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Investigation of site selectivity of the stereoselective deprotonation of cyclohexene oxide using kinetic resolution of isotopic enantiomers in natural abundance

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Abstract—Stereoselective deprotonation of epoxides with lithium amides can occur by abstraction of protons from more than one site. The site selectivity of the deprotonation of cyclohexene oxide by several chiral and achiral lithium amides has been investigated. ^{2}H NMR has been used to measure the relative abundances of the isotopomers of the epoxide containing one deuterium. An isotopic stereoisomer, with deuterium in the site undergoing abstraction, reacts slower than its enantiomer and other isotopomers having protium in the same site due to a kinetic isotope effect. This results in a kinetic resolution yielding a relative excess of the less reactive isotopic stereoisomer. Thus, the relative abundance of such an enantiomer increases when compared with those having protium at the site in question as the reaction proceeds. It can be concluded that deprotonation of cyclohexene oxide using some chiral- and non-chiral lithium amides occurs by β_{syn}-deprotonation.
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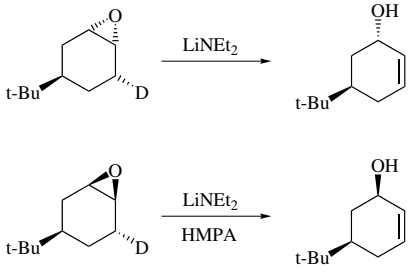
1. Introduction

Lithium amide deprotonation of epoxides is a convenient method for the preparation of allylic alcohols. Since the first report by Cope in 1958,[1] the area has received much attention. In 1980, Whitesell and Felman[2] demonstrated the first asymmetric deprotonation while at present chiral lithium amides for stoichiometric[3–6] as well as catalytic[7–10,3,11,12,6] deprotonations are being developed for highly stereoselective deprotonations.

In the construction of efficient chiral lithium amides for stereoselective deprotonations the structure and energies of the rate limiting diastereoisomeric activated complexes are modelled computationally. Such accurate calculations require knowledge of the molecular composition of the activated complexes and also of which site(s) of the substrate that is preferentially deprotonated. An obvious approach to the solution of the latter problem is to make use of substrates specifically deuterium labelled at the different sites. Such an approach has already been used for a few epoxide substrates.[13–19] Thus, Thummel and Rickborn showed that the deprotonation of *trans*- and *cis*-4-*tert*-butyl-cyclohexene oxide, respectively, by lithium diethylamide, occurs mainly via the β_{syn}-pathway, along with some α-elimination of the *cis*-4-*tert*-butyl-cyclohexene oxide (Scheme 1).[14,18]

Morgan et al. have investigated the deprotonation of deuterium-labelled *cis*-4-*tert*-butyl-cyclohexene oxide by Li–NEt_2, in the presence of HMPA and the β-*anti*-elimination was found to be the major pathway (Scheme 1).[19]

They also investigated the deprotonation of α-labelled cyclohexene oxide by LDA, with the result suggesting



Scheme 1.

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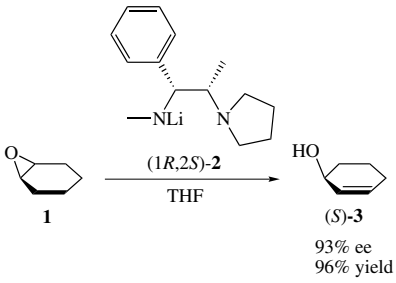
the β-elimination was the major pathway, since no loss of deuterium was found in the deuterium labelled α-position.[19] However, these experiments did not allow a differentiation between β_{syn} and β_{anti} elimination.

Thus, the mechanistic diversity of lithium amide promoted rearrangements of epoxides prompted us to investigate the site selectivity for deprotonation by chiral and achiral lithium amides, in order to establish a basis for the mechanistic investigations by computational chemistry.

Along with the development of NMR spectroscopy and its increased sensitivity over the last few decades, methods have been developed for measurement of ^{2}H and ^{13}C kinetic isotope effects in organic and biochemical reactions using the isotopes in natural abundance.[20–33] Herein, the regioselectivity of stereoselective deprotonations has been investigated by combining ^{2}H NMR studies, chiral isotopomers in natural abundance and kinetic deuterium isotope effects. The approach involves the kinetic resolution of isotopic stereoisomers and was applied to the lithium amide deprotonation of an epoxide.

