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REGIO- AND STEREO-CONTROL OF THE BROMOMETHOXYLATION OF CYCLOHEXENES BY HYDROXY OR METHOXY SUBSTITUENT

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Abstract - Bromomethoxylation of cyclohexenes carrying a hydroxy or methoxy substituent was studied and found to be regiospecific and stereospecific or highly stereoselective. Herein, the inductive effect of the substituents determines the regiochemistry of the products, and steric hindrance directs the stereoselectivity of the reaction.

The bromomethoxylation of cycloalkenes is usually stereospecific in the sense that Br and methoxy substituents in the products are in trans configuration.[1] However, regioisomers and/or stereoisomers were obtained for substituted cyclohexenes even when the Br and methoxy are added trans-diaxially to the double bond as required by the stereoelectronic effect.[2] For example, in the bromomethoxylation of 1-methyl-4-tert-butylcyclohexene[3] and 4-cyanocyclohexene,[4] regioisomers were obtained. Recently, Kočovský and co-workers[5] demonstrated that for biased cyclohexene systems, such as 2- or 5-unsaturated cholestane derivatives, participation of neighboring group, such as hydroxy, methoxy, etc. could very

effectively control the regiochemistry and stereochemistry of the bromohydroxylation reaction.

In this report, we describe that for simple and conformationally mobile cyclohexenes with hydroxy or methoxy substituent (OR group), the bromomethoxylation with N-bromosuccinimide (NBS) in methanol is regiospecific and stereospecific if no steric hindrance interferes with the reaction. Herein, the OR group of the reactants directs the regiochemistry and stereochemistry of the reaction.

RESULTS and DISCUSSION

The bromomethoxylation of alkenes could be achieved by many different brominating agents in methanol.[6-8] In this study, we use NBS in methanol.

The bromomethoxylation of six cycloalkenes carrying OR group (1-6) and three dihydropyrans with methoxy or methoxycarbonyl substituent (7-9) was studied. In all cases the yields are good to excellent. The presence of isomers was studied by GLC analyses at different temperature and confirmed by ^{1}H and ^{13}C NMR spectroscopy. The regiochemistry, configuration, and conformation of the products (Table 1-3) were determined by the chemical shift of the hydrogen geminal to Br, its coupling constants to the vicinal hydrogens, the existence of a reflection symmetry in the molecule as observed in NMR spectra, and for dihydropyrans (7-9), the coupling constants of the anomeric protons. Trans addition of Br and methoxy is assumed in the case 3 where coupling constant is not available for determining the configuration of the methoxy-bearing carbon of the product. Trans configuration in Br and methoxy is observed in the other cases as expected.[6,9]

The bromomethoxylation of 8 by tert-butyl hypobromite in methanol was studied by Duggan and Hall.[7] Therein, products from

cis and trans addition of Br and methoxy were obtained in the ratio of 4:6. However, in our study, two trans addition stereoisomers, 8a1 and 8e2, were obtained in the ratio of 95:5.

Baldwin and Brown[6] had studied the bromomethoxylation of 9 by 1,3-dibromo-5,5-dimethylhydantoin in a mixed solvent of methanol and ether. It was reported that 3(e)-bromo-2(e),4(e)-dimethoxytetrahydropyran (9e1) and 9a were obtained in the ratio of 2:1. However, in their study 9e1 and 9a were not separated. The regiochemistry and stereochemistry of the products were determined by debromination and ^{1}H NMR spectra of the products in mixture. In our study, a different brominating agent was used and two products were obtained and separated. One of them is 9a and the other is its regioisomer, 9e2.

Except for 4a2 and 9e2, all the products from the bromomethoxylation of 1-9 are Markovnikov products. The Markovnikov orientation for the bromomethoxylation of cyclohexenes could be attributed to the ability of the OR group to reduce the stability of a partial charge on the β-carbon.

For 1-3 and 7, the reactions are stereospecific. By contrast, for the five- and seven-membered ring compounds the stereoselectivity is not so pronounced. In those stereospecific reactions, the products have incoming Br and methoxy in cis and trans configuration with respect to the OR group of the reactants. Even for those stereoselective reactions, the stereochemistry of the major products (4a1, 5A, 6A, and 8a1) followed the same generalization. It seems that the OR group of the reactant directs the stereochemistry of the reaction.

