A Generalized *exo*-Anomeric Effect. Substituent and Solvent Effects on the Conformational Equilibria of 2-(Arylseleno)cyclohexanones

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Abstract. The effects of substitution and solvent on the conformational equilibria of 2-[(4-R-substituted-phenyl)seleno]cyclohexanones are described. The conformational equilibria were determined by comparison of the linewidths of the H-2 resonances in the ^{1}H NMR spectra of the conformationally averaged systems with those of the anancomeric (highly biased) 4-isopropyl-2-substituted cyclohexanones. The substituent (R = NMe_2, OMe, Me, H, F, Cl, CF_3, NO_2) and solvent ($(CD_3)_2CO$, CD_3CN, CD_2Cl_2, $CDCl_3$) effects are discussed in terms of electrostatic effects and the possible stabilizing orbital interactions. The values of K_{eq} (axial–equatorial) increase as the substituent becomes more electron withdrawing, in agreement with the dominance of $n_{Se}\rightarrow\pi^*_{C=O}$ or $\sigma_{C-Se}\rightarrow\pi^*_{C=O}$ orbital interactions in the axial conformers. The increase in the proportion of the equatorial isomers in more polar solvents for a given substituent suggests a damping of the dipolar interactions in the equatorial isomers. However, the proportion of the equatorial isomers in a given solvent increases as the substituent becomes more electron withdrawing, indicating that electrostatic interactions do not dominate in controlling the conformational equilibria. Analysis of the equilibrium data by means of a dual substituent parameter approach indicates the best correlation with σ_I and σ^+_R substituent constants in CD_2Cl_2 and with σ_I and σ^o_R substituent constants in CD_3CN, with similar sensitivities to the resonance and polar effects. The correlations are interpreted in terms of accommodation of effective positive charge on the selenium atom in the axial isomers in CD_2Cl_2, and a lesser sensitivity to the buildup of positive charge in the more polar solvent CD_3CN. Comparison of the IR ν_{CO}-stretching frequencies for the axial and equatorial ArSe-substituted anancomeric systems (R = NO_2, NMe_2) indicates a higher stretching frequency for the NO_2-substituted isomers. In the case of the NMe_2-substituted compounds, ν_{CO} appears at a higher frequency in the equatorial isomer, whereas in the case of the NO_2-substituted compounds, ν_{CO} is less sensitive to the axial or equatorial orientation of the substituent. The results are consistent with the operation of $n_{Se}\rightarrow\pi^*_{C=O}$ or $\sigma_{C-Se}\rightarrow\pi^*_{C=O}$ orbital interactions in the axial isomers. The J_{C2-H2} values in the axially-substituted anancomeric isomers are of greater magnitude than those in the equatorially-substituted isomers, which is also consistent with the operation of the orbital interactions described above. There is, however, no marked substituent effect on the J_{C2-H2} values within the series of axial or equatorial isomers. We argue that this does not support the dominance of $\sigma_{C-Se}\rightarrow\pi^*_{C=O}$ orbital interactions. Examination of crystal structures reported in the literature for related compounds indicates a particular gauche orientation about the C_2–Se bond, which lends further support to the operation of an $n_{Se}\rightarrow\pi^*_{C=O}$ orbital interaction. We suggest that the latter interaction is a manifestation of a generalized *exo*-anomeric effect.

This work is dedicated, with respect and affection, to the memory of Ray Lemieux, an inspiring teacher, in celebration of the award of the 1999 Wolf Prize.

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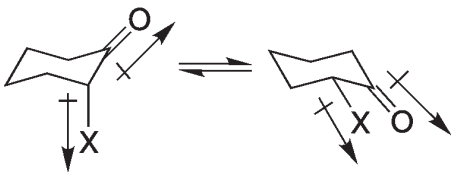


Scheme 1

INTRODUCTION

Conformational effects operating in 2-substituted cyclohexanones (Scheme 1) have intrigued both experimental and theoretical chemists for many years. Thus, the conformational equilibria of 2-halocyclohexanones have been studied extensively and the trends have been rationalized in terms of steric, dipole–dipole, and orbital interaction components.[1–5] It is now clear that the proportion of the axial conformer increases as the substituent changes from fluorine to iodine. The trend has been interpreted in terms of increasing non-bonded repulsion between the carbonyl group and the halogen in the equatorial conformers as the size of the halogen increases. The dipolar repulsion (see Scheme 1) does not dominate since the 2-iodo compound shows the largest proportion of the axial conformer. Alternative explanations have been advanced in terms of stabilizing orbital interactions. Thus, Corey and Burke[2] have attributed the trend to a dominance of $\sigma_{C-X} \rightarrow \pi^*_{C=O}$ orbital interactions in the axial conformer (Fig. 1a), which would be more important for X = I than for X = F. On the other hand, Eisenstein et al.[4] have argued that it is the $n_X \rightarrow \pi^*_{C=O}$ orbital interaction in the axial conformer (Fig. 1b) that leads to the preferred stabilization for the larger halogens, the overlap between the lone pair orbital and the $\pi^*_{C=O}$ orbital being less in the equatorial conformers. The conformational studies have been extended to systems containing substituents that are rotors, e.g., X = OR, NMe_2, SR, and SeR,[5–11] and it appears that the increased axial preference for the heavier chalcogen substituents is due to the increased non-bonded repulsion with the carbonyl group in the equatorial conformer.[5,11] However, theories of stabilizing orbital interactions continued to be advanced. Of particular note, a study with 2-(4-substituted) aryloxycyclohexanones indicated that the percentage of the equatorial isomer increased as the electron-withdrawing character of the substituent increased; a good Hammett correlation was obtained for electron-withdrawing substituents, lending support to the influence of the orbital interactions described above.[6] Curiously, however, the equilibria were insensitive to the effect of electron-donating substituents.[6] An infrared and UV-visible study of 2-alkylthiocycloalkanones has also suggested the existence of $\sigma_{C-X} \rightarrow \pi^*_{C=O}$ orbital interactions and charge transfer from the 3p orbital of sulfur to the carbonyl group.[8]

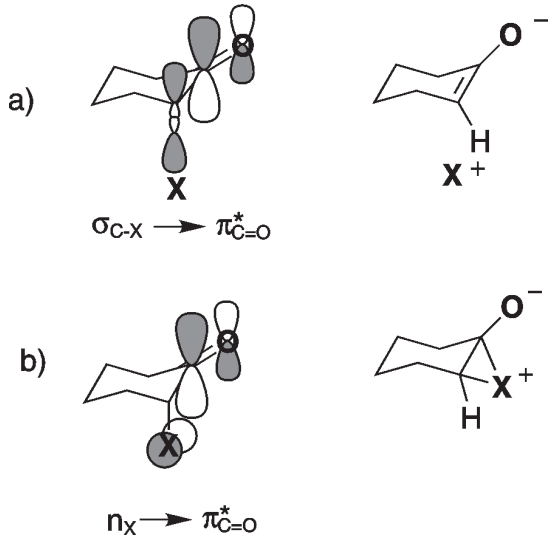


Fig. 1. Molecular-orbital (left) and equivalent valence-bond (right) descriptions of stabilizing interactions in 2-substituted cyclohexanones.

