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Optical Rotatory Dispersion Studies. 138.[1] Synthesis and Conformational Analysis of β-Heteroatom-Substituted Cyclohexanones

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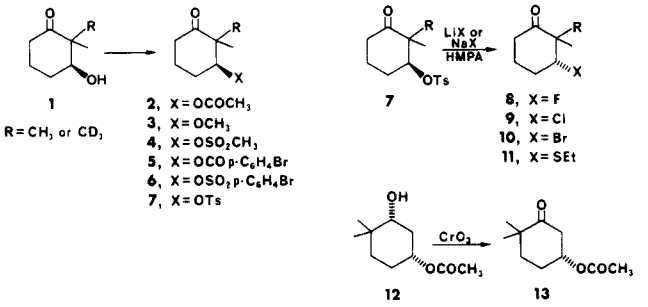
Circular dichroism and proton magnetic resonance spectroscopy were used in the conformational analysis of a series of β-heteroatom-substituted cyclohexanones. It was found that the axial population of the substituted ketone relative to that of the monosubstituted cyclohexanone is enhanced for the more highly electronegative substituents oxygen and fluorine and decreased for the less electronegative substituents chlorine, bromine, and sulfur. Possible mechanisms underlying this behavior, including electrostatic and dipole–dipole interactions as well as through-space and through-bond orbital interactions, are briefly discussed.

The concept of steric size in conformational analysis has frequently been found inadequate in explaining the conformational behavior of systems containing heteroatoms and/or unsaturation.[2] Well-known examples include the anomeric[3] and gauche[4,6] effects and the halo ketone effect.[5] These "anomalous" effects are often explained by electrostatic or dipole–dipole interactions or by interactions of orbitals, particularly lone-pair orbitals in systems containing heteroatoms. The orientation of the functional groups is usually crucial in stabilizing or destabilizing interactions and thus determines the preferred conformation(s) of the system.

A preliminary circular dichroism study of a series of cyclohexanones with oxygen-based substituents in the β-position showed a significantly larger population of the axial conformer that is found in the monosubstituted cyclohexanones.[7] At this point no systematic study of the conformational behavior of β-heteroatom-substituted cyclohexanones had been described in the literature. The purpose of the present study was therefore to extend the range of heteroatom substitution in this series.

Scheme I



Both circular dichroism and proton NMR data were used to investigate the conformational equilibria of the β-heteroatom-substituted cyclohexanones shown in Schemes I and II. Compounds 1–13 are 2,2-dimethyl (or 2-methyl-2-trideuteriomethyl) -substituted because the ketol 1, available in high optical purity from previous work,[7] provided a convenient precursor for a number of differently substituted derivatives. Dimethyl substitution at C-2 has been used in CD studies at a "chiral probe" in order to investigate subtle conformational effects relating to other substituents in the molecule.[8] It does not play any specific role in the current investigation, however. Furthermore, there were a number of difficulties with the CD method (see below) which made it a generally less reliable technique than NMR in studying the conformational behavior of the compounds in question.

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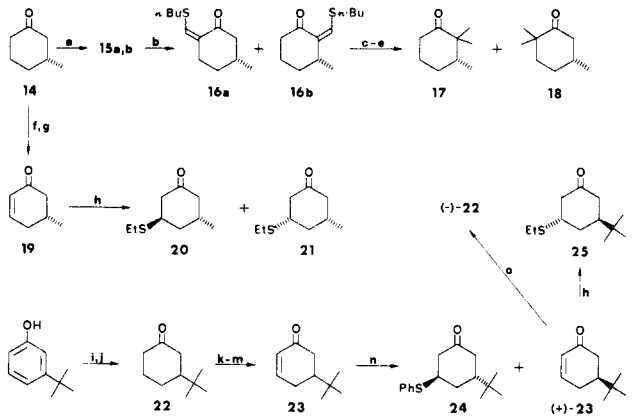
Scheme II[a]



[a] (a) KOMe/HCOOEt/ether; (b) *n*-BuSH/*p*-TsOH/benzene/Δ; (c) KO-*t*-Bu/*t*-BuOH; (d) excess CH_3I; (e) $KOH/H_2O/HOCH_2CH_2OH/\Delta$; (f) Br_2/H_2O; (g) Li_2CO_3/LiBr/DMF/Δ; (h) EtSH/Et_3N; (i) H_2/5% Rh on Al_2O_3/MeOH; (j) H_2CrO_4/acetone; (k) LDA/THF; (l) PhSeBr/THF; (m) HOOH/CH_2Cl_2; (n) 0.5 mol of PhSH/cinchonidine/benzene; (o) H_2/5% Rh on Al_2O_3/hexane.

Synthesis

The chiral ketol **1** was obtained via microbial reduction[9] of 2,2-dimethyl [or 2-methyl-2-(trideuteriomethyl)] -1,3-cyclohexanedione.[7] (The deuterated compound is racemic at C-2 and was used because of its availability. The substitution of CD_3 for CH_3 will have only a negligible effect on the conformational behavior of the molecule.[10]) The optical purity of **1** was determined to be >95% by ^{19}F NMR spectroscopy of its (+)-MTPA ester.[7,11] The conversion of the ketol to its derivatives **2–6** (with retention of sterochemistry at C-3) has been previously described.[7] The 5-acetoxy ketone **13** was prepared by CrO_3 oxidation of the corresponding optically active (ee >95%) alcohol **12**.[12]

The tosylate **7**, obtained from **1** via standard procedures, was converted to the halide and sulfide derivatives **8–11** with overall inversion at C-3 by heating with the appropriate nucleophile in HMPA. The desired substitution products were isolated by preparative TLC or by column chromatography on silica gel. In all cases yields were modest due to competing elimination.

The bromo compound **10**, though obtained optical active, was found to racemize completely when subjected to the reaction conditions (heating with LiBr at 65 °C in HMPA) for 2.5 h. Its optical purity was determined to be <5% by NMR analysis of the mixture of diastereomeric ketals formed by reaction with (2*R*,3*R*)-(−)-butanediol.[13] The signals arising from the proton geminal to bromine are fairly well resolved in the 300-MHz NMR spectrum, as are those assigned to the methyl groups on the dioxolane ring. The latter, however, are more accurately integrable. The low optical purity is consistent with the weak CD signal arising from the ketone **10** (see Experimental Section.) The optical purity of the chloro ketone **9** was determined to be ~87% by the same technique, indicating a loss in ee during displacement reaction of only ~7%. Since only a small amount of racemization took place during the chlorination as compared to the bromination, it was assumed that the fluoride ion would not be a good enough nucleophile or leaving group to lead to any significant racemization in the preparation of **8**. The keto sulfide **11** was found to be configurationally stable under the reaction conditions; reactions performed using varying excesses (15:1; 20:1) of ethyl mercaptide ion yielded products of similar (within 5%) optical purity. Displacement reactions with ethyl mercaptide ion have previously been reported to proceed with 100% inversion.[14]

The methyl analogues **17** and **18** were prepared by selective alkylation of (+)-3-methylcyclohexanone (prepared from (+)-pulegone,[15] >95% ee) according to the method of Ireland and Marshall.[16] Base-catalyzed condensation of **14** with ethyl formate,[17] followed by reaction with *n*-butanethiol, gave a mixture of **16a** and **16b** in a ratio of approximately 4:1. Alkylation of the mixture with a large excess of iodomethane and subsequent hydrolytic removal of the blocking group gave a mixture of mono-, di-, and trimethylated cyclohexanones. The desired trimethyl compounds were isolated, in a ratio of approximately 1:1, by preparative GC on 20% OV-101. The difference in the ratios of **16a** to **16b** and **17** to **18** could be due to more rapid formation of the less hindered 2,2,5-isomer in the alkylation step. When this step was carried out twice on the same material, the ratio of **17** to **18** was approximately 4:1, as expected.

The optically active *trans*- and *cis*-3-(ethylthio)-5-methylcyclohexanones **20** and **21** were also prepared from **14** via α-bromination, dehydrobromination, and base-catalyzed addition of ethanethiol. The isomers (trans:cis ~10:1) were separated by preparative GC on 20% Carbowax.

Kinetic resolution of 5-*tert*-butyl-2-cyclohexen-1-one (**23**) by the method of Wynberg and Hiemstra[18] yielded optically active **23**. The racemic enone was prepared from *m*-*tert*-butylphenol by catalytic hydrogenation, oxidation, phenylselenylation, and oxidative elimination of the selenide.[19] Cinchonidine-catalyzed addition of 40–50 mol % of thiophenol in benzene gave (+)-**23**, the addition product **24**, and a small amount of cis addition product. The optically active enone (+)-**23** was easily isolated by HPLC or by preparative TLC on silica gel. Its optical purity and absolute configuration were determined by conversion to the known[20,21] ketone (−)-**22**. Enantiomeric excesses of 20% and 29% were obtained from reactions employing a thiol/enone ratio of 0.5 and 0.4, respectively. These results correlate well with those of Hiemstra for the same system[22] (23% ee from a 0.5:1.0 thiol:enone ratio, assuming that his value of $[\alpha]^{21}_{578}$ can be compared with our value of $[\alpha]^{20}_{D}$).

