Stereochemistry of Organic Compounds

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only on paper. In that year, Squillacote, Chapman, Anet, et al., (1975) succeeded in capturing the twist form by a matrix isolation technique, which consisted of rapidly cooling to 20 K (−253°C) a mixture of cyclohexane vapor and argon previously heated to about 800°C (see also p. 621). The IR spectrum of the solid matrix indicated that it contained about 25% of a second entity besides the chair conformer. The rate of disappearance of this entity (presumably the twist form) on slight heating suggested a twist-to-chair activation energy of $\Delta G^{\ddagger} = 5.3$ kcal mol^{-1} (22.2 kJ mol^{-1}). With a chair-to-twist activation enthalpy (see above) of 10.7–11.5 kcal mol^{-1}, 44.8–48.1 kJ mol^{-1}, this places the twist 5.4–6.2 kcal mol^{-1} (22.6–25.9 kJ mol^{-1}) in enthalpy above the chair conformation, on the perhaps dubious assumption that $\Delta S^{\ddagger} = 0$ for the twist-to-chair process. Also, if the 25% twist form at 800°C is taken to be an equilibrium value, $\Delta G^0_{\text{chair}\rightarrow\text{twist}}$ at 800°C is about 2.3 kcal mol^{-1} (9.6 kJ mol^{-1}), which requires $\Delta S^0_{\text{chair}\rightarrow\text{twist}}$ to be about 3–4.5 cal mol^{-1} K^{-1} (12.6–18.8 J mol^{-1} K^{-1}). This value is only slightly smaller than that of 4.9 cal mol^{-1} K^{-1} (20.5 J mol^{-1} K^{-1}) reported (Allinger and Freiberg, 1960) from the equilibration of *cis*- and *trans*-1,3-di-*tert*-butylcyclohexanes; in any case the entropy of the twist is substantially above that of the chair, again because of lower symmetry, chirality (it is a racemate), and low-lying vibrational states. Even if $\Delta H^0_{\text{chair}\rightarrow\text{twist}}$ is as low as 4.7 kcal mol^{-1} (19.7 kJ mol^{-1}) and $\Delta S^0_{\text{chair}\rightarrow\text{twist}}$ as high as 4.9 cal mol^{-1} K^{-1} (20.5 J mol^{-1} K^{-1}) one calculates the fraction of twist conformer in cyclohexane at room temperature to be no more than 0.4%.

b. Monosubstituted Cyclohexanes

In monosubstituted cyclohexanes, the topomerization process shown in Figure 11.16 becomes an isomerization process (Fig. 11.18) involving the interconversion of two diastereomers (Jensen and Bushweller, 1971). Like the inversion of cyclohexane itself, this process is very rapid, its rate in most cases being close to that in cyclohexane (ca. 2×10^5 s^{-1} at room temperature). This result explains why temperatures near −150°C were required to isolate conformational isomers of the type shown in Figure 11.18 and why the notion of Sachse's contemporaries that such isomers might be observable under ambient conditions was erroneous. In fact, no conformational isomers of monosubstituted cyclohexanes have ever been isolated at room temperature, several claims to the contrary having been subsequently disproved (but see p. 358). Nonetheless the equilibrium depicted in Figure 11.18 is very real, with most monosubstituted cyclohexanes being mixtures of two conformers with the equatorial one generally predominating (Hassel, 1943). This phenomenon can be readily demonstrated by IR spectroscopy at room temperature [e.g., cyclohexyl bromide (Fig. 11.18, X = Br) shows a C–Br stretching vibration for the equatorial conformer at 685 cm^{-1} and for the axial conformer at 658 cm^{-1} (Larnaudie, 1954)] and by NMR spectroscopy at temperatures below about −50°C (Berlin and Jensen, 1960; Reeves and Strømme, 1960), under which conditions distinct signals of nuclei due to the two conformers are seen. In fact, as

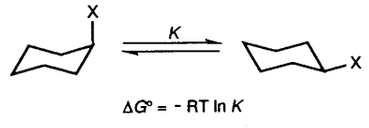

Figure 11.18. Conformational inversion of monosubstituted cyclohexane.

already described in Chapter 10, both methods lend themselves to a *quantitative* determination of the equilibrium depicted in Figure 11.18: IR spectroscopy (cf. Fishman et al., 1981) for determination of ΔH^0 by observation of the change in band area with temperature (cf. Eq. 10.9), NMR spectroscopy through direct measurement of the intensity of the signals due to the two species shown in Figure 11.18. The ratio of these signal intensities gives K, and hence ΔG^0. Either ^{1}H or ^{13}C (or, in the case of fluorinated compounds, ^{19}F) NMR spectroscopy may be used for this purpose. Application of ^{1}H NMR spectroscopy is limited because the signals of the two conformers, with the possible exception of that for the proton geminal to X (C*H*X), are often broad and poorly resolved both within one conformer and between the two. ^{13}C NMR spectroscopy (Anet et al., 1971) is therefore much to be preferred; whereas at room temperature $C_6H_{11}X$ (Fig. 11.18) generally shows four distinct ^{13}C signals [C(2,6) and C(3,5) being enantiotopic, and hence isochronous], at low temperature (−80°C or lower) eight signals (for the two individual conformers) are often seen. This finding allows one to compute four different values for K, the degree of whose agreement reflects the accuracy of the determination. (It has already been implied in Chapter 10, p. 641, that differences in nuclear Overhauser effects (NOE) and relaxation times tend not to affect the determination of K as long as corresponding nuclei in the two conformers are compared.)

