Regio- and stereoselectivity in the solvomercuriation and intramolecular alkoxymercuriation of cyclic unsaturated alcohols

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The regio- and stereoselectivity in the solvomercuriation and intramolecular alkoxymercuriation of several cyclic olefinic alcohols were examined. The regioselectivity is controlled mainly by electronic factors, while the stereoselectivity is controlled by steric factors as well as electronic ones. The optimised structure of the mercurinium ion intermediate suggests that the attractive interaction between the hydroxy group in the molecule and the mercurinium ion moiety affects the selectivity.

Introduction

The oxymercuriation–demercuriation procedure provides a convenient synthetic method for effecting the Markovnikoff hydration of the carbon–carbon double bond. The reaction of (*E*)-pent-2-ene, which has an evenly substituted carbon–carbon double bond with an equal number of substituents on each sp^2 carbon, preferably yielded pentan-2-ol, but there is no clear explanation for this regioselectivity.[1] In cyclic systems, the regio- and stereoselectivity of alkylcyclohexenes are controlled by the torsional strain between the allylic alkyl group and the incoming nucleophile to the mercurinium ion intermediate.[2] Since 3-methylcyclohexene gave mainly *trans*-3-methylcyclohexanol, Brown pointed out that the regio- and stereochemistry are determined by the difference in the relative stabilities of the two possible transition states caused by the *gauche* interactions between the forming bond of the nucleophile with the mercurinium ion moiety and the bonds in the molecule.[3] In this article, we present the results of a study designed to evaluate the role of the polar substituent on the regio- and stereochemistry in the solvomercuriation of cyclic olefinic alcohols. The intramolecular alkoxymercuriation of cyclohexenylalkanols was also examined. Cyclohexenols such as cyclohex-2-enol **1**, 2-methylcyclohex-2-enol **2**, 3-methylcyclohex-2-enol **3**, 3,*cis*-5-dimethylcyclohex-2-enol **4** and cyclopent-2-enol **5** were employed. 2-Isopropylidenecyclohexanol **6** and 2-isopropylidenecyclopentanol **7** were used as substrates which have an equally substituted exocyclic double bond. The regio- and stereoselectivity obtained from the cyclic allylic alcohols were compared with those from 3-methylcyclohexene **8** and 1-isopropylidene-2-methylcyclohexane **9**. The intra- and intermolecular alkoxymercuriations of cyclohex-3-enylmethanol **10**, 4-methylcyclohex-3-enylmethanol **11** and 2-(cyclohex-2-enyl)ethanol **12** were also examined (Fig. 1). Methoxymercuriation was applied to the unsaturated alcohols, and oxymercuriation occurred on the unsaturated hydrocarbons. The analyses of the regio- and stereoselectivity of the reaction were performed on the demercuriated products which were obtained by $NaBH_4$ reduction.

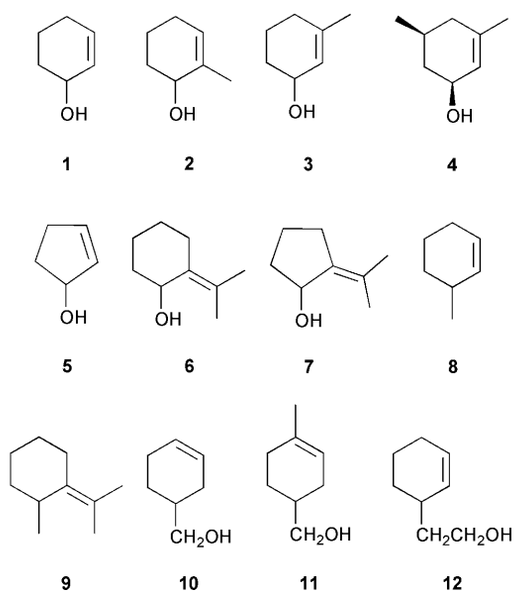

Fig. 1 Olefins.

Results and discussion

In order to examine the consistency of the regio- and stereoselectivity, the reaction was performed at different temperatures and for different times. No appreciable differences in results were observed upon varying the reaction conditions (Table 1, footnote *a*). This indicates that the difference in the entropies of activation between the routes to the diastereomeric products is almost constant. The differences in the free energies of activation giving two diastereomeric products are adequately approximated by the differences in the enthalpies of activation. The regioselectivity in the nucleophilic attack on the mercurinium ion intermediate is controlled generally by the electron density of the attacking site. We previously showed that the regioselectivity varied depending on the substituent(s) on the phenyl group in the methoxymercuriation of substituted phenylalkenols.[4] On the other hand, the regioselectivity as well as the stereoselectivity in the solvomercuriation of cyclic compounds such as the cyclohexene derivatives is considered to be controlled by not only electronic but also steric factors, that is, (i) the electron density of the mercurinium ion moiety, (ii) the energetics of the two different routes to the products *via* skew-boat-like and chair-like transition states, when the ring opening of the mercurinium ion takes place in the diaxial mode, and (iii) the local steric environment of the approaching nucleophile with respect to the substrate (steric and/or torsional strain). In addition, both the regio- and stereoselectivity of the intramolecular alkoxymercuriation forming the new cyclic structure are also controlled by (iv) the steric relationship of the ring

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Table 1 Selectivity in solvomercuriation and intramolecular alkoxymercuriation[a]

Compound	Yield[b] (%)	Regioselectivity[c] α	Regioselectivity[c] β	Stereoselectivity[d] *cis*	Stereoselectivity[d] *trans*
Methoxymercuriation					
1	78	0	100	30	70
1[e]	95	2	98	α 18	80
				β 1	1
2	80	100	0	89[f]	11
3	76	0	100	13[f]	87
4	69	0	100	0[f]	100
5	92	0	100	19	81
6	42	0	100	62	38
7	61	0	100	59	41
8[g]		16	84	α 12	4
				β 6	79
9	5				
10	43	52	48	α 1	51
				β 46	2
11	65	0	100	97[h]	3
Intramolecular alkoxymercuriation					
10	30	100	0	100	0
11	48	0	100	100	0
12	20	100	0	100	0

[a] Reaction time 1 h (solvomercuriation) or 1.5 h (intramolecular alkoxymercuriation). Temperature 25 °C. No apparent discrepancies of regio- and stereoselectivity appeared depending on the reaction conditions (time 24 h, temperature 0 and 40 °C). The discrepancies of selectivity were within 3% except in the case of **6** (6%, time 24 h, temp. 25 °C). [b] Isolated yield. [c] The α is the proximal and the β is the distal carbon atom of the mercurinium ion moiety to the allylic substituent. [d] The relation between the two substituents on the ring unless otherwise indicated. [e] Ref. 12. Oxymercuriation. Accompanied by 2% cyclohexane-1,2-diols. Reaction time not mentioned. No appreciable discrepancy was observed for the selectivity between the oxymercuriation and the methoxymercuriation. [f] The relation between OH and OMe. [g] Ref. 3. The reaction temperature, time and yield not reported. [h] The relation between CH_2OH and OMe.

junction, if a condensed-ring structure is constructed, and (v) the number of atoms in the newly formed ring.

