Cage Return and Solvent Viscosity. Effect of Viscosity on Polar Effects Inherent in Benzylic Bromination[1]

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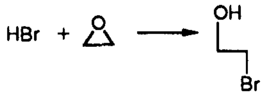
Abstract: Solution-phase free-radical reactions whose rates are near the diffusion limit are strongly influenced by the viscosity of the media in which the reaction is carried out. Since solvent viscosity is temperature dependent, the interpretation of temperature-dependent kinetics must also take into account changes in the rates of diffusion of caged radical–molecule pairs. The competitive bromination of toluene and substituted toluenes is viscosity dependent: $ArCH_3 + Br^\bullet \rightleftharpoons (ArCH_2^\bullet + HBr)_{cage} \xrightarrow{k_{diff}} R^\bullet \rightarrow$ products. The temperature dependence of the Hammett linear free energy relationship obtained from the competitive bromination of a series of substituted toluenes has been studied as a function of the viscosity of the reaction mixture. It had been reported that ρ increased in magnitude as the temperature increased. This observation had been rationalized as being due to entropic control of the free energy of activation. When temperature is held constant and the viscosity of the solvent is changed, the Hammett ρ value increases in magnitude (i.e., becomes more negative). However, when a plot of ρ vs temperature is constructed from values of ρ determined in solvents that at those temperatures had constant viscosities, the slope of the plot reflects normal enthalpy control. The effect of differential internal cage return of the radical–hydrogen bromide pairs explains these results.

Introduction

Hammett linear free energy relationships have been established as one of the most useful mechanistic probes in organic chemistry. Competitive reactivities have been extensively used to obtain these relationships due to the ease of obtaining reliable data and the straightforward interpretation of the results. It is well-recognized that kinetic methods are only useful for the study of competitive reactions when the reactions are carried out under conditions where the reactive intermediates are formed irreversibly. This is particularly the case for reactions such as benzylic bromination with molecular bromine where the reverse reaction is kinetically important.[5-8] External reversal, i.e., reactions of the radicals formed with the hydrogen bromide free in solution, eq 1, has been limited by carrying out the reactions with high concentrations of bromine and running the reactions to low conversion;[9,10] by using a large excess of an epoxide to scavenge the hydrogen bromide formed,[11] eq 3; or by the use of N-bromosuccinimide to scavenge the free hydrogen bromide,[12] eq 4. The reversal reaction was also limited by using a nitrogen flow system where the hydrogen bromide was swept from the system as it was formed.[13]

$$RH + Br^\bullet \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R^\bullet + HBr \qquad (1)$$

$$R^\bullet + Br_2 \longrightarrow RBr + Br^\bullet \qquad (2)$$



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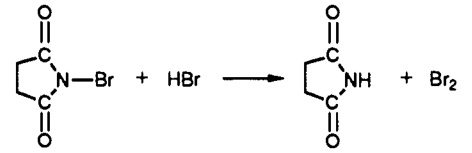

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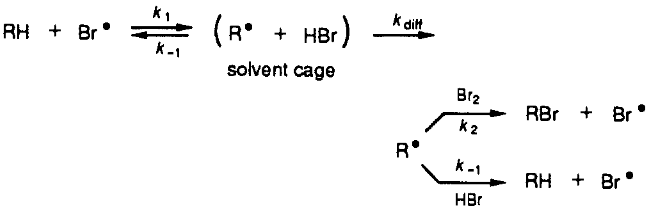
A number of years ago,[8-10] we suggested that, even in the absence of external reversal (external return), cage return (internal return) would likely obscure the interpretation of the kinetic results obtained in solution-phase reactions involving bromine atom abstraction; see Scheme I.

Scheme I



Scheme I was successfully used to rationalize the results obtained in the competitive brominations of cyclohexane and cyclopentane,[9] to explain the magnitude of the deuterium isotope effect determined for the bromination of cyclohexane and perdeuteriocyclohexane,[10] and to explain the difference between the solution-phase and vapor-phase deuterium isotope effect found during benzylic bromination.[10,14] Cage reversal implies a competitive reaction between the transfer of the caged hydrogen bromide–alkyl radical pair and their diffusion from the cage. Since cage diffusion is controlled by solvent viscosity and viscosity is temperature dependent, the latest paper on cage return[14] demonstrated that an analysis of the kinetic results of the effect of temperature on competitive brominations must consider viscosity-dependent cage reversal.

