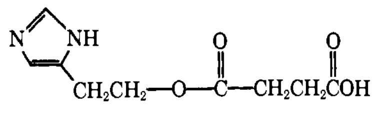
general acid, general base or nucleophilic, general acid catalysis of the hydrolysis of esters in water. (This statement applies to models employing two separate potential catalytic functional groups.) This result is in accord with previous searches for intramolecular bifunctional catalysis: thus, Koshland could find no evidence for concerted catalysis by imidazolyl and carboxyl groups in the hydrolysis of ester **24**,[57] and Coward and Bruice[58] could find no evidence for intramolecular concerted general acid, general base catalysis by tertiary amino groups in the enolization of ketones. Thus, the many postulated mechanisms for enzyme mediated reactions embodying a push-pull mechanism await experimental confirmation that such a mechanism is actually possible.



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Acknowledgment. This work was supported by grants from the National Institutes of Health and the National Science Foundation.

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[57] D. E. Koshland, Jr., *J. Cellular Comp. Physiol.*, 47 (1), 245 (1959); *J. Theoret. Biol.*, 2, 75 (1962).

[58] J. K. Coward and T. C. Bruice, *J. Amer. Chem. Soc.*, **91**, 5339 (1969).

α Effects. III. The Reaction of Malachite Green with Primary Amines, Methoxylamine, and Hydrazines

J. Edward Dixon[1] and Thomas C. Bruice*[1]

Contribution from the Department of Chemistry,
University of California at Santa Barbara, Santa Barbara, California 93106.
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Abstract: The rate and equilibrium constants associated with the addition of hydrazine, methylhydrazine, and methoxylamine (all possessing a pair of unshared α electrons) to malachite green are larger than are corresponding rate and equilibrium constants for primary amines of similar pK_a'. It may be concluded for this reaction that the α effect results in great part from a product of greater stability than predicted from the pK_a' for amines. For the "more stable product" to transmit its stability to the transition state (kinetic α effect) it is essential that a large amount of bond formation has occurred in the critical transition state. Therefore, reactions exhibiting large Brønsted β values exhibit the α effect, whereas those with small β values, where the transition state resembles reactants rather than products, generally do not. The Brønsted β values for the reaction of amines and hydrazines with malachite green are identical at 0.4. Plots of $\Delta F^{\ddagger}$ *vs.* ΔF^0 afford the linear free energy relationship, $\Delta\Delta F^{\ddagger}/\Delta\Delta F^0 = 1.0$. Thus all changes in ΔF^0 are reflected quantitatively in a concomitant change in $\Delta F^{\ddagger}$. However, since ΔF^0 values are close to zero and the Brønsted $\beta \cong 0.4$, so that the transition state must reside *ca.* midway between reactants and products, it would appear as though factors in addition to product stability account for a portion of the kinetic α effect. The possibility that solvent effects or intramolecular general base catalysis are the source of the α effect is ruled out by consideration of activation parameters. Polarizability seems to be of little or no importance in accounting for the hyperreactivity of hydrazines in nucleophilic substitution on dinitrohalobenzenes.

The term α effect[3] has been used to denote the high reactivity of nucleophiles possessing an unshared pair of electrons adjacent (α) to the nucleophilic atom. This phenomenon was probably first placed on a firm experimental footing by Epstein, Demek, and Rosenblatt in their investigations of nucleophilic attack upon phosphonates.[4] Nucleophiles exhibiting the α effect include hydrazines, hydroxylamine, hydroperoxide anions, oxime anions, hypochloride ion, etc. The mechanism by which the α electrons can influence the rate of reaction has been discussed, but it cannot be said that it is understood.[3] Substrates which are susceptible to the α effect include activated esters,[5] tetrahedral phosphorus,[6] etc.[7]

The majority of previous investigations deals solely with the determination of rate constants. In the present study we sought a system that did not involve metastable intermediates and would provide: (a) rate constants, (b) equilibrium constants, and (c) Brønsted β constants. Our objective has been to determine the relationship of the decreased $\Delta F^{\ddagger}$ associated with the α effect to ground state free energies and to the position of the transition state along the reaction coordinate. Such a system has been found in the reaction of malachite green (A) with a number of amines and hydrazines (*i.e.*, eq 1). The choice of amine addition to

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[1] A portion of the material to be submitted by J. E. D. in fulfillment of the requirement for the Ph.D. in Chemistry, University of California at Santa Barbara.

[2] To whom inquiries should be addressed.

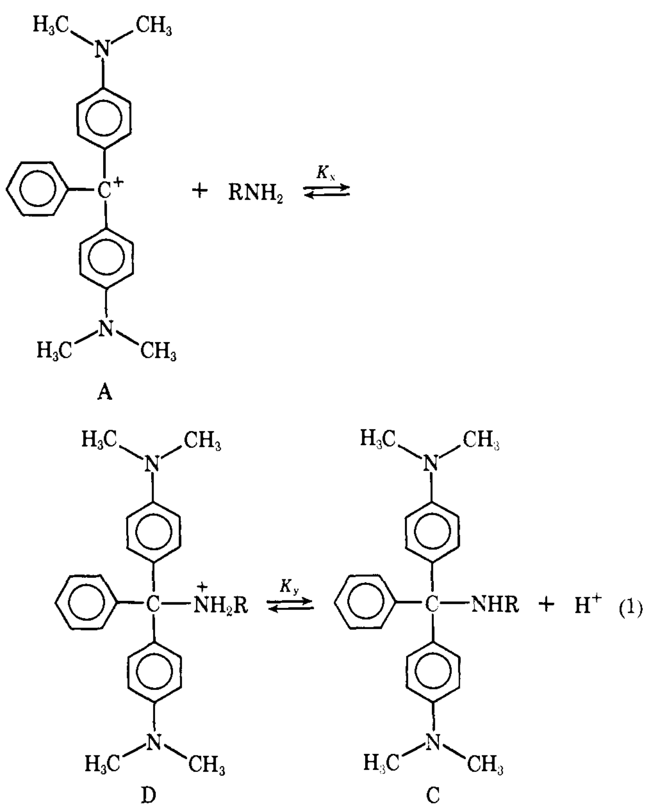
[3] J. O. Edwards and R. G. Pearson, *J. Amer. Chem. Soc.*, **84**, 16 (1962).