2. Results and discussion

Cyclohexene oxide **1**, a *meso*-compound, was reacted with the lithium amide enantiomer (1*R*,2*S*)-**2** in THF to give the (*S*)-enantiomer of 2-cyclohexen-1-ol **3** in high enantiomeric excess and in high yield (Scheme 2).[34]



Scheme 2.

The formation of (*S*)-**3** and (*R*)-**3** may occur via pathways involving abstraction of protons at the α-, β_{syn}- and β_{anti}-sites, respectively.

Herein, the site selectivity of the deprotonation reaction was investigated by using the natural abundance of deuterium in the substrate (ca. 0.015 at. %).[35] The presence of one deuterium in a molecule of cyclohexene oxide makes it chiral. Compound **1** has 10 isotopomers (A–F), thus five pairs of isotopic stereoisomers (Scheme 3). Due to the low natural abundance of deuterium the fraction of isotopologues containing more than one deuterium is insignificant in the present context.

The rate of dehydronation of an isotopomer with a deuterium in the site, at which the abstraction takes place, is expected to be lower than that for the other isotopomers having protium in the site in question due to a kinetic isotope effect larger than 1. As a consequence, the relative abundance of the isotopomer with deuterium in the abstraction site would increase as the reaction proceeded. Thus, a comparison of the relative abundances of the epoxide isotopomers before and after deprotonation as determined by ^{2}H NMR reveals the site(s), which is preferentially undergoing abstraction as well as those which do not significantly contribute to product formation.

In Figure 1 is shown a ^{2}H NMR spectrum obtained from a sample of distilled commercially available cyclohexene

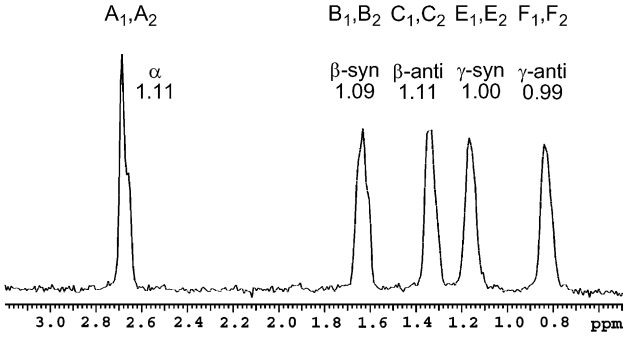
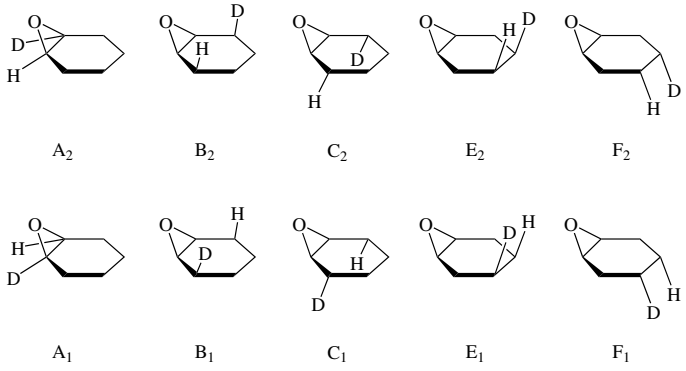


Figure 1. Unlocked ^{2}H NMR spectrum (92 MHz) obtained using ^{1}H-decoupling showing the five signals from unreacted cyclohexene oxide in benzene.



Scheme 3.

Table 1. Results of deprotonations of cyclohexene oxide **1** by the chiral and achiral lithium amides **2**–**13** shown in Scheme 4

Entry	Base	Fraction recovered **1**	ee[a]	Intensities of ^{2}H-signals from recovered **1**[b]				
				α	β_{syn}	β_{anti}	γ_{syn}	γ_{anti}
1	None	1[c]	—[f]	1.09	1.09	1.10	1.00	0.99
2	None	1[d]	—[f]	1.11	1.09	1.11	1.00	0.99
3	(1*R*,2*S*)-**2**	0.50	93.6 (*S*)	1.09	1.58	1.17	1.00	1.02
4	(1*S*,2*R*)-**2**	0.46	93.3 (*R*)	1.12	1.64	1.20	1.00	1.02
5	**4**	0.37	95.9 (*S*)	1.03	1.71	1.15	1.00	0.97
6	**5**	0.47	96.1 (*S*)	1.02	1.63	1.20	1.00	0.97
7	**6**	0.48	78.9 (*S*)	1.09	1.41	1.14	1.00	1.00
8	**7**	—[e]	—[f]	1.02	1.92	1.27	1.00	1.00
9	**8**	0.49	—[f]	1.11	1.47	1.18	1.00	1.01
10	**9**	0.53	—[f]	1.11	1.34	1.16	1.00	1.02
11	**10**	0.42	—[f]	1.11	1.40	1.16	1.00	1.01
12	**11**	0.58	—[f]	1.18	1.30	1.17	1.00	1.01
13	**12**	0.48	—[f]	1.10	1.39	1.15	1.00	0.99

