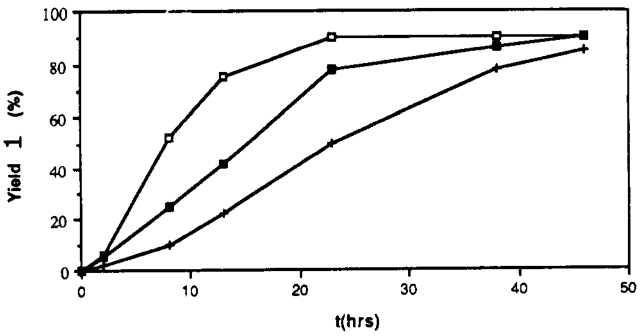


Figure 1. Formation of cyclohexenyl acetate catalyzed by palladium acetate, hydroquinone/molecular oxygen, and (□) copper, (■) manganese, or (+) cobalt acetate.

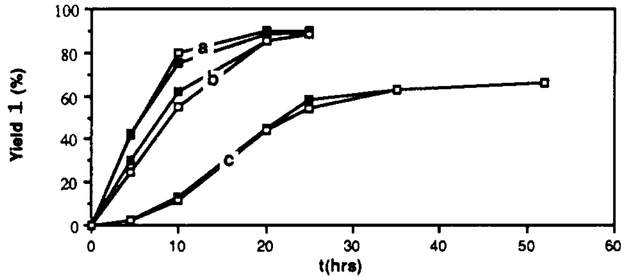


Figure 2. Effect of copper acetate and hydroquinone concentration on the formation of cyclohexenyl acetate. (a) 15% (b) 5%, and (c) 0% of hydroquinone. (■) 15% and (□) 5% of copper acetate.

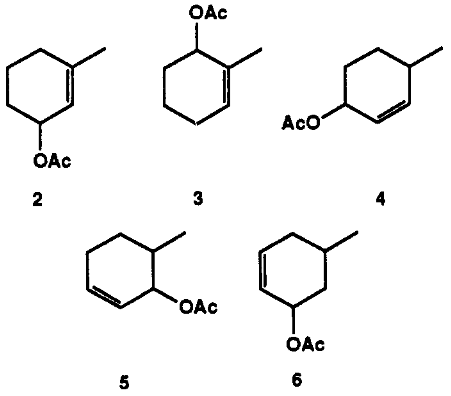
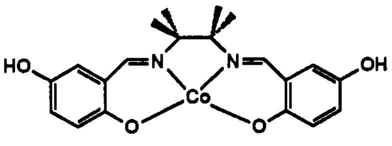
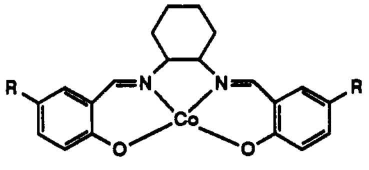


Figure 3.

system, which incorporates the quinone and the cooxidant in one molecule, might be superior to the mixture of metal acetate and hydroquinone. This may also be an advantage in systems where free benzoquinone tends to undergo competing reactions such as Diels–Alder addition.[3] We therefore prepared a Salen[9] type complex 7 in situ by mixing the ligand[10] (5 mol %) with an equivalent amount of cobalt(II) acetate (5 mol %) and then performed acetoxylation as described above but leaving out hydroquinone.



7



8 R = OH

9 R = H

The acetoxylation was somewhat slower than for the copper acetate/hydroquinone system, but about 90% yield of cyclohexenyl acetate was obtained after 40 h. The related compound 8 (5 mol %) gave 68% yield. If the hydroxyl group in 8 was replaced by hydrogen as in 9, only small amounts of cyclohexenyl acetate (19%) were formed together with substantial amounts of benzene from dehydrogenation of cyclohexene, and in this case palladium(0) was also precipitated as a mirror. If instead a mixture of 9 (5 mol %) and hydroquinone (10 mol %) was used, the product cyclohexenyl acetate was again formed in good yield (80%).[7,11] Our results thus show that efficient palladium-catalyzed acetoxylation of cyclohexene can be achieved, using oxygen as oxidant, if a mixture of hydroquinone or benzoquinone and a transition metal acetate is used as cooxidant. Exploratory experiments also suggest that this mixture can be replaced by a compact cooxidant such as 7 which incorporates the quinone moiety and is reminiscent of biological electron transfer systems. This type of oxidation system appears potentially useful for all types of oxidation reactions where a quinone moiety is essential, and the concept is being studied further in our laboratories.

