of two without risk of overlooking any significant peaks in the minimum functions.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICHIGAN
C. E. NORDMAN
KAZUMI NAKATSU

RECEIVED DECEMBER 17, 1962

THE MECHANISM OF BENZYLIC BROMINATION WITH N-BROMOSUCCINIMIDE

Sir:

Studies pertaining to allylic brominations or the apparently analogous benzylic brominations by N-bromosuccinimide (NBS) have been widely accepted as supporting a free-radical chain mechanism involving succinimidyl radicals as the chain-carrying species.[1] The chief alternative to this pathway, one involving free bromine, was originally suggested by Goldfinger,[2] and has been promulgated by Sixma and Riem[3] and by McGrath and Tedder.[4]

The most extensive mechanistic studies of the allylic bromination reaction have been reported by Dauben and his students,[5-7] who have established the radical chain character of the reaction and have determined the over-all kinetics of the bromination of cyclohexene. For the brominations initiated by the decomposition of 2,2'-azo-bis-isobutyronitrile (AIBN), the rate of disappearance of NBS depends upon the concentrations of reactants according to equation 1.

$$-d[NBS]/dt = k[NBS]^0[RH]^1[AIBN]^{1/2} \quad (1)$$

This rate expression corresponds to that derived from these reactions (where C· = initiator fragment; SNBr = N-bromosuccinimide; and RH = hydrocarbon substrate)

$$AIBN \longrightarrow 2C\cdot \quad (2)$$

$$C\cdot + SNBr \longrightarrow CBr + SN\cdot \quad (3)$$

$$SN\cdot + RH \longrightarrow SNH + R\cdot \quad (4)$$

$$R\cdot + SNBr \longrightarrow RBr + SN\cdot \quad (5)$$

$$2SN\cdot \longrightarrow \text{stable product(s)} \quad (6)$$

No corresponding studies have been attempted on benzylic systems, nor have any comparisons been made between benzylic and allylic systems which allow one to state whether or not the same mechanism operates in both cases for brominations by NBS.

Although N-chlorosuccinimide is thought to serve in chlorination reactions only to provide a low, constant concentration of molecular chlorine,[2,8] a similar role for NBS has been rejected on the basis of the studies of Dauben[5-7] and of work by Kooyman,[9] who determined the relative reactivities of a series of substituted toluenes toward bromine and NBS. Both series of reactions obeyed the Hammett correlation, but yielded different values of the reaction constant, rho (−1.55 for NBS and −1.05 for bromine). The postulation of a common hydrogen abstracting species for the two reactions, namely, Br·, would demand identical rho values.

We have determined the relative reactivities of a series of substituted toluenes toward NBS, N-bromotetrafluorosuccinimide (NBTFS), N-bromotetramethylsuccinimide (NBTMS), and molecular bromine, in benzene solution at 80°, and have found all values of the reaction constants to be identical within the limits of experimental error. Further examination of the last two brominating agents at 19° reveals that they also display identical rho values at this temperature.

TABLE I

RELATIVE RATES[a] FOR THE BROMINATION OF SUBSTITUTED TOLUENES LOG $k_{rel.}$ FOR INDICATED SUBSTITUENT

Brominating agent	*p*-OCH_3	*p*-CH_3	*p*-$C(CH_3)_3$	*p*-Cl	*m*-Br	*p*-CN	*T*, °C.	ρ[b]	r[c]
NBS	1.093	0.418	0.464	−0.145		−0.953	80	−1.46 ± 0.07	0.996
NBTFS		.500	.457	− .081		− .875	80	−1.45 ± .07	.996
NBTMS	0.980	.480	.402	− .168	−0.616	− .845	80	−1.36 ± .05	.997
Br_2	0.956	.383	.393	− .138	− .650	− .914	80	−1.36 ± .05	.996
NBTMS		.530		− .168	− .761		19	−1.79 ± .08	.996
Br_2		.506	.551	− .125	− .703		19	−1.76 ± .12	.994

[a] Rates relative to toluene were determined by the study of competitive reactions using quantitative n.m.r. spectroscopy for the requisite product analyses. An integrated rate expression was utilized for the calculations.[11] [b] Uncertainties are expressed as standard deviations. [c] Correlation coefficient.

All data fit the Hammett correlation best when σ^+ values are utilized. Application of standard statistical methods[10] to the data shows that when all series of data at each temperature are treated as belonging to the same set, the fit to a straight line is at least as good as for each of the individual series (see Table I). At 80°, $\rho = -1.39 \pm 0.03$ and at 19°. $\rho = 1.78 \pm 0.06$. For both cases, the correlation coefficients are 0.995.

