



# Advances in Physical Organic Chemistry

## Volume 27

*Edited by*

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# **Advances in Physical Organic Chemistry**

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## Preface

This series of volumes, established by Victor Gold in 1963, aims to bring before a wide readership among the chemical community substantial, authoritative and considered reviews of areas of chemistry in which quantitative methods are used in the study of the structures of organic compounds and their relation to physical and chemical properties.

Physical organic chemistry is to be viewed as a particular approach to scientific enquiry rather than a further intellectual specialization. Thus organic compounds are taken to include organometallic compounds, and relevant aspects of physical, theoretical, inorganic and biological chemistry are incorporated in reviews where appropriate. Contributors are encouraged to provide sufficient introductory material to permit non-specialists to appreciate fully current problems and the most recent advances.

Within the broad definition of physical organic chemistry adopted in this series, the subject of organic reactivity is one of central importance. In this volume, three contributions are concerned with the derivation of detailed information about transition-state structure and bonding from reactivity data by application of linear free energy correlations, particularly those associated with the names Brønsted and Hammett. It is hoped that the juxtaposition of these closely related but distinctive approaches will provide readers with a useful guide to available methodology. Complementary ways of studying transition-state structure should feature in a forthcoming volume. In the fourth contribution to Volume 27, the continuing question of the factors governing the partitioning of electrophiles between mixed nucleophilic solvents is addressed in the light of new results arising from the resurgent interest in quantitative aspects of nucleophilic substitution at saturated carbon.

The Editor would welcome feedback from readers. This might merely take the form of criticism. It might also contain suggestions of developing areas of chemistry that merit a forward-looking exposition or of the need for a new appraisal of better established topics that have escaped the notice of the Editor and his distinguished Advisory Board.

D. BETHELL

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# Effective Charge and Transition-state Structure in Solution

ANDREW WILLIAMS

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## 1 Introduction

### OBJECTIVES

For many years chemists have understood that the effects of polar substituents on rates and equilibria are caused by changes in charge at the reaction centre. The manifestation of these effects in terms of slopes of linear free energy relationships has always seemed false, and recent years have seen the development of the effective charge parameter  $\epsilon$ , which may be derived simply from Brønsted or Hammett slopes. Discussion of the electronic structure of the states of the reaction path is logically better suited to a charge idiom.

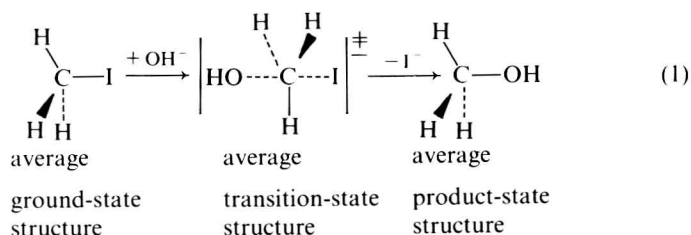
This review, while not comprehensive, aims to cover most aspects of the concept of effective charge in its application to reactions in solution. A case is not being pressed for the application of charge derived from polar effects as the *only* quantity whereby information is obtained about bonding; rather it is recognized that polar substituent effects on rates and equilibria in solution are far more easily and reliably obtained than are other data, and they constitute one of our most powerful mechanistic tools for studies of reactions in solution.

### ASSEMBLIES OF MOLECULES

Chemists still discuss chemical structure in terms of the “Kekulé” model where a molecule is regarded as consisting of a number of atoms disposed in fixed positions in space. Mechanisms are often discussed in terms of change from one Kekulé representation to another, as if atoms in an assembly of reactant molecules have exactly the same disposition relative to each other and these remain constant with time. Of course, individual molecules move relative to one another. The application of this model undoubtedly puts a restriction on our understanding of mechanism and acts as propaganda for a simplistic view of mechanism. An assembly of molecules does not behave as if each constituent were identical at a given instant, and reference to the results of X-ray crystallographic studies indicates that there is an uncertainty

that arises from thermal vibration (Ladd and Palmer, 1977) in the disposition of each atom in a molecule relative to its neighbours even in crystalline solids.