[a] ee of (*S*)-**3** or (*R*)-**3**.
[b] Intensities of ^{2}H NMR signals from recovered **1** after reaction relative to γ_{syn}. Numbers are average values of two or more measurements.
[c] Unreacted **1** from bottle without further treatment.
[d] Unreacted **1** recovered after exposure to workup procedure.
[e] Fraction of **1** not measured.
[f] Not measured since achiral base was used as deprotonating agent.

oxide in benzene using ^{1}H-decoupling. Benzene was used as the solvent in order to observe the expected five deuterium signals as base line separated peaks.

It is interesting to note that the integration of the peaks shows that the abundances of the enantiomer pairs are not equal in the unreacted substrate. For three of the pairs (A_1,A_2; B_1,B_2 and C_1,C_2), the abundances were about 10% larger than that of the remaining two pairs (E_1,E_2 and F_1,F_2) (Fig. 1 and Table 1, entry 1). This shows that the cyclohexene oxide had a chemical formation history during which the relative abundances were made unequal. This knowledge is important for the interpretation of our results (Table 1). The five singlets were assigned to the five enantiomeric pairs of the isotopomers, respectively, using nuclear Overhauser effects (NOE) and computational chemistry (see Experimental).

In the deprotonation experiments described herein, only samples from a single batch of purified cyclohexene oxide were used. Cyclohexene oxide from the batch was also exposed to the workup procedure used in the deprotonation experiments. The relative abundances of the enantiomeric pairs were measured (Table 1, entry 2) and found to be within experimental errors identical to the batch values. The workup procedure did not change the relative abundances of the enantiomeric pairs.

Compound **1** was partially deprotonated by the enantiopure lithium amide (1*R*,2*S*)-**2** in THF (entry 3). The fractions of remaining cyclohexene oxide and product 2-cyclohexen-1-ol were determined using a calibrated quench-extraction GC method (cf. Experimental section).

The remaining cyclohexene oxide from the reaction mixture was isolated using chromatography followed by distillation and analyzed by ^{2}H NMR. The spectrum with

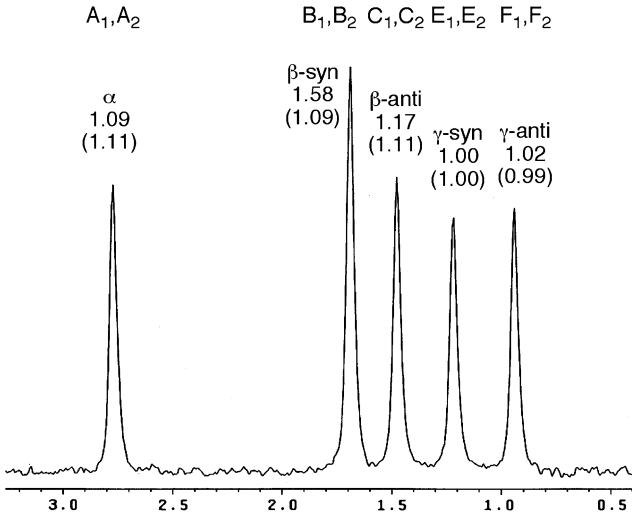


Figure 2. Unlocked ^{2}H NMR spectrum (92 MHz) obtained using ^{1}H-decoupling showing the five signals from recovered cyclohexene oxide in benzene after reaction with (1*R*,2*S*)-**2**.

determined relative abundances of the isotopomer pairs, together with the measured relative abundances of the isotopomer pairs in the starting material (in parentheses) is shown in Figure 2.

Since hydrogens at the γ-positions of cyclohexene oxide were expected to be unreactive towards abstraction under the present reaction conditions, the signals from *syn*- and *anti*-γ-deutrons were used as internal reference signals. The intensity of the signal assigned to E_1,E_2 of **1** was set to 1.00. The fraction of cyclohexene oxide measured by GC, as remaining after quenching of the reaction, was 50%.

