Indian Journal of Chemistry
Vol. 34B, August 1995, pp. 695-701

Conformational analysis: Theoretical study of phenylselenotetrahydropyrans based on molecular mechanics methods

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Received 17 June 1994; revised and accepted 10 April 1995

Theoretical study of selenium compounds is extended to a class of phenylselenotetrahydropyrans. For that purpose the MMX (PC MODEL) force field has been extended with some new parameters.

Introduction

Recently, chemistry of selenium compounds has made a remarkable development. The main reason for this is that selenium reagents have proved to be very suitable for many regio- and stereo-selective reactions[1-3]. Besides, they can be used under very mild conditions.

In spite of great significance of selenium compounds in modern organic chemistry, it is surprising that molecular mechanic's consideration of selenium-containing molecules appeared only recently[4]. One of the most popular and the most exploited molecular mechanics methods is the MM2 developed by Allinger[5]. An extension of MM2 force-field to selenium and tellurium compounds was developed by Allinger and collaborators[4]. The force-field for selenium compounds is not as well established as for majority of the other compounds, but it should be satisfying for most of the conformational problems. The MMX force-field, used by PC MODEL program[6] has been derived from MM2, with π-VESCF routines taken from MMP1 program[7], also developed by Allinger. The π-VESCF routines were modified for open shell species by McKelvey, while improvements to the heat of formation calculations were done by Gajewski[8].

The present study is a continuation of theoretical investigation of selenium compounds. Our aim was to determine geometries and to study conformational equilibria of a series of phenylselenotetrahydropyran molecules (Table I).

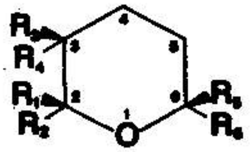
Methodology

In the present work, we have used the interactive molecular mechanics program PC MODEL, version 4.0[6]. The program is based on the MMX force-field. In order to study selenium compounds by this program we have transferred Allinger's parameters[4] for selenium into the MMX force-field. In all the calculations selenium was treated without the lone pairs.

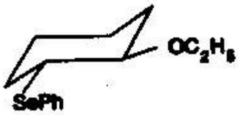
Using such modified force-field we performed calculations of geometries for selenols and selenides (the results are listed in Table II). The standard least squares fitting showed that both the force-fields agreed well with experimental data (correlation coefficients for bond lengths, as calculated by MMX and MM2 force-fields, were 0.998 and 0.999, respectively; whereas for bond angles analogous values were 0.979 and 0.977; correlation constants were negligible).

In order to calculate geometries of phenylselenotetrahydropyrans (Table I) the MMX force-field was further expanded by parameters for bond length C_{sp^2}-Se, bond angle C_{sp^2}-C_{sp^2}-*Se* and torsional angle O-C-C-Se (Table III). The parameters for the bond length C_{sp^2}-Se were present in the program, but their application resulted in an extremely large bond length in methylphenylselenide. The new values of parameters were determined according to the following procedure. The MMX stretching constant was maintained whereas the value for the natural bond length was fitted to reproduce the bond length obtained from the MOPAC-PM3[9,10] calculations[11] and experimentally[12] for the methylphenylselenide. The value of the C_{sp^2}-Se bond dipole was chosen such as to get the experimental value of the dipole moment of methylphenylselenide (Table II). The parameters for the angle C_{sp^2}-C_{sp^2}-Se and the torsional angle O-C-C-Se were taken as those for the angle C_{sp^2}-C_{sp^2}-O and the torsional angle O-C-C-S respectively, calculated by MMX. As there were no parameters for torsional angles *C-C-Se-*C_{sp^2}, C_{sp^2}-C_{sp^2}-C_{sp^2}-Se and H-C_{sp^2}-C_{sp^2}-Se, generalized parameters (Table III) were used in the

Table I—List of the phenylseleno compounds subjected to conformational analysis by MMX force-field, and calculation of ^1H NMR coupling constants



Compound	R_1	R_2	R_3	R_4	R_5	R_6
1	CH_3	H	SePh	H	H	H
2	CH_3	H	H	SePh	H	H
3	H	CH_2SePh	H	H	H	H
4	CH_3	H	H	H	CH_2SePh	CH_3
5	H	CH_3	H	H	CH_2SePh	CH_3
6	CH_3	CH_3	SePh	H	H	H
7	CH_3	CH_3	SePh	H	CH_3	CH_3
8	CH_3	CH_3	H	H	CH_3	CH_2SePh
9	CH_3	CH_3	SePh	CH_3	CH_3	H
10	CH_3	CH_3	SePh	H	CH_3	H
11	CH_3	CH_3	H	SePh	CH_3	H



