Conformational Preference of the Isocyanato-group ¹

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The conformational free energy for the isocyanato-group ($-\Delta G^{\circ}_{NCO}$) in isocyanatocyclohexane is calculated from the n.m.r. spectrum by use of data obtained from the spectra of cis- and trans-4-t-butyl-1-isocyanatocyclohexane. From measurements of the chemical shift and the coupling constants in the spectrum at 35° values for ΔG°_{NCO} of 0.39 ± 0.02 and 0.48 ± 0.15 kcal./mole, respectively, are obtained; from the spectrum at -75° the value calculated for $\Delta G^{\circ}_{\text{XCO}}$ is 0.60 ± 0.1 kcal./mole. An energy barrier for chair-boat interconversion in isocyanatocyclohexane of 10.8 kcal./mole is obtained from the coalescence temperature. The synthesis of the above cis- and transisomers is described.

NUCLEAR magnetic resonance spectroscopy is one of the most accurate methods of determining the freeenergy difference between the axial and equatorial conformations of substituent groups in cyclohexane derivatives.² To obtain the necessary data for calculating $-\Delta G^{\circ}_{\rm NCO}$ for isocyanatocyclohexane (I) and cis- and trans-4-t-butyl-1-isocyanatocyclohexane, (II) and (III) respectively, were prepared and their n.m.r. spectra recorded at ambient temperature. These cisand trans-isomers, hitherto unknown, were prepared from the corresponding acid chloride via the Curtius reaction.

The n.m.r. spectra of (II) and (III) show two main regions of absorption; a large signal at high field and a smaller signal at low field, of relative areas 18:1. The signal at low field is caused by the tertiary proton $(\alpha$ -proton) bonded to the same carbon atom as the isocvanato-group, which has a lower diamagnetic shielding than the other protons. The cis- and trans-isomers are readily characterised from the n.m.r. signal of the Axial and equatorial protons generally α-proton. differ in chemical shift if the chemical environment is otherwise the same ³ and the signal of the axial proton usually appears at higher field. The coupling constant between neighbouring axial protons, Jaa, is generally two to three times as large as the coupling constant between an axial and a neighbouring equatorial proton, Jae.³ The coupling constant between two neighbouring equatorial protons, Jee, is even lower,⁴ although the difference between Jae and Jee is small. For this reason the axial and equatorial protons adjacent to the α -proton are not identical and the signal of the α -proton is the X part of an A₂B₂X system.⁵ The difference in coupling constants results in the signal caused by an axial α -proton being broader than that caused by an equatorial α -proton. The signal of the α -proton in (III) is broader and appears at a higher field than the signal of the α -proton in (II) (Figure 1).

Because of the rapid rate of inversion of the cyclohexane ring in (I) at room temperature, the chemical shift, the coupling constants, and thus the band width,

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1967, 1044. ² N. C. Franklin and H. Feltkamp, Angew. Chem. Internat. Edn., 1965, 4, 774.

of the α -proton signal are averaged values, reflecting the position of the equilibrium between the conformation in which the α -proton is equatorial (Ia) and that in which it is axial (Ib). To calculate the equilibrium constant



FIGURE 1 N.m.r. spectra (100 MHz in CDCl₂ at 35°)

cis-4-t-Butyl-1-isocyanatocyclohexane (II); B, trans-4-t-Α. Butyl-1-isocyanatocyclohexane (III); and C, Isocyanatocyclohexane (I)

for (I) the magnitude of these properties for the individual conformers must be known. These values were determined from the n.m.r. spectra of (II) and (III) since in these compounds, because of the presence of the bulky t-butyl group, the isocyanato-group is fixed axially and equatorially, respectively. In using this method the common assumption was made that the 4-t-butyl group has no influence on the property being measured. Accurate chemical shift measurements were made on expanded spectra of the α -protons and a value for K (1.90 \pm 0.05), and hence for $-\Delta G^{\circ}_{\rm NCO}$ (0.39 \pm 0.02

³ R. U. Lemieux, R. Kullnig, H. J. Bernstein, and W. G. Schneider, J. Amer. Chem. Soc., 1957, 79, 1005.
⁴ F. A. L. Anet, J. Amer. Chem. Soc., 1962, 84, 1053.
⁵ J. A. Pople, W. G. Schneider, and H. J. Bernstein, 'High Resolution Nuclear Magnetic Resonance,' McGraw-Hill, New Nuclear Magnetic Resonance,' McGraw-H York, 1959.