[4] J. Epstein, M. M. Demek, and D. H. Rosenblatt, *J. Org. Chem.*, **21**, 796 (1956).

[5] (a) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Amer. Chem. Soc.*, **89**, 2106 (1967); (b) W. P. Jencks and J. Carriuolo, *ibid.*, **82**, 1778 (1960).

[6] A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1583 (1958).

[7] D. L. Ball and J. O. Edwards, *J. Amer. Chem. Soc.*, **78**, 1125 (1956); K. B. Wiberg, *ibid.*, 77, 2519 (1955); C. A. Bunton and C. J. Minkoff, *J. Chem. Soc.*, 665 (1949); H. O. House and R. S. Ro, *J. Amer. Chem. Soc.*, **80**, 2428 (1958); R. P. Bell, *J. Phys. Chem.*, **55**, 885 (1951).



malachite green was predicated on the reports of reversible reactions with both HO^- and N_3^-.[8]

To assess the importance of polarizability as a contributing factor to the α effect, the reaction of amines and hydrazines with 1-halo-2,4-dinitrobenzenes was also investigated.

Experimental Section

Materials. Glycylglycine (Aldrich) and the hydrochlorides of glycine ethyl ester (Eastman), 2,2,2-trifluoroethylamine (Pierce), ethylamine (Matheson Coleman and Bell), ethylenediamine (Eastman), methoxylamine (Eastman), hydrazine (City Chemical Co.), methylhydrazine (Matheson Coleman and Bell), and phenylhydrazine (Allied Chemical) were recrystallized from ethanol–water mixtures and dried *in vacuo* over phosphorus pentoxide. Glycine (Fisher reagent), semicarbazide hydrochloride (Puriss, Aldrich), malachite green (Matheson Coleman and Bell), 2,4-dinitrofluorobenzene (2,4-DNFB) (Aldrich), 2,4-dinitrochlorobenzene (2,4-DNClB) (K & K), and 2,4-dinitroiodobenzene (2,4-DNIB) (Pfaltz and Bauer) required no further purification.

Apparatus. Kinetic measurements were made with a Gilford Model 2000, Zeiss PMQ II, or the Cary 15 spectrophotometer. The Zeiss was equipped with a thermostated brass cuvette holder and the Gilford with dual thermospacers through which water circulated at the appropriate temperature. The Cary Model 15 was equipped with a thermostated polyethylene cell with quartz windows. The pH of the cell could be monitored continuously as optical density measurements were recorded. The solutions were stirred magnetically.[9]

The pH of a kinetic solution was determined both prior to and at the completion of the reaction, using a Radiometer Model 22 pH meter with a PHA 630 scale expander, and a combined glass calomel electrode (Radiometer GK 2021 C) thermostated at 30 ± 0.1°.

All calculations of rate or equilibrium constants were performed on either an Olivetti Underwood Programma 101 or a Hewlett Packard 9100 A calculator using a least squares fit of points in plots of k_{obsd} *vs.* B_T. A micropipet (Eppendorf) was used to deliver stock solutions in both rate and equilibrium studies.

Kinetics.[10] The rate of disappearance of malachite green with all amines, hydrazines, and hydroxide was followed at 625 or 620 nm. The rate of appearance of the corresponding amines and hydrazine products, resulting from the reaction of 2,4-dinitrofluorobenzene or 2,4-dinitroiodobenzene, was followed near 365 nm. In the case of 2,4-dinitrochlorobenzene, the rates were followed at 345 nm. All reactions were carried out in standard taper cuvettes. Glass-redistilled water was used to prepare all solutions, and serial dilutions were made with 1.0 *M* potassium chloride so that the ionic strength of all solutions was maintained at 1.0 *M*. Stock solutions of malachite green were prepared in acetonitrile; a reaction was initiated by the addition of 10 μl of the stock solution to *ca.* 3 ml of buffer, giving a solution approximately 5×10^{-6} *M* in dye. The concentration of nucleophile was always in large excess over that of malachite green, reactions were followed to completion, and rate constants were calculated from plots of log $(OD_\infty - OD_t)$ *vs.* time. All amines and hydrazines (except ethylamine and ethylenediamine) were used as free bases, and hydroxide functioned as a buffer at pH's near 11.0. When either 2,4-DNFB, 2,4-DNClB, or 2,4-DNIB were used as a substrate (approximately 10^{-3} or 10^{-4} *M*) excess amine or hydrazine served as both buffer and nucleophile. All reactions were thermostated at 30° ± 0.1.

It is noteworthy that phenylhydrazine hydrochloride undergoes oxidation upon neutralization, *i.e.*, a yellow color appears whose absorbance is proportional to the concentration of free phenylhydrazine. All possible precautions to prevent this oxidation met with no success. Therefore the rate constant reported for phenylhydrazine is obtained in the presence of this unknown yellow impurity. Solutions of phenylhydrazine were made up fresh and all rates were run within 10 min of nuetralization.

