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THE CHEMISTRY OF FUNCTIONAL GROUP ARRAYS. ELECTROSTATIC CATALYSIS AND THE "INTRAMOLECULAR SALT EFFECT".

Paul J. Smith and Craig S. Wilcox*

Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260 USA

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Abstract. *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 results reveal that in chloroform the intramolecular salt effect can lead to very large rate enhancements. It is proposed that in this case the local effect of the ion pair probably depends upon two factors: the electrostatic effects of the salt pair and, to a lesser extent, an intramolecular hydrogen bond. This observation of large rate enhancements in nonpolar solvents provides evidence of the substantial effects that ion pairs within the active sites of enzymes could have on reaction rates. The most specific and strongest synthetic molecular associations have been reported for host-guest systems in chloroform, and it is foreseen that hydrogen bond based host-guest systems will be combined with the intramolecular salt effect to bring within reach a large class of new shape selective specific synthetic catalysts and molecular effectors.*

Background. Enzymes represent the most widespread and successful reagents for the catalytic control of chemical reactions. Many organic chemists have been attracted to the enzymes as sources of inspiration for the design of new totally synthetic catalysts. An important function of enzyme active sites is to provide acidic or basic functional groups that facilitate proton transfer.[1] Potential catalysts or enzyme models that mimic such facilitated proton transfers have already been prepared and evaluated in other groups.[2] We are examining another long-recognized aspect of enzyme active sites - the electrostatic field effects that are imposed by the functional groups of the surrounding protein.[3] In a series of influential papers, Warshel has built on the important early discussions by Vernon and by Perutz and emphasized the influence that protein-induced electrostatic fields can have upon substrate reactivity.[4]

Ions and ion pairs are simple structures that are associated with strong electrostatic fields and it is interesting to consider the effects such ions might have on chemical reactions. A valuable series of papers by Haberfield has already broached this subject and examined the effects of proximate charges upon reactions (especially proton transfers) in polar solvents.[5] Most examples of these phenomena have arisen in experiments conducted in polar media.[6] However, it is in nonpolar media that these effects should be greatest and could approach the magnitude of rate acceleration required for practical catalytic control of a chemical reaction.[3,5,7] If large electrostatic field effects could be demonstrated with simple models in nonpolar solvents, then this result could be combined with the growing body of knowledge concerning host-guest interactions in nonpolar solvents and the result would bring within reach a unique class of specific synthetic catalysts.

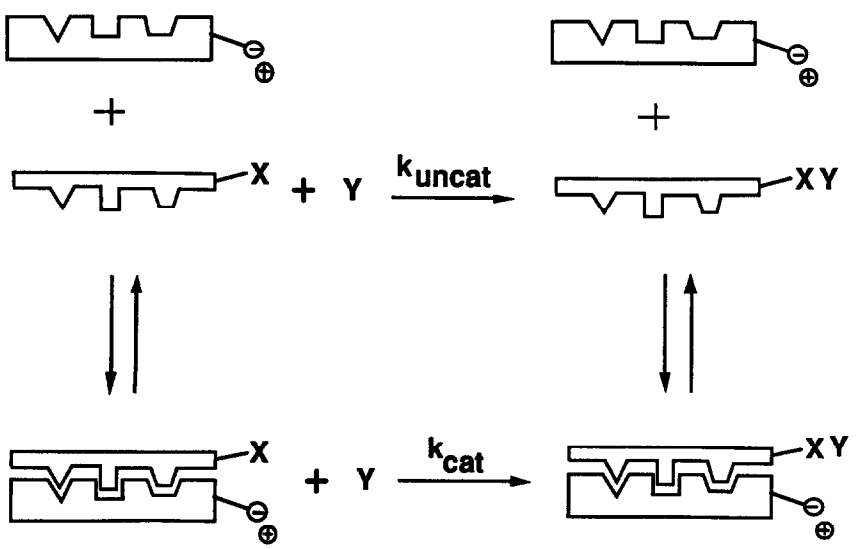
The *inter*molecular effects of added salts upon the rates of nucleophilic substitution reactions were first appraised and categorized many years ago. The total effect of added salts (aside from mass-law effects, the special salt effect and the common ion effect) can be separated into "ionic strength" 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.[7] An example of such effects was provided when Winstein showed that the unimolecular decomposition of neophyl tosylate in many solvents was accelerated upon addition of lithium perchlorate.[8] Not surprisingly, this effect was most pronounced in the least polar solvents; in ether: 0.1 M lithium perchlorate increased rates of ionization by a factor of 10^5. In most solvents this accelerating effect was found to increase linearly with increasing salt concentrations, but it is not unusual to see nonlinear effects, especially at higher concentrations of salt.