Interestingly, one of the peaks that emanated from B_1,B_2, showed a considerably increased relative intensity

(1.58) compared with the corresponding B_1,B_2 signal (1.09) from the starting cyclohexene oxide (entries 3 and 1). Apparently, the dehydronation of the substrate has resulted in a relative enrichment of the B_1,B_2 pair and this shows that the hydrons preferentially abstracted are the β_{syn}-hydrons. This result, together with the high stereoselectivity (93.6% ee of (*S*)-**3**) observed for the deprotonation of **1**, implies that the β_{syn}-proton in B_2 and not the β_{syn}-proton in B_1 is preferentially abstracted. It is concluded that the increased intensity of the B_1,B_2 signal is mainly caused by a primary deuterium kinetic isotope effect (KIE) on the dehydronation of the β_{syn}-hydron in B_1 resulting in relative enrichment of the B_1, that is, the isotopic enantiomer B_1 is kinetically resolved.

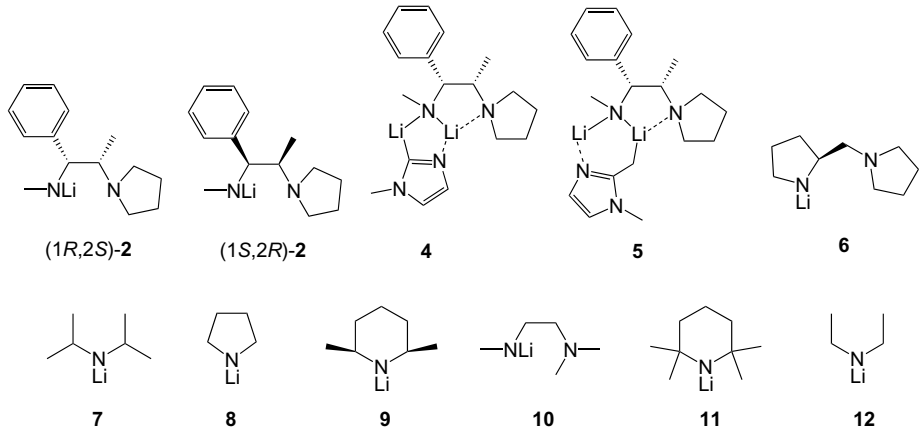
The B_2 enantiomer on the other hand was by analogy predicted to undergo almost exclusive β_{syn}-deprotonation with a rate closely similar to that of unlabelled cyclohexene oxide. The abstraction of the B_2 β_{syn}-deutron was assumed to be much slower due to the combination of the high enantioselectivity and a deuterium isotope effect. Thus, the dehydronation of B_2 resulted in essentially no relative enrichment of this isotopomer. It can be concluded that the relative enrichment of B_1,B_2 almost exclusively emanates from the relative enrichment of B_1.

Another signal, that from the β_{anti}-deuterons in C_1,C_2, also showed some increased relative intensity, from 1.11 in the starting material to 1.17 in the isolated cyclohexene oxide. Apparently, some relative enrichment of one or both of these isotopic enantiomers had occurred (entry 3). This result was consistent with β_{syn}-deprotonation being the major pathway. Some change of hybridization of the β-carbon was expected on going to the activated complex and this is expected to cause a secondary kinetic isotope effect (SKIE) larger than 1 and as a consequence relative enrichment of C_1,C_2 will result. However, some β_{anti}-deprotonation contribution cannot be completely ruled out since such a pathway is also predicted to give enhanced relative intensity of the signal from C_1,C_2 due to a primary isotope effect. Domination of such a mechanism is, however, expected to give only a small increase in the relative intensity of the B_1,B_2 signal due to a secondary deuterium isotope effect. Since this is not in accordance with what has been observed it can be concluded that the *anti*-elimination pathway may at the very most be of minor importance. The relative intensity of the signal from the α-deuterons on the other hand (entry 3) does not show any significant change during the reaction, which suggests that the fraction of α-deprotonation is insignificant.

The chemical origin of the cyclohexene oxide substrate and its precursors is unknown. Therefore, it cannot be excluded that some enantioselection of isotopic enantiomers has taken place during the formation of the cyclohexene oxide molecules and/or its precursors. The observed unequal abundance of the isotopomers may indicate that the isotopic stereoisomers are not present as racemates in the cyclohexene oxide starting material.

