Tetrahedron, 1966. Vol. 22, pp. 515 to 520. Pergamon Press Ltd. Printed in Northern Ireland

THE MAGNITUDE OF THE HYDROGEN ISOTOPE EFFECT IN THE METALATION OF THIOPHENE

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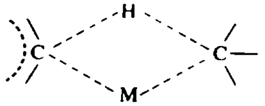
(*Received* 24 *May* 1965; *in revised form* 9 *August* 1965)

Abstract—A determination of the isotope effect (k_H/k_T) for the metalation of 2-t- thiophene with n-butyllithium gives a value of 16 ± 4 compared with the earlier value of at least 5·9 obtained by Gronowitz and Halvarson. The k_H/k_D value for the same reaction was determined to be 6·6 ± 0·3 and this value leads to a calculated value, using the method of Swain, of 16 for k_H/k_T. These values accord with the complete loss of the carbon to hydrogen stretching vibration at the transition state of a "protophilic" metalation process.

INTRODUCTION

The most widely accepted mechanism at the present time for the ring metalation of aromatic and heterocyclic substrates by alkylalkali compounds involves rate determining protophilic attack on a ring carbon to hydrogen bond by the carbanion or incipient carbanion from the organometallic. A four membered ring transition state for this type of process has been proposed by three different workers and is represented in approximate fashion as



This idea was originally put forth by Bryce-Smith[1] in a study of the metalation of alkylbenzenes with alkylsodium and alkylpotassium compounds. Huisgen[2] invoked a similar concept in his study of metalation of halobenzenes with phenyllithium and lithium piperidide leading to benzynes; as has Streitwieser[3] in work on proton abstraction from the alkyl groups of alkylbenzenes with lithium cyclohexylamide. Neither of the latter authors has referred to the earlier paper(s).

These views of the metalation reaction require that substitution of deuterium or tritium for aromatic ring hydrogen undergoing removal during metalation should lead to a lower reaction rate, i.e., a hydrogen isotope effect. Just this outcome has been observed from experiments on the metalation of monodeuterobenzene[4] with ethylpotassium, where a k_H/k_D of 1·7–2·5 was found; and in the metalation of thiophene containing tracer levels of tritium with n-butyllithium.[5] in which case a k_H/k_T

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[1] D. Bryce-Smith, *J. Chem. Soc.* 1086 (1954).

[2] R. Huisgen, *Kekule Symposium on Theoretical Organic Chemistry* p. 165, Butterworth, London (1958).

[3] A. Streitwieser, D. E. Van Sickle and L. Reif, *J. Amer. Chem. Soc.* **84**, 259 (1962).

[4] D. Bryce-Smith, V. Gold and D. P. N. Satchell, *J. Chem. Soc.* 2743 (1954).

[5] S. Gronowitz and K. Halvarson, *Arkiv. Kemi* **8**, 343 (1955).

of at least 5·9 was reported. However, the magnitude of these isotope effects are much smaller than the apparently related removal of an α-proton from ethylbenzene by lithium cyclohexylamide in which a k_H/k_D value of 12±2 was reported.[3] Complete loss of the C—H stretching vibration at the transition state corresponds[6] to k_H/k_D values of about 6·9 at 25° and to k_H/k_T values of about 16.

A careful examination of the published[5] determination of k_H/k_T for the metalation of thiophene reveals that the reported value of 5·9 may indeed be much lower than the true value. The authors point out that the number obtained was a minimum value and that it depended on a quantitative yield in the monometalation of thiophene, containing tracer levels of 2-tritiothiophene, with equivalent amounts of n-butyllithium. The equation derived by Melander[7] covers this case

$$r = \frac{n-1}{\beta + n - 1} \cdot \frac{1}{x} [1 - (1 - x)^{(\beta+n-1)/n}]$$