Reactions carried out at 7, 14.8, 23.8, and 38.4° were run in a manner similar to that described above. Nitrogen was passed through the cell housing of the spectrophotometer to prevent moisture formation on the cell surface at 7 and 14.8°. For all kinetic runs at temperatures other than 30°, the temperature was taken in the cell itself using Anschutz thermometers. Temperature control was approximately ±0.10°. No temperature variations were noted.

Equilibrium Determinations with Malachite Green. The general approach was to have the amine or hydrazine equilibrate with malachite green very rapidly so that the slower reaction with either water or hydroxide could be neglected. For the equilibrium determinations, a constant total buffer concentration was maintained while the pH was varied. Plots of the absorbance proportional to [malachite green] *vs.* pH are shown in Figure 3. From eq 12 (see Appendix), equilibrium constants K_x and K_y are obtained by plots of $(A_T - A)/Q$ against a_H, where Q is a collection of constants. This procedure was possible only for amines or hydrazines of high pK_a' (generally p$K_a > 7$). With amines or hydrazines of lower pK_a' either equilibrium was obtained very slowly or salting out of the dye resulted at the necessary concentrations of buffer. The equilibrium constant reported for methoxylamine is only an approximate value based upon several determinations well above the pK_a' of the buffer, probably introducing considerable error in its determination. Equilibrium constants are not reported for semicarbazide or trifluoroethylamine because of the salting out problem. The equilibrium constant is not reported for phenylhydrazine due to the oxidation problem discussed earlier. A typical equilibrium experiment was carried out as follows: exactly 3 ml of buffer at a given pH was placed in a cuvette and allowed to equilibrate at 30° for 15 min; malachite green was added; the solution was mixed and then allowed to stand for a short period of time, and its absorbance was recorded. The absorbance of the same concentration of malachite green was also recorded in the absence of buffer. The total concentration of malachite green never exceeded 5×10^{-6} *M*; that of the buffer was generally below 0.1 *M*. This procedure was repeated at various pH's at constant buffer concentration.

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[8] C. Ritchie, G. A. Skinner, and V. G. Badding, *J. Amer. Chem. Soc.*, **89**, 2063 (1967).

[9] J. R. Maley and T. C. Bruice, *Anal. Biochem.*, **34**, 275 (1970).

[10] The following abbreviations are used throughout this paper and, although some are in common use, a definition of each has been included for completeness: $[B_T]$ = total concentration of buffer; $[B_f]$ = concentration of free buffer (*i.e.*, amines or hydrazine); $[B_H]$ = concentration of conjugate acid of buffer; μ = ionic strength; pK_a' = the pK_a taken under the conditions employed; $\Delta T\Delta S^{\ddagger} = \Delta TS^{\ddagger} - \Delta TS^{\ddagger}$ differences between entropy of activation; $\Delta\Delta F^{\ddagger} = \Delta F^{\ddagger} - \Delta F^{\ddagger}$ differences in free energy of activation; $\Delta\Delta F^0 = \Delta F^0 - \Delta F^0$ differences in standard free energy.

Table I. Equilibrium and Rate Constants for the Reactions of Nucleophiles with Malachite Green

Nucleophile	k_1, M^{-1} min^{-1}	pK_a	No. of k_{obsd}	Concn range for rate of reaction	K_x, M^{-1}	K_y, M	k_{-1}, min^{-1}
Ethylamine	950	10.69[a]	10	0.001–0.050	14.3	9.67×10^{-10}	66
Glycine	514	9.63[a]	12	0.050–0.0020	3.0	7.72×10^{-9}	172
$CF_3CH_2NH_2$	8.69	5.63[b]	12	0.050–0.80			
Methylhydrazine[f]	1950	8.14	5	0.01–0.03	9.9	1.64×10^{-8}	197
Semicarbazide	36.2	3.25[b]	15	0.03–0.05			
Methoxylamine	72.4	4.81[a]	15	0.01–0.10	2.7		
Glycylglycine	133.3	8.25[c]	10	0.01–0.001	0.60	3.29×10^{-8}	222
Glycine ethyl ester	56.0	7.75[a]	15	0.05–0.50	0.26	5.06×10^{-8}	215
Hydrazine	3750	8.11[a]	15	0.005–0.0005	21.3	2.5×10^{-7}	178
Phenylhydrazine[f]	390	5.27[d]	13	0.010–0.001			
Ethylenediamine	1060	10.10[a]	5	0.003–0.007			

[a] M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 4400 (1967). [b] Reference 5a. [c] T. C. Bruice, J. J. Bruno, and W. S. Chou, *J. Amer. Chem. Soc.*, **85**, 1659 (1963). [d] H. H. Stroh and G. Westphal, *Chem. Ber.*, **96**, 184 (1963). [e] M. Caplow, *J. Amer. Chem. Soc.*, **90**, 6795 (1968). [f] See Experimental Section.

Results

The rate constants for attack of hydroxide and water ($T = 30°$, $\mu = 1.0$) on malachite green were found to be 1.23 M^{-1} sec^{-1} and 3.8×10^{-4} sec^{-1}, respectively. Rate constants (25°) of 1.59,[11] 1.36,[12] and 2.18 M^{-1} sec^{-1} [8] have been reported for the former reaction; moreover, Taft has shown[11] that the rate may decrease by as much as 10% at the ionic strength of this study, so that the results are in reasonable agreement. Rate constants for the addition of water have been reported previously as 2.2×10^{-4},[11] 3.8×10^{-4},[12] 2.11×10^{-4} [8] sec^{-1} at 25°, again showing good agreement.