For the products 1a, 2a, and 4a1, the OR group is in axial, and the incoming Br and methoxy are in trans-diequatorial positions. However, this conformation is not necessarily the initially-formed. It is known from experiences[6] that in the bromomethoxy-

lation of alkenes, Br and methoxy are usually added trans-diaxially. However, the conformation of product having trans-diaxial substituents is less stable than that with trans-diequatorial substituents. Thus conformational conversion is expected. Similarly, the anomeric effect and the tendency of Br to take an equatorial position may force the product from dihydropyrans to undergo conformational conversion. The only exception is the case 3 where an unfavorable 1,3-interaction would be present if conformational conversion occured.

The mechanism involving the transition state with an interaction between the OR group and the bromonium ion (specific directing effect, Fig. 1)[4,6,10] may account for the stereospecificity or high stereoselectivity of the reaction for both cyclohexenes and dihydropyrans. However, if this interaction has an important contribution, the OR group of the cyclohexenes has to be in the less stable pseudo-axial position.[11] And in the case 7, where methoxycarbonyl group replaces OR group and the interaction is expected to be different, nevertheless stereospecificity in the reaction is still observed. Furthermore, for cases 8 and 9, the anomeric effect predicts that the OR group in the reactant prefers to take an axial position and, consequently, the reaction is even more likely to be stereospecific. Nevertheless, results contrary to this expectation were observed. So it is less likely that this interaction has an important contribution to the reaction.

In substituted cyclohexenes there are four pathways for trans-diaxial addition of Br and methoxy group (pathways 1-4). In 1-3, the pathway 1 is followed exclusively. In this pathway, where the OR group is in an equatorial position, bromonium ion is formed reversibly and trans-addition of methanol is followed.

This is another example of the effect of the steric hindrance from the axial substituent on the course of the reaction.

The stereospecificity in the bromomethoxylation of 7, a dihydropyran without the anomeric effect, could be explained by a similar argument. Herein the steric hindrance from the axial substituent against the incoming methanol prevents the reaction from following the pathway 6 so that the pathway 5 is followed exclusively. In this pathway, the substituent is in an equatorial position and the Br and methoxy are added trans-diaxially to the dihydropyran.

Similarly, in the case 8, where the anomeric effect predicts the OR group has a higher tendency to take an axial position in the reactant, the pathway 5 still dominates the reaction and the pathway 6 plays a less important role. The high stereoselectivity in the bromomethoxylation of 10 studied by Sweet and Brown[15] could be explained by the same argument. In these cases, the steric hindrance from the axial substituent in pathway 6 is smaller and the minor product from this pathway is produced. The smaller steric effect from the axial substituent in dihydropyrans is probably a result of the longer C-O bond length and therefore longer distance between the substituent and the incoming methanol.

These results support our suggestion that the steric hindrance from the pseudo-axial OR group against the incmoing methanol will raise the activation energy of the pathway 4, therefore the pathway 1 is followed exclusively in cases 1-3.

In summary, for cyclohexenes without other steric hindrance, the OR group determines the regiochemistry of the bromomethoxylation by the electronic effect and in the mean time, by the steric hindrance from these groups, directs the course of the reaction and the stereochemistry of the product.

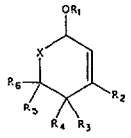
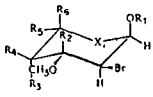
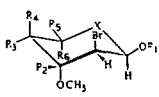
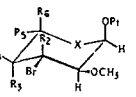
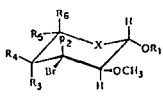
The pathways 2 and 3 are expected to be less favorable because the products from these pathways are anti-Markovnikov.

For the pathway 4, it is very likely that the steric hindrance from the pseudo-axial OR group of the reactant against the incoming methanol will raise the activation energy and renders this pathway not competitive. The steric hindrance from the axial methyl of 3- or 4-methylcyclohexenes was suggested by Rickborn and Lwo[12] to account for the lower rate of the epoxidation of these compounds. Pasto and Klein[13] also proposed the steric hindrance from remote alkyl group playing a predominant role in determining the stereochemistry of hydroboration of alkyl cyclohexenes. Kočovský and co-workers[5] also demonstrated that the steric hindrance from neighboring group in biased cyclohexenes could affect the reaction course.