Further attempts to evaluate the relative contributions of the various orbital interaction components to the composite conformational effects led to the investigation of the conformational equilibria of the related 2-substituted *exo*-methylene cyclohexanes and their derivatives.[12,13] Thus, for example, Lessard and coworkers[12] argued that the main interaction stabilizing the axial conformation of 2-methoxy *exo*-methylenecyclohexane was a $\pi_{C=C} \rightarrow \sigma^*_{C-O}$ orbital interaction (Fig. 2a) that was only possible in the axial conformation. The interaction is analogous to the $n_X \rightarrow \sigma^*_{C-Y}$ orbital interactions (Fig. 3a), proposed to account for the anomeric effect[14–16] in carbohydrate derivatives. The latter effect has been classified further in terms of the *endo*-anomeric effect[17] (Fig. 3a), which refers to the preference of electronegative groups attached to the anomeric carbon for the axial orientation, and the *exo*-anomeric effect,[19] which is the preference for the gauche conformation around the C_1-aglyconic carbon bond of glycopyranosides that permits expression of an $n_Y \rightarrow \sigma^*_{C-X}$ stabilizing orbital interaction (Fig. 3b,c).[18] This explanation for the stabilization of the axial conformers of 2-substituted *exo*-methylenecyclohexanes was initially questioned by Zefirov and coworkers,[13a,b] who argued by examination of the effects of additional substitution on the double bond that it was an $n_X \rightarrow \pi^*_{C=C}$ orbital interaction in the axial conformer (Fig. 2b) that was the dominant contributor to the stabilization, but subsequently concluded[13c] that a $\pi_{C=C} \rightarrow \sigma^*_{C-X}$ orbital interaction was dominant with certain substituents.

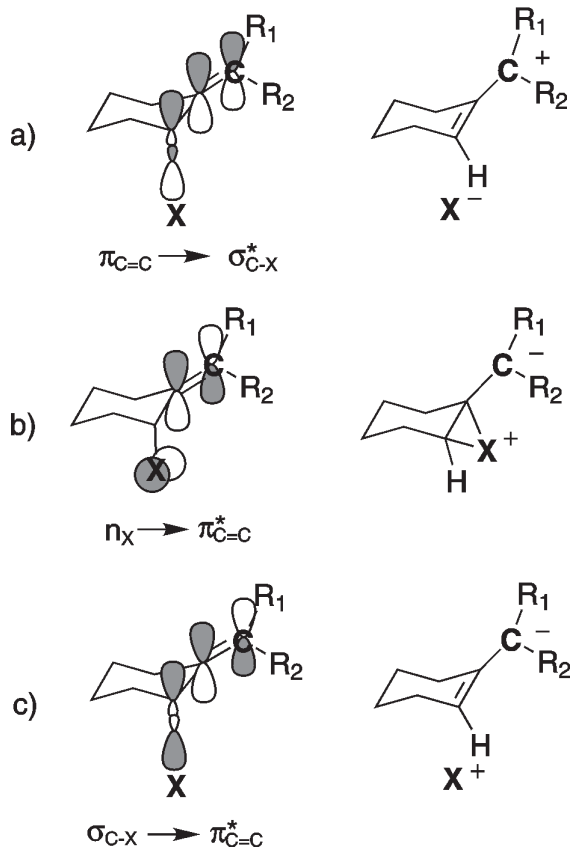


Fig. 2. Molecular-orbital (left) and equivalent valence-bond (right) descriptions of stabilizing interactions in 2-substituted *exo*-methylenecyclohexanes.

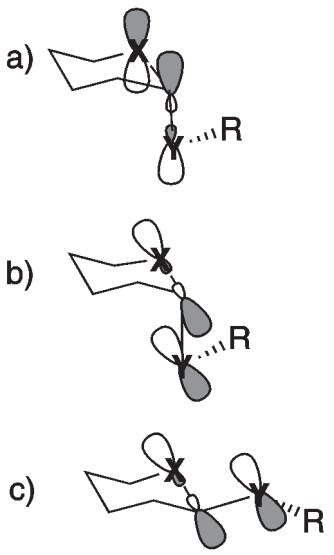
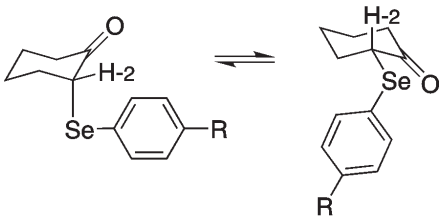


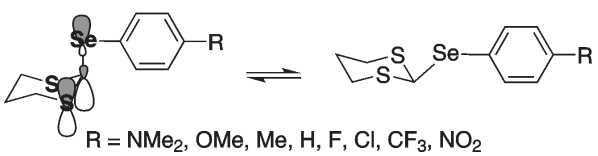
Fig. 3. Stabilizing $n \rightarrow \sigma^*$ orbital interactions associated with the (a) *endo*-anomeric effect and (b), (c) *exo*-anomeric effect in 2-substituted heterocyclohexanes.