Acknowledgment. We are grateful to "Carl Tryggers Stiftelse för vetenskaplig forskning", the Swedish Board of Technical Development, and the National Energy Administration for financial support.

Supplementary Material Available: The preparation of the ligands 7–9 together with ^{1}H NMR data (1 page). Ordering information is given on any current masthead page.

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(9) Salen: *N,N'*-bis(salicylidene)ethyleneamine.

(10) The ligands were fully characterized by elemental analyses (C, H) and NMR spectra.

(11) Similar conditions have been used for diacetoxylation of 1,3-dienes, ref 11.

The Intramolecular Salt Effect[1]

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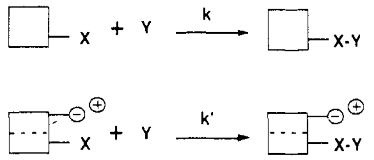
Summary: Ionic groups and salt bridges in the active sites of enzymes are thought to have important effects upon substrate reactivity. This paper describes the evaluation of an ion pair as an intramolecular effector of reaction rate for an addition reaction, the reaction of benzylic primary amines with methyl propynoate.

One of the most interesting challenges for contemporary organic chemists is the design of reaction systems that are catalytically controlled through noncovalent interactions. Control in a catalytic system is limited by the relative rates of the catalyzed (controlled) reaction and the uncatalyzed (uncontrolled) reaction. The microenvironment that imposes selectivity in the reaction must also greatly expedite the reaction or large amounts of substrate will "leak through" to products by the competing uncontrolled processes characterized by more chaotic microenvironments. The catalytically facilitating microenvironment may be attached to a reagent or to one or more substrates through reversible covalent bonds or through noncovalent interactions.[3-5] In all cases, for catalytic control to ensue, the result of the interaction must be to enhance the reactivity of the bound reagents or substrates.

We expect that the intramolecular (or intramolecular-complex) salt effect can be used to enhance the reactivity of substrates that are noncovalently attached to ionic host molecules. This paper describes the evaluation of an ion pair as an intramolecular effector of reaction rate for an addition reaction. The results reveal that in chloroform the intramolecular salt effect can lead to very large rate enhancements. This observation of large rate enhancements in nonpolar solvents may have an important influence in the field of synthetic catalyst design. The most specific and strongest synthetic molecular associations have been reported for host–guest systems in chloroform, and it may be foreseen that hydrogen bond based host–guest systems can be combined with the intramolecular salt effect to bring within reach a large class of new shape-selective specific synthetic catalysts and molecular effectors.

The intramolecular salt effect mimics an aspect of enzyme active sites—the general electrostatic field effects that are imposed by the ionic and nonionic functional groups of the surrounding protein.[6] Following important early discussions by Vernon and by Perutz, Warshel has cogently reemphasized and evaluated the influence that protein-induced electrostatic fields may have upon substrate reactivity.[7] If location-specific (intramolecular) ion pair effects could be demonstrated with simple models in nonpolar solvents, then this result could easily be combined with the growing body of knowledge concerning host–guest interactions in nonpolar solvents and the outcome would be that a large class of specific synthetic catalysts would be within reach. This study of intramolecular salt effects in nonpolar solvents was therefore begun.[8]

Scheme I[a]



[a] This paper examines the effect that an adjacent ion pair has on an addition reaction. The dashed lines in the second reaction represent the possible use of noncovalent forces for enforcing the proximity of the ion pair and a reactant.

Ingold suggested that the total effect of added salts (aside from mass-law effects, and setting aside the special salt effect and the common ion effect) can be separated into "ionic strength" effects, which are understood to be the long-range effects of the ionic atmosphere surrounding the reactant and the activated complex arising from that reactant, and "specific" salt effects, those parts of the total effect which depend on properties of the ions other than their net charge.[9,10] Studies of ionic species in nonpolar solvents are complicated by the nonideal nature of these solutions.[9-12] In nonpolar solvents, a clear view of kinetic phenomena can be further obscured by the aggregation of reactants and products.[13] Perrin and Pressing have discussed these issues and presented a valuable quantitative model for intermolecular salt effects in nonpolar media.[14]

If a reaction is sensitive to ionic cosolutes (Scheme I), it might seem obvious that if the ion pair was held close to the reacting species an even greater result could be expected. In nonpolar solvents, however, the magnitude of the added benefit to be derived by attaching the ionic species to the reactant is uncertain. One reason for this uncertainty is that ionic species aggregate in nonpolar solvents, and if nonionic cosolutes are included in these aggregates (such inclusion might be favored by, for example, hydrogen bond formation), then the added benefits of intramolecularity could be negligible. Furthermore, reactions must be expected to differ in sensitivity to such intramolecular electrostatic effects; some classes of reactions may show large accelerations, some no effect, and some reactions may be inhibited by the effect. Before embarking on a program to design synthetic catalysts

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(2) Fellow of the Alfred P. Sloan Foundation, 1988–1990.

