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STEREOELECTRONIC EFFECTS AT CARBOXYL OXYGEN

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The recent attempts to evaluate the stereoelectronic effects at carboxyl oxygen using Kemp's triacid derivatives are reviewed. Contexts include metal-ion chelation, acidity measurements, intramolecular general base catalysis and nucleophilic substitution. These give a range of 0–8 kcal/mol for the effects, and leave the issue open for more incisive experiments.

One would think that a practitioner with 20 years' experience would be immune to wildly optimistic projects, but only a few years ago we were struck by the unusual structure of Kemp's triacid[1] and the opportunities it provided for studies in molecular recognition. The specific issue was stereoelectronic effects at the carboxyl oxygen. The remarkable characteristics of the molecule, which features a U-shaped relationship between any two carboxyl functions, permits structures to be built in which the region of space near the *syn* lone pairs of a carboxyl can be managed. When we set out to evaluate these effects, we were sanguine; clean incisive experiments would be done, and quantitative values could be obtained for such effects. However, as we shall see, such work is fraught with ambiguities, uncertainties and seductive comparisons.

The focus of attention is shown in Scheme 1 and was described initially and most dramatically by Gandour.[2] Given the greater stability of the (Z)-acid vs the (E)-acid (measured in the gas phase)[3] and as supported by recent calculations,[4,5] what factors on the kinetics of reactions, that is, β values in general base catalysis, can be expected in Z vs E lone pairs? What expression might this have in binding? As Gandour[2] pointed out, enzyme active sites almost invariably[6] have the Z lone pairs directed at the active site or substrate.

Our first attempts involved pK_a measurements of the diacids derived from the condensation of two equivalents of Kemp's triacid **1** with appropriate rigid diamine spacers (Scheme 2). The spectroscopic characteristics of compound **2** (including x-ray evidence) showed an ideal intramolecular hydrogen bonded system characteristic of carboxylic acid dimers in the gas phase.

The pK_a values were extraordinary,[7] the first being normal and the second being *ca* 6 p$K_a$units above it; this suggested that the 6 pK_a units was the price of having two Z lone pairs directed at one another. Would E lone pairs also show such a difference? It is unlikely that anyone will construct a molecule that forces two E lone pairs into such an arrangement.[8] More accessible is the face-to-face arrangement presented by two of the carboxyls in Kemp's triacid. Here the difference in pK_a values is *ca* 3 units[1] and the distance between oxygen involved is comparable to, but not exactly the same as, that present in **2**. The effect, whatever it is due to, also appears in the naphthalene version **3**. The difference in pK_a units there was still considerably higher than in the corresponding model, the ethanoanthracene derivative **4** of Golden and Stock.[9] Perhaps the differences are in solvation; the naphthalene diacid binds alcohols and water within its cavity,[10] presumably through cooperative sets of hydrogen bonds as shown. Breaking up this network must be different for the two types of acids. Indeed, much of the difference between **2** and Kemp's triacid might be due to the ideal hydrogen bond that must exist in the monoanion. If this was worth say, 3–4 kcal (1 kcal = 4·184 kJ) as corresponding situations in enzymes are,[11] then the difference between Kemp's triacid and **1** is entirely accounted for without recourse to arguments concerning stereoelectronic effects in carboxyl oxygen.