12

Ph-SeCH$_2$-CH(OCH$_3$)$_2$

13

Ph-SeCH$_2$-CH(OC$_2$H$_5$)$_2$

14

Table II—The list of structures of selenols, dimethyl selenide, tetrahydroselenophene[a] and methyl phenyl selenide[b]

Bond length (Å)		Methyl-selenol	Dimethyl selenide	Ethylselenol *anti*	Ethylselenol *gauche*	Tetrahydro-selenophene	Methyl phenyl selenide
Se-H	exp[a]	1.473		1.440	1.467		
	MM2	1.472		1.472	1.472		
	MMX	1.472		1.472	1.472		
Se-C	exp	1.959	1.943	1.962	1.957	1.975	1.957
	MM2	1.959	1.946	1.966	1.966	1.971	—
	MMX	1.951	1.950	1.968	1.958	1.952	1.952
	PM3						1.952[c]
C-C	exp			1.525	1.524	1.538	
	MM2			1.537	1.537	1.537	
	MMX			1.534	1.534	1.536	
C_{sp^2}-Se	exp						1.912
	MMX						1.903
	PM3						1.881[c]
Bond angle (°)							
C-Se-H	exp	95.4		93.5	93.1		
	MM2	95.0		95.1	95.2		
	MMX	95.7		95.1	95.2		
C-Se-C	exp		96.2			89.1	
	MM2		96.3			89.3	
	MMX		96.1			90.3	

Contd.

Table II—The list of structures of selenols, dimethyl selenide, tetrahydroselenophene[a] and methyl phenyl selenide[b]

Bond length (Å)		Methylselenol	Dimethyl selenide	Ethylselenol		Tetrahydroselenophene	Methyl phenyl selenide
				anti	*gauche*		
Se-C-H	exp		110.5				
	MM2		110.5				
	MMX		110.5				
C-C-Se	exp			108.7	113.5	105.8	
	MM2			111.1	111.5	106.6	
	MMX			112.2	111.5	106.6	
C-C-C	exp					106.0	
	MM2					107.2	
	MMX					107.3	
C_{sp^2}-Se-H	exp						99.6
	MMX						96.3
	PM3						104.9
C_{sp^2}-C_{sp^2}-Se	exp						—
	MMX						120.3
	PM3						119.0[c]
Dipole moments	exp[d]	1.29	1.41	1.47	1.49	1.93	1.31
	MM2	1.36	1.47	1.36	1.36	1.56	
	MMX	1.36	1.47	1.36	1.36	1.55	1.31
	PM3						1.65[c]

[a] Experimental and MM2 data taken from reference 4.

[b] Experimental data taken from reference 12.

[c] MOPAC data, reference 11.

[d] Experimental data taken from reference 13.

Table III—Parameter set for bond lengths, bond angles and torsional angles involving selenium atom

Bond lengths and stretch constants			
Bond	l_o/Å	K_o /mdyn Å^{-1}	DM/Debye
C_{sp^2}-Se	1.890	3.200	−1.1
Angle bending			
Angle	θ_o/°	K_0 /mdyn Å rad^{-2}	
C_{sp^2}-C_{sp^2}-Se	124.30	0.700	
Torsional parameters/kcal mol^{-1}			
Torional angle	V_1	V_2	V_3
O-C-C-Se	−0.800	0.900	−0.300[a]
	0.300	1.200	0.000[b]
C_{sp^2}-C_{sp^2}-Se-C	−1.800	1.000	−0.700[c]
O-C-Se-C_{sp^2}	0.000	0.000	0.500[c]
O-C_{sp^2}-C_{sp^2}-O	0.000	15.000	0.000[c]

[a] Equal to MMX parameters for sulphur.

[b] Parameters modified in the present work

[c] Generalized parameters of MMX

program. In all molecular mechanics calculations the program option DP-DP was used. It initiated the use of bond dipoles for polar interactions.

Comparison with experimental ^{1}H NMR coupling constants (Table IV) indicated that the choice of parameters for the torsional angle O-C-C-Se was not reasonable, because the stability of the rotamer with O-C-C-Se angle equal to 60° was overestimated. For that reason the parameters were optimized by trial and error method. The proton coupling constants were determined using a highly automated routine procedure based on Altona's formula and implemented in the program. The values were compared with experimental data (Table IV).

