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Review Commentary

Intriguing double-inversion stereochemistry in the denitrogenation of 2,3-diazabicyclo[2.2.1]heptene-type azoalkanes: a model mechanistic study in physical organic chemistry

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ABSTRACT: In this review is given a detailed account of the mechanistic elucidation of the unique stereochemical double inversion observed in the nitrogen extrusion of bicyclic azoalkanes. It is shown that the judicious choice of experimental tools and theoretical approaches provides insight into and understanding of this perplexing stereoselectivity. This long-standing mechanistic query serves as an example *par excellence* of harnessing the structural variation of the DBH-type substrate (internal effects) and the change of medium properties (external effects) to diagnose a complex reaction mechanism. The particular case reviewed here is specific, but the focus in resolving its mechanistic complexities is general and, thus, may be applied to the elucidation of other intricate reaction mechanisms, primarily stereoselective and product-selective organic transformations. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: bicyclic azoalkane denitrogenation; stereochemical double inversion; diazenyl diradicals; free-volume model of viscosity; polarity effects; pressure dependence; substituent effects

INTRODUCTION

The recent definition of physical organic chemistry[1] as '. . . *the application of synthetic methodology to prepare compounds with structures designed to test critical concepts of physical theory* . . . ' fits well to the present model study of the unusual mechanism of the double inversion that is observed in the denitrogenation of DBH-type azoalkanes (**1**) (Scheme 1); this intriguing stereochemical process is exhibited for the parent 2,3-diazabicyclo[2.2.1]heptene, DBH (**1a**). Besides varying the structural features of the bicyclic azoalkane to probe the intrinsic complexities of the molecular dynamics for this remarkable stereoselectivity, the external influence of the medium (viscosity and polarity) is examined to acquire a detailed picture of the transition structures and the intermediates involved in this prototypal process. It is the aim of this review to demonstrate by means of a model study that it is precisely such a combined scrutiny of the internal (substrate structural effects) and external (medium influence) factors which allows us to elucidate complex stereochemical reaction coordinates.

The double inversion of the molecular skeleton upon nitrogen extrusion, first observed for the parent 2,3-diazabicyclo[2.2.1]hept-2-ene, DBH (**1a**), constitutes a unique stereoselective process, much under mechanistic dispute for almost four decades.[2] Preferable formation of the inverted [**2a**(*inv*)] over retained [**2a**(*ret*)] housane represents a general feature for both the photolytic and thermal denitrogenation modes. This stereoselective preference does not change on substitution in the DBH molecule, as is seen from Table 1, which compiles the product distributions for the substituted DBH derivatives studied so far; in most cases the inverted product is favored. This observation qualifies stereochemical double inversion as a general phenomenon with regard to activation modes and conditions. Here we review recent experimental data on the denitrogenation of various

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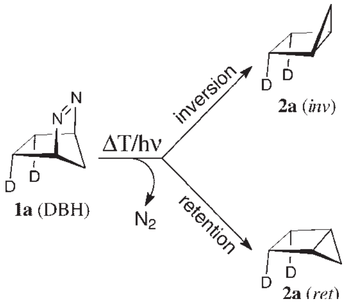
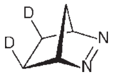
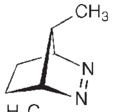
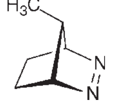
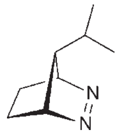
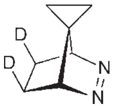
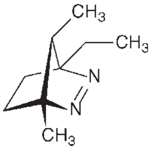
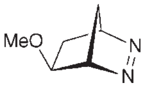
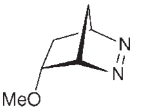
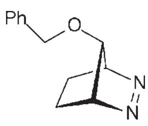


Scheme 1

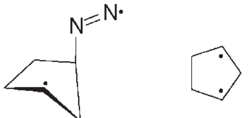
Table 1. Product distributions in the denitrogenation of the DBH-type azoalkanes

Entry	Azoalkane	Ref.	Inversion: retention Singlet conditions[a]	 Triplet conditions[b]
1		2, 3	75:25	50:50
2		3	67:30	44:56
3		3	74:25	56:44
4		3	80:17	77:23
5		4	70:30	—[c]
6		5	81:19	—[c]
7		6	55:45	22:78
8		6	84:16	21:79
9		7	85:15	—[c]

[a] Direct photolysis, $\lambda > 300$ nm.
[b] Triplet-sensitized (benzophenone) photolysis.
[c] Not determined.

substituted azoalkanes and discuss the mechanistic alternatives for this intriguing stereoselective process.

