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Photochemical versus Thermal Skeletal Inversion: Viscosity-Controlled Photodenitrogenation of a Bridgehead-Substituted DBH-Type Azoalkane and Thermal Syn-to-Anti Housane Isomerization

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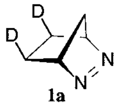
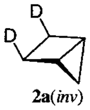
Abstract: Upon photochemical nitrogen extrusion, azoalkane **1b** yields the diastereomeric housane products *syn*-**2b** (inversion) and *anti*-**2b** (retention), whose syn-to-anti isomerization (k_{iso}) is observable already at room temperature. From the similar viscosity dependence of the k_{inv}/k_{ret} data for the photolysis of the azoalkane **1b** and the k_{iso} data for the thermolysis of the housane *syn*-**2b**, we conclude that these skeletal inversions are subject to frictional impediments and these determine the stereoselectivity.

Introduction

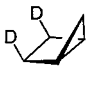
The skeletal inversion observed in the denitrogenation of *2,3-exo-d*$_2$-2,3-diazabicyclo[2.2.1]hept-2-ene (**1a**), the azoalkane DBH, to the housane **2a**(*inv*) constitutes a unique stereoselective process, much under mechanistic dispute for almost four decades.[1] The persisting mechanistic query on this nitrogen extrusion concerns stepwise versus concerted breakage of the two CN bonds in DBH (**1a**): The stepwise CN-bond rupture necessarily implicates a nitrogen-containing intermediate, namely the diazenyl diradical **DZ**, whereas the concerted process passes through the nitrogen-free **DR** species. Nitrogen loss from the singlet ^{1}**DZ** diradical along the S_H2 trajectory leads to the inverted housane **2a**(*inv*); the N_2 molecule is displaced homolytically through backside attack by the radical center.[1]



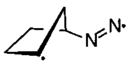
1a



2a(*inv*)



2a(*ret*)



DZ


DR

Alternatively, the nitrogen-free singlet ^{1}**DR** diradical affords both the inverted and the retained housanes **2a**(*inv*) and **2a**(*ret*).[2] To account for the loss of stereoselectivity of the ^{1}**DZ** intermediate, a bifurcation in the product-forming step has been proposed, in which nitrogen extrusion to the singlet ^{1}**DR** diradical competes with the inversion process (S_H2 mechanism).

The stepwise mechanism with the unsymmetrical singlet diazenyl diradical ^{1}**DZ** as pivotal intermediate has been recently verified by means of viscosity effects on the product-forming bifurcation step in the photochemical denitrogenation of DBH.[3] In a more viscous solvent, the inversion process along the S_H2 trajectory is slowed due to frictional impediment on the inversion motion (flap mode[4]) of the methylene bridge, loss of N_2 of the ^{1}**DZ** species to the symmetrical singlet ^{1}**DR** diradical is favored, and, thus, the **2a**(*inv*)/**2a**(*ret*) housane ratio is reduced and a lower stereoselectivity is observed. Computational results confirm that the unsymmetrical singlet diazenyl diradical ^{1}**DZ** is a bona fide intermediate, accommodated in a shallow (ca. 1 kcal mol) energy well.[5] In contrast, theoretical work on the thermal denitrogenation of DBH predicts concerted two-bond cleavage directly to the singlet 1,3-diradical ^{1}**DR**, and the dominant formation of inverted housane **2a**(*inv*) is reconciled in terms of dynamic effects; thus, deazetation is accompanied by the simultaneous flap motion of the methylene bridge.[6] A computational study on the thermal isomerization of the housane **2a** concludes that the intermediary ^{1}**DR** diradical is not subject to dynamic effects even in the gas phase.[4] To date, the latter theoretical prediction has not been subjected to experimental scrutiny. It was, therefore, of mechanistic relevance in regard to the skeletal inversion process to examine the thermal isomerization of a housane and compare the results with that of the photodenitrogenation of the corresponding azoalkane, but in solution, for which viscosity may serve as experimental probe.[3]

