Selectivity of Wohl-Ziegler Brominations of Cyclohexene and *trans*-2-Hexene

Rick W. Dorn, Eden Willcox, Joseph K. West and Thomas W. Nalli

Department of Chemistry, Winona State University, Winona, Minnesota

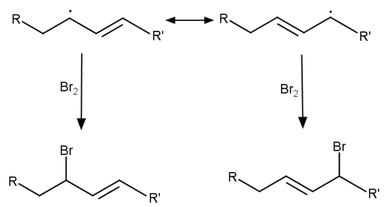
INTRODUCTION

Wohl-Ziegler bromination utilizing N-bromosuccinimide (NBS) is an important reaction in organic synthesis.[1,2,3] The reaction proceeds by a radical chain mechanism **(**eq 1-2), in which the bromination position is determined by which hydrogen the bromine radical abstracts (eq 1).

$$Br\cdot + RH \rightarrow HBr + R\cdot \quad (1)$$

$$R\cdot + Br_2 \rightarrow RBr + Br\cdot \quad (2)$$

Unsymmetrical allylic systems should display multiple isomers according to resonance theory (Scheme 1). However, it has been reported and often claimed that bromination of 2-heptene (**1a**) with NBS yields 4-bromo-2-heptene (**2a**) as the sole product.[4,5,6,7]



Scheme 1: Allylic rearrangement products due to resonance stabilization.

In contrast, it is well established that allylic rearrangement occurs during NBS bromination of terminal alkenes[8,9]. We reinvestigated, both experimentally and computationally, allylic rearrangement during NBS bromination of 2-alkenes (**1a** and **1b**). Furthermore, selectivity was studied for the effect of a bromine atom on radical stability in subsequent bromination steps.

EXPERIMENTAL

General. All reactions used oven dried glassware, dried solvents (4 Å molecular sieves) and were carried out under N_2. NMR spectra were obtained at 300 MHz in $CDCl_3$.

NBS Brominations. To a solution of the alkene (0.5 – 2 M) was added NBS (0.67 – 1 equiv) and benzoyl peroxide (BPO) (if no *hv*). The reaction mixture was stirred rapidly and refluxed in front of a 275 W sunlamp (if no BPO was used). The succinimide was filtered off and solvent removed *in vacuo*.

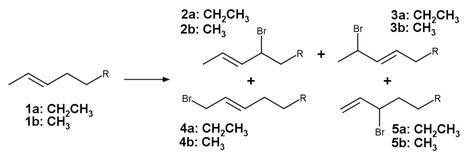
1-Bromo-2-hexene (4b). To a chilled solution (- 8 ºC) of 2-hexen-1-ol (42 mmol) in diethyl ether (0.5 M) was added PBr_3 (17 mmol) dropwise. The solution was stirred (r.t. 2 h) before the addition of ice, extraction with diethyl ether, drying over Na_2SO_4, and concentration *in vacuo* to yield 4.6 g of *trans*-**4b** (67 %). ^{1}H NMR δ 5.72 (m, 2H), 3.96 (d, 2H), 2.02 (q, 2H), 1.40 (sextet, 2H), 0.895 (t, 3H).

4-Bromo-2-hexene/2-bromo-3-hexene (2b/3b) . 2-pentenal was treated with MeMgBr in ether (3.0 M). Neutralization (10 % HCl) followed by extraction (ether), drying (Na_2SO_4.), and PBr_3 treatment (as above) gave **2b**/**3b** (1.3:1). ^{1}H NMR **2b** δ 5.68 (m, 2H), 4.44 (q, 1H), 2.06 (m, 2H), 1.71 (d, 3H), 0.977 (t, 3H). **3b** δ 5.68 (m, 2H), 4.70 (quintet, 1H), 1.90 (m, 2H), 1.77 (d, 3H), 1.00 (t, 3H).

DFT Methods. Structures were modeled (GAMESS[10]) in the gas phase (B3LYP functional set). The 6-311++G** basis (C and H atoms) and the ECP-based LANL2DZ basis (Br atoms) was applied. Vibrational analysis confirmed no imaginary frequencies.