The NMR method usually yields ΔG^0, in the −80 to −100°C region, since area measurements of signals must be made well below the coalescence temperature. It does not, however, lend itself to determination of ΔH^0 and ΔS^0, which requires accurate measurement of K over a sizeable range of temperature. Unfortunately, the accessible temperature range is quite limited, at the upper bound by incipient coalescence, at the lower by crystallization of the solute or solvent or both. The ΔG^0 values measured at low temperature are therefore often reported as if they were the same at 25°C, which implies $\Delta S^0 = 0$ and ΔH^0 independent of temperature. Neither of these assumptions is likely to be correct. If X lacks the local $\mathbf{C}_{\mathbf{nv}}$ symmetry of a methyl group ($\mathbf{C}_{3\mathbf{v}}$) or of a halogen or C≡N group ($\mathbf{C}_{\infty\mathbf{v}}$), there may be entropy-of-mixing differences between axial and equatorial conformers. But even if such is not the case, vibrational and rotational entropies will not be the same for conformational isomers (Reisse, 1971). Thus, while ΔS^0 for X = CN was found to be zero (Höfner, Binsch, et al., 1978) that for X = Cl is 0.32 cal mol^{-1} K^{-1} (1.34 J mol^{-1} K^{-1}) and for X = Br 0.06 cal mol^{-1} K^{-1} (0.25 J mol^{-1} K^{-1}), in both cases favoring the equatorial conformer. For CD_3O, where one might have expected entropy of mixing to favor the equatorial conformer (which has two favorable and one somewhat less favorable conformations by virtue of rotation of CH_3O about the C–O axis, whereas the axial conformer can only have two low-energy rotamers, with the CH_3 group pointing outside the ring), the *axial* conformer is actually favored by 0.42 cal mol^{-1} K^{-1} (1.76 J mol^{-1} K^{-1}). The best that can be said here is that entropy effects (and presumably also effects of temperature-variable enthalpy) are small. In the cases investigated, these entropy effects were much less than 1 cal mol^{-1} K^{-1} (4.2 J mol^{-1} K^{-1}), and therefore caused less than a 0.1 kcal mol^{-1} (0.42 kJ mol^{-1}) difference in ΔG^0 between the measurement range of −80 to −100° and room temperature. Attempts to obtain ΔG^0 at room temperature to a greater accuracy than 0.1 kcal mol^{-1} (0.42 kJ mol^{-1}) require measurements of unusual care (Reisse, Oth, et al., 1969; Eliel and Gilbert, 1969; Höfner, Binsch, et al., 1978) and may

even so be foiled by extraneous factors, such as solvent effects or self-association, not to mention methodological problems.

In general it would be preferable to measure ΔG^0 at 25°C, which is close to the temperature at which one frequently deals with physical, spectral, and pharmacological properties, as well as synthesis, reaction mechanism, and so on. For the reasons already mentioned, accurate extrapolations from low temperatures are rarely feasible. In principle, however, conformational composition can be measured at any temperature by use of the Winstein–Holness equation (Eq. 10.22) which, applied to a cyclohexyl system (Fig. 11.18) with two conformations and generalized to any appropriate property P, becomes

$$P = n_E P_E + n_A P_A \tag{11.1}$$

or

$$K = n_E/n_A = (P_A - P)/(P - P_A) \tag{11.2}$$

where n denotes mole fraction and the subscripts E and A refer to equatorial and axial conformers, respectively. The first application going beyond kinetics (Winstein and Holness, 1955) and dipole measurements (where $P = \mu^2$ is polarization, μ being the dipole moment) was, in fact, in NMR (Eliel, 1959). Application to chemical shifts, δ, and coupling constants, J, gives $\delta = n_E\delta_E + n_A\delta_A$ and $J = n_E J_E + n_A J_A$; that is, both observed chemical shifts and observed coupling constants in an equilibrating system, such as shown in Figure 11.18, are the weighted averages of the corresponding constants in the individual conformers. Using the form of Eq. 11.2 (cf. p. 641), this becomes

$$K = (\delta_A - \delta)/(\delta - \delta_E) = (J_A - J)/(J - J_E) \tag{11.3}$$

Unfortunately, the room temperature shifts of the pure conformers δ_A and δ_E are not readily accessible; because of sizeable variations of chemical shift with temperature, they can*not* be taken to be equal to the low-temperature shifts. The situation is much more favorable with coupling constants which are very nearly temperature independent and can thus be used to estimate K at room temperature from J, if J_E and J_A are known from low-temperature measurement (Höfner, Binsch, et al., 1978). In the past, this method has been limited to proton spectra, but with the increasing availability of ^1H–^{13}C coupling constants (Marshall, 1983), the method may find extension to ^{13}C NMR spectroscopy.

More popular, but less reliable, have been methods to determine ΔG^0 through the use of model compounds. These are compounds confined to a single conformation in which the substituent X is either strictly equatorial or strictly axial. Such confinement may be brought about either by "conformational locking," such as in the *trans*-decalin-2-ols (Fig. 11.19 **A**, R or R′ = OH), or by "conformational biassing," such as in the *cis*- and *trans*-4-*tert*-butylcyclohexanols (Fig. 11.19, **B**, R or R′ = OH, respectively). Conformational locking was present in many of the compounds cited in Barton's 1950 classical paper (q.v.) dealing with physical and chemical properties of axially and equatorially substituted cyclohexyl compounds. However, it has not been used much in quantitative work, perhaps because of concern that the double substitution only two and three

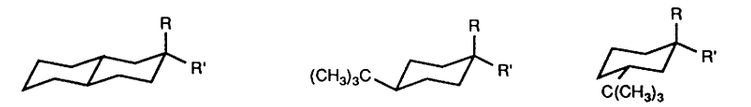

Figure 11.19. Conformationally locked (**A**) and conformationally biassed (*anancomeric*: **B** and **C**) compounds.

positions away from the carbon bearing the substituent X might affect reactivity. Prototypes of the biassed model (Winstein and Holness, 1955) are the 4-*tert*-butylsubstituted compounds (Fig. 11.19, **B**); compounds of this type have also been called "anancomeric" (Anteunis, 1971) meaning "fixed in one conformation" (the word is derived from Greek *anankein* meaning to fix by some fate or law). Models of this type can be used to ascertain appropriate axial or equatorial parameters, such as chemical shifts (of various nuclei), coupling constants, dipole moments, pK_a values of acids, and extinction coefficients for IR determinations (for a review, see Eliel et al., 1965).

