NITRATION AND SUCCINOYLATION OF TRITIUM LABELED TOLUENE

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Abstract—Recent literature is summarized on the question of the nature of secondary hydrogen isotope effects, and on the existence of such effects, in the nitration of toluene. New experimental data presented for the mononitration of α -, *m*- and *p*-tritiated toluene samples, reveals no secondary isotope effects. It is suggested that the remarkable freedom of this aromatic nitration from hydrogen isotope effects (primary or secondary) constitutes evidence that in the transition state for the reaction, the aromatic ring has accepted very little charge from the nitronium ion. In another electrophilic substitution, *p*-succinoylation of toluene-*p*-t, the interesting result that the succinoylation product retains most of the tritium of the starting material is rationalized.

WHILE primary hydrogen isotope effects have been used for some time as criteria for certain reaction mechanisms and are now fairly well interpreted on a theoretical basis,¹ wide use of secondary isotope effects to help reveal intimate details of reaction intermediates has come more recently, and on a much less well-established theoretical basis.² Thus, in the nitration of toluene, it has been well established for some time that tritium and hydrogen are substituted at the same rate and that therefore loss of hydrogen in this substitution reaction requires less activation energy than does formation of some prior transition state, presumably one in which the aromatic ring has become positively charged due to attack by nitronium ion.³ Now, however, there is some question as to the existence of a secondary hydrogen isotope effect in this reaction and as to an interpretation of any secondary effects which may exist. The results of Swain⁴ on the relative (competitive) rates of nitration of toluene and α -deutero (or tritio) toluene showed a $k_{\rm H}/k_{\rm D}$ value of 1.002 \pm 0.002 and reportedly "demonstrated that secondary hydrogen isotope effects are absent from aromatic substitution by nitronium ion".⁵ Very recently though, on the basis of the amount of *m*-nitration in toluene and in its x-deuterated analog (3.41 \pm 0.15%) and $3.63 \pm 0.16\%$, respectively), Suhr and Zollinger have said, "Dieser Isotopen effect ist immer noch sehr klein, es kann jedoch keinem Zweifel unterliegen, dass er real ist."6

Suhr and Zollinger interpreted their results as being a consequence of a greater +I effect of the heavier hydrogen isotope causing a rate enhancement which shows

¹ L. Melander, "Isotope Effects on Reaction Rates" Ronald Press, New York, N.Y. (1960).

² Leading references on the question of the nature of secondary hydrogen isotope effects include K. T. Leffek, R. E. Robertson and S. E. Sujamori, *Chem. & Ind.* 259 (1961); L. S. Bartell, *Tetrahedron Letters*, No. 6, 13 (1960); R. E. Weston, Jr., *Tetrahedron* 6, 31 (1959); E. S. Lewis, *Ibid.* 5, 143 (1959); V. J. Shiner, Jr., *Ibid.* 5, 243 (1959); E. A. Halevi, *Ibid.* 1, 174 (1957); A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *J. Amer. Chem. Soc.* 80, 2326 (1958).

³ For a good summary of the evidence see P. B. D. De La Mare and J. H. Ridd, *Aromatic Substitution* Academic Press, New York, N.Y. (1959).

⁴ C. G. Swain, T. E. C. Knee and A. J. Kresge, J. Amer. Chem. Soc. 79, 505 (1957).

⁵ A. J. Kresge and D. P. N. Satchell, *Tetrahedron Letters*, No. 13, 20 (1959).

⁶ H. Suhr and H. Zollinger, Helv. Chim. Acta 44, 1011 (1961).

up only in the *m*-position. In the *o*- and *p*- positions such as inductive effect would, according to these authors, be just cancelled by an accompanying decrease in hyperconjugation. Results we report here are not consistent with the proposal that isotopic substitution of α -hydrogen in toluene can stabilize a transition state (enhance a rate) by greater inductive electron release during nitration.

The radioactivity in o-nitrotoluene produced from toluene- α -t has been compared with that in the p-isomer produced in the same reaction. If there were a greater +I effect in the tritiated material, one might expect the o-isomer to have a greater radioactivity, which we do not find. From the nitration of toluene- α -t, 0.509 \pm 0.004 mc/mole, the o- and p-nitrotoluenes produced had activities of 0.509 \pm 0.003 and 0.510 \pm 0.004 mc/mole, respectively.⁷ Nor do we find any isotope effect on the over-all reaction rate. Nitration reactions were quenched after consumption of over 90 per cent of the toluene and the unreacted material isolated and assayed to find an activity of 0.508 \pm 0.005 mc/mole.

