748. *Kinetic Studies of the Fluorene Series. Part III.*[1] *The Reaction of 2-Substituted Fluorenones with Sodium Borohydride*

By J. Alwyn Parry and Keith D. Warren

A kinetic study has been made of the reduction of 2-substituted fluorenones with sodium borohydride in isopropyl alcohol. The reaction is inhibited by electron-releasing groups and accelerated by electron-withdrawing groups, although changes in both the energies and entropies of activation are involved.

In contrast with the 9-diazofluorene system, the influence of 2-substituents on the reactivity at the 9-position can be satisfactorily correlated by Hammett-type equations without assuming the operation of abnormally large resonance contributions. This difference is discussed in terms of the aromaticity of the five-membered ring.

The influence of 2- and 3-substituents on the reactivity of fluorenone in oxime formation has been studied by Dickinson and Eaborn.[2] Such condensation reactions are, however, now known [3,4] to be kinetically complex, and substituent effects on carbonyl group reactivity may be more readily assessed from rates of reduction by sodium borohydride in isopropyl alcohol.

Recently, Smith and Bayer [5] recorded results for fluorenone and twelve 2- and 3-substituted derivatives in which the 2-amino- and 2-methoxy-derivatives showed substantial negative deviations from the Hammett, $\rho\sigma$ correlation. This prompted the repetition of the work and the study of six new 2-substituents.

Table 1

Reaction of 2-substituted fluorenones with sodium borohydride in isopropyl alcohol

Substituent	H	Br	NH_2	F	OCH_3	CN	CO_2CH_3
10^4k (l. mole^{-1} sec.$^{-1}$) (25·00°)	80·9	862	17·9	763	113	7350	799
10^4k (l. mole^{-1} sec.$^{-1}$) (10·10°)	29·6	396	7·15	279	36·1	4120	333
E_A (kcal.)	11·3	8·8	10·3	11·3	12·8	6·5	9·9
$-\Delta S\ddagger$ (e.u.)	32·1	36·0	38·4	27·7	26·4	39·3	32·5

Substituent	I	Cl	CH_3	C_6H_5	$NH{\cdot}CO{\cdot}CH_3$	SCH_3	NO_2
10^4k (l. mole^{-1} sec.$^{-1}$) (25·00°)	852	968	65·8	161	129	212	10,500
10^4k (l. mole^{-1} sec.$^{-1}$) (10·10°)	355	410	19·7	59·6	47·4	75·8	4920
E_A (kcal.)	9·9	9·7	13·6	11·2	11·3	11·6	8·5
$-\Delta S\ddagger$ (e.u.)	32·4	32·7	25·0	31·2	31·4	29·4	31·8

Table 2

Spectrophotometric data

Substituent	H	Br	NH_2	F	CO_2CH_3	CN	CH_3
$\lambda_{max.}$ (mμ)	383	403	500	392	383	385	402
ε	251·6	390·0	481·4	192·4	677·5	708·1	275·1

Substituent	I	Cl	OCH_3	C_6H_5	SCH_3	$NH{\cdot}CO{\cdot}CH_3$	NO_2	
$\lambda_{max.}$ (mμ)	406	404	430	415	445	425	410 *	420 *
ε	498·1	319·9	323·8	674·2	577·2	514·0	758·0	468·7

* Not maxima.

The present results (Table 1) differ significantly from the earlier figures and yield an excellent linear Hammett plot in which the 2-amino- and 2-methoxy-derivatives are satisfactorily included.

---

[1] Part II, K. D. Warren, *J.*, 1963, 598.

[2] J. D. Dickinson and C. Eaborn, *J.*, 1959, 3641.

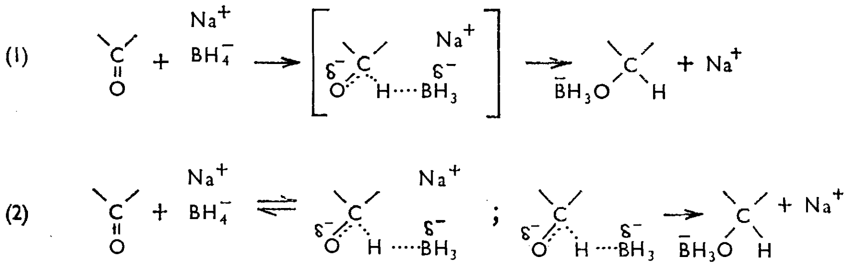
[3] B. M. Anderson and W. P. Jencks, *J. Amer. Chem. Soc.*, 1960, **82**, 1773.