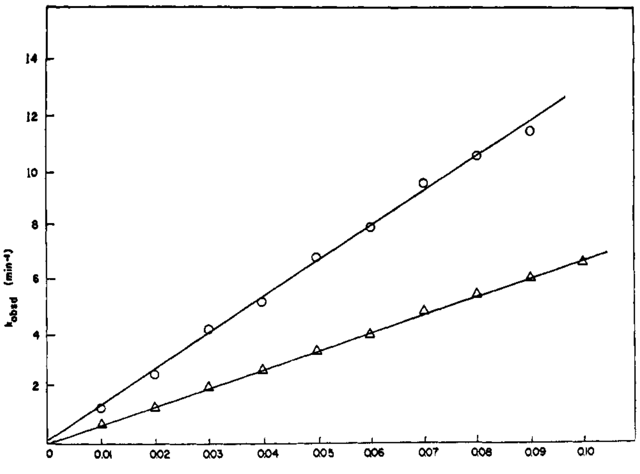


Figure 1. The linear dependence of the pseudo-first-order rate constants on increasing concentrations of glycylglycine (●) and methoxylamine (▲) with malachite green at 30°, $\mu = 1.0$.

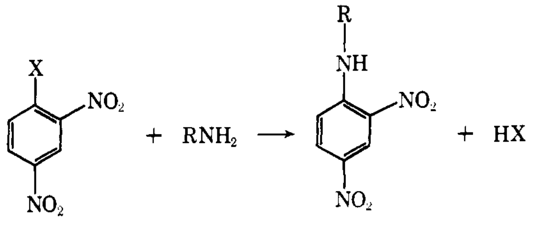
Rates of reaction (k_1) of carbonium ion with amines and α-effect nucleophiles were followed near pH 11, where addition of amine to malachite green proceeds to completion. In the pH range employed, HO$^-$ served as a buffer and no drift in pH was noted in readings taken prior and after completion of the reaction. The disappearance of carbonium ion followed first-order kinetics when the concentration of amine free base ([B$_f$]) was much greater than [A]. The reactions were found to follow the kinetic rate expression (2).

$$k_{obsd} = k_{HO^-}[HO^-] + k_1[B_f] \qquad (2)$$

Plots of k_{obsd} against [B$_f$] at constant pH were linear with slopes of k_1 and intercepts of $k_{HO^-}[HO^-]$ (Figure 1). Reactions were run at sufficiently high [B$_f$] to avoid any possibility that at the completion of the reaction, unreacted dye remained. This was necessitated since, if unreacted malachite green was present at the completion of the reaction, it is slowly scavenged by HO$^-$ so that values of absorbance at t_∞ for reaction with amines were impossible to obtain. This phenomenon was observed for the more weakly basic amines in attempts to follow the reaction both near their pK_a''s and at low amine concentration at pH's near 11.0. Values for k_1 are reported for all nucleophiles investigated in Table I. Rate constants for the reaction of glycylglycine (glygly) and hydrazine with malachite green at 7, 14.8, 23.8, 30, and 38.4° are reported in Table II. Values for $\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$ were derived from an Arrhenius plot of the data in Table II.

Equilibrium studies were not possible for all amines and "α-effect nucleophiles" (see Experimental Section). The equilibria of the system are shown in eq 1. A plot of the absorbance of A against pH at constant [B$_T$] ([B$_T$] = [BH] + [B$_f$]) is shown in Figure 2. From the derivation given in the appendix, K_x is obtained from the slope and K_x/K_y from the intercept of a plot of $(A_T - A)/Q$ *vs.* hydrogen ion activity, where Q is represented by a number of constants (see Appendix) and A_T is the total concentration of A. Values for K_x and K_y are reported in Table I.

The observed pseudo-first-order rate constants for the reaction of glycylglycine and hydrazine with 2,4-DNFB, 2,4-DNClB, and 2,4-DNIB (substrates susceptible to the α effect) afforded linear plots of k_{obsd} *vs.* [B$_f$], from which second-order rate constants for nucleophilic attack (eq 3) were obtained. The rate constants and rate ratios for these nucleophiles, along



(3)

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[11] Rate constant reported by C. Ritchie, G. A. Skinner, and V. G. Badding, *J. Amer. Chem. Soc.*, **89**, 2063 (1967), which was footnoted to R. W. Taft as a personal communication.

[12] E. F. J. Duynstee and E. Grunwald, *ibid.*, **81**, 4542 (1959).

Table II. Values for $T\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta F^{\ddagger}$ for the Reaction of Glycylglycine and Hydrazine with Malachite Green (Standard State for ΔF, ΔH, and $T\Delta S$ was 30°)

	k_1, M^{-1} min^{-1}	Temp, °C	$\Delta F^{\ddagger}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$T\Delta S^{\ddagger}$, kcal/mol
Hydrazine	1060	7	15.3	7.9	−8.4
	1580	14.8			
	2480	23.8			
	3750	30.0			
	4680	38.4			
Glycylglycine	31.4	7	17.3	9.7	−8.6
	52.1	14.8			
	90.2	23.8			
	133	30			
	199	38.4			

with previous results obtained by Bunnett,[13] are given in Table III.

Table III. Rate Constants and Rate Ratios for the Nucleophilic Attack of Glycine, Glycylglycine, and Hydrazine on 2,4-Dinitrohalobenzenes

X	k_{glycine}, M^{-1} min^{-1}	k_{glygly}, M^{-1} min^{-1}	$k_{\text{hydrazine}}$, M^{-1} min^{-1}
F	19.0	4.4	80.5
Cl	0.047	0.007	0.216
I	0.022	0.0037	0.082

X	$k_{\text{hydrazine}}/k_{\text{glygly}}$	$k_{\text{glygly}}/k_{\text{glycine}}$	$k_{C_6H_5S}/k_{^-OCH_3}$	$k_{\text{pip}}/k_{^-OCH_3}$[a]
F	18.3	0.41	59	0.85
Cl	30.8	0.48	1950	0.98
Br			4840	1.43
I	22	0.17	16800	1.48

[a] Data from J. F. Bunnett, *J. Amer. Chem. Soc.*, **79**, 5969 (1957).

