ENTROPY CONTRIBUTIONS TO REMOTE SECONDARY KINETIC HYDROGEN ISOTOPE EFFECTS

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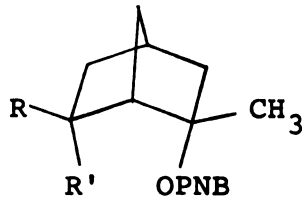
ABSTRACT

ENTROPY CONTRIBUTIONS TO REMOTE SECONDARY KINETIC HYDROGEN ISOTOPE EFFECTS

By

Vincent Francis Smith, Jr.

In an effort to establish the importance of contributions to remote secondary kinetic isotope effects from entropy differences between isotopic substrates, the rates of solvolysis of the 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoates (Ia-c) were measured in 80% ethanol-water over the temperature



Ia: R = R'=CH_3 (d_o)

Ib: R = CH_3; R'=CD_3 (endo-6-CD_3)

Ic: R = CD_3; R'=CH_3 (exo-6-CD_3)

range 100° to 150° by a spectrophotometric technique.

Brown and coworkers[1] have suggested that the ionization process in this system is sterically impeded by the

interaction which develops between the leaving group and the endo-6-methyl group. This, in conjunction with Bartell's theory[2] of steric isotope effects, would lead to the prediction of an inverse effect for both Ib and Ic.

However, the observed effects were normal in both cases and were found to vary with temperature as follows:

Temp.°C	Substrate	k_H/k_D
100.840	endo-6-CD_3	0.997 ± 0.016
125.217	endo-6-CD_3	1.003 ± 0.014
142.244	endo-6-CD_3	1.027 ± 0.013
150.186	endo-6-CD_3	1.026 ± 0.010
100.840	exo-6-CD_3	1.011 ± 0.015
125.217	exo-6-CD_3	1.017 ± 0.014
142.244	exo-6-CD_3	1.043 ± 0.013
150.186	exo-6-CD_3	1.049 ± 0.011

From the activation parameters obtained with these data, it was apparent that the enthalpy differences between the isotopic substrates were consistent with those predicted, and that it was, in fact, entropy differences that gave rise to the surprising normal effects.

Substrate	$\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$ (cal/mole)	$\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$ (cal/deg/mole)
endo-6-CD_3	204 ± 82	0.53 ± 0.20
exo-6-CD_3	244 ± 96	0.67 ± 0.24

Differential solvation and internal rotational differences were considered as possible sources of these entropy-controlled effects.

It was concluded that entropy contributions to effects of a non-bonded nature may indeed be significant and that predictions based upon Bartell's model may be most useful in estimating enthalpy differences alone.

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1. S. Ikegami, C. L. Vander Jagt, and H. C. Brown, J. Am. Chem. Soc., 90, 7124 (1968).

2. L. S. Bartell, Ibid., 83, 3567 (1961).

ENTROPY CONTRIBUTIONS TO REMOTE SECONDARY KINETIC HYDROGEN ISOTOPE EFFECTS

By

Vincent Francis Smith, Jr.

A THESIS

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To Bonnie,

whose patience, tolerance, and hard work has

contributed immeasurably to this thesis.

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INTRODUCTION

It should be obvious to all but the most naive observer, that application of secondary kinetic isotope effects as a mechanistic criterion is useful only to the degree to which the origin of the isotope effect itself is understood. Ironically, it is possible to determine with certainty the factors contributing to a given effect only if the intimate mechanism of the reaction involved is explicitly defined, a situation not often encountered in modern chemistry. One is therefore left with this dichotomous relationship between reaction mechanism and isotope effect, and must bear in mind this interdependence when drawing conclusions from either phenomenon.

Considerable amounts of data have been amassed in efforts directed toward the elucidation of the nature of solvolytic α[1] and β[2] secondary hydrogen isotope effects. However, effects arising from deuterium substitution at sites further removed from the reaction center have received relatively little attention. Almost certainly a prime reason for this lack of data is the generally smaller magnitude of these remote effects. The precision and accuracy required for such studies is often attainable only under the most stringent conditions.

It is generally accepted that secondary isotope effects arise from force constant changes which occur during the progression from ground state to transition state during a given reaction. Figure 1 illustrates that if a reaction proceeds such that the force constant associated with the isotopic bond is decreased (the bond weakened) relative to that in the ground state, the activation energy for the deuterated compound will be greater than that for the unlabeled compound; this is due to the greater zero-point energy difference in the stronger bond of the ground state. This leads to the "normal" isotope effect ($k_H/k_D>1$). On the other hand, if the reaction involves an increase of force constant (bond strengthening) at the site of isotopic substitution, the "inverse" isotope effect ($k_H/k_D<1$) will be exhibited.

Presently, the cause of these force constant changes is discussed in terms of inductive effects,[2,3] hyperconjugative effects,[4] and steric (non-bonded) effects.[5] It is still subject to question as to how much each of these factors contributes to the observed isotope effects, especially β-effects. It has been suggested by Karabatsos, et al.,[6] that, in systems where hyperconjugative stabilization involving the isotopic bond is possible, less than 10% of the observed isotope effect is due to non-bonded interactions.

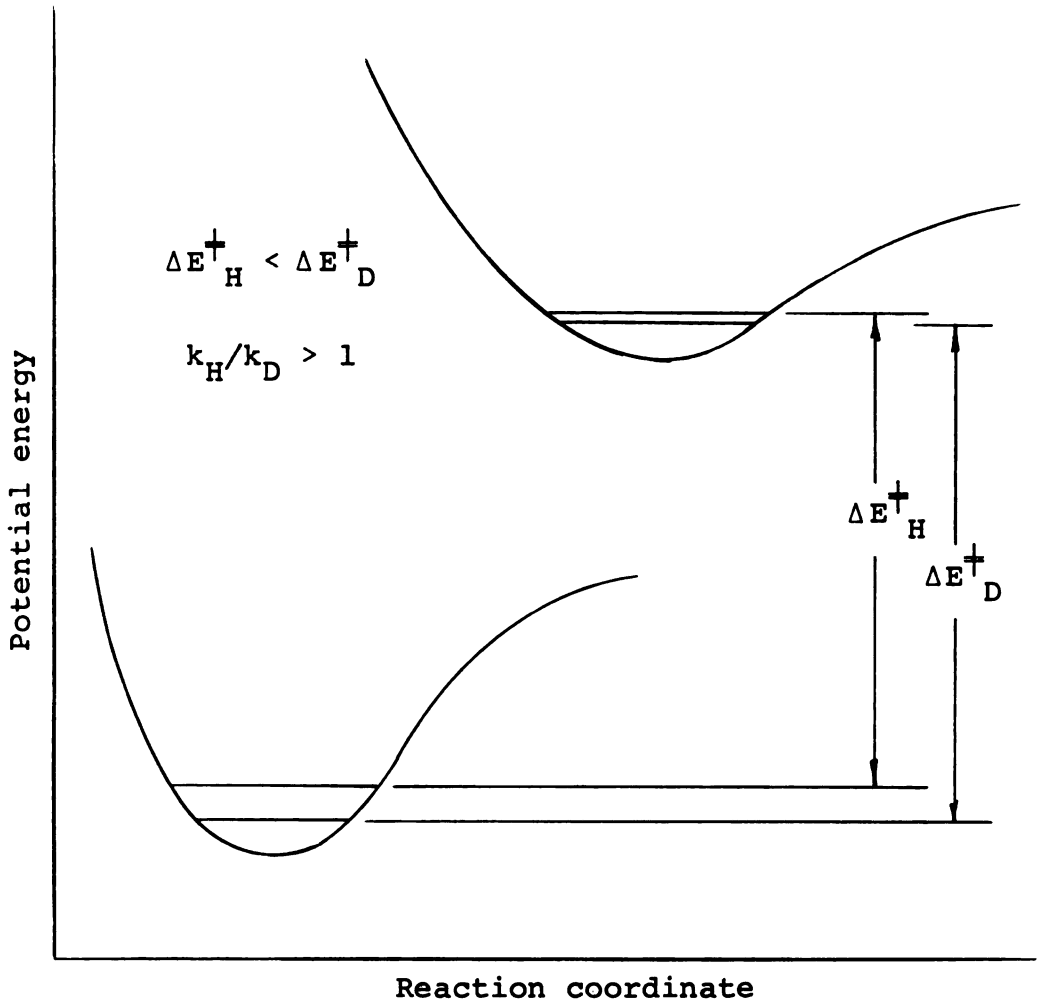


Figure 1a. Potential energy curves for decreasing force constant of isotopic bond.

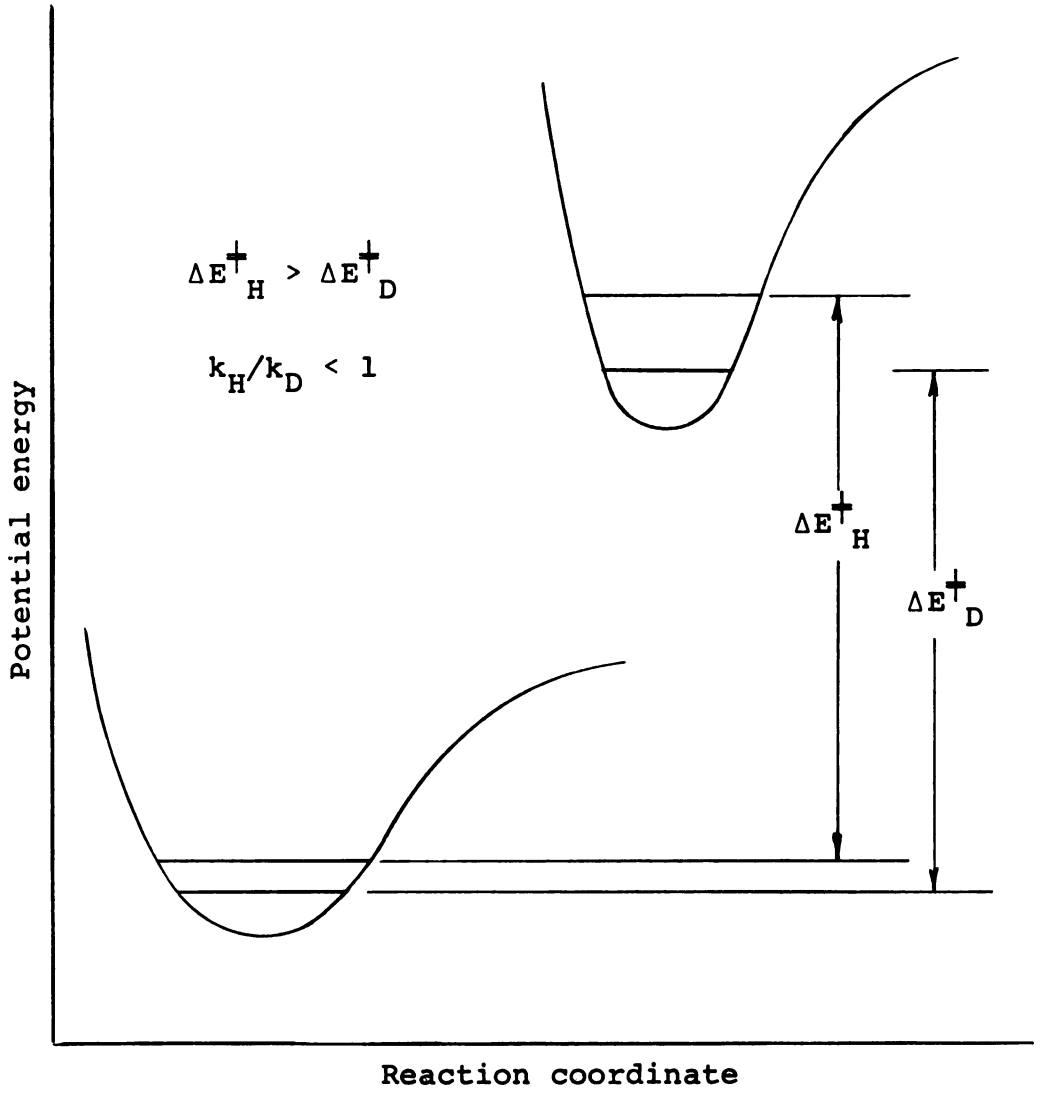
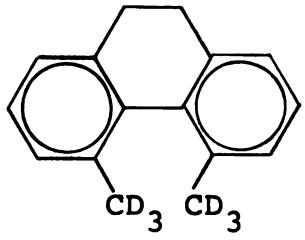


Figure 1b. Potential energy curves for increasing force constant of isotopic bond.