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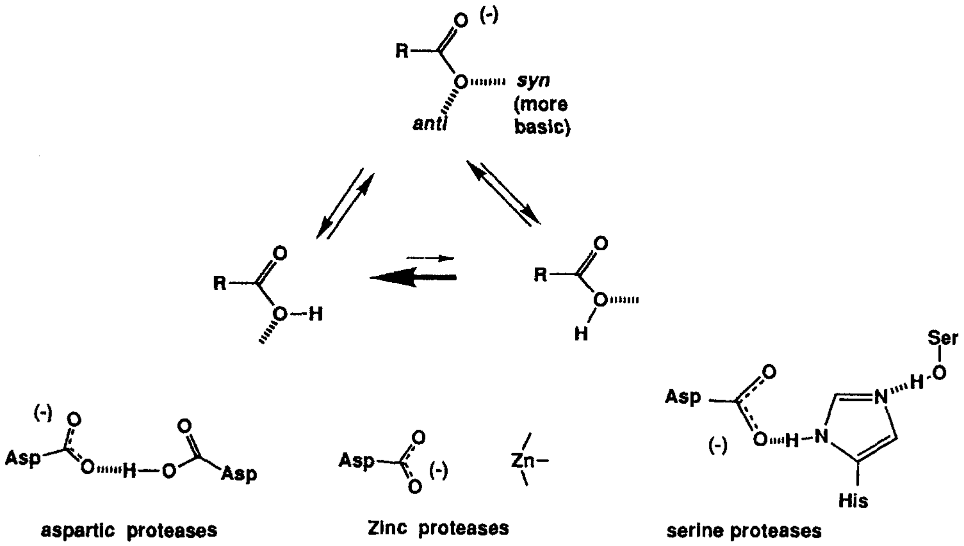
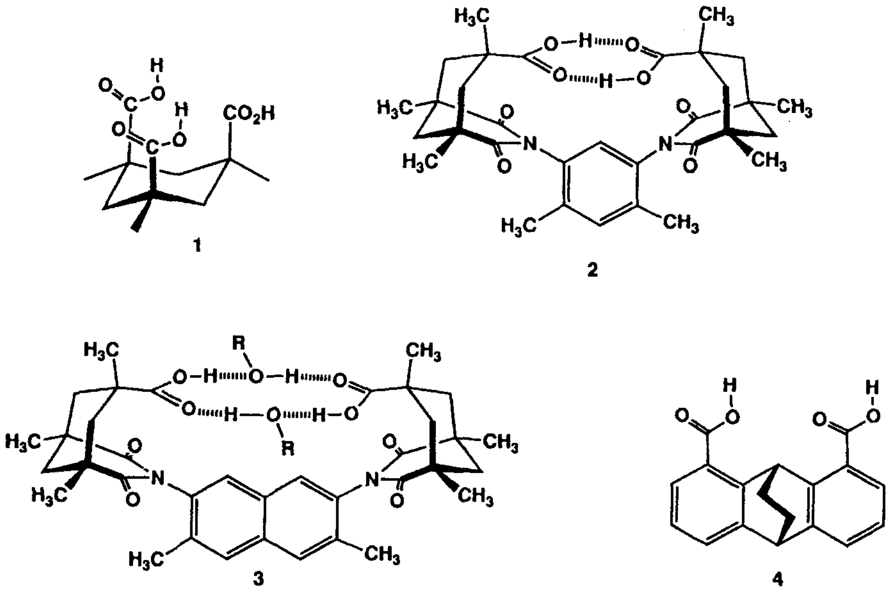
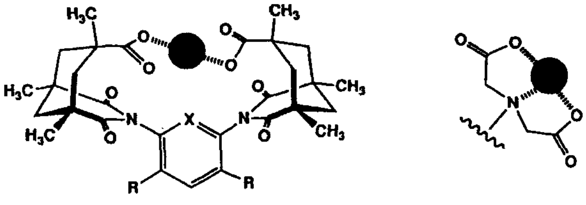


Scheme 1

Another, but related, measure of these effects had to do with the use of the diacid dianions as microenvironments for divalent alkaline earth metal ions (Scheme 3). Derivatives such as **5** can extract stoichiometric amounts of calcium and magnesium ions from aqueous solutions into organic solvents.[12] While the solubilities of these molecules made the complexation constants difficult to measure, our best estimates were that these structures were two or three orders magnitude better than imidodiacetate at calcium binding. Such structures, inducing EDTA and dipicolinate,[13] are constrained by their shapes to involve only the *E* lone pairs in the complexes. But what would be a fairer comparison? After all, the imidodiacetate involves car-



Scheme 2



5 X = N, CH
R = H, alkyl

EDTA etc.

Scheme 3

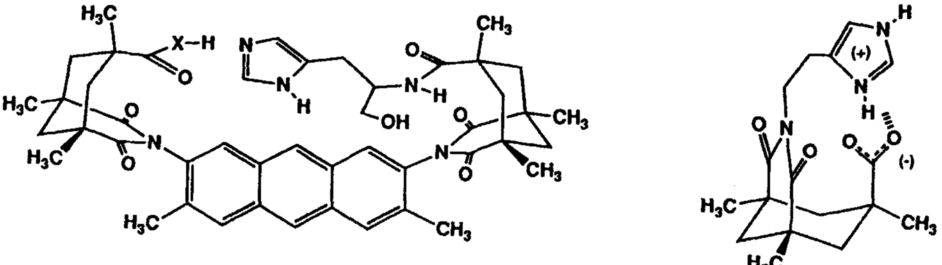
boxyls at different distances, different degrees of rotational freedom and an additional contact point represented by the central nitrogen. So, once again, the stereoelectronic effect is shrouded by uncertainties. A second context in which equilibrium acidities were evaluated involved the carboxyl–imidozolium pair. This arrangement appears in many enzymes of the serine protease and esterase classes.[14] We have described how rotational events might be a key feature in the redirection of protons within such active sites.[15] For the issue at hand, we constructed molecules such as **6a** using the acridine spacer (Scheme 4). Comparison of the pK_a of imidizolium and the carboxylate vs the corresponding primary amide **6b** was made. This is a 'poor man's' version of the site-directed mutagenesis experiments done by Craik *et al.*[16] The result, a difference of 1 pK_a unit is reasonable, but the nearby acridine nitrogen represents a 'wild card' in this comparison. In a smaller version the simple condensation of histamine with Kemp's triacid gave a construct, **7**, in which the appropriate intramolecular contacts were made.[17] The difference in the appropriate pK_a values when compared with dihydrourocanic acid, again suggests about a 1 pK_a enhancement provided by the *Z* lone pairs.