where r is the fraction of tritium retained in the product, n is the number of equivalent positions of the substrate which are involved in reaction, x is the fraction of conversion of substrate to product and β is the isotope effect expressed as k_T/k_H (reciprocal of above expression). The earlier workers[5] determined experimentally for the thiophene case ($n = 2$) that the value of r was $0{\cdot}89 \pm 0{\cdot}03$ for an assumed quantitative conversion of thiophene to 2-lithiothiophene $x = 1{\cdot}0$) and that this gave a value of β of 0·17 and k_H/k_T of 5·9. However, use of the above equation shows that the observed value of r leads to calculated isotope effects which vary from 5·9 if $x = 1{\cdot}00$ to infinity if $x = 0{\cdot}97$; therefore precise determination of the isotope effect is impossible unless x is known very precisely. Since the earlier work involved equimolar quantities of thiophene and n-butyllithium, it was felt likely that the actual value of the isotope effect (k_H/k_T) could indeed be greater than the 5·9 reported.

We have reevaluated the k_H/k_T ratio at 35° for metalation of thiophene containing tracer amounts of 2-tritiothiophene. Several precautions were taken to ensure that the difficulties inherent in the earlier work were avoided. The labeled thiophene (1·00 equiv.) was metalated with 1·05 equiv. of n-butyllithium. This slight excess of metalating agent brought about consumption of all the thiophene. Too large an excess of n-butyllithium would have caused dimetalation, and to the degree this happened the tritium content of the 2-lithiothiophene would have been altered. A few percent dimetalation, however, does not disturb the ratio of labeled to unlabeled 2-lithiothiophene to a significant degree, and a neutralization equivalent on the crude acid from carbonation of the reaction mixture showed that no more than one or two percent thiophenedicarboxylic acid was present. Also the reaction mixture was examined for the presence of unreacted thiophene by vapour phase chromatographic analysis. None was found. These results indicated that a calculation of an isotope effect could be made without the uncertainty of incomplete consumption of thiophene.

Thiophene containing tracer levels of 2–t–thiophene was prepared by monometalation of thiophene and treatment with tritium containing water. The radioactive thiophene substrate and 2–thiophene carboxylic acid product from metalation and carbonation were counted with a liquid scintillation counter. Standard deviations were calculated for all counting data and applied to the resulting specific activities.

[6] J. Hine, *Physical Organic Chemistry* p. 72, McGraw-Hill, New York (1962).

[7] L. Melander, *Isotope Effects on Reaction Rates* p. 56. Ronald Press, New York (1960).

Molar specific activities for the thiophene and 2-thiophene carboxylic acid were 16·38 ± 0·18 and 15·38 ± 0·17 microcuries/mole respectively. These data yield a mean value of 16 for k_H/k_T and a range taken from the standard deviations of the counting statistics of 12 to 20.

We next turned to a determination of the k_H/k_D value for the same reaction. The use of pure 2-deuteriothiophene avoids the requirement of accurate knowledge of fraction of reaction, since isotopic content of the substrate remains constant throughout the reaction. Actually we used thiophene containing 97·70% deuterium in the 2-position and 50% conversion to 2-lithiothiophene. Knowledge of the deuterium content of both unreacted thiophene and 2-thiophene carboxylic acid formed by carbonation allowed a correction for the slight isotopic impurity in the thiophene. This gave a value of $k_H/k_D = 6·6 \pm 0·3$ at about 35°.

The k_H/k_D ratio for proton abstraction from thiophene was calculated assuming loss of the C–H and C–D stretch frequencies at the transition state in accord with the method given by Melander.[8] The C–D stretch frequency was obtained from an IR spectrum of liquid 2–d–thiophene and was found to be approximately 2300 cm^{-1}, while Waddington *et al.*[9] have assigned the C–H stretch for thiophene at approximately 3100 cm^{-1}. The calculated value of k_H/k_D is 6·6 for 35°.