Recently, three papers have reported the temperature dependence of the homolytic abstraction of a benzylic hydrogen by the bromine atom.[15-18] All three papers reported results that showed

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(5) Russell, J. J.; Seetula, J. A.; Thimonen, R. S.; Gutman, D.; Nava, D. F. *J. Am. Chem. Soc.* **1988**, *110*, 3084.

(6) Russell, J. J.; Seetula, J. A.; Gutman, D. *J. Am. Chem. Soc.* **1988**, *110*, 3092.

(7) Thaler, W. A. In *Methods in Free-Radical Chemistry*; Huyser, E.S., Ed.; Dekker: New York, 1969; Vol. 2, Chapter 2, pp 130–141.

(8) Tanner, D. D.; Pace, T.; Ochiai, T. *J. Am. Chem. Soc.* **1975**, *97*, 4303 and references therein.

(9) Tanner, D. D.; Ruo, T. C-S.; Takiguchi, H.; Guillaume, A. *Can. J. Chem.* **1981**, *59*, 1368.

(10) Tanner, D. D.; Ochiai, T.; Pace, T. *J. Am. Chem. Soc.* **1975**, *97*, 6162.

(11) (a) Tanner, D. D.; Wada, N. *J. Am. Chem. Soc.* **1975**, *97*, 2190. (b) Lu, F-L.; Naguib, Y. M. A.; Kitadani, M.; Chow, Y. L. *Can. J. Chem.* **1979**, *57*, 1967.

(12) Tanner, D. D.; Ruo, T. C-S.; Takiguchi, H.; Guillaume, A.; Reed, D. W.; Setiloane, P. B.; Tan, S. L.; Meintzer, C. P. *J. Org. Chem.* **1983**, *48*, 2743.

(13) Pearson, R. E.; Martin, J. C. *J. Am. Chem. Soc.* **1963**, *85*, 3142.

(14) Tanner, D. D.; Nguyen, H. N. *J. Org. Chem.* **1987**, *52*, 4686.

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unusual temperature-dependent effects; however, the three studies neglected to consider internal return as a viable process that affects the relative kinetic methods used to obtain the linear free energy relationships that were reported.

One of the papers[15] reported the temperature dependence of the Hammett linear free energy relationship. The value of ρ became less negative with decreasing temperature and approached an isokinetic temperature (−71 °C). Differential enthalpies and entropies of activation were obtained. The entropic contribution to the rates was reported to be important enough to control the reactivities of the toluenes studied and was used to explain the inverse dependence of ρ with temperature.

A second publication[16] reported that the relative rates of bromination of 4-chlorotoluene vs toluene, k_{ct}/k_t, showed an Arrhenius plot with a positive slope for temperatures from +45 to −32 °C. As the temperature increased, the relative rates appeared to be further from unity. Activation parameters for the higher temperature reactions gave values of $E_t^* - E_{ct}^*$ of 0.592 kcal/mol and $S_{ct}^* - S_t^* = -2.47$ eu, yielding an isokinetic temperature of −33 °C. It was expected that at temperatures <−33 °C the sign of ρ should change from negative to positive. Qualitatively, these results showed the same temperature-dependent behavior as was reported by Kim[17] and suggest the importance of entropy in the control of the reaction kinetic for bromination. In the third paper, the temperature range over which the competitive rates of brominations, k_{ct}/k_t, were studied was extended (+45.0 to −50 °C).[15] An Arrhenius plot of ln (k_{ct}/k_t) vs $1/T$ showed a change in the sign of the slope at −33 °C. A ρ value for the bromination of a series of substituted toluenes was reported[16] at −50 °C, and a linear correlation was best achieved with σ instead of σ^+ substituent constants, $\rho = -0.376$.