A long-standing mechanistic dichotomy on the nitrogen-extrusion process under present consideration 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[8] leads to the inverted housane **2a**(*inv*); the N_2 molecule is displaced homolytically through backside attack by the radical center.[2,4] Alternatively, the nitrogen-free singlet ^{1}**DR** diradical affords both the inverted and the retained housanes **2a**(*inv*) and **2a**(*ret*). 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.

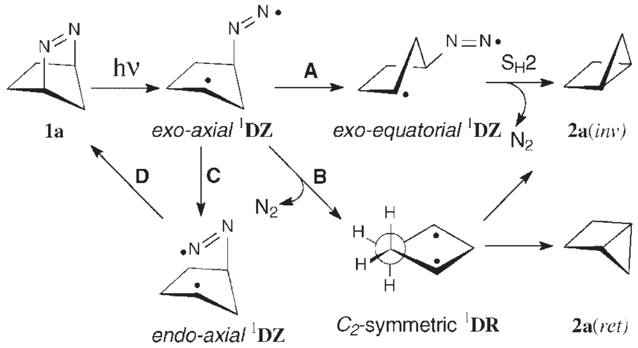


DZ **DR**

A recent computational study on the thermolysis of the parent DBH concluded that the lower energy pathway of deazetation is the concerted expulsion of N_2 directly to the ^{1}**DR** species.[9] The observed stereoselection, namely more **2**(*inv*) than **2**(*ret*), was interpreted in terms of dynamic effects of the non-statistical ^{1}**DR** diradical intermediate.

Computational[10] and experimental[4,11,12] evidence exists in favor of the stepwise nitrogen elimination in the photolysis of azoalkanes, which implicate the intervention of a diazenyl radical species. Thus, a recent theoretical study on the parent DBH discloses the singlet diazenyl diradical ^{1}**DZ** as the lowest-energy transient on n,π* excitation.[10] Similarly, computational results on the photolysis of azomethane suggest a stepwise mechanism for the denitrogenation.[13] Indeed, simple symmetry considerations in terms of the Dauben–Salem–Turro theory on photochemical transformations[14] predict a stepwise process on n,π* excitation.[4]

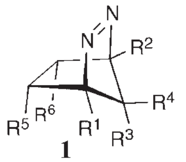
The most recent computational studies on the parent DBH (**1**) provided a detailed mechanistic scenario for the photochemical evolution of the ^{1}**DZ** diradical and its subsequent chemical transformation to the inverted housane **2**; the salient features are displayed in Scheme 2.[15] On n,π* excitation, the DBH (**1**) generates initially the *exo*-axial ^{1}**DZ** by passage through a conical intersection. Thereafter, the ^{1}**DZ** species carries sufficient momentum to convert the *exo*-axial to the *exo*-equatorial conformer along pathway **A** (major route); the latter conformer is predestined for N_2 loss to afford the inverted housane **2**(*inv*) along the S_H2 trajectory. Alternatively, pathway **B** competes to generate the C_2-symmetric ^{1}**DR** diradical on



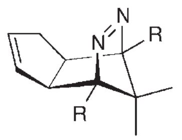
Scheme 2

denitrogenation, which cyclizes in equal amounts to the **2**(*inv*) and **2**(*ret*) housanes. The third pathway **C** entails the rotational change of *exo*-axial to the *endo*-axial ^{1}**DZ** diradical, with subsequent reclosure to the azoalkane **1** along step **D**. For the parent DBH (**1**), pathway **D** may be neglected, since the experimentally determined quantum yield of DBH consumption is unity.[16]

Experimentally, the pertinent query is posed as to whether medium (viscosity and polarity)[17] and substituent (bridgehead and methano bridge)[15] effects allow one to clarify the mechanism of the photodenitrogenation. As will become apparent, the choice of the bicyclic (**1**) and tricyclic (**3**) azoalkanes has been most fortunate in this mechanistic elucidation.



1



3

1a (R^1= R^2= R^3= R^5=H, R^5= R^6= D)
1b (R^1 = R^2= H, R^3= R^4= Me, R^5= R^6= D)
1c (R^1= Me, R^2= Et, R^3= H, R^4= Me, R^5= H, R^6= H)
1d (R^1=R^2=H, R^3-R^4 = CH_2CH_2, R^5= R^6= D)

3a (R = H)
3b (R = Mc)
3c (R = Ph)
3d (R = CH_2-*n*-Pr)
3e (R = CH_2OAc)

Here we present the new developments in this context and offer a contemporary view on the long-standing but fascinating double-inversion phenomenon.

