4MeC5 ester was made as follows. 4-Methylpentanoic acid (1.74 g, 15 mmol), DCC (3.095 g, 15 mmol), and *p*-toluenesulfonic acid (150 mg) were dissolved in pyridine (3 mL) and benzene (50 mL). To the solution was added HNBA (2.75 g, 15 mmol), and the mixture was allowed to react for 4 days at room temperature.[42] The solvents were removed by evaporation, and the product was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$ solution, and water. The residue was dissolved in acetone and filtered. Removal of the acetone gave a noncrystalline product.

2-Carboxy-4-nitrophenyl esters (2) were prepared from the acid anhydrides and 5-nitro-2-hydroxybenzoic acid (5-nitrosalicylic acid, Lancaster Synthesis), using either of the first two procedures outlined above. The melting points were as follows: C2, 159-162 °C; C4, 97-99 °C; C6, 90-92 °C.

The structures of all of the esters were confirmed by their proton NMR spectra and by the UV-vis spectral change that they gave on hydrolysis in aqueous base.

Kinetic Methods. Ester cleavage was followed spectrophotometrically using the same general approach and techniques as in earlier studies.[7,11,26b] The cleavages of **1** and **2** were monitored by the increases at 407 and 370 nm due to release of the dianions of the corresponding carboxynitrophenols. Initial substrate concentrations were 0.01-0.1 mM, depending on the solubility of the ester. Stock ester solutions were made up in methanol so that final solutions contained 0.1% (v/v) MeOH. The reaction medium was a 0.2 or 0.4 M phosphate buffer of pH 11.7, containing [CD] = 0-20 mM (see Tables S1-S3, supplementary material, for the actual concentrations). A high buffer capacity was used to avoid changes in pH caused by the ionization of the CD hydroxyl groups.[44] The observation cell was kept at 25 °C. Absorbance data points (100) were collected for 10 half-lives, and those covering 80-90% reaction gave good first-order behavior.

Fitting of the kinetic expressions (eqs 2, 4, and 6) was carried out with programs based on standard nonlinear least-square methods.[18] The value of k_u was fixed at the observed value, and the remaining constants were the parameters to be determined. In any case where there was little to choose between the qualities of the fits obtained with two different equations, the simpler of the two equations was chosen.[17]

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Registry No. 1 (C2), 1210-97-5; **1** (C3), 86868-06-6; **1** (C4), 56003-42-0; **1** (C5), 67880-44-8; **1** (C6), 65293-27-8; **1** (C7), 43049-38-3; **1** (C8), 113894-26-1; **1** (2E+C6), 137363-36-1; **1** (4MeC5), 137363-37-2; **2** (C2), 17336-14-0; **2** (C4), 93597-98-9; **2** (C6), 93598-00-6; **2** (C8), 115162-19-1; HNBA, 616-82-0; α-cyclodextrin, 10016-20-3; β-cyclodextrin, 7585-39-9; acetic anhydride, 108-24-7; propanoic anhydride, 123-62-6; butanoic anhydride, 106-31-0; pentanoic anhydride, 2082-59-9; hexanoic anhydride, 2051-49-2; heptanoic anhydride, 626-27-7; octanoyl chloride, 111-64-8; 2-ethylhexanoyl chloride, 760-67-8; 4-methylpentanoic acid, 646-07-1; 5-nitro-2-hydroxybenzoic acid, 96-97-9.

Supplementary Material Available: Tables of observed rate constants for the cleavage of 4-carboxyl-2-nitrophenyl and 2-carboxy-4-nitrophenyl alkanoates (**1** and **2**) as a function of the concentration of α- or β-cyclodextrins (Tables S1-S3) (9 pages). Ordering information is given on any current masthead page.

(44) Gelb, R. I.; Schwartz, L. M.; Bradshaw, J. J.; Laufer, D. A. *Bioorg. Chem.* **1980**, *9*, 299. Gelb, R. I.; Schwartz, L. M.; Laufer, D. A. *Bioorg. Chem.* **1982**, *11*, 274.

Hydrogen Bonds to Carboxylate Groups. Syn/Anti Distributions and Steric Effects

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Abstract: The syn/anti distribution for hydrogen bonds to small-molecule carboxylate groups has been analyzed. The data set used consisted of 15 acetate structures, 48 primary carboxylates, 172 secondary carboxylates, and 20 ternary carboxylates retrieved from the Cambridge Structural Database. For 876 interactions there is overall a slight preference for syn geometry with a clear correlation between the syn/anti ratio and steric hindrance in the anti positions between the donor and substituents on the acceptor molecule. In the absence of steric interference, syn H-bonds are not significantly preferred according to statistics. It is shown that the stereoelectronic preferences for catalysis by carboxylate groups do not translate into stereoelectronic preferences for hydrogen-bond formation.

