para-substituted styrene 1,2-dibromides suitable for radioactivity determinations (R_p). Unfortunately, it was not possible to use this procedure with the p-CH_3O compound. Despite repeated efforts, it was not possible to prevent partial polymerization of the p-methoxystyrene, so R_p could not be determined in this case. (Such polymerization reactions are known to significantly alter the molar activities of both vinylic carbons.[75]

Except for the p-CH_3O compound, the carbon-14 contents of the initial and recovered reactants (R_0 and R_r values, respectively) were also determined as their respective styrene dibromide derivatives.[75] Samples of the initial and recovered salts were allowed to undergo 100% elimination[15] under conditions identical with those used to carry out the kinetics runs, except that a reaction temperature of 70 °C was used. The styrenes formed were converted to the dibromides as before. For the p-CH_3O system, the radioactivity measurements were carried out directly on the quaternary ammonium bromides themselves.

The separation procedure described above could not be used for the p-NO_2 system because the salt undergoes further elimination when heated in an aqueous medium. Instead, for the isotope-effect experiments with this compound, the reaction mixture (200 mL) was poured into ether (400 mL) and cooled in ice water. The salt that precipitated (along with sodium bromide) was filtered, washed with ether, and dried under vacuum at 57 °C. This precipitate, which still contained sodium bromide, was then allowed to undergo complete elimination in a separate reaction, and the resulting p-nitrostyrene was brominated, purified, and counted in a similar manner as the other compounds (R_r values). The original filtrate, which contained ether, ethanol, and the product p-nitrostyrene, was poured into cold water and the layers were separated. After the ethereal layer was washed with water and dried ($MgSO_4$), the corresponding styrene dibromide was prepared, purified, and counted as described above (R_p values).

Our standard procedure[19,76] was used for the radioactivity measurements; when the quaternary ammonium bromides were counted, 0.5 mL of methanol was added to solubilize them in the standard toluene-based cocktail-fluor solution (15 mL per sample) normally used. The isotope effects (rate-constant ratios) were calculated from the equations of Tong and Yankwich (see the Procedure and Results Section).[18]

The isotope-effect results are summarized in Table III. Confidence in the results is best gained by close examination of the complete details of the isotope-effect experiments; samples of our results are presented in Tables IV and V for the α- and β-carbon-14 labeled p-Cl quaternary ammonium bromides. Complete details for the other compounds and details of other aspects of the experimental work are available in the Ph.D. dissertation of JRIE.[1]

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Stereoelectronic Effects at Carboxylate Oxygen: Similar Basicity of the *E* and *Z* Lone Pairs in Solution

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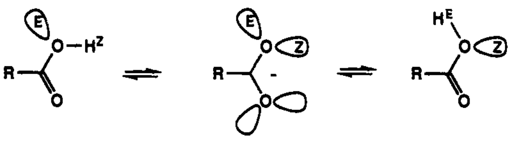
Received March 6, 1991

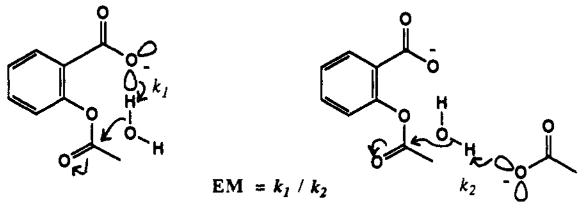
Abstract: Comparisons of effective molarities for intramolecular reactions and bond length-pK_a correlations show no evidence of a significant difference in basicity between the *E* and *Z* lone pairs of carboxylate in the condensed phase.

The realization[1] that the *E* and *Z* lone pairs of carboxylate may differ significantly in basicity, and thus reactivity, has inspired recent calculations[2]—generally supportive—and some elegant experiments[3]—generally inconclusive. It is the purpose of this communication to point out that there is good evidence in the literature to show that any difference cannot be large.[4] This, together with new evidence presented below, suggests that it is not significant in solution.



1. Effective Molarities. It is suggested[1,3] that effective molarities (EM)[5] observed for carboxylate acting as a general base are low because the intramolecular reaction must use the (less basic) *E* lone pair, whereas reference intermolecular processes are free to use the (more basic) *Z* lone pair of electrons. This is not supported by the evidence.

(a) Intramolecular (cyclization) reactions involving carboxylate as a nucleophile must also use the *E* lone pair, yet they show EM's that include the highest measured: typically 10^8-10^9 M, rising to 10^{13} M for systems in which strain in the ground state is relieved on cyclization.[5] EM's for intramolecular general-base catalysis are typically 1-10 M. This difference is far greater than could possibly be accounted for by a stereoelectronic effect on lone pair basicity and reflects primarily the favorable free energy of formation of the ring formed in the nucleophilic reaction.