One must, of course, ask whether such models (Fig. 11.19, **B** and **C**) are adequate; specifically, whether the introduction of a "holding group," such as 4-*tert*-butyl, to make a molecule anancomeric will alter (falsify) the chemical shifts, coupling constants, dipole moments, pK_a values, and so on, of the equatorial or axial conformer of cyclohexyl-X devoid of such a group. The holding group can have two kinds of adverse effects: it may deform the molecule structurally thus altering many of its properties, or it may affect the particular property to be measured in other ways, for example, by inductive effects or through-space interactions. With respect to the first point, crystallographic study (James and McConnell, 1971; Johnson et al., 1972a; also neutron diffraction: James and Moore, 1975) of cyclohexyl *p*-toluenesulfonate (which crystallizes with the toluenesulfonate group equatorial) and its 4-*trans*-*tert*-butyl homologue (Fig. 11.19, **B**, R′ = OTs, R = H) discloses no obvious significant differences except possibly an unusually long C–OS bond (151 pm, 1.51 Å) in the unsubstituted compound (the corresponding bond length in the 4-*tert*-butyl homologue is a more normal 147 pm (1.47 Å). *cis*-4-*tert*-Butylcyclohexyl tosylate (Fig. 11.19, R = OTs, R′ = H) has also been investigated (Johnson et al., 1972b; James and Grainger, 1972); it is dimorphous (i.e., crystallizes in two different forms) but the molecules in the two types of crystal do not differ greatly. As expected, the axial substituent causes some flattening of the ring. Unfortunately, the axial conformer of cyclohexyl tosylate itself cannot be obtained crystalline, so investigation of the effect of the 4-*tert*-butyl substituent on the geometry of the axial OTs group is not possible. However, as far as they go, the crystallographic studies imply no major effect of a 4-*tert*-butyl substituent on molecular shape, though the situation seems to be different for 3-*tert*-butyl substitution (James, 1973) and for the more flexible cyclohexanones (Abraham et al., 1980, 1983). The conclusion with respect to the 4-*tert*-butyl substituent is also supported by force field calculations (Altona and Sundaralingam, 1970).

It has, in fact, been repeatedly found that 3-*tert*-butyl substituents (Fig. 11.19, **C**) as well as *cis*-3,5-dimethyl substituents in cyclohexanes are unsuitable in model studies, either NMR (Eliel and Martin, 1968a) or kinetic or equilibrium studies

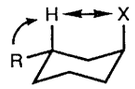

Figure 11.20. "Allinger buttressing."

(Eliel et al., 1966; Eliel and Biros, 1966). The reason has been pointed out by Allinger et al. (1967; see also Burkert and Allinger, 1982): An equatorial alkyl group buttresses the hydrogen geminal with it and thus prevents it from bending outward. If the alkyl group is at position 3 or 5 relative to an axial substituent to be studied, this "lack of give" will increase the synaxial H/X repulsion and thus increase the conformational energy of X as well as cause other changes (Fig. 11.20).

Even though the 4-*tert*-butyl group seems to cause little distortion in model compounds, use of such models in quantitative NMR studies cannot be recommended since it is apt to lead to inaccurate results (e.g., Reisse, 1971). Probably the major reason is a long-range effect of the *tert*-butyl substituent on the chemical shifts. (There are no extensive studies involving coupling constants.) This perturbation is serious in ^{1}H NMR because the whole range of observations (difference between equatorial and axial protons) is usually within less than 1 ppm, and therefore discrepancies of even a few hundredths of a part per million are fatal to accurate determinations. In ^{13}C NMR, the shift differences between equatorial and axial conformers are usually greater, but, unfortunately, this is compensated by the shifts being more sensitive to long-range (δ and ε) effects (cf. Jordan and Thorne, 1986). Fortunately, substituent effects on ^{13}C NMR shifts tend to be additive (see p. 717), and can thus be corrected for on the basis of shifts of suitable reference compounds.

Two methods other than low-temperature NMR studies have been used widely to determine conformational equilibria (Fig. 11.18). One is chemical equilibration of conformationally locked models (Eliel and Ro, 1957a; Fig. 11.21), based on Barton's recognition (1950) that equatorially substituted isomers are generally more stable than axially substituted ones. Since this equilibration is one of cis–trans diastereomers, it requires chemical intervention and one obvious condition for the method to succeed is that equilibrium must be established cleanly, that is, without appreciable side reactions. The second condition is that the equilibria in Figures 11.21 and 11.18 correspond, which again depends on the innocuousness of the holding group. In this situation, experience suggests that a 4-*tert*-butyl substituent does seem to be satisfactory.

Another method consists in the application of the Winstein–Holness equation (Section 10-5) to reaction rates. Using the form of this equation analogous to Eq. 11.2 one has $K = (k_a - k)/(k - k_e)$ (Eliel and Ro, 1956), where K is the conformational equilibrium constant (Fig. 11.18), k is the Winstein–Holness rate constant

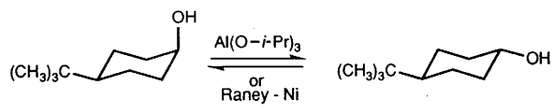

Figure 11.21. Chemical equilibration to determine conformational energies.