Methoxymercuriation of cyclohexenols

We accepted the premise that the oxymercuriation of olefins involves the rapid pre-equilibrium formation of a mercurinium ion as an unstable intermediate followed by the rate- and product-determining attack of a nucleophile.[5] The stereochemistry of the reaction in this study is discussed on the basis of the fact that the attack of the nucleophile occurs *trans* to the mercury and proceeds with preferential diaxial opening of the mercurinium ion in the oxymercuriation of cyclohexenols, similar to the case of simple cyclohexenes.[6] The reaction of **1**, which has the evenly substituted carbon–carbon double bond, gave the product in which the methoxy group was introduced at the β-carbon (Table 1). The terms α and β designate a proximal and a distal carbon of a mercurinium ion moiety from a substituent on a six-membered cyclic system, respectively. A plausible reaction pathway for **1** is illustrated in Scheme 1. There are two conformers for **1**, **1a** and **1e**, the hydroxy group of which is at the pseudo-axial position in the former and the pseudo-equatorial in the latter. The structure optimisation of **1** using MO calculations indicated that **1a** is more stable than **1e** by 0.3 kcal mol^{-1} † (Table 2).[7] The mercuric (Hg^{II}) acetate approaches the two diastereofaces of the carbon–carbon double bond for each conformer to give four mercurinium ions, **1ac1**, **1at1**, **1ec1** and **1et1**. We tried to calculate the optimised structures of these diastereomeric mercurinium ions, the corresponding transition states and the products, the methoxymercurials. At present, the transition-state structures of the reaction cannot be obtained. The mercurinium ion **1at1** whose hydroxy group is placed at the pseudo-axial position and on the same side as the mercurinium ion moiety is the most stable among the four. This infers that the close contact between the hydroxy oxygen and the mercurinium ion moiety results in the generation of the attractive interaction. This is supported by the interatomic distance between the oxygen atom and the mercury atom (Table 3). In this reaction a ligand exchange is also expected between the acetate ion on the mercury and the alkoxide in the solvent or the substrate

† 1 cal = 4.184 J.

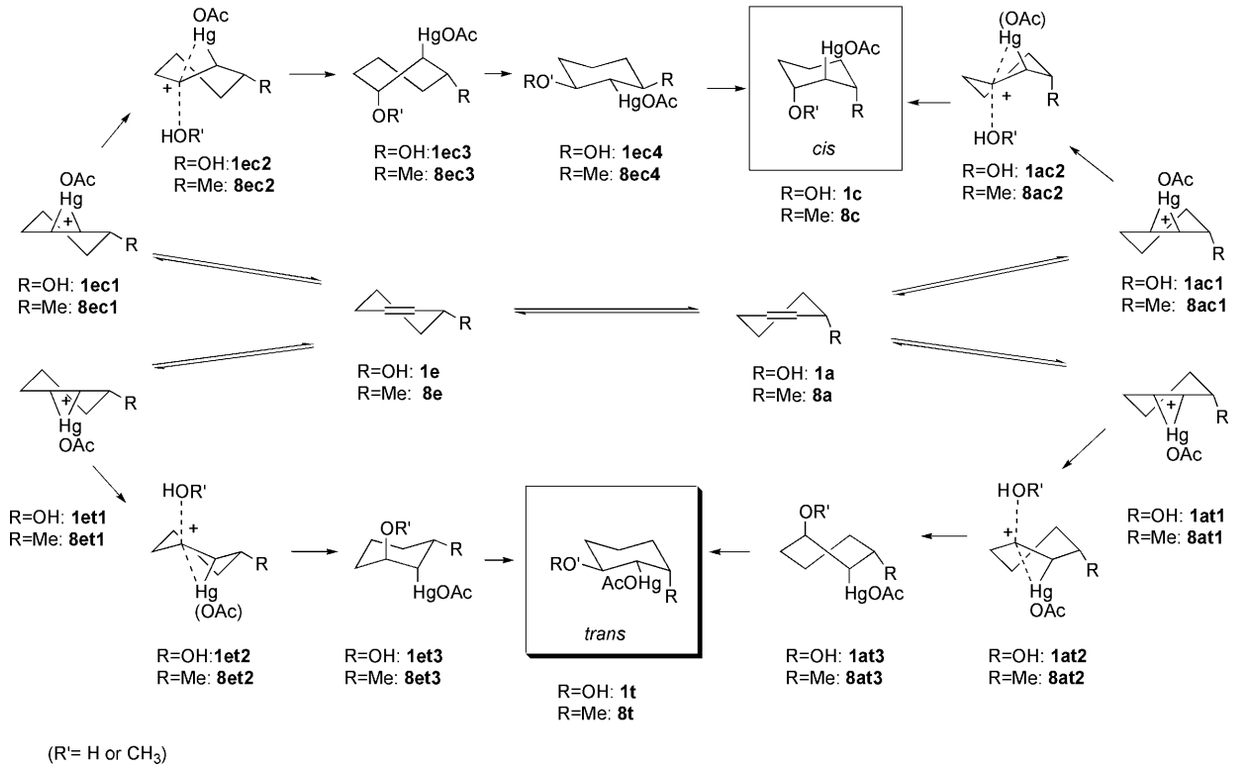
Table 2 Calculated heat of formation for reaction species

Compound	Heat of formation/ kcal mol^{-1}	Compound	Heat of formation/ kcal mol^{-1}
1a	−45.94	**7a**[g]	−63.43
1e	−46.25	**7e**[h]	−63.13
1ac1	27.88	**7ac1**[i]	9.60
1at1	16.45	**7at1**[j]	0.48
1ec1	27.56	**7ec1**[k]	17.01
1et1	20.11	**7et1**[l]	0.49
1et3	−174.57	**7ec3**[m]	−178.26
1ec4	−171.98	**7et3**[n]	−183.36
1c	−174.30	**7c**[o]	−182.25
1t	−178.33	**7t**[p]	−185.84
5	−39.03	**8a**	−9.93
5c1[a]	36.16	**8e**	−10.30
5t1[b]	25.92	**8ac1**	58.78
5c3[c]	−165.28	**8at1**	51.59
5t3[d]	−170.73	**8ec1**	58.95
5c[e]	−169.19	**8et1**	54.14
5t[f]	−171.25	**8at3**	−138.98
6a	−69.12	**8ec4**	−134.94
6e	−65.46	**8c**	−135.69
6ac1	−0.15	**8t**	−141.36
6at1	−5.01	**9a**	−32.68
6ec1	1.08	**9e**	−27.72
6et1	3.05	**9ac1**	32.37
6ac3	−187.18	**9at1**	33.91
6et3	−186.43	**9ec1**	36.20
6c	−187.40	**9et1**	40.63
6t	−186.95		