Since the k_H/k_T value for the metalation of thiophene given above could not be narrowed beyond a range of 12 to 20 by the experimental data used, it was of interest to calculate the k_H/k_T value from the k_H/k_D value which we established with some confidence. Swain *et al.*,[10] have related the two isotope effects by the equation:

$$\frac{k_T}{k_H} = \left(\frac{k_D}{k_H}\right)^{1.44}$$

Using this equation and the 6·6 value for k_H/k_D, the k_H/k_T value is found to be 16. Thus both the deuterium and tritium isotope effects found in this work agree well with the postulated loss of the C–H stretch at the transition state in the metalation reaction. The new results seem more in line with the transition state proposed for the protophilic mechanism than the earlier and lower values; however, it should be pointed out that a recent[11] calculation has indicated disagreement with the view that single temperature observations of k_H/k_D values tell much about the degree of C–H bond breaking or making at the transition state.

EXPERIMENTAL(12)

Preparation of tritium labeled thiophene. A solution of 0·10 mole n-butyllithium in 105 ml ether, prepared by the method of Gilman *et al.*,(13) was added (15 min) to 20 g (0·24 mole) thiophene in

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[8] Ref. 7 p. 22.

[9] G. Waddington, J. W. Knowlton, D. W. Scott, G. D. Oliver, S. S. Todd, W. N. Hubbard, J. C. Smith and H. M. Huffman, *J. Amer. Chem. Soc.* **71**, 797 (1949).

[10] G. D. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Am. Chem. Soc.* **80**, 5885 (1958).

[11] A. V. Willi and M. Wolfsberg, *Chem. and Ind.*, Dec. 19, 1964, p. 2097.

[12] All reactions involving organolithium compounds were conducted under a dry N_2 atm. The n-butyllithium used, unless otherwise indicated, was a n-hexane solution obtained from the Foote Mineral Co., and the concentration of such solutions was determined by titration with standard aqueous acids.

Unless otherwise indicated, vapour phase chromatographic analyses were performed on a Model 154D Perkin–Elmer instrument with a thermal conductivity sensor.

[13] H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, *J. Amer. Chem. Soc.* **71**, 1499 (1949).

100 ml ether. After an additional 15 min, tritium-containing water (0·2 ml of approximately 1 curie/mole radioactivity diluted with 2 ml distilled water) was added during which time the reaction mixture became turbid and heat was evolved. Excess "ordinary" water was then added and the ether layer separated and dried ($MgSO_4$), The labeled thiophene was recovered by distillation through an 18 inch Vigreux column and 9 ml boiling at 82–84° was collected. This was redistilled and approximately the centre half was collected at 83–84°. This was diluted with sufficient ordinary thiophene (ca, 5000 fold) to yield a labeled thiophene of approximately 16 microcuries per mole radioactivity.

Metalation of tritium labeled thiophene. To a solution of 8·41 g (0·10 mole) tritium-labeled thiophene in 150 ml ether was added 62 ml n-butyllithium (0·105 mole) solution over a period of 1·5 hr at 35°. The mixture was stirred vigorously during the addition and for 1·0 hr afterward. It was then poured with rapid stirring on to a slurry of ether and crushed solid CO_2. The mixture was warmed to room temp and hydrolysed by the addition of 60 ml water. The aqueous layer was separated and the ethereal layer washed with 40 ml dil $NaHCO_3$aq. This extract and the original aqueous layer were acidified with HCl to pH 2 and the precipitated carboxylic acid removed by filtration. This acid melted at 127-128° and was obtained in 93% yield based on thiophene. The product was sublimed at 0·3 mm and 110–115° after which it melted at 129–130°, and this material was used for radioassay.

The ethereal layer from the above operation was examined carefully by VPC for small amounts of unreacted thiophene. A number of components were found in this layer due to the presence of alkane hydrocarbon (mostly n-hexane) solvent from the n-butyllithium. This solvent was isolated separately from another sample of n-butyllithium solution and also examined by VPC. The closest peak to the point where added thiophene appeared was due to n-octane and the 20 sec difference of retention time between these two compounds allowed clean separation on the Perkin–Elmer "R" column at 100° and 15 psi He carrier. No thiophene could be found.