Compound	R
1a	NMe_2
1b	OMe
1c	Me
1d	H
1e	F
1f	Cl
1g	CF_3
1h	NO_2

Scheme 2

The unresolved issue of the role of orbital interactions in exerting an influence on the conformational preferences of 2-substituted cyclohexanones and related compounds prompted the present study. Of relevance, Fraser and Faibish[11] have concluded, from an NMR and molecular mechanics investigation of 2-methoxy- and 2-methylthio-cyclohexanone, that the increased preference for the MeS substituent (over the MeO substituent) for the axial orientation results mainly from the variation in non-bonded repulsion between the substituent and the carbonyl group in the equatorial isomer, and that an explanation involving orbital interactions appears unnecessary. However, it is not at all obvious from this one comparison that electronic interactions play no role. In order to systematically probe the effects of substitution on the orbital interaction components, we chose to examine the conformational equilibria and spectroscopic properties of a contiguous series of 2-[(4-substituted-phenyl)seleno]cyclohexanones **1a**–**1h** (Scheme 2). These compounds were chosen as suitable candidates since changes in the nature of the substituent should result in corresponding changes in electronic interactions but only minimal changes in steric effects. The (4-substituted-phenyl)seleno probe has previously served as a sensitive and accurate reporter of electronic perturbation of the conformational equilibria of 2-[(4-substituted-phenyl)seleno]-1,3-dithianes (Scheme 3).[19]



Scheme 3

Table 1. Physical data for the 2-arylselenocyclohexanones **1a–1h**

compound	yield (%)	mp (°C) (cryst. solvent)	ir(cm^{-1})[a]	formula	microanalysis: calcd (found) C	H	N
1a, R=NMe_2	71	49–49.5 (hex./EtOAc)	1692	$C_4H_{19}NOSe$	56.76(56.71)	6.46(6.37)	4.73(4.85)
1b, R=OMe	94	28–29 (EtOH)	1691	$C_{13}H_{16}O_2Se$	55.13(54.88)	5.69(5.73)	
1c, R=Me	76	24–25 (EtOH)	1694	$C_{13}H_{16}OSe$	5843(58.69)	6.03(6.10)	
1d, R=H	93	55–56 (hexane)	1694	$C_{12}H_{14}OSe$	56.92(56.91)	5.57(5.51)	
1e, R=F	94	40–41 (hexane)	1694	$C_{12}H_{13}OFSe$	53.15(52.93)	4.83(4.83)	
1f, R=Cl	84	36–36.5 (EtOH)	1694	$C_{12}H_{13}OClSe$	50.11(49.88)	4.56(4.39)	
1g, R=CF_3	87	63–63.5 (hexane)	1696	$C_{13}H_{13}OF_3Se$	48.61(48.58)	4.08(4.00)	
1h, R=NO_2	65	89.5–90 (hex./EtOAc)	1699	$C_{12}H_{13}NO_3Se$	48.33(48.36)	4.39(4.30)	4.70(4.85)

[a] in CH_2Cl_2, RT.

Table 2. Physical data for the 4-isopropyl-2-arylselenocyclohexanones **2a–2h**

compound	yield (%)	*trans*:*cis* ratio	formula	microanalysis: calcd (found) C	H	N
2a, R=NMe_2	81	10:1	$C_{17}H_{25}NOSe$	60.35(60.55)	7.45(7.60)	4.14(4.22)
2b, R=OMe	74	2:1	$C_{16}H_{22}O_2Se$	59.07(59.24)	6.82(6.87)	
2c, R=Me	73	1.8:1	$C_{16}H_{22}OSe$	62.13(62.29)	7.17(7.30)	
2d, R=H	86	2:1	$C_{15}H_{20}OSe$	61.01(61.14)	6.83(6.98)	
2e, R=F	87	2:1	$C_{15}H_{19}OFSe$	57.51(57.78)	6.11(6.20)	
2f, R=Cl	78	1.8:1	$C_{15}H_{19}OClSe$	54.64(54.81)	5.81(5.98)	
2g, R=CF_3	75	2:1	$C_{16}H_{19}OF_3Se$	52.90(52.93)	5.27(5.18)	
2h, R=NO_2	87	2:1	$C_{15}H_{19}NO_3Se$	52.94(52.95)	5.63(5.72)	4.12(4.02)

Table 3. ^3C NMR data[a,b] for the 2-arylselenocyclohexanones **1a–1h**

compound	C-1	C-2	C-3	C-4	C-5	C-6	Ph[c]	Other
1a, R=NMe_2	207.7	52.03	33.38	22.40	26.70	38.22	113.1, 137.1 112.9, 150.7	40.11 (NMe_2)
1b, R=OMe	207.4	51.95	33.58	22.60	26.70	38.30	118.6, 137.1 115.9, 160.1	55.15 (OMe)
1c, R=Me	207.4	51.59	33.73	22.67	26.72	38.32	124.8, 134.9 129.9, 138.1	21.01 (Me)
1d, R=H	207.6	51.52	33.98	22.86	26.82	38.50	128.6, 134.6 129.1, 128.0	
1e, R=F	207.2	51.94	33.75	22.81	26.70	38.40	123.0, 137.1 116.3, 163.0	
1f, R=Cl	207.1	51.67	33.82	22.89	26.67	38.44	126.7, 135.9 129.2, 134.4	
1g, R=CF_3	207.2	51.25	34.09	23.14	26.80	38.61	134.0, 133.6 125.8, 129.8	123.9 (CF_3)
1h, R=NO_2	206.9	51.02	34.06	23.27	26.80	38.64	139.3, 132.7 123.9, 146.9	

[a] in ppm downfield from $SiMe_4$; [b] in $CDCl_3$ at 294 ± 1 K; [c] aromatic ring carbons are listed in the order C_{ipso}, C_{ortho}, C_{meta}, C_{para}; the fluorinated compounds **2e** and **2f** exhibit the expected C–F coupling.

EXPERIMENTAL

General Information

Melting points were determined on a Fisher-Johns melting-point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer operating at 400.13 MHz for ^{1}H, 100.6 MHz for ^{13}C, and 76.3 MHz for ^{77}Se, respectively. ^{1}H assignments were confirmed with the aid of two-dimensional 1H,1H (COSYDFTP) experiments using standard Bruker pulse programs. ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from $SiMe_4$, and ^{77}Se chemical shifts are reported in ppm downfield from Me_2Se.[19] IR spectra were recorded in CH_2Cl_2 solutions on a Bomem FTIR spectrometer. Flash column chromatography was performed with Kieselgel 60 (230–400 mesh) silica gel. Solvents were distilled before use and were dried, as necessary, by literature procedures. Transfers under nitrogen were effected by means of Schlenk tube techniques. Microanalyses were performed by M.K. Yang of the Simon Fraser University Microanalytical Laboratory.