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(6) Vernon, C. A. *Proc. R. Soc.* **1967**, *B167*, 389. Perutz, M. F. *Proc. R. Soc.* **1967**, *B167*, 448. Perutz, M. F. *Science* **1978**, *201*, 1187. Warshel, A. *Proc. Natl. Acad. Sci.* **1978**, *75*, 5250-5254.

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(8) An insightful series of papers from Haberfield has already examined the effects of proximate charges upon reactions (especially proton transfers) in polar solvents: Haberfield, P. In *Environmental Influences and Recognition in Enzyme Chemistry*; Liebman, J. F., Greenberg, A., Ed.; VCH: New York, 1988; pp 109–137. For a further discussion intramolecular electrostatic effects in polar media, see: Dahlberg, D. B.; Kuzemko, M. A.; Chiang, Y.; Kresge, A. J.; Powell, M. F. *J. Am. Chem. Soc.* **1983**, *105*, 5387–5390.

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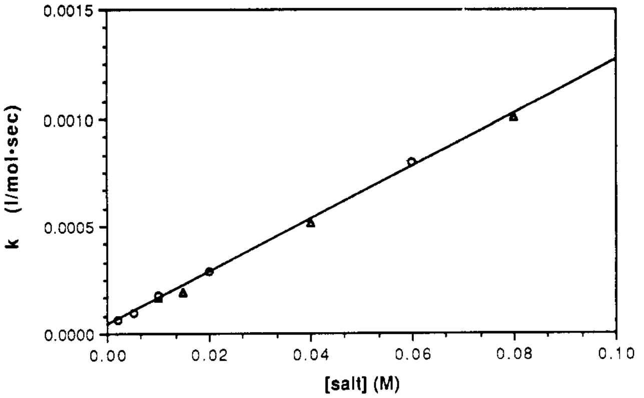
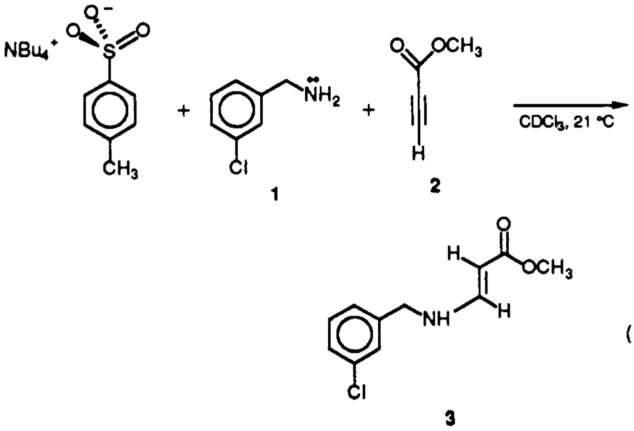


Figure 1. The effects of added tetrabutylammonium tosylate ([salt]) upon the second-order rate constant (*k*) for eq 1. Data acquired under pseudo-first-order conditions (○) and under second-order conditions (△) are included.

based on local ion pair field effects, we undertook to examine the magnitude of the intramolecular salt effect.



(1)

Given the known difficulties that attend kinetic experiments in nonpolar solvents, we sought to identify reactions for study that would not generate products such as salts or strongly acidic or basic species that would further complicate the reaction kinetics. Of course we also sought a reaction that might be susceptible to salt effects. The reaction of primary amines with propynoate esters fulfilled these criteria.[15] The reaction obeys a second-order rate law (first order in each component) in polar and nonpolar solvents, the reaction is accelerated by polar solvents, and the rate-determining step involves an attack of the amine on the unsaturated component to generate a (more or less) polar activated complex.