Discussion

A number of rationales have been provided for the α effect: (a) polarizability in the transition state;[3] (b) diminished solvation, *e.g.*, of HOO$^-$ as compared to HO$^-$;[14] (c) intramolecular general base catalysis by the α-electron pair; (d) factors which stabilize the product also stabilize the transition state, thus lowering the transition state energy;[15,16] (e) hydrogen bonding to the carbonyl group by the hydrogen on the α atom in the transition state,[17] for displacement reactions on esters, etc., (f) stabilization of the transition state by overlap of the orbitals of the lone pair of electrons in the α position in a manner similar to the stabilization of the incipient carbonium ion in α-halo ether solvolysis;[3] (g) destabilization of the ground state[18] due to the repulsion of the nonbonding electron pair, and this repulsion being relieved on covalent bond formation by the other electron pair. The present study deals with an examination of the importance of factors a, b, c, and d.

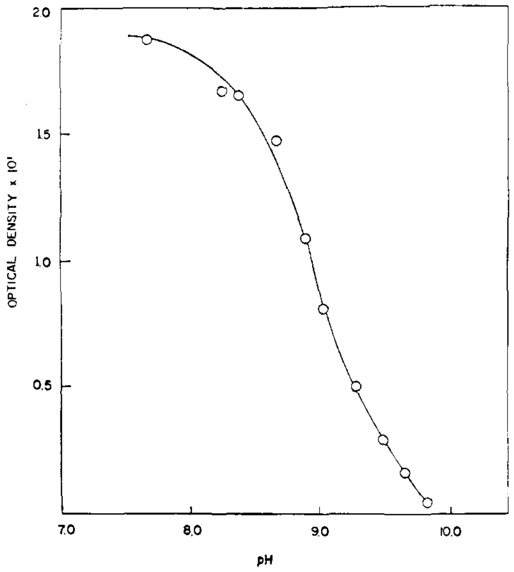

Figure 2. Variation in the optical density of [A] (concentration of carbonium ion) with changes in pH, as B_T remains constant. Glycine is the amine employed at 0.50 M, where t = 30°, A_T = 0.196, units.

Bunnett[14] has interpreted kinetic evidence to indicate (Table III) that as the halogen substituent on 2,4-dinitrohalobenzenes becomes more polarizable, the attack of a polarizable nucleophile (thiophenoxide) has an enhanced rate over that of less polarizable nucleophiles (piperidine or methoxide).[19] If polarizability were responsible for the α effect exhibited by hydrazines, it might be anticipated that hydrazine would show an enhanced rate compared to primary amines when polarizable 2,4-dinitrohalobenzenes are employed as substrates. The results of this study are shown in Table III. A comparison of the rate ratio (Table III) when X is fluoro *vs.* that when X is chloro (with the same nucleophiles) should give a measure of the importance of the polarizability of the two nucleophiles. Clearly the ratio of 1.7 for hydrazine/glygly is much closer to that of 1.0 for glycine/glygly and 1.1 for piperidine/methoxide where polarizability is of little importance, than to the ratio of 33 for thiophenoxide/methoxide, where polarizability has been suggested to contribute significantly to the reaction rate. The same results are obtained by comparing the rate ratio of either 2,4-DNFB or 2,4-DNClB with 2,4-DNIB. Following the rationale of Bunnett, these findings would indicate that polarizability has little significance in the attack of hydrazine on 1-halo-substituted 2,4-dinitrobenzenes. This conclusion is supported by measurements of molar refrac-

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(13) J. F. Bunnett, *J. Amer. Chem. Soc.*, **79**, 5969 (1957).

(14) C. A. Bunton in "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Interscience, New York, N. Y., 1962, p 25.

(15) J. Gerstein and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 4655 (1964).

(16) J. Hine and R. D. Weimar, *ibid.*, **87**, 3387 (1965).

(17) W. P. Jencks, *ibid.*, **80**, 4585 (1958).

(18) K. M. Ibne-Rasa and J. O. Edwards, *ibid.*, **84**, 763 (1962).

(19) This reasoning is also supported by the hard and soft acid-base scale devised by R. G. Pearson, *ibid.*, **85**, 3533 (1963).

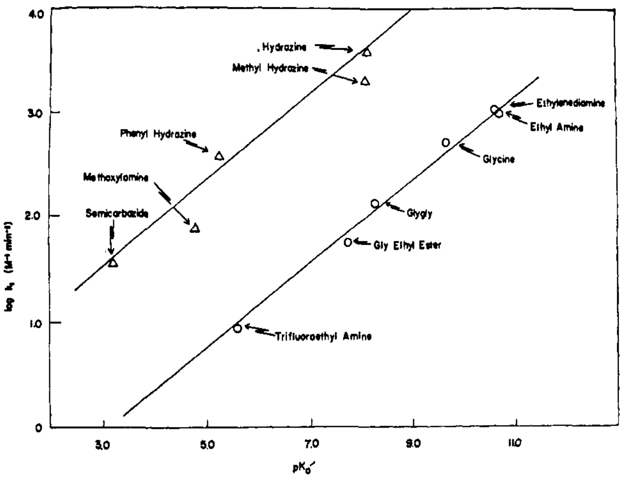

Figure 3. Brønsted plot of the logarithm of the second-order rate constant (k_1) of amines (○) and α-effect nucleophiles (△) as a function of their respective pK_a'.