(cf. Section 10-5) – in this case the rate constant for the reaction to be investigated in the mobile system (Fig. 11.18) – and k_a and k_e are the rate constants for the same reaction with purely equatorial and purely axial conformers. In this form, despite some questions having been raised to the contrary (see Seeman, 1983 for discussion; see also Section 10-5), the equation is unconditionally correct, provided the rate of interconversion of the axial and equatorial conformers (Fig. 11.18) is fast compared to the rate of the reaction being studied. Since we have already seen that the conformer equilibration proceeds at a rate of about $2 \times 10^5\ s^{-1}$ at room temperature, this condition will be fulfilled for all but a few extremely fast reactions, such as protonations, nitrous acid deaminations, and carbene additions of amines. Unfortunately, there is no way of determining k_a and k_e directly. These rates must therefore be determined on model compounds. For example, to use acetylation rates in determination of the cyclohexanol conformational equilibrium (Fig. 11.18, X = OH); Eliel and Lukach, 1957) one must use *cis*- and *trans*-4-*tert*-butylcyclohexanol as models to determine acetylation rate constants k_a and k_e, respectively. In most cases the factors mentioned earlier (ring deformation and long-range effects) will vitiate this attempt (cf. Eliel and Biros, 1966) and the kinetic method is therefore not to be recommended, although there may be special situations (especially when the reaction site is somewhat remote from the ring) in which it may succeed (McKenna, 1974).

"Conformational energies," $-\Delta G^0$ or "A values" (cf. Winstein and Holness, 1955; Fig. 11.18) for a variety of common substituents are summarized in Table 11.7. Since almost all ΔG^0 values are negative, we find it convenient to tabulate $-\Delta G^0$. More detailed tabulations have been compiled by Hirsch (1967), Jensen and Bushweller (1971), and Bushweller (in press) (see also Schneider and Hoppen, 1978). Perusal of the halogen values indicates that ΔG^0 is not solely a function of substituent size. As the halogens get larger (i.e., their van der Waals radius increases), the C–X bond becomes longer (i.e., the bond length increases also), and thus X becomes more distant from the carbon and hydrogen atoms at C(3,5) including, especially, the synaxial hydrogen atoms, which are mainly responsible for crowding of the axial substituent. This result leads to a form of compensation that is reinforced because the substituent with the longer bond also benefits more from the outward bending caused by the flattening of the cyclohexane ring (lever principle). The fact that the larger atoms (in the lower part of the periodic table) are also the softer or more polarizable ones, and therefore the atoms for which the attractive part of the van der Waals potential (London force) is more important (cf. Section 2-6) may be a contributing factor to their apparently low conformational energy values. It should, however, be noted that the drop in $-\Delta G^0$ from Cl to Br is due to entropy, not enthalpy effects (see above). A similar continuous decrease in conformational energy is evident in the series $(CH_3)_3C$, $(CH_3)_3Si$, $(CH_3)_3Ge$, $(CH_3)_3Sn$, and $(CH_3)_3Pb$.

Conformational energies for OX [X = H, CH_3, Ac, Ts, $Si(CH_3)_3$, or $C(CH_3)_3$] vary little with X, presumably because the group X can be turned so as to point away from the ring when OX is axial. At worst this will decrease the number of rotamers (rotational conformers) for the axial OX, and thereby produce a slight drop in its entropy. The OH group itself shows a large solvent effect, $-\Delta G^0_{OH}$ being appreciably larger in hydrogen-bond forming solvents (e.g., isopropyl alcohol) than in those not forming hydrogen bonds (e.g., cyclohexane).

TABLE 11.7. Conformational Energies.