Studies of ionic species in nonpolar solvents are complicated by the non-ideal nature of these solutions.[7-9] In nonpolar solvents even the most lipophilic salts are known to exist as ion pairs (and more complex aggregates) at concentration above 10^{-5} M.[10] A quantitative model of salt effects must therefore include a means for modeling formation of ion pairs, triplets, quadrupoles, and higher order charged and uncharged aggregates. In nonpolar solvents, a clear view of kinetic phenomena can be further obscured by the aggregation of reactants and products.[11]

Perrin and Pressing developed a reasoned approach to the challenge of modeling the effects that salt pairs (dipoles) could exert upon a dipolar transition state.[12] It was concluded that when only one dipolar solute (the ion pair) is considered and interactions with the transition state are integrated over all configurations and distances, then the logarithm of the rate is expected to vary linearly with salt concentration. Perrin pointed out that this result does not fit the observed data (the commonly observed salt effect is linear in k, not log k), but because several dipoles can be effective, higher order effects must be considered. These effects are included in the higher terms of the virial equation that is central to the Perrin and Pressing model. It was argued that these terms would lead to diminished concentration dependence (downward curvature of

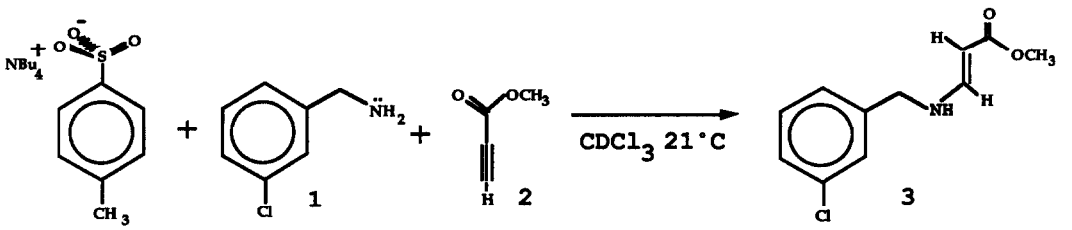
the log k vs [salt] graph) and would explain the observed salt dependence. Aggregation of added salts is another phenomenon that can also lead to downward curvature of the log k vs [salt] graph. The model was based on the proposition that the observed rate accelerations were due to the ability of ionic addenda to affect the free energy (activity coefficient) of a polar activated complex more than the neutral starting material. An alternative view - that the linearity of salt effects arises from the direct presence of the salt in the transition state - cannot be defended.

These and other pioneering studies outlined the intermolecular effects that ionic addenda may exert upon the rates of substitution reactions in nonpolar solvents. Our own interests in this field are summarized by the reactions in Scheme 1. We envisioned a catalytic scheme that is in harmony with the central theme of Warshel's work and is based on local (within the complex) electrostatic field effects. Any rate acceleration for the bound substrate depends on the total effects of the host catalyst and these effects will be exerted on the ground state and the activated complex of the reaction of interest. The principle effects of the ion pair can be divided between hydrogen bond interactions and classical coulombic interactions. Given a reaction sensitive to ionic cosolutes, it might seem obvious that if the ion pair was held close to the reacting species an even greater result could be expected. To commence a program to evaluate synthetic catalysts based on Scheme 1, we undertook to examine the magnitude of the *intra*molecular salt effect.[13]



Scheme 1. A catalytic scheme based on reversible binding of a substrate and activation of the substrate through an intramolecular effect of the ion pair.

Equation 1.



Results. Because of the difficulties that attend kinetic experiments in nonpolar solvents, it was important that the reaction to be studied not generate products such as salts or strongly acidic or basic species that would complicate the reaction kinetics. The reaction of primary amines with propynoate esters fulfilled these criteria.[14] 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 solvent effects reported for the reaction led us to expect that the reaction would be susceptible to dissolved salts.