If internal return is considered an important mechanistic process (see Scheme I), a kinetic expression can be derived that accounts for cage reversal.[6,9] The derivation gives the expression for the relative rates of reaction of any two substrates and assumes that both benzylic radicals diffuse from the cage at the same rate and that any effect of solvent on these competitive rates is negligible; i.e., $(k_1/k_2)^{\text{vp}} = (k_1/k_2)^{\text{soln}}$. See eq 5. If, as the equation suggests,

$$\log([\text{R}_1\text{H}]^0/[\text{R}_1\text{H}]^f)/\log([\text{R}_2\text{H}]^0/[\text{R}_2\text{H}]^f) = (k_1/k_2)^{\text{obs}} = (k_1/k_2)^{\text{vp}}\left(\frac{k_{-2}[\text{HBr}] + k_\text{d}}{k_{-1}[\text{HBr}] + k_\text{d}}\right) \quad (5)$$

the rate of internal return is competitive with diffusion and the diffusive rate is related to the solvent viscosity by the diffusion constant, α, then the observed rates will be an inverse function of the solvent viscosity, eqs 6 and 7. The vapor-phase value of

$$k_\text{d} = \alpha/\eta \quad (6)$$

$$(k_1/k_2)^{\text{obs}} = (k_1/k_2)^{\text{vp}}\left(\frac{\alpha + k_{-2}(\text{HBr})\eta}{\alpha + k_{-1}(\text{HBr})\eta}\right) \quad (7)$$

the relative rates can be estimated by an extrapolation of a plot of viscosity vs the relative rates of reaction.

In this report on the solution-phase benzylic brominations of substituted toluenes, a method is proposed for estimating the Hammett linear free energy parameter, ρ, in the absence of both internal and external return. Furthermore, if the viscosity dependence of the competitive rates is considered, as well as their temperature dependence (at constant viscosity), then normal activation parameters can be determined.

Results

In order to determine the viscosity dependence of the Hammett linear free energy relationship for free-radical benzylic brominations, the brominations were carried out at 23 °C in Freon solvents of varying viscosity. To eliminate external return, two methods were used: the competitive brominations were carried out with *N*-bromosuccinimide (NBS) and added molecular bromine[12] and with molecular bromine and ethylene oxide;[11] see Table I. The ρ values reported gave excellent correlations with σ^+ substituent constants.[18] In all cases, the correlation coefficients were higher than when σ values were used. The results are graphically displayed by Figure 1.

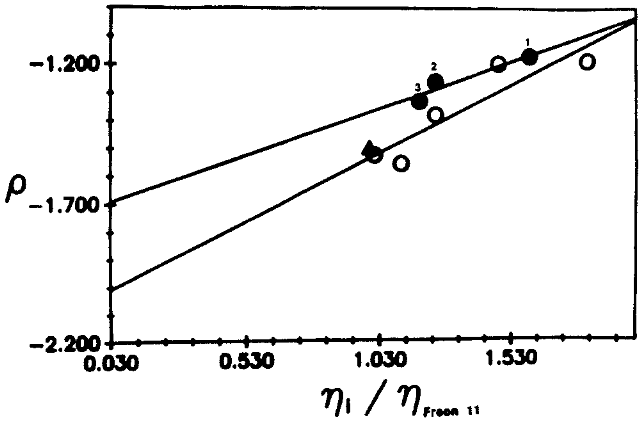

Figure 1. ρ values vs $\eta_i/\eta_{\text{Freon11}}$ (23 °C) for the brominations (23 °C) carried out in Freon: ○, NBS/Br_2; △, Br_2/ethylene oxide; ●, kinetic data given in ref 17. Conditions for data in ref 17: 1, CCl_4, 283 K; 2, CCl_4, 313 K; 3, CCl_4, 333 K.

