

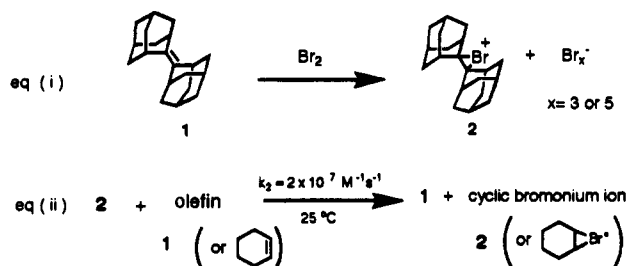
ω -Alkenyl Glycosides Reacting with *N*-Bromosuccinimide: Concerning the Transfer of Br⁺ from Cyclic Bromonium Ions to Olefins¹

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Received December 6, 1993

The addition of bromine to olefins is the prototype electrophilic reaction which students of organic chemistry first encounter.² That a cyclic bromonium ion is the key intermediate was the culmination of intense physical organic investigations,³ but the isolation in Wynberg's laboratory⁴ and subsequent X-ray characterization by Brown and co-workers⁵ of the cyclic bromonium salt **2** from adamantylideneadamantane, **1** (eq i), was of landmark significance since it paved the way for further insights into this "well-known" reaction.^{3–5} Thus the question of reversibility of cyclic bromonium ion formation, long a controversial postulate,⁷ could be revisited, and elegant kinetics experiments by Brown and collaborators have now removed the doubt.⁸ Further refinement by these investigators has revealed the possibility of direct transfer of Br⁺ from the cyclic bromonium ion **2** to alkene **1**, the rate of which (calculated to be $\sim 2 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ at 25 °C)⁹ approaches the diffusion control limit. Transfer to cyclohexene was also observed (eq ii).⁹



The observations (a) that, in the words of Brown,⁹ the structure of **1** "absolutely impedes the progress of Br₂ addition beyond" the formation of **2** and (b) that **2** is sterically unfavorable could imply that the process represented in eq ii might be atypical. However, in this manuscript we show that such transfers occur readily with unhindered, normal, monosubstituted alkenes at room temperature. Our results demand the conclusion that transfer of Br⁺ between alkenes occurs at rates which are competitive with product formation and, therefore, support the postulates of Brown and co-workers based on their detailed kinetic experiments.^{9,10}

(1) This work was supported by grants from the NSF (CHE 9311356) and NIH (GM 41071).

(2) See the chapter on alkenes in any college-level textbook on organic chemistry.

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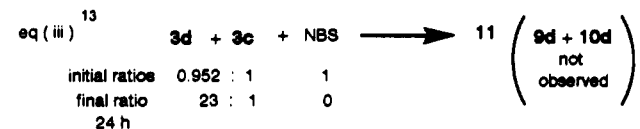
Table 1. Reaction of the ω -Alkenyl Glycosides **3a–d** with *N*-Bromosuccinimide and Water^a

entry	substrate	results	product(s) ^b	TLC ^c
i	3a	bromohydrin	9a + 10a (6.4:1)	10 h 25 min
ii	3b	bromohydrin	9b + 10b (2.4:1)	6 h 45 min
iii	3c	hydrolysis	11	2 h 20 min
iv	3d	bromohydrin	9d + 10d (2.8:1)	5 h 9 min

^a Each ω -alkenyl glycoside was accurately weighed (25–50 mg) into a flask wrapped in aluminum foil. An accurately weighed amount of NBS (recrystallized from H₂O, dried over P₂O₅ under vacuum) was added to 1% H₂O in MeCN to make a standard 75 mM solution. A portion of this solution (40 mL/(mmol of glycoside)) was pipetted into each flask, and the resulting solution was stirred at room temperature. ^b That the products were the Markovnikoff and anti-Markovnikoff bromohydrins was established by treatment with sodium hydride in THF. Both gave the same epoxide quantitatively (albeit at different rates), which was identical (HPLC) with the material obtained by treating the alkene precursor with MCPBA. ^c The progress of the reactions was monitored (TLC; 4:1 light petroleum/EtOAc). The times shown are for the disappearance of the starting materials.

Our interest in this problem arose out of our work on *n*-pentenyl glycosides (NPGs), **3c**, Scheme 1, in mechanistic and synthetic studies of glycosyl activation¹¹ by halonium ions generated from NBS¹² or NIS. The question of how other ω -alkenyl glycosides would behave prompted an examination of the homologous series **3a** → **3d**. The results in Table 1 show that, under the specified conditions, the NPG **3c** is the only substrate that suffers hydrolysis to **11**, bromohydrin mixtures (**9a,b,d** + **10a,b,d**) being obtained from the other three. Control experiments showed that **9d** and **10d** are not interconverted, and indeed are completely unaffected, by independent exposure to the reaction medium.