RESULTS

Table 1: NBS Bromination of 2-heptene and 2-hexene[a]



Entry	Reactant	Solvent	Time (h)	Rel. Yield (%)[b] 2	3	4	5
1	**1a**	CCl_4	3	32[c]	44[c]	21	3
2	**1b**	CCl_4	2	42	33	21	4
3	**1b**	cyclohexane	2	42	33	21	4

[a] Reaction conditions: 0.67 equiv NBS, BPO and reflux. [b] *cis*/*trans* Isomers were added together. Values reported are averaged from ^{1}H NMR and GC peak integrations (± 2 %). [c] ^{1}H NMR peak integration used due to co-eluted peaks in TIC chromatogram.

Figure 1: TIC Chromatogram of Bromohexene Products (Entry 2)

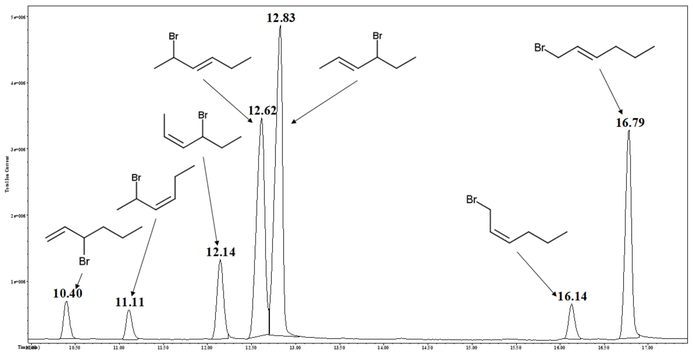
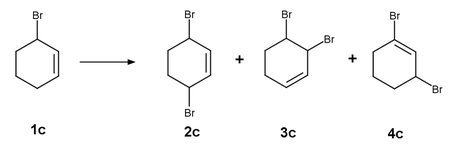


Table 2: NBS Bromination of 3-bromocyclohexene[a]



Entry	Reactant	Solvent	Time (min)	Conversion (%)	Rel. Yield (%)[b] 2	3	4
4	**1c**	CCl_4	11	3	82	17	1
			15	6	83	16	1
			19	90	79	19	2

[a] Reaction conditions: 1 equiv NBS, reflux and *hv* (275 W). [b] *cis*/*trans* Isomers added together from GC peak integration.

Figure 2: ^{1}H NMR Spectrum of Bromohexene Products (Entry 2)

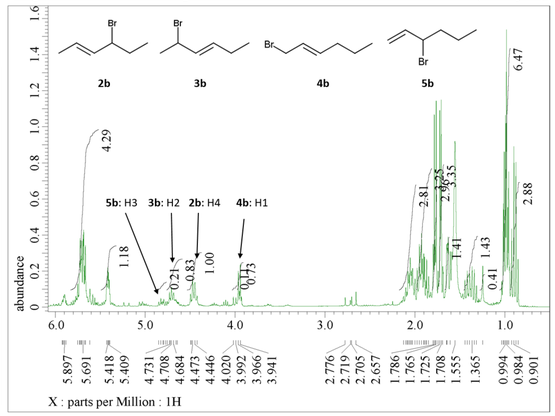


Figure 3: Relative equilibrium geometry energies of reactant, intermediates and products from NBS bromination of *trans*-2-hexene (I), *trans*-4-bromo-2-hexene (II) and 3-bromocyclohexene (III).