[a] Mercurinium ion, OH, Hg: opposite side. [b] Mercurinium ion, OH, Hg: same side. [c] 5-Hydroxy-2-methoxycyclopentylmercuric acetate, OMe, OH, HgOAc: equatorial. [d] 5-Hydroxy-2-methoxycyclopentylmercuric acetate, OH: axial, OMe, HgOAc: equatorial. [e] 5-Hydroxy-2-methoxycyclopentylmercuric acetate, OMe, OH, HgOAc: axial. [f] 5-Hydroxy-2-methoxycyclopentylmercuric acetate, OH: axial, OMe, HgOAc: equatorial. [g] **7**, OH: axial. [h] **7**, OH: equatorial. [i] Mercurinium ion, OH: axial, OH, Hg: opposite side. [j] Mercurinium ion, OH: axial, OH, Hg: same side. [k] Mercurinium ion, OH: equatorial, OH, Hg: opposite side. [l] Mercurinium ion, OH: equatorial, OH, Hg: same side. [m] 2-Hydroxy-1-(2-methoxypropan-2-yl)cyclopentylmercuric acetate, $-CMe_2OMe$: axial, OH, HgOAc: equatorial. [n] 2-Hydroxy-1-(2-methoxypropan-2-yl)cyclopentylmercuric acetate, HgOAc: axial, $-CMe_2OMe$, OH: equatorial. [o] 2-Hydroxy-1-(2-methoxypropan-2-yl)cyclopentylmercuric acetate, OH, HgOAc: axial, $-CMe_2OMe$: equatorial. [p] 2-Hydroxy-1-(2-methoxypropan-2-yl)cyclopentylmercuric acetate, OH, $-CMe_2OMe$: axial, HgOAc: equatorial.

Table 3 The distance between the mercury atom and the hydroxy group oxygen in the mercurinium ion

Mercurinium ion	Hg···OH Distance/Å
1ac1	4.12
1at1	2.19
1ec1	4.07
1et1	2.41
6ac1	4.36
6at1	2.17
6ec1	2.21
6et1	4.00



Scheme 1 Reaction pathway of **1** and **8**.

before addition. In order to compare these two intermediates, *viz.* the mercurinium acetate with which the hydroxy group is undergoing intramolecular interaction (**1at1**) and the ligand-exchanged species, the optimisation was performed on these two different structures. For simplification, the calculation was performed on allyl alcohol as a model compound. The result indicated that the former is far more stable than the latter (the difference in energy is 14.26 kcal mol^{-1}) probably because of the difference in the distances between the mercury atom and the alcoholic oxygen (the former: 2.21 Å and the latter: 1.95 Å). It is likely that the contribution of the species in which the ligand is exchanged with the intramolecular hydroxy group adds little to the reaction. When the hydroxy group is placed pseudo-equatorially, then **1et2**, whose hydroxy group is placed on the same side as the mercurinium ion, is energetically more stable compared with **1ec1** whose hydroxy group is placed on the opposite side to that of the mercurinium ion moiety. This also indicates the presence of the interaction between the hydroxy group and the mercurinium ion moiety.

Since the rate-determining step of the oxymercuriation is the introduction of a nucleophile to the mercurinium ion, then species **1ac1**, **1at1**, **1ec1** and **1et1** are in pre-equilibrium. Since the opening of the three-membered cyclic mercurinium ion by attack of the nucleophile occurs in the diaxial mode, the transition-state structures from **1at1** and **1ec1** take skew-boat-like conformations, while those from **1ac1** and **1et1** take chair-like conformations. These transition-state species will then change to the corresponding, more stable conformers of the two diastereomeric products. The *trans* product will be formed from **1at1** and **1et1**; the former is more stable than the latter by 3.66 kcal mol^{-1}. According to the Curtin–Hammett principle the product ratios depend only on the energy difference in the diastereomeric transition states.[8] Since the energy difference between the chair and skew-boat conformations has been estimated to be about 5.5 kcal mol^{-1},[9] the energy of **1et2** will be smaller than that of **1at2** at the transition state and so *trans*-isomer formation mainly proceeds from the mercurinium ion **1et1** *via* **1et2**. Likewise, *cis*-product formation proceeds from the mercurinium ion, **1ac1** *via* **1ac2**.

Table 4 The calculated formal charge and the coefficient of the LUMO of carbons in the mercurinium ion moiety

Mercurinium ion	Formal charge		|Coefficient of LUMO|[a]	
	α	β	α	β
1ac1	−0.1714	−0.0762	0.0867	0.2263
1at1	−0.1452	−0.0755	0.0321	0.3336
1ec1	−0.1734	−0.0802	0.1587	0.1643
1et1	−0.1401	−0.0791	0.0150	0.2892
6ac1	−0.2278	0.0000	0.0322	0.3339
6at1	−0.1798	−0.0543	0.0300	0.2563
6ec1	−0.1539	−0.0941	0.1146	0.1454
6et1	−0.2203	−0.0124	0.0193	0.2715
8ac1	−0.1098	−0.1069	0.1205	0.1886
8at1	−0.1153	−0.0990	0.0832	0.2175
8et1	−0.1140	−0.1040	0.1780	0.1385
8ec1	−0.1292	−0.0964	0.0512	0.2381
8et1	−0.0961	−0.1158	0.1297	0.1848
10a1	−0.1076	−0.1075	0.1210	0.1902
12a1				

[a] 2pπ component.

Since it is considered that the regio- and stereoselectivity in the solvomercuriation of six-membered cyclic olefins are primarily controlled by the electronic situation of the mercurinium ion moiety and the deformation of the ring during the reaction, the formal charges and coefficients of the LUMO of the carbons in the mercurinium ion moiety were calculated using the MO method (Table 4). The formal charges of the β-carbons for both **1ac1** and **1et1** are apparently higher than those of the α-carbons, and the coefficients of the LUMO of the carbons in the mercurinium ion moiety for **1et1** to the *trans* product are higher than in that of **1ac1** to the *cis* product (Table 4). These are in accord with the experimental evidence that the nucleophile attacked at the β-position and that the *trans* product was preferably formed.

The stabilisation energies obtained using the modified Klopman's equation, which consists of the Coulombic term and the frontier orbital term, give an additional clue to the

Table 5 Stabilisation energy calculated by the modified Klopman's equation (kcal mol^{-1})

Compound	Stereoselectivity		ΔE_C [a]	ΔE_F [b]	ΔE	$\Delta\Delta E$
1	*cis*-β	19	−0.09	0.15	0.06	
	trans-β	81	−0.09	0.54	0.45	0.40
5	*cis*-β	30	−0.07	0.32	0.25	
	trans-β	70	−0.10	0.50	0.40	0.15
6	*cis*-β	59	0.00	0.55	0.55	0.29
	trans-β	41	−0.06	0.32	0.26	
7	*cis*-β	62	0.06	0.58	0.64	0.35
	trans-β	38	−0.06	0.35	0.29	
8	*cis*-α	12	−0.13	0.17	0.04	0.05
	cis-β	4	−0.12	0.10	−0.02	
	trans-α	6	−0.15	0.01	−0.14	
	trans-β	79	−0.11	0.29	0.18	0.32

[a] Coulombic term. [b] Frontier orbital term.

