°C, THF) of the aldehyde obtained upon Collins oxidation of **17** with the lithiated benzoxazole **18**,[18] prepared at −100 °C in the THF by using LDA, provided, as the major product (36%), the C(3)–C(12) fragment **3**.[6] Since **3** has been converted into calcimycin on a previous occasion, the preparation of **3** constitutes a formal total synthesis of the antibiotic.

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Registry No. **3**, 74244-53-4; **4**, 74281-17-7; **5**, 74231-22-4; **6**, 74231-23-5; **7**, 74231-24-6; **8**, 74231-25-7; **9**, 74231-26-8; **10**, 74231-27-9; **11**, 74231-28-0; **12**, 74231-29-1; **13** (R = Si(Me$_2$)-*t*-Bu), 74231-30-4; **13** (R = Me), 74231-31-5; **14**, 74231-32-6; **15**, 74231-33-7; **16**, 74231-34-8; **17**, 74281-80-4; **18**, 72297-84-8; *tert*-butylchlorodiphenylsilane, 58479-61-1; propionyl chloride, 79-03-8; 2,2-dimethyl-1,3-propanediol, 126-30-7; *t*-Bu(Me)$_2$SiCl, 18162-48-6.

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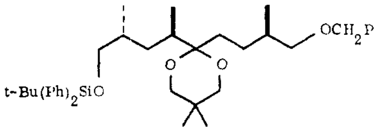
(17) We are grateful to Professor Evans for providing us with a generous sample of compound iv and a detailed procedure for cleaving the benzyl ether.



iv

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Nonlinearity of Hammett $\sigma\rho$ Correlations for Benzylic Systems: Activation Parameters and Their Mechanistic Implications

Summary: Bromide–bromide substitution rates have been measured for a series of *p*-substituted and 1-(3,4-dimethylphenyl)bromoethanes. The activation parameter data support an ion-pair transition state.

Sir: The nonlinearity of Hammett $\sigma\rho$ and related free-energy correlations for benzylic systems has frequently been observed.[1-3] This nonlinearity ranges from curvature to "L"-shaped and even "U"- or "V"-shaped plots. It is in the solvolyses of variously substituted benzyl halides that such behavior has most commonly been observed,[2] but it has been noted for a wide variety of other nucleophilic substitutions with both neutral (Ph_3P, Ph_3As, Et_2S $(NH_2)_2CS$, amines ...) and charged nucleophiles (N_3^-, NCS^-, $S_2O_3^-$, halide ions ...) in a variety of solvents, protic, aprotic, and mixed.[3]

The origins of these frequent failures of the linear free-energy correlations have been extensively discussed over the years with the usual approach being a rationale based upon the relative degree of bond making and breaking at the transition state.[2,3d,4,5] These discussions have varying levels of sophistication, but they all in effect assume an S_N2-type transition state. Given this assumption, it is logical that a system better able to support a positive charge on the carbon attached to the leaving group should have a transition state with a greater degree of bond breaking, one more able to support a negative charge, with a greater degree of bond formation than some "normal" substrate. Consequently the degree and even the sign of the charge developing in the transition state could change with the substituent on the benzylic system. These rather subtle mechanistic changes could account for the changes in slope or even the acceleration of the reaction by both electron-donating and -withdrawing substituents and the resultant V- or U-shaped free-energy correlations.

Unfortunately this facile explanation, which we in fact have ourselves used,[3d] is not consistent with the activation parameters reported here. Bromide–bromide substitutions for a series of *p*-substituted and 1-(3,4-dimethylphenyl)bromoethanes were kinetically followed through the racemization of optically active substrates. These "symmetrical" reactions, where the leaving group and the nucleophile are the same, were chosen to minimize other effects. Data for the racemizations in acetone using LiBr at 0.002 00 M are given in Table I.[6]

The data in Table I have not been corrected for the degree of dissociation of the lithium bromide or the variation in dissociation constant with temperature, but since the same temperature range, 25–45 °C, was used for the whole series, contributions to the observed rate constant and to $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ from incomplete dissociation should be the same for all compounds. Thus while the absolute values may not be "correct", the relative values will be of significance. It is perhaps worth noting that for the unsubstituted case the activation parameters were independent of the concentration of lithium bromide over the range of 5×10^{-4} to 1×10^{-2} M.

The relative rates of the reactions reflect the free energies of activation reported. The enthalpy and entropy terms though are of much greater interest here. If the rationale discussed earlier is accepted, the amount of bond formation should be increasing with the more electron-withdrawing substituents and the enthalpy of bond formation should at least partially compensate for the enthalpy of bond breaking. Thus $\Delta H^{\ddagger}$ should decrease or at least not increase appreciably with such substituents. The

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(1) For access to the earlier literature, see (a) A. Streitweiser, Jr., *Chem. Rev.*, **56**, 571 (1956); (b) O. Exner, "Advances in Linear Free Energy Relationships", N. B. Chapman and J. Shorter, Eds., Plenum Press, London, 1972, Chapter 1.

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(4) (a) K. C. Westaway and S. F. Ali, *Can. J. Chem.*, **57**, 1354 (1979); (b) H. Aronovitch and A. Pross, *J. Chem. Soc., Perkin Trans. 2*, 541 (1978).

(5) The still controversial theoretical basis for free-energy correlations, of which the Hammett equation is but one, and the theoretical implications of their successes and failures are beyond the scope of this communication. Interested readers are referred to reviews such as: (a) ref 1b, pp 4–19; (b) C. D. Johnson, "The Hammett Equation", Cambridge University Press, 1979, pp 133–158; (c) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, 1963.

