streptomycin isolated displayed three enhanced resonances at 13.4 (2.3 times natural abundance), 61.2 (6.5 times natural abundance), and 72.4 (4.5 times natural abundance) ppm from tetramethylsilane, which are the respective signals for carbon-5′ of streptose, carbon-6″ of *N*-methylglucosamine, and carbon-6 of streptidine.[10] The labeling of C-5′ of streptose and C-6″ of *N*-methyl-L-glucosamine is consistent with earlier work.[4,5] Labeling of C-6 of streptidine by [6-^{13}C]glucose provides definitive evidence for the stereochemistry of streptidine formation from glucose (pathway A, Figure 1).

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References and Notes

(1) Presented in part at the 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1974, Abstract No. MICR 19.
(2) (a) Paper V in the series "Carbon-13 as a Biosynthetic Tool"; (b) Paper IV: K. L. Rinehart, Jr., J. M. Malik, R. F. Nystrom, R. M. Stroshane, S. G. Truitt, M. Taniguchi, J. P. Rolls, W. J. Haak, and B. A. Ruff, *J. Am. Chem. Soc.*, **96**, 2263 (1974).
(3) Reviews: (a) J. B. Walker, *Lloydia*, **34**, 363 (1971); A. L. Demain and E. Inamine, *Bacteriol. Rev.*, **34**, 1 (1970).
(4) (a) J. Bruton, W. H. Horner, and G. A. Russ, *J. Biol. Chem.*, **242**, 813 (1967); (b) M. Silverman and S. V. Rieder, *ibid.*, **235**, 1251 (1960).
(5) (a) J. Bruton and W. H. Horner, *J. Biol. Chem.*, **241**, 3142 (1966); (b) D. J. Candy and J. Baddiley, *Biochem. J.*, **96**, 526 (1965); (c) D. J. Candy, N. L. Blumson, and J. Baddiley, *ibid.*, **91**, 31 (1964).
(6) (a) R. M. Bruce, H. S. Ragheb, and H. Weiner, *Biochim. Biophys. Acta*, **158**, 499 (1968); (b) W. H. Horner and G. A. Russ, *ibid.*, **237**, 123 (1971).
(7) M. S. Walker and J. B. Walker, *J. Biol. Chem.*, **246**, 7034 (1971).
(8) Inter alia, K. W. Bentley in "Elucidation of Organic Structures by Physical and Chemical Methods", K. W. Bentley and G. W. Kirby, Ed., Part 2, 2nd ed, Wiley-Interscience, New York, N.Y., 1973, p 177.
(9) J. Fried and O. Wintersteiner, *Science*, **101**, 613 (1945); *ibid.*, **104**, 273 (1946).
(10) M. H. G. Munro and K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, submitted.

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A Kinetic Study of a Friedel-Crafts Ethylation Reaction in Nonpolar Solvent

Sir:

Little has been reported concerning the kinetics of Friedel-Crafts alkylation reactions in nonpolar solvents. Some of the data which has been published appears to be at variance with currently accepted theories.[1] In hopes of clarifying the situation we have determined the kinetics of the $AlBr_3$ catalyzed reaction of ethyl bromide with benzene or toluene in *n*-hexane, using vacuum line procedures to optimize the exclusion of water.[2]

High purity commercially available *n*-hexane and ethyl bromide were dried over CaH_2, degassed, and stored *in vacuo* in break-tip ampoules.[2] $AlBr_3$ was synthesized, purified, and also stored in break-tip ampoules.[3] Known amounts of these reagents were condensed at −196° in a thoroughly flamed reaction flask using usual vacuum line procedures. After the addition of dry nitrogen, the reaction mixture was sealed from the line and brought to reaction temperature (15°) and stirred (spin bar). Reactions were initiated by injecting 15° previously dried (CaH_2) toluene or benzene through a rubber septum on an angled side arm of the reaction flask. Aliquots were periodically removed with a syringe, quenched with H_2O, and analyzed by flame ionization GC.[4]

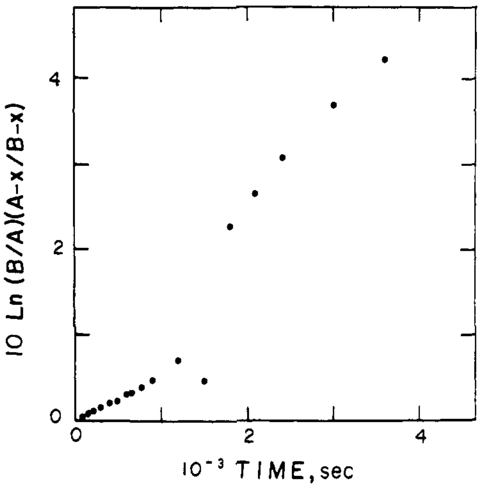

Figure 1. Typical second-order plot for reaction of benzene and ethyl bromide with $AlBr_3$ catalyst in hexane at 15°, mole ratios, 10.37:2.77:0.52:100, respectively.