The optically active enone (+)-**23** was then converted to **25** by base-catalyzed addition of ethanethiol. The desired trans isomer was separated from approximately 5% cis isomer by preparative GC on 20% OV-101. A substantial amount of elimination back to enone always oc-

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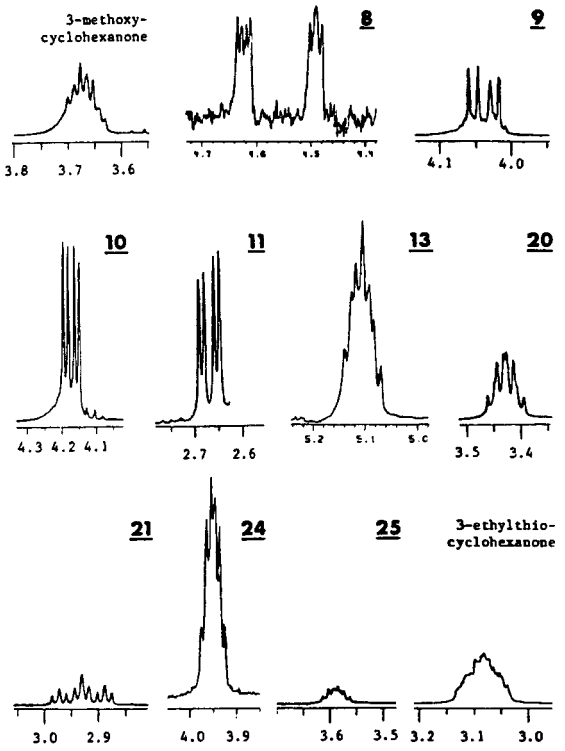

Figure 1. Partial ^1H NMR spectra (proton geminal to heteroatom) of a selection of β-heteroatom-substituted cyclohexanones (see Table I for bandwidths and estimated conformer populations).

curred during preparative GC purification of the β-keto sulfides, but sufficient quantities of the sulfides were still easily obtained.

Racemic 3-(ethylthio)cyclohexanone was prepared similarly from 2-cyclohexen-1-one. Racemic 3-methoxycyclohexanone was prepared from the enone and methanol according to the procedure of Lambert and Clikeman.[23]

Results

NMR Results. The NMR spectra of the β-heteroatom-substituted cyclohexanones in this work always give a well-isolated signal for the proton geminal to the β-substituent (see Figure 1). The correlation between coupling constant and dihedral angle for vicinal protons is well-known.[24] Direct quantitative comparison cannot be made between the coupling constants for different compounds, however, since J is known to vary (i.e., decrease) with the increasing electronegativity of the geminal substituent.[25] Therefore, in as many cases as possible, values of $W_{H\text{-}ax}$ and $W_{H\text{-}eq}$ (bandwidths of axial and equatorial protons, respectively, geminal to the heteroatom X) were obtained from the literature[26-30] or model compounds, anoted in Table I. Most of the cited compounds

Table I. NMR Bandwidths and Corresponding Conformational Preferences

compd, substituent	$W_{obsd,Hx}$, Hz	$W_{H\text{-}ax}$	$W_{H\text{-}eq}$	% X-ax[l]
1, (3*S*)-OH	~10	14.8[a]	6.0[a]	~55
2, (3*S*)-OAc	~12	15.5[b,f]	5.6[b,f]	~35
13, (5*R*)-OAc	21.0	31.0[b]	11.1[b]	50
3-methoxycyclohexanone	20.9	31.0[b]	11.1[b,g]	51
		30.0[c]	12.5[c,g]	52
8, (3*R*)-F	8.5	≲15.7[d,h]	5.8[d,h]	≲73[h]
9, (3*R*)-Cl	12.8	15.7[d]	5.8[d]	29
10, (3*R*)-Br	14.0	≳15.7[d,i]	5.8[d,i]	≳17[i]
11, (3*R*)-SEt	15.0	16.5[e,f]	7.8[e,f]	17
3-(ethylthio)cyclohexanone	30.0	33.0[e]	15.5[e,g]	17
20, see text	20.1	33.0[e]	15.5[e]	75
17, (3*R*)-CH_3	J_{trans} = 11.0[j]	J_{aa} = 13.2[k]	J_{ee} = 1.2[k]	18
18, (5*R*)-CH_3	J_{trans} = 11.5[j]			14

[a] Reference 26 (*cis*- and *trans*-2-*tert*-butyl-4-hydroxycyclohexanones). [b] Reference 27 (4-(benzoyloxy)-2,6-dimethylcyclohexanones). [c] Reference 28 (*cis*- and *trans*-3-methoxy-5-*tert*-butylcyclohexanones). [d] Reference 29 (4-chloro-2,6-dimethylcyclohexanones). [e] This work, compounds **21** and **25**. (Similar bandwidths were reported for a series of related compounds in ref 22.) [f] Obtained by dividing W_H for the compound immediately following by two. [g] May be slightly increased by W coupling. [h] Actual value may be less due to greater electronegativity of F vs. Cl. [i] Actual value may be greater due to greater electronegativity of Cl vs. Br. [j] Based on coupling between trans protons on C-5 and C-6. [k] Reference 30 (4-*tert*-butylcyclohexanone). [l] $CDCl_3$, room temperature.

are stereochemically rigid (by virtue of cis-2,6-dimethyl-substitution) 4-heteroatom-substituted cyclohexanones; coupling constants and/or bandwidths for the corresponding 3-heteroatom-substitued compounds were generally unavailable. While the geometry at C-4 will not be exactly the same as that at C-3 due to the slight flattening of the ring at the carbonyl carbon,[31] a detailed study of proton coupling in 4-*tert*-butylcyclohexanone showed that the calculated bandwidths (excluding J_{gem}) of the axial protons at C-3 and C-4 differed by less than 5% (that at C-3 being slightly greater).[30] Furthermore, estimates of percent axial OCH_3 in 3-methoxycyclohexanone based on 3- and 4-substituted reference compounds agree to within 1% (see Table I).

The following trend of decreasing axial preference (in $CDCl_3$ at 25 °C) emerges from the NMR results: F > OH ~ OCH_3 > OAc > Cl > Br ~ SEt > CH_3. The fact that **20** prefers the conformation with SEt axial at lower temperatures (see Table II) implies that the thioethyl group has a higher axial preference than the methyl group. The CD results for compounds **4–6** are described in ref 6; however, the NMR bandwidth data obtained for these compounds were rather imprecise and thus are not included in Table I. In general, bandwidths for compounds **4–7** were in the range of 10–13 Hz; their conformational preference should therefore be somewhat similar to that of the acetoxy ketone **2**.

CD Results. The circular dichroism data and the corresponding calculated values of percent axial conformational are presented in Table II. Values for the individual contributions to $[\theta]$ of the alkyl and heteroatom substituents were obtained from the literature.[32-34] As mentioned above, a number of difficulties arose in interpreting the CA data. Most of the reference values for the

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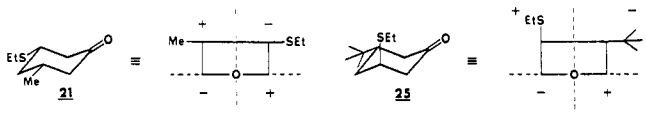
Table II. CD Data and Corresponding Conformational Preferences[a]