Group[a,b]	Conformational Energies (kcal mol^{-1})	Conformational Energies (kJ mol^{-1})	t(°C)	References
D	0.006	0.025	25	*c*
T	0.011	0.046	−88	*d*
F*	0.25–0.42	1.05–1.75	−86 to −93, −25	*e–j*
Cl[a]*	0.53–0.64	2.22–2.68	−80 to −93, 25–27	*e–h, j–m*
Br*	0.48–0.67	2.01–2.80	−81, 25–27	*e–h, j–m*
I*	0.47–0.61	1.97–2.55	−78, −93, 25	*e–h, j*
$OH(C_6H_{12})$*	0.60	2.51	25	*e, n, o*
$OH(CS_2)$	1.04[p,q]	4.35	−83	*f, j*
$OH(CH_3CHOHCH_3)$	0.95	3.97	25	*n*
OCD_3*, OCH_3	0.55, 0.58, 0.63, 0.75	2.30, 2.43, 2.64, 3.14	−82, −93	*e, f, j, k*
$OC(CH_3)_3$	0.75	3.14	36	*r*
OC_6H_5	0.65	2.72	−93	*s*
$OC_6H_4NO_2$-*p**	0.62	2.59	−93	*s*
OC_6H_4Cl-*p**	0.65	2.72	−93	*s*
$OC_6H_4OCH_3$-*p**	0.70	2.92	−93	*s*
OCHO	0.27, 0.60[p]	1.13, 2.51[p]	25, −80 to −93	*e, f, j, t*
$OCOCH_3$*	0.68, 0.71, 0.79, 0.87	2.85, 2.97, 3.31, 3.64	25, −90 ± 3	*e, f, j, u*
$OCOCF_3$	0.68, 0.56	2.85, 2.34	25, −88 to −93	*f, j, t*
$OCOC_6H_5$*	0.5[p]	2.09[p]	−92 ± 1	*f, u*
$OCONHC_6H_5$*	0.77	3.22	−91	*u*
$OSO_2C_6H_4CH_3$-*p*	0.50[p]	2.09[p]	−80 to −83	*e, f, j*
OSO_2CH_3	0.56	2.34	−88	*e, j*
ONO_2	0.59, 0.62[p]	2.47, 2.59	25, −101	*t, v*
$OSi(CH_3)_3$	0.74	3.10	−103	*f*
SH	1.21[p]	5.06[p]	−80	*e, f, j*
SCD_3, SCH_3	1.04[p]	4.35[p]	−79 to −100	*e, j, w*
SC_6H_5	1.10–1.24	4.60–5.19	−80	*x*
$SOCH_3$	1.20	5.02	−90 to −100	*w*
SO_2CH_3	2.50	10.5	−90 to −100	*w*
SCN	1.23	5.15	−79	*e, j*
SeC_6H_5	1.0–1.2	4.2–5.0	−50	*y*
$SeOC_6H_5$	1.25	5.23	−60	*z*
TeC_6H_5	0.9	3.7	−30	*z*
NH_2 (toluene-d_8; $CFCl_3$)	1.23, 1.47[p]	5.15, 6.15[p]	−80 to −100	*f, aa, bb*
$NH_2(CH_3OCH_2CH_2OH/H_2O)$	1.7	7.1	20	*cc*
NH_3^+	1.7–2.0	7.1–8.4	20–25	*cc, kkk*
$NHCH_3(CFCl_3–CDCl_3)$	1.29	5.40	−80	*bb*
$N(CH_3)_2(CFCl_3–CDCl_3)$	1.53	6.40	−90	*bb*
$N(CH_3)_2(CH_3OCH_2CH_2OH/H_2O)$	2.1	8.8	20	*cc*
$NH(CH_3)_2^+$	2.4	10.0	20	*cc*
$NHCOC_6H_5$	1.6	6.7	−90	*dd*
NC	0.20[p]	0.84[p]	−80 to −93	*e, f, j*
NCO	0.44, 0.51	1.84, 2.13	−70 to −80	*e, j, dd*
N_3*	0.45–0.62	1.88–2.59	−183, −93	*f, ee*
NCS	0.25[p]	1.05[p]	−79 to −93	*e, f, j*
$N{=}CHCH(CH_3)_2$	0.75	3.14	32	*dd*
$N{=}C{=}NC_6H_{11}$	0.96	4.02	−80	*j*
NO_2*	1.1[p]	4.8[p]	−80 to −90, 25	*e, f*
PH_2	1.6	6.7	−90, 27	*ff, gg*
$P(CH_3)_2$	1.5, 1.6	6.3, 6.7	−90, 27	*ff*
$P(C_6H_5)_2$	1.8	7.5	37	*hh*
PCl_2	1.9, 2.0	7.9, 8.4	−90, 27	*ff*
$P(OCH_3)_2$	1.9; 1.5	7.9; 6.3	−90, 27	*ff*
$O{=}P(C_6H_5)_2$	2.46	10.3	−80	*ii*
$S{=}P(C_6H_5)_2$	3.13	13.1	−102	*jj*
CHO	0.56–0.73, 0.8	2.34–3.05, 3.35	25	*kk, ll*
$COCH_3$	1.02, 1.21, 1.52	4.27, 5.06, 6.36	−100, 25	*mm, nn*
CO_2H	1.4	5.9	25	*nn*
CO_2^-	2.0	8.4	25	*nn*

TABLE 11.7. (*Continued*)

Group[a,b]	Conformational Energies (kcal mol^{-1})	Conformational Energies (kJ mol^{-1})	t(°C)	References
CO_2CH_3	1.2–1.3	5.0–5.4	25, −78	*e, j, nn, oo*
CO_2Et	1.1–1.2	4.6–5.0	25	*j*
COF	1.4–1.7	5.9–7.1	25	*pp*
COCl*	1.3	5.4	25	*nn*
CN*	0.2	0.84	−79 to −95	*e, f, j, k*
C≡CH	0.41–0.52	1.71–2.18	−91	*e, f, j*
$CH{=}CH_2$	1.49, 1.68	6.23, 7.0	−100	*kk, qq*
$CH{=}C{=}CH_2$	1.53	6.40	−80	*rr*
CH_3*	1.74	7.28	27	*ss*
CD_3	0.0115[q,u]	0.048[q,u]	25–27	*uu, vv*
CH_2CH_3*	1.79	7.49	27	*ss*
$CH(CH_3)_2$*	2.21	9.25	27	*ss*
$C(CH_3)_3$	4.7; 4.9	19.7; 20.5	−120	*ww, xx*
CH_2Br	1.79	7.49	27	*yy*
CH_2OH	1.76	7.36	27	*yy*
CH_2OCH	1.72	7.20	27	*yy*
CH_2CN	1.77	7.41	27	*yy*
$CH_2Si(CH_3)_3$	1.65	6.90	27	*yy*
$CH_2Sn(CH_3)_3$	1.79	7.49	27	*yy*
$CH_2Pb(CH_3)_3$	1.81	7.57	27	*yy*
CH_2HgOAc	2.05	8.57	27	*yy*
CF_3	2.4–2.5	10.0–10.5	27	*zz*
C_6H_5	2.8[p]	11.71[p]	−100, 700	*qq, aaa*
$CH_2C_6H_5$	1.68	7.03	−71	*bbb*
C_6H_{11}	2.2	9.2	36	*ccc*
SiH_3	1.45; 1.52	6.07; 6.36	−85, 75	*ddd, eee*
$Si(CH_3)_3$	2.5	10.5	33	*fff*
$SiCl_3$	0.61	2.55	−80	*e, j*
$Ge(CH_3)_3$	2.1	8.8	−70	*ggg*
$Ge(C_6H_5)_3$	2.90	12.1	not given	*ggg*
$Sn(CH_3)_3$	1.0[p]	4.2	−69 to −90	*ggg, hhh, iii*
$Sn(i\text{-}Pr)_3$	1.10	4.6	not given	*ggg*
$Sn(CH_3)_2C_6H_5$	1.08	4.5	not given	*ggg*
$SnCH_3(C_6H_5)_2$	1.20	5.02	not given	*ggg*
$Sn(C_6H_5)_3$	1.44	6.0	not given	*ggg*
$Pb(CH_3)_3$	0.67	2.80	−69	*ggg*
HgOAc	0, −0.3	0, −1.3	−79, −90	*e, j, jjj*
HgCl	−0.25	−1.05	−90	*jjj*
HgBr	0[p]	0	−79	*e, j, jjj*
MgBr (Et_2O)	0.78	3.26	−75	*j*
MgC_6H_{11} (Et_2O)	0.53	2.22	−82	*j*

