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CONFORMATIONAL ISOMERISM IN A FULLY SUBSTITUTED CYCLOHEXANE [1)]

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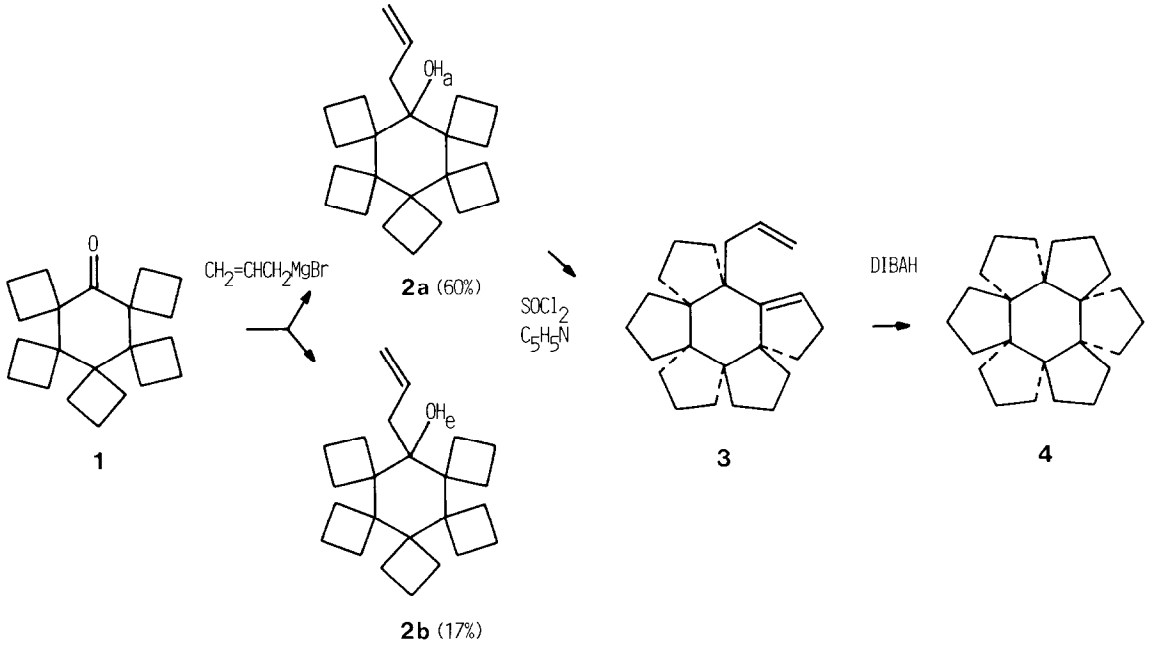
Summary: Conformational isomers 2a (OH_a) and 2b (OH_e) have been obtained through addition of allylmagnesium bromide to ketone 1. Due to the highest barriers of inversion known so far [$\Delta G^{\ddagger}_{413}$ = 134.9 kJ/mol (2a) and 136.9 kJ/mol (2b)] both conformers are indefinitely stable at room temperature in solution.

Caused by the low barriers of inversion normally found in cyclohexanes [$\Delta G^{\ddagger}$ = 40 - 50 kJ/mol [2)]], conformational isomerism [3)] within the cyclohexane family has hitherto been observed only at very low temperatures [4)]. We now report on a cyclohexane whose conformational isomers 2a (OH_a) and 2b (OH_e) are indefinitely stable at room temperature in solution and may be equilibrated at higher temperatures only. Their barriers of inversion [$\Delta G^{\ddagger}_{413}$ = 134.9 kJ/mol (2a) and 136.9 kJ/mol (2b)] exceed those of other cyclohexanes by far [5)].



We made this observation during an attempted synthesis of [6.5]coronane 4 via the sequence 1-2a-3-4 [6)] when we reacted ketone 1 [7)] with allylmagnesium bromide in ether (6h/40°C). To our surprise, not only the expected homoallylic alcohol 2a

(mp 145°C, 60%, OH_a)[8] but also its conformational isomer 2b (mp 154-156°C, 17%, OH_e)[8] was obtained. Both conformers could be separated by column chromatography[9] and have been proved to be indefinitely stable at room temperature in solution.