For the case 9, 9a and 9e2 were obtained and the influence of the solvent on the product ratio was studied. (Table 4) It is observed that, in the less polar solvent where the OR group of the reactant has a higher tendency to take an axial position,[14] the ratio of 9e2 : 9a increases. This result supports that 9a and 9e2 are the products from the pathways 1 and 3 respectively. Despite of anti-Markovnikov, the pathway 3 was followed, instead of the pathway 4, is a manifestation of the influence of the steric hindrance from the axial methoxy group.

For the case 4, pathway 1 gave the product 4a1. However, the steric hindrance from C-4 methyl against the electrophilic bromine raised the energy barrier of this pathway and allowed the pathway 2 becoming competitive to give 4a2. Herein, the Br atom went to C-3 via a chairlike transition state, instead of going to C-2 via a higher energy pathway with a twist-boat transition state. The regiochemistry of this product is anti-Markovnikov.

Table 1. Results of Bromomethoxylation of Substituted Cyclohexenes (1-4) and 2-Methoxy-5,6-dihydro-2H-pyran (9)

					Isolated yield, %
1.* X=CH_2, R_1=CH_3, R_2-R_6=H.	1a	1e	—	—	85
2. X=CH_2, R_1-R_6=H.	2a	—	—	—	86
3. X=CH_2, R_1=R_3=R_4=H, R_2=R_5=R_6=CH_3.	—	3e	—	—	85
4.# X=CH_2, R_3=R_4=CH_3, R_1=R_2=R_5=R_6=H.	4a1	—	4a2	—	90
9.@ X=O, R_1=CH_3, R_2-R_6=H.	9a	—	—	9e2	90

* The products of 1 is in conformational equilibrium of 1a and 1e.
\# 4a1/4a2=5/2.
@ The ratio of 9a/9e2 is dependent on slovents. (See Table 4.)

Table 2. Results of Bromomethoxylation of Substituted Cycloalkenes (5 and 6).

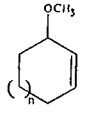
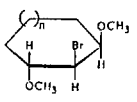
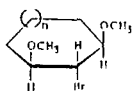
			Ratio (A/S)	Isolated yield, %
5. n=0.	5A	5S	5/4	89
6. n=2.	6A	6S	5/1	82

Table 3. Results of Bromomethoxylation of Substituted Dihydropyrans (7, 8, and 10).

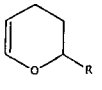
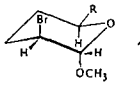
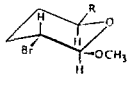
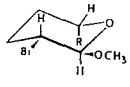
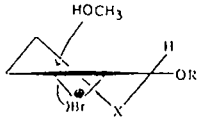
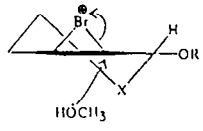
				Ratio	Isolated yield, %
7. R=$COOCH_3$	7e	—	—		82
8. R=OCH_3	—	8e2	8a1	8e2/8a1=5/95	95
10. R=CH_2OCH_3	10e1	10e2	—	10e1/10e2=9/1	87

Table 4. Solvent Effects on Bromomethoxylation of 9 with NBS in different solvent systems.

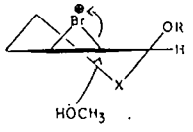
Solvent system(v/v)		9a/9e2
MeOH : Ether	(1:0)	1/0.83
	(1:1)	1/1.18
	(1:1.25)	1/1.46
	(1/10)	1/1.42
MeOH : n-Hexane	(1:1)	1/1.56
	(1:3)	1/1.57
	(1:10)	1/1.96



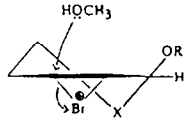
Pathway 1.



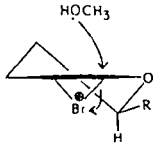
Pathway 2.



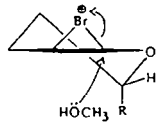
Pathway 3.



Pathway 4.



Pathway 5.



Pathway 6.