compd	substituent	solv	temp, °C	$[\theta]_{max}$	$[\theta]_{X\text{-ax,calcd}}$[b,c]	$[\theta]_{X\text{-eq,calcd}}$[b,c]	% X-az,calcd
1	(3*S*)-OH	EPA[d]	25	+240[e]	−3680[f]	+2660	38
			−190	+430[e]	−4740	+3720	35
		MeOH	25	−510	−4640	+2990	49
2	(3*S*)-OAc	4IPM[g]	25	−2330	−5690	+3680	64
			−30	−2600			67
			−80	−3090			72
			−130	−3940			81
			−190	−4050			83
		EPA	25	−2200	−6190	+3780	60
			−30	−2400			62
			−80	−2850			67
			−130	−3530			73
			−190	−3620			74
		MeOH	25	−2640	−6720	+4510	64
13	(5*R*)-OAc	4IPM	25	+610	+3310	−5330	69
			0	+560			68
			−50	+440			67
			−140	−750			53
			−190	−750			53
		EPA	25	+210[e]	+2690	−5100	68
			0	+160[e]			67
			−50	−510			59
			−100	−1350			48
			−150	−2220			37
			−190	−2320			36
		MeOH	25	−530	+3750	−5960	56
3	(3*S*)-OMe	isooctane	25	−630	−3810	(+)[h]	?
		MeOH	25	−2630	−5110	(+)	?
8	(3*R*)-F	4IPM	25	+460	+4230	−5130	60
			−100	+970			65
			−192	+1720			73
		EPA	25	+1100	+4330	−5070	66
			0	+1270			67
			−52	+1780			73
			−100	+2430			80
			−192	+3420			83
		MeOH	25	+2610	+5090	−6000	78
9	(3*R*)-Cl	4IPM	25	+6025	+5290	+9460	82[i]
			−190	+6150			79
		EPA	25	+5575	+5800	+9250	~100
			−190	+4895			~100
		MeOH	25	+7090	+6620	+5780	~100
11	(3*R*)-SEt	4IPM	25	+9950	+5820[j]	+11010[j]	20
			−190	+11000			~0
		EPA	25	+9800	+6560	+10270	24
			−190	+9400			31
		MeOH	25	+9400	+5760	+11070	23
20	see text	4IPM	25	+5130	+2820[j]	+14940[j]	81 (57)[k]
			−80	+4005			90 (75)
			−102	+3030			98 (90)
		EPA	25	+4660	+3200	+14850	87 (80)[l]
			−71	+3820			95 (92)
			−133	+3355			99 (98)
			−188	+3875			94 (93)
		MeOH	25	+4930	+2950	+14850	83 (80)
17	(3*R*)-Me	4IPM	25	−1570	+3935	−3000	21
			−56	−2120			13
			−117	−2365			9
			−153	−2695			4
		EPA	25	−1690	+3790	−2565	14
			−117	−2910			8
			−163	−3430			2
		MeOH	25	−3830	+4580	−3610	~0
18	(5*R*)-Me	4IPM	25	+2120	−5070	+6005	35
			−83	+2365			33
			−133	+2180			35
		EPA	25	+4560	−5100	+6320	15
			−130	+5320			9
		MeOH	25	+2615	−5895	+6870	33

[a] Compound **10** not included due to uncertain (very low) optical purity; all other compounds except **9** (ee ~87%) have ee ≥95%. [b] Values for alkyl group contributions taken from ref 32. All are derived from 4-*tert*-butylcyclohexanones except β-equatorial methyl, which is derived from a 4-isopropenylcyclohexanone. [c] Values for heteroatom contributions (except SEt) taken from ref 33 and 34. [d] EPA = 5:5:2 ether/isopentane/ethyl alcohol. [e] Very approximate due to weak and/or bissignate curve. [f] All reference values for EPA were actually measured in dioxane (EPA data unavailable). [g] 4IPM = 4:1 isopentane/methylcyclohexane. [h] No data were available for equatorial OMe, but the overall value of $[\theta]$ for this conformation will almost certainly be positive. [i] All % axial values for **9** differ substantially from NMR values (Table I). [j] Approximate values for SEt contributions taken from ref 22; values obtained from **21** and **25** (Table III) give >100% axial SEt for **11** in all solvents. [k] Values in parentheses were calculated with data from compounds **21** and **25** (Table III). [l] Low-temperature behavior of **20** in EPA suggests the possibility of more than two contributing conformations (see text).

Table III. Calculated Octant Contributions of the β-Ethylthio Group (Derived from Compounds 21 and 25)[a]



solv[i]	$[R]_{total}^{obsd\ b}$	$[R]_{eq\text{-}CH_3}^{lit.}$	$[R]_{eq\text{-}SEt}^{calcd\ a}$
	Compound **21**		
4IPM			
rt	−7.76	+1.51[c]	−9.27
−110 °C	−6.53		−8.04
EPA			
rt	−9.47	+1.89[c]	−11.36
−145 °C	−7.82		−9.71
MeOH	−6.09	+1.64[c]	−7.73
	Compound **25**		
4IPM			
rt	−3.32	−3.19[e]	−0.13[g]
−78 °C	−3.18[d]		
−123 °C	−3.42[d]		
−178 °C	−4.12		−0.93
EPA			
rt	−4.23	−3.16[f]	−1.07
−66 °C	−4.59[d]		
−125 °C	−3.22[d]		
−188 °C	−4.73		−1.57
MeOH	−1.80	−3.49[f]	+1.69[h]

[a] These calculated values give unsatisfactory results for % axial SEt in **11**; see text for discussion. [b] [R] may be converted to [θ] by the approximate relation [θ] = 994[R]. [c] Reference 32. [d] These intermediate-temperature values were not used in calculations but are included to show the low-temperature behavior of **25**. [e] This work. [f] Reference 21. [g] Dissignate ("antioctant") contribution. [h] Consignate contribution. [i] Rt = room temperature.

heteroatom substituents were taken from appropriately substituted adamantanones, whose geometry will not be exactly the same as that of the corresponding cyclohexanones.[35] Methyl-group contributions have, in fact, been found to differ substantially for adamantanones[34,36] and 4-alkyl-substituted cyclohexanones.[32,37] The related problems that arise for the ethylthio series (see below) are likely to apply to other substituents as well. Also, data were not always available for the desired solvent systems, especially in the case of EPA, where values obtained in dioxane were substituted. A further complication was the weak and/or bissignate nature of some of the CD curves (see Table II), which made it difficult to obtain reliable values of $[\theta]_{max}$ or [R].

A variable amount of uncertainty sometimes arose from the fact that the overall calculated values of [θ] or [R] for the two chair conformations were of the same sign and similar in magnitude as well; **9** and **11** are most notable in this respect. Finally, the optical purity of **10** was so low (probably less than 5%) as to introduce an unaccetpable amount of error into any calculations.

The case of the ethylthio ketone **11** requires special comment. Values for the contribution of the thioethyl group in the axial and equatorial positions were unavailable in the literature and thus were obtained independently from the CD spectra of compounds **21** and **25** (Table III). The values thus obtained, however, give unreasonable (greater than 100%) estimates of percent axial SEt in **11**. It is therefore likely that **21** and **25** are not suitable models for this purpose. The contribution of β-axial SEt in **25** is seen to be very sensitive to changes in solvent (Table III). The β-axial position in cyclohexanones almost regularly gives rise to fairly weak, dissignate ("antioctant") contributions.[37,38] This phenomenon is commonly attributed to the fact that the substituent is near a nodal plane[39] (the curved third surface of the octant rule[40]), although a discussion by Snatzke[41] attributes the apparent change in sign of the rotational strength associated with this transition ($n \rightarrow \pi^*$) to through-space interactions between the orbitals of the β-substituent and the carbonyl group. In any case, the large change in $[R]_{SEt,\beta\text{-}ax}$ with solvent could be due to changes in the geometry of the molecule or to interactions with the solvent or both. The high sensitivity of the rotational strength of this compound to such factors renders its applicability as a stereochemically rigid model rather tenuous.

The use of **21** may also be problematic, since cyclohexanones with two 1,3-diequatorial groups (specifically, *cis*-2,4-dimethyl- and *cis*-2-methyl-4-*tert*-butylcyclohexanone) are believed to assume alternate geometries such as twist conformations,[42] which have large rotational strengths and thus can lead to large errors even when present in small amounts.[32,43] Compound **25**, although it does not possess this specific substitution pattern, goes through a maximum in the rotational strength as the temperature is lowered (see table III). Compound **20** exhibits similar low-temperature behavior. Such behavior suggests that more than two conformations may be present in significant quantities. (since the CD spectra of **21** were measured at only two temperatures, such a trend could not be observed.)

The approximate values quoted by Hiemstra for β-axial and β-equatorial SAr ([R] = 15.6 consignate and 1.33 dissignate, respectively) in a study of asymmetric thiol addition to enones[22] give results that are much more in accord with the NMR results for **11** (Tables I and II). These values were derived from the observed ellipticities of several optical active β-(arylthio)cyclohexanones with varying methyl substitution. The difficulties encountered with **11**, on the whole, serve to illustrate the possible dangers involved in applying "standard" CD values to differently substituted systems, particularly for quantitative work and for sensitive (e.g., β-axial substituted) systems.

The NMR bandwidth method, in contrast to the CD method, gives satisfactory results when **21** and **25** are used as model compounds. The values for $W_{H\text{-}ax}$ and $W_{H\text{-}eq}$ agree well with the corresponding values cited by Hiemstra[22] (34 and 14 Hz, respectively) for axial and equatorial β-(arylthio)cyclohexanones, as do the calculated conformational preferences of related mobile systems. (The reported *A* values for SCH_3 and SPh are 0.7 and 0.8, respectively; one may therefore expect, to a first approximation, similar conformational behavior.) The better

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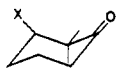
Table IV. Conformational Preferences (% Axial X at Room Temperature) for Various Six-Membered Ring Systems

				
$X^{a,b}$	$CDCl_3{}^a$	$CHFCl_2{}^{c,e}$	$CF_2Cl_2{}^{c,e}$	$CDCl_3{}^{d,f}$
OH	55	23	13	29[g]
OCH_3	51	45	20	27[h]
OAc	35 (50)[i]	34	26	27[g]
F	≲73			44
Cl	29			31
Br	≳17			34
SEt	17	25	11	23[h,j]
CH_3	18 (14)[i]	23	20	5

[a] This work (NMR values, Table I). [b] Compound is 2,2-dimethyl substituted for all X but OCH_3. [c] Reference 23. [d] Reference 44 (calculated from A values). [e] Calculated from low-temperature values via $\Delta G = -RT \ln K$. [f] Unless otherwise noted. [g] This value was selected as the "best value" (in a nonpolar solvent for X = OH) from a large collection of results. [h] Carbon tetrachloride. [i] For the 2,2-dimethyl-5-X cyclohexanone. [j] For SCH_3.

consistency of the NMR results suggests that, at least in the case of β-axial substitution, this method allows more latitude for small changes in geometry than does the CD method.

