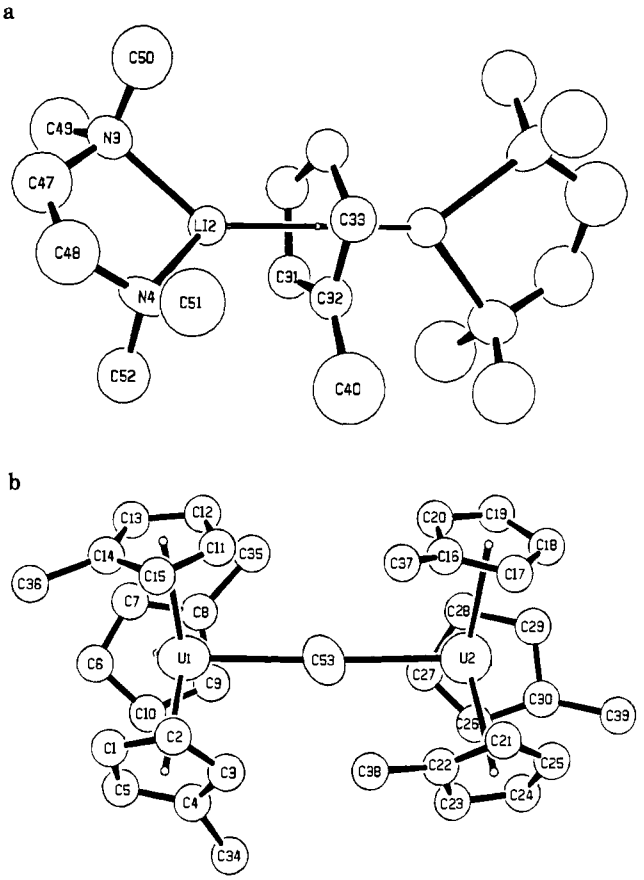

Figure 1. (a) ORTEP drawing of $[Li_2(Me_2NCH_2CH_2NMe_2)_2(\mu\text{-}\eta^5,\eta^5\text{-}MeC_5H_4)]$ fragment: Li-C(av) = 2.31 (3) Å, Li-N(av) = 2.09 (1) Å, N(3)-Li-N(4) = 86.7 (22)°, N-Li-ring centroid(av) = 136°. (b) ORTEP drawing of $[(\eta^5\text{-}MeC_5H_4)_6U_2(\mu\text{-}Me)]$ fragment: U-C(CP)(av) = 2.82 (4) Å, U-ring centroid(av) = 2.57 Å, U-C(53)(av) = 2.72 (1) Å, U-C(53)-U = 176.9 (11)°, ring centroid-U-C(53)(av) = 100°, ring centroid-U-ring centroid(av) = 117°.

have been observed. Addition of 1 molar equiv of methyllithium to $(MeC_5H_4)_3U(thf)$ in diethyl ether in the presence of 1 molar equiv of $Me_2NCH_2CH_2NMe_2$ at -30 °C gives a red precipitate which upon crystallization from diethyl ether gives red crystals which were shown to be $[Li(tmed)_2]\cdot[Li(tmed)]_2[\mu\text{-}MeC_5H_4]\cdot[(MeC_5H_4)_3U]_2[\mu\text{-}Me]$ by X-ray crystallography.[6] The ^1H NMR spectrum of the paramagnetic compound (trivalent uranium has

* Address all correspondence to this author at the Department of Chemistry, University of California, Berkeley, CA 94720.

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(6) (a) Methyllithium (1.7 mL of a 0.97 M diethyl ether solution, 1.7 mmol) was added to $(MeC_5H_4)_3U(thf)$ (0.91 g, 1.7 mmol) in diethyl ether (30 mL) and $Me_2NCH_2CH_2NMe_2$ (0.25 mL, 1.7 mmol) at -30 °C. The red precipitate was stirred at -30 °C for 30 min and then warmed to -10 °C, the volatile material was removed at -10 °C, and then the solid was exposed to a vacuum for 1 h at room temperature. The red solid was extracted with diethyl ether (100 mL) and filtered, and the filtrate was concentrated to ca. 80 mL and then cooled to -20 °C. The red crystals (0.20 g, 19%) were collected, mp 81-85 °C. Additional crops of crystals may be obtained on concentration and cooling the mother liquors [Anal. Calcd for $C_{104}H_{161}Li_3N_8U_4$: C, 50.0; H, 6.50; N, 4.49. Found: C, 49.4; H, 7.26; N, 6.49. ^1H NMR (C_7D_8, -70 °C) δ 14.4 (12 H), 6.17 (2 H), 3.21 (1.5 H), 2.63 (4 H), 2.35 (4 H), 2.10 (12 H), 1.50 (12 H), -8.08 (18 H), -18.7 (12 H), -284.7 (3 H)]. The resonances at δ +14.4 and -18.7 are tentatively assigned to the ring methine protons and the resonance at δ -8.08 to the ring methyl protons of the $(MeC_5H_4)U$ fragment. The resonance at -284.7 is due to the bridging methyl group. The ring methine and methyl group resonance on the $(MeC_5H_4)Li$ fragment are assigned to the resonances at δ 6.17 and 3.21, respectively. The other resonances are due to the $Me_2NCH_2CH_2NMe_2$ protons. The line width, $\nu_{1/2}$, of all the resonances is ca. 10-15 Hz, except that of the resonance at δ -284.7 which is 30 Hz. (b) *X-ray Crystallography* (see Supplementary Material).

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