VISCOSITY EFFECTS

The utility of viscosity as a medium parameter has been of prime importance in understanding the nature of solvent–solute interactions.[18] In this context, the diversity of physical models that have been developed to rationalize the viscosity dependence of molecular transformations is impressive.[19] For example, viscosity has played a definitive role in the detection of reaction intermediates and the elucidation of their chemical behavior. The classical cage-effect studies[20] in radical reactions constitute an example *par excellence* of solvent viscosity as a powerful mechanistic tool in understanding complex chemical events. Also major unimolecular structural rearrangement, e.g. the skeletal inversion during nitrogen extrusion from the DBH-type azoalkanes, should experience frictional effects and thereby depend on viscosity. Hence the solvent viscosity may be an informative medium variable for the exploration of mechanistic aspects of molecular transformation, as was recently demonstrated for a number of cases.[17]

Here, we address two facets of harnessing viscosity for mechanistic studies on the denitrogenation process. These refer to the viscosity effects on (i) the photodenitrogenation quantum yield and (ii) the stereoselectivity expressed in terms of the k_{inv}/k_{ret} ratio for the inversion (k_{inv}) and retention (k_{ret}) channels.

The strategy behind viscosity studies on the denitrogenation quantum yield is based on the fact that the concerted nitrogen extrusion from azoalkane **1** to afford nitrogen-free ^{1}**DR** diradical should not depend on viscosity, while the stepwise process through the intermediacy of the nitrogen-containing ^{1}**DZ** species may exhibit frictional impositions on the denitrogenation quantum yield. Indeed, the recapture of the released nitrogen by the ^{1}**DR** intermediate is unlikely; conversely, the retardation of the flap motion of the methylene bridge in the diazenyl diradical ^{1}**DZ** (inversion process) in viscous medium may result in the regeneration of **1**, which should reduce the quantum yield.

The incentive for the viscosity studies on the stereoselectivity (k_{inv}/k_{ret} ratio) rests on the fact that computationally the putative ^{1}**DR** species of the parent DBH is predicted to possess a C_2-symmetric conformation.[21] This implies identical displacements of the atoms that are involved in the ring closure of the thermally equilibrated, nitrogen-free diradical ^{1}**DR** to the inverted **2**(*inv*) and retained **2**(*ret*) housanes. The consequence of this is that no different viscosity dependence should operate on the k_{inv} versus k_{ret} steps of the parent DBH. In contrast, a viscosity dependence of the k_{inv}/k_{ret} ratio is expected for the diazenyl diradical (^{1}**DZ**). Since during the inversion process **1** → **2**(*inv*) the methylene bridge suffers a major spatial displacement, it is subject to more pronounced frictional interactions with the medium compared with the retention mode. Therefore, we anticipate that viscosity studies may serve as an effective experimental tool to scrutinize the various mechanistic alternatives for the denitrogenation process.

The free-volume model of viscosity for unimolecular transformations

Our approach is based on the simple free-volume model of viscosity, developed by Doolitle,[22] who intuitively pointed out that the translational motion of a molecule in a liquid medium is only possible when sufficient free volume (V_f) is available, i.e. when the free volume V_f per molecule is larger than some 'critical' value V_0. The critical volume (V_0) in the translational diffusion may be considered as the van der Waals volume of the molecule. The fluidity, which is the inverse of viscosity (η^{-1}), is proportional to the probability factor $[\exp(-V_0/V_f)]$ for the translational motion of an ensemble of molecules in the liquid medium. Hence the free-volume dependence of the viscosity may be expressed by the equation

$$\eta = A\exp(V_0/V_f) \qquad (1)$$

where A is a proportionality factor.

In contrast to translational diffusion, molecular rearrangements involve only a portion of the molecule. Thus, only a fraction αV_0 ($\alpha < 1$) of the critical volume V_0 is required to execute the internal molecular motion, for which the rate constant k of the molecular rearrangement is given by

$$k = k^0\exp(-\alpha V_0/V_f) \qquad (2)$$

Substitution of Eqn (1) into Eqn (2) affords

$$k = k^0(A/\eta)^\alpha \qquad (3)$$

for the viscosity dependence of the molecular transformation. This simple expression was first applied to rationalize the viscosity behavior of isomerizations.[23]

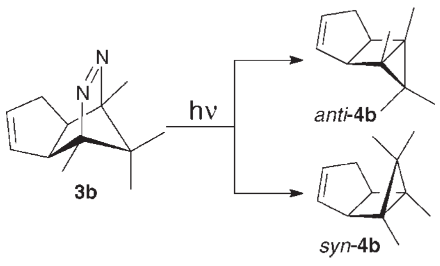
As expected, the α parameter depends decisively on the substituents in the transforming molecule, which suffer major displacements during the reaction; conversely, the α value experiences a nominal effect for remote substituents. Hence the structural dependence of α on strategically placed substituents in the reacting molecule should disclose valuable mechanistic 'fine structure' on the motion of the molecular fragments involved in unimolecular chemical transformations.