Discussion

Table IV compares the values for conformational preference obtained in this work (NMR values) with those obtained previously for β-substituted *exo*-methylenecyclohexanes[23] and the monosubstituted cyclohexanes.[44] The latter are derived from a table of A values (the free energy difference between the axial and equatorial conformations) for the various substituents, in which values based on NMR studies in $CDCl_3$ are usually very close to those chosen as "best values" for the respective substituents. Comparison of the current system with the monosubstituted cyclohexanes shows that in the case of fluoro, hydroxy, methoxy, acetoxy, and methyl substitution, the 3-keto group enhances the axial preference of the substituent, the effect being greater for the more electronegative substituents. The chloro-, bromo-, and ethylthio-substituted ketones, on the other hand, show a reduction in axial preference of the substituent as compared to the cyclohexanes.

The stabilization of the β-axial conformation in cyclohexanones due to the removal of one 1,3-diaxial interaction, known as the "3-alkyl ketone effect",[45-47] is probably not as important for the heteroatom-substituted systems as it is for the methyl-substituted system, due to longer bond lengths (in the case of bromine, chlorine, and sulfur) or smaller van der Waals radii (in the case of fluorine and oxygen) of the groups in question as compared to the methyl group. The clear correlation of axial preference with electronegativity of the substituent, however, suggests that electrostatic or dipole–dipole interactions may be important in the axial–equatorial equilibrium. The possible existence of an electrostatic attraction between the β-substituent and the partially positive center at the carbonyl carbon is given credence by the decreased axial preference of the acetoxy group relative to the hydroxy and methoxy groups. This effect could be due to the fact that the oxygen bonded to the ring in the acetoxy group will have a partial positive charge as a result of ester resonance.

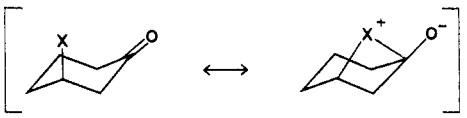


Figure 2. Resonance structures depicting electron donation from axial substituent into carbonyl bond.

Lambert and Taba, in their analysis of 3-methoxy-*exo*-methylenecyclohexane, claim that the equatorial isomer is slightly favored by dipole–dipole interactions.[48] The large decrease in axial conformation with reduced solvent polarity (Table IV) tends to support this conclusion. One should note, however, that a similar solvent effect is observed for cyclohexanol and methoxycyclohexane.[44] It is therefore possible that the exo double bond, with its very weak dipole, actually has little effect on overall dipold–dipole interactions in this system. Furthermore, when the exo methylene group is replaced by dichloromethylene, thus creating a much stronger double bond dipole, there is an increase in axial conformation,which parallels the results seen for the ketone. The authors attribute this effect to increased through-space interaction between the heteroatom substituent and the double bond; chlorine substitution lowers the LUMO of the double bond. The carbonyl group, however, has a higher lying π* orbital than the unsubstituted olefin;[55] thus the same reasoning cannot be applied to the ketone system.

Lambert and Taba also point out that "the center of the C—O dipole, the center of the $C{=}X_2$ dipole, and the role of oxygen and halogen lone pairs are not easily specified".[48] The large variety of substituents in the present study also makes exact analysis of dipole–dipole interactions difficult, since group dipoles will be of different magnitudes and often point in different directions.[49] In many cases, restricted rotation will also play a role in determining the overall group dipole moment. Therefore, while it is likely that dipole–dipole interactions paly an important role in the conformational equilibria of β-heteroatom-substituted cyclohexanones, possibly stabilizing the axial conformation,[50] it is difficult to accurately assess the specific interactions at this level.

Orbital interactions could also have important bearing on the conformational equilibria in question. Numerous studies[5,51] have dealt with interactions between the orbitals of the heteroatom substituent and the carbonyl group in heteroatom-substituted ketones. Although the majority deal with α-substituted systems, several[51a-c] concern β-substituted systems as well.

The donation of electron density into the π^*_{CO} orbital by a β-axial substituent, as described in ref 41, may be represented by a resonance structure[52] as shown in Figure 2. There are some difficulties, however, in involving this mechanism as a stabilizing influence for the axial conformation in the current system. The high energy of the π^*_{CO} orbital was mentioned previously. One would also

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(50) Molecular mechanics calculations by Allinger (personal communication) indicate that 3-hydroxycyclohexanone should favor the axial conformation by ca. 0.15 kcal/mol when dipole–dipole interactions are considered. This value corresponds to an axial population of approximately 56% at room temperature, which fits well with the NMR data for 1.
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(52) Allinger, N. L., personal communication.

expect the second-row and lower elements (chlorine, bromine, and sulfur) to be more effective in electron donation than the first-row elements (fluorine and oxygen) due to greater bond lengths, greater polarizability and nucleophilicity, and, in most cases, higher lying lone-pair orbitals. The opposite trend is apparent here. Furthermore, the distance between these groups (for a C–O bond) has been estimated at approximately 3.0 Å,[23] while Hoffmann[53] contends that through-space interaction should be negligible beyond about 2.5Å.

The β-equatorial position (with respect to the carbonyl orbitals, particularly π^*_{CO}) resembles a trans arrangement of groups while the β-axial position resembles a gauche arrangement,[48] the former being the more effective "coupling path" for through-bond orbital interaction.[53,54] "Indirect" or through-bond interactions have been reported to occur through as many as five bonds[54c] and depend strongly on the path connecting the orbitals.[53,54] Therefore, it is possible that some through-bond stabilizing interaction between the heteroatom and the carbonyl group exists in the equatorial conformation. The interaction between the lone-pair orbitals and π^*_{CO} should be greatest for the less electronegative substituents (Cl, Br, and S) with higher lone-pair orbital energies[55–57] since these will be closest in energy to the π^*_{CO} orbital. As has been seen, these substituents favor the equatorial conformation.

In light of the above discussion, one may propose dipolar or electrostatic interactions as stabilizing influences for highly polar substituents in the axial position, with stabilizing orbital interactions in the equatorial position becoming a factor for less polar, more highly polarizable substituents with higher lone-pair orbital energies. It is apparent, however, that no single mechanism can account for all the experimental results, and at present we can only speculate as to what effects are dominant in this system.

Experimental Section

Circular dichroism spectra were measured on a JASCO J-40 instrument, using a previously described[58] cell for the low-temperature measurements. Absorption spectra were measured with a Hewlett-Packard HP 8450 A UV–vis spectrophotometer. Optical rotations were measured on a Rudolf Autopol III polarimeter in a thermostated 10-cm cell. ^{1}H NMR spectra were obtained on a Varian T-60, a 100-MHz Varian XL-100, or a 300-MHz Nicolet NT 300 WB spectrometer and are given as δ values with $CDCl_3$ as solvent and residual $CHCl_3$ as internal standard. Mass spectra were obtained on a Ribermag R10-10B, a Varian MAT-44, or a finnigan MAT-711 high-resolution mass spectrometer. Preparative gas chromatography was performed with a Varian Aerograph Series 2700 gas chromatograph on a 10-ft columnm of 20% OV-101 on Supelcoport (column A) or 20% Carbowax 20M on 80/100 Chromosorb W (column B).

(3*S*)-2-Methyl-2-(trideuteriomethyl)-3-(tosyloxy)cyclohexanone (7). A stirred solution of 1.0 g (6.9 mmol) of (1*S*)-2-methyl-2-(trideuteriomethyl)cyclohexanol (1, ee >95%[6]) in 18 mL dry pyridine was cooled to 0 °C under N_2. *p*-Toluenesulfonyl chloride (3.0 g, 16 mmol) was added, and the solution was stirred for 3 h at room temperature. The reaction mixture was then poured onto ice water with stirring. The precipitated white solid was filtered and washed with 5% HCl, water, saturated $NaHCO_3$ solution, and water. It was then dried under vacuum to give 0.955 g (46%) of 7: ^{1}H NMR (for protic 7, prepared by the same procedure) 1.015 (s, 3 H), 1.048 (s, 3 H), 1.694 (dddd, J = 13.7, 4.3 (twice), 2.4 Hz, 1 H), 2.06 (m, 3 H), 2.395 (t, J = 6.8 Hz, 2 H), 2.448 (s, 3 H), 4.578 (dd, J = 6.9, 3.5 Hz, 1 H), 7.334 (d, J = 8.0 Hz, 2 H), 7.775 (d, J = 8.3 Hz, 2 H); IR (CCl_4) 1715, 1545, 1190, 1180 cm^{-1}.