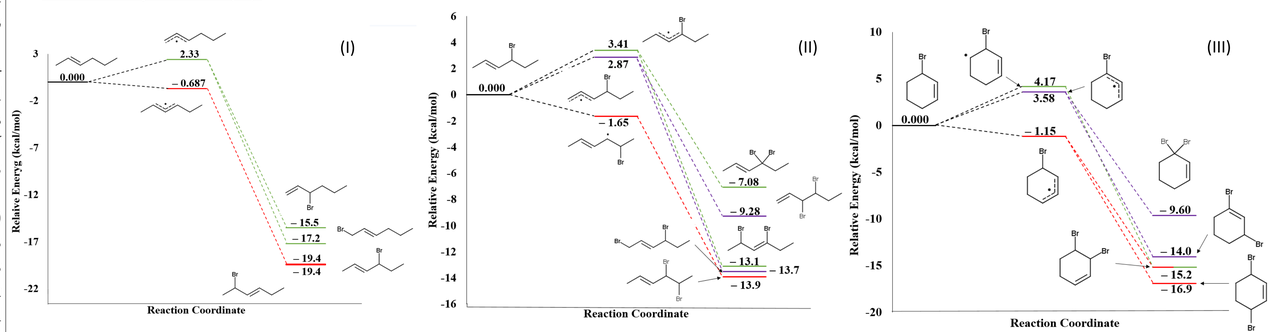
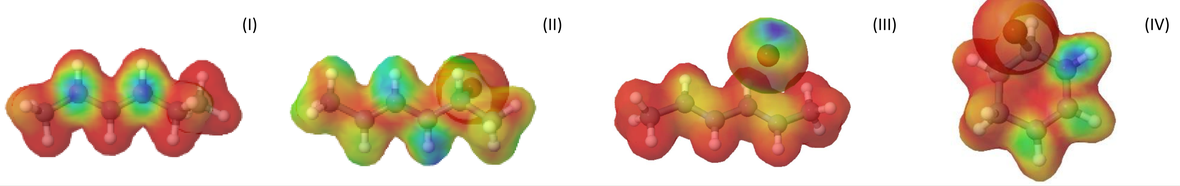


Figure 4: Radical susceptibility maps of *trans*-2-hexen-4-yl (I), *trans*-5-bromo-2-hexen-4-yl (II), *trans*-2,4-hexadiene + Br· (III) and 3-bromocyclohexen-6-yl (IV). Color gradient from red to blue indicates increasing radical susceptibility.

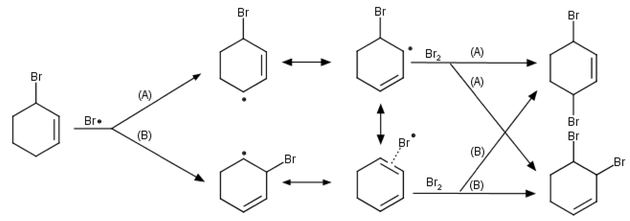


DISCUSSION

Wohl-Ziegler brominations of **1a** and **1b** both yielded a mixture of bromoalkene products (Table 1). We were able to identify the GC peaks (Figure 1) based on retention times of independently prepared bromohexene products (**2b**, **3b**, **4b**) and MS fragmentation patterns. Key ^{1}H NMR peaks of alpha hydrogens were also assignable (Figure 2) and relative yields determined from both methods were remarkably consistent. Our findings that the allylic rearrangement product (**3a**) is the major isomer clearly contradicts previous claims that NBS bromination of 2-heptene yields solely 4-bromo-2-heptene. [4,5,6,7] Moreover, our NMR results show that previously reported NMR spectra of **2a** are incorrect.[11]

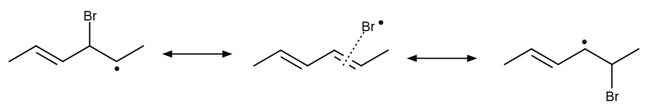
The relative yields of the bromoalkene products were invariant with solvent, time, initiation method and GC injection port temperature, indicating that the products do not equilibrate and the reaction is under kinetic control. Further reinforcing this ideal, our computations indicated reversion of the bromoalkenes to the allylic radicals is prohibitively endergonic (ΔG = 17-19 kcal/mol, Figure 3-I). The 75:25 ratio of products **2b/3b** to **4b/5b** is explained by formation of the H-4 derived radical at a rate 3 times faster than the H-1 derived radical. This would indicate a transition state for H abstraction that is ~ 1 kcal/mol more stable. This is consistent with the computational data, which shows a 3 kcal/mol difference in radical stability (Figure 3-I).

