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A SEARCH FOR A β EFFECT: THE NUCLEOPHILICITY OF THE METHYLENE GLYCOLATE ANION

SHMARYAHU HOZ and DVORA HALTOVSKY
Department of Chemistry, Bar-Ilan University, Ramat-Gan, Israel

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Abstract—The possible existence of a β-effect (effect of a lone pair of electrons located at a β position of a nucleophile) was investigated by reacting methylene glycolate anion with *p*-nitrophenyl acetate, 2,4-dinitro-fluorobenzene and 2,4-dinitrochlorobenzene in water. For these reactions, no enhanced nucleophile reactivity was found. An upper limit of 2.5 was found for the nucleophilicity n of methylene glycolate on the Swain-Scott scale and 6.2±0.2 on Ritchie's N_+ scale.

Lone pair-lone pair interactions play an extremely important role in determining the stereochemistry of many molecules. When the lone pairs are located α to each other, these interactions dictate the most stable conformation as well as the rotational barrier about the central bond in molecules such as hydrogen peroxide, hydrazine, hydroxylamine etc.[1] When located β to each other, various stereochemical features are induced. For example, in pyranose rings, contrary to expectations based on 1,3 diaxial interactions, there is a clear preference for axial over equatorial positioning of C_1 electronegative substituents.[2] This same type of interaction is also responsible for the chiral structure of polyoxymethylene,[3] the preference of certain conformations in substituted 1,3 diazanes and related molecules[4] etc. These phenomena were given the names "Anomeric effect", "Edward-Lemieux effect", "Gauche effect" and the "Rabbit ear effect". In spite of the multitude of names given, all these phenomena probably have a common origin. Although most can be explained on the basis of repulsion of unshared electron pairs,[5] current theories based on semi-empirical and *ab initio* calculations, point to lone pair-polar bond and polar bond-polar bond interactions as the major cause for these phenomena.[1,4,6]

The energy associated with these 1,3 interactions appears generally to be on the order of 0.5–3 Kcal/mol.[7]

While the study of the kinetic effect of a lone pair at an α position of a nucleophile on its nucleophilicity has attracted the attention of many chemists revealing the enhanced nucleophilicity of the so-called α-nucleophiles,[8a] and while some studies were also reported for other α–ω interactions,[8b] the theoretical and thermodynamical studies of the 1,3-interactions (whether they be lone pair-lone pair, lone pair-polar bond or polar bond-polar bond interactions), were not accompanied by analogous kinetic studies. This is probably due to the fact that aliphatic acyclic β-nucleophile (termed analogously to α-nucleophile) such as H_2NCHO^-, $ClCH_2O^-$, FCH_2NH_2, $CH_2(NH_2)_2$ etc. appear mainly as unstable intermediates which undergo very fast decompositions.

In 1948 Bruson and Riener reported the exothermic formation of methoxy-methoxy-propionitrile ($CH_3OCH_2OCH_2CH_2CN$) when potassium hydroxide is added to a mixture of formaldehyde, methanol and acrylonitrile at ordinary temperatures.[9] This undoubtedly involves the production of methyl hemiformal anion ($CH_3OCH_2O^-$), which is a β-nucleophile, as a reaction intermediate. A similar result was also reported for the reaction with methyl acrylate.[10] Encouraged by the observations that β-nucleophiles compete successfully with the other nucleophiles present in the solution, we investigated the possible existence of a β-effect in nucleophilic reactions.

The simplest nucleophile which can be defined as a β nucleophile is the anion of methylene glycol (MG^-). This anion is readily obtained by dissolving formaldehyde in basic aqueous solution. Since practically nothing is known about its nucleophilicity, we also report data establishing its location on Swain-Scott and Ritchie nucleophilicity scales.

RESULTS AND DISCUSSION

General. In aqueous solutions, formaldehyde exists as the monohydrate–$CH_2(OH)_2$ and as a series of low molecular weight polymeric hydrates. (The concentration of the unhydrated monomeric formaldehyde is well under 0.1 per cent even in concentrated solutions). Low formaldehyde concentration favours methylene glycol while high concentrations favours the polyoxymethylene glycols.[11]

Nucleophilic attack of MG^- on an electrophilic center (E) results in a hemiformal ($E'OH_2OH$) formation (eqn. 1) which is in equilibrium with the corresponding alcohol and methylene glycol (eqn. 2). The hemiformal formation might occur in a single reaction step as in S_N2 reactions or via a tetrahedral intermediate, depending on the nature of the substrate E.

$$HOCH_2O^- + E \rightarrow E'OCH_2OH \qquad (1)$$

$$E'OCH_2OH \underset{}{\overset{H_2O}{\rightleftharpoons}} E'OH + CH_2(OH)_2 \qquad (2)$$

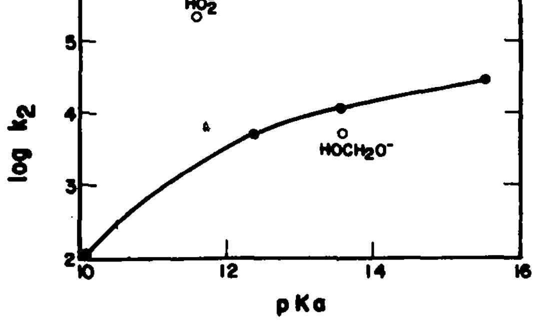
Basic conditions catalyze the rate at which equilibrium is attained in reaction 2. For the reactions reported here, this equilibrium lies to the far right of equation 2.

