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Conformational energy (A-value) of the 4-phenyl-1,2,3-triazolyl group

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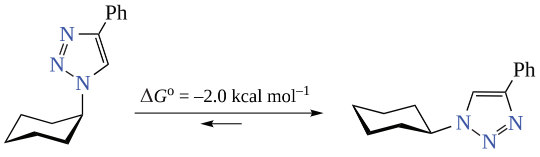
Conformational energy (A-value) of the 4-phenyl-1,2,3-triazolyl group was estimated as 2.0 kcal mol^{-1} (8.5 kJ mol^{-1}) using ^{1}H NMR-based conformational study for a set of (4-phenyl-1,2,3-triazol-1-yl)cyclohexanes. This provides a reasonable estimation also for the conformational energy of 1,2,3-triazolyl group itself and its substituted analogues.



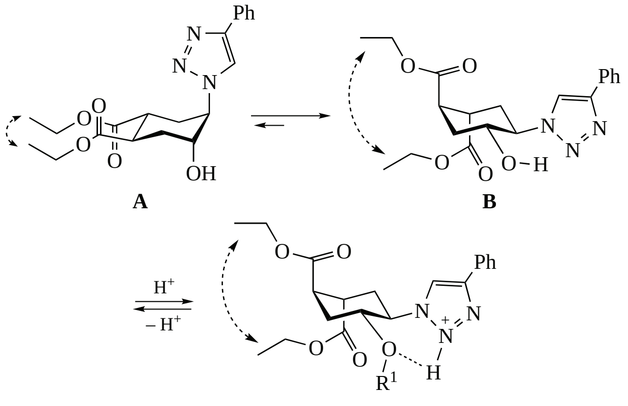
Keywords: (1,2,3-triazol-1-yl)cyclohexane conformations, cyclohexyl-1,2,3-triazol, triazolyl conformational energy, click reaction.

In memory of academician Nikolay S. Zefirov, a Teacher and Friend

Conformational switches are molecules that reversibly change the relative orientation of their parts when triggered by external stimuli: metal cation complexation, electric field, light at specific wavelength, pH changes, *etc*. They are useful in designing controllable compounds with a variety of functions which may include drug release, sensor techniques, or information storage and transmission.[1–5] The cyclohexane-based molecular systems provide an efficient prototype for such devices. For instance, *trans*-2-aminocyclohexanols[5–7] and *trans*-2-(azaarylsulfanyl)-cyclohexanols[8,9] were successfully used as the pH-triggered conformational switches. The variation of amino groups and other substituents allows a broad adjustment of the structure, so that the system could be tuned for a desired conformational response affecting a variety of properties.

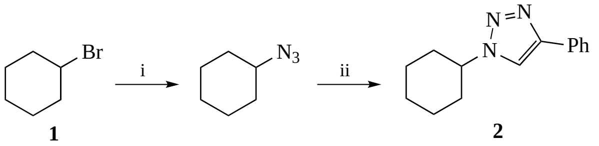
The 'click' reaction (the Huisgen alkyne–azide cycloaddition) may serve as a convenient approach to equip the cyclohexane and similar scaffolds with a virtually unlimited variety of substituents for different desired applications (see, *e.g*., refs. 10–12). Inspired by our abovementioned results, we used this cycloaddition for the synthesis of a series of structurally similar *trans*-2-(4-phenyl-1,2,3-triazol-1-yl)cyclohexanols in order to test their conformational switching abilities (Scheme 1).[13]

The initial study of these compounds showed they were largely restricted to conformation **B** with equatorial positions of the 4-phenyltriazolyl (Tz) and hydroxy groups,[13] contrasting with the cited above models that mostly preferred an opposite conformation **A**. This conformational bias could be explained by a strong attraction between Tz and OH, and/or by a large preference for the equatorial position (conformational energy, A-value) of the triazolyl group. The latter seemed to be unlikely, considering the opposite bias of the previously studied analogues with noticeably bulkier 5- and 6-membered cyclic amino groups. However, to the best of our knowledge, the conformational energy of the 1,2,3-triazolyl group was never estimated before, and we decided to measure it experimentally.

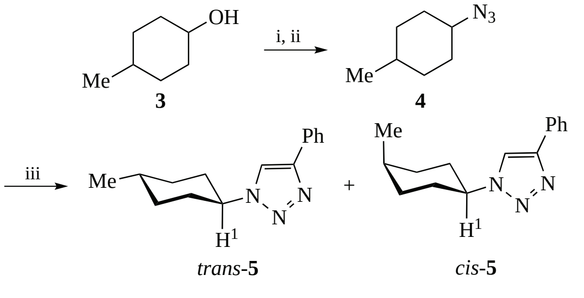


Scheme 1

A set of model (4-phenyl-1,2,3-triazol-1-yl)cyclohexanes was synthesized according to Schemes 2 and 3 (see Online Supplementary Materials for the synthetic procedures). The conformational behavior of the obtained compounds **2**, *trans*- and *cis*-**5** was evaluated by ^{1}H NMR spectroscopy (Table 1).