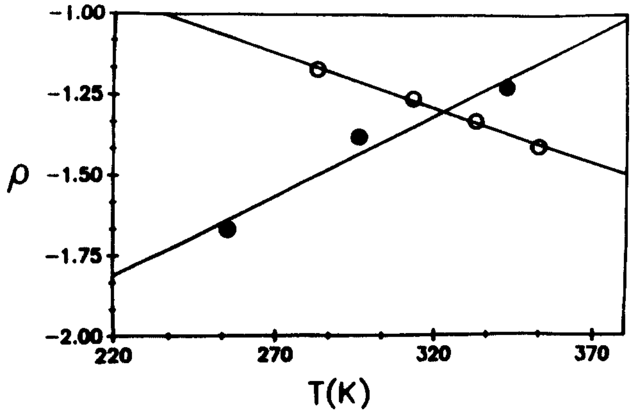

Figure 2. ρ values obtained for benzylic brominations in Freon vs the temperature of each reaction at constant viscosity $\eta_i/\eta_{\text{Freon11}}$ (23 °C) = 1.250 ± 0.009 (●). ρ values for bromination at different temperatures (taken from ref 17) for reaction carried out in CCl_4 vs the viscosity of the solutions at those temperatures (○).

Although internal return is significant during competitive cage reactions, reversal may not be as kinetically important during the external return processes since its effects are attenuated by the faster reactions of the radicals with molecular bromine. In the last two entries of Table I, the reactions carried out with molecular bromine are reactions that result from both internal and external return. The ρ values obtained from these reactions are almost the same as those carried out in the same solvents in the absence of external return (NBS/Br_2).

The temperature dependence of ρ has recently been reported for benzylic brominations with NBS.[17] When the reaction mixtures used for these studies were heated to the reported temperatures and the viscosity of the mixtures was determined (see Table II), the viscosity dependence of ρ as well as its temperature dependence could be compared to the viscosity dependence of ρ determined at 23 °C; see Figure 1.

The temperature dependence of ρ at constant viscosity was determined for the NBS brominations carried out in Freon solutions; see Table III. A graphical display of the temperature dependence of ρ at constant viscosity is compared to the temperature dependence previously reported without considering the viscosity changes; see Figure 2.

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[15] Wright, J. G.; Gilliom, R. D. *J. Am. Chem. Soc.* **1986**, *108*, 2340.

[16] Gilliom, R. D.; Brewer, R. M.; Miller, K. R. *J. Org. Chem.* **1983**, *48*, 3600.

[17] Kim, S. S.; Choi, S. Y.; Kang, C. H. *J. Am. Chem. Soc.* **1985**, *107*, 4234.

[18] Russell, G. A. *J. Org. Chem.* **1958**, *23*, 1407.

Table I. Relative Rates of Bromination of Meta- and Para-Substituted Toluenes vs Toluene at 23 °C

solvent	rel viscosity[a]	reagent	*p*-MeO	*p*-Me	*p*-F	H	*p*-Cl	*m*-F	*m*-Cl	$\rho(\sigma^+)$	*r*
Freon 11	1.01	NBS/Br_2	12.63 ± 0.51	2.13 ± 0.02	0.762 ± 0.014	1	0.649 ± 0.021	0.227 ± 0.005	0.195 ± 0.009	−1.53	0.992
Freon 11/113	1.11 ± 0.01	NBS/Br_2	15.47 ± 0.18	1.81 ± 0.06	0.794 ± 0.012	1	0.634 ± 0.012	0.242 ± 0.002	0.203 ± 0.005	−1.56	0.990
Freon 113	1.24 ± 0.01	NBS/Br_2	11.58 ± 0.30	1.52 ± 0.04	0.825 ± 0.029	1	0.545 ± 0.006	0.297 ± 0.009	0.245 ± 0.007	−1.38	0.987
Freon 113/112	1.48 ± 0.02	NBS/Br_2	5.71 ± 0.13	2.03 ± 0.05	0.817 ± 0.016	1	0.622 ± 0.004	0.243 ± 0.009	0.257 ± 0.007	−1.20	0.989
Freon 112	1.82 ± 0.03	NBS/Br_2	6.26 ± 0.08	1.72 ± 0.04	0.859 ± 0.017	1	0.683 ± 0.004	0.268 ± 0.010	0.254 ± 0.007	−1.19	0.991
Freon 11	0.99 ± 0.002	Br_2/ ethylene oxide		3.74 ± 0.61	0.650 ± 0.013	1	0.596 ± 0.075	0.420 ± 0.051	0.189 ± 0.015	−1.50	0.965
Freon 11		Br_2		2.82 ± 0.35	0.783 ± 0.012	1	0.693 ± 0.007	0.203 ± 0.001	0.201 ± 0.020	−1.65	0.980
Freon 112		Br_2		1.53 ± 0.11	0.733 ± 0.018	1	0.655 ± 0.007	0.303 ± 0.004	0.220 ± 0.020	−1.16	0.958