stereoselectivity of the reaction,[10] as shown in eqn. (1) in

$$\Delta E = -Q_r Q_s / R_{rs} \cdot \varepsilon + 2(c_r c_s \cdot \Delta\beta)^2 / |E_{LUMO\ (mercurinium\ ion)} - E_{HOMO\ (MeOH)}| \quad (1)$$

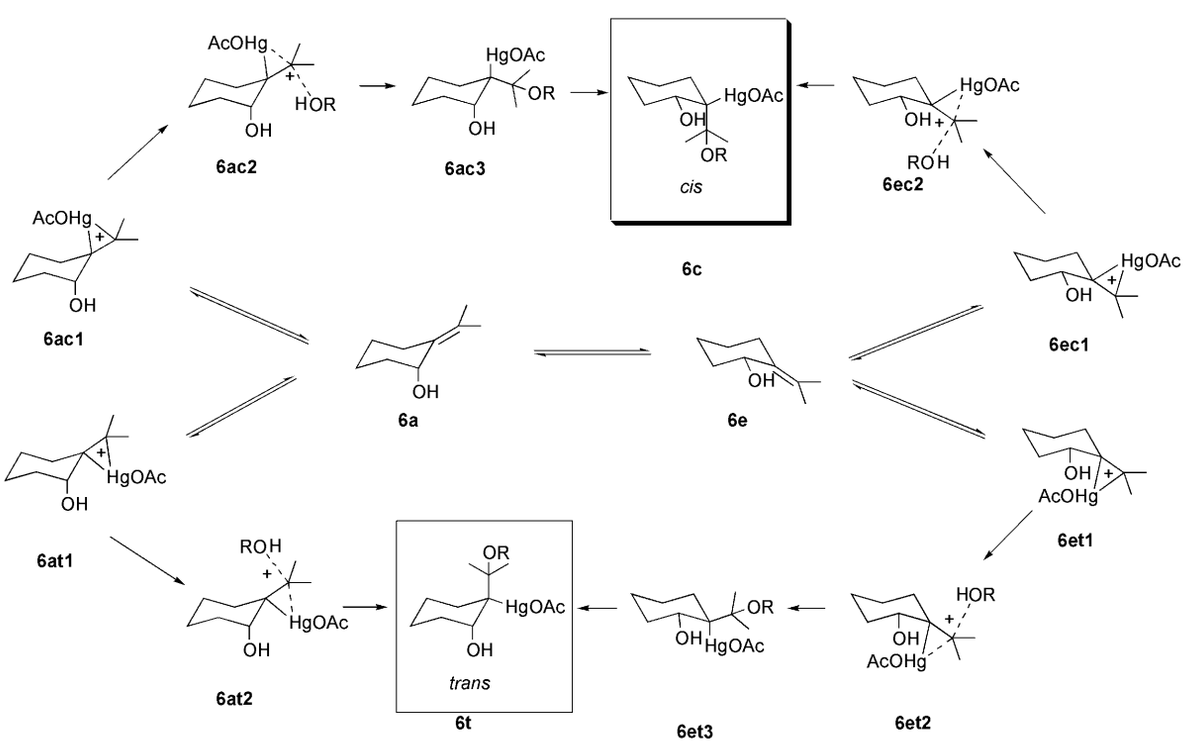
which Q_r is the charge of the methanol oxygen (−0.309), Q_s is the charge of the β-carbon atom of the mercurinium intermediate, R_{rs} is the distance between the methanol oxygen and the β-carbon of the mercurinium intermediate at the transition state of 2.70 Å (although it was impossible to find the transition state of the reaction for **1** by MO calculations, we succeeded in determining the transition state of the more simple substrate, cyclohexene, in which the distance between the methanol oxygen and the β-carbon atom is 2.70 Å), ε is the relative permittivity of methanol (32.6), c_r is the AO coefficient of the methanol oxygen (0.805), c_s is the AO coefficient of the β-carbon of the mercurinium ion intermediate, $\Delta\beta$ is the C–O resonance integral at 2.70 Å (−1.02), E_{LUMO} is the energy level of the LUMO for the mercurinium ion intermediate, and E_{HOMO} is the energy level of the HOMO for methanol (−11.1). The calculated stabilising energies are summarised in Table 5. Since the product distribution is controlled by the energy difference in the transition states, the fact that the ΔE for the *trans* β-isomer is larger than that of the *cis* β-isomer is one of the reasons why the formation of the *trans* product is preferred.

The regiochemistry in the methoxymercuriation of **2**, **3**, and **4** followed the Markovnikoff rule. The methoxy group was introduced at the carbon with a methyl group. When a nucleophile is introduced at the 2-position, the *cis*-isomers were preferentially obtained, and at the 3-position the *trans* ones were preferred.

Methoxymercuriation of 2-isopropylidenecyclohexanol 6

The nucleophile was introduced at the β carbon of the olefinic double bond in the methoxymercuriation of **6** which has an exocyclic double bond, and the stereochemistry of the preferred product was *cis*. The presumed reaction pathways are illustrated in Scheme 2. The geometry optimisation of the two possible conformations for **6** by theoretical calculations indicated that the one (**6a**) in which the hydroxy group takes the axial position is more stable than the alternative (**6e**) by 4.5 kcal mol^{-1}. This may be due to the torsional strain between the hydroxy group and the neighboring exocyclic carbon–carbon double bond. The mercuric acetate attacks these two conformers to give four different mercurinium ion intermediates, **6ac1**, **6at1**, **6ec1** and **6et1**. The conformer whose hydroxy group is placed on the same side as the mercurinium ion is more stable than the alternative by 4.8 kcal mol^{-1} when the hydroxy group is in the axial direction. This suggested the presence of an interaction between the hydroxy group and the mercurinium cation. In contrast to the conformer whose hydroxy group takes the axial position, the conformer (**6ec1**) whose hydroxy group is placed on the opposite side to that of the mercurinium ion moiety is more stable than the alternative (**6et1**). The distance between the hydroxy group and mercury atom is shorter in **6ec1** (2.17 Å) than in **6et1** (4.00 Å).

Since the introduction of the nucleophile to these four diastereomeric mercurinium ion intermediates of **6** is considered not to cause an appreciable deformation in the ring structure, the reaction will mainly produce the *cis* isomer from **6ac1** and the *trans* from **6at1**, which are energetically more stable than the corresponding alternatives, **6ec1** and **6et1**, respectively. The heats of formation for the two isomeric



Scheme 2 Reaction pathway of **6**.

product oxymercurials are reversed in magnitude compared with the corresponding substrates, the mercurinium ion intermediates, in this reaction step. The preferred formation of the *cis* product indicates that the energy of **6ac2** is smaller than that of **6at2** in the transition state; even the heat of formation for **6at1** is smaller than that of **6ac1**. Again, the formal charges of the β-carbons of both **6ac1** and **6at1** are larger than those of the corresponding α-carbons and the coefficients of the LUMO of **6ac1** are larger than those of **6at1** (Table 4). The stabilisation energy for the *cis* β-product is higher than that for the *trans* β-product **6t**.