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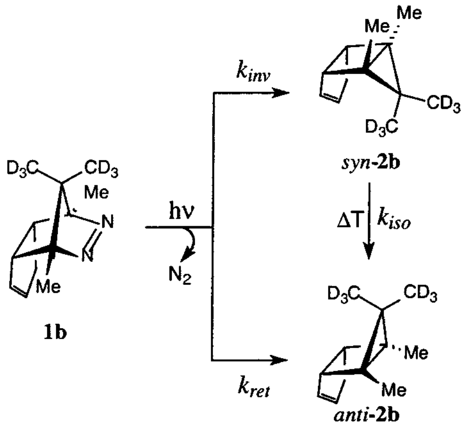
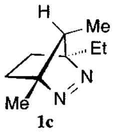
Scheme 1



Herein we show that the photochemical denitrogenation of the azoalkane **1b** to the inverted (k_{inv}) housane *syn*-**2b** and the retained (k_{ret}) *anti*-**2b** displays similar viscosity effects as the thermal isomerization (k_{iso}) of the *syn*-**2b** to the *anti*-**2b** diastereomer (Scheme 1). Therewith, we demonstrate that also for the more complex azoalkane **1b** frictional impediments control the flap motion of the methylene bridge during the inversion process, as previously established for the parent DBH photodenitrogenation;[3] moreover, we confirm experimentally that similar frictional effects operate in the thermal inversion of the *syn*-**2b** to the *anti*-**2b** housane. The reason for having selected the structurally more elaborate housane *syn*-**2b** to probe viscosity effects in the thermal isomerization rests on the practical fact that for the housane **2a** too high temperatures are required to obtain sufficiently accurate rate constants (k_{iso}); for the 2-methyl derivative of the housane **2a**, >200 °C is necessary.[7] One may argue that such sterically loaded DBH derivatives as the housane **2b** (bridgehead and methylene-bridge disubstitution, as well as cyclopentene annelation) are no longer representative as a test system on the mechanistic intricacies for the viscosity-dependent double inversion process in the thermal isomerization of the deuterium-labeled parent housane **2a**. Nonetheless, for the related double-inversion process in the photodenitrogenation of azoalkanes, we have shown[3b] that the sterically loaded DBH derivative **1c** (bridgehead and methylene-bridge substitution) is subject to a viscosity dependence like the deuterium-labeled parent DBH (**1a**). Thus, the viscosity effects observed in the photodenitrogenation of azoalkanes are frictional in nature and reflect the ease of the flap motion for the methylene bridge during the double inversion and are not in a decisive way obscured by the steric bulk through bridgehead and methylene-bridge substitution, as well as cyclopentene annelation. We infer that similar frictional effects of the medium also operate in the thermal isomerization of the housanes **1a** and **1b**, irrespective of the extent of steric loading.



1c

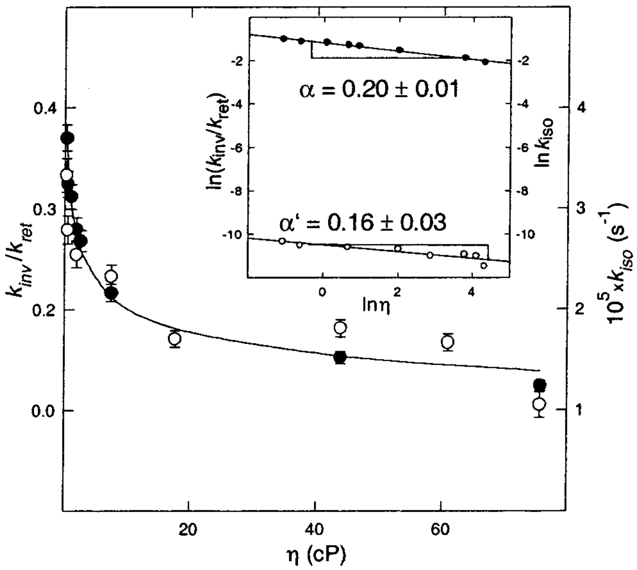


Figure 1. Viscosity dependence of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio for the diastereomeric housane products (Scheme 1) of the azoalkane **1b** photolysis (solid symbols) and k_{iso} for the thermal isomerization of the *syn*-**2b** to the *anti*-**2b** housanes (open symbols) at 25 °C; the insert displays the double-logarithmic plot of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ (solid symbols) and k_{iso} (open symbols) data. The experimental results are given in the Supporting Information.