Experiments with *m*-tritiotoluene also fail to reveal any secondary isotope effect. If the aromatic ring accepts charge in going to the transition state, surely an inductive effect which could be exerted from a position α to the ring would be even more influential from a position on the ring. However, after 91 per cent nitration of a toluene-*m*-t, 0.327 \pm 0.003 mc/mole, recovered unreacted material assayed 0.326 \pm 0.002 mc/mole. After 11 per cent nitration of a toluene-*p*-t, 0.262 \pm 0.001 mc/mole, the o-nitrotoluene produced had an activity of 0.262 \pm 0.0005 mc/mole.⁸

While the spread of our radioassay values do not absolutely preclude the possible existence of a secondary hydrogen isotope effect in the nitration of toluene, the values do reduce the possible magnitude of such an effect to somewhat less than even that allowed by the values of Swain *et al.* i.e., to a magnitude whose mechanistic significance might better be discussed on the basis of why there is little or no isotope effect rather than what inductive and resonance phenomena might be blended to cause the effect.

One attractive hypothesis to explain the remarkable freedom of aromatic nitration from hydrogen isotope effects (primary or secondary) is that the energy maximum from attack of nitronium ion is not very far along the reaction co-ordinate, i.e., that in the transition state the aromatic ring has accepted so little charge that relative stabilization of this charge by isotope effects is negligible. Whereas the transition state for this type of reaction is usually pictured as being closely related to the ion $I,^9$ this hypothesis is that the transition state more nearly corresponds to structure II. This hypothesis has been previously supported by Dewar *et al.* in a theoretical interpretation of partial rate factors in aromatic nitration.¹⁰ One would predict that

⁷ Unless otherwise indicated, activities reported are mean values and total spread from four assays, duplicate samples from duplicate nitration experiments. To obtain the duplicability reported using liquid scintillation counting, it was necessary to purify samples by gas chromatography just before assay, to use a solid internal standard, and to count samples for a long period of time (cf. ref. 12).

⁸ Duplicate samples analyzed from only one experiment.

Probably the first suggestion of an intermediate like I for electrophilic aromatic substitution was by P. Pfeiffer and R. Wizinger, *Liebigs Ann.* 461, 132 (1928). Apparently, use of the term "transition state" in connection with structure I was first made by E. D. Hughes and C. K. Ingold, J. Chem. Soc. 608 (1941) and by G. W. Wheland, J. Amer. Chem. Soc. 63, 2025 (1941) at about the same time.

¹⁰ M. J. S. Dewar, T. Mole and E. W. T. Warford, J. Chem. Soc. 3581 (1956). Added in proof: After this paper was submitted, there appeared another proposal of transition state II, G. A. Olah, S. J. Kuhn, and S. H. Flood, J. Amer. Chem. Soc., 83, 4571 (1961).

with a transition state like II, substitution by nitronium ion would be quite susceptible to a primary isotope effect.



A mildly interesting experiment done as an aside to this work was the *p*-succinoylation of *p*-tritiated toluene by addition of anhydrous aluminum chloride to a solution of succinic anhydride and the toluene in tetrachloroethane. The β -(*p*-toluyl)propionic acid produced had a radioactivity which at first seemed consistent neither with direct substitution of *p*-hydrogen nor with prior exchange of aromatic hydrogen by aluminum chloride catalysis. The starting toluene-*p*-t had 0.262 mc/mole and the succinoylated product had 88 per cent of that molar activity. Repetition of this *p*-succinoylation with *m*-tritiated toluene gave a product with the same large retention of activity. The 88 per cent retention of tritium was also observed using *o*-tritiated material. The 12 per cent activity which is lost in the reaction goes into water added to work up the reaction. The 88 per cent retained activity is all on the aromatic ring, since oxidation of the active toluylpropionic acid to terephthalic acid occurs without loss of radioactivity.

One can explain retention of tritium on the ring (even from the *para* position) in *p*-succinoylation of toluene with two assumptions: (1) the tritium and hydrogen on all positions of toluene are continuously maintained in equilibrium by exchange with the carboxyl group (or its $AlCl_3$ complex) of the product, and (2) tritium or hydrogen on the ring positions of the product does not exchange.¹¹ The consequence of these assumptions is that tritium removed into the carboxyl group of product is rapidly reintroduced onto the ring of unreacted toluene, thereby giving little net loss of activity.

EXPERIMENTAL

Preparation of labeled toluene samples. Ring tritiated toluene samples were prepared by hydrolysis of appropriate tolyllithium solutions, and α -tritiated toluene was prepared by the same reaction of benzylmagnesium chloride. For example, to a filtered *p*-lithiotoluene solution, prepared by reaction of *p*-bromotoluene with an emulsion of lithium in ether, there was added water containing tracer amounts of tritium. The resulting organic solution was filtered, washed free of ether with 60% perchloric acid, dried and fractionally distilled. Before use, the toluene-*p*-t (and each other labeled sample) was fractionated by preparative scale gas chromatography.

Chromatographic purification. All gas chromatography was done with the Aerograph Model A-110-C using a silicone on firebrick absorbent packed in a five foot steel column of one half inch diameter. For the isolation of toluene, a temp of 100° was ordinarily used, and for the separation of nitrotoluenes, a temp of 150° was used. For the purpose of quantitative analysis of a reaction mixture of toluene and its nitration products, the syringe used for sample injection was weighed before and after injection to accurately determine sample size, and, to determine constituent amounts in the sample, areas under the peaks were compared with corresponding areas from standardization chromatographs of known quantities of toluene and nitrotoluenes.