Synthesis

The required diaryl diselenides and aryl selenocyanates were prepared as described in our previous work.[19] 2-Chlorocyclohexanone was prepared by standard methods.[20] 4-isopropylcyclohexanone is commercially available (Phalz and Bauer) or was conveniently prepared by hydrogenation (Pd/C, 1 atm. H_2) of 4-isopropyl-2-cyclohexenone (Aldrich), followed by reoxidation (Jones reagent) of the alcohol/ketone mixture.

*General Procedure for the Preparation of **1a–1g***

To a solution of the appropriate diaryl diselenide (2.5 mmol) in dry THF (15 mL), was added freshly prepared sodium sand (5.5 mmol) and benzophenone (30 mg). The reaction mixture was placed in an ultrasonic bath and sonicated until a permanent blue color appeared. The reduction rate was dependent on the specific diselenide substrate and the particle size of the sodium, but the reaction was generally complete within 2 h. The resulting sodium arylselenolate suspension was cooled with a dry-ice/acetone bath and a solution of 2-chlorocyclohexanone (0.60 mL, 5.2 mmol) in dry THF (10 mL) was added dropwise. The mixture was allowed to warm to room temperature, poured into saturated NH_4Cl (30 mL), and extracted with ether. The ether extract was washed with saturated NaCl (20 mL) and dried ($MgSO_4$). Removal of the solvent gave a yellow oil that was purified by flash chromatography (hexanes-EtOAc) to yield pure 2-arylselenocyclohexanones **1a–1g** as colorless solids. Analytically pure samples were obtained by recrystallization. Yields and melting points are presented in Table 1. The ^{13}C NMR data appear in Table 3.

*General Procedure for the Preparation of **1h** and **2a–2h***

A solution of lithium diisopropylamide (12.5 mmol) in dry THF (30 mL) was prepared from diisopropylamine (1.85 mL, 13.2 mmol) and 2.5 M *n*-BuLi in hexane (5.0 mL) and cooled to –78 °C. The appropriate ketone (12.3 mmol) was added and the reaction mixture was stirred for 30 min. A solution of the required selenium electrophile (12.5 mmol) in dry THF (10 mL) was prepared. In the cases of **1h**, **2a**, and **2h**, the electrophile was the selenocyanate. In the cases of **2b**-**2g**, THF solutions of the selenenyl bromides were prepared by treatment of THF solutions of diaryldiselenides with 1 equivalent of Br_2. The solutions of the electrophile were added dropwise over 5–10 min and the reaction mixture was stirred briefly (≈15 min) before being quenched by pouring into saturated NH_4Cl solution. Processing and purification as in the previous procedure yielded the pure α-selenenyl ketones. Compound **1h** was obtained as a yellow crystalline material while **2a**–**2h** were obtained as colorless or light yellow oils consisting of cis/trans mixtures. Physical data are presented in Tables 1 and 2. Complete separation of the isomers was generally impossible since they appeared to interconvert during silica gel chromatography. In certain cases (e.g., **2a** and **2h**), pure isomers could be obtained by careful fractional crystallization.

Trans-*2-(4 dimethylaminophenylseleno)-4-isopropylcyclohexanone (**2a** trans)*. Pale-yellow microcrystalline solid. Mp 78 °C (hexanes). ^{1}H NMR ($CDCl_3$) δ 7.40 (d, 2H, *J* 8.8 Hz, Ar), 6.67 (bs, 2H, Ar), 3.69 (dt, 1H, $J_{2,3a}$ 4.6, $J_{2,3e} = J_{2,6e}$ = 2.3 Hz, H-2), 3.15 (ddd, 1H, $J_{6e,6a}$ 14.8, $J_{5a,6a}$14.1, $J_{5e,6a}$ 6.1 Hz, H-6a), 2.96 (s, 6H, N(CH_3)$_2$), 2.27 (ddd, 1H, $J_{5a,6e}$ 4.3, $J_{5e,6e}$ 3.0 Hz, H-6e), 2.23 (dtd, $J_{3e,3a}$ 14.2, $J_{3e,4} = J_{3e,5e}$ = 3.0 Hz, H-3e), 2.00 (ddq, $J_{5e,5a}$ 13.2, $J_{4,5e}$ 3.0 Hz, H-5e), 1.91 (ddd, $J_{3a,4}$ 12.3 Hz, H-3a), 1.79 (tdt, $J_{4,5a}$ 12.1, $J_{4,CH}$ 6.7 Hz, H-4), 1.54 (d of septets, C*H*(CH_3)$_2$), 1.40 (dddd, 1H, H-5a), 0.91 (d, 6H, *J* 6.7 Hz, CH(CH_3)$_2$. IR: ν_{CO} 1696 cm^{-1}.

Cis-*2-(4-dimethylaminophenylseleno)-4-isopropyl-cyclohexanone (**2a** cis)*. Pale-yellow needles. Mp 85–86 °C (hexanes). ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 2H, Ar), 6.61 (m, 2H, Ar), 3.89 (ddd, 1H, $J_{2,3a}$ 12.5, $J_{2,3e}$ 6.1 $J_{2,6a}$ 1.3 Hz, H-2), 2.95 (s, 6H, N(CH_3)$_2$), 2.57 (ddd, 1H, $J_{6e,6a}$ 14.2, $J_{5a,6e}$ 4.5, $J_{5e,6e}$ 3.2 Hz, H-6e), 2.35 (dddd, 1H, $J_{5a,6a}$12.8, $J_{5e,6a}$ 6.3 Hz, H-6a), 2.24 (dddd, $J_{3e,3a}$ 12.8, $J_{3e,4}$ 3.1, $J_{3e,5e}$ 2.8 Hz, H-3e), 2.00 (dddd, $J_{5e,5a}$ 12.7 Hz, H-5e), 1.66 (td, $J_{3a,4}$ 11.2 Hz, H-3a), 1.58–1.40 (m, 3H, H-4, C*H*(CH3)$_2$, H-5a), 0.86 (d, 3H, *J* 6.5 Hz, CH(CH_3) 0.84 (d, 3H, *J* 6.5 Hz, CH(CH_3)$_2$. IR: ν_{CO} 1708 cm^{-1}.