Results and Discussion

Upon deazetation, azoalkane **1b**[8] yields the stereoisomeric housane products *syn*-**2b** (inversion) and *anti*-**2b** (retention). For our experiments on the syn-to-anti isomerization (k_{iso}), we have chosen 25 °C, a temperature at which the *syn*-**2b** to *anti*-**2b** housane isomerization is measurable, but slow enough not to affect the experimental data on the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio in the photolysis of the **1b** azoalkane (Scheme 1). The deuterium labeling was utilized for convenience, since it permits ^2H NMR monitoring of the *syn*-**2b**/*anti*-**2b** product ratio ($k_{\mathrm{inv}}/k_{\mathrm{ret}}$) and the kinetics of the *syn*-**2b**-to-*anti*-**2b** thermal isomerization (k_{iso}) in nondeuterated solvents; some of the solvents employed in this study would be difficult to come by in deuterated form. The viscosity at constant temperature (25 °C) and ambient isobaric conditions was varied over a wide range (from ca. 0.34 to 75.6 cP) through the proper choice of solvents (acetonitrile, methanol, *n*-propanol, *n*-octanol, 1,2-ethanediol, 1,2-propanediol, 1,4-butanediol, and a 1:1 mixture of 1,2-propanediol and 1,4-butanediol).

Figure 1 displays the experimental data on the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ housane ratio (solid symbols) of the photolysis of azoalkane **1b** and k_{iso} (open symbols) of the *syn*-**2b** to *anti*-**2b** housane isomerization for a large (ca. 220-fold) viscosity variation. As seen from Figure 1, the viscosity profiles of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ and k_{iso} values match well, with a bigger scatter for the k_{iso} data. Both the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio and the isomerization rate constant k_{iso} depend on viscosity to the fractional power, i.e., $k_{\mathrm{inv}}/k_{\mathrm{ret}} \sim \eta^{-\alpha}$ and $k_{\mathrm{iso}} \sim \eta^{-\alpha'}$. This becomes evident from the double-logarithmic plots of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ and k_{iso} data versus viscosity (cf. insert in Figure 1), whose slopes take the values $\alpha = 0.20 \pm 0.01$ ($R^2 = 0.982$) for the azoalkane **1b** photolysis and $\alpha' = 0.16 \pm 0.03$ ($R^2 = 0.927$) for the *syn*-**2b** housane isomerization (cf. Supporting Information for details).