In order to assess the relative magnitude of purely steric isotope effects, a system must be considered wherein hyperconjugative and inductive involvement of the isotopic bond is minimal. Mislow and coworkers[7] provided the first unambiguous demonstration of such an effect in their study of the rate of racemization of 9,10-dihydro-4,5-bis(trideuteriomethyl)phenanthrene (I); at 42° in benzene, $k_H/k_D = .885$.

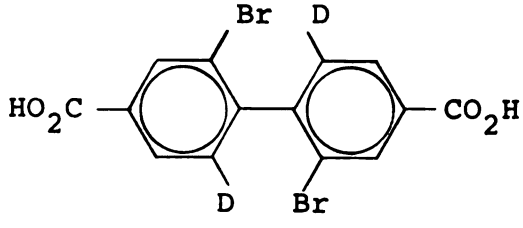


I

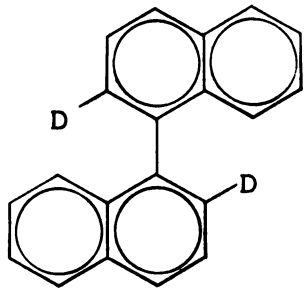
Measurement at three other temperatures allowed the determination of activation parameters. Thus $\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$ and $\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$ were found to be 240 cal/mole and 0.53 e.u. respectively. Consequently, although enthalpy favored the isotopic substrate by a relatively large amount (corresponding to a $k_H/k_D = .682$), entropy favored the unlabeled compound by an amount such that at 42° $\Delta G^{\ddagger}_H - \Delta G^{\ddagger}_D$ was only 80 cal/mole.

It must be noted at this point that steric isotope effects, as developed by Bartell,[5] result from internal energy changes alone and consequently require activation entropy differences to be zero, i.e., $\Delta G^{\ddagger}_H - \Delta G^{\ddagger}_D = \Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$ and $\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D = 0$. Clearly, the data of Mislow and coworkers do not lend support to this hypothesis.

Similar studies of racemization rates in the biphenyl (II)[8,9] and binaphthyl (III)[10] systems have been reported. As expected, both systems gave inverse isotope effects.



II



III

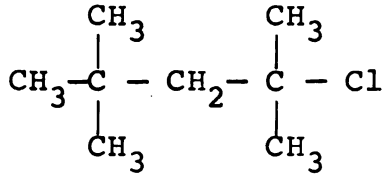
In the biphenyl study, at -19.8° in ethanol k_H/k_D was found to be 0.84. Rate measurements over a 20° range yielded isotope effects which were the same within experimental error. No meaningful activation parameter differences could be obtained. For III, Carter and Dahlgren[10] found k_H/k_D = .88 at 64.2° in N,N-dimethylformamide solution. The effect increased to a maximum of 0.83 over a 42° range. Here again activation parameter differences did not provide support for the assumption that $\Delta G^{\ddagger}_H - \Delta G^{\ddagger}_D = \Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$ according to Bartell's theory. $\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$ was found to be 270 cal/mole and $\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$ 0.54 e.u. In this as well as the other racemization studies, the activation parameters were shown to be essentially independent of the nature of the solvent, confirming the expectation that little charge development occurs along the reaction coordinate.

Earlier, Robertson, et al.,[11] had reported a solvolytic isotope effect that was assumed to be free of complicating hyperconjugative or inductive contributions. Thus, examination of the hydrolyses of a series of n-propyl derivatives containing a terminal trideuteriomethyl group yielded the results collected in Table 1. It was suggested that steric inhibition of vibrations involving the terminal methyl group was responsible for the observed 5-8% inverse isotope effects. This inhibition could arise from interactions between the methyl group and either the leaving group, or the incoming solvent molecule. In the view of the authors, the former was considered more important.

Table 1. γ-d_3 Isotope effects for the hydrolyses of n-propyl derivatives.

Leaving Group	T,°C.	k_H/k_D ($\pm$ .006)
Benzenesulfonate	54.18	0.947
Methanesulfonate	60.00	.943
Bromide	80.01	.921
Iodide	90.00	.924

More recently, a similar effect was reported by Jewett and Dunlap[12] who studied the aqueous ethanolysis of dimethylneopentylcarbinyl chloride (IV) and its δ-nonadeuterated analog. At a



IV

temperature unspecified by the authors k_H/k_D was 0.983 in 80% aqueous ethanol. This effect might similarly be explained as the result of an increase in non-bonded interactions between the γ-methyl groups and the (solvated) leaving group, although the authors implied that the effect was inductive in origin.

In view of previous success in determining the significance of steric factors by studying heats of reaction of pyridine bases with Lewis acids and the rates of reaction with alkyl halides, Brown and McDonald[13] reported the data shown in Table 2. Although the authors favored a purely steric explanation for the effects observed, the evidence cited does not appear particularly compelling. An inductive contribution may also be present. However, it was shown in a succeeding paper,[14] that the reaction between 2,6-bis(trideuteriomethyl)pyridine and boron trifluoride was more exothermic than the reaction

Table 2. Kinetic isotope effects for the reaction of various pyridines with methyl iodide at 25°.

Pyridine	k_H/k_D
4-Methyl-$\underline{d}_3$	0.999 ± .003
3-Methyl-$\underline{d}_3$	.991 ± .002
2-Methyl-$\underline{d}_3$	.971 ± .003
2,6-Dimethyl-$\underline{d}_6$	.913 ± .003
Pyridine-4-$\underline{d}_1$	.988 ± .002
Pyridine-$\underline{d}_5$	.970 ± .006

with the unlabeled substrate by 230 cal/mole; when a sterically less demanding Lewis acid like diborane[15] was used, this effect apparently vanished. Since these two Lewis acids are thought to be equally sensitive to polar influences,[15] these results may be taken as evidence against the operation of an inductive effect in this equilibrium reaction. Implications that similar inductive effects are operable in the kinetic process are valid only to the extent to which the transition state resembles the product of this equilibrium.

It is interesting that the authors also noted that a steric explanation would predict an increasing effect with increasing bulkiness of the alkyl iodide. Thus, the effects of 2-methyl-$\underline{d}_3$-pyridine with ethyl and isopropyl

iodides were determined at 75° and 100° respectively; calculations based on the assumption that $\Delta S^{\ddagger}_{H} - \Delta S^{\ddagger}_{D} = 0$ were then performed and the isotope effects compared at 25°! A comparison of predicted and experimental effects is in this case of questionable utility for two reasons. Firstly, the trend predicted is reasonable only if it is assumed that as one proceeds from methyl and ethyl to isopropyl, the transition state "tightness" remains unchanged, i.e., that the nucleophile approaches the central carbon to the same extent in each case, thus experiencing greater non-bonded repulsions with any increased substitution about that carbon. In fact, it may be argued[16] that as substitution is increased, transition state distances also increase and the attacking nucleophile thus experiences lesser non-bonded repulsions, leading to smaller isotope effects. Secondly, without a better understanding of the contribution (if any) of entropy differences to determining non-bonded isotope effects,* values obtained by extrapolations based upon only one temperature should be treated with due caution.

In this light it is interesting to note the observations of Karabatsos, et al.,[6,18] in their studies of the 8-trideuteriomethyl-1-naphthoyl chlorides (V) and the

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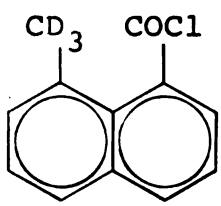
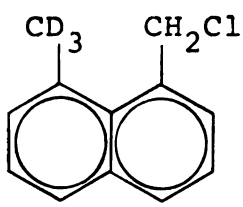
*Robertson, et al.,[17] have presented certain data which would indicate that some β-effects are entirely due to entropy differences.

8-trideuteriomethyl-1-chloromethyl-naphthalenes (VI). Available evidence would indicate that both systems undergo solvolysis by a limiting mechanism.[6] Use of Bartell's



V



VI

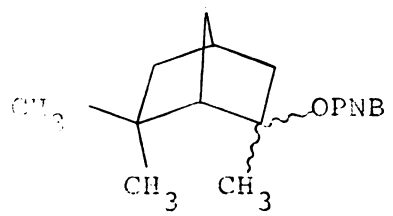
procedure[5] results in calculated $\Delta\Delta E$ values of about -100 to -300 cal/mole for V and +70 to +49 cal/mole for VI.[19] When the acid chloride V was solvolyzed in 95% aqueous acetone at 25° $k_H/k_D = 1.029 \pm .015$ corresponding to $\Delta G^{\ddagger}_H - \Delta G^{\ddagger}_D = -16.6 \pm 8.3$ cal/mole; and in 75% aqueous acetone over the temperature range -20° to -34° $\Delta G^{\ddagger}_H - \Delta G^{\ddagger}_D =$ -60 to -74 cal/mole. The data yielded $\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D =$ -308 ± 102 cal/mole, a value in agreement with that calculated. Similarly, when the carbinyl chloride VI was solvolyzed in 67% aqueous acetone at 25°, $k_H/k_D = 1.013 \pm .022$ and $\Delta G^{\ddagger}_H - \Delta G^{\ddagger}_D = -8 \pm 13$ cal/mole, an effect in direction opposite to that calculated! However, from kinetic measurements at 15° and 35°, it was established that $\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D = 140 \pm 300$ cal/mole and $\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D =$ $0.49 \pm .44$ e.u. Again it would appear that the enthalpy of activation agrees with the effect calculated by Bartell's procedure, but the free energy of activation does not!

Thus, it appears that entropy differences may indeed play an important role in determining the

magnitude of experimental non-bonded isotope effects, and this research was initiated to further understand this contribution.