[a] Starred values mean that ΔH^0 and ΔS^0 are available in the original reference. [b] The solvent is in parentheses in cases where large solvent dependence is observed. [c] Anet and Kopelevich, 1986. [d] Anet et al., 1990. [e] Jensen et al. 1969. [f] Schneider and Hoppen, 1978. [g] Bugay, Bushweller et al., 1989. [h] Subbotin and Sergeyev, 1975. [i] Chu and True, 1985. [j] Jensen and Bushweller, 1971. [k] Höfner, Binsch et al., 1978. [l] Shen and Peloquin, 1988. [m] Considerably smaller ΔH^0 values were reported by Gardiner and Walker, 1987, by Gardiner et al. 1987, and by Bugay, Bushweller et al., 1989. [n] Eliel and Gilbert, 1969. [o] See also Aycard, 1989. [p] Averaged value; all values given are within experimental error of each other. [q] The alcohol may have been self-associated (oligomeric). [r] Senderowitz, Fuchs et al., 1989. [s] Kirby and Williams, 1992. [t] Allan, Reeves et al., 1963. [u] Jordan and Thorne, 1986. [v] Klochkov et al., 1989. [w] Eliel and Kandasamay, 1976. [x] Subbotin, Zefirov et al., 1978. [y] Duddeck et al., 1985. [z] Duddeck et al., 1991. [aa] Buchanan and Webb, 1983. [bb] Booth and Josefowicz, 1976. [cc] Sicher et al., 1963. [dd] Herlinger and Naegele, 1968. [ee] Sülzle, Klaeboe et al., 1988. [ff] Gordon and Quin, 1976. [gg] Pai and Kalasinsky, 1990. [hh] Juaristi and Aguilar, 1991. [ii] Juaristi et al., 1986. [jj] Juaristi et al., 1987. [kk] Buchanan, 1982. [ll] Buchanan and McCarville, 1972. [mm] Buchanan et al., 1984. [nn] Eliel and Reese, 1968. [oo] Booth et al., 1992. [pp] Della and Rizvi, 1974. [qq] Eliel and Manoharan, 1981. [rr] Gatial et al., 1990, 1991. [ss] Booth and Everett, 1980a. [tt] Difference between CH_3 and CD_3; CD_3 has lesser equatorial preference than CH_3. [uu] Baldry and Robinson, 1977. [vv] Booth and Everett, 1980b, c. [ww] Calculated value: van de Graaf, Webster, et al., 1978. [xx] Manoharan and Eliel, 1984a. [yy] Kitching et al. 1981. [zz] Della, 1967. [aaa] Squillacote and Neth, 1987. [bbb] Juaristi et al., 1991. [ccc] Reisse et al., 1964. [ddd] Penman, Kitching et al., 1989. [eee] Shen et al., 1992. [fff] Kitching et al., 1982b. [ggg] Kitching et al., 1982a. [hhh] Moder, Jensen et al., 1980. [iii] Kitching et al., 1976. [jjj] Anet et al., 1974. [kkk] Eliel et al., 1962.

The value for OH obtained by low-temperature NMR in CS_2 seems to be out of line; it must be strongly suspected that solutions about 0.2 *M* in cyclohexanol (concentrations appropriate for an NMR experiment) at −80°C are subject to extensive oligomerization of the solute by intermolecular hydrogen bonding, so that the measured $-\Delta G^0$ is not that of the monomeric alcohol.

The value of $-\Delta G^0$ for SH is slightly larger than that for OH. That for SCH_3 is somewhat smaller; that of $SOCH_3$ is similar to SCH_3, but that of SO_2CH_3 is considerably larger. The former three groups presumably confront the ring with their lone electron pairs, which are evidently not greatly repulsive, but SO_2CH_3 must confront the ring with an O or CH_3 moiety (probably the former), which is sterically much more demanding. The progression of $-\Delta G^0$ in the series NH_2, $NHCH_3$, $N(CH_3)_2$ is also slight, for the same reasons adduced for OH versus OCH_3, but $(CH_3)_3\overset{+}{N}$, as expected, has a very large $-\Delta G^0$ value (too large to be measured). The values for PR_2 are of the same magnitude as those for NR_2; the diminution in $-\Delta G^0$ seen for Group 14(IVA) and Group 17(VIIA) elements as one goes down the periodic table is not evident in Group 15(VA) and Group 16(VIA), though in the latter groups there are data for only the first two members. Linear substituents, such as –NC, –NCO, N_3, CN, and C≡CH have expectedly small conformational energy values and those of planar groups, such as COR, CO_2R, $CH{=}CH_2$ are intermediate between those of linear and those of tetrahedral groups, such as CH_3. The vinyl group has the largest conformational energy in this series; apparently, when it is axial, one of its β (methylene) hydrogen atoms interferes seriously with one of the equatorial ring hydrogen atoms of the cyclohexane.

The sp^2 hybridized groups orient themselves so as to confront the ring with their flat sides, in other words the plane of the substituent is perpendicular or nearly perpendicular to the bisector plane of the cyclohexane ring. In the case of axial phenyl, this rotational conformation, though optimal, imposes steric crowding of the ortho hydrogen atoms (*o*-H) of the phenyl with *both* adjacent equatorial hydrogen atoms (e-H) of the cyclohexane chair (Fig. 11.22*a*); this explains the high conformational energy of the phenyl group (Table 11.7; Allinger and Tribble, 1971). Equatorial phenyl, in contrast, is most stable in the bisector plane of the cyclohexane chair (Fig. 11.22*b*) where the unfavorable *o*-H/e-H interaction is avoided (see also Section 2-6, Fig. 2.26).