The identity of the rho values for this widely differing series of brominating agents forces us to conclude that the same radical serves as the hydrogen abstractor in every case.[12] Supporting evidence can be found in the data of Wiberg and Slaugh,[13] who discovered that reactions involving NBS and bromine exhibit essentially the same kinetic isotope effect in the removal of α-hydrogens from toluene.

Any other conclusion would necessitate arguing that identical rho values for four different brominating agents, and identical temperature dependence of rho for two of them, is strictly coincidental. This means postulating that changes in structure of the attacking radical have essentially no effect on its sensitivity to the polar effect. Such a postulate lacks support from consideration of the different values of rho found for radical attack at the side chain of toluene, values of which vary from −0.6 through −1.8.[14-16] Hydrogen abstraction from substituted benzaldehydes has been found to be sensitive to the structure of the

(1) C. Walling, "Free Radicals in Solution," John Wiley and Sons, New York, N. Y., 1957, p. 381.
(2) J. Adams, P. A. Gosselain and P. Goldfinger, *Nature*, **171**, 704 (1953).
(3) F. L. J. Sixma and R. H. Riem, *Koninkl. Ned. Akad. Wetenschap., Proc.*, **61B**, 183 (1958).
(4) B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc.*, 80 (1961).
(5) H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 4863 (1959).
(6) H. J. Dauben, Jr., and L. L. McCoy, *J. Org. Chem.*, **24**, 1577 (1959).
(7) H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 5404 (1959).
(8) J. Adams, P. A. Gosselain and P. Goldfinger, *Bull. Soc. Chim. Belges*, **65**, 523 (1956).
(9) E. C. Kooyman, R. van Helden and A. F. Bickel, *Koninkl. Ned. Akad. Wetenschap., Proc.*, **56B**, 75 (1953).
(10) H. H. Jaffé, *Chem. Revs.*, **53**, 253 (1953).
(11) C. Walling and B. Miller, *J. Am. Chem. Soc.*, **79**, 4181 (1957).
(12) A similar conclusion has been reached through selectivity studies on benzylic halogenations leading to secondary and tertiary bromides. Private communication from Professor G. A. Russell, Iowa State University.
(13) K. B. Wiberg and L. H. Slaugh, *J. Am. Chem. Soc.*, **80**, 3033 (1958).
(14) C. Walling, ref. 1, pp. 418, 366.
(15) C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, **82**, 6113 (1960).
(16) E. S. Huyser, *ibid.*, **82**, 394 (1960).

attacking species. For perbenzoate radicals, $\rho = -0.448$ as compared with -1.668 for *p*-chloroperbenzoate radicals.[11]

If the same species indeed serves as the hydrogen abstractor in each reaction, only bromine atoms could reasonably fill this role. Presumably the halogen arises from reaction of NBS with hydrogen bromide. Equations 7, 8 and 9 represent a likely chain-propagating sequence for the reaction. Step 8 is a fast, probably ionic, reaction which can be shown to occur essentially instantaneously at $-80°$ in toluene solution.

$$Br\cdot + RH \longrightarrow R\cdot + HBr \quad (7)$$

$$HBr + SNBr \longrightarrow SNH + Br_2 \quad (8)$$

$$Br_2 + R\cdot \longrightarrow RBr + Br\cdot \quad (9)$$

The process by which molecular bromine is formed initially in the reaction mixture is not specified, but many possible sources of this chain-carrying species can be postulated.

Two groups of workers, Sixma and Riem[3] and McGrath and Tedder,[4] have shown that at very low concentrations of molecular bromine allylic substitution, rather than addition to double bonds, may be the predominant reaction with olefins. The report[3] that NBS and bromine yield the same product mixtures in the bromination of two particular toluenes with a selectivity corresponding to a rho value of about -1.2 favors the mechanism involving molecular bromine. The indicated selectivity is, however, considerably less than that observed in the present work, a difference which is thought[17] to be too large to be explained on the basis of the change in solvent from carbon tetrachloride to benzene.

Low values for the selectivity of attack by bromine may arise as a result of the operation of the reverse reaction of hydrogen bromide with benzyl radicals,[13] a difficulty which we have avoided by greatly increasing the concentration of bromine relative to hydrogen bromide in the reaction mixture. Kooyman's selectivity ratios have been reproduced under conditions involving low Br_2/HBr ratios.

The conclusions which we have reached concerning the mechanism of benzylic bromination are not necessarily valid for the analogous allylic bromination reactions. Other free-radical reactions of NBS, notably its rearrangement to β-bromopropionyl isocyanate,[18] have been shown[19] to follow courses greatly influenced by the presence of traces of olefin. It is of interest, however, that a mechanistic scheme involving the three propagating steps (7, 8 and 9), which are postulated as being consistent with our results, can be reconciled with the over-all experimental rate law observed by Dauben for the allylic bromination of cyclohexene.