In selecting a system with which the steric isotope effect would be most effectively investigated, it is necessary that, as previously noted, contributions from hyperconjugation or induction be minimized. Consideration should also be given Mislow's conclusion[7] "...that steric hydrogen isotope effects are plainly operative only under special conditions of severe overcrowding," and Bartell's observation[5b] "...that if the number of carbons separating the hydrogen and the leaving group, X, is greater than two or three, the purely steric effect may be very small even if standard molecular models suggest an unusually close H···X distance...because the skeletal flexibility increases substantially with increasing links in the chain unless unusual constraints are imposed, and the steric effect vanishes rapidly with modest increases of flexibility." In addition, the mechanism of the reaction under observation must be understood and defined as completely as possible.

Since special conditions of severe overcrowding have been suggested as the cause of the abnormally high solvolytic exo/endo rate ratio for the 2,6,6-trimethyl-2-norbornyl-p-nitrobenzoates (VII),[20] it seemed that this



VII

system would serve as a convenient probe for further examination of the steric isotope effect. It has generally been accepted that the rigid norbornane structure constitutes an ideal system for the investigation of large steric effects,[21] thereby providing the "unusual constraints" deemed necessary by Bartell. Mechanistically, the solvolysis of VII is well established in that a wide variety of evidence now indicates that tertiary norbornyl substrates react via classical carbonium ions.[22] In particular, the successful trapping of the optically active 1,2-dimethyl-2-norbornyl cation or ion pair reported by Goering and Humski[23] provides convincing support for this mechanism.

Brown and coworkers[20] have presented kinetic data which indicate that the large repulsive forces between the endo-6-methyl and the endo-2-methyl of the exo-p-nitrobenzoate substrate are effectively relieved as the transition state geometry is approached. In fact, at 25° in 80% aqueous acetone, exo-VII solvolyzed at a rate 726 times greater than endo-2-methyl-exo-2-norbornyl-p-nitrobenzoate.

Therefore, based upon steric considerations alone,* it would be expected that substitution of a trideuteriomethyl group in the endo-6-position would produce a rather large normal isotope effect. On the other hand, as the transition state is approached by the endo-p-nitrobenzoate substrate, the already crowded endo-6-methyl group becomes even more constrained by the (solvated) leaving group. Thus, when compared at 25° in 80% aqueous acetone, endo-VII is about 6 times less reactive than the exo-2-methyl-endo-2-norbornyl derivative. This increased crowding of the endo-6-methyl group would be expected to lead to an inverse isotope effect with substitution by a trideuteriomethyl group. Similar substitution in the exo-6-position of either substrate may be expected to produce an effect reflecting the nature of the interaction (if any) between the geminal methyl groups as well as that between the exo-6-methyl and the 7-hydrogen syn to it. It would seem reasonable that these effects should be in the same direction as those associated with the endo-6-position but smaller in magnitude (perhaps undetectable).

It is interesting to note that Goering and Humski[24] also reported on the γ-isotope effect for the previously mentioned 1,2-dimethyl-exo-2-norbornyl-p-nitrobenzoate (VIII). It was found that at 78.5° in 90% aqueous acetone

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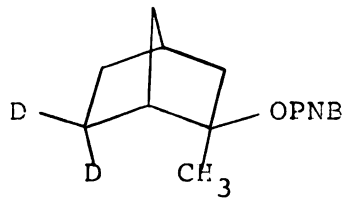
*Both hyperconjugative and inductive effects should be negligible in this δ-isotope effect.



VIII

k_H/k_D = 1.02 ± .01. In the words of the authors, "The present results show that the γ-isotope effect for unassisted ionization in an exo-norbornyl system is small, as previously assumed..." It must be pointed out, however, that the previous assumption[25] was made for solvolysis at 25°. Again, the need for a better understanding of entropy differences in reactions of isotopic substrates is well illustrated.

EXPERIMENTAL

I. Synthesis

Preparation of 2-methyl-5-norbornene-2-carboxylic acid[26]

To a 1000ml round-bottomed flask equipped with a reflux condenser was added 181g (2.1mol) glacial methacrylic acid (Rohm & Haas) and 168g (2.5mol) freshly distilled cyclopentadiene (dimer from Eastman). The mixture was allowed to react at reflux on a steam bath for 3.5 hrs. Immediate distillation of the product under reduced pressure afforded 170g (1.1mol, 53% theoretical amount) 2-methyl-5-norbornene-2-carboxylic acid, bp. 126-7° at 5mm.

Separation of epimeric carboxylic acids[27]

To a 2000ml round-bottomed flask equipped with an addition funnel and magnetic stirring bar was added 170g (1.1mol) 2-methyl-5-norbornene-2-carboxylic acids and an equimolar amount of sodium bicarbonate in a minimum amount of water such that a homogeneous solution was obtained. To this magnetically stirred solution was added dropwise a stock solution of iodine and potassium iodide (300g I_2 and 600g KI in 1800ml water). The addition was continued

until a yellow color persisted. The precipitate which formed was filtered and washed with bicarbonate solution and dried. Nearly colorless crystals weighing 98.3g (0.355mol), mp. 84-6° without recrystallization, were obtained. The filtrate was carefully acidified by dropwise addition of dilute hydrochloric acid with stirring; the pH was monitored with pH paper and was taken to ca. 3-4. Extraction with ether followed by washing the combined extracts with water and then saturated salt solution, drying over anhydrous magnesium sulfate, and evaporation of the solvent yielded 103g (0.68mol) endo-2-methyl-5-norbornene-exo-2-carboxylic acid. The product was twice recrystallized from aqueous acetic acid to mp. 80-3°. The iodolactone obtained previously was reduced with zinc dust.[28] Thus, to a 1000ml round-bottomed flask equipped with a reflux condenser and magnetic stirring bar was added 98.3g (0.354mol) iodolactone and 400ml glacial acetic acid. To this magnetically stirred solution was added 120g (1.85g-at) zinc dust in portions; heat was evolved after a short induction period. After 3hrs. the mixture was filtered and the solid residue washed with 500ml hot water. The filtrates were diluted with 1500ml water and then extracted with ether. The ether extracts were combined and washed with 5% sodium bicarbonate solution; these washings were acidified in the manner described for the exo-acid. This procedure

yielded 40.9g solid material which was recrystallized from aqueous ethanol; recovered yield was 32.6g (0.214mol, 61% theoretical amount), mp. 86-98°. Vacuum (12mm) sublimation of this material yielded 29.8g pure exo-2-methyl-5-norbornene-endo-2-carboxylic acid, mp. 107-109°. The identity of each pure epimer was confirmed by its NMR spectrum.

Preparation of exo-2-methyl-endo-2-hydroxydideuteriomethyl-5-norbornene

To a thoroughly dried 500ml three-necked round-bottomed flask equipped with reflux condenser, addition funnel and mechanical stirrer was added 200ml anhydrous ether (dried by distillation from lithium aluminum hydride) and 5.0g (0.12mol) lithium aluminum deuteride (Merck, Sharp and Dohme, 99%). To this stirred suspension was added dropwise a solution of 24.3g (0.16mol) exo-2-methyl-5-norbornene-endo-2-carboxylic acid dissolved in a minimum amount of anhydrous ether. This mixture was then heated at reflux for two days. After cooling, the mixture was treated successively with 100ml water and 100ml dilute hydrochloric acid. The ether layer was separated and the aqueous layer extracted with fresh ether; then the combined ether extracts were washed with 10% sodium hydroxide, water, and saturated sodium chloride, then dried over anhydrous magnesium sulfate.

Removal of solvent by distillation left a residue weighing 17.2g. On the basis of the amount of unreduced acid recovered from the basic wash solution above, the product yield was 13.0g (.093mol, 58% theoretical amount). This product was used in the next step without further purification.

Preparation of endo-2-methyl-exo-2-hydroxydideuteriomethyl-5-norbornene

By the same procedure as described for the epimeric compound, 18.8g (0.134mol, 84% theoretical amount) endo-2-methyl-exo-2-hydroxydideuteriomethyl-5-norbornene was obtained.

Preparation of exo-2-methyl-endo-2-tosyloxydideuteriomethyl-5-norbornene

To a 500ml round-bottomed flask fitted with a drying tube was added 17.2g (0.12mol) exo-2-methyl-endo-2-hydroxydideuteriomethyl-5-norbornene and 100ml dry pyridine. The solution was cooled in an ice bath, then 24.8g (0.13mol) p-toluenesulfonyl chloride was added in two equal portions. The mixture was kept at 0° until pyridine hydrocholoride began to precipitate. Then the reaction mixture was transferred to the refrigerator (ca. 3°) for two days. The product was isolated by the addition of ice chunks to the reaction flask. The white solid which formed was taken up in ether and the ether

solution extracted with 10% hydrochloric acid until the odor of pyridine was no longer detectable in the neutralized extract. After a final washing with water and saturated sodium chloride, the product solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded a crystalline solid weighing 28.3g. Theoretical yield was 27.3g. This material was used in the next step without further purification.

Preparation of endo-2-methyl-exo-2-tosyloxydideuteriomethyl-5-norbornene

A procedure similar to that described for the preparation of the epimeric compound yielded 38.3g (0.13 mol, 97% theoretical amount) tosylate from 18.8g (0.134 mol) endo-2-methyl-exo-2-hydroxydideuteriomethyl-5-norbornene.

Preparation of endo-6-trideuteriomethyl-exo-6-methyl-2-norbornene

To a thoroughly dried 250ml round-bottomed flask equipped with reflux condenser, addition funnel, and mechanical stirrer was added 100ml dry tetrahydrofuran (distilled from lithium aluminum hydride) and 1.5g (0.036mol) lithium aluminum deuteride (Merck). To this stirred suspension, which was protected from moisture by a drying tube, was added dropwise a solution of 27.3g (o.093mol) exo-2-methyl-endo-2-tosyloxydideuteriomethyl-5-norbornene dissolved in 25ml dry tetrahydrofuran. The reaction

mixture was then heated at reflux for two days. At this time an additional 2.6g (0.062mol) lithium aluminum deuteride was added and heating at reflux was continued for another four days. After cooling, the mixture was treated with water; after the initial reaction had subsided, the mixture was added to ca. 2000ml water made slightly acidic by the addition of dilute hydrochloric acid. After the resulting solution was extracted with ether, the combined extracts were washed with fresh water, then saturated sodium chloride, and dried over anhydrous magnesium sulfate. Slow distillation thru a short Vigreux column yielded 9.3g colorless liquid which was about 60% desired hydrocarbon and 40% 1-butanol (identified by mixed injection VPC). Passage of this mixture thru an alumina column (activated, chromatographic grade, 80-200 mesh, Matheson) by using pentane as eluant afforded a clean separation of the hydrocarbon product. Distillation yielded 4.4g (0.035mol, 37% theoretical amount) endo-6-trideuteriomethyl-exo-6-methyl-2-norbornene, bp. 131-2° at prevailing atmospheric pressure. The identity of the product was confirmed by NMR; no contamination by the epimeric hydrocarbon was detectable.