(3R)-2,2-Dimethyl-3-fluorocyclohexanone (8). A solution of 7 (150 mg, 5 mmol) and 440 mg of $(n\text{-Bu})_4NF$ in 10 mL of dry THF was stirred and heated at 70–75 °C under anhydrous conditions for 28 h. The reaction mixture was then treated with 50 mL of water and extracted with ether. The ether extracts were washed with water and dried ($MgSO_4$); removal of solvent yielded 86 mg of a yellow oil. GC analysis showed peaks corresponding to 2,2-dimethyl-3-cyclohexen-1-one, 8, and 7 in a ratio of approximately 7:2:1. A mixture of the olefin and 8 was obtained by chromatography of the crude product on 20 g of silica gel, eluting with CH_2Cl_2. Pure 8 was isolated by preparative GC (column A) as a colorless liquid: ^{1}H NMR 1.17 (s, 6 H), 1.77 (m, 1 H), 2.05 (m, 3 H), 2.42 (m, 2 H), 4.49, 4.63 (dd, m, J_{HF} = 48 Hz, J = 6 Hz, J = 2.5 Hz, 1 H); MS, m/s (relative intensity) 144.09460 (25.3, M^+), 82.07895 (63.1, C_6H_{10}), 73.04598 (21.4, C_4H_6F), 69.07071 (100, C_5H_9), 59.02968 (9.25, C_3H_4F).

(3*R*)-2-Methyl-2-(trideuteriomethyl)-3-chlorocyclohexanone (9). Anhydrous LiCl (400 mg, 0.105 mol) was added to a solution of 100 mg (0.33 mol) of 7 in 10 mL dry HMPA. The mixture was stirred and heated at 85 °C under anhydrous conditions for 3 h and worked up as described for 8 above. The crude product (49 mg) was chromatographe over silica gel, eluting with CH_2Cl_2. Two overlapping spots were collected together and characterized by NMR as 9 and the corresponding elimination product. This mixture was rechromatographed, and the pure chloro compound (21 mg, 42%) was isolated as a colorless liquid: ^{1}H NMR 1.23 (s, 3 H), 1.25 (s, 3 H), 1.70 (m, 1 H), 2.12 (m, 2 H), 2.27 (m, 1 H), 2.38 (ddd, J = 13, 5.2, 3.8 Hz, 1 H), 2.51 (ddd, J = 13, 8.8, 6.0 Hz, 1 H), 4.04 (dd, J = 8.8, 3.8 Hz, 1 H); MS, m/z (relative intensity) 165.08167 ($M^+/^{37}Cl$, 3.59), 163.08344 ($M^+/^{35}Cl$, 11.12), 85.09982 ($C_6H_{11}D$, 100), 72.09133 ($C_5H_8D_2$, 28.88).

(3*R*)-2,2-Dimethyl-3-bromocyclohexanone (10). The compound was prepared as described for 9 above, by using anhydrous LiBr in place of LiCl and heating at 65 °C for 3 h. (The use of shorter reaction times and lower temperatures and/or lower concentrations of LiBr did not lead to any significant improvement in the optical purity of the product.) The product was isolated by preparative TLC on silica gel as colorless, low-melting crystals in 32% yield: ^{1}H NMR 1.254 (s, 3 H), 1.258 (s, 3 H), 1.688 (dddd, J = 15.2 (twice), 10.0, 4.8 Hz, 1 H), 2.12 (m, 1 H), 2.249 (ddd, J = 14.1, 10.0, 4.2 Hz, 1 H), 2.342 (dd, J = 9.3, 4.7 Hz, 1 H), 2.404 (dd, J = 9.4, 6.5 Hz, 1 H), 2.549 (ddd, J = 14.7, 11.0, 6.2 Hz, 1 H), 4.171 (dd, J = 9.7, 4.2 Hz, 1 H); MS, m/z (relative intensity) 209 ($M^+/^{81}Br$, 5.1), 207 ($M^+/^{79}Br$, 5.5), 128 (100), 100 (30.7), 58 (18.5), 57 (16.9), 56 (19.7), 55 (36.2); CD (MeOH) $[R]_{obsd}$ = +0.194, $[R]_{calcd}$ (equatorial Br, 100% ee) = +18.4, $[R]_{calcd}$ (axial Br, 100% ee) = +7.2.[32,33]

Ketalization of 10 with (−)-(2*R*,3*R*)-2,3-Butanediol. A solution of 8.3 mg (0.0405 mmol) of 10, 13 mg (0.144 mmol) of the title diol, and a few crystals of *p*-TsOH in 25 mL of benzene was reflected in a Dean-Stark apparatus for 6 h. The solution was then washed with saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. Removal of solvent yielded 8.0 mg (71%) of a colorless oil: ^{1}H NMR (two diastereomers in nearly equal amounts) 1.061 (s, 6 H), 1.091 (s, 3 H), 1.127 (s, 3 H), 1.197 (d, J = 5.9 Hz, 3 H), 1.206 (d, J = 5.9 Hz, 3 H), 1.239 (d, J = 5.9 Hz, 3 H), 1.245 (d, J = 5.9 Hz, 3 H), 1.58 (m, 6 H), 1.76 (m, 2 H), 2.04 (m, 4 H), 3.60 (m, 4 H), 4.271 (dd, J = 8.4, 4.6 Hz, 1 H), 4.312 (dd, J = 8.8, 4.7 Hz, 1 H). The intensities of peaks assigned to the two isomers are nearly identical; this observation and the very low rotational strength of 10 (see above) indicate a very low ee, probably <5%.

Ketalization of 9 with (−)-(2*R*,3*R*)-2,3-Butanediol. The chloro ketal was obtained similarly from 9-d_3 as a colorless oil:

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^{1}H NMR (major isomer) 1.046 (s, 3 H), 1.194 (d, J = 5.9 Hz, 3 H), 1.244 (d, J = 5.9 Hz, 3 H), 1.5–2.0 (series of m, 6 H), 3.59 (m, 1 H), 3.62 (m, 1 H), 4.093 (dd, J = 12.1, 4.4 Hz, 1 H). Corresponding signals for the minor isomer appear most clearly at δ 1.082 (s), 1.205 (d, J = 5.8 Hz), 1.239 (d, J = 5.8 Hz), and 4.06 (dd, J = 12, 4.5 Hz). Relative intensities indicate an ee of approximately 87%.

(3*R*)-2-Methyl-2-(trideuteriomethyl)-3-(ethylthio)cyclohexanone (11). A solution of 200 mg (0.67 mmol) of **7** in 5 mL of dry HMPA was cooled in an ice bath under N_2. This mixture was added to a cold solution of 900 mg of NaSEt (10 mmol) in 20 mL of dry HMPA (prepared from 400 mg of sodium and excess EtSH in dry ether, which was subsequently removed and replaced with HMPA). After the addition, the yellow solution was stored in the freezer (−15 °C) for 14 h. It was then treated with 100 mL of water and extracted three times with ether. The ether extracts were washed three times with 5% aqueous NaOH and four times with water and dried over $MgSO_4$. The solvent was then removed under vacuum and the residue (140 mg) chromatographed over silica gel to give **11** contaminated with minor impurities. The product was isolated by preparative GC (column A) in 20% yield: ^{1}H NMR 1.151 (s, 3 H), 1.248 (*t*, J = 12.8 Hz, 3 H), 1.62 (m, 1 H), 1.94 (dddd, J = 20.8, 9.5, 3.3, 1.3 Hz, 1 Hz), 2.09 (m, 2 H), 2.32 (d of m, J = 11.5 Hz, 1 H), 2.53 (m, 1 H), 2.57 (d of q, J = 6.7, 2.8 Hz, 2 H), 2.67 (ddd, J = 11.1, 3.8 Hz, 1 H); MS, m/z (relative intensity 189.12673 (M^+, 76.36), 128.1151 ($C_8H_{10}OD_3$, 54.51), 101.04231 (C_5H_9S, 100), 100.1191 ($C_7H_{10}D_3$, 24.14), 99.11991 ($C_7H_9D_3$, 28.64), 72.08969 ($C_5H_6D_3$, 25.3); IR 1708, 1250 cm^{-1}.