[a] Viscosity of each reaction mixture is relative to Freon 11 at 23 °C.

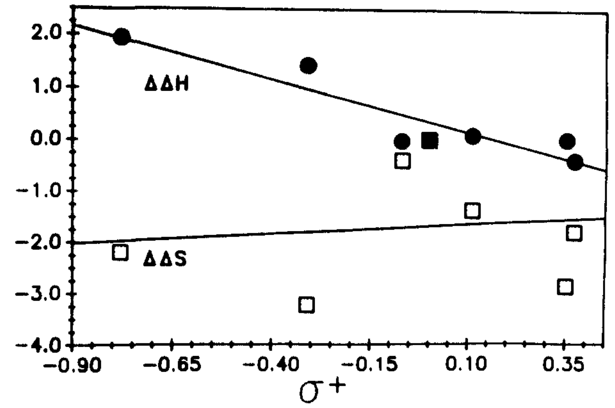

Figure 3. Plot of the activation parameters ΔΔ*H* (●) and ΔΔ*S* (□) vs σ^+ calculated for the temperature-dependent relative rates of bromination in Freon solutions at constant viscosity.

Discussion

The viscosity dependence of the Hammett linear free energy relationship at constant temperature is described by a complex function; see eqs 5–8.

$$\rho^{\text{obs}} = \log\,(k_1/k_0)^{\text{obs}}/\sigma^+ =$$
$$\log\,(k_1/k_0)^{\text{vp}}/\sigma^+ + \log\left(\frac{\alpha + k_0(\text{HBr})\eta}{\alpha + k_{-1}(\text{HBr})\eta}\right)\Big/\sigma^+ \quad (8)$$

The function has a positive slope; i.e., as the viscosity becomes smaller, the value of ρ becomes more negative. See Figure 1. As predicted, the more viscous the media the more important is cage reversal. Since the least reactive substrates show the smallest amount of reversal, the apparent ρ values become less negative (i.e., less selective) as more of the least reactive radicals escape cage reaction and form brominated products; see Table I. When molecular bromine was used as a brominating agent (see the last two entries in Table I), the resulting benzylic radicals are subject to both internal and external return, although external return may not be kinetically important, reversal affects the product ratios from both of these processes simultaneously, and in the same solvent an even more positive ρ value should be obtained. When compared with the values obtained from NBS/Br_2 reactions carried out in the same solvent, the ρ values are almost the same. However, in the reactions carried out with molecular bromine the kinetics for the *p*-methoxy substituent could not be obtained since nonbenzylic halogenation takes place. Without this point, the $\rho(\sigma^+)$ values were less accurate and the small difference between the ρ's obtained by the two methods is probably not experimentally meaningful. The use of NBS as the brominating agent assured the absence of external return[19] and established cage reversal as the only kinetically complicating reaction. An extrapolation of the function to the vapor-phase viscosity, η_{vp}, where cage reversal will be 0 yields an approximate ρ in the absence of reversal reactions. Since it is not possible to evaluate the function, the intercept, ρ at $\eta_{\text{vp}}/\eta_{\text{Freon11}}$, can be approximated by a straight line to give an extrapolated value, ρ_{ext}, for the vapor-phase value of $\rho_{\text{ext}} = -2.0$. In the absence of reversal, the value of $\rho_{\text{ext}} = -2.0$ suggests that benzylic abstraction by a bromine atom is the reaction most sensitive to polar effects that is to date reported. The observation of a linear free energy correlation with σ^+ substituent constants has been interpreted as evidence for a polar transition state. The excellent correlation with σ^+, while only fair correlations were obtained with σ substituent constants, was consistent with previously reported correlations[13,17,21] but is contrary to the correlation with σ value that was reported at low temperature.[17]

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[19] Tanner, D. D.; Meintzer, C. P.; Dionarian, N.; Singh, H.; Tsai, E. C.; Oumar-Mahamat, H. *J. Am. Chem. Soc.* **1990**, *112*.