Preparation of exo-6-trideuteriomethyl-endo-6-methyl-2-norbornene

A procedure similar to that described for the preparation of the epimeric compound yielded 6.5g (0.052mol, 40% theoretical amount) exo-6-trideuteriomethyl-endo-6-methyl-2-norbornene, bp. 131-2°, from 38.3g (0.13mol) endo-2-methyl-exo-2-tosyloxydideuteriomethyl-5-norbornene treated with 5.7g (o.136mol) lithium aluminum deuteride in tetrahydrofuran at reflux over a period of seven days. Again there was no contamination by the epimeric hydrocarbon as shown by NMR.

Preparation of exo-2,3-epoxy-endo-6-trideuteriomethyl-exo-6-methylnorbornane[29]

To a 250ml three-necked round-bottomed flask equipped with reflux condenser, addition funnel, thermometer, and magnetic stirring bar was added 4.4g (0.035mol) endo-6-trideuteriomethyl-exo-6-methyl-2-norbornene and 50ml methylene chloride. To this magnetically stirred solution was added dropwise a solution of 7.0g (0.040mol, 8.2g of Aldrich 85% prue) m-chloroperbenzoic acid dissolved in 100ml methylene chloride. The temperature during the addition was maintained <25°. After stirring for 2hrs., the mixture was treated with 10% sodium sulfite solution until a test with starch-iodide paper was negative. The precipitated solid m-chlorobenzoic acid was filtered and the filtrate was washed with 5% sodium

bicarbonate, water, and then saturated sodium chloride. After drying over anhydrous sodium sulfate and removal of the solvent by evaporation, the theoretical amount of desired epoxide was obtained. This material was used in the next step without further purification.

Preparation of exo-2,3-epoxy-exo-6-trideuteriomethyl-endo-6-methylnorbornane

Treatment, similar to that described for the preparation of the epimeric compound, of 6.5g (0.052mol) exo-6-trideuteriomethyl-endo-6-methyl-2-norbornene with 10.4g (0.060mol, 12.2g of Aldrich 85% pure) m-chloroperbenzoic acid again yielded the desired epoxide quantitatively.

Preparation of endo-6-trideuteriomethyl-exo-6-methyl-exo-2-norbornanol[30]

To a 250ml three-necked round-bottomed flask equipped with reflux condenser, addition funnel, and mechanical stirrer was added 100ml N-methylmorpholine (Aldrich, bp. 118-9° and 2.7g (0.070mol) lithium aluminum hydride; this stirred suspension soon became quite thick and paste-like in appearance. Then, with continued stirring, was added dropwise a solution of 4.9g (0.035mol) corresponding epoxide dissolved in 25ml N-methylmorpholine. The mixture was heated at reflux for 62hrs. After cooling, the mixture was hydrolyzed by the cautious addition of

water. This mixture was then transferred to a 1000ml three-necked round-bottomed flask equipped with a distillation head, a steam inlet tube and a glass stopper. Steam distillation was continued until 500ml of distillate had been collected. This distillate was then extracted with ether and the combined extracts were washed with water, 10% hydrochloric acid, again with water, and then dried over anhydrous sodium sulfate. Distillation of the solvent afforded 4.4g of residue which contained about 90% desired alcohol as determined by VPC. Therefore the actual yield was ~4.0g (0.028mol, 80% theoretical amount). This material was used in the next step without further purification.

Preparation of exo-6-trideuteriomethyl-endo-6-methyl-exo-2-norbornanol

Reduction, similar to that described for the epimeric compound, of 7.3g (0.052mol) exo-2,3-epoxy-exo-6-trideuteriomethyl-endo-6-methylnorbornane with 3.8g (0.10mol) lithium aluminum hydride yielded 6.7g (0.047mol, 90% theoretical amount) desired alcohol.

Preparation of endo-6-trideuteriomethyl-exo-6-methyl-2-norbornanone[31]

A stock solution was prepared by diluting a mixture of 10g (0.0336mol) sodium dichromate dihydrate and 7.50ml (0.134mol) concentrated sulfuric acid to 50ml with

water. To a 100ml three-necked round-bottomed flask equipped with reflux condenser, small addition funnel, and thermometer was added 4.4g (0.031mol) of the corresponding exo-2-norbornanol material (ca. 90% pure) dissolved in 20ml ether. To this magnetically stirred solution was added 15.0ml (contains 0.010mol sodium dichromate) oxidizing solution at a rate such that the temperature was maintained ≤30°. After continued stirring for 2hrs. at room temperature, the ether layer was separated and the aqueous layer extracted with fresh ether. The combined ether extracts were washed with water, saturated sodium bicarbonate, again with water, and then dried over anhydrous sodium sulfate. After removal of the solvent by careful distillation thru a short Vigreux column, the residue was distilled thru a short-path condenser under reduced pressure. A clear colorless liquid weighing 2.01g was collected over the range 75-100° at 12mm. This material was analyzed by VPC and was found to contain about 59% (1.2g, 8.5mol, 31% theoretical amount) of the desired ketone. The major impurity was apparently unoxidized alcohol as indicated by VPC retention times. The material was used in the next step without further purification.

Preparation of exo-6-trideuteriomethyl-endo-6-methyl-2-norbornanone

Treatment, similar to that described for the preparation of the epimeric compound, of 7.4g (0.052mol) corresponding exo-2-norbornanol material (90% pure) with 25.4ml (contains 0.017mol sodium dichromate) oxidizing solution yielded 3.27g product which was collected over the range 74-98° at 11mm. This material was about 70% (2.3g, 0.016 mol, 34% theoretical amount) desired ketone. Again the major impurity was unoxidized alcohol, and the material was used without further purification.

Preparation of 2,6-dimethyl-endo-6-trideuteriomethyl-endo-2-norbornanol

To a 50ml two-necked pear-shaped flask equipped with reflux condenser, serum cap, and magnetic stirring bar, was added 0.35g (0.014g-at) magnesium metal turnings. After the flask had been flame-dried, protected from moisture by a drying tube, and cooled, 15ml of anhydrous ether and 0.9ml (2.04g, 0.014mol) methyl iodide (Aldrich) were added and allowed to react. After stirring at room temperature for 0.5hr., the reagent was treated with 0.5g of the corresponding ketone solution (about 0.3g, 2.1mmol of endo-6-trideuteriomethyl-exo-6-methyl-2-norbornanone); this mixture was heated at reflux overnight. After 18hrs. the mixture was allowed to cool and

was hydrolyzed by the addition of saturated ammonium chloride solution. The two clear phases that were obtained were separated and the aqueous phase extracted with fresh ether. The combined extracts were washed with 20% sodium thiosulfate, water, and saturated sodium chloride, then dried over anhydrous sodium carbonate. The solvent was removed by slow distillation thru a 16cm. Vigreux column. The residue was transferred to a small sublimation apparatus and heated at 80° under a pressure of 12mm. The solid obtained was recrystallized from pentane and allowed to dry. The yield was 0.22g (1.4mmol, 66% theoretical amount) desired tertiary alcohol, mp. 77-81°. The alcohol was not further purified before conversion to its p-nitrobenzoate.

Preparation of 2,6-dimethyl-exo-6-trideuteriomethyl-endo-2-norbornanol

Treatment, similar to that described for the preparation of the epimeric compound, of 0.5g of corresponding ketone material (about 0.35g, 2.5mmol of exo-6-trideuteriomethyl-endo-6-methyl-2-norbornanone) with 0.014mol methyl Grignard reagent yielded 0.24g (1.5mmol, 60% theoretical amount) desired tertiary alcohol, mp. 69-75°. Again this material was not further purified before conversion to the p-nitrobenzoate.

Preparation of 2,6-dimethyl-endo-6-trideuteriomethyl-endo-2-norbornyl p-nitrobenzoate[32]

To a 50ml two-necked pear-shaped flask equipped with reflux condenser, nitrogen inlet, serum cap, and magnetic stirring bar, was added 0.22g (1.4mmol) tertiary alcohol and 5ml anhydrous ether. Then by syringe was added 1.0ml (1.6mmol) of n-butyllithium (1.6M solution in hexane, Foote Mineral Co.) and the reaction mixture stirred at room temperature under nitrogen for 1.5hrs. Meanwhile, to a 50ml three-necked round-bottomed flask equipped with reflux condenser fitted with a nitrogen inlet, serum cap, glass stopper, and magnetic stirring bar, was added 0.27g (1.4mmol) p-nitrobenzoyl chloride (recrystallized from ligroine immediately prior to use) and 5ml ether. Then by syringe was added the previously formed lithium alkoxide under an atmosphere of nitrogen. The reaction mixture was allowed to stir at room temperature for 4 hrs.; then the product was isolated by pouring the mixture into 10% sodium carbonate and separating the ether layer. After washing with saturated sodium chloride, the ether solution was dried over anhydrous sodium sulfate. After removal of the solvent by evaporation, the residue was induced to crystallize by cooling to ca. -25°. The yellow crystals were collected and dried; the product weighed 0.148g and melted over the range 103-13°.

After ten successive recrystallizations from pentane at 0°, 0.061g, mp. 119-20°, was obtained. The NMR of this compound was obtained and compared to that of the unlabeled material; with the exception of the absence of the signal for the endo-6-methyl group, the spectra were identical.

Preparation of 2,6-dimethyl-exo-6-trideuteriomethyl-endo-2-norbornyl p-nitrobenzoate

Treatment, similar to that described for the preparation of the epimeric p-nitrobenzoate, of 0.24g (1.5 mmol) of the appropriate tertiary alcohol with 1.1ml (1.7mmol) n-butyllithium solution, followed with 0.29g (1.53mmol) p-nitrobenzoyl chloride and the usual isolation procedure yielded 0.123g p-nitrobenzoate, mp. 120-2°. Again the NMR of this material showed that the exo-6-methyl group was specifically and completely deuterated.

Preparation of unlabeled compounds

Instead of the 2-methyl-5-norbornene-2-carboxylic acids, the corresponding methyl esters were prepared in 55% yield by Diels-Alder condensation of cyclopentadiene with methyl methacrylate (Eastman). An excess of lithium aluminum hydride in those steps requiring the deuterated reagent in the preparation of the labeled compounds, allowed the synthesis of the 6,6-dimethyl-2-norbornene

in 69% yield from the initially prepared bicyclic methyl esters. Subsequent preparations were performed in the same manner as previously described for the labeled compounds; similar yields were also obtained. The end product, 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate, melted at 120-1°.

II. Solvolysis Product Study

Examination of products generated under solvolytic conditions

To a thick-walled glass ampoule was added 0.1g 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate dissolved in about 5ml warm ethanol and about 45ml of 80% aqueous ethanol. The ampoule was sealed and the contents heated at 150° for 20hrs. After cooling, the ampoule was broken and the contents added to 300ml saturated sodium chloride solution containing 0.02g sodium carbonate. The mixture was extracted with several portions of pentane. The combined extracts were washed with water and then dried over anhydrous sodium carbonate. The solvent was removed by slow fractionation and the residue was examined by VPC (column: 25% SE-52, Chrom. W-AW/DMCS; 70/80 mesh; 6'-7"x 1/4"; temperature: 111°; carrier gas: helium, 25ml/min).