Neglecting stereo chemistry, we found that bromination of 3-bromocyclohexene yields 3 isomers (79 % **2c**, 19 % **3c**, 2 % **4c**, Table 2). According to resonance theory, the major and minor products (**2c** and **3c**) can come from the same radical intermediate, with the major product (**2c**) being more stable than the minor (**3c**) (Figure 3-III). However, our preliminary DFT calculations suggest H abstraction at C4 could occur and represent another pathway (path b) to the observed products (Scheme 2).



Scheme 2: Resonance structures from two separate pathways (A and B) due to bromines effect on the radical stability.

DFT calculations relating to the bromination of 4-bromo-2-hexene indicate that the most stable radical intermediate occurs due to H abstraction at C5 (Figure 3-II) with a bromine shift from C4 to C5 and the radical ending up on C4 (Scheme 3). Interestingly, the DFT minimization pathways suggest a transition state in which the bromine has all of the radical and is hovering over 2,4-hexadiene **(**Figure 4-II and 4-III). The possibility that bromine preferentially abstracts a H at C5 will be tested.



Scheme 3: Bromine shift to yield most stable radical intermediate when H abstraction occurs adjacent to Br.

CONCLUSION

Wohl-Ziegler brominations of 2-alkenes (**1a**, **1b**) do in fact display multiple isomers in accord to resonance theory. TIC chromatograms, MS fragmentation patterns and ^{1}H NMR spectra confirmed identification of all isomers. Previous claims stating **2a** is the sole product of NBS bromination of **1a** have been shown to be incorrect. The bromohexene products were determined to be under kinetic control since equilibrium is thermodynamically prohibitive and relative yields are invariant with solvent, time, initiation method and GC injection port temperature.

DFT calculations suggest that radical susceptibility increases near a bromine atom and thus bromine helps stabilize the radical. This finding gave rise to a new possible mechanism where H abstraction occurs adjacent to Br. Further DFT calculations show Br dissociates and hovers over the diene to induce a Br shift to a more favorable radical.

ACKNOWLEDGEMENTS

We thank WSU Chemistry Club, WSU Student Senate, WSU Academic Affairs and the ACS Lacrosse-Winona Local Sectional for the financial support to attend this conference.

REFERENCES

(1) Dauben, HJ.; McCoy, L. *J. Chem. Soc.* **1959**, 81 (18), 4863 – 4873. (2) Winkler, M.; SteinbiB, M.; Meier, M. *Eur. J. Lipid Sci. Technol*. **2013,** 116, 44 – 51. (3) Klein, D. Wiley: New Jersey, **2012**. (4) Greenwood, F.; Kellert, M. *J. Am. Chem. Soc*. **1953**, 75, 4842 – 4843. (5) Greenwood, F.; Kellert, M.; Sedlak, J. *Org. Syn.* **1963**, 4, 108. (6) Saikia, I.; Borah, A.; Phukan, P. *Chem. Rev.* **2016**, 116, 6837 – 7042. (7) N-Bromosuccinimide. https://en.wikipedia.org/wiki/N-Bromosuccinimide (accessed Nov. 2017). (8) Kharasch, M.; Malec, R.; Yang, N. *J. Org. Chem.* **1957**, 22, 1443 – 1444. (9) Bateman, L.; Cunneen, J.; Fabian, J.; Koch, H. *J. Chem. Soc*., **1950**, 936 – 941. (10) Schmidt, M.; Baldrige, K.; Boatz, J.; Elbert, S.; Gordon, M.; Jensen, J.; Koseki, S.; Matsunaga, N.; Nguyen, K.; Su, S.; Windus, T.; Dupuis, M.; Montgomery, J. *J. Comput. Chem*. **1993**, 14, 1347 – 1363. (11) Khazaei, A.; Vaghei, R.; Karkhanei, E. *Syn. Comm.* **2002**, 32 (14), 2107 – 2113.