[20] Gussell, G. A.; Desmond, K. M. *J. Am. Chem. Soc.* **1986**, *85*, 3139.

[21] Walling, C.; Rieger, A. L.; Tanner, D. D. *J. Am. Chem. Soc.* **1963**, *85*, 3129.

Table II. Relative Reactivities for Benzylic Bromination of Substituted Toluenes vs Toluene and Their Mixture Viscosities

temp, °C	solvent	rel viscosity[a]	log (k_Y/k_H)								
			p-CH_3	*m*-CH_3	*p*-F	*p*-Cl	*m*-F	*m*-Cl	*p*-*t*-Bu	ρ	*r*
10	CCl_4[b]	1.61 ± 0.01	0.260	−0.032	−0.056	−0.260	−0.337	−0.481		−1.04	0.945
60	CCl_4[b]	1.18 ± 0.01	0.364	0.029	−0.022	−0.187	−0.444	−0.585		−1.37	0.966
10	CH_2Cl_2[c]	1.02 ± 0.01	0.608		−0.122	−0.249	−0.595	−0.748	0.472	−1.83	0.980
23	CH_2Cl_2[c]		0.592		−0.138	−0.264	−0.639	−0.732	0.492	−1.86	0.980

[a] Viscosity of each reaction mixture relative to Freon 11 at 23 °C. [b] The relative rates were taken from ref 17, NBS bromination. [c] Benzylic bromination with the ethylene oxide/bromine reagent.

Table III. Relative Rates of Bromination of Meta- and Para-Substituted Toluenes vs Toluene at Constant Relative Viscosity ($\eta_i/\eta_{Freon11}$ (23 °C) = 1.253 ± 0.009) and at Different Temperatures

solvent	temp, °C	reagent	*p*-MeO	*p*-Me	*p*-F	H	*p*-Cl	*m*-F	*m*-Cl	ρ	*r*
Freon 11	−18	NBS/Br_2	13.80 ± 0.43	3.95 ± 0.14	0.765 ± 0.006	1	0.66 ± 0.017	0.216 ± 0.001	0.171 ± 0.001	−1.67	0.987
Freon 113	23	NBS/Br_2	11.58 ± 0.30	1.52 ± 0.04	0.825 ± 0.029	1	0.545 ± 0.006	0.29 ± 0.009	0.245 ± 0.007	−1.38	0.987
Freon 112	70	NBS/Br_2	5.05 ± 0.17	1.98 ± 0.01	0.772 ± 0.012	1	0.583 ± 0.021	0.211 ± 0.005	0.206 ± 0.007	−1.22	0.981

Table IV. Differential Activation Parameters of Photobromination (−18 to +70 °C) of Substituted Toluenes by NBS/Br_2 in Freon Solution at Constant Viscosity ($\eta_i/\eta_{Freon11}$ = 1.250 ± 0.009)

differential activation parameter	*p*-OCH_3	*p*-CH_3	*p*-Cl	*m*-F	H	*p*-F	*m*-Cl
$\Delta\Delta H^{\ddagger}$	1.9	1.4	0.086	0.0073	0	−0.022	−0.40
$\Delta\Delta S^{\ddagger}$	−2.2	−3.2	−1.4	−2.7	0	−0.40	−1.8

Temperature Dependence of the Activation Parameter. A calculation of the activation parameters, $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$, for each of the substrates when the temperature dependence of each competitive rate is determined at constant viscosity is given in Table IV. A plot of the relative activation parameters determined at constant viscosity, Table IV, for each substituent vs the σ^+ values illustrates the dependence of the relative rate to either enthalpy or entropy; see Figure 3.