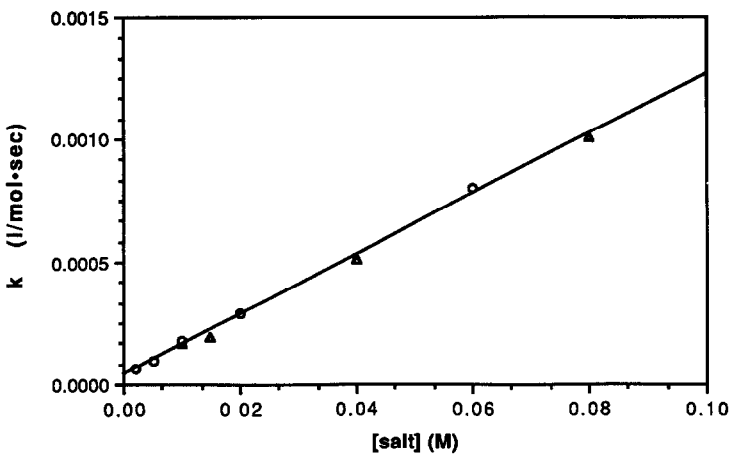


Figure 1. The effects of added tetrabutylammonium tosylate ([salt]) upon the second order rate constant (k) for equation 1. Data acquired under pseudo-first order conditions (O) and under second order conditions (Δ) are included.

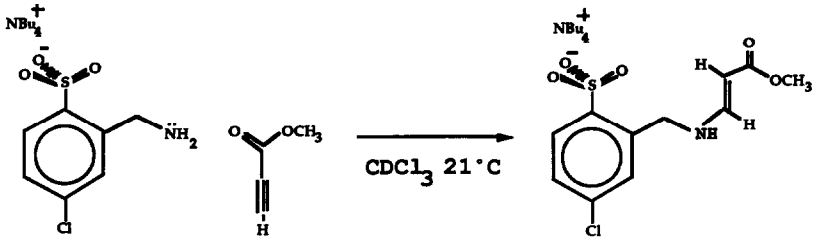
The effects of tetrabutylammonium tosylate on the rate of reaction of 3-chlorobenzylamine with methyl propynoate (equation 1) are presented in Figure 1. The reaction showed good overall second order behaviour and it was observed that the rate constant increased

Equation 2.

$$k = 3.6 \times 10^{-5} + 1.23 \times 10^{-2} \bullet [Bu_4N^+ Ts^-] \quad (L \bullet mol^{-1} \bullet sec^{-1})$$

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. The observed second order rate constant (**k**) can be calculated for salt concentrations in this range according to equation 2 (R^2=0.997). A single determination of the rate constant in deuteriochloroform without added salt gave k = 2.5 x 10^{-5} $L \bullet mol^{-1} \bullet sec^{-1}$, in reasonable agreement with the extrapolated value, 3.6 x 10^{-5} $L \bullet mol^{-1} \bullet sec^{-1}$.

Equation 3.



4 **2** **5**

To test the effectiveness of the *intramolecular* salt effect (equation 3), tetrabutylammonium sulfonate **4** was prepared from **1** via the known corresponding sulfonyl chloride.[15] In reactions with methyl propynoate in deuteriochloroform, this ionic reactant showed good kinetic behaviour. The reaction was second order overall, first order in amine **4** and first order in propynoate **2** (k = 0.0156 $L \bullet mol^{-1} \bullet sec^{-1}$). An important result is illustrated in Figure 2: A 10 mM solution of the ionic amine containing 19.1 mmolar methyl propynoate reacts 100 times faster than a mixture of 10 mM neutral amine and 10 mM tetrabutylammonium tosylate containing 19.1 mmolar methyl propynoate.

The ionic amine **4** is 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 faster 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 as would be expected based on the rate constants measured in the noncompetitive experiments.

These data can be used to determine an "effective molarity" (EM) for the salt. 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. Of course this extrapolation cannot be tested: higher order aggregates and 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.