Oxymercuriation of 3-methylcyclohexene 8 and 1-isopropylidene-2-methylcyclohexane 9

To compare the role of the methyl and the hydroxy groups, the regio- and stereoselectivity in the oxymercuriation of **8** and **9** were examined. The oxymercuriation of **8** has already been reported, by Brown *et al.* in 1979.[3] The reaction pathways for **8** are illustrated in Scheme 1. The heats of formation for the two conformers of **8** and four diastereomeric mercurinium ion intermediates were calculated using the MO method (Table 2). Similar to the case of **1**, the reaction of **8** will also proceed mainly through **8et1** to the *trans* and through **8ac1** to the *cis* oxymercurial. Again, the calculated formal charges, the coefficients of the LUMO of the possible mercurinium ion intermediates, and the stabilisation energies were calculated and are consistent with the experimental results.

The reaction of **9** occurred with much difficulty. The conversion of the substrate to the product was less than 10% and most of the starting olefin was recovered unchanged. The product was not the expected oxymercurial but was instead 2-(6-methylcyclohex-1-enyl)propan-2-ol **9a4** which indicates the double-bond migration and the introduction of the hydroxy group during the reaction. In general, the allylic position is oxidised by mercuric acetate to give unsaturated acetates in acetic acid at high temperature.[11] We confirmed that **9** was oxidised at the allylic position under the oxymercuriation conditions. We would like to propose the following reaction pathways shown in Scheme 3.[5] Compound **9** exists in two conformations (**9a** and **9e**), on which the attack by mercuric acetate produces four diastereomeric mercurinium ion intermediates (**9at1**, **9ac1**, **9et1** and **9ec1**). The oxymercuriation should have occurred by the introduction of a water molecule, whereas the elimination of the allylic hydrogen and the cleavage of the C–Hg bond occurs to give the allylic mercurials. If this elimination is supposed to be of the *E*2 type, the axial hydrogen at the C-6 position of **9ac1** participates to give allylic mercurial (**9a2**), followed by the formation of the allylic cation (**9a3**) by the elimination of Hg^0. The nucleophile then attacks the more stable tertiary cation to form **9a4**. Since there are two axial hydrogens at C-2 and C-6 in **9et1**, the formed allylic cations should be **9a3** and **9e3**, which produce two allylic alcohols, respectively. Consequently, four kinds of allylic alcohols, one of which consists of two stereoisomers, would be expected. Only the formation of **9a4** is consistent with the theoretical parameters of the two allylic cations, that is, the nucleophilicity is the highest and the coefficient of the LUMO is the largest at the β position of **9a3** among the allylic cations (Fig. 2).

Methoxymercuriation of other cyclohexenyl compounds

The methoxy group was introduced at the *cis* 4-position in 46% yield and the *trans* 3-position in 51% yield accompanied by *trans*-4-methoxycyclohexanemethanol (2%) and *cis*-3-methoxycyclohexanemethanol (1%) in the methoxymercuriation of **10**, in which the hydroxymethyl group is at the homoallylic position. This result was analogous to the oxymercuriation of 4-*tert*-butylcyclohexene whose *tert*-butyl group is at the homoallylic position.[7] The calculated formal charges and

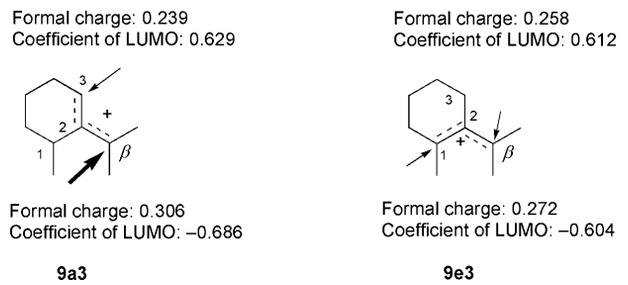


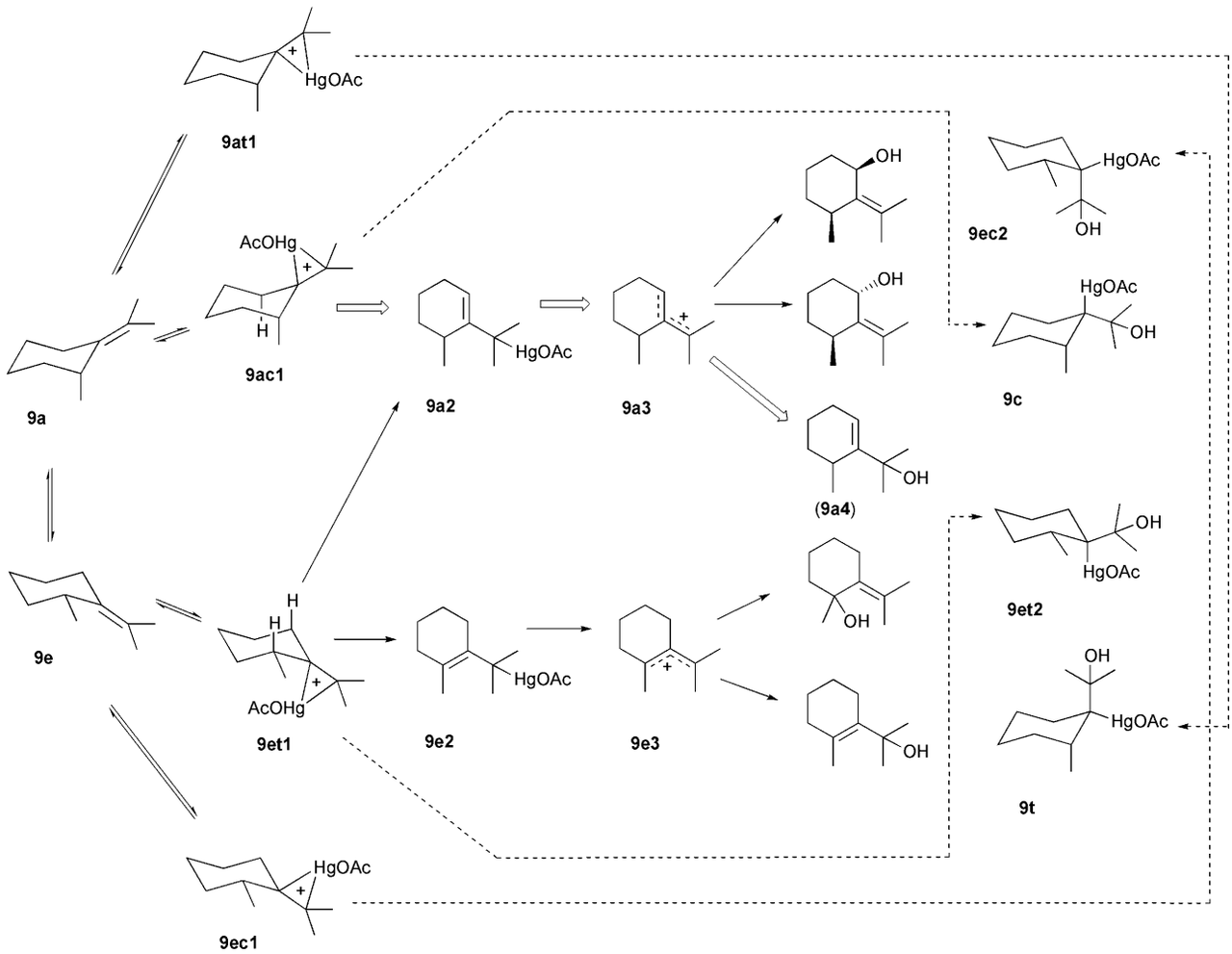
Fig. 2 Calculated parameters of cations from **9**. The LUMO coefficient indicates the 2pπ component.