(6) For a discussion of the experimental procedures employed see A. R. Stein, *J. Org. Chem.*, **41**, 519 (1976); **38**, 4022 (1973).

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Table I. Kinetic and Thermodynamic Data for Racemization of Substituted 1-Phenylbromoethanes in Acetone

substituent	k,[a] L/(mol·s)	$\Delta G^{\ddagger}$,[b] kJ/mol	$\Delta H^{\ddagger}$,[b] kJ/mol	$\Delta S^{\ddagger}$,[b] J/(deg·mol)
3,4-$(CH_3)_2$	7.74×10^{-3}	87.6 ± 1.5	54.2 ± 3.0	−110 ± 10
p-CH_3	7.90	86.9 ± 0.9	56.6 ± 1.5	−100 ± 5
p-H	3.65	88.4 ± 0.3	64.19 ± 0.09	−79.9 ± 0.7
p-Br	8.77	87.1 ± 0.9	66.2 ± 2.6	−69 ± 10
p-NO_2	16.75	84.8 ± 1.1	69.5 ± 1.8	−50 ± 8

[a] Observed value for [LiBr] = 0.002 M, T = 303.15 K. All reactions are kinetically second order, but the observed rate constants decrease with increasing lithium bromide concentration due to ion pairing of the salt (see ref 6). [b] Averages of the values obtained for several concentrations of lithium bromide between 5.00×10^{-4} and 1.000×10^{-2} M. The temperature range for each determination was 25–45 °C.

values in Table I are clearly inconsistent with that rationale.

If on the other hand we are dealing with an ionization process, perhaps to an ion pair,[7,8] it is the C–Br bond strength, moderated of course by solvation, that would determine $\Delta H^{\ddagger}$. The enthalpy of activation would then be expected to decrease progressively as the carbon becomes more able to support the developing positive charge; this is exactly what is found. Clearly an ionization model is a more acceptable one than the classical S_N2 transition state required by the usual rationale.

The decrease in enthalpy of activation with the increase in stability of the expected carbocation is compensated for by the entropy term which rapidly gets more negative. Such a "compensation effect" of enthalpic and entropic contributions is well-known and seems to be one of the reasons the Hammett and like equations are so broadly applicable.[5,9] Of course $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are not "independent" variables since changes in the former will affect the transition state structure and hence its solvation. It is usual to assume the bulk of the entropy of activation comes from the resolvation in going from the reactants to the transition state so that, if this assumption is valid, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are affected by the same factors.

Again, the observed range in $\Delta S^{\ddagger}$ with substituent is more consistent with a larger change in charge separation and hence in solvation than would be expected if the usual explanation for the nonlinear Hammett behavior of such systems is valid. Both the enthalpic and entropic data then are consistent with an ionization process rather than the one usually invoked.

Shiner and his colleagues[8] have done extensive studies of m- and p-substituted 1-phenylethyl halides and have concluded that internal return from an ion pair is important in alcoholysis and hydrolysis. From deuterium isotope effects, they concluded that for the solvolysis of unsubstituted 1-phenylethyl bromide in 80:20 ethanol–water and even of the p-nitro analogue in 5:95 acetone–water ionization was nearly complete at the transition state, with nucleophilic attack probably occurring at the contact ion-pair stage. Acetone is of course much less ionizing than aqueous ethanol or water and is incapable of hydrogen bonding, but his results lend support to our conclusions. Unfortunately Shiner did not report activation parameters.

There have, however, been a few reports of activation parameters, or data from which they can be calculated, for benzylic systems[2b,c,3b,c,f–h] but only two report data for a range of substituents and reactions that are at all comparable to the system reported here. The data of Sugden and Willis[3h] for the bromide–*radio*-bromide exchanges in ethylene diacetate show precisely the same pattern in and comparable values for the activation parameters. The results of Brown et al.[2c] for the solvolysis of p-nitrobenzoate esters of benzylic systems show similar patterns. Thus the dramatic dependence of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ on substituents is not limited to racemizations in the phenylethyl system or the solvents studied to date.

Clearly the nonlinearity of the Hammett equation is due to the fact that the enthalpic parameter is more than compensated for by the entropic one. In the system in question the range of $\Delta H^{\ddagger}$ is 15.3, that of $T\Delta S^{\ddagger}$ is 18.2 kJ/mol at 303.15 K. Undoubtedly for proponents of the usual rationale for the nonlinearity, it will be possible to "fit" the activation data to their mechanism,[10] but we feel that the data supports an ion-pair scheme. Obviously more data for benzylic systems must be obtained before any extensive mechanistic discussion is undertaken so that we conclude with a plea that such measurements be made. Rate and isotope effect measurements clearly are not enough to sort out the origins of the nonlinearity of Hammett $\sigma\rho$ correlations.

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(10) For example, the changes in $\Delta S^{\ddagger}$ can be explained by assuming the transition state changes from "very tight" to "very loose" as the substituent changes from electron withdrawing to electron donating and considering the effects upon solvation. The fact that $\Delta H^{\ddagger}$ continues to increase markedly as the substituents become quite electron withdrawing is difficult to explain in this way though. In any event, when does a "loose" transition state with almost no bonding to the leaving group become an ion pair?

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Structure Determination of the Active Sulfhydryl Reagent in Gill Tissue of the Mushroom *Agaricus bisporus*[1]

Summary: The red pigment found in sporulating gill tissue of the mushroom *Agaricus bisporus*, which is a potent inhibitor of a number of enzymes containing sulfhydryl groups at their active sites, is shown to be 2-hydroxy-4-imino-2,5-cyclohexadienone (4).

Sir: A potent sulfhydryl reagent appears in the gill tissue of the mushroom *Agaricus bisporus* in the period prior to

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