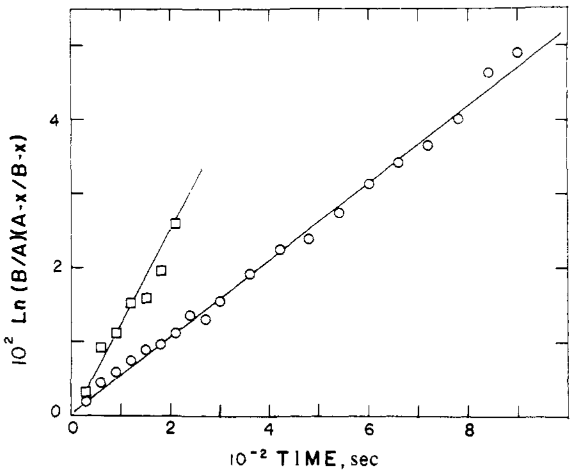

Figure 2. Typical second-order plots at short times for reaction of aromatic and ethyl bromide with $AlBr_3$ catalyst in hexane at 15°: mole ratios, circles, 10.37 (benzene):2.77:0.52:100; squares, 9.91 (toluene):0.58:0.42:100.

In both systems, layer separation occurred and was heralded by a moderately fast color change followed by a swift change from clear to slightly turbid. The colored, separated phase then finally formed either tiny droplets on the inside of the reaction walls or a very small puddle beneath the spin bar, either of which was difficult to detect. It is significant that this phenomenon occurred in either system within 30 min.

Pseudo-second-order rate plots were obtained in both systems assuming

$$d[\text{product}]/dt = k_{\text{app}}[\text{aromatic}][\text{ethyl bromide}]$$

where $k_{\text{app}} = k[AlBr_3]_0^n$. A typical graph of ln $(B/A)(A - x/B - x)$ plotted against time is presented in Figure 1. The plot is fairly linear at short times, i.e., up to the time of layer separation, and then monotonic albeit nonlinear for long times, i.e., after the time of layer separation.

Typical data for benzene and toluene systems at short

Table I. Calculated Slopes and Intercepts (with 95% Confidence Limits), and Linear Correlation Coefficients for the Aluminum Bromide Catalyzed Ethylation of Benzene and Toluene with Ethyl Bromide in *n*-Hexane at 15°

Run no.	Aromatic	Slope ± 95% C.L.	Intercept ± 95% C.L.	*r*-coef
1	Benzene	$(5.20 \pm 0.19) \times 10^{-5}$	$(4.75 \pm 9.00) \times 10^{-4}$	0.997
2	Benzene	$(8.22 \pm 0.75) \times 10^{-5}$	$(1.19 \pm 1.62) \times 10^{-3}$	0.998
3	Toluene	$(1.27 \pm 0.05) \times 10^{-4}$	$(-3.07 \pm 8.23) \times 10^{-4}$	0.999
4	Toluene	$(4.05 \pm 1.23) \times 10^{-4}$	$(1.3 \pm 7.9) \times 10^{-3}$	0.999

Table II. Rate Constants for the Aluminum Bromide Catalyzed Ethylation of Benzene and Toluene with Ethyl Bromide in *n*-Hexane at 15°

Run no.	Initial concn, *M* [Aromatic]	[alkyl halide]	[Catalyst]	Rate constant k, $l^3\ mol^{-3}\ sec^{-1}$
1	0.732^a	0.196	0.0365	7.3×10^{-2}
2	0.716^a	0.266	0.0507	7.1×10^{-2}
3	0.702^b	0.0417	0.0299	2.2×10^{-1}
4	0.708^b	0.0500	0.0450	3.1×10^{-1}

^{a} Benzene. ^{b} Toluene.

times are presented in Figure 2. The linearity of the plotted data is noteworthy. Using the usual least-squares method approach, the slopes and intercepts, along with their 95% confidence limits, and the linear correlation coefficients, were calculated and are presented in Table I.

Rates for these reactions showed a second-order dependence on $[AlBr_3]_0$. Therefore, the rate constants could be calculated from slope $= k\ (A - B)(C)^2$, where A, B, and C are the initial concentrations of aromatic, ethyl bromide, and catalyst, respectively. These data are summarized in Table II. The relative rate of toluene to benzene, k_T/k_B, is calculated from these data to be 3.7 in reasonably good agreement with Brown's selectivity relationship[5,6] (*vide infra*).

Our findings are not in harmony with recent reports by Nakane and workers.[1] From competitive and noncompetitive studies on similar systems, using ethyl or isopropyl fluoride or ethyl iodide as alkylating agent and BF_3 or $AlBr_3$ as catalysts, they reported first-order dependence on the catalyst and k_T/k_B ~0.6 in three nonpolar solvents: CCl_4, cyclohexane, and *n*-hexane. These writers further reported difficulty in maintaining homogeneity in some of their solutions.[7] Therein may lie one explanation for the apparent discrepancy between their and our findings.