(5*R*)-2,2-Dimethyl-5-acetoxycyclohexanone (13). Jones reagent[59] (0.1 mL) was added to a cooled (0 °C) solution of 37.2 mg (0.26 mmol) of **1** in 2 mL of ether, and the mixture was stirred for 2 h. The reaction mixture was then treated with water and extracted twice with ether. The ether extracts were washed with water (7 × 10 mL), dried over $MgSO_4$, and concntrated to a white solid, which was purified by column chromatography over silica gel to give 19 mg (52%) of crystalline **13**: mp 56–75 °C; ^{1}H NMR 1.065 (s, 3 H), 1.072 (s, 3 H), 1.53 (ddd, J = 14, 4.8, 4.0 Hz, 1 H), 1.78 (ddd, J = 14, 10, 3.2 Hz 1 H), 1.82 (m, 1 H), 1.956 (s, 3 H), 2.46 (ddd, J = 14.9, 6.6, 1.1 Hz, 1 Hz), 2.50 (ddd, J = 14.9, 4.4, 0.8 Hz, 1 H), 5.11 (ddd, J = 10.6, 6.6, 4.2 Hz, 1 H); MS, m/z (relative intensity) 184.10994 (M^+, 15.54), 124.08818 ($C_8H_{12}O$, 46.85), 95.08644 (C_7H_{11}, 30.94), 81.07117 (C_6H_9, 32.58), 68.02606 (C_4H_4O, 53.25), 56.06268 (C_4H_8, 33.98), 43.01847 (C_2H_3O, 100); IR 1747, 1720, 1550, 1243 cm^{-1}.

Formylation of (+)-(3*R*)-3-Methylcyclohexanone (14). To a stirred suspension of 25 g (0.36 mol) of KOMe in 400 mL of dry ether at 0 °C under N_2 were added 20.0 g (0.178 mol) of **14** (obtained from the retro-aldol reaction of (+)-pulegone; ee >95%) and 13.3 g (0.18 mol) of ethyl formate (purified by stirring sequentially with anhydrous K_2CO_3 and $MgSO_4$ and then distilling). The mixture was allowed to come to room temperature and stirred for 72 h. It was then poured into ice water, and the separated organic layer was washed with cold 5% aqueous NaOH. The combined aqueous phase was washed with ether, acidified with 5% HCl, and again extracted with ether. The latter extracts were dried over $MgSO_4$ and concentrated to an orange-red oil, which was distilled under reduced pressure to give 13.0 g (52%) of a colorless oil, bp 72.5–73.5 °C (3.6 mm). NMR analysis indicated a 4:1 ratio of regioisomers, with the less hindered predominant: ^{1}H NMR (both isomers) 1.01 (d, J = 6 Hz), 1.13 (d, J = 7 Hz) [total 3 H], 1.2–1.8 (overlapping m, 7 H), 8.65 (br s, 1 H).

(5*R*)-2-[(*n*-Butylthio)methylene]-5-methylcyclohexanone (16a) and (3*R*)-[(*n*-Butylthio)methylene]-3-methylcyclohexanone (16b). A solution of 6.5 g (46 mmol) of the hydroxymethylene ketone mixture (above), 5.75 mL (54 mmol) of *n*-BuSH, and a spatula tip of *p*-toluenesulfonic acid in 100 mL of benzene was refluxed under N_2 in a Dean–Stark apparatus for 18 h. The solution was cooled, washed with saturated $NaHCO_3$ solution and water, filtered through $MgSO_4$, and concentrated to a dark brown oil. The oil was distilled under reduced pressure to give 0.55 g of pale yellow liquid, bp 156–158 °C (4.5 mm), followed by 6.80 g (69%) of pale yellow liquid, bp 158–161 °C (4.5 mm): ^{1}H NMR (mixture of isomers) 0.83–1.03 (overlapping signals), 1.11 (d, J = 7 Hz), [total 6 H], 1.27–2.20 (overlapping signals, total 8 H), 2.50 (m, 3 H), 2.84 (t, J = 7 Hz, 2 H), 7.47 (s), 7.57 (t, J = 2 Hz) [total 1 H].

Methylation of Thioenol Ethers 16a,b. The thioenol ether mixture (above) (4.53 g, 16.6 mmol) was added dropwise via syringe to a stirred solution of 7.44 g (66.4 mmol) of potassium *tert*-butoxide in 125 mL of dry (distilled from CaO) *tert*-butyl alcohol. The resulting deep red solution was stirred at room temperature for 10 min and then cooled in an ice bath as 6.2 mL (0.1 mol) of CH_3I was added. The mixture was stirred at room temperature for 20 m and then refluxed for 2.5 h, during which time the color faded to a pale yellow. The mixture was cooled, 200 mL of water was added, and the organic layer was separated. The aqueous layer was saturated with NaCl and extracted with ether, and the combined organic fractions were dried over $MgSO_4$ and concentrated to 4.7 g of a dark greenish brown oil. Attempts to distill this material under reduced pressure led to extensive decomposition, so it was generally hydrolyzed without further purification. NMR analysis of a small sample of distilled material (pale orange liquid) showed an approximately 3:2 ratio of the precursors to **17** and **18**, respectively: ^{1}H NMR (distilled mixture; methyl assignments are tentative) 0.923 (t, J = 7.3 Hz, 6 H), 0.952 (d, J = 6.8 Hz, >3 H), 0.989 (s, >3 H), 1.090 (s, <3 H), 1.091 (d, J = 7.2 Hz, <3 H), 1.129 (s, <3 H), 1.144 (s, >3 H), 1.418 (q, J = 7.9 Hz, 4 H), 1.648 (d of q, J = 6.6, 1.2 Hz, 4 H), 1.35–2.06 (overlapping m, 7 H), 2.34 (m), 2.49 (m) [total 3 H], 2.823 (d of q, J = 7.3, 1.8 Hz, 4 H), 7.367 (s), 7.494 (t, J = 2.1 Hz) [total 2 H].

(+)-(3*R*)-2,2,3-Trimethylcyclohexanone (17) and (−)-(5*R*)-2,2,5-Trimethylcyclohexanone (18). A 2.48-g portion of the methylated ene thioether mixture (above, undistilled) was refluxed under N_2 with 10 mL of 25% aqueous KOH solution in 10 mL of ethylene glycol for 16 h. The reaction mixture was then steam-distilled and the distillate (50 mL) saturated with NaCl and extracted with ether. The extracts were dried over $MgSO_4$ and the solvent removed by distillation to give 0.4 g of a complex mixture of mono-, di-, and trimethylated cyclohexanones. (Hydrolysis of distilled material gives predominantly trimethylated products; see Synthesis section for further discussion of product ratios.) The desired products were isolated by preparative GC (column A, 155 °C); **18** has the shorter retention time on this column. **17**: $[\alpha]^{20}_D$ +39.1° (*c* 0.0043, $CDCl_3$); ^{1}H NMR 0.941 (d, J = 6.5 Hz, 3 H), 1.015 (s, 3 H), 1.090 (s, 3 H), 1.64 (m, 4 H), 1.96 (m, 1 H), 2.297 (dtd, J = 13.8, 4.4, 1.4 Hz, 1 H), 2.476 (ddd, J = 14.0, 11.5, 6.1 Hz, 1 H); MS, m/z (relative intensity (140.2 (M^+, 31.9), 98.1 (33.8), 97.1 (19.3), 96.1 (85.0), 84.1 (28.0), 83.1 (22.7), 70.1 (33.3), 69.01 (100), 56.2 (19.8), 55.1 (50.7) 41.2 (76.8). **18**: $[\alpha]^{20}_D$ −47.0° (*c* 0.0020, $CDCl_3$); ^{1}H NMR 1.005 (d, J = 6.5 Hz, 3 H), 1.051 (s, 3 H), 1.136 (s, 3 H), 1.55 (m, 2 H), 1.72 (m, 2 H), 2.213 (dd, J = 14.0, 10.9 Hz, 1 H), 2.288 (ddd, J = 14.1, 5.3, 1.4 Hz, 1 H); MS, m/z (relative intensity) 140.2 (M^+), 18.9, 96.1 (100), 69.1 (48.0), 56.1 (30.3), 55.1 (35.7), 42.2 (15.6), 41.1 (53.9).

Bromination of 14. Bromine (11.4 mL, 0.223 mol) was added dropwise over a period of 9 h to a vigorously stirred mixture of 25.0 g (0.223 mol) of **14** and 2 mL of glacial AcOH in 75 mL of water. The reaction vessel was cooled in tap water throughout the addition. The mixture was then saturated with NaCl and the organic layer separated. The aqueous layer was extracted with ether, and the combined organic phase was washed three times with saturated $NaHCO_3$ solution and once with brine, dried over $MgSO_4$, and concentrated to 39.8 g of yellow oil. The oil was distilled under reduced pressure to give 2.8 g of a colorless liquid, bp 42–47 °C (2.6 mm) (recovered starting material), 0.23 g of a material boiling from 50 to 81 °C (2.7 mm), and 31.0 g of a yellow oil, bp 81–87 °C (2.7 mm). The final fraction was stored in the refrigerator for 3 days after which time 13.2 g (31%) pinkish white crystals were collected. (Alternatively, the oil may be dissolved in a small amount of pentane and cooled to −78 °C to induce crystallization.) Recrystallization from 2:1 pentane/ether gave 10.7 g (25%) of pinkish white crystals: mp 82–84 °C (lit.[60] mp 83–85 °C); $[\alpha]^{20}_D$ −62.8° (*c* 0.0197, toluene) [lit.[61] $[\alpha]^{25}_D$ −64.8° (toluene)]; ^{1}H NMR 1.02 (d, J = 7 Hz, 3 H), 1.53 (m, 1 H), 2.08

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(m, 4 H), 2.58 (m, 1 H), 2.81 (ddd, J = 10, 5.7, 1.2 Hz, 1 H). NMR data shows ~8% isomeric bromo ketones.