In order to calculate ΔG for compounds containing sulphur, the MMX force-field had to be supplemented by the following parameters: for dihedral angles C-C-S-C_{sp^2}, S-C_{sp^2}-C_{sp^2}-C_{sp^2} and S-C_{sp^2}-C_{sp^2}-H the corresponding generalized parameters from MMX were used. For the angle S-C_{sp^2}-C_{sp^2} and dihedral angle C-S-C_{sp^2}-C_{sp^2} corresponding parameters of selenium were used. As the value of C_{sp^2}-S bond dipole does not exist in either MMX or MM2 force-fields, it had to be determined by reproducing the experimental value of the dipole moment of methyl phenyl thioether. The experimental value of the dipole moment of methyl phenyl thioether was reproduced using 0.155 D for the C_{sp^2}-S bond dipole (experimental and calculated values of dipole moments of methyl phenyl thioether were 1.38 D and 1.39 D respectively). The consistency of new parameters was tested by analysing a series of analogous compounds given in Table V.

Results and Discussion

The experimental values of ΔG for methyl and methoxy substituted cyclohexanes, tetrahydropyrans and 1,3-dioxanes were in good agreement with those obtained by our calculations (Table V). In case of $S\text{-}CH_3$ and SPh groups, the MMX followed the trend of increasing ΔG from cyclohexane to 1,3-dioxane, although the S/O gauche effect was somewhat overrated within the MMX (Table V). The compounds containing Se ($Se\text{-}CH_3$ and SePh groups) generally followed the same trend.

The decreasing value of ΔG in a series of methylcyclohexane, 3-methyltetrahydropyran and 5-methyl-1,3-dioxane is a consequence of decreasing steric energy of the axial-conformation due to reduced number of *syn*-axial interactions.

Table IV—Experimental ^1H NMR coupling constants and coupling constants calculated using published parameters in MMX (calcl) and refined parameters (calc2).

Compd		exp	calcl	calc2	
1	$J_{2,Me}$	6.7	5.8	5.9	
	$J_{2,Me}$	6.1	5.9	5.9	
	$J_{3,2}$	10.0	10.2	10.3	
2	$J_{3a,4a}$	11.9	12.3	12.4	
	$J_{3a,4e}$	4.1	3.7	3.7	
3	J_{BX}	6.8	9.0	7.1	
	J_{AX}	5.8	3.6	6.2	
6	$J_{3,4trans}$	11.5	11.7	12.2	$J_{3a,4a} = 11.9^a$
	$J_{3,4\text{-}cis}$	4.5	3.6	3.7	$J_{3e,4e} = 2.06^b$
	$J_{5e,6a}$	2.4	2.4	2.4	
	$J_{5a,6a}$	11.3	11.6	11.6	
11	$J_{6,Me}$	6.1	5.8	5.8	
	$J_{3,4a}$	11.8	12.1	12.2	
	$J_{3,4e}$	5.5	3.6	3.7	
13	J_{CH_2CH}	6		6.7	
14	J_{CH_2CH}	6		6.6	
	$J_{CH_2CH_3}$	7		7	

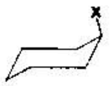
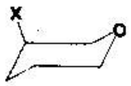
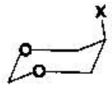
[a] Value of the $J_{3a,4a}$ for compound **2**.

[b] Calculated

The trends in ΔG values for the compounds in Table V containing -OR, -SR and -SeR ($R=CH_3$, Ph) substituents, are the result of fine balance between electrostatic and orbital interactions reflected in the two-fold term[25] of the torsional component of steric energy. Highly electronegative oxygen has negative two-fold torsional constant and its torsional energy counterbalances the increasing electrostatic energy as we go from methoxycyclohexane to 5-methoxy-1,3-dioxane. In the case of -SR and -SeR substituted compounds, positive two-fold term adds the steric energy to the energy of electrostatic interactions.

Our MMX force-field, made suitable for calculations on selenium compounds, was applied for the calculations of geometry and ^1H NMR coupling constants of phenylselenoethers. List of selenium compounds studied in the present work is given in Table I. Syntheses of all the substituted tetrahydropyrans mentioned in this study have been described earlier[23]. For every structure all the possible rotamers were calculated. The phenyl group was rotated 45°, 90°, 120° and 180°. A systematic examination of the tetrahydropyran derivatives (by rotation of the phenyl group around C_{sp^2}-Se bonds) revealed that the orientation of phenyl group was related to the number of substituents on the C atom bonded to Se. For primary carbon, the dihedral angle (C_{sp^2}-C_{sp^2}-Se-C) amounted roughly to 60° [2-(phenylselenomethyl)-tetrahydropyran(**3**)], whereas in the case of tertiary carbon atom, the angle amounted roughly to 90° [2,2,3,6-tetramethyl-3-(phenylseleno)tetrahydropyran (**9**)]. Compounds **2-5** and **9-11** (cf. Table I) exist in only one tetrahydropyran chair-conformation; other possible conformations are hampered by unfavourable *syn*-axial interactions (Table VI).