The pKa of methylene glycol was conductometrically determined by Bell *et al.* in water at 25°C to be 13.27[12] and should be statistically corrected to 13.57 for its use in Bronsted type correlation.

The reactions studied are first order in the substrate and first order in the catalytic MG^-. The pH remained constant during the reaction times.

Reactions of MG^- with p-nitrophenyl acetate (PNPA). The reactivity of nucleophilic reagents towards PNPA has been thoroughly studied.[13] Strongly basic oxygen anions show only a slight increase in reactivity with increasing basicity and thus deviate from the Bronsted relationship (slope 0.76–0.80) observed with less basic oxygen anions.[14] The levelling off of the Bronsted plot commences with nucleophiles having a pKa around 11. In this region of basicity, nucleophilic attack on the carbonyl function is the rate limiting step. As the pKa of methylene glycol is 13.57 its reaction rate constant with PNPA is a direct measure of its nucleophilicty toward the substrate. The small slope of the Bronsted line (*ca.* 0.3 above pKa 11) affords an additional advantage since at a larger slope a relatively small erroneous change in the nucleophile's pKa determination might result in an artificially amplified deviation from the plot.

The reactions of MG^- with PNPA were conducted in aqueous solutions at 25°C with a borax buffer (pH 8). In order to enable the use of the Bronsted line reported by Jencks for our study, it was necessary to anchor our results to his scale. For this purpose the rate constants of the reaction of trifluoroethoxide with PNPA under our reaction conditions were determined. The value obtained is in reasonable agreement with the value 3850 M^{-1} min^{-1} reported by Jencks.[14] Interpolation of Jencks' data to a pKa of 13.57 results in a predicted log k of 4.04 for ther reaction of MG^- with PNPA. The experimentally determined value of 3.73 reveals a negative deviation of 0.3 log units (see Figure). It should be noted that the α-effect nucleophile HO_2^-, exhibits a positive deviation of two log units for the same reaction under the same conditions.



Logarithmic plot of rate constants for the reactions of anionic oxygen nucleophiles with PNPA against the basicity of the nucleophiles.

Table 1. Second order rate constants for nucleophilic attacks on PNPA, DNFB and DNCB in water at 25°C. Formaldehyde concentrations ranged between 0.01 and 1.5 M.

Substrate	Nucleophile	pH	k_2 M^{-1} min^{-1}
PNPA	MG^-	8[a]	5360
PNPA	$CF_3CH_2O^-$	8[a]	4250
DNFB	MG^-	10[a]	75
DNFB	OH^-	10[a]	8.9
DNCB	MG^-	12[b]	0.135
DNCB	OH^-	12[b]	$8.6 \cdot 10^{-3}$

[a] 0.04 M Borax buffer.
[b] 0.04 phosphate buffer.

Reactions of MG^- with 2,4-dinitrochlorobenzene and 2,4-dinitrofluorobenzene. The reaction of nucleophiles with dinitrohalobenzenes has been subjected to numerous studies and its mechanism with oxyanions is well defined.[15] The reaction of MG^- with 2,4-dinitrochloro-(DNCB) and 2,4-dinitrofluorobenzene (DNFB) in water at 25°C was studied. The reactions were followed spectrophotometrically at the λ_{max} of the liberated phenoxide. As evidenced from a control experiment in which formaldehyde was added to a phenoxide solution and no change in the solution absorbance was observed, there is practically no interaction between formaldehyde and the phenoxide, namely, the equilibrium of eqn. 2 where E' = 2,4-dinitrobenzene, lies far to the right. The second order reaction rate constants are given in the table.

For the reactions with DNFB, a plot of k_1 *vs.* the concentration of formaldehyde is linear up to 0.5 M formaldehyde where the reaction order in formaldehyde gradually decreases. (The k_2 value depicted in the table was taken from the linear portion of the graph). Since this behaviour has not been observed either with PNPA or with DNCB, it is reasonable to assume that the DNFB activity coefficient is reduced by specific interaction with methylene glycol or its higher homologues.[16]

The element effect $k_F/k_{Cl} = 555$ clearly indicates that the rate limiting step is the nucleophilic attack on the aromatic substrate.[15]