The trend observed in the TLC times for reaction in Table 1 are in keeping with that found for cyclic oxonium ion intervention in the pioneering study by Winstein and Grunwald on neighboring-group participation in the solvolysis of ω -methoxyalkyl brosylates, i.e., $3 \approx 4 < 5 > 6$,¹³ except that, in our case, the three-center reaction of **3a** is very much slower than the four-center reaction of **3b**. This circumstance could be attributed to the negative inductive effect of the glycosidic, allylic oxygen in **3a**, an effect which should depreciate completely in **3c** and **3d**. Thus the latter two substrates were subjected to closer scrutiny.



We were surprised to find that when equimolar amounts of **3c** and **3d** were allowed to compete for 1 equiv of NBS (eq iii),¹⁴ the *n*-pentenyl glycoside **3c** reacted to give the aldose **11**, while the hexenyl homologue **3c** was recovered completely with no evidence for **9d** and **10d**. Refined rates, rather than the TLC approximations in Table 1, were therefore warranted, and the pseudo-first-order rate constants were determined by using a 10-fold excess of the alkene over NBS and by following the disappearance of NBS by iodometric titration.¹⁵ The rates for **3c** and **3d** were found to be $2.39 \times 10^{-4} \text{ s}^{-1}$ ($r = 0.994$) and $6.3 \times 10^{-5} \text{ s}^{-1}$ ($r = 0.994$), respectively. This small difference in rates rules out the possibility that the high reactivity of **3c** arises because the double

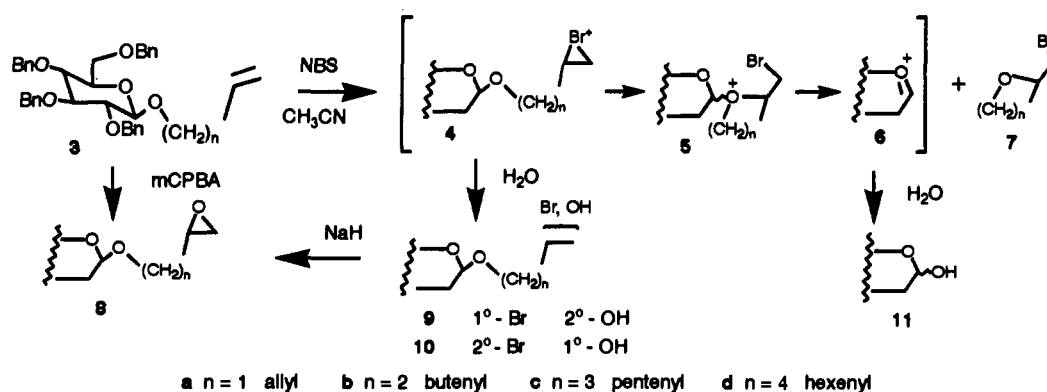
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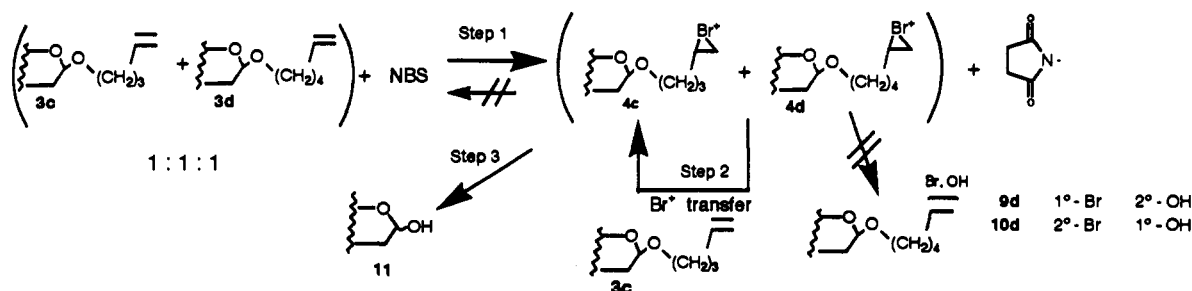
(12) (a) That *N*-bromoamides react with alkenes to give cyclic bromonium ions has been established. Winstein, S.; Ingraham, L. L. *J. Am. Chem. Soc.* 1952, 74, 1160. (b) For extension to NBS, see: Guss, C. O.; Rosenthal, R. *J. Am. Chem. Soc.* 1955, 77, 2549.

(13) Winstein, S.; Grunwald, E. *J. Am. Chem. Soc.* 1948, 70, 828.

Scheme 1



Scheme 2



bond enjoys substantial ground-state activation by five-center interaction with the glycosidic oxygen.