For the analysis of our results, it is important to know the composition of isotopic enantiomers in the starting material. Application of (1*S*,2*R*)-**2**, the enantiomer of (1*R*,2*S*)-**2**, together with the results obtained with (1*R*,2*S*)-**2** gives us the wanted information (Scheme 4). The use of (1*S*,2*R*)-**2** results in a relative enrichment of the enantiomer B_2 rather than B_1. If dealing with a substrate containing isotopic racemates, that is, $[B_1] = [B_2]$ and $[C_1] = [C_2]$, then the measured increased relative intensity of the B_1,B_2 peak is equal to that observed using (1*R*,2*S*)-**2**. If on the other hand $[B_1] > [B_2]$ in the starting material the reaction with (1*S*,2*R*)-**2** results in a smaller relative enrichment of B_2 and thus a smaller increase of the relative intensity of the B_1,B_2 peak can be predicted than in the corresponding reaction with (1*R*,2*S*)-**2**. In contrast, if initially $[B_2] > [B_1]$, a relatively larger enrichment of B_2 occurs and a larger increase in the relative intensity of the B_1,B_2 peak is going to be observed.

Thus, the enantiomer (1*S*,2*R*)-**2** of chiral lithium amide (1*R*,2*S*)-**2** was used as the deprotonating base with the relative abundances of the isotopic isomers being obtained (Table 1, entry 4). A comparison of the relative abundances of the isotopomers with those obtained in the deprotonation using (1*R*,2*S*)-**2** (entry 3), when taking into account the difference in reaction time, reveals



Scheme 4.

that the measured relative abundances with (1*R*,2*S*)-**2** and (1*S*,2*R*)-**2** are closely similar. This result suggests that cyclohexene oxide, which has been used in the present experiments contains isotopomers that are racemates, that is, $[B_1]=[B_2]$ and $[C_1]=[C_2]$. Thus, the results show that the favoured pathway with all lithium amides used is β_{syn}-deprotonation.

3. Conclusion

It is noteworthy that the previously reported computational investigations of the diastereoselecting activated complexes, that have assumed that the deprotonations are of the β_{syn}-type, are modelling a real situation.[36–38] Except for the deprotonation using base **11**, the data in Table 1 do not indicate that significant fractions of the product are formed by α-deprotonations of the epoxide. Along with the formation of the allylic alcohol using **11**, some cyclohexanone is formed as expected from α-deprotonation. Such an observation has been reported earlier.[39] Furthermore, the data reveal no evidence for which β_{anti}-elimination is important. In a few cases (Table 1, entries 5, 6 and 8), the relative abundance relating to the isotopomer with deuterium in the α-position has decreased, which could be explained by a reversible D–H exchange in the α-position between the epoxide and lithium amide as previously reported for substituted cyclopentene oxides[40] and *exo*-norbornene oxide.[41]

4. Experimental

4.1. General

All glassware used for the epoxide deprotonation was dried in an oven (150 °C). Dry THF (max 0.005% H_2O) was used without further purification. *n*-BuLi (2.5 M in hexane) concentrations were determined according to Gilman (ASTM standard E233-90) with some modification. Amines (1*R*,2*S*)-**2** and (1*S*,2*R*)-**2**[34] and amine **6**[42] were prepared as previously described. Cyclohexene oxide was distilled from $CaCl_2$.

4.2. ^{2}H NMR

Samples of cyclohexene oxide (30–50%) and benzene (total volume of 700 μL) were prepared in 5 mm NMR tubes. All ^{2}H NMR spectra were obtained in a ^{1}H-decoupled, unlocked mode at 92 MHz using a Varian INOVA 600 equipped with a 5 mm broadband probe. Relaxation times (T_1) were determined for the deuterium isotopomers of cyclohexene oxide by the inversion-recovery method (largest T_1-value, 0.85 s). Spectra were recorded using 16,384 transients and 90°-pulses with a 2 s acquisition time and 2.25 s delay. The total time between each pulse corresponds to $5T_1$.