The Kekulé model has many advantages, despite its shortcomings. The method of representing a reaction path as if it were for a single molecule presents the problem that the intervening structures in even the simplest mechanism, for example the hydrolysis of methyl iodide (1), do not



correspond to real molecular entities; these structures have no existence comparable to that of a compound and they do not survive even for a time of about  $kT/h$  (the period of a half-vibration,  $10^{-13}$  s) (Kreevoy and Truhlar, 1986). Normal instrumental methods for determining structure are not applicable to transition states, which require observation times of less than  $10^{-13}$  s. An individual particle with a Kekulé structure at an energy maximum on the reaction path takes a longer time to equilibrate into another structure than it takes to decay to product or reactant. The transition-state concept was invoked to deal with this problem, and it turned out that the transition state could be treated as if it were an assembly of molecules (at an energy maximum) in equilibrium with the assembly of real molecules in ground and product states (Ross and Mazur, 1961). The Kekulé representation of the transition state involves full bonds, which are not significantly changed on reaction, and partial bonds for the bonding changes. Thus in (1) the C—H bond-length and bond-angle changes are only second-order effects compared with the bonding changes between carbon and the entering and leaving atoms.

It is important to reiterate these ideas, which indeed form part of the basic physical chemistry in undergraduate classes (Maskill, 1985), because the measurements we shall be considering are made on *assemblies* of molecules and of the intervening “structures” in the reaction pathway. Thus the representations of reactions normally made in mechanistic discussions are not directly related to the experiments, and it is important to remember this.

## MOLECULAR ORIGINS OF POLAR SUBSTITUENT EFFECTS

There are substantial changes in electrical charge on atoms in reacting bonds during a reaction. Development of charge implies that there is an energy change, so that any effect to neutralize charge will be relayed into an energy difference, resulting in a faster or slower rate (Hine, 1960). Thus substituents that withdraw electrons and hence "spread" charge will tend to make reactions go faster if there is a negative charge increase at the reacting bond from ground to transition state; this assumes that the polar substituent is located close enough on the molecule for the effect to be transmitted to the reaction site.

## QUANTITATIVE MEASURES OF POLAR EFFECTS

Polar substituent effects have been measured by a number of similar approaches [for example Hammett plots, Brønsted-type plots,<sup>1</sup> Taft plots and Charton plots, to name the most used (Williams, 1984a)]. None of these methods is intrinsically superior to the other, as each is based on the same principle. The criterion of use is that the standard reaction should resemble as closely as possible the reaction in hand so that there is not too great an extrapolation from known to unknown. Inspection of (2) indicates that, for



example, a Brønsted-type plot of the logarithm of the rate constant for reaction of phenolate ions with methyl iodide against the  $\text{p}K_{\text{a}}$ -value of the phenol is more appropriate than a Hammett plot, where the parameter is the unrelated ionization of a benzoic acid. The approach employed in a particular case is largely a matter of convenience given the above criterion, but it turns out that the Brønsted-type plot is generally more useful than is the Hammett family of plots.

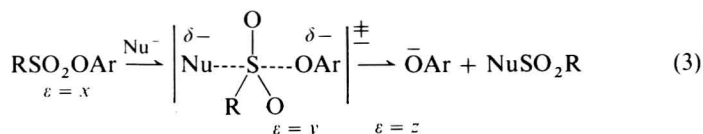
## ELECTRONIC CHARGE AND MECHANISM

Given the above assumptions, the polar substituent effect reveals information about change in charge or dipole moment at the reacting bond

<sup>1</sup> Strictly the Brønsted plot refers only to proton-transfer reactions, but there is an increasing use of the  $\text{p}K_{\text{a}}$  of the conjugate acid of a nucleophile for reactions of nucleophiles with species, and we shall refer to this type of plot as "Brønsted-type".

(Hine, 1960). If a particular atom is being considered then the polar substituent effect refers to change in charge on the atom from ground through transition to product state. The change in charge on a particular atom is probably the most fundamental result of a reaction; any method for studying charge change is therefore a very important method for demonstrating mechanism, and the polar substituent effect is one of the major tools for chemists interested in mechanism.