(b) Of course this argument does not rule out a *contribution* from such a stereoelectronic effect, which might be detected by comparing EM's for cyclizations involving carboxylate with similar reactions of other oxy anions that have only one sort of lone pair. In fact there is no discernible difference: neighboring carboxylate is certainly no less effective a nucleophile than an alkoxide or aryloxide anion.[5]

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[5] Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183-278.

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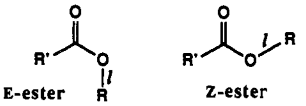
(c) Low EM's are observed for *all* intramolecular general-base-catalyzed reactions, not just for those of carboxylate. They are also observed—one special case apart[6]—for all reactions involving general-acid catalysis,[5] though here the theory would predict little disadvantage for the intramolecular reaction (the postulated higher acidity of the *E* proton largely compensating for its lower equilibrium concentration).

2. Bond Length—pK_a Correlations in Crystals. The length l of the C–O bond in a given system ROX is a linear function of the pK_a of (the conjugate acid of) the leaving group XO^-; the better the leaving group (i.e., the stronger the acid HOX), the longer the bond.[7] This correlation has been established for a dozen different series of compounds and appears to be general in the absence of significant conformational variation at the C center concerned. Thus primary and secondary alkyl systems, where good data are abundant, give excellent linear correlations,[7,8] which can in principle be used to predict the pK_a's of unstable acids HOX. If the intrinsic basicity of the *E* lone pair of carboxylate is indeed lower than that of the *Z* lone pair, then an *E*-carboxylate is, by definition, a better leaving group.[9] Consequently, the C–OCOR′ bond l should be longer in lactones, constrained into the *E* conformation, than in ordinary esters, which exist in the *Z* conformation.



E-ester **Z-ester**

A published analysis of the X-ray crystal structures of a large number of esters by Schweitzer and Dunitz[11] supports this idea: the mean C–O ester bond length l is 1.448 (12) Å for esters, but 1.462 (11) Å for lactones. However, C–O bond lengths are also sensitive to substitution at C, being significantly longer for a more substituted carbon,[7,8] and it turns out that the small lactone data set available at the time (ten γ- and six δ-lactones) contained a built-in bias. We have updated the Schweizer and Dunitz analysis, comparing structures of esters and lactones with a CH_2–OCOR′ bond, and find no significant difference in this parameter. Specifically, for 98 lactones the mean C–O bond length is 1.454 (1) Å; for 213 open-chain esters it is 1.453 (1) Å.[11] If there were a difference in intrinsic basicity between *E* and *Z* lone pairs of 4 pK_a units, we would expect the lactone bond to be longer by 0.008 Å.[8]

3. Correlations of Calculated Data. A possible objection to this argument is that bond lengths in rings are subject to steric and strain effects absent from acyclic systems. The only logical effect of ring strain would be to lengthen an endocyclic C–O bond, but the crystallographic data show that there is no significant difference in this parameter between γ- and δ-lactones, and in any case this is the reverse of the effect needed to explain the results described above. Furthermore, we have shown[7] that steric effects are not responsible for bond-length variations, even in derivatives of tertiary alcohols (though they are well-known to cause bond lengthening in highly substituted systems like hexasubstituted ethanes). Most pertinent would be C–O bond lengths for acyclic *E* esters, but open-chain esters exist and always crystallize in the *Z* conformation. However, the properties of acyclic *E* esters are readily calculable.

Table I. Calculated C–O Bond Lengths, l, and Conformational Preferences for Selected Formate Esters[9,13]

ester	C–O bond length (Å)[13]		ΔE (kcal)[a]
	Z	*E*	$Z \rightleftharpoons E$
g-FCH_2CH_2OCHO	1.4202	1.4095	4.75
t-FCH_2CH_2OCHO	1.4213	1.4132	5.37
CH_3CH_2OCHO	1.4289	1.4208	5.47
g-$H_3SiCH_2CH_2OCHO$	1.4305	1.4222	5.30
t-$H_3SiCH_2CH_2OCHO$	1.4294	1.4217	5.35

[a] Relative energies were calculated at the MP2(DZP) level by using the SCF(DZP) geometries. ΔE did not change significantly when *E*- and *Z*-ethyl formate were geometry-optimized at the higher level.

The preference of both carboxylic esters and acids for the *Z* conformation is well-reproduced by high-level calculations. So too is the observed dependence of the length of the C–OX bond length l on the pK_a of HOX. We have recently reported SCF-(DZP) calculations[9,13] on the *E* and *Z* conformations of five formate esters $HCOOCH_2CH_2Y$, where Y = H and trans and gauche F and SiH_3, and we find in every case that the C–O ester bond is actually shorter (Table I) rather than longer for the *E* conformation.[14] This is consistent with a ***higher*** "intrinsic" basicity for the *E* lone pair of carboxylate.