¹ A note of some of these results appeared in Chem. Comm.,

kcal./mole) and the proportion of equatorial conformer (ca. 66%) calculated.¹



An alternative method ¹ for determining $-\Delta G^{\circ}_{\rm NCO}$ is to use the band widths of the α -proton multiplet. These widths were measured between the outermost lines of the multiplet (Figure 2). In (II) the α -proton signal is largely unresolved but the outermost lines are



FIGURE 2 *a*-Proton signal of compounds as in Figure 1

apparent from inflections in the curve. The α -proton signal in (I) is not completely resolved but the outermost peaks were seen reasonably clearly. The corresponding signal in (III) showed a fine structure as expected, the signal being a triplet, separating Jaa, each component itself a triplet, separations Jae. The value of $-\Delta G^\circ_{\rm NCO}$ obtained in this way ¹ is 0.48 \pm 0.15 kcal./mole.

The magnitude of the coupling constants, Jaa, Jae, and Jee can be obtained from these spectra. Direct measurement on the observed nonet of the α -proton of (III) gave Jaa = 10.88 Hz and Jae = 4.00 Hz. Calculation from the band width of the α -proton signal of (II) (=2Jae + 2Jee) gave Jee = 2.55 Hz. It is assumed that Jea = Jae although it has been pointed out that this need not necessarily be so.⁶ Errors in the coupling sum may be caused by second-order effects as a result of strong coupling between the geminal protons, but these effects are minimised in the spectra recorded at 100 MHz. The average $-\Delta G^{\circ}_{NCO}$ value obtained from these two methods represents a preference of the isocyanato-group for the equatorial position to the extent of about 67% at 35°.

The only direct method available for investigating conformational equilibria is the measurement of the area under the n.m.r. signal at low temperature. The α -proton signal of (I) was recorded at 37°, -50°, -55°, -65°, and -75°. At 37° the signal appears as a broad band *ca*. 17 Hz in half-width. On cooling the solution a gradual broadening and then separation of the signal is observed and at -75° the spectrum shows two distinct bands separated by about 37 Hz (Table 1). The separation of the single peak into two bands shows that

TABLE 1 N.m.r. spectrum of isocyanatocyclohexane at 60 MHz

		α-Protor	ı	
Temp.	Chemic (p.p.m. fro	al shift om Me ₄ Si)	½-Width (Hz)	-CH ₂ - protons ‡-Width (Hz)
37°	3.42		17	40
-50	3.47		25	54
-55	3.83	3.40		57
-65	3.92	3.35		65
-75	3.95	3.35		67

the rate of chair-chair interconversion has been slowed sufficiently at low temperature that the mean lifetime in any given conformation is larger than the transition time of a nuclear spin. The peak at low field is assigned to the equatorial protons and the peak at high field to the axial protons. Marked changes also occurred as the temperature was lowered in the shape of the high-field signal due to the ring methylene protons.

The populations of the equatorial and axial α -protons in equilibrium were measured at -75° by weighing the peaks and from integrams of the peaks. Five copies of the spectrum were obtained and the total weight of the α -proton signal determined. The smaller peak was then cut off and the remaining axial proton peak weighed. Two integrams of the spectrum were recorded and the relative heights for the axial and equatorial protons measured. The summarised results (Table 2) give a value for $-\Delta G^{\circ}_{\rm NCO}$ at -75° of 0.60 ± 0.1 kcal./mole.

⁶ D. H. Williams and N. S. Bhacca, J. Amer. Chem. Soc., 1964, 86, 2742.

TABLE 2

Conformational equilibrium for isocyanatocyclohexane $at - 75^{\circ}$

	Axial		$-\Delta G^{\circ}_{NCO}$
Method	NCO (%)	K	(kcal./mole)
Weighed peak areas	17.5 ± 3	4.72 ± 1.2	0.61 ± 0.11
Integrated peak areas	18.5 + 2	4.41 ± 0.65	0.59 ± 0.05

The low-temperature spectra obtained were very similar to those published recently by Herlinger and Naegele,⁷ although the latter spectra recorded at 100 MHz showed considerably sharper bands than we obtained. These authors, from the ratio of the two peak areas, give a value for $-\Delta G^{\circ}_{\rm NCO}$ of 0.44 kcal./mole at -70° .