For comparison with literature data, we have also measured the reaction rate constants for OH^- attack on these two aryl halides. The results obtained (see table) are in agreement with those of Bunton,[17] Murto[18] and Ritchie[19] for DNFB (7.2, 7.7 and 7.2 M^{-1} min^{-1}, respectively) and for DNCB ($8.5 \cdot 10^{-3}$, $1.11 \cdot 10^{-2}$, $7.4 \cdot 10^{-3}$ M^{-1} min^{-1}, respectively). A Bronsted correlation for alkoxide attack on DNFB under similar conditions was reported by Murto.[20] By using this correlation (eqn. 3) we find that MG^- negatively deviates from the Bronsted line by ca. 0.25 log units.

$$\log k = 0.215\,\mathrm{pKa} - 2.564 \qquad (3)$$

Another commonly used criterion for the existence of the α-effect in nucleophilic reactions with 2,4-dinitrohalobenzenes is the ratio $k_{\alpha\text{-nucleophile}}/k_{OH^-}$. For the reaction of DNCB with HO_2^- the following ratios were reported: 600,[21] 1860[19] and 7.8×10^4.[22] Values of 550[19] and 4.5×10^4 [22] were reported for the analogous reaction with DNFB. These are to be compared with values of 16 and 8.4 found for k_{MG^-}/k_{OH^-} in the reactions with DNCB and DNFB respectively. It should be noted that this criterion is somewhat unreliable since it is known that hydroxide ion exhibits an exceptionally low reactivity in aromatic nucleophilic substitution.[23]

Nucleophilic parameters. In order to quantitatively describe the nucleophilicity of MG^-, it was reacted with methyl bromide under the same conditions used by Swain and Scott for establishing their nucleophilic reactivity scale.[24] It was found that the presence of formaldehyde in concentrations as high as 1.5 M did not alter the rate of release of Br^-. Assuming an error of 5% in rate determination and the absence of any side reactions, the upper limit for the nucleophilicity parameter n of MG^- is 2.5.

For reactions in which nucleophilic attack is not accompanied by expulsion of a nucleofuge, the two parameter Swain-Scott equation is replaced by a single paramter equation $\log k/k_0 = N_+$ introduced by Ritchie.[25] In this equation k and k_0 are rate constants for nucleophile and water attack on the substrate, and N_+ is the nucleophilic parameter of the nucleophile. Although it was shown that in some cases the equation must be modified by a selectivity parameter S_+,[26,27] it was recently shown that for nucleophilic attacks on esters[28] and 2,4-dinitrohalobenzenes[19] $S_+ = 1$.

For reactions with esters, the overall kinetic equation is $\log k_{obs} = \log k_0 + N_+ - \log(1 + k_{-x}/k_{-y})$ where k_0 is the rate constant for the reaction of water with the substrate, k_{-x} and k_{-y} are rate constants for the decomposition of the tetrahedral intermediate in the reverse and forward directions respectively. Since it is assumed that the reaction of MG^- with PNPA is essentially irreversible, the last term in the equation is negligible. The $MG^-(H_2O)N_+$ value calculated in this manner is 6.4. The N_+ value can also be evaluated from the reactions of MG^- with DNFB and DNCB in water. The good agreement between results obtained in this laboratory and those reported by Ritchie[19] for reaction rate constants of OH^- with DNFB and DNCB, (8.9 and $8.6\cdot10^{-3}$ compared to 7.2 and $7.4\cdot10^{-3}\ M^{-1}\,min^{-1}$ respectively) permits the use of Ritchie's data for the $MG^-(H_2O)\ N_+$ determination. Two N_+ values are obtained: 6.2 from the data of DNFB and 6.0 from the DNCB reactions. The three N_+ values which were independently obtained average to 6.2 ± 0.2. The close agreement among these three values reinforces the assumption made about the identity of the rate limiting step in these reactions.

CONCLUSIONS

Analysis of the data reported here indicates that unlike lone pair-lone pair 1,2 interactions, the 1,3 interactions do not manifest themselves in enhancing the rate of nucleophilic reactions. The superiority of the β-nucleophiles as demonstrated by the example cited in the introduction, probably results from the fact that in these cases they were allowed to compete with the lyate ions for the substrates. Since lyate ions are notorious for their sluggishness in many reactions,[29] the apparent enhanced reactivity of the β-nucleophiles in these cases might be explained as a result of the choice of the reference reactions.

Jencks has shown that formaldehyde electrophilically catalyses the hydrolysis of phosphoramidate.[30] The results reported here point toward the possible use of formaldehyde in aqueous solution as a nucleophilic catalyst for synthetic purposes.

EXPERIMENTAL

Aqueous solutions of formaldehyde were obtained by pyrolysis of paraformaldehyde (Chemorad) into a water filled receiver. Formaldehyde concentration was determined by the bisulfite method.[31] Solution pH was measured before and occasionally after the kinetic runs. A Digital pH meter (PHM 52 Radiometer) with a multipurpose glass electrode was used for the pH determination. The kinetics of PNPA and 2,4-dinitrohalobenzenes were followed spectrophotometrically (Gilford 2400 single beam spectrophotometer) at the λ_{max} of the liberated aryloxides according to published procedures.[14,17a] Reaction rate constants of MG^- with methyl bromide were measured according to the original Swain-Scott procedure.[23]

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