Trans-*2-(4-nitrophenylseleno)-4-isopropyl-cyclohexanone (**2h** trans)*. Pale-yellow gummy amorphous solid. ^{1}H NMR ($CDCl_3$) δ 8.12 (m, 2H, Ar), 7.65 (m, 2H, Ar), 4.02 (dt, 1H, $J_{2,3a}$ 4.9, $J_{2,3e} = J_{2,6e}$ = 2.2 Hz, H-2), 3.14 (ddd, 1H, $J_{6e,6a}$ 15.0, $J_{5a,6a}$13.8, $J_{5e,6a}$ 6.2 Hz, H-6a), 2.39–2.29 (m, 2H, H-3e, H-6e), 2.09 (ddd, $J_{3e,3a}$ 14.5, $J_{3a,4}$ 12.2 Hz, H-3a), 2.07 (dddd, $J_{5e,5a}$ 12.8, $J_{4,5e}$ 3.0 Hz, $J_{5e,6e}$ 3.0 Hz, H-5e), 1.71 (tdt, $J_{4,5a}$ 12.0, $J_{4,CH}$ 6.8 Hz, $J_{3e,4}$ 3.0 Hz, H-4), 1.59 (d of septets, C*H*(CH_3)$_2$), 1.48 (dddd, 1H, $J_{5a,6e}$ 4.3, $J_{3e,5e}$ 3.2 Hz, H-5a), 0.94 (d, 6H, J 6.7 Hz, CH(CH_3)$_2$. IR: ν_{CO} 1712 cm^{-1}.

Cis-*2-(4-nitrophenylseleno)-4-isopropyl-cyclohexanone (**2h** cis)*. Pale-yellow needles. Mp 96–97 °C (EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ 8.08 (m, 2H, Ar), 7.57 (m, 2H, Ar), 4.31 (ddd, 1H, $J_{2,3a}$ 12.7, $J_{2,3e}$ 5.9 $J_{2,6a}$ 1.2 Hz, H-2), 2.66 (ddd, 1H, $J_{6e,6a}$ 14.1, $J_{5a,6e}$ 4.5, $J_{5e,6e}$ 2.8 Hz, H-6e), 2.48 (dddd, 1H, $J_{5a,6a}$13.5, $J_{5e,6a}$ 6.2 Hz, H-6a), 2.34 (dddd, $J_{3e,3a}$ 12.5, $J_{3e,4}$ 3.0, $J_{3e,5e}$ 2.3 Hz, H-3e), 2.11 (dddd, $J_{5e,5a}$ 13.0 Hz, H-5e), 1.73 (td, $J_{3a,4}$ 11.8 Hz, H-3a), 1.72–1.48 (m, 3H, H-4, C*H*(CH3)$_2$, H-5a), 0.88 (d, 3H, *J* 6.8 Hz, CH(CH_3) 0.87 (d, 3H, *J* 6.7Hz, CH(CH_3)$_2$. IR: ν_{CO} 1713 cm^{-1}.

The ^{13}C NMR data for **2a–2h** appear in Table 4. The ^{1}H H-2 and ^{77}Se NMR data for **1a–1h** and **2a–2h** appear in Table 5.

Table 4. ^{13}C NMR data[a,b] for the 2-arylselenocyclohexanones **2a–2h**

compound	C-1	C-2	C-3	C-4	C-5	C-6	Ph[c]		Other	
2a, R=NMe_2										
trans	208.3	51.19	35.58	38.48	29.48	36.54	113.5	137.0	40.18(NMe_2)	31.87
							112.9	150.8	19.81	19.76($CHMe_2$)
cis	208.3	51.44	38.78	43.62	29.14	40.51	112.5	137.7	40.22(NMe_2)	31.85
							112.9	150.6	20.04	19.45($CHMe_2$)
2b, R=OMe										
trans	208.0	50.93	35.72	38.65	29.46	36.47	119.1	136.9	55.19(OMe)	31.79
							114.7	160.2	19.75	19.71($CHMe_2$)
cis	207.9	52.61	38.82	43.70	29.29	40.59	118.0	137.7	40.22(NMe_2)	31.82
							115.0	159.9	19.96	19.47($CHMe_2$)
2c, R=Me										
trans	208.0	50.48	35.91	38.76	29.50	36.50	125.3	134.7	21.06(CH_3)	31.80
							130.0	138.4	19.73	19.70($CHMe_2$)
cis	207.7	52.45	38.96	43.78	29.34	40.61	124.4	135.5	21.06(CH_3)	31.80
							129.8	137.8	19.95	19.45($CHMe_2$)
2d, R=H										
trans	208.1	50.23	36.07	38.89	29.52	36.57	d	134.2	31.78	19.75
							129.2	128.1	19.72($CHMe_2$)	
cis	207.6	52.50	39.02	43.86	29.45	40.68	d	135.2	31.78	19.92
							129.0	127.7	19.49($CHMe_2$)	
2e, R=F										
trans	208.0	50.75	35.85	38.86	29.43	36.44	123.6	136.8	31.76	19.72
							116.4	162.9	19.70($CHMe_2$)	
cis	207.3	52.78	38.86	43.82	29.43	40.62	122.5	137.8	31.76	19.89
							116.1	d	19.50($CHMe_2$)	
2f, R=Cl										
trans	207.8	50.42	35.93	38.94	29.42	36.43	127.2	135.6	31.76	19.75
							129.4	134.6	19.70($CHMe_2$)	
cis	d	52.81	38.94	43.86	29.42	40.67	126.1	136.6	31.80	19.95
							129.2	134.2	19.47($CHMe_2$)	
2g, R=CF_3										
trans	207.8	49.66	36.10	39.17	29.44	36.44	134.4	133.1	d (CF_3)	31.75
							125.9	d	19.71	19.66($CHMe_2$)
cis	d	52.65	38.95	43.95	29.55	40.96	d	134.2	d (CF_3)	31.75
							112.9	112.5	19.86	19.44($CHMe_2$)
2h, R=NO_2										
trans	208.2	49.36	36.12	39.43	29.52	36.48	139.4	132.1	31.76	19.73
							123.8	146.9	19.67($CHMe_2$)	
cis	206.8	52.75	38.76	43.95	29.48	40.73	139.6	139.6	31.74	19.88
							133.0	146.8	19.47($CHMe_2$)	

[a] in ppm relative to $CDCl_3$ at 77.0 ppm; [b] in $CDCl_3$ at 294 ± 1 K; [c] aromatic ring carbons are listed in the order C_{ipso}, C_{ortho}, C_{meta}, C_{para}; the fluorinated compounds **2e** and **2f** exhibit the expected C–F coupling; [d] resonance not observed.