In a separate experiment it was determined that there was no loss of radioactivity from a sample of 2-thiophene carboxylic acid containing tracer levels of tritium in the 5-position when such a sample was put through the work-up procedure described above.

Orientation in thiophene metalation. Calculations of the magnitude of the H-isotope effect would become quite complicated if thiophene should undergo appreciable monometalation in the 3-position. The m.p. of the "crude" 2-thiophene carboxylic acid given above indicates that there is likely little if any contamination by 3-acid but it seemed necessary to evaluate this possibility more carefully. This was done by a VPC analysis of the methyl esters of 2- and 3-thiophene carboxylic acids.

An ethereal solution of diazomethane (0·07 mole) was poured into an ethereal solution of 2·56 g (0·20 mole) "crude" carboxylic acid (m.p. 127–128°) obtained from the metalation run described above. The resulting solution was allowed to stand at room temp until the excess diazomethane and most of the ether had evaporated and the residual oil was subjected to VPC. Resolution of pure samples of methyl 2- and 3-thiophene carboxylate could not be made on the Perkin–Elmer "P", "Q" or "R" columns; however, the separation could be accomplished on a $\frac{3}{8}$ inch × 20 ft column packed with Apiezon M grease on $\frac{60}{80}$ mesh firebrick in an Aerograph Model A-700 instrument at 210°. Even here, however, the lower limit of detection of the 3-isomer in the presence of 2-isomer was about 3%. The ester from the metalation acid showed no indication of the presence of the 3-isomer and it was concluded that if it is present at all its concentration is below 3%.

Radioassay of thiophene and 2-thiophene carboxylic acid. Liquid scintillation counting was conducted on a Packard Tricarb dual channel counter with automatic readout and repetitive counting capability. Triplicate samples of each solution to be counted were run through six counting cycles of 10 min each. The samples were made up using a toluene "counting solution" of 4·0 g 2,5-diphenyloxazole (primary scintillator) and 50 mg of 2,2′-*p*-phenylene-bis-(5-phenyloxazole) (wave length shifter) in 1000 ml toluene. Three solutions were made up as follows (a) 1·0970 g tritium labeled thiophene in 100 ml counting solution (b) 1·0 ml tritium labeled toluene "standard" (ca. 4·77 microcuries (μc)/mole) in 100 ml counting solution and (c) 1·00064 g tritium labeled 2-thiophene carboxylic acid in 100 ml counting solution. Four different types of samples were prepared in triplicate as follows: Type I 10·0 ml of (a) plus 10·0 ml of counting solution, Type II 10·0 ml of (a) plus 10·0 ml of (b), Type III 10·0 ml of (c) and 10·0 ml of counting solution, and Type IV 10·0 ml of (c) plus 10·0 ml of (b). A sample of "dead" thiophene for background counting was prepared from 0·10 ml of thiophene to 20 ml of counting solution as was a solution of "dead" 2-thiophene carboxylic acid (0·10 g) in 20 ml of counting solution. The counting results are summarized in Table 1. None of the individual

TABLE 1. SUMMARY OF COUNTING DATA

Labeled thiophene (Type I)	36,062 ± 194 counts(a)
Thiophene + internal std (Type II)	100,665 ± 578 counts
Average background (thiophene)	309 ± 10 counts
Net for Type I	35,753 ± 195 counts
Net for Type II	100,354 ± 579 counts
Net for internal std (Type II-Type I)	64,601 ± 610 counts
Molar specific activity of thiophene	16·38 ± 0·18 μc/mole(b)
Labeled 2-thiophene carboxylic acid (Type III)	8,836 ± 60 counts
Acid + internal std (Type IV)	36,089 ± 201 counts
Average background (acid)	318 ± 10 counts
Net for Type III	8,518 ± 61 counts
Net for Type IV	35,888 ± 202 counts
Net for internal std (Type IV-Type III)	27,370 ± 210 counts
Molar specific activity of carboxylic acid	15·38 ± 0·17 μc/mole(b)

[a] All data on number of counts is for a 10 min counting period.