Table V-Conformational free energies (kcal/mol) of substituted cyclohexanes, tetrahydropyrans and 1,3-dioxanes

X						
	Exp.	Calc.	Exp.	Calc.	Exp.	Calc.
CH_3	1.56-1.75[15]	1.78	1.27[16]	1.27	0.80[17]	0.71
OCH_3	0.6[14]	0.52		0.69	0.89[14]	0.82
$S\text{-}CH_3$	1.01-1.07[18,19]	1.06	1.43[16,19]	1.63	1.55-1.73[17,19]	2.32
S-Ph	0.7-1.24[20,21]	0.99		1.43		1.97
$Se\text{-}CH_3$		1.35		1.79		2.19
Se-Ph	1.1[22]	1.24	1.9*	1.64		2.00

* The experimental value refers to compound **6**.

Table VI—Conformational energies and equilibrium equatorial: axial molar ratios

Compd	$\Delta\Delta G = \Delta G_a - \Delta G_e$ (kcal/mol)	Molar ratio of equatorial versus axial conformer
1	0.07	53:47
2	3.40	1:0
3	2.55	99:1
4	5.31	1:0
5	5.66	1:0
6	2.20(1.9)(1.64)	98:2
7	2.41	99:1
8	0.55	72:28
9	6.64	1:0
10	7.52	1:0
11	2.98	1:0
12	0.95	83:17
13	0.9	82:18[a]
14	1.11	87:13[a]

[a] Rotamers 1 and 2 versus 3 in Figure 6.

For any compound in Table I, with 3-SePh substituent, three rotamers around the C-Se bond are possible.

In the case of conformers with an equatorial SePh group, the situation is as follows. In the case of *cis*-2-methyl-3-(phenylseleno)tetrahydropyran (**1**) rotamer 1 is more stable than rotamers 2 and 3 (Figure 1). Rotamers 1 and 2 of 2,2-dimethyl-3-(phenylseleno)tetrahydropyran (**6**) participate equally whereas rotamer 3 is of higher energy. For *trans*2-methyl-3-(phenylseleno)tetrahydropyran (**2**), rotamers 2 and 3 participate almost equally while rotamer 1 is of higher energy. In all other compounds studied, rotamer 2 is the most stable conformer. One can observe that participation of rotamer 2 increases with increasing number of substituents on the ring. If SePh group occupies an axial position, the rotamer 2 is always the most stable whereas rotamer 3 is the least stable conformer, as expected.

In the case of *cis*-2-methyl-3-(phenylseleno)tetrahydropyran (**1**), conformational equilibrium (Figure 2) indicates that conformation with equatorial SePh group is slightly favoured ($\Delta\Delta G = 0.07$ kcal/mol, $\Delta\Delta G = \Delta G_a - \Delta G_e$, where *a* and *e* refer to the axial and equatorial SePh group, respectively).

Calculations performed on the molecules such as 2,2-dimethyl- (**6**) and 2,2,6,6-tetramethyl-3-(phenyseleno)tetrahydropyrans (**7**) revealed that the isomer with equatorial SePh group was more stable by 2.20 kcal/mol and 2.41 kcal/mol, respectively. The calculated $\Delta\Delta G$ value for compound **6** agreed with the estimated $\Delta\Delta G$ value (Table V) obtained using the calculated coupling constants of individual conformers and the experimentally determined value of $J_{3,4\text{-}trans}$ for the mixture of conformers ($J_{trans} = n_e^* J_{aa} + n_a^* J_{ee}$; Table IV).

The CH_2SePh group in 2-(phenylselenomethyl)-tetrahydropyran (**3**) (Figure 3) is involved in a *syn*-axial interaction with H(6-*a*) as well as with the more distant H(4-*a*); the $\Delta\Delta G$ value (2.55 kcal/mol) is close to the value, 2.6 kcal/mol, determined experimentally[14] for 2-methyltetrahydropyran. The analysis of energy partition shows that this preference for equatorial conformation is mainly due to bending and torsion (Table VII).