An alternative, kinetic, approach was also undertaken in an attempt to evaluate the significance of these stereoelectronic effects (Scheme 5). Condensation of the anhydride acid chloride of Kemp's triacid with amino ketones derived from Dakin–West reactions of amino acids gave the appropriate enolizable carbonyl compounds, **8**.[18] These feature hydrogens suspended in a region of space accessible to the *Z* but not *E* lone pairs. Nuclear Overhauser enhancement data suggested C—N (imide) bond rotation in the keto acid **8a**, it also showed that the keto acid **8b** was conformationaly biased owing to the presence of the bulky isopropyl group. Molecular mechanics calculation[19] showed that the approach of the carboxylate can be nearly perpendicular to the plane of carbonyl as prescribed by Corey and Sneen[20] for optimum reaction rate. The intramolecular general base-catalyzed reaction (IGBC) was followed by deuterium exchange and the comparison was made with the corresponding methyl esters **9** using pivalate as the base (since the basicity of the privalate is different from that of the carboxylate groups in the substrates **8a** and **8b** (p$K_a = 6{\cdot}40$) under identical conditions, bimolecular rate constants were corrected for the basicity using a β value of 0·8). Here the appropriate comparison involved effective molarities (EMs), which are known to be generally low for IGBC-type processes.[21] The best measurement of the EM for this system was 17 (Table 1), a modest value but certainly higher than most in these situations. Invariably, other cases of carboxylate in IGBC systems involve the *E* lone pairs and the effective molarities are generally much less than 1.[22,23] Hence in this context a lower limit of 2 kcal is indicated for the stereoelectronic effect.

Because molecular mechanics calculations suggested that proton transfers within this system could not reach an ideal trajectory, we next examined the xanthene skeleton shown in Scheme 6.[24] In structure **10** an

Table 1. First-order rate constants, equilibrium acidities and effective molarities of the keto acids

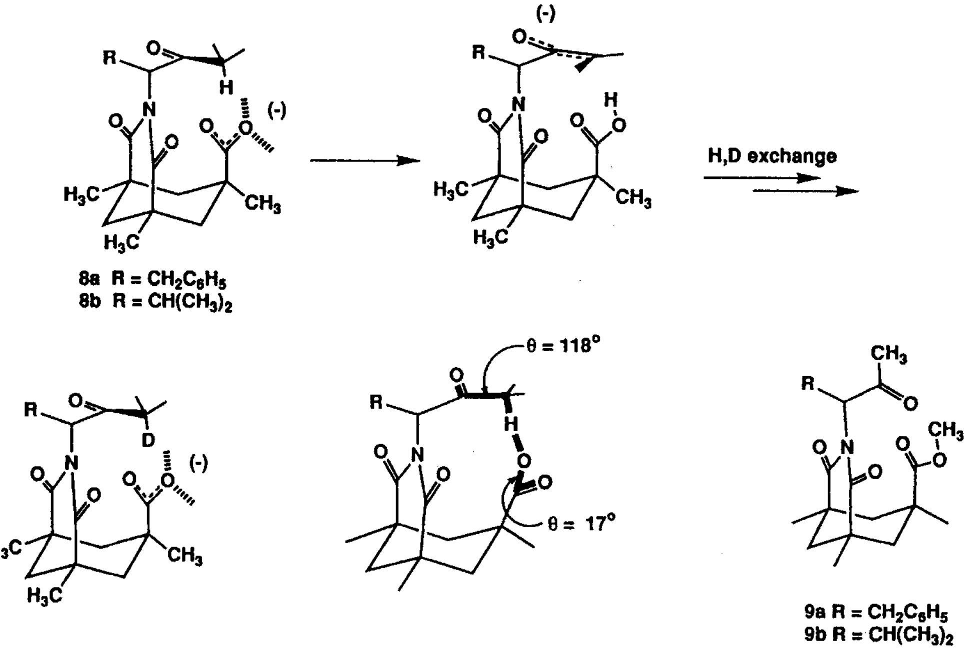
Substrate	k (s^{-1})	pK_a	EM (M)
8a	$6{\cdot}60 \times 10^{-6}$	6·23	7·0
8b	$2{\cdot}14 \times 10^{-5}$	6·23	17·0