[b] These values do not represent absolute radioactivities since they depend directly on the radioactivity of the toluene internal standard and this is known only to about ±10%. However, the ratio of these values (r in the Melander equation) is correctly stated, within the statistical limits indicated, since both values are derived from the same internal standard.

10 min counts could be rejected by Chauvenet's criterion[14] and all of the data (18 counting periods on samples of Type I, II, III and IV) were treated to yield the standard deviations for the average values (6 avg)[15] shown in the Table.

The Melander equation given above simplifies for cases in which all of the substrate is consumed ($x = 1$) to

$$r = \frac{n-1}{n-1+\beta}$$

Using this equation for our $n = 2$ case and the molar specific activities of thiophene and 2-thiophene carboxylic acid given in Table 1, the value of the isotope effect k_H/k_T (or $1/\beta$) is 16 ± 4. This may seem to be a larger uncertainty in the value of k_H/k_T than the data should generate; however, in the range of large isotope effects the ratio (r) of molar specific activity in substrate and product molecules rapidly approaches unity and relatively minor uncertainties in the specific activities translate into large uncertainties in the value of $1/\beta$.

Preparation of 2-d *thiophene.* A sample of 2-bromothiophene which was shown to be pure by VPC was converted to the Grignard reagent in the usual fashion in ether solution. The Grignard reagent was treated with excess D_2O (99·5%) and worked-up in conventional fashion. The product was purified in a preparative Perkin-Elmer "P" column at 100° and a sample of the product was shown to be pure on the analytical "R" column at 100°.

Metalation of 2-d *thiophene.* To 5·00 g (0·0588 mole) thiophene in 150 ml ether was added (1 hr) 19·0 ml (0·0294 mole) 1·54 molar solution of n-butyllithium in hexane. The temp of the reaction mixture was maintained at about 35° during the addition and for 1 hr longer, after which it was carbonated with solid CO_2 and worked up in usual fashion for isolation of the carboxylic acid. A sample for deuterium analysis was sublimed at 100–115° at 0·3 mm press. Unreacted thiophene was isolated from the ether layer by distillation and VPC over the preparative "P" column at 100° with isolation in a cold (−80°) trap. Injection of a small sample of the thiophene so obtained into the analytical "R" column showed that it was pure.

Deuterium analyses. Deuterium analyses were performed by Dr. Josef Nemeth of Urbana, Illinois, by the "falling drop" method. The thiophene used initially contained 97·70% of monodeuteration (mole per cent of molecules containing one deuterium atom); the thiophene remaining after approximately 50% had been metalated contained 99·14% monodeuteration; the 2-thiophene carboxylic acid formed by metalation and carbonation contained 83·80% monodeuteration.

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[14] G. D. Chase, *Principles of Radioisotope Methodology* pp. 65–67. Burgen, Minneapolis, Minn. (1959).

[15] C. H. Goulden, *Methods of Statistical Analysis* p. 12. J. Wiley, New York (1939).

Calculation of the k_H/k_D isotope effect is independent of the fraction of reaction of thiophene only if the initial thiophene is pure 2-d thiophene (100% monodeuteration). Since it was actually 97·70%, there should be enrichment of the deuterium content of unreacted thiophene as reaction proceeded. Knowledge of the fraction of reaction and the deuterium content of *both* unreacted thiophene and 2-thiophene carboxylic acid allows for a correction for the small amount of unlabeled thiophene present in the reactant and for the small change in reactant isotopic composition during reaction. These considerations plus the uncertainty in the deuterium analyses of ±0·5% lead to the k_H/k_D value of 6·6 ± 0·3.

Acknowledgement—The authors would like to express appreciation to C. J. Collins of Oak Ridge National Laboratory for use of the liquid scintillation counter and to both C. J. Collins and J. F Eastham for helpful discussions.