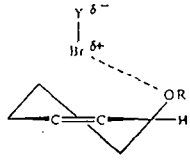


Figure 1.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu IR-440 grating spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were determined on a JEOL JNM-FX100 or a Brucker AM-300 WB FT-NMR spectrometer using TMS and $CDCl_3$ as internal standards, respectively. The mass spectra were obtained on a JEOL JMS-D100 spectrometer operating at 12 eV. The elemental compositions of compounds were determined by a JEOL JMS HX-100 high resolution mass spectrometer or a Heraeus CHN-O-RAPID elemental analyzer. GLC analyses were performed by a Shimadzu GC-9A gas chromatograph equipped with an SE-30 column.

Materials. 3-Methoxycycloalkenes and 2-methoxy-5,6-dihydro-2H-pyran were prepared according to the literature method.[16] Methyl 3,4-dihydro-2H-pyran-2-carboxylate was prepared by esterification of the corresponding acid. 2-Cyclohexen-1-ol, 2-methoxy-3,4-dihydro-2H-pyran, 3,5,5-trimethyl-2-cyclohexen-1-ol, and NBS were purchased (Aldrich).

Bromomethoxylation of Substituted Cycloalkenes and Dihydropyrans with NBS in Methanol.

General procedure. 3 mmol of substituted cycloalkene or dihydropyran was added dropwisely to a mixture of 3.1 mmol of NBS and 40 ml of dry methanol at 0 °C. The mixture was stirred overnight at room temperature and then salted out with 30 ml of saturated aqueous NaCl. The aqueous layer was further extracted with ether. The combined organic layers were washed sequently with saturated aqueous NaCl and water. The ether solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The oily residue was directly analyzed by GLC to study the presence of isomers and then purified or seperated by chromatography on a silica gel column, eluting with n-hexane. Solid products were further recrystallized from n-hexane, and all products were further identified by GLC analyses.

2(e)-Bromo-1(a),3(e)-dimethoxycyclohexane (1a). Oil (85%); ^{1}H NMR δ 1.37-1.53 (m, 4 H), 1.64-1.75 (m, 1 H), 1.92-1.99 (m,1 H), 3.29 (s,6 H), 3.60 (m,2 H), 4.29 (dd,J = 5.6, J = 3.0 Hz,1 H); ^{13}C NMR δ 18.7 (t), 26.1 (t), 26.8 (t), 55.8 (d), 55.9 (q), 56.7 (q), 77.2 (d), 79.9 (d); IR (film) 2900, 1460 cm^{-1} ; MS m/e 223 (M^++1, 20), 221 (M^+-1, 17), 41(100).

2(e)-Bromo-3(e)-methoxy-1(a)-hydroxycyclohexane(2a). Oil (86%); ^{1}H NMR δ 1.56-1.84 (m,6 H), 2.26 (br s,1 H), 3.41 (s,3 H), 3.62 (ddd,J = 7.4, J = 3.8 Hz,1 H), 4.03 (m,1 H), 4.27 (dd, J = 2.8, J = 7.4Hz,1 H); ^{13}C NMR δ 18.2 (t), 27.2 (t), 30.2 (t), 56.9 (q), 62.0 (d), 69.2 (d), 79.7 (d); IR (film) 3430, 2950, 2870, 2830, 1460, 1450 cm^{-1} ; MS m/e 211 (2), 209 (2), 178 (4), 176 (4), 97 (100); calcd for $C_7H_{13}BrO_2$ 210.0104, found 210.0098.

2(a)-Bromo-1(e)-hydroxy-3(a)-methoxy-3,5,5-trimethylcyclohexane (3e). White crystals (85%); mp 66-68 °C; ^{1}H NMR δ 0.87 (s, 3 H), 1.00 (s,3 H), 1.29 (s,3 H), 1.42 (s,2 H), 1.19-1.58 (m,2 H), 1.73 (br s, 1 H), 3.13 (s, 3 H), 3.83 (ddd, J = 3.3, J = 10.4, J = 4.0 Hz, 1 H), 4.35 (d,J = 3.3 Hz,1 H); ^{13}C NMR δ 24.8, 28.0, 31.7, 34.0, 40.6, 42.8, 50.0, 65.7, 67.9, 79.2; IR (KBr) 3300, 2925, 2900, 2825, 1450 cm^{-1} ; MS m/e 237 (M^++2-15, 4), 235 (M^+-15, 4), 220 (6), 218 (6), 139 (100). Anal. Calcd for $C_{10}H_{19}BrO_2$ C, 47.99; H, 7.66, found: C, 47.76; H, 7.56.