The effects of tetrabutylammonium tosylate on the rate of reaction of 3-chlorobenzylamine[16] with methyl propynoate (eq 1) are presented in Figure 1. The reaction showed good overall second-order behavior, and it was observed that the rate constant increased with added tetrabutylammonium tosylate. The largest salt concentration used was 320 mM. Over the concentration range from 2 to 80 mM the rate was found to vary linearly with salt concentration, and the observed second-order rate constant (*k*) can be calculated for salt concentrations in this range according to eq 2 ($R^2 = 0.997$). The rate constant in deuteriochloroform without added salt (by extrapolation) is 3.6×10^{-5} L·mol^{-1}·s^{-1}.

$$k = 3.6 \times 10^{-5} + (1.23 \times 10^{-2})[\mathrm{Bu_4N^+Ts^-}] \quad (2)$$
$$\text{or } k = (3.6 \times 10^{-5})(1 + 340[\mathrm{Bu_4N^+Ts^-}])$$

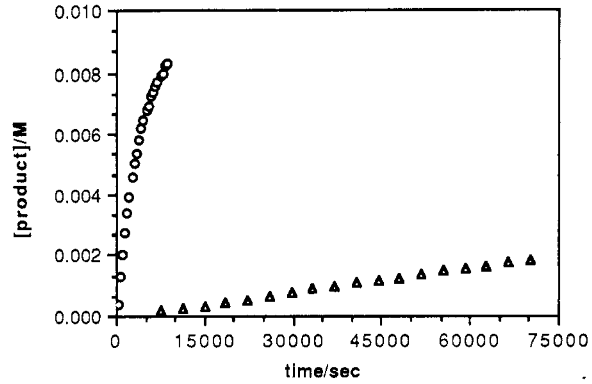
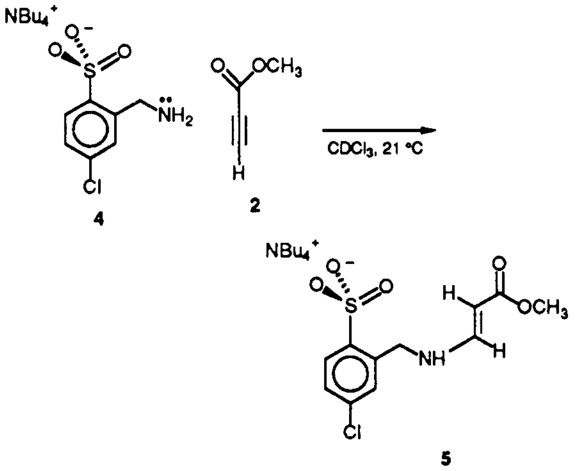


Figure 2. Illustration of the relative rates of reaction of alkyne **2** with the ionic amine **4** (○) and the nonionic amine **1** (△) in solutions of equal salt concentration.

To test the effectiveness of the *intramolecular* salt effect (eq 3), tetrabutylammonium sulfonate **4** was prepared from **1** via the known corresponding sulfonyl chloride.[17] In reactions with methyl propynoate in deuteriochloroform, this ionic reactant showed good kinetic behavior.[18] The reaction was second order overall, first order in amine **4** and first order in propynoate **2** ($k = 0.0156$ L·mol^{-1}·s^{-1}). An important result is illustrated in Figure 2. A 10 mM solution of the ionic amine containing 19.1 mM methyl propynoate reacts 100 times faster than a mixture of 10 mM neutral amine and 10 mM tetrabutylammonium tosylate containing 19.1 mM methyl propynoate. The ionic amine **4** is certainly a stronger base than the neutral amine **1**. To be assured that this increase in basicity did not lead to a change in mechanism to a fast base-catalyzed process, a competitive experiment was carried out. A mixture containing 10 mM ionic amine, 10 mM neutral amine, and 19.1 mM propynoate was prepared, and the reaction was followed using NMR spectroscopy. The results were entirely consistent with the rate constants measured in the noncompetitive experiments.



(3)

These data can be used to determine an "effective molarity" for the tetrabutylammonium sulfonate group. If salt above 80 mM behaved like the solutions observed here the concentration of salt required to induce the neutral amine to react at a rate equal to the ionic amine would be 1.25 M. However, experiments with concentra-

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tions of salt from 80 to 320 mM show that this extrapolation is not appropriate. Higher order aggregates and even microcrystalline precipitates form long before such high concentrations are reached, and it is not surprising that the nearly linear change of rate with added salt that is observed between 2 and 80 mM salt is not continued at higher concentrations.