Continuing efforts in this Laboratory are designed to determine the relationship between brominations in the allylic and benzylic systems and to elucidate the nature of the chain initiating steps.

Acknowledgment.—This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of these funds.

THE NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS R. E. PEARSON
URBANA, ILLINOIS J. C. MARTIN

RECEIVED OCTOBER 8, 1962

(17) G. A. Russell, *Tetrahedron*, **8**, 101 (1960).

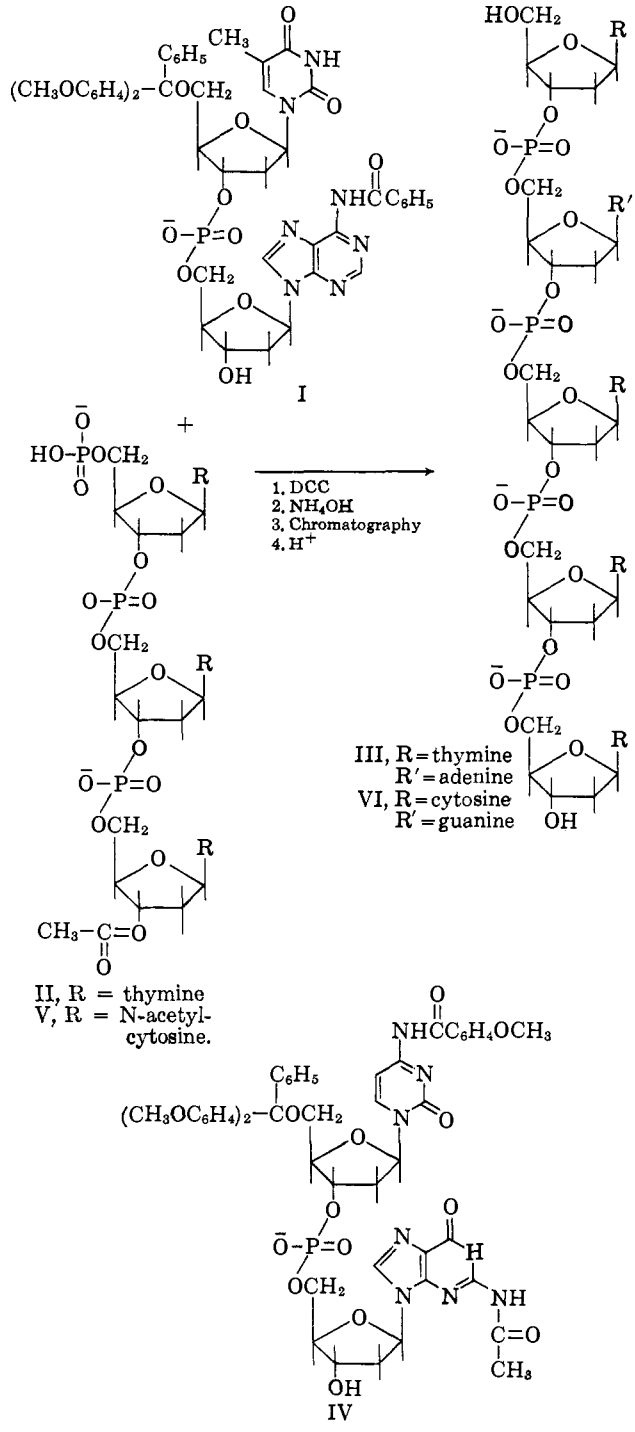
(18) J. C. Martin and P. D. Bartlett, *J. Am. Chem. Soc.*, **79**, 2533 (1957); H. W. Johnson and D. E. Bublitz, *ibid.*, **79**, 753 (1957).

(19) Unpublished work of Leslie Freiburg, Thomas Brownlee and Richard Panich.

THE SYNTHESIS OF DEOXYRIBO-POLYNUCLEOTIDES CONTAINING SPECIFIC NUCLEOTIDE SEQUENCES[1]

Sir:

Previously, methods have been reported for the preparation of suitably protected mononucleotides and for their polymerization to form homologous series of polynucleotides.[2] In the area of stepwise synthesis of oligonucleotides, studies have so far been carried out mostly with thymidine oligonucleotides[2-4] and the single synthetic experience with the mixed trinucleotide



(1) This work has been supported by grants from the National Science Foundation, Washington, D. C., the National Cancer Institute of the National Institutes of Health and the Life Insurance Medical Research Fund, New York, N. Y.

(2) H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest," John Wiley and Sons, N. Y., 1961, Chapter 5.

(3) P. T. Gilham and H. G. Khorana, *J. Am. Chem. Soc.*, **81**, 4647 (1959).

(4) G. Weimann and H. G. Khorana, *ibid.*, **84**, 419 (1962).