[4] W. P. Jencks, *J. Amer. Chem. Soc.*, 1959, **81**, 475.

[5] G. G. Smith and R. P. Bayer, *Tetrahedron*, 1962, **18**, 323.

Mechanism of Reaction.—The borohydride reduction of carbonyl groups has been shown [6] to proceed *via* rate-determining transfer of the first hydrogen atom to the carbon atom of the keto-group, followed by rapid replacement of the remaining hydrogens by alkoxy-residues. This may involve either (1) the direct reaction of the borohydride ion with the carbonyl function or (2) the initial formation of a complex and subsequent hydride ion transfer.

For several ketones, in addition to the present series, substantial negative entropies of activation are found.[6] Also, in isopropyl alcohol, lithium borohydride is about three times more reactive than sodium borohydride,[7] presumably because of the strong polarising field of the small lithium ion, since the salts are known to react as ion pairs.[7] These observations, though, are consistent with either mechanism, particularly when solvation and ion-pairing are likely to contribute to the process.



Hammett treatment of the present data, using σ_m constants, yields however, a ρ value of $+3{\cdot}06$, suggesting that sodium borohydride is a moderately strong nucleophile and that a fairly polar transition complex, involving the formation of a C–H bond, with some loss of conjugation is likely. In addition, preliminary molecular orbital calculations indicate that reactivity at the 9-position is here better correlated against charge densities than against localisation energies, and also suggests an early transition state.

Energy–Entropy Relationships.—As expected, the reaction is inhibited by electron-supplying substituents, and facilitated by electron-withdrawing groups. The normal increase in activation energy with decrease in $\log_{10} k_{\mathrm{rel}}$ is observed, and $-\Delta S^{\ddagger}$ increases as E_{A} decreases.

This compensating variation of E_{A} with $\Delta S^{\ddagger}$ is often observed;[8,9] in Part II it was found for the acid-catalysed solvolysis of 2-substituted 9-diazofluorenes, and explained in terms of solute–solvent interactions. Whilst this factor may contribute,[10,11] the relationship is now thought to arise normally from the invariant shapes of the potential-energy surfaces for a series of similar reactants.[11,12]

The E_{A} *vs.* $\Delta S^{\ddagger}$ plot gives an isokinetic temperature of 210°, compared with a value of 340° for the diazofluorene series. Both values differ sufficiently from the observation temperatures for Hammett correlations to be fully reliable.

Application of the Hammett Equation.—In Part II,[1] the influence of 2-substituents on reactivity at the 9-position of fluorene derivatives was considered. It was postulated that such groups, formally *meta*-substituents, could sometimes, depending on reaction type, transmit T effects to the reaction site *via* the unsubstituted ring, thus showing partial *para*-character. Equations involving σ_m and σ_p constants, based on the Taft [13] and

---

[6] H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, 1957, **1**, 214.
[7] H. C. Brown and K. Ichikawa, *J. Amer. Chem. Soc.*, 1961, **83**, 4372.
[8] R. A. Fairclough and C. N. Hinshelwood, *J.*, 1937, 538.
[9] J. Leffler, *J. Org. Chem.*, 1955, **20**, 1202.
[10] K. J. Laidler, *Trans. Faraday Soc.*, 1959, **55**, 1725.
[11] A. V. Willi, *Chimia (Switz.)*, 1961, **15**, 558.
[12] P. Ruetschi, *Z. phys. Chem. (Frankfurt)*, 1958, **14**, 277.
[13] R. W. Taft and I. C. Lewis, *J. Amer. Chem. Soc.*, 1958, **80**, 2436.

Yukawa-Tsuno[14] treatments, were therefore used. However, results of no physical significance can arise (*viz.*, the constants relating to the two σ_R or σ^+ terms may be of opposite sign) and the equation below containing only *meta*-constants is now used. The operation of T effects is assessed from any abnormal enhancement of the resonance contributions to the σ-constants. (The use of equations based on σ^+ values is now less satisfactory, since for many substituents the values of σ^+ and σ scarcely differ significantly.)