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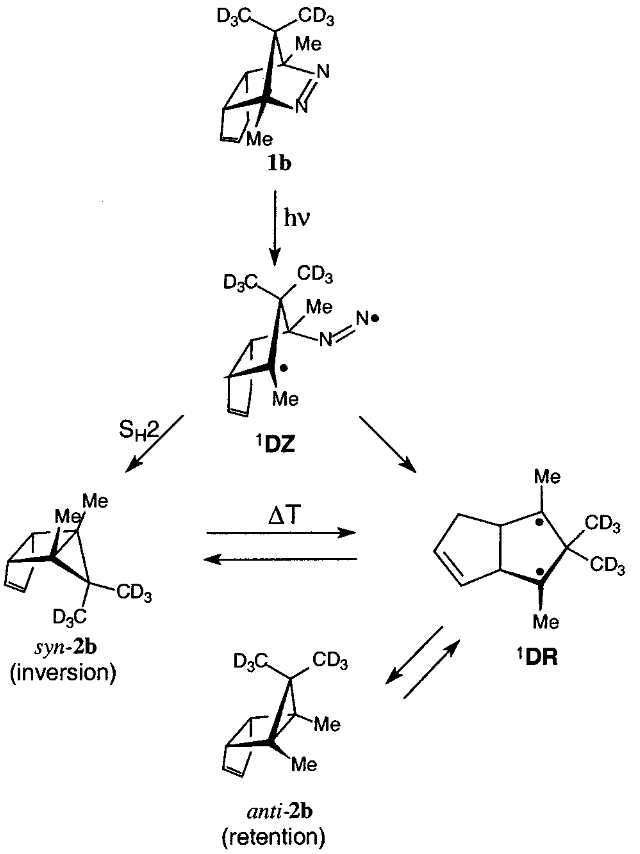
The α value in the viscosity dependence of the k_{inv}/k_{ret} ratio ($k_{inv}/k_{ret} \sim \eta^{-\alpha}$) for the photodenitrogenation of the azoalkane **1b** refers to the fraction of the free volume (per molecule) involved in the molecular reorganization (flap motion of the substituted methylene bridge in the inversion process),[3] while the α′($k_{iso} \sim \eta^{-\alpha'}$) pertains to the free-volume fraction available in the thermal *syn*-**2b** → *anti*-**2b** housane isomerization. The comparable α and α′ values, within experimental error, manifest the similar free-volume requirements and thereby reflect similar frictional impositions on the skeletal inversion for both the azoalkane photolysis and the housane isomerization.

A point of concern is the choice of the *diverse* solvents to assess the viscosity behavior, which requires justification. In other words, is the observed solvent dependence (Figure 1) solely accounted for in terms of viscosity or do other solvent properties based on electronic interactions (e.g., hydrogen bonding for the alcohols) play a decisive role? Our recent study on the parent DBH (**1a**)[3d] has disclosed that, besides viscosity, also bulk polarity of the solvent influences the stereodifferentiation[3d,9] and specific electronic interactions, such as hydrogen bonding, have little if any effect on the inversion stereoselectivity.[3d] In the present case, hydrogen bonding is also not important, since the data point for acetonitrile fits well within the viscosity correlation (Figure 1). For substrate **1a**, we contend that the similar viscosity profile in protic and nonprotic solvents demands the same free-volume requirements and thereby reflects similar frictional impositions.[3d] To assess the viscosity dependence, it is customary to utilize either nonpolar ($\epsilon < 3$) or polar ($\epsilon > 10$) media and avoid solvents of intermediate polarity ($3 < \epsilon < 10$).[3d] The remarkable feature of the present study is the use of polar solvents (for all of them $\epsilon > 10$), whose viscosity range may be spanned ca. 220-fold! Indeed, the good linear correlation ($R^2 = 0.982$) between the $\ln(k_{inv}/k_{ret})$ and $\ln \eta$ data infers that viscosity constitutes the determinant solvent property and, thus, frictional rather than electronic effects operate in the double-inversion process.

The mechanistically common feature for the photolysis[3] of azoalkane **1** and the thermal isomerization[4] of its housane product **2** resides in the intermediacy of the nitrogen-free cyclopentanediyl ^{1}**DR** species (Scheme 2). As is evident from the composite mechanism in Scheme 2, the substituted methylene bridge in the inversion processes ^{1}**DZ** → *syn*-**2b** and *syn*-**2b** → *anti*-**2b** experiences a flap motion of similar amplitude. Thus, one may expect for these rearrangements similar viscosity effects, as is manifested by the values for α (photolysis of the azoalkane **1b**) and α′ (thermolysis of the housane *syn*-**2b**) [Figure 1]. The inverted housane is formed from the azoalkane through the intramolecular homolytic displacement of the nitrogen molecule by backside attack (S_H2 process[1]) in the diazenyl diradical ^{1}**DZ**. Loss of inversion selectivity derives from the common ^{1}**DR** species, experimentally directly assessed for the first time through the facile thermal syn-to-anti isomerization of the housane **2a**. The reason the anti housane (retention) eventually persists is dictated by the fact that this diastereomer is thermodynamically preferred by ca. 6 kcal/mol.[10]