tions which indicate that hydrazine has no unusual polarizability.[20]

The importance of solvation in contributing to the α effect was investigated by comparison of activation parameters for the bases glycylglycine and hydrazine. These two compounds were selected on the basis of their nearly identical proton basicity (p$K_a' = 8.25$ *vs.* 8.11, respectively). A comparison of the $\Delta H^{\ddagger}$ terms for the two bases indicates a $\Delta H_{\text{glygly}}^{\ddagger} - \Delta H_{\text{hydrazine}}^{\ddagger} = \Delta\Delta H^{\ddagger}$ of 1.8 kcal mol^{-1}, whereas $\Delta T\Delta S^{\ddagger}$ is only 0.2 kcal mol^{-1} (Table II). Thus, the entropy terms are dramatically similar, in contrast to the enthalpy terms, which account for the entire differences in $\Delta\Delta F^{\ddagger}$. If $T\Delta S^{\ddagger}$ is taken to reflect structural or environmental changes,[21] it follows that the small value of $\Delta T\Delta S^{\ddagger}$ must indicate that unusual solvation effects or intramolecular general base catalysis cannot serve as rationales for the α effect in the reaction of hydrazine with malachite green.

Comparison of rate constants for hydrazines to those for amines has been most useful in determining the nature of displacement reactions in which the α effect is manifested. For example, in the reaction of primary and secondary amines with nitroethane[22] and methyl iodide,[23] hydrazine falls on the Brønsted plot for primary amines and methylhydrazine on the Brønsted plot for secondary amines (no α effect). In contrast, for nucleophilic displacement reactions on substituted phenyl acetates, hydrazine and methylhydrazine exhibit large positive deviations from the Brønsted plots for amines. Therefore, in the case of hydrazines the α effect can be quantitatively expressed as the extent of positive deviation of the log $k_{\text{rate}}^{\text{hydrazine}}$, from plots of log $k_{\text{rate}}^{\text{amine}}$ *vs.* the pK_a' values of the hydrazines and amines.[24] Thus, in the present study the convention previously adopted[22,23] of comparing a series of amines and hydrazines *via* the Brønsted equation has been retained.

The rate constants (k_1) for nucleophilic attack on malachite green by six amines and five "α-effectors" (collectively referred to as hydrazines) are given in Table I. A least squares fit of log k_1 *vs.* pK_a' (Figure 3) gave Brønsted equations for amines (4) and α-effect nucleophiles (excluding methoxylamine) (5).

$$\log k_1 = 0.41\text{p}K_a' - 1.32 \qquad (4)$$

$$\log k_1 = 0.42\text{p}K_a' + 0.18 \qquad (5)$$

No statistical correction has been applied to any nucleophiles possessing a pair of α electrons. Examples exist in the literature where corrections have been applied[23] and where they are omitted.[5a] Although *N*-alkylhydrazines associate with a proton through the electron pair on the alkyl-substituted *N*-nitrogen,[25] it is quite certain that in the case of the substituted hydrazines (and other α-effect nucleophiles), where electron withdrawing groups are present on the *N*-alkyl nitrogen, protonation is on the nucleophilic and unsubstituted nitrogen. This is probably why methylhydrazine, which presumably reacts through the *N*-alkyl nitrogen, falls below the line for other substituted hydrazines (*i.e.*, greater steric hindrance) in the attack on malachite green. Comparison of eq 4 and 5 indicates that the Brønsted plots for hydrazines and amines are, within experimental error,[26] parallel. The rate constants for the hydrazines fall approximately 1.5 orders of magnitude above those for the corresponding amines. This value compares well with that observed for nucleophilic attack on esters.

It is generally accepted that the amount of bond making in the transition state can be described in terms of the sensitivity of the reaction to the pK_a' of the attacking nucleophile (Brønsted β value).[27] Such descriptions presuppose that β ranges in value from 0 to 1.0 or, alternatively, depend upon educated guesses as to the maximum value of β. Supposition that the range of β is from 0 to 1.0 stems from studies of nucleophilicity toward hydrogens bonded to nitrogen or oxygen. Thus, employing Brønsted β values in reactions other than proton transfer processes to arrive at a description of the extent of bond making or breaking in the transition state is undesirable. However, when both rate and equilibrium data are present, a reasonable correlation of transition state structure with β values is possible. Because the average ΔF^0 for the reaction of an amine or hydrazine with malachite green is small (*e.g.*, glycylglycine, +0.36; hydrazine, −1.81 kcal/mol), one would conclude that the transition state is approximately half-way along the reaction coordinate. A β value of 0.4 is in accord with this supposition so that a

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(20) J. W. Brühl, *Ber.*, **26**, 2508 (1892); **30**, 162 (1897), as noted in ref 5b.

(21) R. W. Taft, "Steric Effects in Organic Chemistry," Wiley, New York, N. Y., 1956, p 556.

(22) M. J. Gregory and T. C. Bruice, *J. Amer. Chem. Soc.*, **89**, 2327 (1967).

(23) See Table I, footnote *a*.

(24) It is worthy to note that a large number of comparisons between the nucleophiles HO$^-$ and HOO$^-$ and between NH_3 and NH_2NH_2 exist in the literature,[5a] and that these comparisons are given to indicate the presence of the α effect. The fact that both NH_3 and ^-OH fall below the Brønsted plots for primary amines and alkoxide ions, respectively, indicates that these comparisons reflect factors other than the enhanced nucleophilicity due to the presence of the unshared pair of electrons.

(25) F. E. Condon, *J. Amer. Chem. Soc.*, **87**, 4481 (1965).