RESULTS AND DISCUSSION

Synthesis

Compounds **1a–1g** were prepared by the reaction of the respective sodium arylselenolates (generated by sodium metal reduction of the corresponding diselenides, as described by Ley et al.[21]) with 2-chlorocyclohexanone.[20] Compound **1h** was synthesized by the reaction of the lithium enolate of cyclohexanone with 4-nitrophenylselenocyanate. Compounds **2b–2g** were synthesized by the reaction of the lithium enolate of 4-isopropylcyclohexanone with the freshly prepared arylselenenyl bromides using the general protocol of Reich et al. [22] In the case of **2a** and **2h** it proved to be advantageous to use the corresponding arylselenocyanates as the electrophiles.

Conformational Analysis

The ^1H NMR spectra of **1a–1h** measured in CD_2Cl_2, $CDCl_3$, CD_3CN, and $(CD_3)_2CO$ at ambient temperature

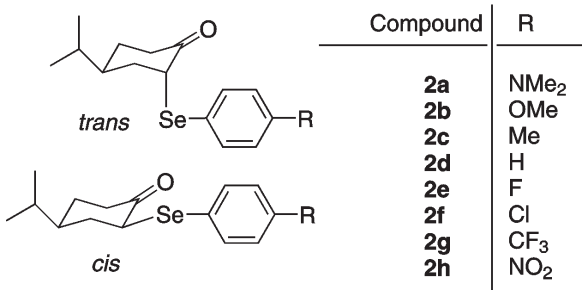
Table 5. ^{1}H H-2[a,b] and ^{77}Se[b,c] NMR chemical-shift data for 2-arylselenocyclohexanones

	^{1}H chemical shift			^{77}Se chemical shift		
compound	1	2_{trans}	2_{cis}	1	2_{trans}	2_{cis}
a, R=NMe_2	3.74	3.66	3.88	386	409	341
b, R=OMe	3.80	3.78	3.96	386	411	345
c, R=Me	3.85	3.78	4.03	391	414	349
d, R=H	3.91	3.84	4.15	397	420	358
e, R=F	3.90	3.85	4.05	391	414	354
f, R=Cl	3.84	3.76	4.02	389	413	351
g, R=CF_3	4.01	3.93	4.18	397	420	362
h, R=NO_2	4.10	4.01	4.28	404	426	371

[a] in $CDCl_3$; ppm downfield from Me_4Si; [b] in $CDCl_3$; at 294 ± 1K; [c] in $CDCl_3$; ppm downfield from Me_2Se.

showed a similar pattern. As the 4-substituent of the arylseleno moiety became more electron withdrawing or as the solvent polarity increased, the width at half-height of the H-2 resonance increased and appeared at lower field. Since the H-2 signal is the X part of an ABX system, these data are consistent with the presence of a higher proportion of the equatorial conformer with increasing substituent electronegativity or solvent polarity.

Direct examination of the conformational equilibria by means of low-temperature ^{77}Se NMR spectroscopy was attempted with the hope that the large chemical-shift range of ^{77}Se (≈2000 ppm for organic compounds),[23] coupled with a known sensitivity to conformational environment,[19,24,25] might permit observation of individual conformer resonances within the accessible temperature range. Unfortunately, only one sharp ^{77}Se resonance could be detected at temperatures down to 165 K, indicating that the barriers to ring interconversion are too low (~21 kJ mol^{-1} for cyclohexanones[26]) to permit observation of coalescence behavior even on the ^{77}Se chemical shift scale.



Scheme 4

Thus, indirect quantitation of the conformational equilibria was effected by comparison of the H-2 linewidths at half-height in the ^{1}H NMR spectra of **1a–1g** (Scheme 2) with those in the spectra of compounds *trans*-**2a–2g** and *cis*-**2a–2g** (Scheme 4), which served as anancomeric (highly biased) systems for *axial* and *equatorial* 2-arylselenocyclohexanones, respectively. Attempts to use the average chemical shift method[27] using data from ^{1}H, ^{13}C, and ^{77}Se spectra were not judged to be reliable. Thus, although all three methods confirmed the general trend of increasing K_{A-E} for more electronegative substituents, there were some ambiguities and the agreement between methods was marginal at best, most likely because the isopropyl group is not merely a spectator group and does have an effect on the chemical shifts of interest. The equilibrium data obtained at 294 K by application of the Eliel equation[27] to the ^{1}H H-2 linewidths[28] are summarized in detail for $CDCl_3$ in Table 6 and for several other solvents of varying polarity in Table 7.

The data indicate that K_{eq} (axial–equatorial) increases as the electron-withdrawing character of the substituent increases. It is noteworthy that Cantacuzène and Tordeux[6] observed a similar trend with the equilibria of 2-(4-substituted) phenoxycyclohexanones. The trend is opposite to that observed in our previous study

Table 6. ^{1}H NMR H-2 linewidths[a] and equilibrium data[b] for 2-arylselenocyclohexanones

	H-2 linewidths				$-\Delta G°_{294K}$ (error)
compound	**1**	$\mathbf{2}_{trans}$[c]	$\mathbf{2}_{cis}$[c] (kJ mol^{-1})	K_{A-E} (error)	(kJ mol^{-1})
a, R=NMe_2	11.8	9.6 2	1.2	0.23 (0.02)	3.56 (0.24)
b, R=OMe	c	9.5	21.5	—	—
c, R=Me	12.4	10.0	21.4	0.27 (0.02)	3.24 (0.21)
d, R=H	12.5	10.0	21.4	0.28 (0.02)	3.11 (0.20)
e, R=F	13.0	10.0	21.1	0.37 (0.02)	2.44 (0.15)
f, R=Cl	12.6	10.1	21.8	0.27 (0.02)	3.20 (0.21)
g, R=CF_3	13.0	10.0	21.2	0.37 (0.02)	2.47 (0.15)
h, R=NO_2	13.1	10.1	21.0	0.38 (0.02)	2.37 (0.15)

[a] at half-height in Hz; [b] in $CDCl_3$ at 294 ± 1 K; [c] obscured by other resonances.