Charge change can be related to the extent of change in bonding in a transition state by suitable calibration. The best polar effect for calibration is that measuring the change in charge from *ground* to *product* states for the bonding change in question, and this reaction is termed the "calibrating" equilibrium. In (3) the charges on ground and product states are  $x$  and  $z$



respectively for the oxygen atom. The difference  $z - x$  represents the charge change in a full bond fission. The difference  $z - y$ , where  $y$  is the charge on the oxygen in the transition state, is the charge change from transition state to product state, and thus the "bonding" in the transition state can be defined as  $(z - y)/(z - x)$  of the total change. Trying to relate charge change, derived from polar effects on states, with Pauling-type bond order is not very useful. It is simplest to *define* bond order in the context of charge, and we shall defer to a little later the meaning of bond order under these conditions.

Other experimental approaches to bond order depend on energy measurements where means of regulating the energies other than by effects on charge are employed. Invariably these methods are experimentally much more demanding than polar substituent effect studies. They include steric effects (Taft's  $\delta$ ), pressure effects ( $\Delta V$ ), isotope effects (vibration), temperature effects (entropy) and stereochemistry. The stereochemical method, although not usually regarded as an energy method, involves comparisons of product ratios which thus reflect differing energies of particular reaction paths as affected by molecular chirality. In order for these various approaches to be applied quantitatively, some calibration process is required so that energy changes to the transition state from ground state can be compared with that for a bonding change between two known states; a recent study with heavy atom secondary isotope effects underlines the requirement of the proper calibration process (Hengge and Cleland, 1990).

## DOES THE POLAR EFFECT MEASURE CHANGE IN BOND ORDER?

It is perfectly true to say that in solution chemistry no experimental method gives the bond order of an isolated bond in ground, transition or product states. The transition state is an assembly of unstable structures, each with an average lifetime less than that of a vibration. It might be considered that, since the molecule does not exist in the transition state for more than  $10^{-13}$  s, there will be no time for the solvent to redistribute and thus one should not be able to assume that the solvating groups are in equilibrium in ground and transition state. Since the solvent is part of the state, solvation must behave as if it were in equilibrium in transition and ground and product states (Kreevoy and Truhlar, 1986). In other words, the transition state refers to the *whole* system and not just to the isolated molecule undergoing reaction.

It is important to emphasize that the index of bonding refers to *states* and not to Kekulé *bonds*. There is an unfortunate neglect of solvent in discussing reaction mechanisms of solution reactions (or reactions in the liquid phase), which are documented as if they were carried out in the gas phase.<sup>2</sup> Confusion arises as to the applicability of polar substituent effects in estimating bonding. Polar substituent effects estimate charge or dipole-moment change that is the result of both bonding *and* solvation changes. It is also more correct (this applies to all methods) to discuss states rather than bonds, and the shorthand approach to graphics neglects this. Kinetic isotope effects are dependent on the solvent (Keller and Yankwich, 1973, 1974; Williams and Taylor, 1973, 1974; Burton *et al.*, 1977), and it is probable that strong solvation of the isotopically substituted atom will make a substantial contribution. In practice, however, only the effects of the first solvation shell need be considered. The stereochemistry of a reaction also is dependent on the solvent, as is manifest from Cram's classic text (Cram, 1965).

## 2 Effective charge

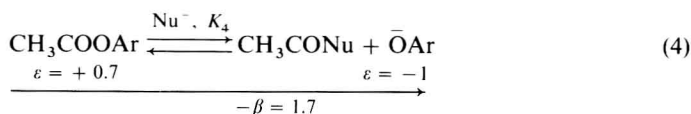
### EQUILIBRIA

Change in effective charge  $\Delta\epsilon$  on an atom in a reaction centre is formally defined as a quantity obtained by comparison of the polar effect on the free

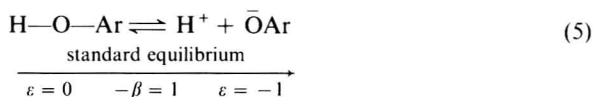
<sup>2</sup> Descriptions of mechanism in *this* article are couched in a language devised for structural studies (naturally) and can therefore be misleading if the assumptions are forgotten. For convenience, and following precedent, solvent is often omitted from descriptions of state in this text; moreover the term "bonding change" is invariably used to mean the summation of change in bonding (in its literal sense) and solvation.

energies of rate or equilibrium processes with that on a standard ionization equilibrium (Jencks, 1971; McGowan, 1948, 1960; Williams, 1984b; Thea and Williams, 1986). Thus the value of Brønsted's  $\beta$  is an effective charge change where the standard ionization equilibrium has a defined change in effective charge of unity. The absolute effective charge may be obtained from  $\Delta\epsilon$  by defining its value for one of the states in the standard equilibrium.