The conformational energy of methyl in methylcyclohexane (a key datum; cf. Anet et al., 1971) has been determined with great accuracy by low-temperature ^{13}C NMR spectroscopy (Booth and Everett, 1976, 1980a). Since the contribution

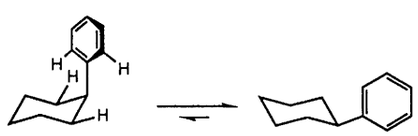

Figure 11.22. Equatorial and axial conformers of phenylcyclohexane; $\Delta G^0 = -2.87$ kcal mol^{-1} (12.0 kJ mol^{-1}).

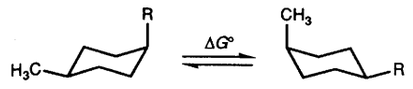

Figure 11.23. Counterpoise method.

of the axial conformer in the temperature range of the experiment (140–195 K) is only about 1%, it was necessary to work with ^{13}C enriched material to see the methyl peak of the minor conformer. With the value for methyl in hand, values for ethyl and isopropyl were determined (Booth and Everett, 1980a) by use of the so-called "counterpoise method" (Eliel and Kandasamy, 1976; see also Eliel et al., 1963) employing *cis*-1-alkyl-4-methylcyclohexanes as objectives of low-temperature NMR investigation (Fig. 11.23). Making the reasonable assumption that the conformational energies of CH_3 and R are additive, one has $\Delta G^0 = \Delta G_R - \Delta G_{CH_3}$, where ΔG^0 is the free energy change for the process shown in Figure 11.23; hence $\Delta G_R = \Delta G^0 + \Delta G_{CH_3}$. By carrying out the equilibration over a range of temperature, it was possible to determine both ΔH^0 and ΔS^0 as well as ΔG^0. The results (axial→equatorial conformer) are shown in Table 11.8 (Booth and Everett, 1980a), along with values calculated by molecular mechanics (Allinger et al. 1968a); the agreement between experimental and calculated values is good. It is of interest that $-\Delta H^0$ *de*creases in the series CH_3, C_2H_5, *i*-Pr whereas ΔS^0 *in*creases. The reason for this finding may be gleaned from Figure 11.24. In ethylcyclohexane the axial conformer has two rotamers (**A** and its mirror image); the third rotamer, in which the methyl group points into the ring, is of very high energy [cf. the $-\Delta G^0$ value of $(CH_3)_3C$–, where one methyl must point into the ring, see Table 11.7]. The equatorial conformer, in contrast, has three populated rotamers: **B** and its mirror image, and **C**. Therefore the equatorial conformer will

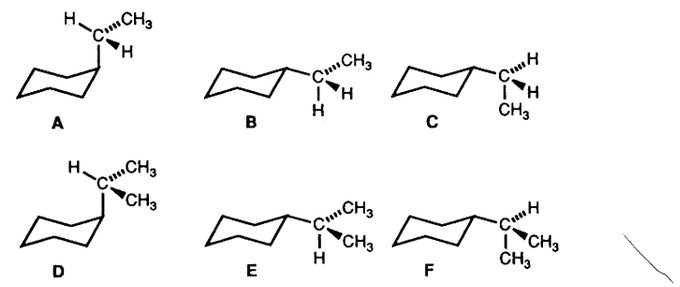

Figure 11.24. Rotamers of ethylcyclohexane and isopropylcyclohexane.

TABLE 11.8. Conformational Thermodynamic Parameters for Alkyl Groups.

	$-\Delta H^{0\,a}$		$-\Delta S^{0\,b}$		$-\Delta G^{0\,a}_{25}$	
Alkyl	Found	Calculated	Found	Calculated	Found	Calculated
CH_3	1.75 (7.32)	1.77 (7.41)	−0.03 (0.13)	0 (0)	1.74 (7.28)	1.77 (7.41)
C_2H_5	1.60 (6.69)	1.69 (7.07)	0.64 (2.68)	0.61 (2.55)	1.79 (7.49)	1.87 (7.82)
$(CH_3)_2CH$	1.52 (6.36)	1.40 (5.86)	2.31 (9.67)	2.18 (9.12)	2.21 (9.25)	2.05 (8.58)

[a] In kilocalories per mole (kcal mol^{-1}); values in parentheses are in kilojoules per mole (kJ mol^{-1}).
[b] In calories per mole per degree kelvin (cal mol^{-1} K^{-1}); values in parentheses are in joules per mole per degrees kelvin (J mol^{-1} K^{-1}).

have a larger entropy of mixing. On the other hand, since the enthalpy of each conformer is the weighted average of the enthalpy of the rotamers, the enthalpy of the equatorial conformer is enhanced by the contribution of the high-enthalpy rotamer **C** in which the terminal methyl of the CH_2CH_3 group is subject to *two* butane–gauche interactions with the ring. (In **A** and **B** there is only one such interaction.) The difference in enthalpy between axial and equatorial conformers for ethyl is thus somewhat diminished relative to the difference for methyl. The same argument applies, a fortiori, to the isopropyl group in which the axial conformer exists as the single rotamer **D**, whereas the equatorial conformer still has three rotamers: The lowest-energy rotamer **E** and the slightly higher energy rotamer **F** and its mirror image (see also Anderson, 1992, p. 118).

> The validity of the frequently used counterpoise method rests on the assumption that the reorientation (axial–equatorial) of one substituent does not affect the ease of reorientation of the other. To the extent that axial and equatorial substituents deform a cyclohexane ring unequally (cf. p. 693), this assumption is probably not strictly correct, but for pairs of small substituents (e.g., CH_3 and C_2H_5, CH_3 and SCH_3) it may be an adequate approximation.