Introduction

The question of stereoelectronic preferences for catalysis by carboxylate groups has received detailed attention from mechanistic, structural, and functional perspectives.[1-4] Gandour used the equilibria for deprotonation of the syn and anti conformation of simple carboxylic acids to show that syn lone pairs are $>10^4$ times more basic than anti lone pairs ($K_a' > 10^4$ larger than K_a).[1] Hence, in biologically active systems, a syn lone pair of a carboxylate group is catalytically more active than the anti lone pair.[5]

Our research interests have focused on the forces that affect molecular association and preorganization of hydrogen-bonded aggregates, whether or not such aggregates are reactive or show catalytic behavior.[6] Carboxylate groups, like other hydrogen-bonding groups, can play just as important a role as a site for directing molecular organization of catalytic components as they do in actually promoting catalysis. Here we seek to decouple the organizational properties of carboxylate groups from their reactivity properties and, in the process, to address the question of whether stereoelectronic preferences are similar for the two very different roles that carboxylate groups assume. Using data from

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(1) Gandour, R. D. *Biorg. Chem.* **1981**, *10*, 169-176.
(2) (a) Gandour, R. D.; Nabeel, A. R.; Nabulsi, R.; Fronczek; F. R. *J. Am. Chem. Soc.* **1990**, *112*, 7816-7817. (b) Tadayoni, B. M.; Parris, K.; Rebek, J. *J. Am. Chem. Soc.* **1989**, *111*, 4503-4505. (c) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1989**, *111*, 4505-4507. (d) Cybulski, S. M.; Scheiner, S. *J. Am. Chem. Soc.* **1989**, *111*, 23-31.
(3) (a) Zimmerman, S. C.; Cramer, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 5906-5908. (b) Huff, J. B.; Askew, B.; Duff, R. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5908-5909.
(4) Carell, C. J.; Carell, H. L.; Erlebacher, J.; Glusker, J. *J. Am. Chem. Soc.* **1988**, *110*, 8651-8656.
(5) For a general description, see: Fersht, A. *Enzyme Structure and Mechanism*, 2nd ed.; W. H. Freeman: New York, 1985; Chapter 15.
(6) Etter, M. C. *J. Phys. Chem.* **1991**, *95*, 4601-4610.

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Table I. Syn/Anti Distributions and Hydrogen Bond Geometries for Different Categories of Carboxylate Groups

	N^a	%	φ(C=O···H) (deg)	O···H (Å)	O···D (Å)[b]	α(O···H–D) (deg)
			syn			
acetates (AC)	28	53.8	118.4 (2.7)[c]	1.870 (41)	2.845 (36)	166.5 (2.2)
primary (PC)	95	57.2	119.4 (1.3)	1.816 (14)	2.787 (12)	165.1 (1.1)
secondary (SC)	359	60.7	118.9 (0.7)	1.818 (8)	2.774 (6)	162.5 (0.7)
ternary (TC)	45	67.2	119.8 (1.8)	1.809 (19)	2.764 (12)	165.7 (1.7)
			anti			
acetates (AC)	24	46.2	121.8 (1.3)	1.863 (27)	2.826 (20)	166.0 (3.2)
primary (PC)	71	42.8	126.4 (1.3)	1.822 (16)	2.777 (11)	164.9 (1.5)
secondary (SC)	232	39.3	132.0 (0.7)	1.872 (9)	2.817 (7)	160.0 (0.8)
ternary (TC)	22	32.8	135.1 (2.3)	1.876 (23)	2.830 (18)	161.3 (2.4)

[a] Number of hydrogen bonds used in the analysis. [b] D = O or N. [c] Standard deviations for mean values given in parentheses.

the Cambridge Crystallographic Database[7] on small-molecule carboxylates, we found that the inherent syn preferences observed for catalysis were not observed for intermolecular hydrogen bonds to carboxylate groups. In addition, we recognized that steric hindrance from C^α substituents greatly reduces the number of occurrences of anti hydrogen bonds. A detailed statistical analysis of the crystallographic data provides a convincing case that hydrogen bonds to carboxylate groups have no significant preference for the syn or anti lone pairs in the absence of steric effects from neighboring groups.

Terminology

The symbols r(O···D) and r(O···H) are used to denote the hydrogen bond distance between $O_{carboxylate}$ and a donor D or a hydrogen, respectively. α(O···H–D) is used for the hydrogen bond angle O···H—D, φ(C=O···H) is used for the C=O···H angle, and ω(O–C–O···H) is used for the torsion angle O—C—O···H. Regular A–B–C–D torsion angles are denoted θ(A–B–C–D).

