Thermodynamically Preferred Axial Allylic –NHTs Substituent in Simple 1-Triisopropylsilyl(oxy) Cyclohexenes: Solid State Conformation by X-Ray Crystallography

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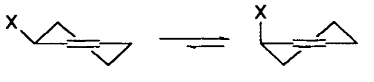
For a series of 6-(4-methylphenylsulphonyl)amino-1-triisopropylsilyl(oxy)-cyclohexenes the preferred conformation, in the solid state, has the –NHTs (Ts = 4-methylphenylsulphonyl) group in an axial orientation; if the axial-NHTs group experiences a 1,3-diaxial interaction with a methyl group, the equatorial conformation becomes the thermodynamically more stable form.

The preferred conformation of cyclohexene has been the subject of extensive investigation for many years.[1] Both ^1H and ^{13}C NMR studies appear to indicate that cyclohexene, substituted by an electronegative allylic group, shows a preference for an axial orientation (see Scheme 1).[2] This reversal of the normal predilection for thermodynamic equatorial orientation has been ascribed to stabilization of the pseudo axial orientation through π–σ^*_{C-X} interactions (lower σ^*_{C-X} energy).[3] Unfortunately, because simple monocyclic cyclohexene derivatives are usually liquids, there is paucity of X-ray crystallographic data that would define, in the solid state, the thermodynamically preferred disposition of allylic substituents.[4] Our recent investigation of the chemistry of triisopropylsilyl enol ethers has indicated that an allylic -NHTs group prefers an axial conformation.[5] Here we report the solid state structures for a number of monocyclic 6-(4-methylphenylsulphonyl)amino-1-triisopropylsilyl(oxy)-cyclohexenes that clearly show, in the absence of other axial interactions, the allylic -NHTs (Ts = 4-methylphenylsulphonyl) group prefers an axial conformation.

Treatment of the triisopropylsilyl enol ethers **1–5** with the Sharpless aminating reagent $(TsN)_2Se$[6] in dichloromethane at 25 °C gave the α-aminated adducts **6–10** in the yields shown in Scheme 2. All of the α-animated adducts **6–10** gave suitable crystals for single crystal X-ray crystallographic analysis.‡ In **6, 7, 8** and **9** the -NHTs group is in an axial conformation, and Fig. 1 shows an ORTEP diagram of **7** which is representative



Scheme 1

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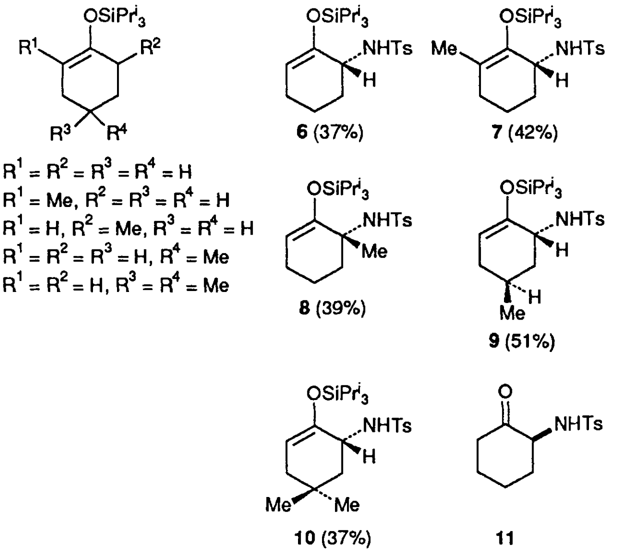
† Author for correspondence concerning X-ray crystallographic data.