The conformational free energy of 2,6,6-trimethyl-2-(phenylselenomethyl)tetrahydropyran (**8**) ($\Delta\Delta G$ = 0.55 kcal/mol) is in favour of conformation with equatorial CH_2SePh group. It is obvious that 1,3-diaxial repulsions between the two CH_3 groups are comparable to those between CH_3 and CH_2SePh groups.

In the case of compounds **3-5** and **8** three rotamers of SePh group, as represented in Figure 4, are possible around the C2-CH_2 bond. Calculations performed on **3** and **4** using conformers with equatorial SePh group (Figure 4) reveal that for compound **3** rotamers 1 and 2 are almost equally stable, while 3 is of higher energy. In the case of

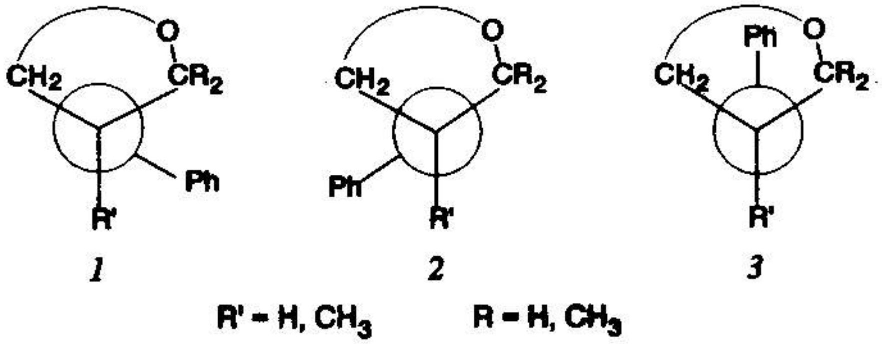


Figure 1—Possible rotamers around C-Se bond (Se in the rear) in tetrahydropyrans substituted at position-3

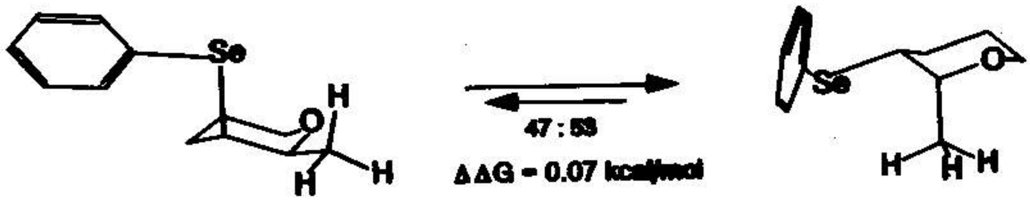


Figure 2—Conformational equilibrium of *cis*-2-methyl-3-(phenylseleno)tetrahydropyran. Calculated conformational free energy and axial/equatorial ratio are given

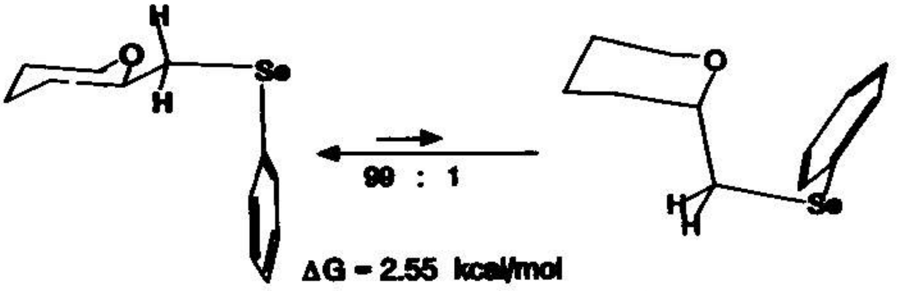


Figure 3—Conformational equilibrium in 2-(phenylselenomethyl)-tetrahydropyran 3

compound 4, rotamers 1 and 3 are almost equally stable (R' = H and CH_3), whereas rotamer 2 is of higher energy.

Using the same force-field and procedure described here, all rotamers for compounds 12-14 (Table V) were calculated. The diequatorial isomer is favoured in the equilibrium mixture of 12 ($\Delta\Delta G$ = 0.95 kcal/mol) (Figure 5), but less than one may expect on the basis of the known $\Delta\Delta G$ values for the conformational equilibria of ethoxycyclohexane ($\Delta\Delta G$ = 0.9 kcal/mol)[14] and phenylselenocyclohexane ($\Delta\Delta G$ = 1.11 kcal/mol)[22].