the coefficients of the LUMO of the mercurinium ion moiety in the optimised structure of **10a1** are tabulated in Table 4. The substituents, which are separated from the double bond, do not appear to contribute to the regioselectivity of the nucleophilic attack. It has been reported that the oxymercuriation of homoallylic cyclohexenol, cyclohex-3-enol, predominantly gave the product in which the nucleophile is introduced at the 4-position and the stereochemical relationship between the hydroxy group and the incoming nucleophile is *trans*.[6] When the substituent at the homoallylic position is the *tert*-butyl or hydroxymethyl group, these substituents are fixed in the equatorial position on the mercurinium ion intermediate, while the hydroxy group is placed in axial as well as equatorial positions. The interaction between the mercurinium ion and the hydroxy group at the axial position may affect the stereochemistry of the reaction.

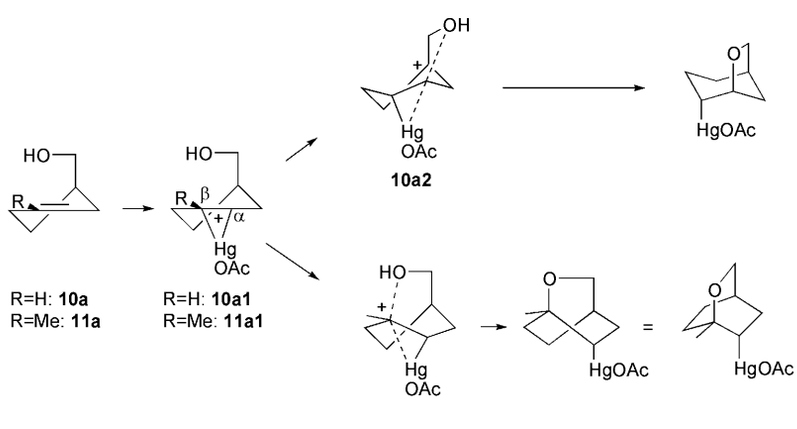
The methoxymercuriation of **11** followed the Markovnikoff rule to give only 4-methoxy products in which the *cis* ($CH_3O\cdots CH_2OH$) isomer was 97% of the total and the *trans* isomer was 3%. The reaction of **12** in methanol did not proceed to give the methoxylated product.

Intramolecular alkoxymercuriation

The intramolecular alkoxymercuriations of **10**, **11** and **12** were examined in 2-methylpropan-2-ol. Although the reaction of **10** was expected to produce two types of compound, only 6-oxabicyclo[3.2.1]octane was obtained after demercuriation. The methoxymercuriation of **10** did not show any regioselectivity, while the intramolecular reaction proceeded with the attack of the nucleophile in the molecule to the α position to form the tetrahydrofuran ring. On the other hand, the reaction of **11** followed the Markovnikoff rule to give only 1-methyl-2-oxabicyclo[2.2.2]octane. The different selectivity depending on the intra- or intermolecular reaction of **10** indicates that the nucleophilic reaction is controlled not only by the electronic effect but also by other factors. The possible reaction pathways for **10** and **11** are shown in Scheme 4. In the intramolecular alkoxymercuriation, the addition of mercuric acetate to the two diastereofaces of the olefinic bond of each of the two cyclohexene conformers results in the formation of four kinds of mercurinium ion intermediates. In order to form the new ring system, the hydroxymethyl groups of **10** and **11** have to be placed in the axial position and the attack should be in the *cis* direction to it because the intramolecular nucleophile at the equatorial position would have difficulty in attaining a trajectory to attack the mercurinium ion moiety. The nucleophilic attack on **11** follows the Markovnikoff rule and the reaction is forced to proceed *via* the energetically unfavorable skew-boat-like transition state. The nucleophilic attack on **10** occurred only at the α carbon of the mercurinium ion moiety, and the reaction proceeds *via* the energetically favorable chair-like transition state (**10a2**) to form the five-membered tetrahydrofuran ring. The energy-minimised structure of **10a1** in which the hydroxymethyl group is in the axial position and on the opposite side of the mercurinium ion moiety indicated that the formal charge is higher at the α carbon than at the β, and that the



Scheme 3 Reaction pathway of **9**.



Scheme 4 Reaction pathway of **10** and **11**.

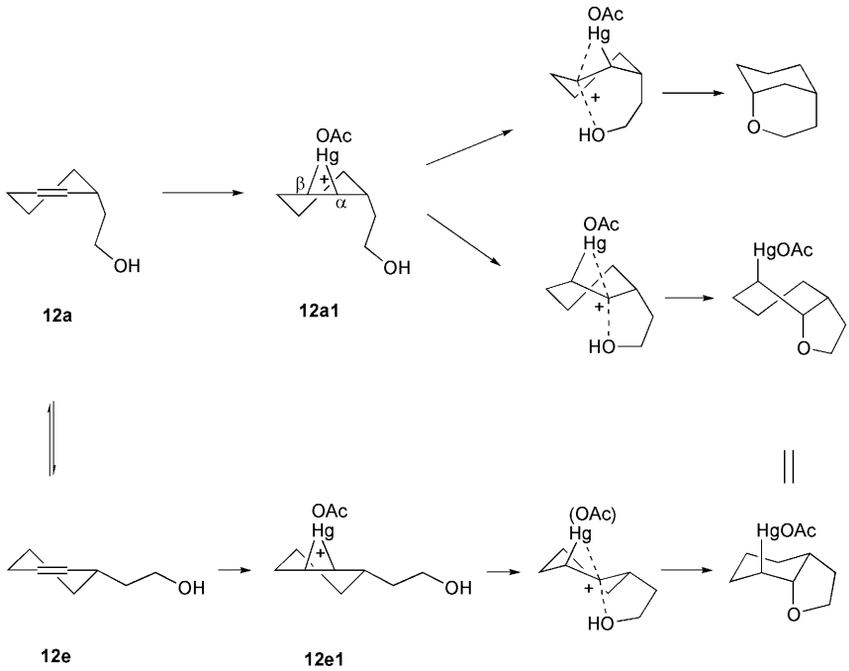
coefficient of the LUMO of the β carbon is higher than that of the α.