(−)-(5*R*)-5-Methyl-2-cyclohexen-1-one (19). A mixture of 0.95 g of anhydrous Li_2CO_3 and 0.75 g of anhydrous LiBr in 50 mL of DMF (stored over molecular sieves) was stirred and heated to 125 °C under N_2. A solution of 1.0 g (5.2 mmol) of the bromo ketone (above) in 3 mL of DMF was added via syringe, and heating and stirring were continued for 1 h and 45 m. The mixture was cooled, diluted with 150 mL of ether, washed several times with saturated $NaHCO_3$ solution and water and once with brine, and dried over $MgSO_4$. The solvent was removed by distillation to give 0.38 g (69%) of yellowish liquid; GC analysis showed only one peak. Repetition on 10 times the scale followed by distillation at reduced pressure (receiver cooled in an ice–salt bath) gave 2.90 g (50%) of **19**: bp 34–35 °C (2.0 mm), [lit.[62] bp 54 °C (5 mm)]; $[\alpha]^{25}_D$ −89.2° (*c* 0.00536, $CHCl_3$) [lit.[63] $[\alpha]^{25}_D$ −90.17° (*c* 0.797, $CHCl_3$)]; ^{1}H NMR 1.07 (d, J = 5.7 Hz, 3 H), 2.30 (m, 3 H), 6.02 (d of m, J = 10.1 Hz, 1 H), 6.95 (ddd, J = 10.1, 5.1, 2.5 Hz, 1 H); IR 3030, 2920, 1660, 1380 cm^{-1}.

Addition of Ethanethiol to 19. Ethanethiol (0.48 mL, 6.5 mmol) (distilled from NaSEt) and Et_3N (0.35 mL, 2.5 mmol) (distilled from CaH_2) were added sequentially via syringe to 350 mg (3.2 mmol) of **19** in an oven-dried flask fitted with a serum stopper. The contents were swirled briefly and left at room temperature for 21 h. The solution was then diluted with 2 mL of ether and washed three times with cold 2% HCl and once with cold water. Drying over $MgSO_4$ and removal of solvent gave 0.55 g (~100%) colorless oil. GC analysis indicated a trans:cis (**20**:**21**) ratio of approximately 10:1. Preparative GC on column B effected a base line separation of the two isomers. **20**: $[\alpha]^{20}_D$ +62° (*c* 0.0204, $CDCl_3$); ^{1}H NMR (1.128 (d, J = 6.5 Hz, 2 H), 1.237 (t, J = 7.4 Hz, 3 H), 1.789 (ddd, J = 13.3, 9.2, 3.8 Hz, 1 H), 1.93–2.05 (overlapping m, 2 H), 2.39 (m, 1 H), 2.45 (dd of m, J = 12, 2 Hz, 2 H), 2.537 (d of q, J = 7.4, 2.3 Hz, 2 H), 2.65 (ddd, J = 14, 5.0, 1.5 Hz, 1 H), 3.43 (ddd, J = 10.6, 5.4, 3.9 Hz, 1 H); MS, *m/z* (relative intensity) 172.3 (M$^+$, 36.4), 115.3 (10.6), 111.3 (27.6), 110.3 (90.1), 95.2 (21.0), 82.3 (25.3), 69.1 (36.0), 68.2 (100), 67.2 (50.9); IR 1700, 1220 cm^{-1}. **21**: ^{1}H NMR 1.062 (d, J = 6.4 Hz, 3 H), 1.257 (t, J = 7.4 Hz, 3 H), 1.38 (dd, J = 25, 13 Hz, 1 H), 1.86 (m, 1 H), 1.999 (dd, J = 13.4 Hz (twice), 1 H), 2.16 (d of m, J = 13.2 Hz, 1 H), 2.266 (dd, J = 13.3 Hz (twice), 1 H), 2.379 (ddt, J = 13.6, 3.6, 1.9 Hz, 1 H), 2.596 (q, J = 7.4 Hz, 2 H), 2.674 (ddt, J = 13.9, 4.3, 2.0 Hz, 1 H), (dddd, J = 12.7 (twice), 4.0 Hz (twice), 1 H); MS, *m/z* (relative intensity) 172.3 (M$^+$, 39.0), 115.2 (14.1), 111.3, (36.1), 110.3 (72.8), 95.3 (18.4), 82.3 (20.1), 69.2 (37.9), 68.2 (100), 67.2 (43.4).

Asymmetric Thiol Addition/Kinetic Resolution of 5-*tert*-Butyl-2-Cyclohexen-1-one (23).[64] To a solution of 52 μL (0.51 mmol) of freshly distilled PhSH in 2 mL of benzene in an oven-dried flask were added 4 mg of cinchonidine (recyrstallized twice from EtOH and dried under vacuum, mp 263–264 °C; $[\alpha]^{20}_D$ −98.3° (*c* 0.002336, EtOH), lit.[65] $[\alpha]^{20}_D$ −109.2° (EtOH)). To this mixture was added 238 mg of **23** containing (by GC analysis) 18% 3-*tert*-butylcyclohexanone (**22**)[66] and 3-*tert*-butyl-2-cyclohexen-1-one (**26**)[67] (corresponds to 195 mg or 1.28 mmol of **23**) in benzene. (The impurities do not interfere noticeably with the desired reaction; see Synthesis section.) The flask was stoppered and left at room temperature for 13 h. The solution was then diluted with 3 mL of benzene, washed with 2% HCl, water, and brine, dried over $MgSO_4$, and concentrated to 285 mg of yellowish oil. This material was passed through a short column of silica gel, eluting with hexane, for preliminary purification, and then reconcentrated to 265 mg. Separation of the mixture of HPLC (silica gel column, eluting with 2% ether/CH_2Cl_2) gave 89 mg (68% of theoretical) of **24** (cis sulfide appears as a small shoulder), 74 mg (63% of theoretical) of (+)-**23**, and 18 mg of **26** along with a few other impurities. (+)-**23**: ^{1}H NMR identical with that of the racemic material (above); $[\alpha]^{20}_D$ +2.80° (*c* 0.0647, hexane), $[\alpha]^{20}_D$ +5.02 (*c* 0.0566, CCl_4); CD (hexane) $[\theta]_{339}$ = −292. The optical rotation in hexane corresponds to an ee of 21.7%, while the CD in hexane indicates an ee of 19.4% (both by comparison with another sample which was converted to (−)-**22**; see below). The latter value is probably more accurate. **24**: ^{1}H NMR 0.891 (s, 9 H), 1.744 (ddd, J = 14.0, 12.0, 3.7 Hz, 1 H), 2.08 (overlapping m, 3 H), 2.52 (m, 2 H), 2.627 (dd, J = 14.8, 5.4 Hz, 1 H), 3.948 (ddd, J = 5.4, 2.4 Hz (twice), 1 H), 7.31 (m, 3 H), 7.43 (m, 2 H); MS, *m/z* (relative intensity) 262.1 (M$^+$, 45.3), 205.0 (7.7), 153.0 (14.4), 110.0 (69.3), 97.0 (56.4), 96.0 (55.0), 69.0 (43.7), 57.0 (100).

Catalytic Hydrogenation of (+)-23. A balloon filled with H_2 was connected, via a three-way stopcock, to a two-necked flask containing 1 mL of hexane, 5 mg of 5% Pd/C catalyst, and a stirring bar. The second neck was closed with a serum stopper (previously soaked in concentrated NaOH solution to remove catalyst poisons). The system was alternately evacuated and filled with H_2 three times, followed by 5 min of stirring. A solution of 14 mg (+)-**23** ($[\alpha]^{20}_D$ +3.75° (*c* 0.0128, hexane); CD (hexane) $[\theta]_{339}$ = −437) in 1 mL of hexane was added via syringe, and stirring was continued for 1.5 h. The solution was then diluted with pentane, filtered through $MgSO_4$, and concentrated to 13 mg of (−)-**22**: ^{1}H NMR identical with that of the racemic material; $[\alpha]^{25}_D$ −8.24° (*c* 0.0017, $CDCl_3$) [lit.[21] $[\alpha]^{25}_D$ (for *S* isomer) +24.1° ($CHCl_3$)]; CD (4:1 methylcyclohexane/isopentane) $[\theta]_{301}$ = −910 [lit.[21] $[\theta]_{297}$ (for *S* isomer) = +3168 (4:1 methylcyclohexane/isopentane)]. The absolute configuration of (−)-**22** and (+)-**23** is thus determined to be *S*, and a correlation between their chiroptical data and enantiomeric purity is established. Again, the CD value is probably more accurate than the rotation value, although the agreement between the two (29% and 32% ee, respectively, in this case) is fairly good.