Examination of the stability of 2,6,6-trimethyl-endo-2-norbornanol in the presence of p-nitrobenzoic acid

To another ampoule was added about 45ml of 80% aqueous ethanol and 0.05g 2,6,6-trimethyl-endo-2-norbornanol with 0.055g p-nitrobenzoic acid (recrystallized from water). The sealed ampoule was heated at 150-5° for 18hrs. After treatment as described above, the product mixture was again examined by VPC under conditions identical to those described above.

III. Kinetics

Constant temperature bath

A 5gal. glass (Pyrex) jar was placed in a wooden (3/4" plywood) box large enough to accommodate the jar and allow about 1 1/2" between the jar and the box walls on all sides except the top. This space around the jar was filled with vermiculite; the top was covered with a sheet of 1/2" asbestos. The most suitable bath medium was found to be HTF-100 Ucon Fluid (available from Matheson Scientific) which is a mixture of polyalkylene glycols. This medium was heated to within about 2° of the desired operational temperature by means of a 500W heater. The heater was operated continuously at an appropriate voltage that was controlled by means of a Variac. The medium was stirred rapidly by a 2 1/2" aluminum

propeller with 20 blades which was positioned near the bottom of the bath and was driven by a Talboys, No. 104, 1/18 H.P. electric motor. It was necessary to cool the rheostat with a continuous stream of air so as to prevent excessive heating. Excellent temperature control was maintained using a mercury filled temperature regulator (-35 to 500°F., Micro-Set, Precision No. 62541) in conjunction with a knife heater (125W, Cenco) and an electronic buffer relay (Precision No. 62690). The voltage supplied to the intermittent heater was adjusted so that heating and non-heating periods were of approximately equal duration. Temperature changes were observed with a Beckmann differential thermometer; over the range 100-160°, bath temperatures were found to vary within the limits of $\pm$0.010°.

Sample ampoules and holder

Individual ampoules were made from 1/4" regular wall Pyrex tubing; each was about 3 1/4" in length and had a neck constriction to facilitate subsequent opening. A wire basket was constructed from wire mesh such that a maximum of 45 of these ampoules could be simultaneously introduced into the bath thru an opening in the asbestos top. The basket was made deep enough to allow the ampoules to set below the surface of the bath top so that a cover could be placed over the opening.

Calibration of Beckmann differential thermometer

The actual temperatures corresponding to each of the settings of the Beckmann differential thermometer were determined with either a Hewlett-Packard Quartz Thermometer or a precalibrated platinum resistance thermometer.

Preparation of solvents

Water.--House-supplied distilled water was redistilled in an all-glass apparatus.

Ethanol.--Absolute ethanol was prepared by treating the commercial material with sodium metal and diethyl succinate as described by Fieser.[33] The anhydrous material was distilled thru a 30cm. Vigreux column.

Mixed solvent.--The solvent used for the kinetic runs was 80/20 ethanol-water (V/V). It was prepared in bulk by weighing the appropriate quantities as calculated from densities at 25°.

Determination of Beer's Law

p-nitrobenzoic acid.--A series of solutions of p-nitrobenzoic acid (recrystallized from water) in 80% ethanol-water was prepared by weighing and by the appropriate dilution procedures. Then a 1.0 ml sample of each of these was transferred to a 10 ml volumetric flask containing 1.0 ml of sodium hydroxide solution (0.1M). Each sample was then diluted to 10 ml with 95% ethanol and

the absorbance determined on a Unicam SP.800 spectrophotometer.

2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate.--A similar series of solutions of this p-nitrobenzoate (recrystallized from hexane) in 80% ethanol-water was prepared and treated as described above. The absorbances were determined in the same manner. Additionally, a 1.0 ml sample of each of the solutions was added to 1.0 ml of 10% sodium hydroxide solution in a small separatory funnel. 10 ml of cyclohexane (Spectro-Grade) was added and the mixture was shaken. After settling of the layers, a sample of the cyclohexand portion was withdrawn and its absorbance determined on a Cary 14 spectrophotometer.

Kinetics of solvolysis

To each of 10 to 14 ampoules was added about 2 ml of substrate solution (about 8.0×10^{-4}M, typically 0.061g/250ml) by using a syringe. After all the ampoules had been filled, each was successively cooled in ice water while it was sealed with a gas torch. The ampoules of a given run were placed in the wire basket such that a maximum amount of space was left between them; the basket was then placed in the bath. At this point, the bath temperature decreased rapidly and the 500W heater was adjusted so as to minimize the temperature drop; after the original temperature had again been attained (after

3-5min) the voltage supplied to the heater was returned to its original value. After 40 to 65 min. allowed for equilibration, the first ampoule was withdrawn and immediately quenched in an ice-water mixture with rapid shaking. This was taken as time zero and subsequent ampoules were removed and quenched in the same manner at appropriate time intervals. The ampoules were stored at -5° until the run was completed, when they were collectively allowed to warm to room temperature in a water bath. Each ampoule was broken open and 1.00ml was withdrawn by syringe. This aliquot was treated by one of the following:

Simple dilution procedure.--The sample was added to a 10 ml volumetric flask containing 1.0 ml of sodium hydroxide solution (0.1M). After at least 10min, this mixture was diluted to volume with 95% ethanol. The absorbance of this solution was measured on a Cary 14 spectrophotometer against a solvent blank prepared in the same manner. The measurements were performed at various wavelengths around the absorption maximum for the ester (around 256-257nm).

Extraction procedure.--The sample was introduced into a 60ml separatory funnel containing 10ml of 10% sodium hydroxide solution. After having set for about 10min, this mixture was shaken for 1min. with 10ml of cyclohexane (Spectro-Grade) which was added by pipette.

After 5 min., the aqueous layer was drawn off and the cyclohexane layer allowed to stand an additional 3 min. Then a sample was withdrawn and transferred to a cuvette wherein the absorbance was measured against a solvent blank prepared in exactly the same manner. The absorbance of each sample was determined at four separate wavelengths (250, 255, 260, and 265nm) on a Cary 14 spectrophotometer.

Thus from each kinetic run, at least four values for the first order rate constant were determined from the appropriate kinetic expression. The average of these values was taken as the rate constant for that run.

RESULTS AND DISCUSSION

In order to probe the origin of kinetic isotope effects, it is first necessary to establish the exact nature of the kinetic process itself. For this reason, an analysis of the solvolysis products from 2,6,6-trimethyl-*endo*-2-norbornyl p-nitrobenzoate in 80% ethanol-water at 150° was performed. The results in Table 3 show that 68% of the products formed are olefinic and 32% are substitution. These compounds were identified by their VPC retention times determined by the mixed injection technique. The production of 32% rearranged alcohol was interesting, although not surprising, in view of the results obtained when 2,6,6-trimethyl-*endo*-2-norbornanol was treated with formic acid at room temperature.[34] Under these conditions a 90% yield of the 1,6,6-trimethyl-*exo*-2-norbornyl formate was obtained presumably through a carbonium ion rearrangement mechanism. Therefore, all the solvolysis products may be reasonably assumed to germinate from the 2,6,6-trimethyl-2-norbornyl cation, or ion pair.*

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*Bimolecular elimination from tertiary substrates under solvolytic conditions have been shown to be negligible.[16b,35]

However, the possibility that the kinetic process might have produced the 2,6,6-trimethyl-endo-2-norbornanol which subsequently, under the unbuffered conditions of the solvolysis, may have undergone further reaction to yield the observed products could not be dismissed. Such instances of acyl-oxygen cleavage under solvolytic conditions have been observed previously with rather unreactive p-nitrobenzoates. Thus Bunton, et al.,[36] found that a comparison of the ionization rates of isobornyl and 2-methylisobornyl p-nitrobenzoates in 80% ethanol-water was frustrated by the fact that the isobornyl system underwent acyl-oxygen cleavage. Goering and Closson[37] have suggested that cyclodecyl p-nitrobenzoate solvolyzes by acyl-oxygen cleavage in 90% acetone-water at 119°. However, from the results collected in Table 4, it may be concluded that if acyl-oxygen cleavage occurs at all in the present system, it does so at a rate which is at least thirty times slower than the rate of ionization at 150°. This is evidenced by the fact that after ten solvolytic half-lives, 83% of the 2,6,6-trimethyl-endo-2-norbornanol is recovered unchanged. Therefore any isotope effects observed in this investigation may safely be attributed to the ionization process itself or some other process involving the corresponding ion pair.

The suitability of ultraviolet spectrophotometry as the analytical tool for this investigation was

Table 3. Products from the solvolysis of 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate in 80% ethanol-water (V/V) at 150°.

Product	Retention Time(min.)	%(normalized)
A	3.5	7.7
C	5.2	60.4
E	20.4	31.8

A = 1,6,6-trimethyl-2-norbornene

C = 2,6,6-trimethyl-2-norbornene and 6,6-dimethyl-2-methylenenorbornane (roughly a 40:60 mixture)

E = 1,6,6-trimethyl-exo-2-norbornanol

VPC analysis conditions: column- 25% SE-52 (Chrom.W-AW/DMCS), 70/80 mesh, 6'-7"x 1/4", 111°; carrier gas- He @ 25ml/min.

confirmed by Beer's Law determinations for the p-nitrobenzoate ester in cyclohexane as well as in 95% ethanol and for the p-nitrobenzoate anion in 95% ethanol. The determinations were made at two different wavelengths in 95% ethanol and at four in cyclohexane. The results of the measurements are collected in Tables 5, 6, and 7; typical plots of the data are shown in Figures 2 and 3. No systematic deviations from Beer's Law were apparent over the concentration range up to 1.2×10^{-4}M for the ester in cyclohexane. Similar results were obtained for the p-nitrobenzoate anion in 95% ethanol. However, substantial negative deviations from Beer's Law were

Table 4. Products from the treatment of 2,6,6-trimethyl-endo-2-norbornanol with p-nitrobenzoate acid under solvolytic conditions at 150-5° for the equivalent of 10-11 half-lives.

Product	Retention Time (min.)	%(normalized)
A	3.5	2.7
B	4.1	1.3
C	5.2	2.0
D	14.6	82.9
E	20.7	11.1

A = 1,6,6-trimethyl-2-norbornene

B = unidentified

C = 2,6,6-trimethyl-2-norbornene and 6,6-dimethyl-2-methylenenorbornane

D = 2,6,6-trimethyl-endo-2-norbornanol

E = 1,6,6-trimethyl-exo-2-norbornanol

VPC analysis conditions: column- 25% SE-52(Chrom.W-AW/DMCS), 70/80 mesh, 6'-7"x 1/4", 111°; carrier gas- He @ 25ml/min.

Table 5. Beer's Law determination for 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate in 95% ethanol.

Molar Concentration ($\times 10^5$)	Absorbance at	
	255nm	258nm
13.0	1.541	1.575
10.4	1.355	1.379
6.5	0.902	0.922
5.2	0.727	0.741
2.6	0.373	0.372
1.3	0.200	0.201

$\varepsilon_{255} = 14{,}000$

$\varepsilon_{258} = 14{,}300$

Table 6. Beer's Law determination for 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate in cyclohexane.