2(e)-Bromo-1(a)-hydroxy-3(e)-methoxy-4,4-dimethylcyclohexane (4a1). Oil (64%); ^{1}H NMR δ 0.89 (s, 3 H), 1.07 (s, 3 H), 1.74-1.87 (m, 4 H), 2.51 (br s, 1H), 3.25 (d, J = 10.5 Hz, 1 H), 3.57 (s, 3 H), 4.16 (m, 1 H), 4.27 (dd, J = 10.5, J = 2.6 Hz, 1 H); ^{13}C NMR δ 16.0 (q), 27.3 (t), 29.5 (q), 32.4 (t), 39.5 (s), 62.4 (q), 63.8 (d), 71.5 (d), 86.5 (d).

3(e)-Bromo-1(a)-hydroxy-2(e)-methoxy-4,4-dimethylcyclohexane (4a2). White crystals (26%); mp 58-60 °C; ^{1}H NMR δ 1.04 (s, 3 H), 1.09 (s, 3 H), 1.30-1.90 (m, 4 H), 2.56 (br s, 1 H), 3.25 (dd, J = 3.2, J = 10.4 Hz, 1 H), 3.50 (s, 3 H), 4.10 (d, J = 10.4 Hz, 1H), 4.14 (m, 1 H); ^{13}C NMR δ 20.9, 25.5, 31.0, 32.7, 37.2, 58.0, 66.0, 66.5, 83.0; IR (KBr) 3300, 2800, 1450 cm^{-1}; MS m/e 238 (10), 236 (10), 207 (5), 205 (5), 157 (100). Anal. Calcd for $C_9H_{17}BrO_2.H_2O$: C, 42.37; H, 7.51. Found: C, 42.38, H, 7.49.

t-2-Bromo-r-1,t-3-dimethoxycyclopentane (5A). Oil (48%); ^{1}H NMR δ 1.58-2.27 (m, 4 H), 3.36 (s, 3 H), 3.38 (s, 3 H), 3.80 (m, 1 H), 4.00 (m, 1 H), 4.30 (dd, J = 4.4, J = 2.2 Hz, 1 H); ^{13}C NMR δ 26.4, 26.6, 55.4, 57.3, 57.4, 81.2, 87.1; IR (film) 2900, 2800, 1450 cm^{-1}; MS m/e 179 (M^++2-31, 10), 177 (M^+-31, 10), 129 (40), 97 (100).

t-2-Bromo-r-1,c-3-dimethoxycyclopentane (5S). Oil (41%); ^{1}H NMR δ 1.77-2.08 (m, 4 H), 3.40 (s, 6 H), 3.94 (m, 2 H), 4.00 (t, J = 3.8 Hz, 1 H); ^{13}C NMR δ 28.7 (t), 54.9 (d), 57.3 (q), 88.7(d); MS m/e 179 (M^++2-31, 6), 177 (M^+-31, 7), 129 (35), 97 (100).

t-2-Bromo-r-1,t-3-dimethoxycycloheptane (6A). Oil (63.7%); ^{1}H NMR δ 1.58-2.65 (m, 8 H), 3.35 (s, 3 H), 3.36 (s, 3 H), 3.54 (m, 2 H), 4.40 (dd, J = 5.7, J = 2.0 Hz, 1 H); ^{13}C NMR δ 20.6 (t), 23.2 (t), 28.7 (t), 29.1 (t), 56.5 (q), 56.7 (q), 60.1 (d), 79.9 (d), 83.1 (d); IR (film) 2900, 1460 cm^{-1}; MS m/e 238 (5), 236 (5), 124 (100); calcd for $C_9H_{17}BrO_2$ 238.0399, found 238.0392.

t-2-Bromo-r-1,c-3-dimethoxycycloheptane (6S). Oil (18.8%); ^{1}H NMR δ 1.37-1.79 (m, 8 H), 3.35 (s, 6 H), 3.57 (m, 2 H), 4.12 (t, J = 5.4 Hz, 1 H); ^{13}C NMR δ 23.5 (t), 27.9 (t), 56.8 (d), 59.5 (q). 80.0 (d).