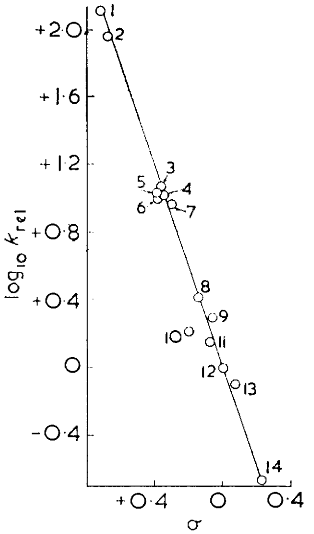


FIGURE 1. Relationship between substituent constants and relative rates of reduction of 2-substituted fluorenones

2-Substituents: 1, NO_2; 2, CN; 3, Cl; 4, I; 5, Br; 6, CO_2CH_3; 7, F; 8, SCH_3; 9, C_6H_5; 10, $NH{\cdot}CO{\cdot}CH_3$; 11, OCH_3; 12, H; 13, CH_3; 14, NH_2.

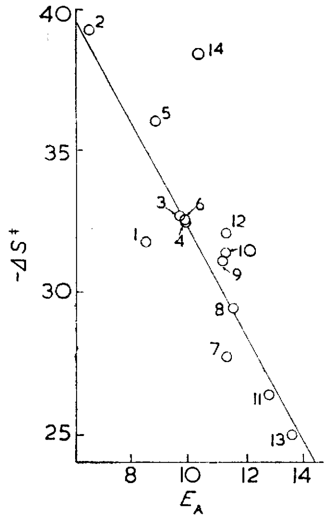


FIGURE 2. Relationship between energies and entropies of activation. (The numbers have the same meaning as in Figure 1.)

$$\log_{10} k_{\text{rel}} = \rho(\sigma_I + a\sigma_{R,m})$$

The results at 25·00° gave the correlation (Figure 1) $\rho = +2{\cdot}950$, $a = +1{\cdot}228$ ($\rho = +2{\cdot}975$, $a = +1{\cdot}182$ excluding the 2-$NH{\cdot}CO{\cdot}CH_3$ value) whilst correlation by the standard σ_m values requires $a = 1{\cdot}00$.

For the 9-diazofluorene series, the addition of values for the 2-phenyl and 2-thiomethyl derivatives[15] ($k_{\text{rel}} = 0{\cdot}956$ and $0{\cdot}887$, respectively, at 25·00°) to those previously reported yields the correlation $\rho = -1{\cdot}637$, $a = +1{\cdot}795$.

Clearly, resonance effects of 2-substituents appear to operate far more efficiently in 9-diazofluorenes than in fluorenones. This could be a composite effect. Reactions involving loss of conjugation between ground and transition states may produce[16] a values of less than unity; such loss of conjugation, if offset by abnormally large tautomeric effects in the ground state, could produce the present result.

However, direct hydrogen transfer is probably rate-determining and loss of conjugation incomplete. Furthermore, in the diazo-series, where hydrogen transfer is also rate-controlling, some loss of conjugation must occur too. Since the delocalisation energy of 9-diazofluorene is substantially greater than that of fluorenone,[17] and this loss therefore likely to be the more significant, greater resonance effects in the diazofluorenes are then implied.

---

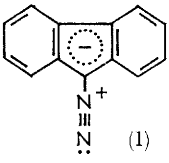
[14] Y. Tsuno, T. Ibata, and Y. Yukawa, *Bull. Chem. Soc. Japan*, 1959, **32**, 960; Y. Yukawa and Y. Tsuno, *ibid.*, pp. 965, 971.

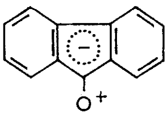
[15] J. A. Parry and K. D. Warren, unpublished results.

[16] J. D. Dickinson and C. Eaborn, *J.*, 1959, 3036.

[17] K. D. Warren and J. R. Yandle, unpublished calculations.

Mechanistically similar reactions of the diazo-group do not usually show abnormal resonance effects; the reaction of benzoic acid with substituted diphenyldiazomethanes in toluene [18] shows a similar ρ value but nearly normal resonance contributions ($\rho = -1{\cdot}513$, $a = +1{\cdot}186$). When, however, the diazo-function is attached to a cyclopentadiene ring, structures such as (I) can contribute, producing substantial aromatic character in the


(I)


(II)

central ring, but the analogous form for fluorenone (II) requires a polarity contrary to the normal tautomeric displacement in carbonyl linkages.

It is tempting then to infer that the more effective transmission of *T* effects to the 9-position in the diazofluorene system is due to the greater ground state aromaticity of the five-membered ring, as reflected also in the delocalisation energies. This, though, is an oversimplification; molecular orbital calculations based on the localisation approximation,[17] and borne out by preliminary results,[19] indicate that, in the 4-position, resonance effects should be greater in the ketone series than in the 9-diazofluorenes. A full treatment will therefore be presented when studies of 3- and 4-substituted derivatives are complete.