‡ *Crystal data* for **7**: $C_{23}H_{39}NO_3SSi$, monoclinic, space group $P2_1/c$ (No. 14), a = 16.182(3), b = 12.548(3), c = 12.742(2) Å, β = 104.350 (13)°, V = 2506.6(9) Å^3, D_c = 1.16 g cm^{-3} for Z = 4 and F (000) = 952. Data were collected at −75 °C on a Nicolet R3 diffractometer using a graphite monochromator Mo-Kα radiation (λ = 0.7107 Å) and equipped with an LT-2 low temperature delivery system. The data were collected from 4.0 to 50° in 2θ using the ω-scan technique, with a 1.2° scan range in ω at a constant 10° min^{-1}. The structure was solved by direct methods and refined by full-matrix least squares with anisotropic thermal parameters for all the non-H atoms. All hydrogen atoms were located from a difference electron density map and refined with isotropic thermal parameters. A total of 4806 reflections were measured of which 4414 were unique (R_{inf} = 0.0384). Reflections having $F_o < 4\sigma(F_o)$ were considered unobserved (972 reflections).

For **10**: $C_{24}H_{41}NO_3SSi$, orthorhombic, space group $Pbca$ (No. 61), a = 11.982(3), b = 13.493(3), c = 32.579(6) Å, V 5267(2) Å^3, D_c = 1.14 g cm^{-3} for Z = 8 and F(000) = 1968. The data were collected at −100 °C and refined as for compound **7**. A total of 9947 reflections were measured of which 4665 were unique (R_{inf} = 0.0343). Reflections having $F_o < 4\sigma(F_o)$ were considered unobserved (2008 reflections). All hydrogen atoms were calculated in idealized positions.

Atomic coordinates, bond lengths and angles, and thermal parameters for compounds **6–11** and **13–16** have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 2

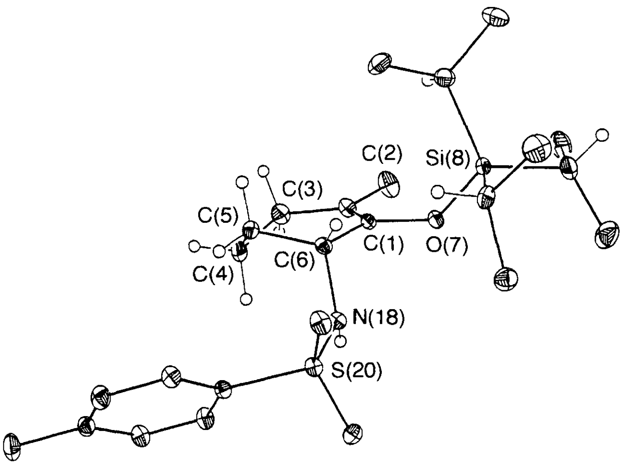


Fig. 1 ORTEP diagram of **7**. Selected bond lengths (Å) and angles (°): C(1)–C(2) 1.33, C(1)–C(6) 1.50, C(1)–O(7) 1.38, C(6)–N(18) 1.48, Si(8)–O(7) 1.66; C(2)–C(1)–C(6) 123.4, C(6)–C(1)–O(7) 115.3, O(7)–C(1)–C(2) 121.2, N(18)–C(6)–C(1) 107.9, Si(8)–O(7)–C(1) 131.4.

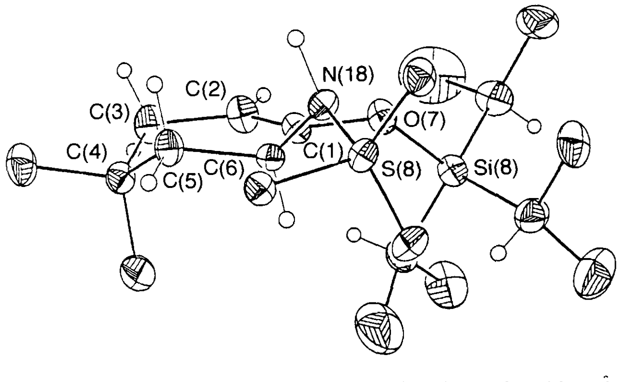
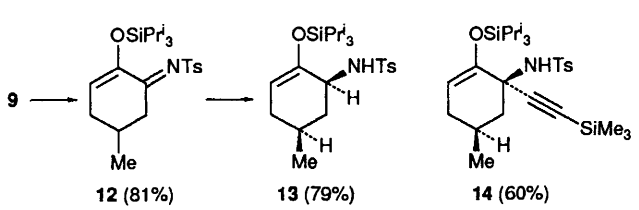
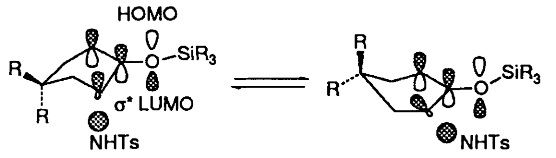