Methods

Small-molecule carboxylate structures without metal ions were retrieved from the Cambridge Structural Database[7] (CSD, June 1990 release) by means of the CSD program, QUEST89, and divided into four categories: AC = acetates (C^α-substituents: H, H, H), PC = primary carboxylates (C, H, H), SC = secondary carboxylates (C, C or N, H), and TC = ternary carboxylates (C, C, C, or N). A maximum crystallographic R factor of 0.08 was used for PC and SC, while 0.10 was used for AC and TC to increase the number of data points in these classes. The total data set consisted of 255 structures: 15 AC, 48 PC, 172 SC, and 20 TC.[8] In the succeeding geometry calculations with the GSTAT89 program, only contacts with α(O···H–D) > 90° (D = O or N) were retained. A 2.95-Å upper limit for r(O···H) was used in the preliminary runs, giving the distance distribution shown in Figure 1. In the remainder of the paper, our discussion is limited to 876 O···H–D interactions that occur below 2.35 Å. A few O···H–C contacts of >2.35 Å undoubtedly have hydrogen bond character,[9] but they were found to be less directional with respect to the oxygen lone pairs than regular hydrogen bonds and were not included in the statistical material. According to recommendations by Taylor and Kennard, normalized H-atom positions were used.[10] Torsion angles for D-amino acid residues were converted to correspond to those of the equivalent L enantiomers.

Results and Discussion

The experimental results may be summarized by stating that there are correlations between steric hindrance in the anti position, out-of-plane location of bonded H-atoms, orientation of H-atoms relative to the carbonyl lone pair directions, and the observed

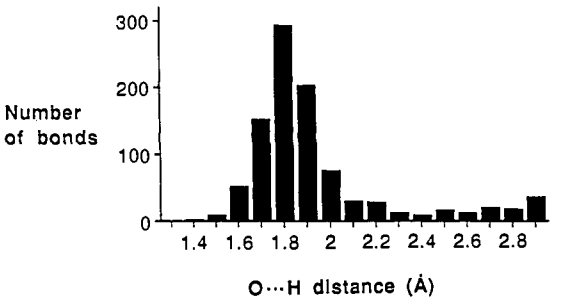

Figure 1. Distance distribution for 974 carboxylate O···H–D (D = O or N) contacts shorter than 2.95 Å.

frequency of hydrogen bonds. We find no indication, either statistically or geometrically, that syn hydrogen bonds are inherently more favorable than anti.

Although these results seem paradoxical given the well-established syn preference for catalysis, the dilemma is simply that of the difference between hydrogen bond ability and basicity. As is well-known, these phenomena are related but are *not* the same, and there is no fundamental reason why the stereoelectronic preferences for one process should be the same as for the other. Indeed, ab initio calculations for formate–water and formate–planar ammonia complexes indicated the energy difference between the two orientations to be very small.[11] Our results show that sets of crystallographic data are useful for analyzing the hydrogen-bond-promoted organizational potential and stereoelectronic preferences of carboxylate groups, independent of their catalytic potential. Similar types of analyses could readily be done for other types of functional groups, and the results should be useful for predicting self-association potentials and patterns of any molecules, large or small, containing the functional group in question. Several earlier works show how useful the crystallographic database is for studying molecular self-association properties.[4,12,13]

Principal statistical and geometrical results are given in Table I. Syn φ(C=O···H) values are all near the 120° lone pair angle, in agreement with previous surveys of carboxylate groups in small molecules[12] and proteins.[14,15] For anti interactions, however, a significant and steady increase occurs in φ(C=O···H) from 121.8° in AC to 135.1° in TC as the carboxylate R group is enlarged (Table I). H-atoms in the plane of the carboxylate group are characterized by having ω(O–C–O···H) close to 0° (syn orientation) or 180° (anti orientation). For all categories, syn H-atoms cluster near the carboxylate plane (Figure 2). Such a preference