Methyl 5(a)-bromo-6(a)-methoxytetrahydropyran-2(e)-carboxylate (7e). Oil (82%); ^{1}H NMR δ 1.18-2.44 (m, 4 H), 3.37 (s, 3 H), 3.70 (s, 3 H), 4.00 (m, 1 H), 4.35 (dd, J = 2.7, J = 8.1 Hz, 1 H), 4.83 (d, J = 2.7 Hz, 1 H); ^{13}C NMR δ 23.1, 26.8, 48.8, 52.1, 55.4, 88.2, 100.5, 171.0; IR (film) 2925, 2830, 1740 cm^{-1}; MS m/e 253 (M^++1, 4), 251 (4), 223 (20), 221 (10), 113 (100); calcd for $C_8H_{13}BrO_4$ 253.9984, found 253.9985.

3(e)-Bromo-2(e),6(a)-dimethoxytetrahydropyran (8a1). Oil (90%); ^{1}H NMR δ 1.78-2.29 (m, 4 H), 3.48 (s, 3 H), 3.51 (s, 3 H), 3.89 (m, 1 H), 4.75 (d, J = 6.6Hz, 1 H), 4.85 (dd, J = 3.4 Hz, 1 H); ^{13}C NMR δ 28.2 (t), 29.2 (t), 48.3 (d), 54.6 (q), 55.6 (q), 99.3 (d), 99.7 (d); IR (film) 2950, 2850, 1440 cm^{-1}; MS m/e 225 (M^++1, 10), 223 (10), 138 (100). Anal. Calcd for $C_7H_{13}BrO_3$: C, 37.35; H, 5.82. Found: C, 37.18; H, 5.74.

3(e)-Bromo-2(e),6(e)-dimethoxytetrahydropyran (8e2). 5% [in admixture with (8a1)]; part of ^{1}H NMR spectrum that is not covered up by the major product δ 4.16 (m, 1 H), 4.48 (d, J = 7.1 Hz, 1 H), 4.57 (dd, J = 7.8, J = 2.2 Hz, 1 H).

3(e)-Bromo-2(a),4(e)-dimethoxytetrahydropyran (9a). Oil (49%); ^{1}H NMR δ 1.57-1.73 (m, 1 H), 2.16-2.26 (m, 1 H), 3.44 (s, 6 H), 3.60-3.85 (m, 3 H), 3.91 (dd, J = 2.9, J = 7.5 Hz, 1 H), 4.77 (d, J = 2.9 Hz, 1 H); ^{13}C NMR δ 31.6 (t), 53.1 (t), 55.1 (q), 56.5 (q), 57.4 (d), 79.3 (d), 94.5 (d); IR (film) 2900, 2800, 1450 cm^{-1}; MS m/e 225 (1), 223 (1), 136 (100); calcd for $C_7H_{13}BrO_3$ 226.0034, found 226.0032.

4(e)-Bromo-2(e),3(e)-dimethoxytetrahydropyran (9e2). White crystals (41%); mp 51-52 °C; ^{1}H NMR δ 1.52-1.78 (m, 1 H), 2.10-2.22 (m, 1 H), 3.30-3.50 (m, 2 H), 3.46 (s, 3 H), 3.53 (s, 3 H), 3.66 (dd, J = 7.5 Hz, 1 H), 4.05 (ddd, J = 7.5, J = 2.9 Hz, 1 H), 4.35 (d, J = 7.5 Hz, 1 H); ^{13}C NMR δ 31.3, 54.0, 57.4 (two peaks overlapped), 61.1, 81.0, 103.9; IR (KBr) 2920, 2820, 1440 cm^{-1}; MS m/e 225 (M^++1, 1), 223 (1), 195 (10), 193 (10), 75 (100); calcd for $C_7H_{13}BrO_3$ 226.0034, found 226.0035.

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