It is virtually certain that step 1 in Scheme 2 is irreversible,¹⁶ and hence the failure of 4d to proceed to products supports the notion that 4d transfers its bromonium ion to 3c in step 2 to give 4c, which then reacts to give 11 (step 3). Steady-state production of the pentenyl intermediate 4c results, its rate of decomposition being leveraged according to LeChatelier's principle, leading to production of 11 and the absence of 9d and 10d.

The data in eq iii show that the ratio of 3d → 3c fell from ~1:1 at the start of the reaction to 23:1 at the end. Adjusting for the changing concentration as the reaction proceeds, the pseudo-first-order rate constants quoted above predict a final 3d:3c ratio of 2.6:1. Accordingly a series of competition experiments with

(14) Compounds 3c (50.0 mg, 0.0821 mmol) and 3d (51.2 mg, 0.0821 mmol) were weighed into a flask covered with foil. The initial 3d:3c ratio was determined by dissolving the starting materials in CHCl_3 and injecting an aliquot onto a Rainin Dynamax HPLC system (column = Dynamax 60-A, silica, analytical column; UV detector = 265 nm; flow rate = 1.0 mL/min; 93:7 hexanes:EtOAc → 20:80 hexanes:EtOAc over 50 min). The 3d:3c ratio was determined as 0.971:1.000 by area. The CHCl_3 was then evaporated, and the residue was dried under vacuum. The residue was then diluted to 40 mM with a 1% $\text{H}_2\text{O}/\text{MeCN}$ solution containing 1 equiv of NBS (0.0821 mmol). Aliquots (0.5 mL) of this reaction solution were then diluted to various concentrations (25 mM → 0.200 mM) in separate flasks covered with foil, and the mixtures were stirred at room temperature until complete disappearance of NBS as determined by treatment of aliquots with 10% KI solution and starch indicator solution. The reactions were then quenched with 10% Na_2SO_3 solution, diluted with CH_2Cl_2 , and extracted with brine. The organic layer was dried with Na_2SO_4 , filtered, and concentrated. Each reaction was analyzed by HPLC using the same conditions as above to determine the final 3d:3c ratios.

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(16) This conclusion is indicated by the ΔH_f° values of NBS and succinimide, -80.35 and -109.72 kcal/mol, respectively. The succinimidyl anion would therefore pick up a proton much more readily than it would attack the cyclic bromonium ion. Coleman, D. G.; Skinner, H. A. *Trans. Faraday Soc.* 1966, 62, 2057. Howard, P. B.; Skinner, H. A. *J. Chem. Soc. A* 1966, 1536.

(17) An exponential curve gave the best fit to data points in the graph of the final 3d:3c ratios versus concentration. *Cricket Graph*, version 1.3, 1988, Cricket Software, Malvern, PA.

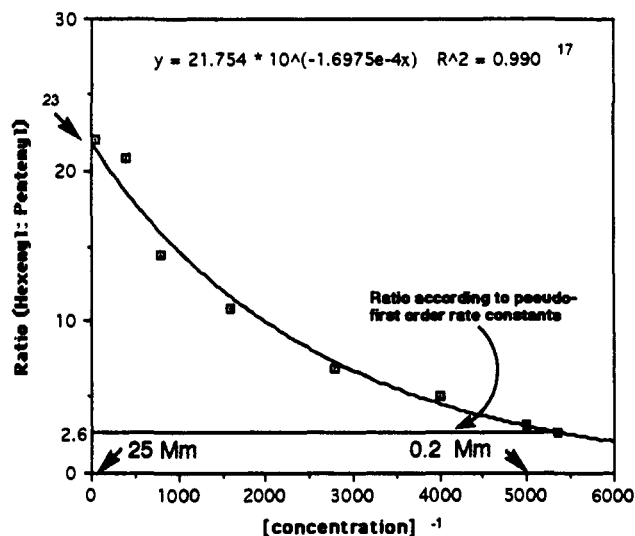


Figure 1. Competition experiment between pentenyl (3c) and hexenyl (3d) for 1 equiv of NBS at increasing dilutions:¹⁴ □, equimolar amounts of final (hexenyl: pentenyl) ratio.

increasingly dilute solutions ranging from 25 mM to 0.200 mM is shown on the abscissa of Figure 1. The premise was that the final 3d:3c ratio after the disappearance of NBS (shown on the ordinate) should change from 23:1 to 2.6:1 as the concentration is lowered.

Indeed it is seen that the curve approaches this final value.¹⁷ Thus it can be concluded that, at low concentration, both substances are reacting in the ratio predicted by their rate constants, whereas at high concentration, the transfer reaction shown in step 2 of Scheme 2 is of overwhelming significance.

Acknowledgment. We are greatly indebted to Professor R. S. Brown of the University of Alberta for his enthusiastic and perspicacious help and for sharing details of investigations currently underway in his laboratory.