Molar Concentration ($\times 10^5$)	Absorbance at			
	250nm	255nm	260nm	265nm
14.4	1.848	---	---	1.822
12.0	1.621	1.772	1.756	1.567
9.6	1.283	1.405	1.397	1.244
7.2	0.990	1.082	1.070	0.950
4.8	0.619	0.677	0.673	0.602
2.4	0.334	0.360	0.357	0.318

$\varepsilon_{250} = 13{,}500$ $\varepsilon_{255} = 14{,}600$

$\varepsilon_{260} = 14{,}600$ $\varepsilon_{265} = 13{,}000$

Table 7. Beer's Law determination for sodium p-nitrobenzoate in 95% ethanol.

Molar Concentration ($\times 10^5$)	Absorbance at 255nm	Absorbance at 258nm
16.8	1.267	1.343
13.4	1.071	1.142
8.4	0.662	0.722
6.7	0.532	0.572
3.4	0.281	0.298
1.7	0.151	0.160

$\varepsilon_{255} = 7900$

$\varepsilon_{258} = 8900$

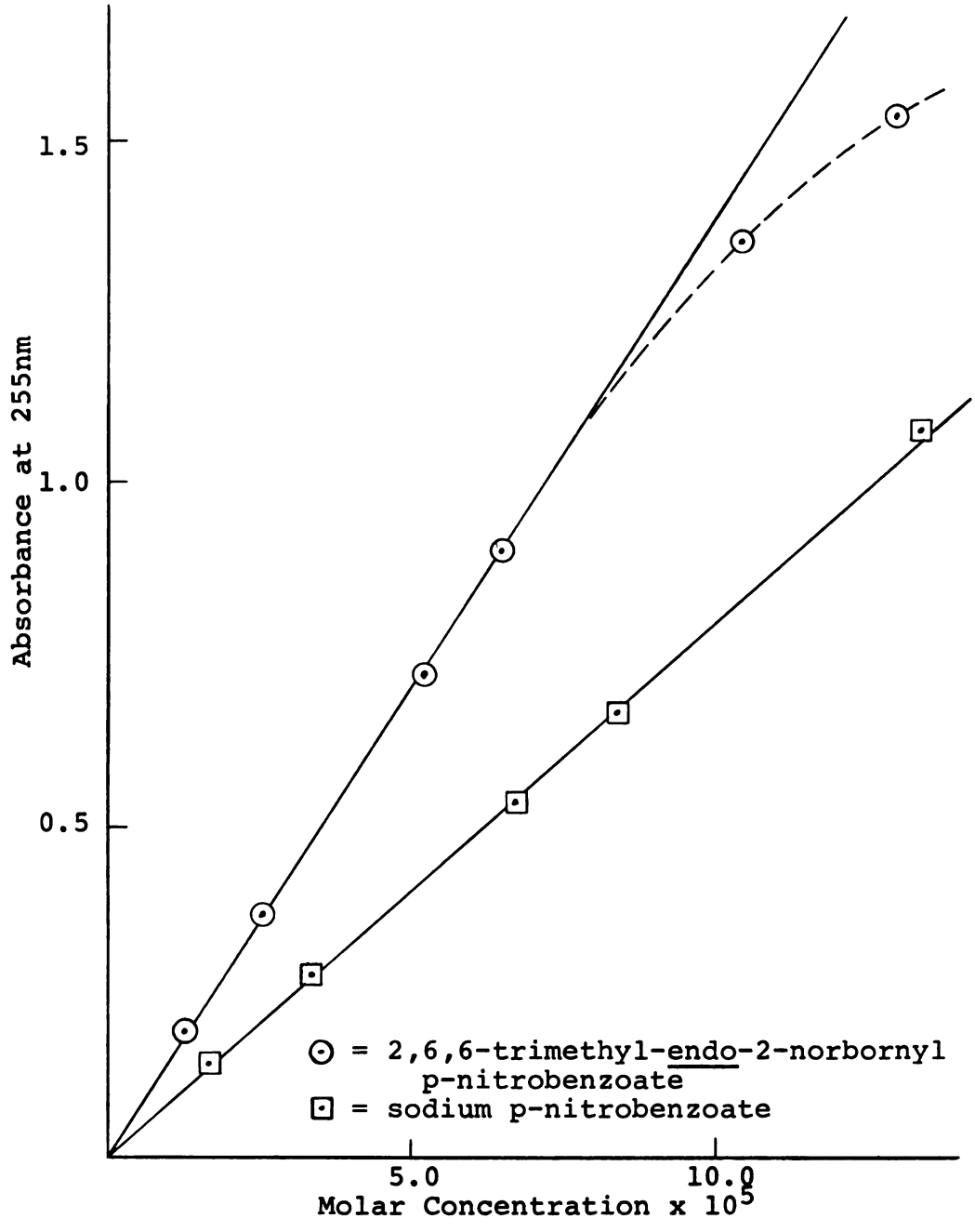


Figure 2. Beer's Law plots of 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate, and sodium p-nitrobenzoate, in 95% ethanol.

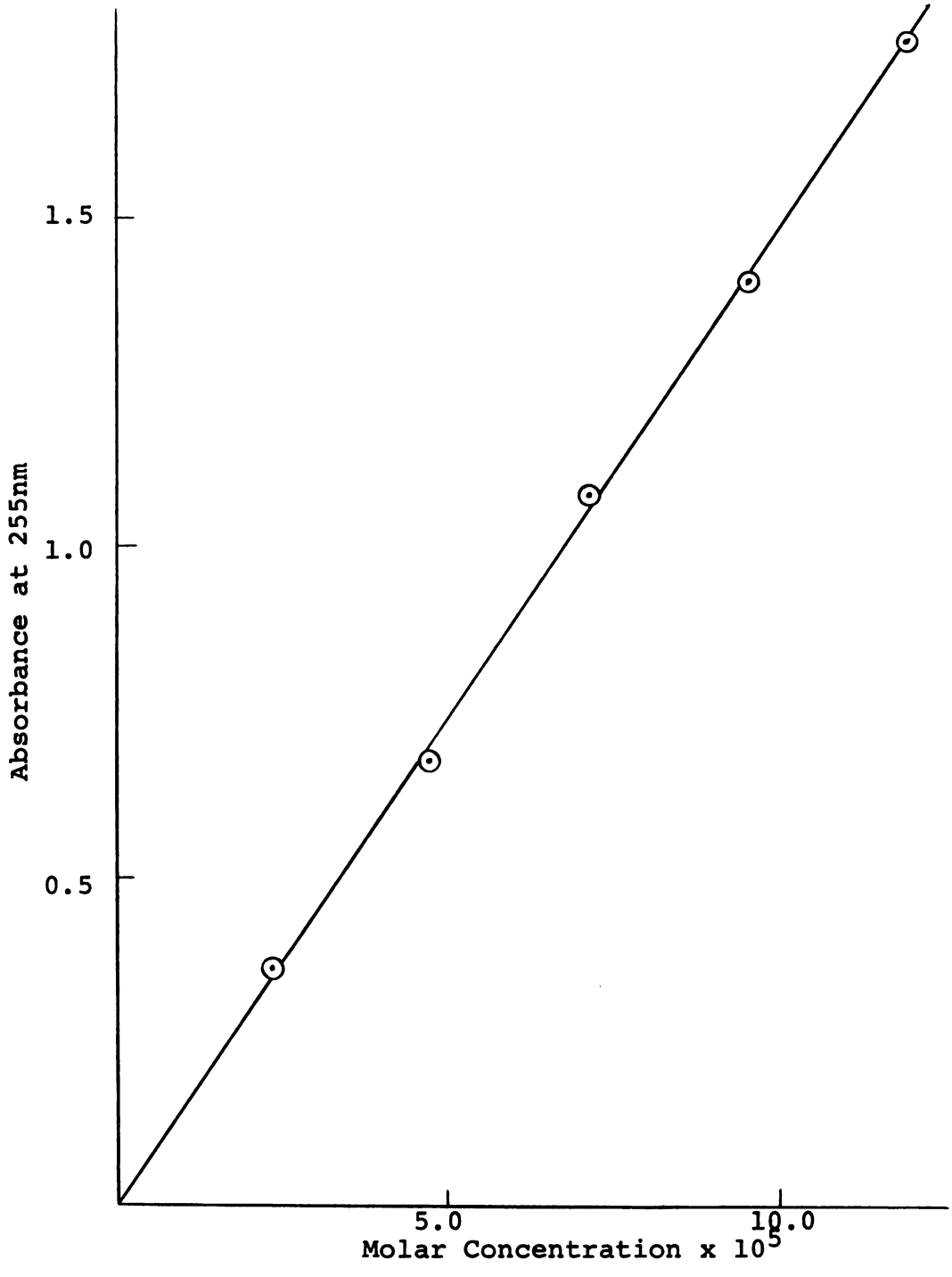
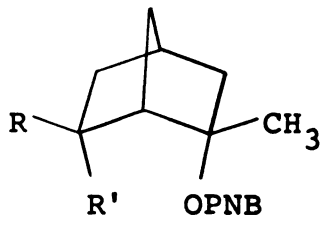


Figure 3. Beer's Law plot of 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate in cyclohexane.

encountered with the p-nitrobenzoate ester in 95% ethanol at concentrations greater than about 8.0×10^{-5}M. This may have been a reflection of the limited solubility of the ester at higher concentrations. The calculated molar absorptivities (ε) ranged from 13,000 to 14,600 for the ester in either solvent and 7900 to 8900 for the acid anion in 95% ethanol.

Thus the kinetics of solvolysis of the 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoates (Ia-c) in 80% ethanol-water were determined by using the ampoule



Ia: R = R'=CH_3 (d_o)

Ib: R = CH_3; R'=CD_3 (endo-6-CD_3)

Ic: R = CD_3; R'=CH_3 (exo-6-CD_3)

technique and analyzing the contents of each ampoule by measuring its absorbance at four different wavelengths. In this system, an absorbing ester solvolyzes to yield an absorbing acid among the products. The observed decrease in absorbance with time may be treated by the scheme developed by Roy[38] wherein allowance is made for the generation of an absorbing product. Thus, if

ε_e = molar absorptivity of ester at given wavelength

ε_a = molar absorptivity of acid at given wavelength

A_t = absorbance of sample at time t

A_o = absorbance of sample at time = 0

A_∞ = absorbance of sample after 10-11 half-lives

a = ester concentration at time 0

c_e = ester concentration at time t

c_a = acid concentration at time t

then $A_t = c_e\varepsilon_e + c_a\varepsilon_a$

$= c_e\varepsilon_e + (a-c_e)\varepsilon_a$

$$c_e = \frac{A_t - a\varepsilon_a}{\varepsilon_e - \varepsilon_a}$$

$$kt = \ln \frac{a}{c_e}$$

$$= \ln \frac{a\varepsilon_e - a\varepsilon_a}{A_t - a\varepsilon_a}$$

but $a\varepsilon_e = A_o$

and $a\varepsilon_a = A_\infty$

Therefore $kt = \ln(A_o - A_\infty) - \ln(A_t - A_\infty)$

Unfortunately, the absorption spectra of the ester and the acid are similar, such that a direct analysis of the solvolysis mixture is impossible. However, the spectrum of the acid anion is substantially different from that of the ester and thus addition of dilute solutions of sodium hydroxide to each sample would allow the determination of the set of points comprising a kinetic run.