(7) Cambridge Structural Database, University Chemical Laboratory, Lensfield Road, Cambridge, England, 1988.
(8) Originally, formates were included as a fifth category, but the results were not statistically dependable (4 structures).
(9) Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063–5070.
(10) Corrects X–H bond lengths from X-ray data to correspond to neutron diffraction distances (Taylor, R.; Kennard, O *Acta Crystallogr.* **1983**, *B39*, 133–138). X–H distances used: N–H = 1.009 Å, O–H = 0.983 Å (Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–S19).
(11) Results from ab initio calculations at the MP2 level: formate–planar ammonia complex, syn 1.2 kJ mol^{-1} lower than anti;[2c] formate–water complex, anti 1.2 kJ mol^{-1} lower than syn (global minimum is cyclic structure with two H-bonds).[2d]
(12) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761–5766.
(13) (a) Vedani, A.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 7653–7658. (b) Murray-Rust, P.; Glusker, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1018–1025.
(14) Ippolito, J. A.; Alexander, R. S.; Christianson, D. W. *J. Mol. Biol.* **1990**, *215*, 457–471.
(15) Thanki, N.; Thornton, J. M.; Goodfellow, J. M. *J. Mol. Biol.* **1988**, *202*, 637–657.

Table II. Geometries for $NH_3^+\cdots{}^-OOC$ Hydrogen Bonds

	N^a	φ(C=O···H) (deg)	O···H (Å)	O···N (Å)	α(O···H–N) (deg)
			syn		
acetates (AC)	2	108.9 (5.6)[b]	1.828 (130)	2.833 (150)	164.5 (6.7)
primary (PC)	43	121.1 (1.9)	1.820 (17)	2.816 (12)	164.6 (1.8)
secondary (SC)	164	118.0 (1.1)	1.832 (9)	2.820 (6)	162.1 (0.9)
ternary (TC)	26	117.3 (2.2)	1.786 (18)	2.793 (12)	167.7 (2.1)
			anti		
acetates (AC)	5	120.7 (2.9)	1.812 (43)	2.830 (47)	169.4 (3.0)
primary (PC)	23	130.9 (2.0)	1.797 (24)	2.774 (10)	161.9 (3.2)
secondary (SC)	112	131.3 (0.9)	1.875 (12)	2.839 (7)	158.2 (1.3)
ternary (TC)	11	135.0 (3.8)	1.864 (24)	2.846 (16)	159.9 (3.2)

[a] Number of hydrogen bonds used in the analysis. [b] Standard deviations for mean values given in parentheses.

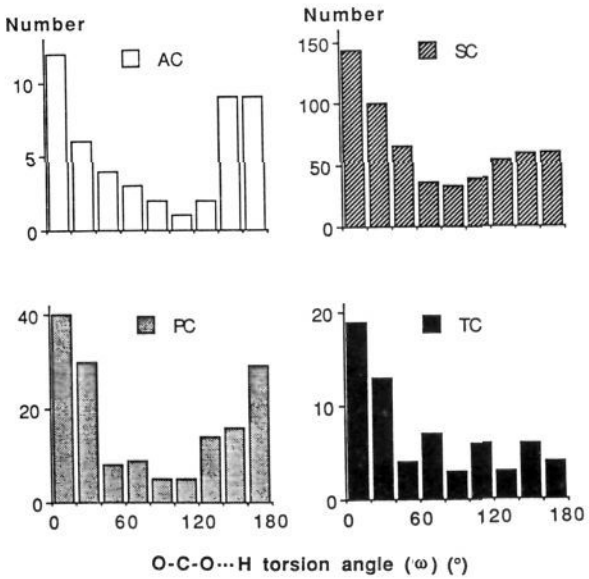

Figure 2. Distribution for ω (values averaged from $\omega > 0°$ and $\omega < 0°$). H-atoms in the carboxylate plane have $\omega = 0°$ (syn geometry) or $\omega = 180°$ (anti geometry).

is also observed for anti H-atoms in AC and PC but is less obvious for SC. The in-plane preference for anti H-atoms is completely lost for TC, as indicated by the lack of an ω(O–C–O···H) peak at 180° in Figure 2. The resulting difference between anti H-atom positions in AC and TC is easily observed in Figure 3. These trends for both φ(C=O···H) and ω(O–C–O···H) are consistent with progressively larger substituent groups blocking access to the optimal anti positions. As a result, the syn/anti distribution shifts from 53.8%/46.2% in AC to 67.2%/32.8% in TC (Table I). The intermediate syn/anti ratio for PC (57.2%/42.8%) agrees closely with the observed ratio for Glu residues in protein crystal structures, 57%/43%.[14,16] If the H-atom is substituted with a much larger metal ion, steric conflicts in the anti position are accentuated. A 77.3%/22.7% syn/anti distribution was reported for metal ion–carboxylate interactions.[4,17]

Steric hindrance in acetates is minimal, readily recognizable, and independent of rotation around the C′–C$^\alpha$ bond. For the other three categories, however, Table I describes average values for a wide range of different molecules and conformations.