It was reported by Smith and Bayer [5] that strongly electron-supplying (+*T*) groups, 2-OCH_3, 2-NH_2, and 2-F, diverged markedly from the Hammett $\rho\sigma_m$ plot, reacting more slowly than predicted. The results of Table 1, though, yield almost as good a correlation with the standard σ_m constants as when the above equation is used. In particular, the methoxy-group is found to activate, not deactivate, and neither this point nor those for the fluoro- and amino-groups deviate seriously from the regression line. In any case, although Smith and Bayer ascribed their low values for these groups to loss of conjugation in the transition state, such a process should reduce the +*T* effects of the substituents and thereby enhance the rate.

Other +*T* substituents, 2-SCH_3, 2-C_6H_5, and 2-CH_3, conform satisfactorily to the $\rho\sigma_m$ plot, the latter two derivatives in fact reacting slightly more rapidly than predicted; in the diazo-series large +*T* contributions operate in both the 2-phenyl and 2-thiomethyl compounds. Only the 2-NH·CO·CH_3 group (also +*T*) behaves anomalously; here the large uncertainty ($\pm 0{\cdot}1$) in the σ_m value may be responsible.[20] A reduced −*T* effect is found for the 2-CO_2CH_3 compound; the rate here compares with those of the halogen derivatives, whereas in the diazofluorenes the group is appreciably more electron-withdrawing.

Comparison with Other Ketones.—At 25·00° benzophenone reacts with sodium borohydride in isopropyl alcohol about five times more slowly [6] than fluorenone; a considerable increase in activation energy ($E_A = 13{\cdot}6$ kcal.) is only partially offset by a more positive entropy ($\Delta S^\ddagger = -27{\cdot}7$ e.u.). Acetone ($E_A = 9{\cdot}3$ kcal., $\Delta S^\ddagger = -39{\cdot}1$ e.u.) is about 1·5 times as reactive as fluorenone.[6]

The more positive $\Delta S^\ddagger$ value for benzophenone as compared with acetone has been ascribed to the restriction of rotation of the phenyl groups, required for conjugation with the keto-function, in the ground state. Reduced conjugation in the transition complex should then make $\Delta S^\ddagger$ more positive than otherwise expected. For fluorenone, $\Delta S^\ddagger$ is therefore more negative than for benzophenone, since, in the transition state, the 4a,5a-bridge will still restrict the rotation of the phenyl residues.

The decrease in E_A from benzophenone to fluorenone may also be due to differences in

---

[18] C. K. Hancock, R. F. Gilby, and J. S. Westmoreland, *J. Amer. Chem. Soc.*, 1957, **79**, 1917.
[19] K. D. Warren and J. R. Yandle, unpublished results.
[20] Y. Okamoto and H. C. Brown, *J. Org. Chem.*, 1957, **22**, 485.

conjugation; molecular orbital calculations [17] indicate that the localisation energy for nucleophilic attack at the central carbon atom should be smaller for the latter. The value of E_A and $\Delta S^\ddagger$ found for fluorenone thus suggest that some loss of conjugation occurs in the rate-determining step as here proposed.

EXPERIMENTAL

Reagents.—Isopropyl alcohol, heated under reflux for 6 hours with calcium hydride and redistilled therefrom, had b. p. 82·5° and d_4^{25} 0·7829. Sodium borohydride was recrystallised from diglyme [21] and stock solutions filtered (sinter) if necessary before use. The use of filtered solutions obtained from reagent grade material [5] is unsatisfactory, since the reaction is extremely sensitive to trace impurities.

Kinetic Runs.—The sparing solubility of some fluorenones necessitated the use of sodium borohydride concentrations of about $2{\cdot}5 \times 10^{-3}$M, at which the iodimetric determination used by Brown *et al.*[6] was inapplicable. The initial concentration of sodium borohydride was therefore calculated from the standardisation of the stronger stock solutions, and the reaction followed by spectrophotometric determination of the ketone concentrations.