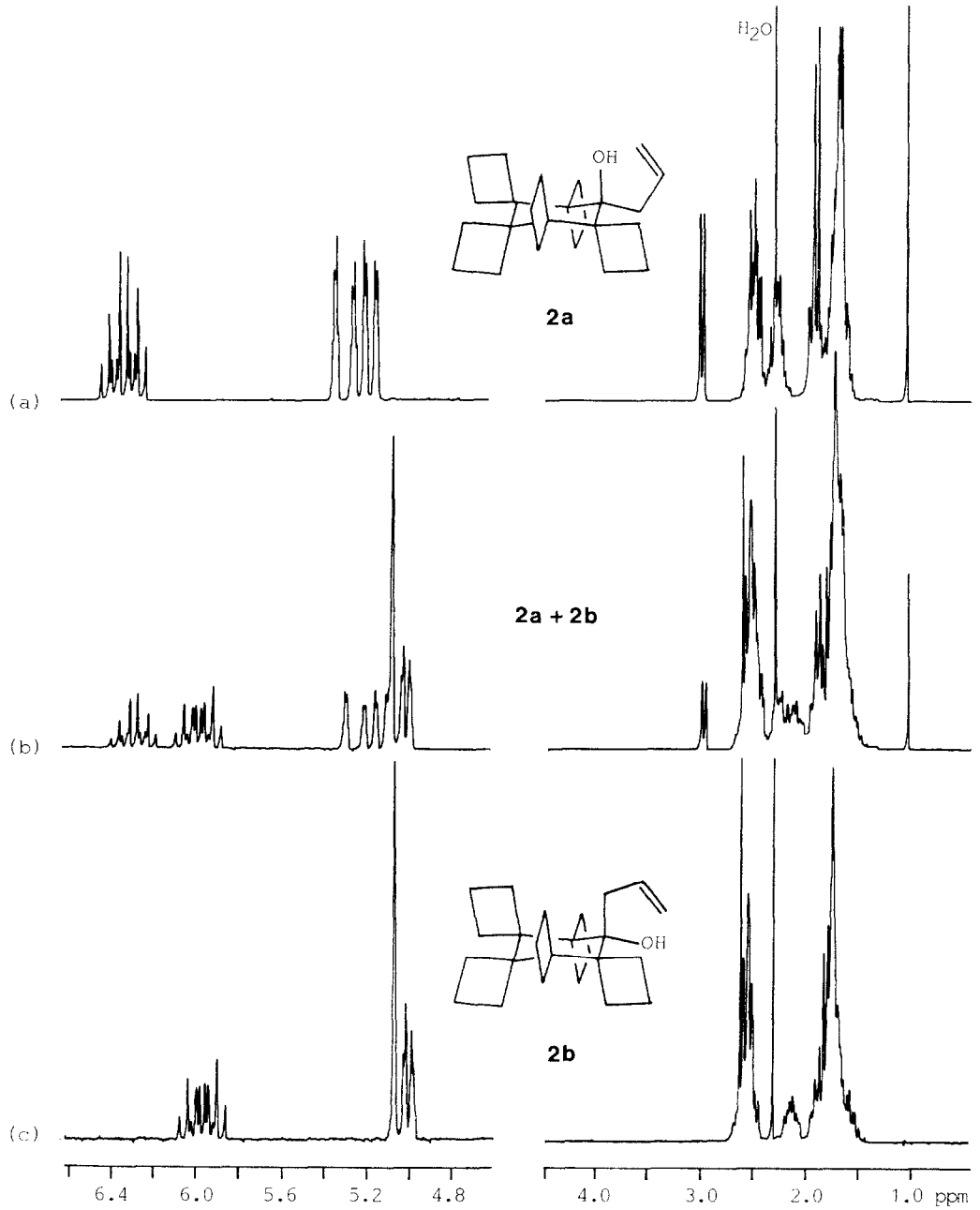


Fig.1. ^1H NMR spectra (200 MHz, d_5-nitrobenzene, 30°C) of 2a (a), an equilibrium mixture of 2a and 2b obtained by heating 2a to 140°C (b), and 2b (c); for clarity, vinylic absorptions (δ = 4.9-6.5 ppm) have been spread and scaled up by a factor of 2.

It thus became obvious that a stereoselective addition of allylmagnesium bromide to ketone 1 had led to 2a and 2b in nonequilibrium concentrations which had been preserved by sufficiently high barriers of inversion at the temperature employed (40°C).

Conformational assignements are based on the known [10] downfield shift of the protons attached to equatorial substituents. Accordingly, the conformer with $\delta(O\underline{H}) = 1.08$ and $\delta(C\underline{H}_2\text{-}CH{=}CH_2) = 3.03$ is recognized as 2a (OH_a) and that with $\delta(O\underline{H}) = 2.65$ and $\delta(C\underline{H}_2\text{-}CH{=}CH_2) < 2.70$ as 2b (OH_e) (fig.1).