Intramolecular nucleophilic reaction occurred to give *cis*-7-oxabicyclo[4.3.0]nonane in the reaction of **12**. The formation of a new oxygen-containing ring was examined using a Dreiding model. When the hydroxyethyl group is placed at the pseudo-axial position, the intramolecular nucleophile can possibly attack both the α and β carbon atoms. On the other hand, when the hydroxy group is at the pseudo-equatorial position, the hydroxy oxygen can be introduced only at the α carbon because the stereochemistry of the ring junction of the forming oxabicyclo[3.3.1]nonane-type compound should be diaxial (Scheme 5). Similarly to the case of the intramolecular alkoxymercuriation of **10**, the electronic situation cannot be the definitive factor determining the selectivity because the formal charges of both carbons of the mercurinium ion moiety for **12a1** showed almost the same values, and the coefficient of the LUMO was larger at the β carbon than at the α one (Table 4).

The results obtained from **10** and **12** indicate that the regioselectivity is not mainly determined by electronic factors, but by steric ones, that is, the formation of the five-membered ring is kinetically preferable to that of the six-membered ring.[12] Baldwin proposed that the opening of three-membered rings to form cyclic structures generally follows the *exo*-mode.[13]

Methoxymercuriation of five-membered cyclic compounds

The regio- and stereochemistry of the oxymercuriation of **5**[3]



Scheme 5 Reaction pathway of **12**.

and **7** showed similar trends to those seen in the corresponding six-membered-ring compounds. The methoxymercuriation of **5** exclusively gave the product in which the methoxy group was introduced at the β-carbon, and the stereochemistry was 33% *cis* and 67% *trans*. The reaction of **7** also gave only the product in which the methoxy group was introduced at the β-carbon, and the stereochemistry was 65% *cis* and 35% *trans*. The energy-minimised structure of **5** exists as only one conformer whose ring is nearly flat. The two diastereomeric addition products (the one: the hydroxy group and mercurinium ion moiety are placed on the same side, and the other: the hydroxy group and mercurinium ion moiety are placed on opposite sides) of mercuric acetate from **5** had a difference in their heats of formation of 10.24 kcal mol^{-1}. The former is more stable than the latter. On the other hand, there are two conformers for **7**, one of which has a pseudo-axial hydroxy group and the other has a pseudo-equatorial one. The difference in the heats of formation for these two diastereomers is only 0.30 kcal mol^{-1}, which is smaller than that of **9**. Among the four mercurinium ions obtained by the addition of mercuric acetate, the two which have the hydroxy group and the mercurinium ion moiety on the same side are apparently more stable than the others.

Conclusions

(1) The regioselectivity in the solvomercuriation of an evenly substituted olefin is mainly controlled by electronic conditions (shown by the formal charge and the coefficient of the LUMO) of the mercurinium ion intermediate. In particular, MO considerations using the modified Klopman's equation shows that the contribution of the frontier orbital term is larger than that of the Coulombic term in determining the stabilisation energy. In the intramolecular alkoxymercuriation, the regioselectivity is controlled not only by electronic factors but also by steric factors.

(2) The stereoselectivity of the solvomercuriation of evenly substituted olefins is controlled by both steric and electronic factors. The degree of stabilisation by the interaction between the substrate and the nucleophile in the transition states also contributes to the stereochemistry.

(3) The intramolecular electrostatic interaction between any polar substituent and the mercurinium ion is responsible for the selectivity of the reaction.

Experimental

General

^{13}C NMR and ^{1}H NMR spectra were obtained with a JEOL JNM α-400 instrument in the pulse Fourier mode. *J*-Values are in Hz. Gas chromatographic analyses were performed on a Shimadzu model GC-8AIF with a Carbowax 20M chemical bonded silica capillary column (0.25 mm × 25 m) at a column temperature of 120 °C. The isomeric ratios were determined by the comparison of NMR and GLC analyses with authentic samples. Mps are uncorrected. Methanol for methoxymercuriation was distilled from Mg foil. THF for oxymercuriation was simply distilled. Solvents for column chromatography ethyl acetate was dried over K_2CO_3 and hexane was dried over $CaCl_2$, and both were distilled before use. Column chromatography was achieved using Nacalai Tesque silica gel 60 (70–230 mesh). SiO_2–$AgNO_3$ was prepared by mixing SiO_2 and aq. $AgNO_3$ followed by drying. This was activated at 120 °C for 2 h before use.

Substrates

Cyclohex-2-enol[14] **1**, 2-methylcyclohex-2-enol[15] **2**, 3-methylcyclohex-2-enol[16] **3**, 3,*cis*-5-dimethylcyclohex-2-enol[17] **4**, cyclopent-2-enol[18] **5**, 2-isopropylidenecyclopentanol[19] **7**, cyclohex-3-enylmethanol[20] **10**, 4-methylcyclohex-3-enylmethanol[21] **11**, and 2-(cyclohex-2-enyl)ethanol[22] **12** have been previously reported.

2-Isopropylidenecyclohexanol 6

2-Isopropylidenecyclohexanol was prepared by the $LiAlH_4$ reduction of 2-isopropylidenecyclohexanone,[23] mp 56 °C (Found: C, 77.2; H, 11.3. $C_9H_{16}O$ requires C, 77.1; H, 11.5%); δ_H (400 MHz; $CDCl_3$) 1.15–1.26 (1H, m), 1.40 (1H, s), 1.42–1.46 (2H, m), 1.67 (3H, s, CH_3), 1.73 (3H, s, CH_3), 1.75–1.80 (2H, m), 1.92 (1H, d, *J* 13.4), 2.10 (1H, t, *J* 9.1), 2.78 (1H, t, *J* 13.9), 4.83 (1H, br t, *J* 1.79, 1-H); δ_C (100 MHz; $CDCl_3$) 19.6, 20.1, 20.2, 24.9, 27.0 (C-3), 33.7 (C-6), 66.5 (C-1), 125.1 (C=), 132.8 (C-2).

2-Isopropylidene-1-methylcyclohexane 9

Methyl 2-methylcyclohexanecarboxylate (10.0 g, 0.064 mol, *cis*/*trans* 93/7) as a solution in diethyl ether (30 cm^3) was added to a

solution of CH_3MgI in the same solvent prepared from methyl iodide (36.4 g, 0.256 mol) and Mg (6.14 g, 0.256 mol) at 0 °C. After the addition was complete, the mixture was heated under reflux for 3 h. The product was hydrolysed with dilute HCl to give 2-(2-methylcyclohexyl)propan-2-ol (8.60 g, 86.0%), bp 84–102 °C/50–53 mmHg.

Dehydration of 2-(2-methylcyclohexyl)propan-2-ol (23.6 g, 0.151 mol) was catalysed by toluene-*p*-sulfonic acid (0.1 g) in boiling benzene (150 cm^3). The reaction mixture was treated in the usual manner. The dehydrated product [16.9 g, 81.1%; bp 74–80 °C/40 mmHg; two other isomers as well as 1-isopropylidene-2-methylcyclohexane **9** were detected by GLC] was partially hydrogenated over Rh–C catalyst. The product composition was monitored by GLC. After diminution of the less substituted olefinic isomers by the hydrogenation, the reaction mixture was separated by column chromatograpy [SiO_2–$AgNO_3$ (25%), hexane–ethyl acetate 9 : 1]. 1-Isopropylidene-2-methylcyclohexane **9** (2.1 g, 12.3%) had bp 71 °C/19 mmHg (Found: C, 86.5; H, 13.3. $C_{10}H_{18}$ requires C, 86.9; H, 13.1%); δ_H (400 MHz; $CDCl_3$) 1.00 (3H, d, *J* 7.32, CH_3), 1.05–2.00 (7H, m), 1.63 (3H, d, *J* 1.47, CH_3), 1.65 (3H, d, *J* 2.2, CH_3), 2.48 (1H, ddq, *J* 14.1, 2.86, 1.47), 2.92 (1H, m); δ_C (100 MHz; $CDCl_3$), 18.0 (CH*C*H_3), 20.4 (CH_3), 20.5 (CH_3), 20.8, 24.9, 27.7, 31.1 (C-2) , 33.2 (C-6), 124.1 [=*C*$(CH_3)_2$], 134.9 (C-1).