Addition of Ethanethiol to (+)-23. The reaction was carried out as described for **19**, using 39.5 mg (+)-**23**, 100 mL of EtSH, and 20 μL of Et_3N. After 24 h at room temperature the reaction mixture was worked up as before to give 41 mg (71%) yellowish oil. GC analysis showed a trans:cis ratio of approximately 20:1. The major isomer **25** was isolated by preparative GC (column A), although this technique did cause substantial β-elimination. **25**: ^{1}h NMR 0.898 (s, 9 H), 1.248 (t, J = 7.5 Hz, 3 H), 1.76 (m, 1 H), 2.06 (overlapping m, 3 H), 2.50 (dd, J = 7.4 Hz (twice), 1 H), 2.51 (m, 1 H), 2.513 (q, J = 7.5 Hz, 1 H), 2.654 (dd, J = 14.6, 5.4 Hz, 1 H), 3.58 (m, 1 H); MS, *m/z* (relative intensity) 214.3 (M$^+$, 15.0), 157.2 (17.3), 152.3 (19.0), 96.2 (100), 57.2 (97.7).

3-(Ethylthio)cyclohexanone.[68] A mixture of 1.0 g of freshly distilled 2-cyclohexen-1-one (Aldrich), 1.2 mL of EtSH, and 0.5 mL of Et_3N was left at room temperature for 22 h. It was then worked up as before to give 1.48 g (90%) of a colorless oil: ^{1}H NMR 1.253 (t, J = 7.4 Hz, 3 H), 1.72 (m, 2 H), 2.14 (m, 2 H), 2.33 (m, 1 H), 2.38 (ddd, J = 14, 11.5, 1.5 Hz, 2 H), 2.578 (q, J = 7.4 Hz, 2 H), 2.716 (dd of m, J = 14.2, 4.5 Hz, 1 H), 3.08 (m, 1 H); IR 1692, 1310, 1260, 1220 cm^{-1}.

3-Methoxycyclohexanone was prepared according to the method of Lambert and Clikeman[23] and purified by preparative GC (colum A) to yield a colorless liquid: ^{1}H NMR 1.69 (m, 1 H), 1.82 (m, 1 H), 2.00 (m, 2 H), 2.313 (dd, J = 6.4 Hz (twice), 2 H), 2.458 (dd, J = 14.2, 6.9 Hz, 1 H), 2.614 (dd, J = 14.0, 4.0 Hz, 1 H), 3.321 (s, 3 H), 3.662 (ddd, J = 10.8, 7.0, 3.8 Hz, 1 H).

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Registry No. 1 (R = CH_3), 87655-21-8; *cis*-1 (R = CD_3), 87655-22-9; *trans*-1 (R = CD_3), 87725-92-6; **2** (R = CH_3), 87655-26-3; *cis*-**7** (R = CD_3), 97570-02-0; *trans*-**7** (R = CD_3), 97643-02-2; **8** (R = CH_3), 97551-76-3; **9** (R = CH_3), 97551-95-6; *cis*-**9** (R = CD_3), 97551-77-4; *trans*-**9** (R = CD_3), 97590-73-3; **9** (R = CD_3; 2,3-butanediol ketal), 97551-81-0; (*R*)-**10** (R = CH_3), 97551-79-6; (*R*)-**10** (R = CH_3; (*R*,*R*)-2,3-butanediol ketal), 97551-80-9; (*S*)-**10** (R =

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CH_3; (*R,R*)-2,3-butanediol ketal), 97590-63-1; **11** (R = CH_3), 97551-96-7; *cis*-**11** (R = CD_3), 97551-82-1; *trans*-**11** (R = CD_3), 97590-74-4; **13**, 97551-83-2; **14**, 13368-65-5; **14** (6-bromide), 97590-65-3; **14** (2-bromide), 97590-66-4; **15a**, 97551-84-3; **15b**, 97590-64-2; **16a**, 97551-85-4; **16a** (α,α-dimethyl deriv), 97551-87-6; **16b**, 97551-86-5; **16b** (α,α-dimethyl deriv), 97551-88-7; **17**, 97551-89-8; **18**, 97551-90-1; **19**, 54307-74-3; **20**, 97551-91-2; **21**, 97590-67-5; (−)-**22**, 57287-85-1; (+)-**23**, 97590-69-7; (±)-**23**, 97551-92-3; **24**, 97590-68-6; **25**, 97551-93-4; *cis*-**25**, 97551-93-4; NaSEt, 811-51-8; HCOOEt, 109-94-4; *n*-BuSH, 109-79-5; EtSH, 75-08-1; PhSH, 108-98-5; 2,2-dimethyl-3-cyclohexen-1-one, 73374-47-7; (±)-2-methyl-2-(trideuteriomethyl)-3-cyclohexen-1-one, 97551-78-5; (−)-(2*R*,3*R*)-butanediol, 24347-58-8; (+)-pulegone, 89-82-7; (±)-3-(ethyl(thio)cyclohexanone, 97590-71-1; (±)-3-methoxycyclohexanone, 97551-94-5; (±)-3-methylenecyclohexanol, 97551-97-8; (±)-3-methoxy-1-methylenecyclohexane, 97551-98-9; (±)-3-methylenecyclohexyl acetate, 97551-99-0; (±)-3-(ethylthio)-7-methylenecyclohexane, 97552-00-6; (±)-3-methyl-1-methylenecyclohexane, 97590-72-2; cyclohexanol, 108-93-0; methyoxycyclohexane, 931-56-6; cyclohexyl acetate, 622-45-7; cyclohexyl fluoride, 372-46-3; cyclohexyl chloride, 542-18-7; cyclohexyl bromide, 108-85-0; (methylthio)cyclohexane, 7133-37-1; methylcyclohexane, 108-87-2; cinchonidine, 485-71-2; 2-cyclohexen-1-one, 930-68-7.

Conformational Analysis of Steroids in Solution: 17β-Hydroxy-19-nor-5α,17α-pregn-20-yn-3-one and Its 5β-Isomer Studied by Nuclear Magnetic Resonance

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The information obtained from two-dimensional NMR spectroscopy at 200 and 500 MHz allowed the complete assignment of the ^1H and ^{13}C NMR spectra of 17β-hydroxy-19-nor-5α,17α-pregn-20-yn-3-one and of its 5β-isomer. The conformation of these molecules in solution was probed by comparing the observed vicinal coupling constants in rings A, B, and C with the corresponding couplings calculated by means of a generalized Karplus relation using the proton–proton torsion angles derived from the steroid conformation in the solid state and/or the conformation calculated by general valence force field methods. The puckering and conformation of the five-membered ring D were determined directly by an analysis of the experimental vicinal couplings by using the generalized Karplus relation in combination with the concept of pseudorotation. It was thus found that the solution conformation of these molecules corresponds with the conformation determined by X-ray crystallography and/or molecular mechanics (MM2). This conclusion is important for establishing the structure–function relation of steroids. The chemical shift and coupling constant features displayed by the NMR spectra of the title compounds are correlated with the conformation of these steroids. For instance, the relatively small $^3J_{15\alpha-16\alpha}$ is explained by the through-space interactions between the carbon–hydrogen orbitals of the C_{15}–C_{16} fragment and the orbitals about the C_{13}-methylene bridge in the distorted $^{13}T_{14}$ envelope conformation of ring D.

Many physiological functions are directed by hormonal steroids, but the mechanism by which a biomolecular event is evoked by a particular steroid is not fully understood. In general, it is presumed that a steroid exerts its biological action after interaction with a protein, e.g., a receptor.[1] Since the physiological response to the distinct steroids appears to be highly specific, it may be deduced that, next to the chemical composition, the steroid conformation plays an important role in the physiological processes. Therefore conformational analysis of steroid molecules is clearly important for establishing the structure–function relation involved.

Most of the present knowledge about steroid conformations stems from X-ray crystallographic studies, but also molecular mechanics (force field calculations) as well as ^1H and ^{13}C NMR studies have contributed. Of course, the ^1H NMR technique is very advantageous to study the steroid conformation as it is able, at least in principle, to yield detailed information about the molecular structure *in solution*. However, the assignment of the ^1H NMR spectra involved is in that case a conditio sine qua non.

Until recently[2] the full analysis of ^1H NMR spectra of steroids has been seriously hampered by the fact that the greater part (>20) of the mutually coupled protons resonate within the 1–2.5 ppm region of the spectrum. The unraveling of the many overlapping signals in this small part of the spectrum presents an extremely difficult task. It was not until developments in NMR instrumentations, i.e., highly stable superconducting magnets interfaced to modern computer-controlled spectrometers, together with the rise of the so-called two-dimensional (2D) NMR techniques revolutionized the field that it was indeed possible to assign the complex ^1H and ^{13}C NMR spectra of steroid molecules.

Recently, a 2D NMR strategy was developed in our laboratories to identify 19-nor steroids.[3] This type of steroid has an even more extended and therefore more complicated network of coupled spins than the common

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