We observed layer separation to occur in toluene reactions as early as 4-5% reaction and to be complete well within an hour. In Figure 3 we have plotted the data for typical reactions of benzene and toluene at long times. The result of the layer separation phenomenon is to reverse the relative order of the rates at long times. Indeed, the ratio k_T/k_B becomes 0.53 at long times, a value that agrees with Nakane's report, in which reported reaction times are on the order of 5-6 hr.

In sampling the primary layer we find the relative amount of *meta* ethylated toluene product remains constant at about 20%, then falls to 15% during the appearance of turbidity and then to 6% during the early existence of the second layer,[8] and finally rises to the thermodynamic value of 40% at long times (>120 min) which is a sure sign of isomerization. During the two-phase period in the toluene reactions we observe a continued increase in diethylated products[9] and an appearance of significant amounts of benzene (3-5%),[10] which together indicate a concomitant disproportionation reaction. Thus, our evidence suggests that side reactions, including disproportionation and isomerization, become important with the onset of the second layer.

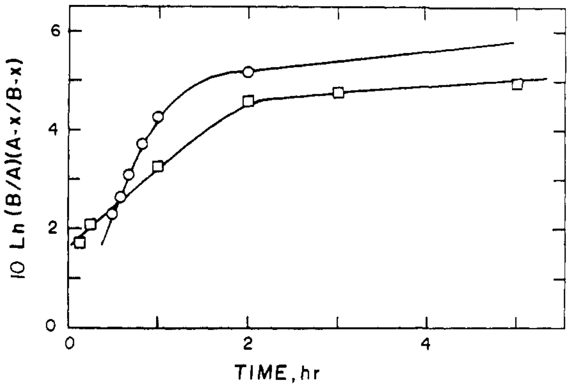

Figure 3. Typical second order plots at long times for reaction of aromatic and ethyl bromide with $AlBr_3$ catalyst in hexane at 15°: mole ratios, circles, 10.37 (benzene):2.77:0.52:100; squares, 9.91 (toluene): 0.58:0.42:100.

On the basis of the low k_T/k_B value, our system appears to involve a strong electrophile.[11] With *no* evidence of isomerization prior to the formation of the second phase,[12] we find a relatively high percentage of the *meta* isomer. Our results support Brown's theory that an attacking species of high activity (low k_T/k_B) would also show low selectivity (relatively high meta per cent).[13]

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References and Notes

(1) (a) R. Nakane, O. Kurihara, and A. Natsubori, *J. Am. Chem. Soc.*, **91**, 4528 (1969); (b) A. Natsubori and R. Nakane. *J. Org. Chem.*, **35**, 3372 (1970); (c) R. Nakane, O. Kurihara, and A. Takematsu, *ibid.*, **36**, 1753(1971).

(2) For experimental approach, see F. P. DeHaan and H. C. Brown, *J. Am. Chem. Soc.*, **91**, 4844 (1969).

(3) H. Jungk, C. R. Smoot, and H. C. Brown, *J. Am. Chem. Soc.*, **78**, 2185 (1956).

(4) Good separation of the three monoethylated toluene products was obtained with a 20 ft column containing 5% disodecylphthalate and 5% bentone 34 on 60–80 mesh Chromosorb W, at 150°.

(5) L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, **1**, 35 (1963).

(6) The average values (with standard deviation) of the monoethylated products were: 20 ± 2% meta, 49 ± 2% ortho, 31 ± 2% para. From these values partial rate factors were calculated to be $m_f = 2.2$, $o_f = 5.4$, $p_f = 6.9$, and the selectivity factor $S_f = 0.50$.

(7) Nakane observed second layer formation whenever a trace of water existed in the solution[1b] and in his last paper[1c] admits complete removal of traces of water was impossible with his experimental techniques.

(8) This may be due to the greater stability of the *meta* isomer σ-complex in the second (lower) layer. H. C. Brown and J. D. Brady, *J. Am. Chem. Soc.*, **74**, 3570 (1952).

(9) Prior to the onset of phase separation the amount of diethylated product was negligible in toluene systems and <5% of ethylated product in benzene reactions.

(10) Relative to toluene. GC analysis of reactant toluene indicated a maximum impurity level of 0.007% benzene. Thus the marked increase in benzene at long reaction time cannot be accounted for by their k_T/k_B ratio.

(11) G. A. Olah, S. Kobayashi, and M. Tashiro, *J. Am. Chem. Soc.*, **94**, 7448 (1972).

(12) In all cases the per cent meta remained constant within experimental error up to the onset of phase separation.

(13) Alkylation mechanisms for second order catalyst dependence have already been proposed: ref 2 and C. R. Smoot and H. C. Brown, *J. Am. Chem. Soc.*, **78**, 6245 (1956).

(14) Undergraduate research assistant, 1972–1974. Summer support from Research Corp. and NSF–URP.

(15) Teaching–Research Postdoctorial Fellow, 1974. Supported by Research Corporation.

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