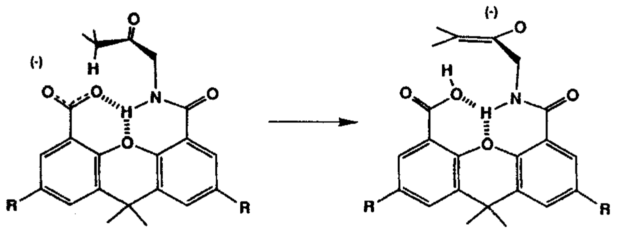
6a X = O
6b X = NH

7

Scheme 4



Scheme 5



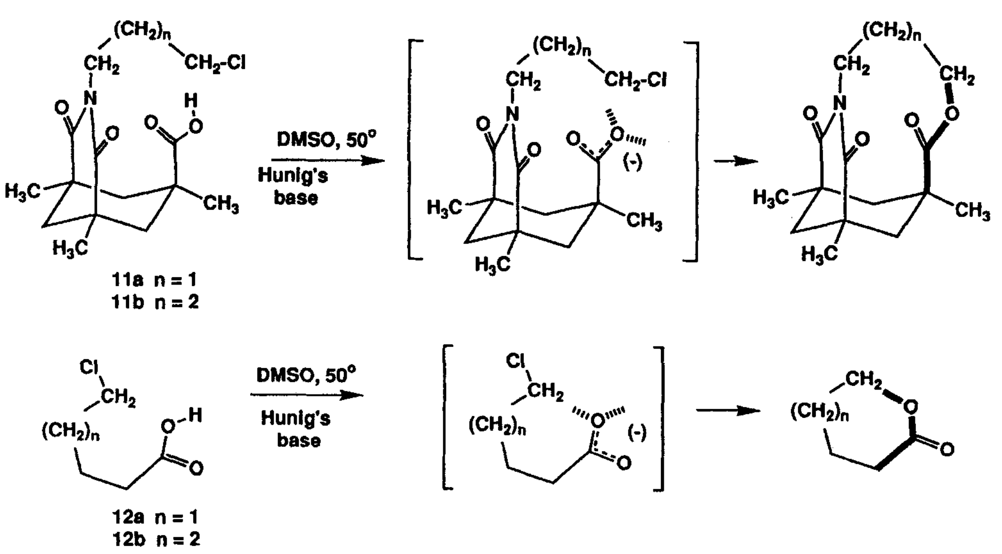
10

Scheme 6

idealized, linear intramolecular proton transfer can be achieved even though it involves a $12\frac{1}{2}$-membered transition state.[25] The effective molarity here, compared with the rate of enolization of the benzoyl derivative of 2-aminopropanone, was only 0·5 M, but even the methylene protons showed intramolecular exchange. Modeling shows that the angle and the distance for this type of proton transfer lead to an unreasonable looking carboxylic acid. Even so, these protons exchange only two times slower than those of the methyl group. Toward external bases, however, they are 20 times faster. Perhaps an 'outer-sphere' reaction, mediated by a water molecule, is responsible for the methylene exchange.[26] If not, the stereoelectronic effects around the carboxyl may not have much of a directional component.[5] This interpretation would be supported by the earlier studies of Harper and Bender[22] involving *ortho*-substituted benzoic acids.

Our most recent attempt involved lactonization. Unlike proton transfers and metal ion binding, where large electrostatic considerations are involved, the covalent formation of a carbon–oxyen bond could involve more directionality. We studied the cyclization of the chloro acids **11** (Scheme 7) and their rates[27] were identical in DMSO compared with the lactonizations involving the *E* lone pairs **12**. Since some strain is involved in the formation of the three-carbon bridge system in **11a**, the comparison with **12** is compromised. These two show about the same cyclization rate, but are they really comparable? Who knows if *any* bimolecular reaction can be compared with an intramolecular one? For example, in lactonization reactions and other nucleophilic processes in which high effective molarities are seen, there is invariably a relief of strain in the intramolecular reaction as the non-bonded components on the periphery of the reacting canters are fused into a ring. In bimolecular cases very different trajectories are involved and strain or steric effects are not issues. Intramolecular cases must be very carefully designed, and recent studies by Kemp *et al.*[28] involving intramolecular acyl transfers define the leading edge of this technology.

The cases described above can be interpreted to support the stereoelectronic effect as being worth anywhere from 0 to 8 kcal mol^{-1}. Measurements in other laboratories[29,30] support the low end of this estimate



Scheme 7

but the large range suggests that this physical organic study has done its job—it has raised more questions than it has answered.

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