Methoxymercuriation

A solution of a substrate (0.600 mmol) in methanol (1 cm^3) was added to a solution of $Hg(OAc)_2$ (0.230 g, 0.723 mmol) in methanol (4 cm^3) and the mixture was stirred at room temperature. Sodium hydroxide (3.0 M; 1.08 cm^3) and $NaBH_4$ (20.4 mg, 0.537 mmol) in aq. NaOH (3.0 M; 1 cm^3) were added at 0 °C. The precipitated Hg was removed by filtration. The product was isolated by diethyl ether extraction. After drying over Na_2SO_4, the solvent was removed and the residue was analysed by GLC.

Oxymercuriation

A solution of a substrate (0.320 mmol) in THF (5 cm^3) was added to a solution of $Hg(OAc)_2$ (0.123 g, 0.386 mmol) in water (5 cm^3) and the mixture was stirred for 60 min at room temperature. Sodium hydroxide (3.0 M; 0.576 cm^3) and $NaBH_4$ (10.9 mg, 0.287 mmol) in aq. NaOH (3.0 M; 0.576 cm^3) were added at 0 °C. The precipitated Hg was removed by filtration. The product was isolated by diethyl ether extraction. After drying over Na_2SO_4, the solvent was removed and the residue was analysed by GLC. In the case of **9** the precipitation of Hg^0 was observed during the reaction. At the end of the reaction the mixture was treated with $NaBH_4$ in the usual manner to remove toxic $Hg(OAc)_2$ from the solution.

Products

Among the reaction products, 3-methoxycyclohexanol,[24] 2-methoxy-2-methylcyclohexanol,[25] 3-methoxy-3-methylcyclohexanol,[25] 3-methoxy-3,5–dimethylcyclohexanol,[25] 3-methoxycyclopentanol,[26] (3-methoxycyclohexane)methanol,[27] 6-oxabicyclo[3.2.1]octane,[28] 1-methyl-2-oxabicyclo[2.2.2]-octane,[29] and 7-oxabicyclo[4.3.0]nonane[30] have been previously reported.

2-(2-Methoxypropan-2-yl)cyclohexanol, bp 121–126 °C/27 mmHg (Found: C, 69.5; H, 11.5. $C_{10}H_{20}O_2$ requires C, 69.7; H, 11.7%); the isomers were separated by column chromatography (SiO_2; hexane–ethyl acetate 9 : 1). *cis*-isomer; δ_H (400 MHz; $CDCl_3$) 1.19 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.16–1.29 (4H, m), 1.56–1.88 (5H, m), 3.20 (3H, s, OCH_3), 4.11 (1H, d, *J* 1.95, 1-H), 4.33 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 19.6 (CH_3), 20.1 (CH_3), 23.0, 23.4, 26.4, 33.2, 48.9 (C-2), 50.5 (OCH_3), 66.6 (C-1), 78.2 [*C*$(CH_3)_2OCH_3$]; *trans*-isomer; δ_H (400 MHz; $CDCl_3$) 0.91 (1H, m), 1.17 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.19–1.32 (3H, m), 1.55 (1H, m), 1.64–1.74 (3H, m), 1.99 (1H, m), 3.26 (3H, s, OCH_3), 3.60 (1H, dt, *J* 10.0, 4.42, 1-H), 5.31 (1H, s); δ_C (100 MHz; $CDCl_3$) 19.9 (CH_3), 23.5 (CH_3), 24.6, 26.1, 27.1, 35.3, 48.5 (C-2), 50.7 (OCH_3), 72.5 (C-1), 80.8 [*C*$(CH_3)_2OCH_3$].

(4-Methoxy-4-methylcyclohexyl)methanol, bp 109.0–115.3 °C/20 mmHg (Found: C, 68.6; H, 11.5. $C_9H_{18}O_2$ requires C, 68.3; H, 11.5%); δ_H (400 MHz; $CDCl_3$) 1.10 (3H, s, CH_3), 1.17–1.23 (4H, m), 1.44 (1H, m), 1.53 (2H, q, *J* 4.14, 7.81), 1.86 (2H, dd, *J* 2.86, 8.56), 1.99 (1H, br s, OH), 3.15 (3H, s, OCH_3), 3.46 (2H, d, *J* 6.34, CH_2O); δ_C (100 MHz; $CDCl_3$) 24.4 (C-2, -6), 24.8 (CH_3), 34.9 (C-3, -5), 39.6 (C-1), 48.3 (OCH_3), 68.3 (CH_2O), 72.8 (C-4).

2-(2-Methoxypropan-2-yl)cyclopentanol, bp 120–121 °C/30 mmHg (Found: C, 68.1; H, 11.3. $C_9H_{18}O_2$ requires C, 68.3; H, 11.5%). The *cis*-isomer was separated by column chromatography (SiO_2; hexane–ethyl acetate 9 : 1), *cis*-isomer; δ_H (400 MHz; $CDCl_3$) 1.19 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.55–1.69 (4H, m), 1.86–1.96 (3H, m), 3.24 (3H, s, OCH_3), 4.37 (1H, br s, C-1), 4.58 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 21.4 (CH_3), 22.2 (CH_3), 24.0, 24.1, 34.9, 48.9 (C-2), 55.0 (OCH_3), 73.9 (C-1), 77.0 [*C*$(CH_3)_2OCH_3$]. It was impossible to isolate the *trans*-isomer.

2-(6-Methylcyclohex-1-enyl)propan-2-ol 9a4. The crude oxymercuriation-demercuriation product of **9** was purified by column chromatography (SiO_2; hexane–ethyl acetate 9 : 1). **9a4**, (Found: C, 77.8; H, 11.7. $C_{10}H_{18}O$ requires C, 77.9; H, 11.8%); δ_H (400 MHz; $CDCl_3$) 1.14 (3H, d, *J* 6.83, axial-CH_3), 1.35 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.52–1.78 (5H, m), 2.05 (2H, m), 2.46 (1H, m, 2H), 5.72 (1H, t, *J* 3.91, =CH); δ_C (100 MHz; $CDCl_3$) 16.9 (axial-CH_3), 21.6 (CH_3), 25.0 (CH_3), 28.0, 30.3, 30.8, 31.4 (*C*HCH_3), 73.5 (*C*OH), 120.0 (=CH), 148.7 (=C).

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