These three sets of evidence together constitute a strong case against a significant difference in basicity between the *E* and *Z* lone pairs of CO_2^- in the condensed phase. We note that the original estimate of the difference in basicity refers to single molecules in the gas phase: the best calculations indicate that the *Z* isomer is more stable by about 5 kcal/mol for an aliphatic carboxylic acid,[15] in reasonable agreement with the measured (microwave[16]) value of 3.9 kcal/mol for formic acid. Since both isomers are in equilibrium with the same anion, this is a direct measure of the difference in basicity between the two lone pairs. The simplest rationalization of all the evidence is that this difference disappears in solution (as does the 340 kcal/mol difference in energy[15] between the *Z* isomer of formic acid and formate anion on transfer from the gas phase to aqueous solution at a pH equal to the pK_a of the acid).[17]

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(6) Kirby, A. J.; Percy, J. M. *J. Chem. Soc., Perkin Trans.* **1989**, 907–912.

(7) Allen, F. H.; Kirby, A. J. *J. Am. Chem. Soc.* **1984**, *106*, 6197–6200. This relationship is formally between a structural parameter, measured in the crystal, and a thermodynamic parameter measured in (aqueous) solution. In fact, bond lengths in organic molecules are hardly affected by packing forces, as long as charge–charge or specific H-bonding interactions are involved, and differ little even between the solid state and the gas phase. (See, for example: Beagley, B. In *Molecular Structure by Diffraction Methods*; Chem. Soc. Special Publication: London, 1975; Vol. 3, p 52.) Differences between a molecule in the crystalline state, effectively a structured, fairly polar solid solution, and in solution in a polar solvent are still smaller. Thus, bond lengths are not expected to be significantly different in solution from those measured in the crystal.

(8) The best correlations are as follows: for RCH_2OX, $l = (1.458-2.02) \times 10^{-3}\ pH_{HOX}$ ($r = 0.995$). For RR′CHOX, $l = (1.475-2.90) \times 10^{-3}\ pH_{HOX}$ ($r = 0.999$).[9]

(9) Amos, R. D.; Handy, N. C.; Jones, P. G.; Kirby, A. J.; Parker, J. K.; Percy, J. M.; Su, M. D. Submitted for publication.

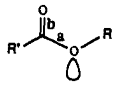
(10) Linear free energy relationships between kinetic (reactivity) and thermodynamic parameters (e.g. basicity) in solution are the well-established experimental basis of much of physical organic chemistry. We can confidently expect such a relationship between the pK_a of HOX and the rate constants for a reaction involving C–OX bond breaking.

(11) Schweizer, W. B.; Dunitz, J. D. *Helv. Chim. Acta* **1982**, *65*, 1547–1554.

(12) The Cambridge Crystallographic Database, Version 4.4 (Jan 1991), was searched for the substructure C–CO–O–CH_2–C* (C* attached to H or C only), setting limits of 0 ± 20° and 180 ± 20° for the dihedral angle indicated and ≤7.0% for the *R* factor. The errors quoted are standard deviations of the mean.

(13) Stationary point geometries were determined with the restricted Hartree–Fock scheme and double-ζ plus polarization basis sets. All calculations used CADPAC (Amos, R. D.; Rice, J. E. Cambridge Analytical Derivatives Package, Issue 4, Cambridge, 1988).

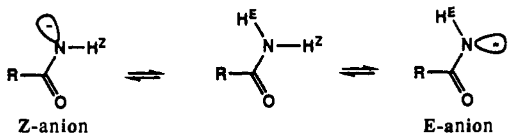
(14) This appears to be normal for calculated ester structures, in particular it is not a special property of formate esters. See, for example: Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935–43. Wang, X.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 1872–4. It is most simply explained in terms of the stronger $n-\sigma^*_{C=O}$ interaction possible in the *Z* isomer. Consistent with this (anomeric-type[4]) effect is the pattern of C–O bond lengths at the carbonyl carbon in calculated ester structures. For seven esters for which high-level calculations are available (five from Table I plus methyl acetate and formate (Wiberg and Laidig, loc. cit.)), bond a is shorter (by 0.007 (2) Å) and bond b is longer (by a similar amount) in the *Z* compared with the *E* isomer. (For the set of 98 + 213 crystal structures discussed above, *both* bonds are shorter for open-chain esters, again by a similar amount.)



(15) Csizmadia, I. G.; Peterson, M. R.; Kozmuta, C.; Robb, M. A. In *The Chemistry of Acid Derivatives*, Supplement B; Patai, S., Ed. Wiley: New York, 1979; Part 1, Chapter 1. Peterson, M. R.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1981**, *101*, 1076–9.