Let us consider the simple reaction (4) of a nucleophile with aryl acetates.

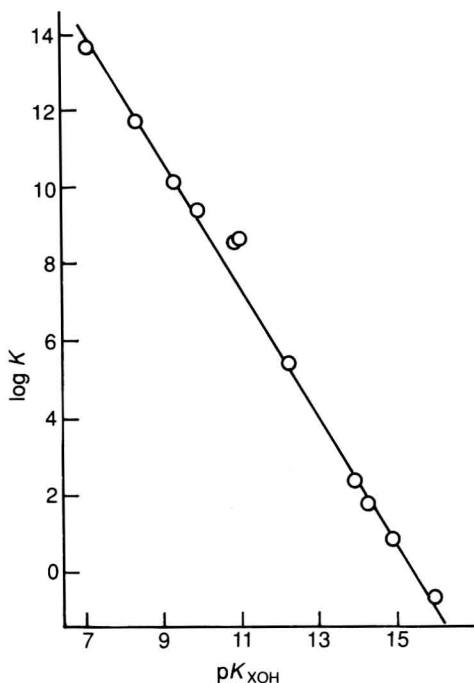


The equilibrium constant for this reaction of hydroxide ion may be plotted as a Brønsted plot against  $\text{p}K_a$  for the appropriate phenol (Fig. 1). The slope of the linear Brønsted-type plot is  $-1.7$  (Ba-Saif *et al.*, 1987); qualitatively this indicates that there is a larger charge change on the aryl oxygen than in the ionization of the phenol (5). The substituent "sees" charge change that



can be defined in terms of that occurring on the oxygen atom in the ionization of the phenol. Thus, if the charges on the oxygen in the phenolate ion and phenol are defined as  $-1$  and  $0$  respectively, the charge change on the corresponding oxygen in the ester reaction is  $-1.7$ . Simple arithmetic shows that there must be  $+0.7$  units of "effective" charge on the oxygen in the ester in the ground state. The charge derived in this way is designated "effective" charge because it is measured against a *defined* standard charge change. The real electronic charges on the oxygen in (5) are certainly not integral because of solvation and of charge removal from the oxygen by its neighbouring atoms. Linearity of the Brønsted line indicates that to a first approximation the charge on the oxygen is not altered by the substituent, at least over the ranges of  $\text{p}K_a$  normally studied. The location of effective charge depends entirely on the standard equilibrium employed and the definition of effective charge therein. The ionization of any acidic species formally places charge change on the atom undergoing proton removal (Williams, 1984b). The polar effect measures charge change at the reaction centre, which will derive mainly from solvation and bonding differences between the measured states.





**Fig. 1** Brønsted dependence of equilibrium constants for reaction of acetate esters with hydroxide ion in aqueous solution. Data from Gerstein and Jencks (1964); the product state is oxyanion and acetic acid and the hydroxy species range from phenols to alcohols.

Little work has been done to correlate effective charges with charge determined by other physical methods because there is little in the way of comparable data. The most obvious comparison is with electronic charge distributions obtained by quantum mechanical calculations (see, for example, Pople and Beveridge, 1970; Dewar, 1969); these calculations refer to isolated molecules and there are as yet no reliable calculations for states, in particular in solution, where molecules will be interacting with each other. The most obvious methods for charge measurement, namely  $^{13}\text{C}$  nmr and esr spectroscopy, are only for ground or product states, and the data refer to the solvated species; the field awaits comparative work.

#### MEASUREMENT OF EFFECTIVE CHARGE IN EQUILIBRIA

The kinetic approach offers the best approach for measuring effective charge. Explicit measurements of equilibrium constants over ranges of