Substituents on C$^\beta$ cause steric hindrance in primary carboxylates. The distribution for θ(O′–C′–C$^\alpha$–C$^\beta$) (confined to [−90°, 90°] by symmetry) for molecules with sp^3-hybridized C$^\beta$-atoms is shown in Figure 4a. When the torsion angle is close to 90°, both anti positions are affected by steric hindrance. We therefore chose to look at only 25 carboxylates which had θ(O′–C′–C$^\alpha$–C$^\beta$) in [−30°, 30°]. The results are given in Figure 4b. It is obvious that anti H-bonds to O″ are not affected; the φ(C=O···H) value and relative frequency compared to the two syn positions resemble closely the data observed for acetates. In contrast, the number of anti H-bonds to O′ is smaller, while φ(C=O···H) is up to 133.2°, clearly indicating that the most favorable anti position on O′ is no longer easily accessible.

Secondary carboxylates were defined as having one C-atom, one H-atom, and one C- or N-atom bonded to C$^\alpha$. Of 194 carboxylates, 22 have C as the third atom. These structures constitute a fairly nonuniform mixture, with a multitude of substituents, C-atom hybridizations, etc. The group was therefore not well-suited for further statistical investigations. N-substituents occur for 172 carboxylates: 94 NH_3^+, 37 NHCO (peptides), and 41 others. The two uniform groups, amino acids (with derivatives) and peptides, were investigated in more detail.

Data for 82 amino acid carboxylates with sp^3-hybridized C$^\beta$-atoms are given in Figures 4c,d. The distribution for θ(O′–C′–C$^\alpha$–N) peaks at about −20°. This derivation from planarity somewhat reduces the steric effect of the A1 substituent in Figure 4d. Thus, there are a relatively large number of H-bonds to O″ anti lone pairs, while the O′ anti lone pairs accept many fewer H-atoms with a larger value for φ(C=O···H). It is important to note that we found no intramolecular $NH_3^+\cdots{}^-OOC$ H-bonds, in agreement with a survey of amino acid structures determined by neutron diffraction by Koetzle and Lehman.[18] They also noted that the ammonium groups shield O′ from proton donors belonging to neighboring molecules, making O′ accept fewer H-atoms than O″.

The distribution of H-bonds to the C-terminal carboxylate group of 36 peptides with sp^3-hybridized C$^\beta$-atoms are described in Figures 4e,f. As for amino acids, θ(O′–C′–C$^\alpha$–N) is shifted somewhat from 0°, facilitating access to O″ anti lone pairs. The relative frequency of anti H-bonds to this atom is also comparable to what was observed for amino acids. The situation for O′ is different. If the carboxylate group had been coplanar with the peptide unit, there would have been considerable steric conflict in the anti position of O′. However, the two groups are twisted out of the plane, giving θ(C′–C$^\alpha$–N–C) in the [−160°,−65°] interval with a peak around −80°. Thus, the steric hindrance is modest, and there is a large number of anti H-bonds to O′. Interestingly, this means that peptide carboxylates accept almost the same number of H-atoms on each lone pair.

Of the 22 ternary carboxylate groups studied, 19 have N-atoms bonded to C$^\alpha$, of which 17 are NH_3^+ substituents. Data for nine molecules with sp^3-hybridized C$^\beta$-atoms, but without cyclopropyl or cyclobutyl groups, are given in Figures 4g,h. The number of samples is small, but large φ values for both anti positions are evident.

We also note that in Figure 4d φ(C=O···H) values are larger for syn H-bonds to O′ than to O″, while the opposite occurs in

(16) The ratio for Asp was 51%/49%, but the authors note[14] that the side chain of this residue has less conformational mobility and propose that the inherent preference for *syn*-carboxylate H-bonds is best represented by the statistics for Glu residues. Asp residues have been observed to more often take part in "local" H-bonds with main-chain NH groups (Baker, E. N.; Hubbard, R. E. *Prog. Biophys. Mol. Biol.* **1984**, *44*, 97–179), presumably promoting anti geometry.

(17) The syn percentage includes a 14.4% fraction classified as "direct", corresponding to an almost or fully symmetric position between the two carboxylate O-atoms.

(18) Koetzle, T. H.; Lehmann, M. S. In *The Hydrogen Bond—Recent Developments in Theory and Experiments*; Schuster, P., Ed.; North-Holland: Amsterdam, 1976; Chapter 9.