(26) Caplow[26a] has noted similar parallel Brønsted lines for the reaction of amines and hydrazine with CO_2. However, results obtained in this laboratory[26b] with the same nucleophiles but with 2,4-dinitrophenyl acetate as substrate revealed Brønsted slopes that are not at all parallel. Initial observations indicate that parallel Brønsted plots for amines and hydrazines may be characteristic of one-step addition reactions. This phenomenon is now under further investigation: (a) see Table I, footnote *e*; (b) J. E. Dixon and T. C. Bruice, unpublished results.

(27) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, p 27.

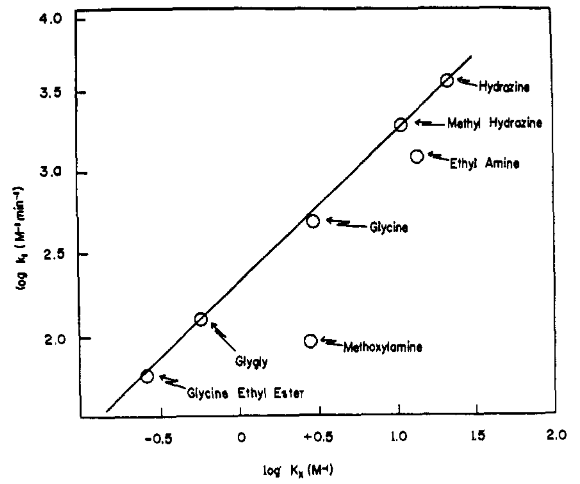


Figure 4. Plot of the logarithm of the second-order rate constant (k_1) *vs.* logarithm of the equilibrium constant (K_x) in the nucleophilic addition to malachite green.

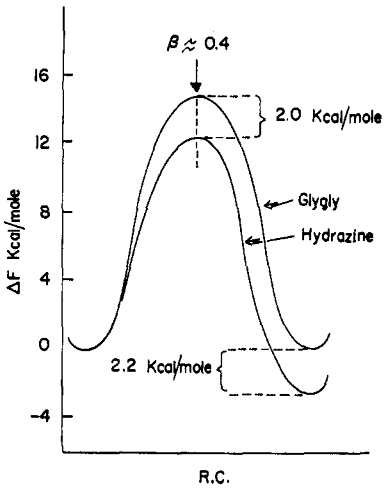
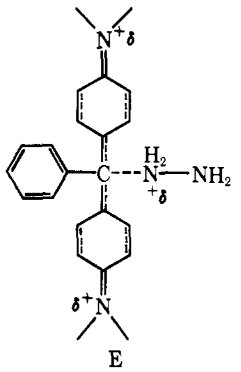


Figure 5. A plot of $\Delta F^{\ddagger}$ (kcal/mole) *vs.* reaction coordinate for glycylglycine and hydrazine addition to malachite green. Transition states for both reactions are placed approximately half-way along RC and exact ground-state energies are unknown.

considerable amount of bond formation in the transition state is occurring for reaction of the nitrogen bases of this study with malachite green. The same pertains to reactions of these nucleophiles with activated esters ($\beta \approx 0.8$).[28,29] It has been argued[29] that a β value of 0.8 for amine attack on *p*-nitrophenyl acetate represents 50% bond formation in the transition state. This was based upon an estimated maximum β value of 1.7.

Measurement of equilibrium constants (K_x, Table I) for the addition of nitrogen bases to malachite green was possible with seven of the eleven nitrogen bases of this study. Inspection of Table I reveals that product formation is increasingly favored with an increase in pK_a of the conjugate acid of the nucleophile. Also, the equilibrium constants for addition of the α-effect bases hydrazine and methoxylamine are greater than anticipated on the basis of pK_a''s when primary amines are employed as standards. Thus a plot of log K_x *vs.* pK_a' shows the same positive deviation for α-effect nucleophiles from the Brønsted equation that is observed for primary amines as was noted in the plot of log k_1 *vs.* pK_a' (Figure 2). Therefore, kinetic and thermodynamic measurements indicate that hydrazines are both more reactive and their products more stable than would be predicted from their pK_a's. When one plots log rate of the forward reaction (k_1) against log K_x (Figure 4) all amines and hydrazines fall on a single line. The slope of this plot gives a linear free energy relationship of $\Delta\Delta F^{\ddagger}\Delta\Delta F^0 = 1.0$; therefore, all changes in ΔF^0 result in a similar change in $\Delta F^{\ddagger}$. This relationship can be seen in the reaction coordinate diagrams of Figure 5 for glycylglycine and hydrazine which are of like pK_a. Within experimental error, the stabilizing influence of the α-electron pair upon the transition state E is quantitatively the same as the stabilizing influence of the electron pair upon the product D of eq 1 (*i.e.*, the transition states for these reactions resemble product about as much as reactant). Thus, the new carbon–nitrogen bond resulting from hydrazine attack on malachite green is more stable than would be predicted from formation of the corresponding hydrogen–nitrogen bond (*i.e.*, the pK_a of the amine). Therefore, the α effect results in this reaction to a great part from the fact that the carbon basicity of hydrazines is greater than the carbon basicity of amines. These results find a parallel in equilibrium determinations for the reaction of HOO$^-$ with methyl iodide in the gas phase,[16] and equilibrium determinations for formation of esters or amides of acetic acid by various nucleophiles.[15] This unusual thermodynamic stability toward carbon is also noted for some "α-effect" compounds in the addition to aldehydes. Therefore, it would seem that the more stable products (based upon comparison of pK_a''s) resulting from attack of compounds possessing a lone pair of α electrons is associated with the kinetic α effect when the substrate is an ester, aldehyde, or malachite green.