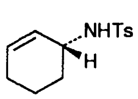
Fig. 2 ORTEP diagram with **10**–Ts removed. Selected bond lengths (Å) and angles (°): C(1)–C(2) 1.31, C(1)–C(6) 1.51, C(1)–O(7) 1.38, C(6)–N(18) 1.48, Si(8)–O(7) 1.65; C(2)–C(1)–C(6) 122.7, C(6)–C(1)–O(7) 114.4, O(7)–C(1)–C(2) 122.9, N(18)–C(6)–C(1) 109.8, Si(8)–O(7)–C(1) 133.9.



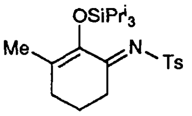
Scheme 3



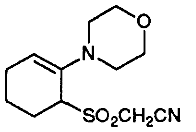
Scheme 4 Competing π–σ* stabilization against 1,3-diaxial interactions



15



16



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of these structures. The 4,4-dimethyl adduct **10** prefers the –NHTs substituent to occupy an equatorial conformation, see Fig. 2.‡ Mild acidic hydrolysis of **6** gave the ketone **11** in which the α-NHTs group is shown from the X-ray data to now be in an equatorial conformation. The indicated bond angles and lengths do not vary significantly throughout the series **6–10**, and notably there are no appreciable differences between these values for the axial-NHTs *versus* equatorial-NHTs.

Oxidation of **9** with SeO_2–dioxane gave the imine **12** (Scheme 3; 81%)[7] which upon reduction with $NaBH_4$ or $LiAlH_4$ gave exclusively the equatorial adduct **13** (79%). This corresponds to the delivery of hydride from an axial trajectory. Similarly, addition of lithium trimethylsilylacetylide gave only axial addition, resulting in **14** (60%). The equatorial –NHTs group in both **13** and **14** was confirmed by X-ray crystallography. All of the crystal structures show the cyclohexenyl ring in a sofa conformation.[1]

The π–σ* interaction depicted in Scheme 4 stabilizes the axial conformer and we have called this interaction a cross-conjugated stabilization effect. For the compounds **6**, **7**, **8** and **9**, which lack any 1,3-NHTs–methyl diaxial interactions, the axial conformer is the thermodynamically more stable conformer. When the π–σ* stabilization is allowed to compete against 1,3-NHTs–methyl diaxial interactions, substrates **10**, **13** and **14**, orientate the –NHTs group in an equatorial conformation.

It is interesting to note that there is hardly any difference in the carbon resonance (C-6) through the series **6**, **7**, **9**, **10** and **13** (δ 52.5, 53.6, 53.0, 53.3 and 52.0, respectively). It would be misleading to use *A*-values to estimate the degree of stabilization imparted by the π–σ* interaction,[8] (there may also be an $A_{1,3}$-strain contribution to axial stabilization),[9] but since a 1,3-diaxial interaction (Me) is enough to overwhelm it, and the *gem*-adduct **8** prefers equatorial Me, the π–σ* stabilization is probably between 1.5–2.0 kcal mol^{-1} (1 cal = 4·184 J). Finally, it should be noted that in the solid state the parent cyclohex-2-enyl-1-NHTs[10] **15** is in a twist-chair conformation with the –NHTs group in an equatorial position (from X-ray data). This of course should be contrasted with **6** (sofa-conformation, –NHTs axial).§

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§ The H_X (methine) vicinal coupling constants (^1H NMR) for **6** and **15** are both small (*J* 3–4 Hz) but the dihedral angles are similar if one assumes that, in solution, the major conformer of **6** is in the sofa form and for **15** the twist-chair dominates.

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