Thermodynamic parameters (ΔH^0 and ΔS^0) have been determined for some of the other substituents in Table 11.7; ΔG^0 values in such cases have been starred; ΔH^0 and ΔS^0 may be found in the original references.

The difference between CO_2^- and CO_2H and between NH_3^+ and NH_2 is of note; in both cases $-\Delta G^0$ for the ion is considerably larger than that for the uncharged species. One way of explaining this is to say that the axial group, when ionic, is swelled by solvation, and therefore more subject to steric repulsion than the neutral ligand. Another complementary explanation implies that the axial substituent, because of crowding, is less readily solvated than the equatorial one, and therefore benefits less from the diminution in free energy than any charged species experiences when it is solvated. (In the case of NH_3^+ vs. NH_2, the steric effect of the extra hydrogen may, of course, also contribute to the larger $-\Delta G^0$ of the former.) The true answer probably lies somewhere in between.

A similar argument applies (if less strongly) to an uncharged but polar substituent and, in general, one might expect conformational energies in such cases to be solvent dependent. However, little solvent dependence of ΔG^0 was found with cyclohexyl fluoride, chloride, and bromide (Eliel and Martin, 1968b).

c. Disubstituted and Polysubstituted Cyclohexanes

1,2-, 1,3- and 1,4-Disubstituted cyclohexanes each exist as cis and trans isomers (Section 11-1). When the two substituents are identical, the cis-1,2 and cis-1,3 isomers are meso forms, whereas the corresponding trans isomers are chiral. In the 1,4-disubstituted series, both the cis and the trans isomers are achiral, regardless of whether the substituents are the same or not.

When one considers conformational factors, the situation becomes somewhat more complex. The 1,4-dimethylcyclohexanes are shown in Figure 11.25. The cis isomer exists as an equimolar mixture of two indistinguishable conformers. Its steric energy (cf. Section 2-6, p. 33) is that of the axial methyl group or

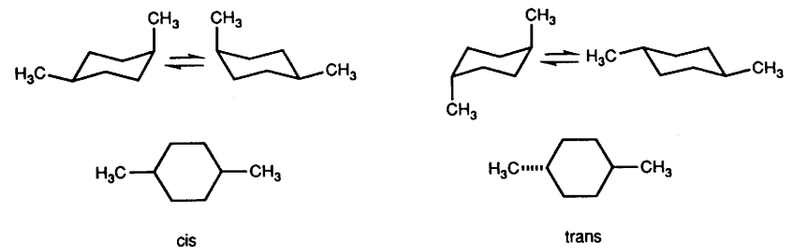

Figure 11.25. 1,4-Dimethylcyclohexanes.

1.74 kcal mol^{-1} (7.28 kJ mol^{-1}). It has no entropy of symmetry (symmetry point group $\mathbf{C_s}$; $\sigma = 1$) and no entropy of mixing, since the two conformers are superposable. The trans isomer consists of two conformers, the predominant e,e and the much less abundant a,a whose energy level is 2×1.74 or 3.48 kcal mol^{-1} (14.56 kJ mol^{-1}) above the e,e, since it has two axial methyl groups. The Boltzmann distribution thus corresponds to 99.7% e,e conformer and 0.3% a,a at 25°C (the amount of the diaxial conformer is less at lower temperatures and more at elevated ones). Use of Eq. 10.1 thus leads to an overall conformational enthalpy of $0.997 \times 0 + 0.003 \times 3.48$ or 0.01 kcal mol^{-1} (0.04 kJ mol^{-1}). The entropy of symmetry is $-R \ln 2$ (symmetry point group $\mathbf{C_{2h}}$; $\sigma = 2$) or -1.38 cal mol^{-1} K^{-1} (-5.76 J mol^{-1} K^{-1}) and the entropy of mixing of the two conformers is $-R(0.997 \times \ln 0.997 + 0.003 \times \ln 0.003)$ or 0.04 cal mol^{-1} K^{-1} (0.17 J mol^{-1} K^{-1}). One thus calculates an enthalpy difference between the two diastereomers of 1.73 (1.74 − 0.01) kcal mol^{-1} (7.24 kJ mol^{-1}) and an entropy difference of $-0.04 + 1.38$ or 1.34 cal mol^{-1} K^{-1} (5.59 J mol^{-1} K^{-1}), the enthalpy favoring the trans isomer and the entropy the cis. The experimental data, along with the calculations, are shown in Table 11.9. It must be kept in mind that the 1.74 kcal mol^{-1} (7.28 kJ mol^{-1}) value for the conformational energy of methyl is a liquid-phase value and that, as already explained in the case of the butane conformers (p. 601), gas-phase enthalpy differences differ from liquid-phase ones because of differences in heats of vaporization. In the case of enthalpy differences between dimethylcyclohexane diastereomers, such differences can be determined experimentally, and therefore ΔH^0 values are available for both liquid and vapor (Table 11.9).

The situation in 1,3-dimethylcyclohexane (Fig. 11.26) is simpler because both diastereomers exist in single conformations: the trans isomer because the two

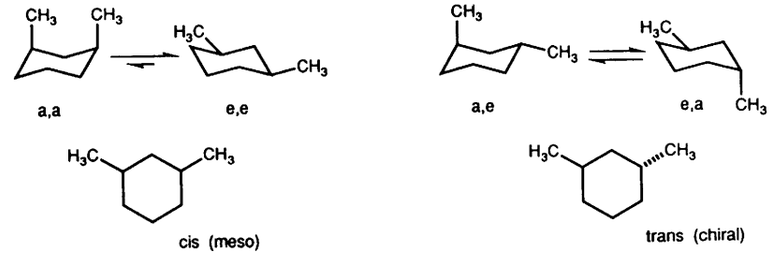

Figure 11.26. 1,3-Dimethylcyclohexane.