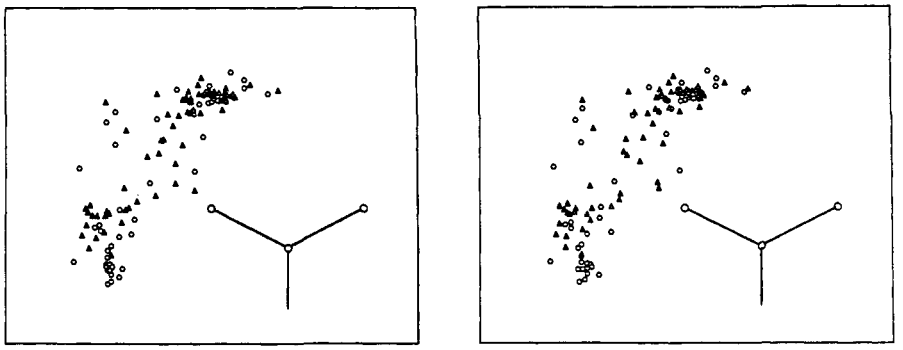

Figure 3. Stereo diagram of the distribution of H-atoms around one oxygen of AC (O) and TC (+). While all syn H-atoms are close to the carboxylate plane, TC anti H-atoms are more dispersed, with a substantially larger C=O···H angle than for AC.

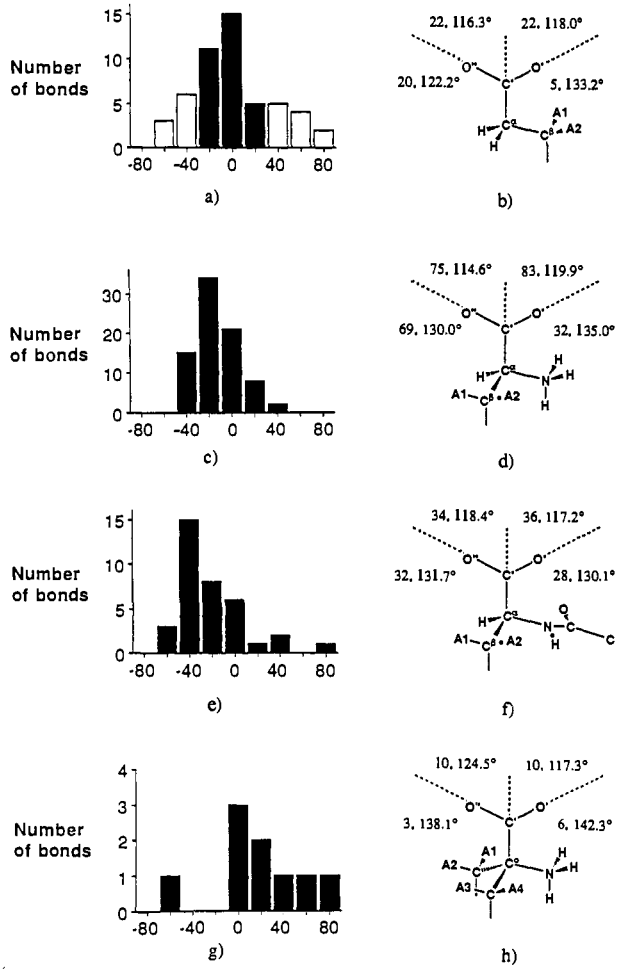

Figure 4. Graphs a, c, e, and g give torsion angle distributions for the fragments shown to their right. a refers to O′–C′–C$^{\alpha}$–C$^{\beta}$, and c, e, and g refer to O′–C′–C$^{\alpha}$–N (O′ label assigned to give torsion angles in the [−90°,90°] interval). Fragment drawings give data for (b) 25 primary carboxylates, (d) 80 amino acid carboxylates, (f) 36 peptide carboxylates, and (h) nine ternary carboxylates. The paired numbers on the figures indicate the number of hydrogen bonds to each lone pair and the associated mean values for their C=O···H angles. Values in b were obtained by using structures only from the three black columns in the a distribution. A complete list of distances and angles is available as supplementary material. The distribution of (H, C, N, O) for the An atoms are as follows: (b) A1 (13, 7, 4, 1), A2 (11, 4, 8, 2); (d) A1 (58, 21, 0, 0), A2 (57, 16, 0, 7): (f) A1 (27, 9, 0, 0), A2 (24, 11, 0, 1); (h) A1 (7, 2, 0, 0), A2 (5, 4, 0, 0), A3 (5, 4, 0, 0), A4 (9, 0, 0, 0).

Figure 4h. These features have no obvious explanation. It has been suggested that in amino acids (Figure 4d) O′ has more sp^2 character than O″ because it accepts fewer H-atoms, making the C′=O′ bond shorter than C′=O″.[18] It is uncertain how such subtle differences might affect the geometry of the accepted H-bonds.