The reaction between the unsolvolyzed ester and the added base was shown to be negligibly slow at room temperature, as the absorption spectrum of the pure ester

remained unchanged upon standing for 1hr. in the presence of a 10-fold molar excess of base. The average time required for analysis of a particular kinetic sample was 20min. During this study it was noted, however, that some of the later samples taken during a kinetic run did indeed exhibit a small decrease in absorbance with time upon standing with base. The production of small amounts of ethyl p-nitrobenzoate from a reaction between the solvent and the liberated acid was suspected. When a sample of a solution of pure p-nitrobenzoic acid in 80% ethanol-water was exposed to the conditions of the solvolysis for the equivalent of twenty half-lives, the initial absorbance of that base-treated sample was indeed observed to decrease to an equilibrium value identical to that of a base-treated sample of the original solution. Therefore, in all subsequent analyses a 10 to 15min. period was allowed for the base treatment of each sample before dilution and measurement.

An extensive series of kinetic measurements was initially carried out using the dilution procedure described in the EXPERIMENTAL section of this thesis. The collected data for each run were fitted to the kinetic equation derived previously:

$$kt = \ln(A_o - A_\infty) - \ln(A_t - A_\infty)$$

by a non-linear least-squares computer program provided by Professor J. L. Dye of this department (see Ref. 39). The results presented in Table 8 are typical of those obtained using this procedure.

Three factors are particularly noteworthy among these results. Firstly, it may be seen that the maximum change in absorbance, i.e., the difference between the absorbances of the initial and the final kinetic points, is only 0.262 units. Secondly, it is apparent that the errors in the individual rate constants are on the order of 2.5%, a value approaching that of the unacceptable in view of the small differences in rates which are being measured. Finally, it is obvious that the precision with which the infinity point may be measured by this technique leaves much to be desired. Thus, from the same kinetic points two infinity values which differ by only 0.006 absorbance units (see for example the data taken at 265nm) yield two rate constants which differ by 4.4%! Clearly, this technique depends too heavily on the apparently unreliable value for the absorbance at infinite time.

A dependable alternative to this procedure was developed and carried out as described in the EXPERIMENTAL section of this thesis. This extraction technique afforded data which are typically represented by those of Table 9. Ironically, the three factors mentioned which render the

Table 8. Data for the solvolysis of 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate in run 35 at 149.790° in 80% ethanol-water (V/V).

Time (min.)	Absorbances at			
	250nm	255nm	260nm	265nm
0	0.766	0.892	0.978	0.991
35	0.739	0.861	0.948	0.967
70	0.718	0.836	0.922	0.948
111	0.701	0.813	0.902	0.928
155	0.667	0.779	0.867	0.901
200	0.638	0.742	0.830	0.868
251	0.611	0.716	0.804	0.850
310	0.594	0.694	0.783	0.833
372	0.577	0.673	0.762	0.816
440	0.558	0.657	0.748	0.802
515	0.544	0.640	0.731	0.789
582	0.538	0.630	0.719	0.776
3033	0.477	0.561	0.656	0.725
3033	0.480	0.569	0.661	0.731

Wavelength (nm)	$k \times 10^5$ (sec^{-1})	Average $k \times 10^5$ (sec^{-1})
250	4.791 ± 0.120	
255	4.783 ± 0.106	
260	4.893 ± 0.117	from first ∞ value:
265	4.819 ± 0.111	4.822 ± 0.114*
250	4.889 ± 0.122	
255	5.017 ± 0.108	
260	5.046 ± 0.119	from second ∞ value:
265	5.038 ± 0.116	4.998 ± 0.118*

*This error is the average deviation.

Table 9. Data for the solvolysis of 2,6,6-trimethyl-*endo*-2-norbornyl p-nitrobenzoate in run 59 at 150.186° in 80% ethanol-water (V/V).

Time (min.)	Absorbances at			
	250nm	255nm	260nm	265nm
0	0.862	0.955	0.956	0.856
30	0.790	0.876	0.874	0.782
60	0.720	0.793	0.793	0.712
100	0.638	0.707	0.708	0.632
140	0.560	0.622	0.621	0.557
190	0.472	0.523	0.523	0.467
241	0.409	0.454	0.454	0.407
307	0.321	0.359	0.359	0.322
360	0.277	0.303	0.305	0.273
430	0.223	0.249	0.251	0.225
500	0.176	0.197	0.200	0.182
570	0.140	0.158	0.160	0.144

Wavelength (nm)	$k \times 10^5$ (sec^{-1})	Average $k \times 10^5$ (sec^{-1})
250	5.288 ± 0.035	
255	5.266 ± 0.034	
260	5.243 ± 0.032	
265	5.232 ± 0.033	5.257 ± 0.034*

*This error is the average deviation.

former method unreliable, make the new procedure extremely attractive. Thus the maximum change in absorbance is now 0.798 units, more than three times larger than that by the former technique; the errors in the rate constants are only 0.7%, almost four times smaller than previously; and finally, and perhaps most importantly, the determination of infinity absorbance values is eliminated. In control experiments, it was determined that the experimental infinity absorbances measured after ten or eleven solvolytic half-lives were all zero within the limits of the reproducibility of the instrument zero. Therefore, all of the subsequently discussed results are based on the data determined by this latter technique.

The rate constants collected in Table 10 were determined from the rate of absorbance decrease over a period of 2 to 2 1/2 half-lives in most cases. However, the runs conducted at 100° were followed for only 0.6 half-life since one half-life at this temperature was twenty days! The individual rate constants in the table are the average of the values determined at four wavelengths for each kinetic run. If any one of these four values appeared inconsistent with the other three, the 4d Rule[40] was applied. That is, the average of the three unquestioned values was used to calculate the deviation of each of the four original values. The questionable value was retained only if its deviation was within four

Table 10. Rates of solvolysis of 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoates in 80% ethanol-water (V/V).

Run	Temp,°C.	Substrate	k x 10^6 (sec^{-1})	Average k x 10^6* (sec^{-1})
78	100.840	d_o	.3878	
80	100.840	d_o	.3920	
82	100.840	d_o	.3892	.3897 ± .0037
79	100.840	endo-6-CD_3	.3857	
83	100.840	endo-6-CD_3	.3962	.3910 ± .0052
81	100.840	exo-6-CD_3	.3853	.3853 ± .0044
52	125.217	d_o	5.033	
54	125.217	d_o	4.985	
57	125.217	d_o	5.084	5.034 ± .050
56	125.217	endo-6-CD_3	5.070	
58	125.217	endo-6-CD_c	4.965	5.018 ± .052
53	125.217	exo-6-CD_3	4.922	
55	125.217	exo-6-CD_3	4.983	4.952 ± .044
71	142.244	d_o	25.42	
74	142.244	d_o	25.09	25.26 ± 0.22
72	142.244	endo-6-CD_3	24.65	
75	142.244	endo-6-CD_3	24.52	24.58 ± 0.23
73	142.244	exo-6-CD_3	24.03	
76	142.244	exo-6-CD_3	24.39	24.21 ± 0.21

*Errors quoted are maximum deviations from the average, or the average error of the individual rate constants of a given set, whichever is larger.

Table 10. (continued)

Run	Temp,°C.	Substrate	k x 10^6 (sec^{-1})	Average k x 10^{6*} (sec^{-1})
59	150.186	$\underline{d}_o$	52.57	
62	150.186	$\underline{d}_o$	51.99	52.28 ± 0.29
60	150.186	endo-6-CD_3	51.22	
63	150.186	endo-6-CD_3	50.70	50.96 ± 0.38
61	150.186	exo-6-CD_3	49.86	
64	150.186	exo-6-CD_3	49.80	49.83 ± 0.44
65	160.671	$\underline{d}_o$	116.8	
68	160.671	$\underline{d}_o$	119.4	118.1 ± 1.4
66	160.671	endo-6-CD_3	117.3	
69	160.671	endo-6-CD_3	119.6	118.4 ± 1.2
67	160.671	exo-6-CD_3	115.5	
70	160.671	exo-6-CD_3	114.4	115.0 ± 1.9

times the average deviation of the other three. The errors associated with these individual rate constants of the table were taken as the average standard deviations of the four (or three) rate constants from each run. The errors reported with the average rate constants of Table 10 are of two kinds. The average standard deviation of the individual constants was calculated as well as the maximum deviation of the values comprising a given set

from the average of that set. The error reported in the table is the larger of these two.

The variation of isotope effect with temperature is shown by the results collected in Table 11. The errors associated with k_H/k_D values were determined from the formula:

$$\sigma = k_H/k_D(\sigma_H^2/k_H^2 + \sigma_D^2/k_D^2)^{1/2}$$

where k_H is the average rate constant for the unlabeled compound, k_D is the average rate constant for the appropriate deuterated compound and σ_H and σ_D are the errors in the respective rate constants. From the results obtained, it is clear that a trend toward increasing normal isotope effect with increasing temperature occurs with both epimerically deuterated compounds, although the results obtained at 160° are inconsistent with this trend. Suspicions of extraneous errors arising from possible decomposition or oxidation of the solvent at this temperature were supported when the thermodynamic activation parameters were calculated. The average rate constants at the different temperatures were fitted to the equation:

$$\ln(k_r/T) = \ln(k/h) - \frac{\Delta H^{\ddagger}}{R}(\frac{1}{T}) + \frac{\Delta S^{\ddagger}}{R}$$

where k_r is the rate constant, T is the absolute temperature, R is the gas constant, k is Boltzmann's constant,

Table 11. Temperature dependence of isotope effects in the solvolysis of 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoates in 80% ethanol-water (V/V).

Temp,°C.	Substrate	k_H/k_D
100.840	endo-6-CD_3	0.997 ± 0.016
125.217	endo-6-CD_3	1.003 ± 0.014
142.244	endo-6-CD_3	1.027 ± 0.013
150.186	endo-6-CD_3	1.026 ± 0.010
160.671	endo-6-CD_3	0.997 ± 0.015
100.840	exo-6-CD_3	1.011 ± 0.015
125.217	exo-6-CD_3	1.017 ± 0.014
142.244	exo-6-CD_3	1.043 ± 0.013
150.186	exo-6-CD_3	1.049 ± 0.011
160.671	exo-6-CD_3	1.027 ± 0.021

and h is Planck's constant. The values for $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ listed in Tables 12 and 13 were obtained from the slope and intercept of a plot of $\ln(k_r/T)$ versus 1/T by using a linear least squares computer program (ACTIV) written by Dr. George C. Sonnichsen. The errors reported with the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values are two times the standard deviation obtained by using the ACTIV program; this allows the error limits to be known with 95% certainty. From the fact that these errors calculated from data collected at

Table 12. Activation parameters for the solvolysis of 2,6,6-trimethyl-*endo*-2-norbornyl p-nitrobenzoates in 80% ethanol-water (V/V), calculated from results obtained at all temperatures.

