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ISOTOPE EFFECTS AND MECHANISM IN THE BROMINATION OF ALPHA- AND BETA-CARBON-14 LABELED 4-NITRO-4'-METHYLSTILBENES[1]

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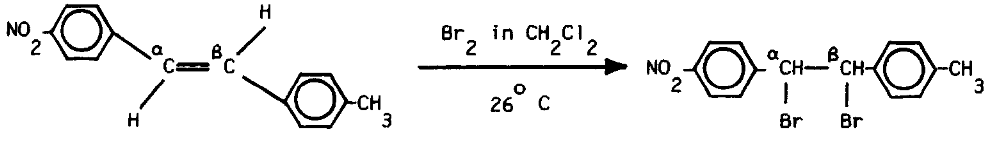
Abstract: In the bromination of 4-nitro-4'-methylstilbene, the carbon-14 $^{\alpha}C$ isotope effect is larger, $k/^{\alpha}k = 1.013$, than the $^{\beta}C$ one, $k/^{\beta}k = 1.0035$. These results support an open carbocation intermediate mechanism with the positive charge on the carbon adjacent to the methyl-containing ring.

The fundamental tenet of the mechanistic use of isotope effects is that isotope effects are to be expected when and only when there are bonding changes at the labeled position in the rate-determining step of the reaction.[2] This isotope effect mechanistic tool is especially valuable when the successive labeling technique is used,[3] and when experimental results are compared to isotope effect results calculated for different activated complex models.[4]

Very little isotope effect research has been carried out on simple electrophilic addition reactions,[5] and there are no prior reports of the finding of carbon isotope effects in simple bromination reactions. We now report the first case of such a finding in the bromination of first, $^{\alpha}C$- and second, $^{\beta}C$-carbon-14 labeled 4-nitro-4'-methylstilbenes: (The equation below summarizes the two separate experiments on the same formulas.)



erythro 76 %, threo 24 %

$$k/^{\alpha}k = 1.013 \pm 0.003 \text{ (Table 1)}$$
$$k/^{\beta}k = 1.0035 \pm 0.003 \text{ (Table 2)}$$

The only report in the literature on carbon isotope effects in the bromination of alkenes is that of Ropp, Raaen and Weinberger,[6] who reported that there were no carbon-14 isotope effects in the bromination of alpha- or beta-labeled styrene or methyl cinnamate. This is puzzling, since all of the likely mechanisms for the bromination of these compounds involve bonding changes at both the alpha and beta positions, and thus isotope effects would be expected. These results[6] were puzzling to the authors as well, who said, "There seems to be no obvious explanation for the lack of isotope fractionation in addition reactions of (this type)". (These isotope effects might be expected to be small, since they involve bond formation; such effects are expected to be small, perhaps even inverse.[2] There are questions about the error limits and other aspects of the early report[6] but there is no doubt from the experimental data presented that the isotope effects, if any, must be very small. (Experiments are in progress in this laboratory to elaborate on this early work, using ring-substituted cinnamic acid derivatives.)

The carbon-14 labeled stilbenes were synthesized by relatively conventional means, starting with commercially available benzoic-7-^{14}C acid or sodium cyanide-^{14}C. Full details will be published later. The reactions were carried out at 26° C, in dry methylene chloride. The fractions of reaction, **f**, were established by using limited amounts of bromine. The recovered alkene and product dibromide were separated by differential solubility in carbon disulfide, and exhaustively purified by column chromatography and repeated recrystallizations. Although it would have been very desirable, the ~ 24 % of the *threo* dibromide could not be isolated in sufficient purity for quality radioactivity measurements. Radioactivities of the starting materials, R_o, the recovered reactant, R_r, and the product dibromide, R_p were measured by liquid scintillation counting[7], and the kinetic isotope effects, $k/^{\alpha}k$, and $k/^{\beta}k$, were calculated by the Tong and Yankwich equations[8]. The results are presented in detail in **Tables 1** and 2, and are summarized under the equation above.

Table 1. Fractions of Reaction, Molar Activities and Carbon-14 Kinetic Isotope Effects in the Bromination of $^{\alpha}$C-Labeled 4-Nitro-4′-methylstilbene in Methylene Chloride at 26° C.[a]

Fraction of Reaction f	R_r mCi/mole	R_p mCi/mole	$k/^{\alpha}k$ obtained from:[b] R_o, R_r, R_p	R_o, R_r, f	R_o, R_p, f	R_r, R_p, f
0.30	0.43439	0.42901	1.011	1.010	1.011	1.011
0.40	0.43560	0.42886	1.013	1.011	1.013	1.012
0.50	0.43675	0.42915	1.013	1.012	1.013	1.013
0.60	0.44245	0.43161	1.011	1.024	1.010	1.016

[a] R_o = 0.43309; [b] Overall mean: $k/^{\alpha}k = 1.013 \pm 0.003$ (standard deviation).