Scheme 2 *Reagents and conditions*: i, NaN$_3$, DMSO, 189 °C, 12–24 h; ii, PhC≡CH, CuSO$_4\cdot$5H$_2$O, ascorbic acid, H$_2$O, 1,4-dioxane, room temperature, 4 h.



Scheme 3 *Reagents and conditions*: i, MsCl, pyridine, 0 °C, 3 h; ii, NaN$_3$, DMSO, 189 °C, 48 h; iii, PhC≡CH, CuSO$_4\cdot$5H$_2$O, ascorbic acid, H$_2$O, 1,4-dioxane, room temperature, 8 h.

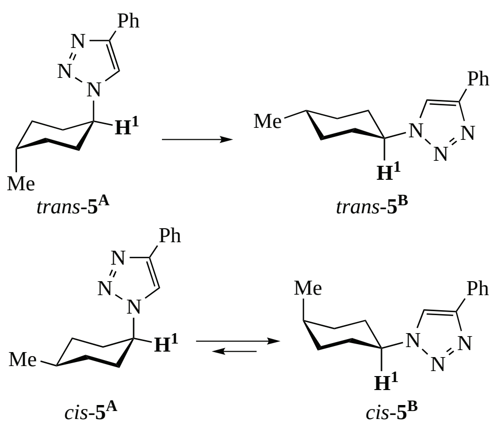
Table 1 ^{1}H NMR data for H^1 and conformational parameters for compounds **2** and *trans*/*cis*-**5**.[a]

Solvent, acid	δ/ppm	W/Hz	n_B (n_{BD}^+) (%)	$\Delta G^o_{\mathbf{B-A}}$/ kJ mol^{-1}	$\Delta G^o_{\mathbf{B-A}}$/ kcal mol^{-1}
2					
$CDCl_3$	4.50	31.5	$97._0$	-8.5_1	-2.0_3
CD_3OD	4.53	31.3	$96._0$	-7.7_8	-1.8_6
$CD_3OD + CF_3COOD$[b]	4.55	31.3	$96._0$	-7.7_8	-1.8_6
trans-**5**					
$CDCl_3$	4.47	32.1[c]	~100	< -13	< -3
CD_3OD	4.50	31.6	$97._5$	-8.9_7	-2.1_4
$CD_3OD + CF_3COOD$[b]	4.52	31.6[d]	$97._5$	-8.9_7	-2.1_4
cis-**5**					
$CDCl_3$	4.55	24.5	$62._2$	-1.2_2	-0.2_9
CD_3OD	4.59	24.3	$61._2$	-1.1_1	-0.2_7
$CD_3OD + CF_3COOD$[b]	4.62	24.3[d]	$61._2$	-1.1_1	-0.2_7

[a] 600 MHz; 0.02-0.03 M solutions; 294 K. [b] CF_3CO_2D was added in large excess (×10–15) to CD_3OD solution. [c] Used as W_B. [d] Poorly resolved signal.

The fast equilibrium [**A**] ⇄ [**B**] (Scheme 4) was examined by ^{1}H NMR spectroscopy (600 MHz). The vicinal coupling constants $^3J_{HH}$ between several protons attached to the cyclohexane moiety are strongly conformation-dependent, which allows an assignment of a predominant conformation and an evaluation of the position of conformational equilibrium. Large vicinal couplings, 9–12 Hz, are observed between the *trans*-diaxial protons, and small values, 2–5 Hz, are measured for the axial-equatorial and equatorial-equatorial vicinal couplings.[14–16] The observation of a single set of well-resolved multiplets with the averaged NMR parameters attests to high rates of both conformational and acid–base equilibria on the NMR time scale. The conformer populations ($n_\mathbf{A}$, $n_\mathbf{B}$) in dilute solutions were estimated as described previously[6–14] using Eliel's equation[15] applied to the averaged signal width $W = \Sigma J_{HH}$ (a sum of spin–spin couplings) of the protons H^1 geminal to the triazolyl groups (see Scheme 4): $W_{\text{observed}} = W_\mathbf{A} n_\mathbf{A} + W_\mathbf{B} n_\mathbf{B}$. These signals were usually well resolved and had chemical shifts in a region apart from the signals of other protons. The parameter W was measured as a distance between terminal peaks of a multiplet (Figure 1). We did not use the averaged chemical shifts for the equilibrium estimation because of their narrow range of variation, general sensitivity to temperature, to the nature of a solvent, additives, complex formation, *etc*. (see Table 1 and Online Supplementary Materials).