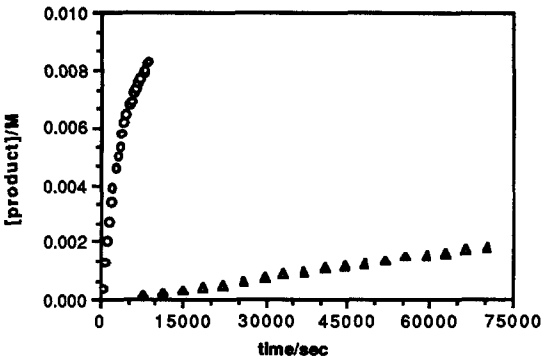


Figure 2. Illustration of the relative rates of reaction of alkyne 2 with the ionic amine 4 (O) and the non-ionic amine 1 (Δ) in solutions of equal salt concentration.

Discussion. These data reveal the effects that coincide with attachment of an ionic group (a salt pair) in a site adjacent to a reaction center. The experiments call attention to the intramolecular electrostatic effects of ion pairs and give credence to the idea that this phenomenon, when coupled with a noncovalent process for salt-substrate association, might lead to new catalysts.

The "intramolecular salt effect" should be considered, after all, as a subsitutuent effect. As demonstrated above, the magnitude of the effect may be estimated only after the intermolecular (cosolute) effects of the electrolyte have been evaluated in model studies. The intramolecular effects of an ion pair can be discussed using the usual vocabulary appropriate to substituent effects. The effects of the ion pair may differ from non-ionic substituents in quantity, but qualitative changes are not expected.

a. Through bond effects. *Inductive effects* (through-bond effects that can be judged by NMR chemical shift data - of course many "inductive" effects in reactions are in fact through space electrostatic interactions)[16] and resonance effects should be judged after evaluating the meta and para analogs of 4. Such experiments are underway. It is possible to predict now that these effects are probably unimportant. It has been reported that the inductive effect of an $-SO_3^-$ group is the same as for -N(H)Ac, it is a relatively small effect, and electron withdrawing.[16] It is not credible that this through-bond effect could lead to activation of the benzylic amine. *Resonance effects* in the transition state would require an unlikely homoconjugative interaction and even direct resonance effects with SO_3^- are very weak.[17] Inductive and resonance effects could have a small part in these observations - but our observation of the large *inter*molecular salt effect leads us to conclude that polar through-space effects of the salt are likely to be much more influential.

b. Hydrogen bond effects. A more important component of this salt effect might be *the intramolecular hydrogen bond* that can form between the amino group (in the initial reaction

state or in the activated complex) and the sulfonate group in the initial reaction state or in the activated complex. If this H-bond is much stronger in the transition state than in the initial state then rate acceleration may be observed. Tetrabutylammonium tosylate (more precisely, the mixture of aggregates of this salt that predominate between 2 and 80 mM concentrations) forms a complex with the product vinylogous carbamate (K_a = 20 M^{-1}) and interactions with the starting amine are weaker than this. The entropic advantages attending intramolecular hydrogen bond formation offer reasonable assurance that such hydrogen bonding will be very important for substrate **4** and product **5**. A dipolar intermediate will be a better hydrogen bond donor than either **4** or **5** (it is a stronger acid) and catalysis through hydrogen bond formation is not unreasonable on that basis.

Separating hydrogen bond effects from electrostatic effects requires some delicacy. All chemical interactions are electrostatic. Hydrogen bonds can be defined on the basis of energy as an interaction between X-H and Y wherein the interaction energy is greater than the sum of the electrostatic interaction and the van der Waals interaction.[18] A common structurally based definition requires that the H---Y distance be less than the sum of the van der Waals radii of H and Y. At "long" X---Y distances, (over 3-3.5 Å) the interaction is predominantly electrostatic and is best understood as a local dipole-dipole interaction.[18,19] These interactions are much less dependent on distance (varying in proportion to the distance raised to the third power) than any proposed orbital overlap effects. On the other hand, at short H---Y distances four components of the total interaction can be recognized: electrostatic, London dispersion, charge-transfer, and delocalization (both intra- and intermolecular). This special aspect of the hydrogen bond is a very short range effect and is usually represented as an additional attractive term (to be added to the electrostatic term) falling off in proportion to the distance raised to the tenth power.[20] These generalizations apply to neutral donor-acceptor combinations.