Determinations of radioactivity. Radioassays were made by scintillation counting with a Baird-Atomic Model 745 scintillation spectrometer. Each sample assayed was purified by gas chromatography just before dissolution in the counting solution. More or less standard liquid scintillation,

¹¹ With these assumptions we have actually derived a simple equation which satisfactorily predicts the radioactivity of the product as a function of percentage reaction, assuming no equilibrium isotope effects.

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internal standardization technique was used,¹² with the exception that we found better reproducibility obtained when the internal standard was added to the sample solution as a solid measured gravimetrically rather than as a liquid measured volumetrically. When adding a solid internal standard, 10 mg of tritium labeled naphthalene, the counting solution used consisted of 15 ml of a toluene solution containing 10 to 100 mg of radioactive sample, 60 mg of 2,5-diphenyloxazole, 0.75 mg of 2,2-*p*-phenylene-bis-(5-phenyloxazole), and 500 mg of naphthalene.

Nitration of labeled toluene samples. Determination of the percentage reaction as a function of time in the nitration of unlabeled toluene was accomplished by analysis of organic products in aliquots which were removed at time intervals from reaction mixtures, shaken with potassium carbonate, and subjected to gas chromatography. Nitration by excess conc sulfuric and nitric acids at room temp was too fast for convenient study, even when the toluene was diluted with inert solvent. For example, aliquots were removed at 30 sec intervals after 1 ml of toluene was diluted with 20 ml of cyclohexane and shaken with 16 ml of a mixture of two parts (by volume) conc sulfuric acid and one part nitric acid (sp. gr. 1.40) at room temp; unreacted toluene was found in only the first aliquot (30 sec reaction time), which contained largely mononitrotoluene; in the fourth aliquot all of the reaction product was dinitrotoluene. Repetition of this experiment at -10° showed that dinitration was considerably slowed, but that all of the toluene was mononitrated in 1 min. After studying several variations in reaction conditions, a convenient reaction time for mononitration was accomplished by use of a limited amount of nitric acid at ice bath temp. Dropwise addition over a period of 2 min of a cold mixture of acids (6.25 g cone nitric acid (sp. gr. 1.42) and 7.5 g cone sulfuric acid (sp. gr. 1.84) to 5 ml of stirred toluene maintained at 0° resulted in the following approximate percentage reactions: 2.5 min (i.e., 30 sec after mixing), 10%; 30 min, 60%; 60 min, 75%; 120 min, 85%; 180 min, 90%.

In experiments with labeled toluene, conditions were those just given except that only 1 ml of toluene (and proportionately less acid) was used. Aliquots were not removed from these reactions but the necessary reaction time to get a desired percentage conversion was estimated from the runs with unlabeled toluene. The exact percentage reaction was measured in each experiment with labelled toluene by the gas chromatographic techniques described. Preparative gas chromatography was used to isolate materials for radioassay. Results of these experiments are given in the discussion.

Succinoylation of labeled toluene samples. Samples of o-, m- and p-tritiated toluene were converted to β -(p-toluyl)propionic acid using aluminum chloride. In each experiment the radioactivity of the acid produced was approximately 88% of that of the starting toluene. For example, to a solution of 1 g of succinic anhydride and 1 ml of toluene-p-t, 0.262 mc/mole, in 10 ml of sym-tetrachloroethane stirred at room temp, there was slowly added 2.7 g of anhydrous aluminum chloride. The reaction mixture was further stirred at room temp for 2 hr and poured onto crushed ice. Fifty milliliters of ether was added to the mixture. The organic layer was separated, washed with dil hydrochloric acid, and extracted with 3 20-ml portions of 10% aqueous sodium carbonate. Acidifying the aqueous extract yielded crude β -(p-toluyl)propionic acid, m.p. 125–126°, which was recrystallized to give 0.95 g of purified acid, m.p. 126–127.5°, 0.230 mc/mole. Oxidation of this material to terephthalic acid was accomplished in the following manner.

Oxidation to terephthalic acid. A 0.2 g sample of the labeled β -(p-toluyl)propionic acid, 0.230 mc/ mole, and 0.6 g of chromium oxide were dissolved in 20 ml of glacial acetic acid and heated on a steam bath for 2 hr. The acid solution was diluted with cold water and the fine white crystals which slowly precipitated were collected. The product, which was identified as terephthalic acid by its infrared absorption spectrum, sublimed > 300° and assayed 2.28 mc/mole.

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¹² For maximum reproducibility, we find it absolutely necessary to recount every sample, before and after addition of the internal standard, until the counting rate varies randomly with time and shows no observable drift. The time required for the counting rate to become steady varies from one sample to another and may be as much as two or more hours in the counter. A large source of error in much scintillation counting technique probably results because the sample in the counter is ordinarily allowed insufficient time to settle down before its counting rate is recorded. This is particularly true where counting has been done by a technician or on automatic equipment instructed to count on some particular schedule.