E

If our deductions concerning a transition state structure midway between reactants and products is correct then it might be anticipated that product stability associated with the α effect should be only partially transferred to the transition state. That the α-effect associated stability of the product is essentially completely transferred to the transition state may then indicate that other factors are equally important in decreasing $\Delta F^{\ddagger}$. The determining factors leading to what is collectively referred to as the α effect are probably many and depend not only on substrate but the type of α-effect nucleophile (*e.g.*, hydrazines *vs.* peroxide ions). Nevertheless, a considerable amount of bond formation in the

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(28) T. C. Bruice and R. Lapinski, *J. Amer. Chem. Soc.*, **80**, 2265 (1958).

(29) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968).

transition state is generally required to observe the kinetic α effect.[30] This may, in general, point to product stability as a usual contributing factor.[15,16] Thus, the attack of amines or hydrazines on methyl iodide,[23,31] and on sulfate[30] and phosphorus esters[32] does not exhibit the α effect and the Brønsted β constant is small.[33]

Rationales for the greater carbon basicity of hydrazines as compared to amines of the same pK_a' in reactions as those dealt with herein are made difficult by the fact that the α effect may appear for general base catalyzed reactions. For example, methoxylamine and diethyl ketoxime exhibit rate constants *ca.* 10^2 greater than anticipated for general base catalyzed hydrolysis of ethyl trifluorothiolacetate,[34] and diethyl ketoxime exhibits a rate constant *ca.* 10^2 for a Brønsted plot for the dehydration of acetaldehyde hydrate, respectively.[35] Furthermore for the former reaction $\beta \cong 0.3$. On the other hand the α effect does not appear in proton abstraction by amines and hydrazines from nitroethane ($\beta = 0.5$).[22] Equilibrium constants indicate that the products resulting from hydrazine attack on nitroethane are no more stable than those from an amine of the same pK_a.

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Appendix

The derivation by which the equilibrium constants were obtained follows from eq 1

$$A + RNH_2 \overset{K_x}{\rightleftharpoons} D \overset{K_y}{\rightleftharpoons} C + H^+ \qquad (1)$$

where

$$K_x = \frac{[D]}{[A][RNH_2]}$$

$$K_y = \frac{[C]a_H}{[D]}$$

The total concentration of A at equilibrium is $[A_T] = [A] + [D] + [C]$; substitution of D and C affords

$$A_T = A + K_x[A][RNH_2] + \frac{K_xK_y[RNH_2][A]}{a_H} \qquad (6)$$

Solving the preceding equation for A and substitution for $[RNH_2]$, where $[RNH_2] = B_T[K_e/(K_e + a_H)]$ and K_e is the dissociation constant of the respective amine or hydrazine, thus gives

$$A = \frac{A_T}{1 + \frac{K_xK_e[B_T]}{K_e + a_H} + \frac{K_xK_yK_e[B_T]}{a_H[a_H + K_e]}} \qquad (7)$$

which upon rearrangement affords

$$A[a_H(K_e + a_H) + a_HK_xK_e[B_T] + K_xK_yK_e[B_T]] = A_T[a_H(K_e + a_H)] \qquad (8)$$

following collection of terms

$$A[a_HK_xK_e[B_T] + K_xK_yK_e[B_T]] = A_T[a_H(K_e + a_H)] - A[a_H(K_e + a_H)] \qquad (9)$$

which gives

$$\frac{[A]K_xK_e[B_T][a_H + K_y]}{a_H(K_e + a_H)} = A_T - A \qquad (10)$$

defining Q as

$$Q = \frac{[B_T][A]K_e}{a_H(K_e + a_H)} \qquad (11)$$

where Q is a collection of known values, thereby obtaining

$$K_x(a_H) + K_xK_y = \frac{A_T - A}{Q} \qquad (12)$$

which upon plotting $(A_T - A)/Q$ against a_H one obtains K_x as a slope and K_xK_y as an intercept.

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[30] For an additional and valuable discussion of the point, see S. J. Benkovic and P. A. Benkovic, *J. Amer. Chem. Soc.*, **88**, 5504 (1966).

[31] Although it is not necessarily correct to indicate that small values of β are associated with a small amount of bond formation in the transition state [R. A. Marcus, *ibid.*, **91**, 7224 (1969)], it is generally accepted that substitution at sp^3 carbon results in less bond formation than at unsaturated carbon. M. H. Abraham [*Chem. Commun.*, 1307 (1969); 293 (1970)] has shown that in attack of amine on methyl iodide the transition state resembles reactants rather than products.

[32] A. J. Kirby and W. P. Jencks, *J. Amer. Chem. Soc.*, **87**, 3209 (1965).

[33] In the reaction of amine nucleophiles with highly activated esters, as 1-acetoxy-4-methoxypyridinium perchlorate, an increase in pK_a of the conjugate acid of the amine is accompanied by a decrease in the Brønsted slope (β) from *ca.* 0.8 to *ca.* 0.4 or less. In the region of the break in the Brønsted plot there is noted a considerable α effect (see ref 29). Examples of this type may well not involve product stability as a contributing factor. It should be noted, however, that the details of mechanism are muddied by the fact that tetrahedral intermediates may follow the rate-determining step and that a small value of β is obtained at rate constants of the order of 10^5 M^{-1} min^{-1}, a value below that anticipated of an uncomplicated diffusion controlled process.

[34] L. R. Fedor and T. C. Bruice, *J. Amer. Chem. Soc.*, **87**, 4138 (1965).

[35] R. P. Bell, *J. Phys. Chem.*, **55**, 885 (1951).