Scheme 2



Should a *statistically equilibrated* ^{1}**DR** species[4] intervene in the thermal syn-to-anti housane isomerization, the medium effect on the latter transformation would reduce to a mere *frictional* imposition on the flap motion of the substituted methylene bridge. For a dynamic ^{1}**DR** species, however, the solvent effect should have another origin, namely, randomization of the excess internal energy along the flap (inversion) coordinate through the collisional momentum transfer in the liquid medium.[6] The similar viscosity profiles for the k_{iso} and k_{inv}/k_{ret} data (Figure 1) imply that the nature of the medium effect on the thermal housane isomerization is the same as that for the azoalkane photolysis, i.e., a frictional retardation of the skeletal inversion. The optimal scenario for dynamic effects during the double-inversion process in the thermal isomerization of housanes would be expected in the gas phase, since collisional deactivation would be minimal. Yet, the theoretical work[4] on the thermal isomerization of the parent housane **2a** in the gas phase concluded that a statistically equilibrated singlet diradical, namely the C_2-symmetric ^{1}**DR**, intervened even under these conditions. Our small (ca. 2-fold variation in the k_{iso} values) but measurable viscosity dependence observed for the thermal isomerization of the more elaborate DBH derivative **2b** in solution can hardly be of dynamic nature, since optimal conditions have been provided for collisional deactivation by

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[9] It is noteworthy to point out that a bulk-polarity effect on the stereoselective inversion was so far *only* noticed for the parent DBH (**1a**), and even for this case it was only a ca. 1.3-fold variation in the k_{inv}/k_{ret} values over a range in the dielectric constant of ca. 20-fold (ref 3d). Such modest polarity effects do not operate in the structurally more elaborate DBH derivatives **1b** (present work) and **1c** (ref 3b), which is evidently a consequence of steric bulk through bridgehead and methylene-bridge substitution and cyclopentene annelation. In fact, for the azoalkane **1c**, a *single* viscosity profile has been observed for all polar, nonpolar, protic, and aprotic solvents (ref 3b). We suspect that dipolar stabilization of the intermediary diradicals by the medium is subject to steric effects, such that the modest bulk-polarity dependence observed for the quite exposed parent DBH (**1a**) is erased for the sterically loaded azoalkanes **1b** and **1c**. These observations conspicuously justify the use of diverse solvents for the viscosity studies on the azoalkane denitrogenation.

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the medium. Instead, the more viscous medium impedes more effectively the flap motion of the methylene bridge through frictional interactions and the extent of double inversion is reduced, as experimentally observed (Figure 1). Since a C_2-symmetric ^{1}**DR** does not qualify (it cannot display any viscosity dependence), presumably the statistically equilibrated ^{1}**DR** species possesses a puckered conformation, whose double inversion is encumbered through the frictional interactions imposed by the medium. The intervention of a puckered ^{1}**DR** diradical implies a “stereochemical memory effect”, which deserves further elucidation.

We conclude from the similar viscosity dependence of the k_{inv}/k_{ret} data for the azoalkane **1b** photolysis and the k_{iso} data for the housane *syn*-**2b** thermolysis (Figure 1) that these skeletal inversions are subject to frictional impediments, which determine the stereoselectivity and kinetics. Testing whether frictional effects also operate in the thermal denitrogenation of the azoalkane **1b** would have been mechanistically instructive, but at the temperatures required for the thermolysis of azoalkane **1b**, unfortunately, the resulting housane *syn*-**2b** does not persist and isomerizes completely to *anti*-**2b**. It would be happenstance to find a common DBH derivative for which the viscosity effects of all three inversion processes, namely, the thermal and photochemical denitrogenation of the azoalkane, as well as the thermal isomerization of the corresponding housane, could be determined in a common temperature range.

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Supporting Information Available: Experimental details and results (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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