The limiting parameter $W_\mathbf{B}$ = 32.1 Hz for the conformers **B** was obtained from the measurements for the *trans*-**5** with a complete bias towards the diequatorial conformation *trans*-$\mathbf{5^B}$ (see Scheme 4, Table 1). The limiting parameter $W_\mathbf{A}$ was set as 12 Hz based on analogous compounds.[14]



Scheme 4

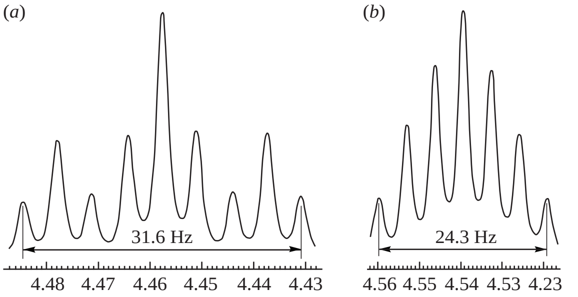


Figure 1 Appearance of CH^1 multiplets in ^{1}H NMR of isomers (*a*) *trans*-**5** and (*b*) *cis*-**5**.

In all studied compounds, the triazolyl ring had a phenyl group attached to position 4. It is reasonable to assume that this remote group does not affect the interactions of triazolyl moiety with the cyclohexane scaffold in both conformers. The data for triazolylcyclohexane **2** demonstrate an almost complete shift of the conformational equilibrium towards the equatorial conformer (~97%). Thus, the latter is more stable than the axial conformer by $\Delta G^\circ_{Tz} = \Delta G^\circ_{\mathbf{2B-2A}} = -2.0$ kcal mol^{-1} (-8.5 kJ mol^{-1}) (see Table 1). This value is between the known conformational energies for the quite bulky methyl and phenyl groups: $\Delta G^\circ_{Me} = -1.74$ kcal mol^{-1} (-7.28 kJ mol^{-1}) and $\Delta G^\circ_{Ph} = -2.8$ kcal mol^{-1} (-11.7 kJ mol^{-1}),[16] and much smaller than for phthalimido group,[17] $\Delta G^\circ_{Phth} = -3.8$–$3.9$ kcal mol^{-1} (-15.9–16.3 kJ mol^{-1}).

However, a direct estimation of the energy parameters for strongly biased equilibria may produce substantial errors. We verified the obtained value of ΔG°_{Tz} by use of the classical 'counterpoise method'[16] employing isomer *cis*-**5** for the NMR measurements (see Scheme 4). Since the competing preferences of two substituents for the equatorial position are partially balanced, the shares of conformers in the *cis*-$\mathbf{5^A}$ ⇄ *cis*-$\mathbf{5^B}$ equilibrium are comparable (see Table 1). Based on the reasonable assumption that the conformational energies of CH_3 and Tz groups are additive, the free energy change for this equilibrium is $\Delta G^\circ(cis\text{-}\mathbf{5^B}\text{–}cis\text{-}\mathbf{5^A}) = \Delta G^\circ_{Tz} - \Delta G^\circ_{Me}$. Therefore, $\Delta G^\circ_{Tz} = \Delta G^\circ(cis\text{-}\mathbf{5^B}\text{–}cis\text{-}\mathbf{5^A}) + \Delta G^\circ_{Me} = -0.29 - 1.74 = -2.03$ kcal mol^{-1} (-8.50 kJ mol^{-1}), which is in a good agreement with the estimation done for compound **2**.

The conformational energy of polar substituents is generally expected to increase in polar hydrogen-bonding solvents due to increase in effective bulkiness. However, for the triazolyl group we observed rather a slight decrease of $-\Delta G^\circ_{Tz}$ in methanol compared to chloroform. Addition of excess CF_3CO_2D did not change the relative population of conformers.

Since the 4-phenyl group in our models is far from the cyclohexane ring and does not create steric repulsions or electrostatic interactions with the cyclohexane scaffold in both conformers, the obtained value provides a reasonable estimation also for the conformational energy of 1,2,3-triazolyl group itself and its 4-substituted analogues. The measured value of the triazolyl conformational energy will be considered in the future design of the cyclohexane-based conformational switches. The substantial magnitude of this parameter may allow a use of this easy-to-make group as a conformational anchor or counterbalance for certain cyclohexane-based derivatives.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.09.006.

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