As can be expected, the calculations on acyclic compounds showed that compounds 13 and 14 exist solely in conformations 1 and 2 (Figure 6) because the third rotamer is significantly destabilized by steric factors.

Conclusion

The MMX force-field, supplemented with parameters for selenium, taken from ref.4 and determined in this work, is found to be adequate for structural and conformational study of organoselenium compounds with C_{2sp^3}-Se bond. Table IV shows that the coupling constants, calculated using literature parameters[4,6], as described above (Table IV, calc.1) for the molecule of 2-(phenylselenomethyl)tetrahydropyran (3) are quite different from the experimental values. Using our modified paramet-

Table VII—Contributions to conformational energy of 3

Contributing factor	Conformer	
	Equatorial	Axial
Strain	0.73	0.78
Bending	1.87	3.18
S-B	0.20	0.28
Torsion	8.32	9.44
Van der Waals	7.25	7.23
Dipolar	0.39	0.39

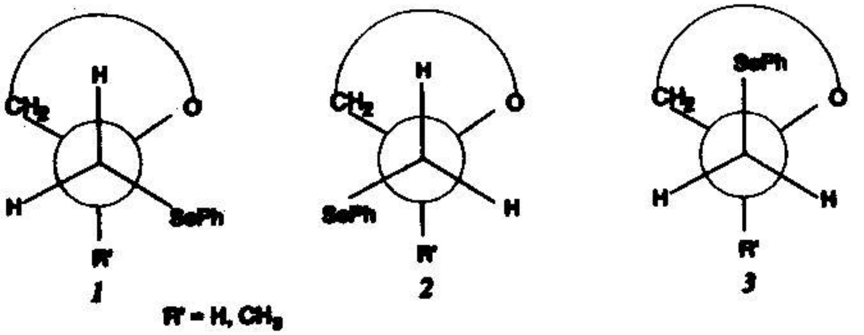


Figure 4—Possible conformers around exocyclic C-C bond in 2-phenylselenomethyl substituted tetrahydropyrans

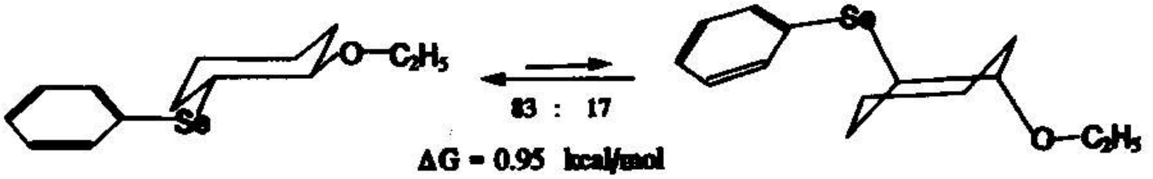


Figure 5—Conformational equilibrium of compound 12

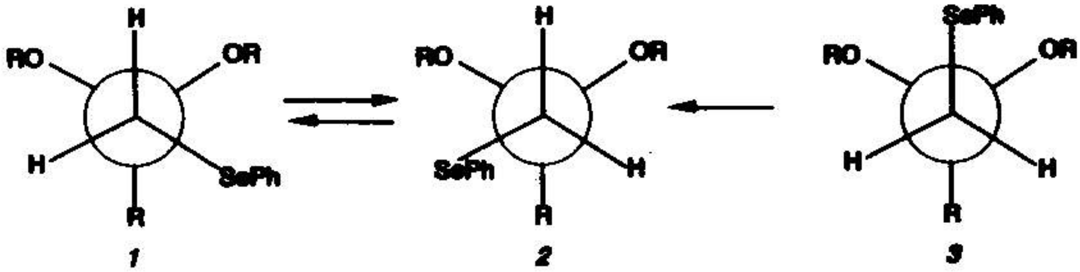


Figure 6—Rotational isomers of compounds 13 and 14

ers, calculations on the series of phenylselenotetrahydropyran molecules were repeated (Table IV, calc 2), and the agreement was within the estimated average deviation for the coupling constants calculated by Altona's equation.

The results presented here reveal that the -SR and SeR groups ($R = CH_3$, Ph) are bulkier than the $-OCH_3$ group on cyclohexane. Their relative size increases from 3-substituted tetrahydropyrans to 5-substituted 1,3-dioxanes due to electrostatic and orbital interactions with oxygen. The position of -SePh group gauche to C – O bond is unfavourable unless counterbalanced by steric factors.

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