The salt effect at low concentrations (≤2 mM, Figure 1) is relevant to our ultimate goal of combining this salt effect with a noncovalent process for assuring salt/substrate proximity (Scheme I). The direct experiments described here show that for this addition reaction, at 2 mM ionic catalyst, we can expect an amine noncovalently attached to a ion pair to react up to 250 times more quickly than unbound amine because unbound amine will be affected only by the general salt effect while bound amine (in the best circumstance) will experience an intracomplex salt effect similar to that measured for the amine 4. At lower concentration than 2 mM catalyst, it may be predicted that bound amine may react up to 430 times faster than unbound amine. These values are at the level of rate acceleration that is required for practical control of organic reactions. They do not approach the accelerations required for control if very small amounts of catalyst/reagent are to be used, but economically acceptable and technically practical control does not always require small amounts of reagent when the reagent is recyclable. Because association constants of 10^3 M^{-1} are readily obtained for hydrogen bonding systems in nonpolar solvents, we anticipate that this intramolecular salt effect can be applied to the design and synthesis of new selective catalysts and we have begun experiments along those lines.

Conclusions. These results reveal the effects that coincide with attachment of an ionic group (a salt pair) in a site adjacent to a nucleophilic reaction center. This paper calls attention to the intramolecular electrostatic effects of ion pairs and suggests that, when coupled with a noncovalent process for solute association, this phenomenon might lead to new selective catalysts. Salt effects on substitution reactions are a classic subject in physical organic chemistry. The experiments discussed above examine for the first time the normal salt effects and the "intramolecular salt effect" for a simple addition reaction. The results are relevant to discussions of enzyme mechanisms because they constitute permissive evidence of the substantial effects that ion pairs within the active sites of enzymes can have on reaction rates. Further data will be required to illuminate the origin and nature of this intramolecular effect on reaction rate. Discussion of hypotheses concerning these matters will be presented in the full paper.[19]

The effects that salts and intramolecular or intramolecular complex electrostatic fields may have on the activity coefficients and free energies of reactants and activated complexes lie at the heart of our ongoing studies.

Acknowledgment. This work was supported by funds provided by the Sloan Foundation and by the University of Pittsburgh. We thank Dr. Peter F. M. Koehler, Dean of the Faculty of Arts and Sciences, for his support of this work. Dr. Fu-Tyan Lin of this Department continues to provide essential support and advice in our NMR experiments. Help from Dr. Greg Meisner, Laboratory Instrumentation Manager in the Department, benefits all our projects.

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(19) A possibility that the effect of tetrabutylammonium sulfonate in eq 1 is due to hydrogen bond formation is doubtful. Two facts are noted: first, because the product binds to the salt more strongly (K_a = 18 M^{-1}) than the starting amine, the product should be an inhibitor of any sulfonate-induced catalysis that is based on hydrogen bond formation. The reaction shows excellent fit to a simple model (second order overall) over 3 half-lives. The buildup of an inhibitory product should cause a detectable deviation of the data from this model and no deviation was observed. Second, we have tested a good H-bond acceptor as a catalyst for this reaction. Triphenylphosphine oxide is not a catalyst of this reaction under the same conditions where tetrabutylammonium tosylate is effective.

Conjugate Reduction of α,β-Unsaturated Carbonyl Compounds by Catecholborane

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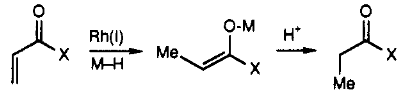
Received August 2, 1990

Summary: α,β-Unsaturated ketones which can readily adopt an s-cis conformation undergo conjugate reduction by catecholborane at room temperature. α,β-Unsaturated imides, esters, and amides are unreactive under the same conditions. However, catalytic quantities of $Rh(PPh_3)_3Cl$ greatly accelerate the 1,4-addition process, effecting conjugate reduction of these substrates by catecholborane at −20 °C. The resulting boron enolates may be reacted with electrophiles to provide functionalized products.

A number of synthetic methods have been developed which effect the conjugate reduction of α,β-unsaturated carbonyl compounds.[1] For example, it has been demonstrated that rhodium(I) complexes catalyze the 1,4-addition of silicon hydrides to enones and enoates (eq 1, M = SiR_3).[2] The purpose of this paper is to report that the analogous rhodium(I)-catalyzed hydroboration[3] with catecholborane may also be realized (eq 1, M = $B(OR)_2$) and to outline the scope and limitations of this complementary reaction, which affords boron enolate intermediates of considerable synthetic utility.



(1)

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