The interesting issue at hand is the relative importance of a hydrogen bond in relation to the total stabilization of the (presumably) charge separated transition state. *Direct experience suggests that in ionic interactions in nonpolar solvents electrostatic interactions will be much more important than H-bond interactions.* For example, in chlorobenzene (ε = 5.63, chloroform ε = 5.02) the Gibbs free energy of association for tetrabutylammonium picrate amounts to 10.4 kcal/mol while for tributylammonium picrate the association free energy is 17 kcal/mol.[21] At most, therefore, the opportunity for H-bond formation seems to provide only 6.6 of the 17 kcal/mol association energy measured for the trialkylammonium picrate. But this is a much stronger H-bond (ΔG) than any common H-bond between neutral molecules. The real contribution of the H-bond is probably less than 5 kcal because the picrate can approach the trialkylammonium ion more closely and therefore the electrostatic component of the interaction should be greater than 10.4 out of 17 kcal/mol. Grunwald found the association energy of octanoic acid with tosylate in benzene to amount to only about 2 kcal/mol and this demonstates that the sulfonate ion is not an unusually active hydrogen bond acceptor toward this donor.[22]

It can be tentatively concluded that for interaction in nonpolar solvents between ionic components that can hydrogen bond, the hydrogen bond component of the interaction is much

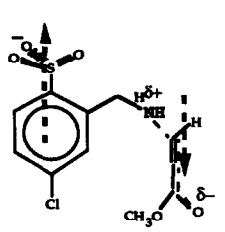
less than the total energy of interaction and the total interaction is dominated by the coulombic attraction between the charged components. It seems reasonable on this basis to expect that in nonpolar solvents the predominant cause of the intramolecular salt effect is not dependent on the hydrogen bond aspects of the interactions. Further experiments that may provide data relevant to this discussion are underway.

(It may be pointed out here that hydrogen bonds do not seem important in the intermolecular case. The product binds to the sulfonate more strongly than the starting amine, so the product should be an inhibitor of sulfonate catalysis if it was based on H-bond formation. The reaction shows excellent fit to a simple second order model over several half-lives. The buildup of an inhibitory product would cause a detectable deviation from this model and no deviation was observed. A good H-bond acceptor has been tested as a catalyst for this reaction. Triphenylphosphine oxide is not a catalyst of this reaction under the same conditions where tetrabutylammonium tosylate is very effective. In the presence of 10 mM triphenylphosphine oxide, $k = 3.6 \times 10^{-5}$ $L \cdot mol^{-1} \cdot sec^{-1}$. It is unlikely therefore that H-bonding is important in the intermolecular case, but in the intramolecular case it may yet be shown to have a role.)

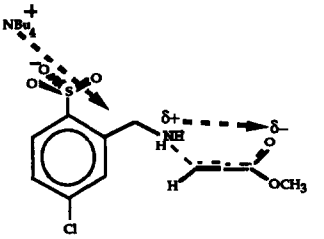
c. Dipole effects not related to the salt *vs* the effects of the ion pair. Finally one must ask if the effect introduced by attaching a salt to a reactive molecule is greater than or less than the effect of attaching any other polar group to that molecule. Any polar group attached close to a reactive site will change the electric field at that site and this change may lower the reaction activation energy.[23] Is the salt pair especially effective for this purpose? There are reasons why the salt effect in this specific case may be larger than the simple effect of the adjacent $-SO_3^-$ group. In chloroform, the tetraalkylammonium tosylates have a larger dipole moment (11 D) than the tosylate group alone (4.58 D).[22] The dipole is not only larger, but (at some entropic price) can be directed appropriately to maximize stabilization of a positive charge at the benzylic site. Therefore the ion pair could be more influential than a fixed neutral functional group because the ion pair is more polar and it can freely adjust to developing charge. A less likely reason that the effect may be especially pronounced with salts is that salts may be aggregated at these concentrations. If so, the effect of a single dipole induced electric field is not relevant and the overall effect of the salt aggregate would be the cause of the observed rate effect. These data would then be of interest as examples of the effects of proximate salt clusters. Grunwald's data suggests that, at up to 5 mM concentrations, tetraalkylammonium salts in benzene are only ion pairs and are probably not aggregated.[22] For the case presented here, the good fit of the reaction data to a simple second-order model over several half-lives indicates that aggregation, if present, is either not changing over the concentration range of the experiment or the changing population of aggregates does not differ detectably in reactivity. For these reasons and because the effective molarity found at several different concentrations of **4** does not significantly vary from 1.25 M, we conclude that aggregation is unlikely.