An additional piece of information can be obtained from the low-temperature spectrum of (I). The coalescence temperature for axial and equatorial α -protons is related to the rate constant for interconversion,⁸ as $k' = \sqrt{2\pi}(Va - Ve)$, where (Va - Ve), the frefrequency separation of the axial and equatorial lines at low temperature, is equal to $37 \cdot 2$ Hz. The total rate constant (k') is calculated to be 165.3 sec.⁻¹ at the coalescence temperature of approximately 219°K. The above rate constant is the total for the forward and reverse reactions; thus, if it is assumed that these are identical, the desired rate constant for the chair-chair interconversion is 82.6 sec.⁻¹. Using the Eyring equation (1), where k is the rate constant and K the transmission coefficient (assumed = 1), we calculate that the energy

$$k = \frac{KkT}{h} \exp\left(\frac{-\Delta G^{\ddagger}}{RT}\right) \tag{1}$$

barrier that must be surmounted to convert a chair form to a boat form is 10.8 kcal./mole. This value does not differ significantly from that observed for cyclohexane and substituted cyclohexanes.⁹

The $-\Delta G^{\circ}_{NCO}$ values obtained from the chemical shift and band widths of the α -protons in the 4-t-butyl substituted systems are in good agreement, considering the assumptions made, with the value obtained by the low-temperature method. Doubts about the validity of these assumptions have been expressed on various occasions and recently Wolfe and Campbell¹⁰ have produced evidence which suggests that for some cyclohexane compounds the 4-t-butyl group affects the chemical shift of protons at the 1- and 2-positions. However, more recently, Eliel and Martin¹¹ concluded that whereas a 3-t-butyl group does somewhat affect the proton shift at C(1), a 4-t-butyl group in a carbocyclic system apparently does not and it therefore appears that the n.m.r. method as originally suggested 12 is suitable for determining conformational equilibria in cyclohexanes. The only theoretically unobjectionable approach is to use the mobile system itself and to slow the interconversion of conformational isomers at low temperature.

In general the magnitude of $-\Delta G^{\circ}$ is controlled by the number rather than the type of substituents on the atom next to the cyclohexane ring. For example, $-\Delta G^{\circ}$ decreases through the series CH₃, CH=CH₂ (or CHO), CN. It might be expected that the $-\Delta G^{\circ}$ value would similarly decrease through the series NH₃⁺, NH₂, NCO and this appears to be so, $-\Delta G^{\circ}$ for NH₃⁺ and NH₂ being 1.9 and 1.2 kcal./mole respectively.

The low experimental value for the conformational free energy of the isocyanato-group indicates that it is of relatively small steric size with respect to the cyclohexane ring. The isocyanato-group, when in the axial position, would be expected to prefer an orientation such that the plane of the group is perpendicular to the plane of the **3**,5-syn-axial carbon-hydrogen bonds, with the carbonyl group directed away from this plane. An alternative, favourable conformation is that in which the plane of the isocyanato-group is parallel to the plane of the 3,5-syn-axial carbon-hydrogen bonds. However there could be some repulsion in this orientation from the equatorial 2-hydrogen and the axial 3-hydrogen.

EXPERIMENTAL

Melting points, determined on a Gallenkamp apparatus (design no. 889, 339), are uncorrected. Refractive indices were determined on a Bellingham and Stanley Abbé 60 refractometer. Vapour-phase chromatograms were recorded on a Pye Argon Chromatograph with 20% silicone elastomer E301 on a 30/80 mesh Celite column 1.2 metres long. I.r. spectra were recorded as liquid films or as potassium bromide discs on a Perkin-Elmer 'Infracord'. N.m.r. spectra at normal temperature were determined for deuteriochloroform solutions, with tetramethylsilane (τ 10) as internal standard, on a Varian Associates HA-100 high-resolution spectrometer and at low temperatures for the same solutions on a Varian Associates A-60 spectrometer.

Isocyanatocyclohexane (I) was redistilled before use, b.p. $66^{\circ}/20$ mm., and was pure by v.p.c.

4-t-Butylcyclohexanecarboxylic Acids.—4-t-Butylbenzoic acid (89 g., 0.5 mole) was suspended in hot water (100 ml.) and sodium hydroxide (20 g., 0.5 mole) was added gradually, with stirring, to obtain a clear solution. This solution was boiled with activated charcoal (25 g.) and filtered, and after repetition of the charcoal treatment the solution was warmed at 100° for $2\frac{1}{2}$ hr. with fresh Raney nickel catalyst [W5 ¹³ from 40 g. of nickel-aluminium alloy (1 : 1)]. After filtration a fresh portion of Raney nickel catalyst, as above, was added and the solution hydrogenated at 180°/ 110 atm. of hydrogen in a 2 1. rocking autoclave. The catalyst was filtered off from the hot solution and on allowing the solution to stand a sodium salt (25 g.) crystallised. Acidification with 5N-hydrochloric acid of an aqueous

⁷ H. Herlinger and W. Naegele, *Tetrahedron Letters*, 1968, 4383.