Hydrogen bond lengths were compared for all groups of carboxylates. From Table I it is seen that syn H-bonds get shorter with increased substitution, while an opposite trend (except AC) is observed for anti H-bonds. As each category encompasses a wide range of donor molecules, we picked the most abundant, the CNH_3^+ group, to study bond-length variations in more detail. The results are given in Table II. Data for AC are inconclusive due to the small number of interactions, but trends for the three other categories can be studied. Both syn and anti H-bonds are longer to SC than to PC, though the difference is much larger for anti interactions. It is noteworthy that the O···N distance for anti H-bonds to PC is only 2.774 Å, the shortest in Table II and significantly shorter than the corresponding value for syn H-bonds, 2.816 Å. Syn H-bonds to TC are more linear than to SC, which could explain why they are also shorter. An inductive effect from the added C substituent might be an additional factor involved. We have already shown how steric crowding in TC led to less favorable anti H-atom positions as reflected by ω(O–C–O···H) and φ(C=O···H). It is then not surprising that the O···N distance for anti H-bonds to TC is the longest in Table II.

Studies of intramolecular H-bonds between imidazole groups (Im) and carboxylates have shown that the pK_a value of Im was raised more by a syn Im$^+$–H···$^-$OOC H-bond than by an anti H-bond,[3] interpreted as an indication of a stronger syn hydrogen bond due to the greater *basicity* of the syn lone pair. A geometrical analysis of the model molecules showed that anti H-bonds were present in six- or seven-membered rings where α(N–H···O) < 140°, whereas syn H-bonds were more linear and, hence, more favorable. Thus, the pK_a value of the Im group may actually depend only to a minor extent on whether it is hydrogen bonded to a syn or anti carboxylate lone pair, since the two sites have nearly equal abilities to accept hydrogen bonds.

The results imply that if the transition state of a general acid–base-catalyzed enzymatic reaction[1] involves primarily formation of a hydrogen bond to a catalytic carboxylate group, there is no obvious advantage to a syn approach of the donor relative to anti. On the other hand, if a proton is fully transferred (or nearly so) in the transition state, giving a neutral carboxyl group, the syn approach would be much preferred as the resulting syn orientation of the carboxyl H-atom is energetically much more favorable than anti.[1,19] This kind of analysis provides a new perspective on the roles of carboxylates in catalytic systems: one role is that of organizing the components, in which case stereoelectronic preferences are not operative, and the other is the catalytic function where the syn approach is clearly preferred.

Conclusion

A statistical analysis of hydrogen bonds to carboxylate groups is presented. H-atoms bonded to syn lone pairs display a strong tendency to be close to the carboxylate plane with φ(C=O···H) close to 120°. Substituents on C$^{\alpha}$ may preclude access to the equivalent (and optimal) anti positions, giving φ(C=O···H) > 120° and fewer H-atoms in the carboxylate plane. These geometrical

(19) ΔE > 24 kJ mol^{-1} calculated for acetic acid with ab initio methods (Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935–5943).

changes are accompanied by a general reduction in the relative number of observed anti interactions. Thus, the slight overall dominance of syn geometry arises from steric repulsion in the anti position. In the absence of steric hindrance, syn H-bonds are not significantly preferred.

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Supplementary Material Available: Listings of references to all crystal structures retrieved from the CSD, graphs showing the α(O···H–D) distribution for the 876 H-bonds used in the survey, φ distributions for all carboxylate categories, and listings of H-bond geometries for interactions shown in Figure 4 (16 pages). Ordering information is given on any current masthead page.

Kinetics of Deprotonation of Arylnitromethanes by Benzoate Ions in Acetonitrile Solution. Effect of Equilibrium and Nonequilibrium Transition-State Solvation on Intrinsic Rate Constants of Proton Transfers