Our present thoughts concerning the effects of the ion pair vis-á-vis other effectors may be generalized by pointing out that the dipole moment for an ion pair can exceed the local dipole moment of neutral functional groups. The *optimum* electrostatic effect of an ion pair should

therefore in most cases exceed the *optimum* electrostatic effect of a single functional group, but the geometrical factors of any single case will be of greatest importance. Of course, optimally oriented *arrays* of functional groups (the α-helix is an important example) can produce electric fields greater than that provided by a common ion pair.[24,25] Experiments designed to evaluate the effect of a well positioned and rigidly fixed salt pair are underway.



a group dipole effect



an ion-pair dipole effect

Conclusions. *Inter*molecular 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 clear 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.

It seems likely that the rate determining step involves formation of a dipolar intermediate and (following the Perrin and Pressing model) this dipole is stabilized by the adjacent dipolar ion pair. Prior work by Huisgen and Giese supports this picture of the transition state for the rate determining step. The intramolecular salt effect is enhanced over the cosolute ("normal") salt effect predominantly because of the shorter distance of interaction. Because the two dipoles are not free to assume all possible relative orientations, a subset of unfavorable orientations (where the dipolar interactions would be repulsive) may be disallowed by the geometry of the molecule and therefore the intramolecular effect could be advantageous for reasons of orientation as well as distance.

The intramolecular salt effect is a subsituent effect. The magnitude of the effect is potentially larger than most substituent effects due to the large electrostatic field of the ion pair. Because the effect is a through-space phenomenon and it is strongest in nonpolar solvents we anticipate that this intramolecular salt effect can be applied to the design and synthesis of new selective catalysts based on hydrogen bonded docking interactions and we have begun experiments along those lines.

The effects that salts and intramolecular or (especially) intra-molecular-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.

Experimental Section.

General. Deuteriochloroform (Cambridge Isotope Labs, 99.8%) was dried over molecular sieves. Methylene chloride (used as an internal standard) was distilled once. Methyl propynoate (Aldrich, 99%) was used without further purification. Triphenylphosphine oxide (Aldrich, 98%) was crystallized from absolute ethanol and dried at 100 °C and 1 mm. 3-Chlorobenzylamine (1) was prepared from 3-chlorobenzyl chloride by the method of Graymore and Davies in 85% yield.[26] The amine was purified by crystallization of the hydrochloride salt from absolute ethanol (mp 224.5-226°C), and the free base was distilled under vacuum (oven temp 40°C, 0.8 mm) immediately prior to preparation of stock solutions.

2-(Aminomethyl)-4-chlorobenzenesulfonic Acid.[15] Chlorosulfonic acid (13 mL, 195 mmol) was combined with the amine hydrochloride of (1) (1.40 g, 7.9 mmol) and this was heated to 130 °C for 18 hours. The hot solution was then carefully pipetted over 70 g of ice. The resulting suspension was filtered to remove a small amount of tarry material, and the filtrate was heated in a water bath at 55 °C for one hour. During this time the desired compound precipitated from solution as a fine white flocculant, which was isolated by filtration and dried at 100 °C overnight to provide 0.93 g (53%) of the product: mp > 300 °C; IR (nujol) 3141, 3075, 1633, 1564, 1497, 1225, 1177, 1087, 1026 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 8.08 (bs, 3 H); 7.78 (d, 1 H, J = 8.2 Hz), 7.54 (d, 1 H, J = 1.6 Hz), 7.50 (dd, 1 H, J = 8.2 Hz, J = 1.6 Hz), 4.36-4.29 (m, 2 H). Anal. Calcd for $C_7H_8ClNO_3S$: C, 37.93; H, 3.64; Cl, 15.99; N, 6.32; S, 14.46. Found: C, 37.69; H, 3.56; Cl, 15.85; N, 6.25; S, 14.39.