Table 2. Fractions of Reaction, Molar Activities and Carbon-14 Kinetic Isotope Effects in the Bromination of ${}^{\beta}$C-Labeled 4-Nitro-4′-methylstilbene in Methylene Chloride at 26° C.[a]

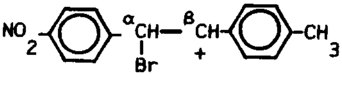
Fraction of Reaction f	R_r mCi/mole	R_p mCi/mole	$k/^{\beta}k$[b] obtained from: R_o, R_r, R_p	R_o, R_r, f	R_o, R_p, f	R_r, R_p, f
0.30	0.19715	0.19634	1.005	1.006	1.005	1.005
0.35	0.19694	0.19616	1.004	0.998	1.006	1.003
0.50	0.19669	0.19618	1.004	0.997	1.007	1.002

[a] R_o = 0.19709; [b] Overall mean: $k/^{\beta}k$ = 1.0035 ± 0.003 (standard deviation).

Since the isotope effects are so very small, it seems appropriate to present the results in full detail in order to establish their credibility. It should be noted that there are no significant trends outside the experimental errors in the data in either table, either as the fraction of reaction changes, or as the equation by which the calculation is made is changed. This type of behavior is observed only when the chemical and radiochemical purities of the starting materials and products are very high, and when the reaction and workup procedures are adequate[5]. Furthermore, the radioactivity of the starting alkene agreed precisely with the radioactivity of the product dibromide at 100 % reaction, as it should.

The isotope effect at ${}^{\alpha}$C, $k/^{\alpha}k$ = 1.013 ± 0.003, is undoubtedly real; an effect of this magnitude might very well have been lost in the experimental error of the earlier work[6]. There is no isotope effect at ${}^{\beta}$C, within experimental error, $k/^{\beta}k$ = 1.0035 ± 0.003. As suggested much earlier,[2] such a "no isotope effect result" could come about from a balancing of bond rupture and bond formation effects. In their discussion of the mechanisms of addition of 2,4-dinitrobenzenesulfenyl chloride to substituted styrenes-^{14}C, Kanska and Fry[5] noted that this balancing of bond rupture and bond formation was the probable cause for the trend in the isotope effects with substituent, for the generally low values of the isotope effects for the carbon adjacent to the ring, and for the "no isotope effect result" for the p-methyl compound.

For this preliminary report, discussion of the present results is couched[9] in terms of possible limiting intermediates **1**, **2**, and **3**. If the mechanism involves the formation of a cationic center at ${}^{\beta}$C, intermediate **1**, the hybridization of that carbon will not have changed



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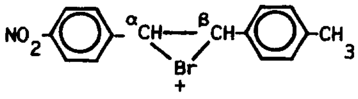

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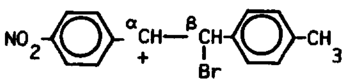

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in going from alkene to activated complex, so very little bonding change will have taken place, and little or no isotope effect would be expected, as is observed. Furthermore, the electron donating ability of the p-methyl group would increase bonding between the ring and ${}^{\beta}C$, leading to a lowering of the ${}^{\beta}C$ isotope effect. No such bond formation isotope effect-lowering factors would be present at ${}^{\alpha}C$, and a "normal bond formation in bromination" isotope effect should be observed. What is "normal" for such a reaction is not established at present; the present work provides the only calibration point to date. The ${}^{\beta}C$ effect is substantially lower than the corresponding effect in the addition of 2,4-dinitrobenzenesulfenyl chloride to substituted styrenes.[5] The reason for this is not firmly established at this time, but it seems likely that the activated complex for this reaction is quite reactant-like, with minimal bonding changes at both alkene carbons (and therefore small isotope effects). Note that reaction through **1** would be expected to give some threo product.

This analysis is also in line with the very extensive, elegant kinetics work of Ruasse and Dubois,[9] and, as a matter of fact, it was their analysis which led us to choose this particular substituted stilbene for our isotope effect studies. Their curved Hammett-type plots, with changing substituents at the two ends of the molecule, were interpreted as arising from competition among mechanistic paths involving intermediates similar to **1-3**. They had contended that our 4-nitro-4'-methylstilbene would react through carbocation **1** and not bromonium ion **2** or carbocation **3**. We take the present isotope effect data to confirm this contention. Of course it is the cation-stabilizing ability of the methyl group which causes the reaction to go through intermediate **1**.

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1. The financial support of U.S. NSF Grant CHE-8314767 is gratefully acknowledged.
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