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Abstract: Second-order rate constants for benzoate ion promoted deprotonation reactions of (3-nitrophenyl)nitromethane, (4-nitrophenyl)nitromethane, and (3,5-dinitrophenyl)nitromethane have been determined in acetonitrile solution at 25 °C. These data were obtained at low benzoate buffer concentrations (<0.01 M), utilizing tetraethylammonium benzoate salts, and benzoate ion concentrations corrected for homoconjugation with data previously reported by Kolthoff and Chantooni. Acidity constants in acetonitrile have also been determined: (3-nitrophenyl)nitromethane, pK_a = 21.7; (4-nitromethyl)nitromethane, pK_a = 20.6; and (3,5-dinitrophenyl)nitromethane, pK_a = 19.8. A Brønsted β_B value of 0.56 and an α_{CH} value of 0.79 have been calculated for the benzoate, 3-bromobenzoate, and 4-nitrobenzoate ion promoted reactions of (3,5-dinitrophenyl)nitromethane and for the benzoate ion promoted reactions of (3-nitrophenyl)nitromethane and (3,5-dinitrophenyl)nitromethane, respectively; (4-nitrophenyl)nitromethane deviates negatively from the Brønsted plot due to the resonance effect of the 4-nitro group. The logarithms of the *intrinsic* rate constants for benzoate promoted deprotonations of (3-nitrophenyl)nitromethane, (4-nitrophenyl)nitromethane, and (3,5-dinitrophenyl)nitromethane are 4.81, 4.58, and 5.27, respectively, and these values are 1.43, 1.70, and 1.30 log units, respectively, higher in acetonitrile than in dimethyl sulfoxide. Transfer activity coefficients from dimethyl sulfoxide (D) to acetonitrile (A) solution, log ${}^{D}\gamma^{A}$, for (3-nitrophenyl)nitromethyl anion (0.28), (4-nitrophenyl)nitromethyl anion (0.56), (3-nitrophenyl)nitromethane (0.18), and (4-nitrophenyl)nitromethane (0.16) have been calculated, and log ${}^{D}\gamma^{A}$ for benzoic acid (~1.9) and the benzoate ion (~0.25) have been estimated. The solvent effects on the intrinsic rate constants are analyzed within the framework of the Principle of Nonperfect Synchronization (PNS) in terms of contributions by late solvation of the arylnitromethyl anion, late solvation of the benzoic acid (produced as a product of the reaction), early desolvation of the benzoate ion and the arylnitromethane, and by a classical solvent effect. The results are also compared with predictions by a theoretical model recently proposed by Kurz. For the comparison of intrinsic rate constants in water and dimethyl sulfoxide there is good agreement between the Kurz model and the experimental results as well as the PNS analysis, but there is a discrepancy between the results and the predictions of the Kurz model for the comparison of intrinsic rate constants in dimethyl sulfoxide and acetonitrile solutions.

Studies of the effects of solvent on proton-transfer reactions of carbon acids have helped clarify the factors that contribute to the relatively high energy barriers in these reactions[2] compared to proton transfers of oxygen and nitrogen acids.[3] One important factor appears to be nonperfect synchronization,[4] or imbalance,[5] in the transition state with respect to the extent to which proton transfer, the delocalization of negative charge, and solvent reorganization have progressed. These imbalances can be described by structure–reactivity parameters, such as Brønsted β and α values, and differences in these parameters, which can provide a measure of the extent to which the various processes have developed in the transition state.

When discussing solvent effects on proton transfers, it is particularly useful to focus on the *intrinsic* rate constant, k_0 (rate constant for the reaction when $\Delta G^\circ = 0$), so as to clearly separate the kinetic from thermodynamic effects.[4] There is growing experimental evidence that the lag in the solvation of developing ions behind charge transfer (or desolvation of disappearing ions being ahead of charge transfer) increases the barrier of the reaction and hence lowers k_0. This increase in the barrier can be understood as the result of nonequilibrium solvation of the transition state caused by the asynchrony or imbalance between charge transfer and the reorganization of the solvation of that charge.[6]

The extent to which k_0 is decreased by nonequilibrium transition-state solvation depends on the solvent.[4,7] In order to further

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(2) (a) Caldin, E. F. *J. Chem. Soc.* **1959**, 3345. (b) Cox, B. G.; Gibson, A. *Faraday Symp. Chem. Soc.* **1975**, *10*, 107. (c) Ritchie, C. D.; Uschold, R. E. *J. Am. Chem. Soc.* **1968**, *90*, 3415. (d) Bernasconi, C. F. *Pure Appl. Chem.* **1982**, *54*, 2335.

(3) (a) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1. (b) Crooks, J. E. *Compr. Chem. Kinet.* **1977**, *8*, 197.

(4) (a) Bernasconi, C. F. *Tetrahedron* **1985**, *41*, 3219. (b) Bernasconi, C. F. *Acc. Chem. Res.* **1987**, *20*, 301.

(5) (a) Hupe, D. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451. (b) Jencks, D. A.; Jencks, W. P. *Ibid.* **1977**, *99*, 7948. (c) Jencks, W. P. *Chem. Rev.* **1985**, *85*, 511.

(6) (a) Kurz, J. L. *J. Am. Chem. Soc.* **1989**, *111*, 8631. (b) Kurz, J. L.; Kurz, L. C. *Isr. J. Chem.* **1985**, *26*, 339.

0002-7863/92/1514-631$03.00/0