Tetrabutylammoniun 2-(aminomethyl)-4-chlorobenzenesulfonate (4). A solution of tetrabutylammonium hydroxide was prepared by dilution of a 40%(w/w) aqueous solution with methanol in a volumetric flask. The solution was standardized by titration of benzoic acid solutions in 50%(v/v) aqueous methanol to a phenolphthalein endpoint. A volume of this solution containing one equivalent of base was added to the above sulfonic acid and the methanol was removed under reduced pressure. The resulting yellow glass was dried by lyophilization and stored under vacuum. IR (CH_2Cl_2) 3413, 3372, 3058, 2967, 2879, 1587, 1539, 1465, 1258, 1202, 1074, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.97 (d,1 H, J = 8.3 Hz), 7.29 (d, 1 H, J = 2.0 Hz), 7.16 (dd, 1 H, J = 8.3 Hz, J = 2.0 Hz), 4.20 (s, 2 H), 3.33-3.27 (m, 8 H), 1.71-1.60 (m, 8 H), 1.50-1.37 (m, 8 H), 1.00 (t, 12 H, J = 7.3).

Tetrabutylammonium Tosylate. One equivalent of 40% aqueous tetrabutylammonium hydroxide was added to 45 mL of a 0.24 M solution of p-toluenesulfonic acid (monohydrate) in methanol. The methanol was removed under vacuum leaving a clear glass which was taken up in 50 mL of methylene chloride, washed twice with 50 mL of water, dried with $MgSO_4$ and filtered. Removal of volatile materials from the filtrate afforded a clear glass which gave crystals on addition of about 5 mL of ethyl acetate. The crystals were isolated by filtration, washed with

cold ethyl acetate and dried under vacuum. Dissolution of the crystals in benzene and freeze-drying gave a white powder which was stored under vacuum (mp 70.5-72 °C).

Rate measurement Procedure. Stock solutions, prepared at 25 °C in volumetric glassware prior to kinetic runs, were sealed and stored in a dessicator containing calcium sulfate in the refrigerator. Before preparing for an experiment the dessicator and its contents were allowed to come to 25 °C. All the reagents required for a given experiment with the exception of the alkyne were transferred to an NMR tube using gas-tight syringes. It was assumed that any volume changes due to mixing were negligible. The tube was capped and equilibrated to temperature (21 °C) in the NMR magnet. An initial spectrum was acquired and the run was started by adding the alkyne. The volume added to initiate the reaction never exceeded 5% of the total reaction volume.

NMR spectra for kinetic runs were acquired on a Bruker AF300 Spectrometer at 21 °C. A program was used to obtain spectra at fixed intervals. Overall time for a given run ranged from 3 to 12 hours, and twenty to thirty spectra were recorded for each run.

Methylene chloride was used as an internal standard in the experiments. Its concentration in a given experiment was confirmed by integration relative to non-volatile components in the initial spectrum (before addition of the alkyne). The relative integrals of all unchanging components (the ratio of CH_2Cl_2 to tosylate, for example) remained constant throughout an experiment indicating that there was not appreciable evaporative loss during an experiment.

Determination of Rate Constants. In all experiments the reactions were followed by NMR by observing the disappearance of the benzylic signal of the starting amine or the appearance of the benzylic signal of the product. The initial products are of *E* configuration. These isomerize relatively slowly and not completely to give some amount of the Z-isomers. The Z isomer was included in the calculation of product concentration for the very slow reactions whenever it was detected. The benzylic signals of the products are as follows: *E*-**3**, δ 4.18 (d, J = 5.5 Hz); Z-**3**, δ 4.31 (d, J = 6.1Hz); *E*-**5**, δ 4.64 (d, J = 6.6 Hz); Z-**5**, δ 4.91 (d, J = 6.6 Hz). The data were fitted to canonical integrated rate equations to obtain rate constants.[27] Reactions of **4** were normally followed for >85% reaction. Reactions of **1** were usually followed for three half-lives, though some experiments at low salt concentration (slow reactions) were observed for two half-lives or less. Measurements of correlation (R^2) for individual runs were all better than 0.98 and were typically better than 0.99.

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References.