The reaction vessels were immersed in a Townson and Mercer E27 Major thermostat maintained at 25·00° ± 0·01° or 10·10° ± 0·01°, and standard borohydride and the appropriate ketone, at reaction temperature, mixed with thorough shaking; 10-ml. samples were withdrawn at intervals, quenched with 5 ml. of a 10 : 1 mixture of isopropyl alcohol and 1N-sulphuric acid, and set aside for about 4 hours. These were then drawn through a No. 5 porosity sinter into a 25-ml. graduated flask, rinsed through with isopropyl alcohol, and made up to the mark. The optical densities were determined at the wavelengths shown, at which the absorptions of the reaction products were negligible, using a Unicam S.P. 500 spectrophotometer. From the previously determined extinction coefficients the concentrations of unreacted ketone were found.

The values of k, the second-order rate constant, were calculated from the expression [6] $k = (1/t)[2{\cdot}303/(4b - a)] \log_{10} [a(b - x)/b(a - 4x)]$, where a = initial ketone concentration, b = initial borohydride concentration, and $x = \frac{1}{4}$ amount of ketone that has reacted after a time t. The reaction gave good second-order kinetics for at least 60% of its course. A tendency to reversal towards the end was due to dissolved oxygen and the effects were minimised by studying only the first 60% of the process, using sodium borohydride in excess. The back reaction is possibly more pronounced at high dilutions since in comparison runs on benzophenone it supervened at an early stage. However, at 25·00°, initial rates gave $k = 14{\cdot}0 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$, in satisfactory agreement with the recorded value [6] of $15{\cdot}8 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

For each fluorenone not less than five consistent values of k were obtained, for widely different values of $(a - 4b)$. With two exceptions, the standard deviation from the mean was less than ±3% and the probable errors in E_A and $\Delta S^\ddagger$ not more than ±0·6 kcal. and ±2·0 e.u. The sparing solubility and extreme reactivity of the 2-cyano- and 2-nitro-compounds resulted in deviations of ±5% and the corresponding energies and entropies are correct to within ±1·1 kcal. and ±4·0 e.u., respectively.

Ketones.—These were all recrystallised to constant melting point and with two exceptions were prepared by recorded methods. Except for the 2-thiomethyl derivatives, which is new, the melting points (uncorr.) agreed satisfactorily with literature values.

2-*Phenylfluorenone.* 2-Aminofluorenone (2·0 g.) was converted by the Gomberg–Hey technique into N-*nitroso*-2-*acetamidofluorenone* (2·5 g.), m. p. 85° (expl.). This was heated in dry benzene (150 ml.) at 55° for 6 hours. Removal of solvent, chromatography on neutral alumina, and recrystallisation from ethanol gave 2-phenylfluorenone (0·9 g., 35%), m. p. 139° (lit.,[22] 140—141°).

2-*Thiomethylfluorenone.* 2-Aminofluorenone (2·0 g.) was diazotised at 2° with 40% w/w sulphuric acid (9 ml.), glacial acetic acid (30 ml.), and sodium nitrite (0·9 g.) in water (10 ml.). The diazonium sulphate was separated, washed with ethanol and ether, suspended in water (50 ml.), and added to potassium xanthate (1·7 g.) in water (25 ml.) at 70°. After ½ hr. the aqueous layer was removed and the tarry product dissolved in benzene, chromatographed on neutral alumina, and recrystallised from methanol, giving S-9-*oxofluoren*-2-*yl ethyl xanthate,*

---

[21] H. C. Brown, E. J. Mead, and B. C. Subba Rao, *J. Amer. Chem. Soc.*, 1955, **77**, 6209.

[22] C. Weizmann, E. Bergmann, and L. Haskelberg, *J.*, 1939, 391.

yellow needles (0·60 g., 26%) m. p. 130—131° (Found: C, 63·85; H, 4·2; S, 21·1. $C_{16}H_{12}S_2O_2$ requires C, 64·0; H, 4·0; S, 21·4%). The above product (0·45 g.) was heated under reflux in ethanol with sodium hydroxide (0·5 g.) for 10 min. and treated with methyl iodide (5 ml.). After 15 min. the solvent was removed, the residue dissolved in benzene, chromatographed on neutral alumina, and recrystallised from ethanol, yielding 2-*thiomethylfluorenone* (0·20 g., 60%), orange-yellow plates, m. p. 84—85° (Found: C, 73·5; H, 4·1; S, 13·8. $C_{14}H_{10}OS$ requires C, 74·3; H, 4·45; S, 14·2%).

One of us (J. A. P.) thanks the University College of South Wales and Monmouthshire for financial assistance.

University College of South Wales and Monmouthshire,
Cathays Park, Cardiff.

[*Received, November* 30*th*, **1964.**]