Substrate	$\Delta H^{\ddagger}$ (cal/mole)	$\Delta S^{\ddagger}$ (cal/deg/mole)
d	30,148 ± 342	-7.67 ± 0.84
endo-6-CD_3	30,065 ± 204	-7.89 ± 0.50
exo-6-CD_3	29,993 ± 234	-8.11 ± 0.58

Substrate	$\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$ (cal/mole)	$\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$ (cal/deg/mole)
endo-6-CD_3	83 ± 398	0.22 ± 0.98
exo-6-CD_3	155 ± 414	0.44 ± 1.02
endo-6-CD_3	83 ± 168*	0.22 ± 0.42*
exo-6-CD_3	157 ± 134*	0.44 ± 0.32*

*Calculated from a least-squares treatment of a plot of $\ln(k_H/k_D)$ vs. 1/T.

Table 13. Activation parameters for the solvolysis of 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoates in 80% ethanol-water (V/V), omitting results obtained at 160.671°.

Substrate	$\Delta H^{\ddagger}$ (cal/mole)	$\Delta S^{\ddagger}$ (cal/deg/mole)
d_0	30,402 ± 118	-7.02 ± 0.30
endo-6-CD_3	30,204 ± 124	-7.54 ± 0.32
exo-6-CD_3	30,160 ± 116	-7.68 ± 0.28

Substrate	$\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$ (cal/mole)	$\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$ (cal/deg/mole)
endo-6-CD_3	198 ± 171	0.52 ± 0.44
exo-6-CD_3	242 ± 165	0.66 ± 0.41
endo-6-CD_3	204 ± 82*	0.53 ± 0.20*
exo-6-CD_3	244 ± 96*	0.67 ± 0.24*

*Calculated from a least-squares treatment of a plot of $\ln(k_H/k_D)$ vs. 1/T.

all five temperatures over a 60° range (Table 12) are two to three times larger than the corresponding errors determined from the same data after deletion of the results obtained at 160° (Table 13), it was concluded that the results obtained at this higher temperature were inaccurate; they were consequently discarded.

The values obtained for the activation parameters in Table 13 are in good agreement with those reported by

Brown, et al.,[20] who studied the solvolysis of 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoate in 80% acetone-water. From kinetic measurements at 125° and 150° they determined $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ to be 31.5 kcal/mole and -6.4 eu. respectively. The values for $\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$ and $\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$ were determined by two different methods. Subtraction of the appropriate individually determined $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values gave differences which were in close agreement with those determined from the equation:

$$\ln(k_H/k_D) = \frac{\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D}{-R}\left(\frac{1}{T}\right) + \frac{\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D}{R}$$

A linear least squares computer program (HANDS) written by Dr. George C. Sonnichsen was used to calculate $\Delta H^{\ddagger}_H - \Delta H^{\ddagger}_D$ and $\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$ from the slope and intercept of a plot of $\ln(k_H/k_D)$ versus 1/T. The errors listed with these values are again two times the standard deviation obtained by using the HANDS program. It was felt that these limits of error were more realistic than those obtained from a statistical combination* of the errors associated with the individual $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values.

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*The errors from such a combination were calculated from the formula:

$$\sigma = (\sigma_A^2 + \sigma_B^2)^{1/2}$$

where σ_A and σ_B are the errors in the individual values whose difference has been determined.

From these data, it is apparent that the enthalpy contribution to the isotope effects is substantial and in the direction one would predict from consideration of the arguments of Brown, et al.,[20] for steric hindrance to ionization in this system, and of Bartell[5] for the consequential increase in the carbon-hydrogen force constant resulting in an inverse isotope effect. In fact, at 150°, if enthalpy alone were important in determining the isotope effects, the calculated k_H/k_D of 0.78 for the endo-6-CD_3 compound and 0.74 for the exo-6-CD_3 compound are rather impressive. It is somewhat surprising to find that the exo-6-CD_3 not only exhibits an isotope effect, but that it is of about the same magnitude as that of the endo-6-CD_3. This suggests that there occurs a substantial increase in the repulsive interactions between the exo-6-methyl group and the syn-hydrogen in the 7-position as well as the geminal endo-6-methyl group, as the transition state geometry is approached. It would be interesting to investigate this possibility by measuring the isotope effect in the solvolysis of 2,6,6-trimethyl-7,7-dideuterio-endo-2-norbornyl p-nitrobenzoate.

It is entropy, however, which is apparently responsible for the unusual effect observed in this system. A comparison of experimental and calculated isotope effects based on the activation parameter differences

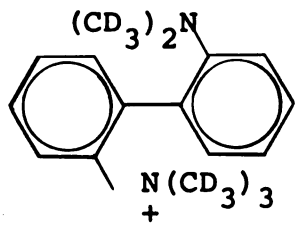
obtained from the HANDS computer program is presented in Table 14.

Table 14. Comparison of isotope effects calculated from activation parameters and those experimentally measured.

Temp,°C.	Substrate	$\Delta G^{\ddagger}_H - \Delta G^{\ddagger}_D$(calc) (cal/mole)	k_H/k_D (calc)	k_H/k_D (exp)
100.840	endo-6-CD_3	6	0.992	0.997
125.217	endo-6-CD_3	-7	1.009	1.003
142.244	endo-6-CD_3	-16	1.020	1.027
150.186	endo-6-CD_3	-20	1.024	1.026
100.840	exo-6-CD_3	-7	1.008	1.011
125.217	exo-6-CD_3	-23	1.029	1.017
142.244	exo-6-CD_3	-34	1.042	1.043
150.186	exo-6-CD_3	-40	1.048	1.049

The observed values of 0.53 and 0.67 cal/deg/mole for $\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$ of the endo and exo trideuteriomethyl groups respectively are not particularly large for an interaction of this nature. It may be recalled that the effect observed by Mislow, et al.,[7] with 9,10-dihydro-4,5-bis(trideuteriomethyl)phenanthrene exhibited $\Delta S^{\ddagger}_H - \Delta S^{\ddagger}_D$= 0.53 to 0.36 cal/deg/mole. Similarly, the 1,1'-binaphthyl-2,2'-d_2 system studied by Carter and Dahlgren[10] gave values

of $\Delta S^{\ddagger}_{H} - \Delta S^{\ddagger}_{D} = 0.54$ to 0.60 cal/deg/mole. The important difference between these previous studies and the present investigation is the temperature at which the kinetic measurements were performed. If the 2,6,6-trimethyl-endo-2-norbornyl p-nitrobenzoates had been studied in the range 22-64° as were these other systems, inverse isotope effects ranging from 0.92 to 0.96 would have been expected. It is interesting to note that in another higher temperature study, Heitner and Leffek[41] found that the isotope effect on the rate of racemization of optically active II d-camphor-10-sulfonate in water at 100.0° and 119.9° was



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0.996 and 1.02 respectively. As in the present system, enthalpy considerations alone would lead to a predicted large inverse effect.

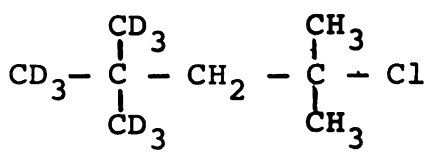
Although suggestions as to the source of these observed entropy contributions would be purely speculative at this point, it may be useful to consider the possibilities. Specific solvation effects have been considered[42] as a source of β-deuterium isotope effects in solvolytic reactions, but considerable amounts of data have been presented which indicate this to be an unlikely cause of these effects. Data collected by Kang[43]

on the solvolyses of the 8-trideuteriomethyl-1-naphthoyl chlorides in aqueous acetone solvents of varying compositions showed isotope effects which were independent of solvent composition, a result which would argue against differential solvation. The fact that in the present study the exo-6-CD_3 compound exhibits an effect similar to that for the endo-6-trideuteriomethyl compound also argues against specific solvation, since one would expect that a differential involvement of solvent as the transition state is approached would be important only in the immediate vicinity of the ionizing bond.

A more likely source of the entropy contribution to the isotope effect depends upon internal rotational differences between deuterated and non-deuterated molecules. In their study of the temperature dependence of the β-deuterium isotope effects in the solvolysis of isopropyl substrates, Robertson, et al.,[17] suggested that the major portion of the observed (normal) effects was a result of such differences. Although no clear evidence that CH_3 groups possess higher barriers to rotation than CD_3 groups in hydrocarbon-like molecules has been experimentally obtained, it may be argued that the larger steric requirements of a normal methyl group, as compared to a trideuteriomethyl group, would result in an increased barrier height. This argument seems reasonable in view of the calculations made by Kreevoy and Mason[44] which

indicate that as van der Waals repulsions increase, barriers to rotation also increase. Application of these arguments to the 2,6,6-trimethyl-endo-2-norbornyl system allows the rationalization of the observed entropy effects in a strictly qualitative sense. Thus, if it is assumed that as the transition state is approached, the van der Waals repulsions involving the trideuteriomethyl groups increase (as indicated by the enthalpy contributions to the isotope effect); and that once the transition state has been reached, these repulsions have become so large that internal rotational differences due to deuteration have become obscured; then, the lower barrier to internal rotation of the ground state trideuteriomethyl group will manifest itself as a greater decrease in activation entropy for the deuterated molecule.

In view of these ideas it is interesting to reconsider the unusual effect reported by Jewett and Dunlap,[12] and mentioned previously in the INTRODUCTION. It may be recalled that in the aqueous ethanolysis of III,



III

an inverse isotope effect of $k_H/k_D = 0.983$ was measured at an unspecified temperature (probably around 25°). The rate of solvolysis of the unlabeled compound was found to

be greater than that of tert-butyl chloride by a factor of twenty. This rate enhancement was attributed to steric acceleration arising from a severly crowded ground state.[45] On this basis, one would have predicted a substantial normal isotope effect from enthalpy considerations alone. If, however, entropy contributions are also taken into account in a manner completely analogous to that just described, it is quite reasonable to rationalize the inverse effect observed. Thus, with $\Delta H^{\ddagger}_{H} - \Delta H^{\ddagger}_{D} = -300$ cal/mole and $\Delta S^{\ddagger}_{H} - \Delta S^{\ddagger}_{D} = -1.06$ cal/deg/mole (admittedly convenient values, but nonetheless reasonable), at 25° the isotope effect would be 0.98 corresponding to a $\Delta\Delta G^{\ddagger}$ of +16 cal/mole. It would be extremely interesting to examine the temperature dependence of the isotope effect for this system.

Although providing an entertaining and interesting rationalization for the effects observed in the present study as well as the study of Mislow, et al.,[7] this approach would appear inappropriate in explaining the results of Carter and Dahlgren[10] where a substantial entropy contribution was found in the absence of deuterated substituents subject to internal rotational differences.

CONCLUSION

It would thus appear that the present study has afforded a conclusive demonstration of the existence and the importance of entropy contributions to those isotope effects which arise from interactions between non-bonded atoms or groups of atoms. The utility of isotope effects of this nature in determining reaction mechanisms has been illustrated, while at the same time the futility of conclusions drawn from their measurement at a single temperature has been clearly established. Consideration of the erroneous conclusions which may have been reached regarding Brown's explanation for the decreased reactivity of 2,6,6-trimethyl-*endo*-2-norbornyl p-nitrobenzoate if the *normal* isotope effect at 150° had been assumed to reflect enthalpy differences alone, makes the importance of these results clear.

It would appear that future efforts in this area should be directed toward a better understanding of the underlying source of the entropy contributions that have been observed.

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LIST OF REFERENCES

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