Table 7. Equilibrium data[a] for 2-arylselenocylcohexanones **1a–1h** as derived from ^{1}H NMR H-2 linewidths[b] in various solvents

compound	solvent	K_{A-E} (error)	$-\Delta G°_{294K}$ (error) (kJ mol^{-1})
	$(CD_3)_2CO$	0.65 (0.04)	–1.05 (0.06)
1a, R=NMe_2	CD_3CN	0.42 (0.03)	–2.12 (0.15)
	CD_2Cl_2	0.24 (0.02)	–3.53 (0.29)
	$CDCl_3$	0.23 (0.02)	–3.56 (0.24)
	$(CD_3)_2CO$	0.69 (0.03)	–0.92 (0.04)
1b, R=OMe	CD_3CN	0.47 (0.03)	–1.85 (0.12)
	CD_2Cl_2	c	—
	$CDCl_3$	c	—
	$(CD_3)_2CO$	0.59 (0.04)	–1.28 (0.09)
1c, R=Me	CD_3CN	0.53 (0.03)	–1.54 (0.09)
	CD_2Cl_2	0.35 (0.02)	–2.61 (0.15)
	$CDCl_3$	0.27 (0.02)	–3.24 (0.21)
	$(CD_3)_2CO$	0.78 (0.05)	–0.62 (0.04)
1d, R=H	CD_3CN	0.67 (0.04)	–0.99 (0.06)
	CD_2Cl_2	0.42 (0.03)	–2.15 (0.15)
	$CDCl_3$	0.28 (0.02)	–3.11 (0.20)
	$(CD_3)_2CO$	1.04 (0.06)	0.09 (0.01)
1e, R=F	CD_3CN	0.91 (0.05)	–0.23 (0.01)
	CD_2Cl_2	0.53 (0.03)	–1.57 (0.09)
	$CDCl_3$	0.37 (0.02)	–2.44 (0.15)
	$(CD_3)_2CO$	0.81 (0.05)	–0.53 (0.03)
1f, R=Cl	CD_3CN	0.68 (0.04)	–0.96 (0.06)
	CD_2Cl_2	0.47 (0.03)	–1.87 (0.12)
	$CDCl_3$	0.27 (0.02)	–3.20 (0.21)
	$(CD_3)_2CO$	1.06 (0.06)	0.13 (0.01)
1g, R=CF_3	CD_3CN	1.30 (0.07)	0.64 (0.03)
	CD_2Cl_2	0.53 (0.03)	–1.57 (0.09)
	$CDCl_3$	0.37 (0.02)	–2.47 (0.15)
1h, R=NO_2	$(CD_3)_2CO$	1.57 (0.09)	1.10 (0.07)
	CD_3CN	1.63 (0.09)	1.20 (0.07)
	CD_2Cl_2	0.60 (0.04)	–1.24 (0.08)
	$CDCl_3$	0.38 (0.02)	–2.37 (0.15)

[a]at 294 ± 1 K; [b]at half-height in Hz; [c]obscured by other resonances.

Table 8. $^1J(C_2–H_2)$ coupling constants (H_z) for compounds **1a–1h** and **2a–2h**

compound	$^1J(C_2–H_2)$	compound		$^1J(C_2–H_2)$
1a, R=NMe_2	147	**2a**, R=NMe_2	*trans*	a
			cis	140
1b, R=OMe	148	**2b**, R=OMe	*trans*	150
			cis	139
1c, R=Me	145	**2c**, R=Me	*trans*	151
			cis	142
1d, R=H	147	**2d**, R=H	*trans*	151
			cis	142
1e, R=F	147	**2e**, R=F	*trans*	148
			cis	a
1f, R=Cl	146	**2f**, R=Cl	*trans*	150
			cis	136
1g, R=CF_3	142	**2g**, R=CF_3	*trans*	150
			cis	140
1h, R=NO_2	142	**2h**, R=NO_2	*trans*	147
			cis	138

[a] Could not be assigned with certainty.

of 2-[(4-substituted-phenyl)seleno]-1,3-dithianes (Scheme 3),[19] in which the dominant $n_S \rightarrow \sigma^*_{C-Se}$ interaction led to an *increase* in the proportion of the axial conformer with increasing electron-withdrawing ability of the substituent. The present data are consistent with the existence of either $n_{Se} \rightarrow \pi^*_{C=O}$ or $\sigma_{C-X} \rightarrow \pi^*_{C=O}$ orbital interactions, as defined above, since electron-withdrawing substituents would be predicted to lower the energy of the n_{Se} or σ_{C-X} fragment orbitals and therefore lead to a weaker interaction with the $\pi^*_{C=O}$ acceptor orbital,[29] thereby destabilizing the axial conformer. That electrostatic interactions, as depicted in Scheme 1, are not dominant is indicated by the fact that the proportion of the equatorial isomers in a given solvent increases as the substituent becomes more electron withdrawing; the opposite would have been predicted if dipole–dipole interactions were dominant. There is, however, an increase in the proportion of the equatorial isomers in more polar solvents for a given substituent, indicating that dipolar interactions are present and that there is a damping of such interactions in the equatorial isomers.

In order to assess the relative importance of the $n_{Se} \rightarrow \pi^*_{C=O}$ and $\sigma_{C-Se} \rightarrow \pi^*_{C=O}$ orbital interactions, we chose to examine the one-bond J_{C2-H2} coupling constants (see Table 8). It has been shown previously that these coupling constants are directly related to the magnitude of C–H bond strengths[30] and can be correlated with the operation of different orbital interactions.[30,31] The smaller J_{C2-H2} values noted for the conformationally averaged systems **1g** and **1h** (with the most powerful electron-withdrawing substituents) relative to the other compounds in the series are consistent with the lesser proportion of axial isomers for these two compounds since either orbital interaction would lead to a strengthening of the C–H bond and an increase in J_{C2-H2} values (see valence bond representations in Fig. 1). This conclusion is supported by the trend in the values for the anancomeric compounds **2a–2h**. The J_{C2-H2} values in the axially-substituted anancomeric isomers **2a–2h** are of greater magnitude than those in the equatorially-substituted isomers, which is also consistent with the operation of an $n_{Se} \rightarrow \pi^*_{C=O}$ or $\sigma_{C-Se} \rightarrow \pi^*_{C=O}$ orbital interaction in the axial isomers that leads to a stronger $C–H_{equatorial}$ bond. Significantly, however, there is no marked sub-