1. Westheimer, F. H. *Adv. Phys. Org. Chem.* **1985**, *21*, 1-35; Lipscomb, W. N. *Acc. Chem. Res.* **1982**, *15*, 232; Fersht, A. *Enzyme Structure and Mechanism*; Freeman: New York; **1985**.
2. Westheimer, F. H. *Ann. N.Y. Acad. Sci.* **1940**, *39*, 401; Breslow, R. *Science*, **1982**, *218*, 532.; D'Souza, V. T.; Bender, M. *Acc. Chem. Res.* **1987**, *20*, 146-152; Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York; **1969**.
3. 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.
4. Warshel, A. *Acc. Chem. Res.* **1981**, *14*, 284-290.;
5. Haberfield, P. In *Environmental Influences and Recognition in Enzyme Chemistry*; Liebman, J. F.; Greenberg, A., Ed.; VCH:New York, **1988**; pp. 109-137.
6. For a discussion, see Dahlberg, D. B.; Kuzemko, M. A.; Chiang, Y.; Kresge, A. J.; Powell, M. F. *J. Amer. Chem. Soc.* **1983**, *105*, 5387-5390.
7. Hughes, E. D.; Ingold, C. K.; Patai, S.; Pocker, Y. *J. Chem. Soc.* **1957**, 1206-1219.
8. Winstein, S.; Smith, S.; Darwish, D. *J. Amer. Chem. Soc.* **1959**, *81*, 5511. Winstein, S.; Friedrich, E. C.; Smith, S. *J. Amer. Chem. Soc.* **1964**, *86*, 305. Allred, E. L.; Winstein, S. *J. Amer. Chem. Soc.* **1967**, *89*, 4012.
9. Bateman, L.C.; Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1940**, 960.
10. Davies, C. W. *Ion Association*; Butterworths:London; **1962**.
11. Swain, C. G.; Pegues, E. E. *J. Amer. Chem. Soc.* **1958**, *80*, 812.
12. Perrin, C. L.; Pressing, J. *J. Amer. Chem. Soc.* **1971**, *93*, 5705.
13. A preliminary report of the results described here has recently appeared: Smith, P. J.; Wilcox, C. S. *J. Org. Chem.* **1990**, *55*, xxxx.
14. Giese, B.; Huisgen, R. *Tetrahedron Lett.* **1967**, 1889. Neuenschwander, M.; Bigler, P. *Helv. Chim. Acta* **1973**, *56*, 959.
15. Nitta, Y.; Shindo, M.; Takasu, T.; Isono, C. *Yakugaku Zasshi*, **1964**, *84*, 493. (*Chem. Abs.* **1965**, *61*, 8291.
16. Taft, R. W.; Price, E.; Fox, I. R.; Lewis, I. C.; Andersen, K. K.; Davis, G. T. *J. Amer. Chem. Soc.* **1963**, *85*, 709.
17. McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420.
18. Kollman, P.; Allen, L.C. *Chem. Rev.* **1972**, *72*, 283.
19. Vedani, A.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 7653.
20. (a) Gelin, B. R.; Karplus, M. *Biochem.* **1979**, *18*, 1256. (b) Weiner, P. K.; Kollman, P. A. *J. Comput. Chem.* **1981**, *2*, 287.
21. McIntosh, R. L.; Mead, D. J.; Fuoss, R. M. *J. Amer. Chem. Soc.* **1940**, *62*, 506.
22. (a) Begum, M. K.; Grunwald, E. *J. Amer. Chem. Soc.* **1990**, *112*, 5104. (b) Dominey, L. A.; Comeford,L.; Chen. S. J.-H.; Grunwald, E. *J. Phys. Chem.* **1987**, *91*, 2211-2216.
23. Evans, D. P.; Morgan, V. G.; Watson, H. B. *J. Chem. Soc.* **1935**, 1174-1178.
24. Hol, W. G. T.; van Duijnen, P. T.; Berendsen, H. J. C. *Nature*, **1978**, *273*, 443.
25. Van Duijnen, P. t.; Thole, B. T.; Broer, R.; Nieuwpoort, W. C. *Int. J. Quant. Chem.* **1980**, *17*, 651.
26. Graymore, J.; Davies, D. R.; *J. Chem. Soc.* **1945**, 293-4.
27. Capellos, C.; Bielski, B. *Kinetic Systems. Mathematical Description of Chemical Kinetics in Solution*; Wiley:New York; **1972**.