⁸ H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, 1956, **25**, 1228.

⁹ F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *J. Chem. Phys.*, 1964, **40**, 3099.

¹⁰ S. Wolfe and J. R. Campbell, Chem. Comm., 1967, 872.

¹¹ E. L. Eliel and R. J. L. Martin, J. Amer. Chem. Soc., 1968, 90, 682.

¹² E. L. Eliel, Chem. and Ind., 1959, 568.

¹³ A. A. Pavlic and Homer Adkins, J. Amer. Chem. Soc., 1946, 68, 1471.

J. Chem. Soc. (B), 1969

solution of this salt gave *trans*-4,t-butylcyclohexanecarboxylic acid (21 g.), m.p. 173—174° (lit.,¹⁴ 174—174·5°).

The filtrate from the sodium salt crystallisation was acidified with 5n-hydrochloric acid. The precipitated acids were removed, dissolved in boiling aqueous ammonia (1, concentrated ammonia solution: 9, water), and, on cooling the solution, white needles of an ammonium salt separated. These were filtered off, washed thoroughly with aqueous ammonia, dissolved in hot water, and the solution acidified with 5n-hydrochloric acid to yield *cis*-4-t-butylcyclohexanecarboxylic acid (7 g.), m.p. 116—118° (lit.,¹⁴ 117—118°).

A further 40 g. of a mixture of acids was obtained by acidifying the combined mother liquors. The i.r. spectrum showed that these acids contained considerable residual aromatic unsaturation.

trans-4-*t*-Butylcyclohexanecarbonyl Chloride.—trans-4-tbutylcyclohexanecarboxylic acid (9·2 g., 0·05 mole) and thionyl chloride (7·7 ml., 0·1 mole) were refluxed gently together for 2 hr., after the initial reaction had subsided. The excess of thionyl chloride was removed in vacuo at room temperature and the residue distilled to give trans-4-t-butylcyclohexanecarbonyl chloride (8·6 g. 85%), b.p. 113°/7 mm. cis-4-t-Butylcyclohexanecarbonyl chloride was similarly prepared, but the crude product was not purified since distillation causes isomerisation.¹⁴

trans-4-*t*-Butyl-1-isocyanatocyclohexane (III).—*trans*-4-t-Butylcyclohexanecarbonyl chloride (4.05 g., 0.02 mole) and a solution of sodium azide (2.6 g., 0.04 mole) in toluene (25 ml.) was heated under reflux for 5 hr. The mixture was then filtered, the toluene removed from the filtrate under reduced pressure, and the residue distilled to give *trans*-4-t-butyl-1-isocyanatocyclohexane (2.0 g., 55%), b.p. 57°/0.5 mm., $n_{\rm D}^{20}$ 1.4618, $\nu_{\rm max}$, 2255 cm.⁻¹ (very strong,

-N=C=O), which was characterised as the *phenylurea* (by treatment with aniline), m.p. 192—195° (from ethanol-water), (Found: C, 74·4; H, 9·5; N, 10·0. $C_{17}H_{26}N_2O$ requires C, 74·41; H, 9·55; N, 10·21%), and as the *diallylurea* (by treatment with diallylamine), m.p. 114—115° [from light petroleum (b.p. 60—80°)] (Found: C, 73·35; H, 10·9; N, 10·2. $C_{17}H_{36}N_2O$ requires C, 73·33; H, 10·86; N, 10·06%).

cis-4-*t*-Butyl-1-isocyanatocyclohexane (II).—Crude cis-4-tbutylcyclohexanecarbonyl chloride (prepared from 5 g. of the cis-acid) and sodium azide (3 g.) in toluene (30 ml.) were heated under reflux for 17 hr. The mixture was filtered and the toluene removed from the filtrate under reduced pressure. The residue (3.6 g.) was a mixture of the isomeric isocyanates (60% cis by v.p.c.). Distillation with a spinning-band column gave a first fraction which, on redistillation, gave pure cis-4-t-butyl-1-isocyanatocyclohexane, b.p. 62°/0.9 mm., $n_{\rm D}^{20}$ 1.4647, $\nu_{\rm max}$. 2255 cm.⁻¹ (very strong, -N=C=O), characterised as the *phenylurea*, m.p. 232—233.5° (from ethanol-benzene) (Found: C, 74.2; H, 9.3; N, 10.35. C₁₇H₂₆N₂O requires C, 74.41; H, 9.55; N, 10.21%).

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¹⁴ H. H. Lau and H. Hart, J. Amer. Chem. Soc., 1959, **81**, 4897.