stituent effect on the J_{C2-H2} values within the series of axial or equatorial isomers. We argue that if $\sigma_{C-Se} \rightarrow \pi^*_{C=O}$ orbital interactions were dominant, then different contributions of the cyclohexene-like resonance hybrid (Fig. 1a) as a function of substituent would lead to a more pronounced variation in coupling constants, given the significant difference in C–H bond strengths for ethylene (720 kJ mol^{-1}) [32] and cyclohexane (399.6 kJ mol^{-1}).[32] The operation of $n_{Se} \rightarrow \pi^*_{C=O}$ interactions in the axial isomers would lead to a cyclopropyl-type resonance contributor (Fig. 1b). Since the C–H bond strengths of cyclopropane (444.8 kJ mol^{-1})[32] and cyclohexane (399.6 kJ mol^{-1})[32] are more similar in magnitude than the cyclohexane/cyclohexene pair, we suggest that $n_{Se} \rightarrow \pi^*_{C=O}$ orbital interactions are more important than $\sigma_{C-Se} \rightarrow \pi^*_{C=O}$ interactions in controlling the conformational equilibria.

Further support for the controlling $n_{Se} \rightarrow \pi^*_{C=O}$ orbital interactions was provided by a dual substituent parameter analysis[33] of the equilibrium data. A two-parameter model was judged to be significant by means of an *f*-test.[34] Of the resonance substituent constants, σ^-_R, σ^o_R, σ^{BA}_R, and σ^+_R, the best correlation for the data in CD_2Cl_2 was obtained with σ^+_R, as judged by the lowest sum of squares of the residuals and the best percent variation explained by the model. Thus, correlations of the type $\log (K_x/K_H) = \rho_I\sigma_I + \rho^+_R\ \sigma^+_R$ gave, for the equilibrium data in Table 7, $\rho_I = 0.24 \pm 0.04$; $\rho^+_R = 0.14 \pm 0.02$. A similar treatment of the data in CD_3CN gave the best correlation with σ^o_R, and $\rho_I = 0.53 \pm 0.08$; $\rho^o_R = 0.48 \pm 0.06$, that is, similar sensitivity of the equilibria to the resonance and polar effects exerted by the substituent. We interpret the correlations in terms of accommodation of effective positive charge on the selenium atoms in the axial isomers in CD_2Cl_2 (Fig. 1b), and a lesser sensitivity to the buildup of positive charge in the more polar solvent CD_3CN because of solvation.

We turned next to an examination of the carbonyl stretching frequencies as a probe of the $n_{Se} \rightarrow \pi^*_{C=O}$ orbital interactions operative in the axial isomers. Comparison of the IR ν_{CO} stretching frequencies for **1a** (R = NMe_2) vs. **1h** (R = NO_2) (Table 1) indicates a higher stretching frequency for the 4-NO_2 compound, consistent with the lesser proportion of the axial isomer and therefore a lesser $n_{Se} \rightarrow \pi^*_{C=O}$ orbital interaction. The IR ν_{CO} stretching frequencies for the axial and equatorial isomers of **2a** (R = NMe_2) were 1696 cm^{-1} (axial) and 1708 cm^{-1} (equatorial). The corresponding frequencies for the isomers of **2h** (R = NO_2) were 1712 cm^{-1} (axial) and 1713 cm^{-1} (equatorial). The higher stretching frequencies for the NO_2-substituted isomers, as compared to the NMe_2-substituted isomers, indicates a lesser $n_{Se} \rightarrow \pi^*_{C=O}$ orbital interaction in the former compounds.

Finally, we comment on some data in the literature on related compounds. Kazakova et al.[10] have studied the electrical and electrooptical properties of 2-(4-substituted) phenoxycyclohexanones and 2-phenylthiocyclohexanones in solution. In the former case, molecular mechanics calculations have also been performed. The results indicate a preference for the gauche arrangement about the C_2–X bond that would permit expression of an $n_X \rightarrow \pi^*_{C=O}$ orbital interaction. Similarly, X-ray structural data for acyclic α-phenylselenenyl ketones[9a] or axially-substituted phenylselenocyclohexanones[9b,c] indicate that the orientation about the C_2–Se bond is in a gauche arrangement that optimizes the $n_{Se} \rightarrow \pi^*_{C=O}$ orbital interaction.

CONCLUSIONS

This work was intended to establish whether orbital interactions were significant contributors to the conformational preferences of 2-arylselenocyclohexanones and if so, to identify the dominant orbital interactions that might constitute a particular conformational effect. The evidence presented in the foregoing sections suggested that orbital interactions were operative and it remained to choose between $n_{Se} \rightarrow \pi^*_{C=O}$ or $\sigma_{C-Se} \rightarrow \pi^*_{C=O}$ interactions as the dominant contributors. Much of the evidence could be reconciled with either one of these interactions. However, arguments were presented in terms of the trends in one bond J_{C2-H2} coupling constants and from X-ray structural data to suggest that the $n_{Se} \rightarrow \pi^*_{C=O}$ interactions dominate. We suggest further that $n_X \rightarrow \pi^*_{C=O}$ interactions, as shown in Fig. 1b, play a role in the stabilization of the axial conformers of 2-substituted cyclohexanones in general. We conclude that the latter orbital interactions lead to a conformational preference about the exocyclic C–Se bond in 2-arylselenocyclohexanones that is shown in Fig. 4. This type of interaction is reminiscent of that proposed to account for the *exo*-anomeric effect in carbohydrates by R.U. Lemieux (Fig. 3b,c),[18] and we suggest that the $n_{Se} \rightarrow \pi^*_{C=O}$ interactions expressed in the 2-arylselenocyclohexanones are a manisfestation of a generalized exo-anomeric effect.

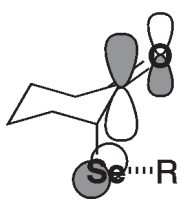


Fig. 4. Stabilizing $n_{Se} \rightarrow \pi^*_{C=O}$ orbital interaction associated with the generalized *exo*-anomeric effect in 2-arylselenocyclohexanones.

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