(16) Bjarnov, E.; Hocking, W. *Z. Naturforsch.* **1976**, *31A*, 1113–1121.

A close and relevant parallel is the ionization of (the isoelectronic) primary amides. Here too calculations indicate that the *Z* isomer (of the anion) is more stable in the gas phase by about 5 kcal/mol.[18] Since the isomeric anions are in equilibrium with the same conjugate acid, this is a direct measure of the difference in acidity between the *E* and *Z* protons. In this case it is possible



to measure the equilibria, and the proton-transfer processes involved, in solution. In aqueous solvent, the base-catalyzed exchange of H^E is never more than a few times faster than that of H^Z; the *E*/*Z* ratio is strongly solvent-dependent, and under some conditions the solvated *E* isomer is actually preferred.[19]

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(17) The calculated (>5 kcal/mol) preference of esters for the *Z* conformation is also much reduced in solution, as indicated by a measured (^{13}C NMR) value of 1.67 kcal/mol for ethyl formate. (Grindley, T. B. *Tetrahedron Lett.* **1982**, 1757-60.) Increasing the size of either the acyl or the alkyl substituent increases the preference for the *Z* conformation, presumably for steric reasons, so any stereoelectronic preference should be most clearly expressed in formate esters.

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Kinetic Studies and Modeling of a Self-Replicating System[†]

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Contribution from the Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. Received April 29, 1991

Abstract: The design, synthesis, and study of a molecular template, **11a**, that catalyzes its own formation from simpler components, **9** and **10d**, is described. Autocatalysis is shown by the following: (1) the increase in rate of reaction of **9** and **10d** in the presence of **11a**; (2) the reduction in rate of reaction in the presence of 2,6-bis(acetylamino)pyridine inhibitor; and (3) the reduction in rate of reaction when a component incapable of template behavior, **10h**, is substituted for **10d**. Three kinetic pathways are elucidated: (1) the background bimolecular reaction (eq 6); (2) the preassociative mechanism (eq 7); and (3) the template termolecular process (eq 8). A kinetic model for the replication process is introduced, and equilibrium and rate constants are determined. Predictions for the shapes of the product growth curves are made.

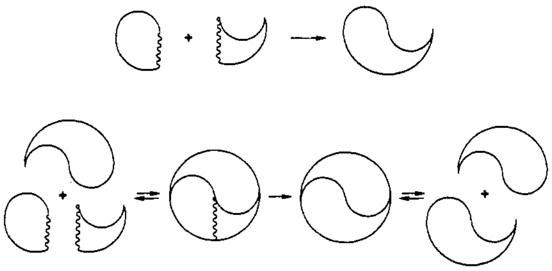
Introduction

Replicating molecules stand on the boundary of chemistry and biology. Replication itself bears no structural content, yet the process invariably involves molecules that are complementary. This feature is apparent in the structure of double-stranded nucleic acids, and perhaps it is too obvious or self-evident to have warranted much discussion in the past. Whereas complementarity implies the presence of "positive" and "negative" molecules (e.g., strands of nucleic acids), *self-complementarity* transcends the need for a "negative" and thus provides a minimal system for replication. We have used *the principle of self-complementarity* as our polar star in this badly trampled terrain; it gives our structures design, shape, and ultimately, function.[1]

Scheme I provides a two-dimensional example of self-complementarity and geometrically illustrates the minimal requirements of a self-replicating system. The sigmoid line represents the intermolecular contact between the two complementary and identical components. These units can be further broken along the jagged line into two different, yet complementary, pieces. The fusion of these pieces leads to a shape that can act as a template for the assembly of an identical unit. (A three-dimensional case has been described elsewhere.[2]) In this paper, we apply this concept in the context of chemical structures.

A brief time ago, we introduced a synthetic system capable of self-replication.[3] Unlike nucleic acids, replication occurs without the aid of enzymes or ribozymes.[4] In contrast with natural systems and other synthetic self-replicating molecules,[5] the new system involves the formation of an amide bond rather than a phosphate bond in the assembly step. Nevertheless, base-pairing provides the recognition and organization of the reacting components. Here, we report the experimental details of the reactions and describe the pecularities of its autocatalytic behavior. In a sequel, we shall address issues concerned with information, growth, and chemical evolution.

Scheme I



Catalysis. One goal of molecular recognition is the merger of the binding and catalytic steps, to make these events converge in space and in time. For the most part, this aim is a restatement of the Pauling principle.[6] It involves the maximum binding to, or recognition of, transition states. The recognition of transition states (rather than, say, their nearby high-energy intermediates) in small model systems is the challenge. Recent progress on this

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[†] Dedicated to Professor George Büchi on the occasion of his 70th birthday.

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