Quite a good correlation was obtained for the $\Delta\Delta H^{\ddagger}$ plot, which showed a negative slope. The $\Delta\Delta S^{\ddagger}$ correlation, while extremely scattered, appeared to be, within experimental error, temperature independent. For reactions considered to be isoentropic, the absolute value of ρ decreases with temperature as expected for reactions controlled by enthalpy. The parameters do not show an isokinetic relationship.

Conclusions

The interpretations of the kinetic results obtained from studies of the temperature dependence of competitive benzylic brominations of toluene and substituted toluenes are in error due to masking of the desired structure–reactivity relationships by viscosity-dependent internal return of the radical–hydrogen pair. As the relative rates of cage return are not in the same ratio as the rates of abstraction, the effect of a change of structure on the reactivity of the substrates is masked by extensive cage return. In these reactions, which are near thermoneutral, the actual temperature-dependent kinetic behavior must be determined in solvents at constant viscosity.

In general, solution-phase reactions whose rates are near the diffusion limit must all be strongly influenced by the viscosity of the media in which the reaction is carried out. Since solvent viscosity is temperature dependent, the interpretation of temperature-dependent kinetics must also take into account changes in the rates of diffusion of the caged reactants.

Experimental Section

Materials. All reagents were commercially available and were distilled or recrystallized before using. GLPC analyses showed all materials to be >99 mol % pure. Ethylene oxide was distilled before use. *N*-Bromosuccinimide, NBS (Aldrich Chemical Co.), was recrystallized from hot water and dried over P_2O_5. Bromine (Chemonics Scientific Ltd., reagent grade) was washed three times with concentrated sulfuric acid and distilled from P_2O_5 through an 18-in. Vigreux column.

Viscosity Measurements. The viscosities of all the solvent mixtures reported in this work were determined at the temperatures indicated with an Ostwald viscometer, calibrated with Freon 11 as a standard (23 °C).[14]

NBS–Bromine Reactions. Weighed amounts of NBS were placed in Pyrex reaction ampules. A mixture of 2–4 of the toluene, substrates, internal standard (*p*-dichlorobenzene), and solvent was prepared and analyzed by GLPC, and its viscosity was measured at 23 °C. In the absence of light, an aliquot of this solution and an aliquot of a dilute solution of bromine were added to each ampule. The reaction ampules were degassed by freeze–thaw (three cycles), sealed, thermostated at 23 °C, and irradiated through a Pyrex water bath with a 300-W incandescent lamp. During irradiation, the nonhomogeneous mixture was continuously shaken. After the reactions were completed or nearly completed, the mixture was treated with moist potassium iodide, and sodium thiosulfate, dried over anhydrous sodium carbonate, and analyzed by GLPC using a 50-m glass capillary column (SE-30). The relative rates of reaction were calculated from the disappearance of reactants.[20] All quantitative values were determined from three or more experiments, and the molar values were determined by using standard calibration curves. The areas were measured by using a HP5840A GC terminal interfaced to a HP5840A gas chromatograph fitted with an FID detector.

Typical NBS–Br_2 Competitive Bromination. In the absence of light, an aliquot of Freon 11 solution (2 mL) of four substrates, toluene (0.2 M), *p*-xylene (0.25 M), *p*-fluorotoluene (0.2 M), and *m*-chlorotoluene (0.2 M); an internal standard, *p*-dichlorobenzene (0.04 M); and molecular bromine (10 μL of 10% solution in Freon 11, (10^{-2} M)) were placed in a Pyrex ampule that contained a weighed amount of NBS (0.212 g (0.60 M)). The mixture was degassed, and the ampule was sealed. After the reaction vessel had been thermostated at the desired temperature, it was exposed to irradiation while the nonhomogeneous mixture was continuously shaken. In all reactions, enough NBS was used to ensure that at least 10% of each substrate had reacted. After reaction, the mixture was treated as described earlier.

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