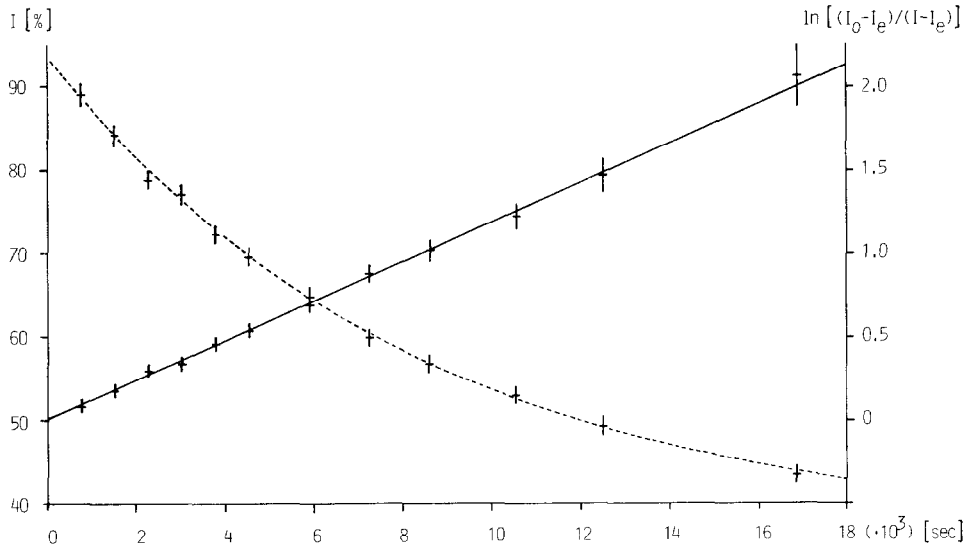


Fig.2. Time course of the decrease in concentration of 2a at 140°C, and least square approximation of $\ln[(I_o\text{-}I_e)/(I\text{-}I_e)] = (k_{2a} + k_{2b})t$; I_o, I and I_e refer to the initial, actual, and equilibrium concentrations of 2a, respectively.

Equilibration could be accomplished on heating solutions of pure 2a and 2b in d_5-nitrobenzene to 140°C. Identical mixtures composed of 34% 2a and 66% 2b indicated that 2b is slightly favoured over 2a ($\Delta G^o = 2.0 \pm 0.1$ kJ/mol). The rate constants of the forward (k_{2a}) and reverse process (k_{2b}) were then determined at 140°C from the time course of the decrease in concentration of 2a. Careful integration of the vinylic absorptions in the 4.9-6.5 ppm region of the ^{1}H NMR spectra (fig.1) were substantial. As could be expected, the equilibration followed opposing first order kinetics [11] (fig.2) and led to $k_{2a} = 7.568 \cdot 10^{-5}$ sec^{-1} and $k_{2b} = 4.277 \cdot 10^{-5}$ sec^{-1} at 140°C. Insertion of these data to the Eyring equation then yielded the free energies of activation as $\Delta G^{\ddagger}_{413} = 134.9 \pm 0.2$ kJ/mol (2a) and $\Delta G^{\ddagger}_{413} = 136.9 \pm 0.2$ kJ/mol (2b) and thereby the highest barriers of inversion of a cyclohexane derivative known so far [5].

It may be expected from the above that other cases of conformational isomerism in fully substituted cyclohexanes will be detected and that still higher inversion barriers than those of 2a and 2b will be met.

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References and notes

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3) We use the term 'conformational isomerism' in a sense defined by Dale (J.Dale, Stereochemie und Konformationsanalyse, Verlag Chemie, Weinheim 1978); for this and other definitions see also L.Ernst, Chem. Unserer Zeit 17,21(1983).

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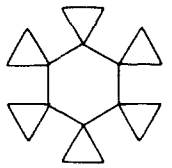
5) Until now the highest barriers of inversion of a cyclohexane derivative were those of 5 ($\Delta G^{\ddagger}_{298}$ = 89.4 kJ/mol) and 6 ($\Delta G^{\ddagger}_{298}$ = 92.0 kJ/mol): L.Fitjer, U.Klages, W.Kühn, D.S.Stephenson, G.Binsch, M.Noltemeyer, E.Egert and G.M.Sheldrick, Tetrahedron 40, 4337 (1984).



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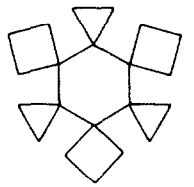

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6) D.Wehle and L.Fitjer, to be published.

7) L.Fitjer, M.Giersig, W.Clegg, N.Schormann and G.M.Sheldrick, Tetrahedron Lett. 24, 5351 (1983).

8) 2a and 2b gave correct elemental analyses and/or high resolution mass spectral data. IR, ^{1}H NMR and mass spectral data are in accord with the structures given. ^{13}C NMR data are as follows: 2a (C_6D_6): = 16.70, 17.03, 17.15, 25.42, 26.37, 26.89, 27.59, 28.47, 28.73, 38.76, 49.33, 50.39,52.39, 79.14, 116.76,137.67; 2b (C_6D_6): = 16.66, 17.19, 17.49, 25.70, 27.04,27.27, 28.22, 28.49 (coincidence of two lines), 39.75, 50.46, 50.51, 54.13, 77.23, 117.44, 137.19; by use of $CDCl_3$ as solvent the line at = 28.49 is resolved, but the lines at = 50.46 and 50.51 coincide instead.

9) Gas chromatography resulted in partial (210°C / 4min) to full conversion (240°C / 4min) to ketone 1 via a retro-ene-reaction.

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