4.3. Typical epoxide deprotonation

The amine of (1*R*,2*S*)-**2** (13.2 g, 61 mmol) was dissolved in dry THF (581 mL) under a nitrogen atmosphere. To the solution was added *n*-BuLi (24.4 mL, 61 mmol, 2.48 M in hexane) and the solution stirred for 30 min at room temperature. Cyclohexene oxide (6.0 g, 61 mmol) was then added and the reaction mixture stirred at room temperature. The reaction was monitored using a calibrated quench-extraction-GC method.[43] Small samples (50 μL) were withdrawn from the reaction mixture and quenched by saturated NH_4Cl (100 μL). After extraction with carbon tetrachloride (500 μL) containing 1-hexanol as GC-standard (3.07 mM), the organic layer was analyzed by GC. After 16 h of reaction, the GC-analysis showed that remaining cyclohexene oxide was 50%. The reaction mixture was then quenched by saturated NH_4Cl (300 mL) and extracted with diethyl ether (1×300 mL, 2×150 mL). The combined organic phase was dried over $MgSO_4$. After

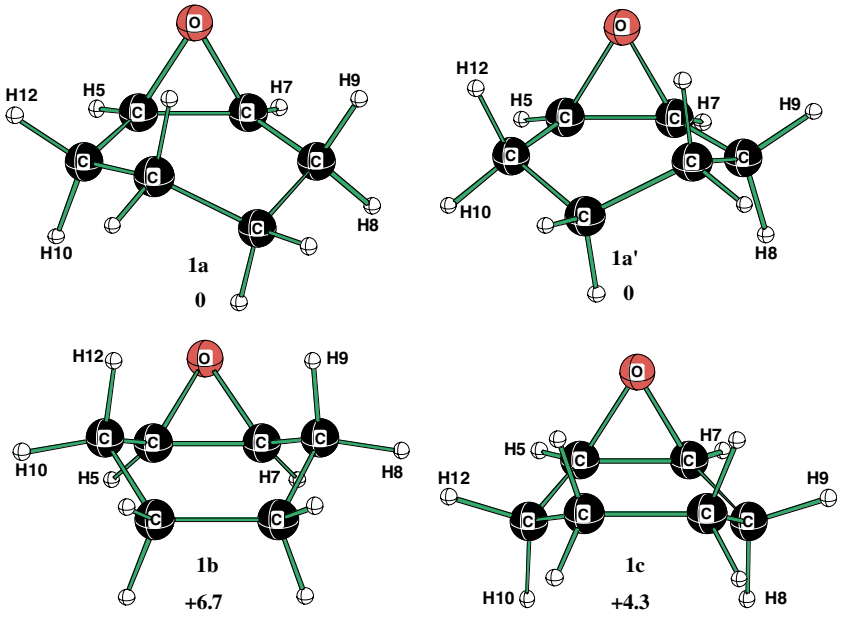


Figure 3. Optimized structures of isomers of **1** at the B3LYP/6-311+G(2d,p) level of theory. Relative energies are given in kcal mol^{-1}.

filtration, the organic phase was carefully distilled (at 760 mm), in order to remove the solvents and fractions containing epoxide with some allylic alcohol being obtained. The epoxide was separated from the allylic alcohol by flash chromatography (Silica, 230–400 mesh) eluating with chloroform (stabilized with 0.6–1.0% EtOH). The cyclohexene oxide fractions were combined and careful distillation (at 760 mm) to give pure cyclohexene oxide.

4.4. NMR assignment

The assignment of the different signals in cyclohexene oxide has been performed using NOE measurements and computational chemistry. For interpretation of the NOE results, the four conformers of cyclohexene oxide were optimized at the B3LYP/6-311+G(2d,p) level of theory: the half-chair conformers **1a** and **1a**′, which are enantiomers, the *exo*-boat **1b** and the *endo*-boat **1c** conformers (Fig. 3). The calculated energy differences indicate that **1** essentially is present as the half-chair enantiomers simplifying the NMR-assignment.[44]

From the optimized structure of **1a**, distances between the α- and β-protons were obtained with the results showing the α-protons (H7 and H5) to be closer in space to the β_{anti}-protons (H8–H7: 2.38 Å, H10–H5: 2.48 Å) than to the β_{syn}-protons (H9–H7: 2.75 Å, H12–H5: 2.57 Å) (Fig. 3). The NOE measurements show that the strongest (fastest build-up) NOE to the α-protons were observed for the more shielded (∂ 1.49) protons, while the less shielded (∂ 1.74) protons show a weaker NOE. By this analysis, it can be concluded that the β_{anti}-protons are more shielded and the β_{syn}-protons are less shielded. The calculated proton chemical shifts for the β_{anti}- and β_{syn}-protons are consistent with this assignment. The γ-protons show no NOE to the α-protons. The calculated chemical shifts show that the γ_{anti}-protons are more shielded than the γ_{anti}-protons.

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