VISCOSITY DEPENDENCE OF THE QUANTUM YIELD FOR THE NITROGEN LOSS IN AZOALKANE PHOTOLYSIS: EXPERIMENTAL EVIDENCE FOR REVERSIBLE FORMATION OF THE DIAZENYL DIRADICAL

In a liquid medium, frictional forces should oppose the conformational motion necessary for pathway **A** in Scheme 2 and diminish the population of the *exo*-equatorial ^{1}**DZ** species so that other pathways may compete. Thus, if denitrogenation of the *exo*-axial ^{1}**DZ** is enhanced along pathway **B** versus pathway **A** to generate the C_2-symmetric ^{1}**DR**, diminution of the diastereoselectivity is expected. Should pathway **C** be more populated, the consequences would be reclosure of the *endo*-axial ^{1}**DZ** to the azoalkane along pathway **D**, which should manifest itself in a lower quantum yield for the photodenitrogenation in more viscous solvents. Although formation of the diazenyl radical intermediate has been reported for both the photolysis[11] and thermolysis[24,25] of acyclic azoalkanes through traditional cage-effect studies on the intermolecular process, it had to be yet documented for the intramolecular case of cyclic azoalkanes. Such a study of the dependence of the quantum yield of azoalkane disappearance on solvent viscosity has recently been conducted, through which ring closure of the ^{1}**DZ** diradical to its azoalkane was unequivocally demonstrated.[26] In this work, the photodenitrogenation efficiency (Φ) as a function of viscosity (η) in Nujol–isooctane mixtures for the structurally elaborate tricyclic azoalkane **3b** was examined, which affords the *anti*-**4b** (retention) and *syn*-**4b** (inversion) housanes (Scheme 3). Figure 1 displays a definite decrease in Φ as the viscosity increases. To rationalize this viscosity behavior of the photodenitrogenation efficiency (Φ), the equation

$$\Phi = k_r/(k_r + k_f + k_{IC}) \qquad (4)$$

needs to be considered, expressed in terms of the rate constants of the denitrogenation reaction (k_r), fluorescence (k_f) and internal conversion (k_{IC}). [As for possible singlet-to-triplet intersystem crossing (k_{ISC}) in azoalkane **3**, recent studies[15] have disclosed that at room temperature this deactivation pathway does not compete with the photodenitrogenation and, therefore, need not to be considered in Eqn (4).] In Eqn (4), the fluorescence rate constant (k_f), an intrinsic photophysical property of the excited molecule, should be relatively independent of the medium. Moreover, comparison of the quantum yields of photodenitrogenation ($\Phi = 0.61$)[26] and fluorescence ($\Phi_f < 0.05$)[15] of the azoalkane **3b** under similar experimental conditions (isooctane at ca 20 °C) reveals that k_f is more than an order of magnitude lower than k_r ($\Phi/\Phi_f = k_r/k_f > 0.61/0.05 > 10$) and may be neglected in



Scheme 3

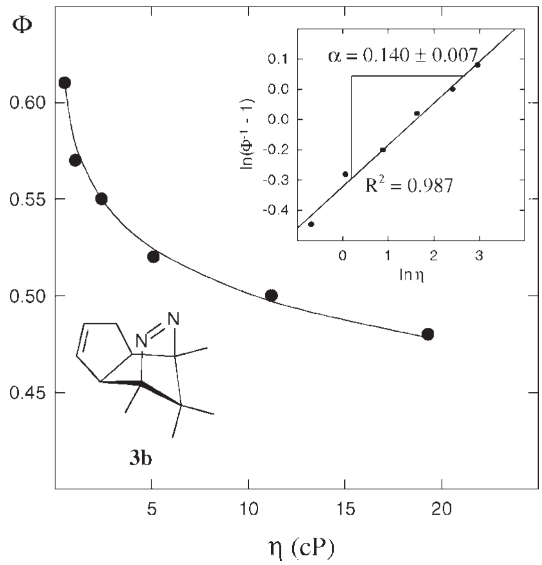


Figure 1. Viscosity dependence of the denitrogenation quantum yield in the photolysis of azoalkane **3b**. The inset displays the linearity of the experimental data according to Eqn (6)

Eqn (4). With regard to the internal conversion (k_{IC}), it is expected that a more viscous medium (less mobility) should decrease this radiationless deactivation (k_{IC}).[26] As becomes apparent from Eqn (4), a decrease in k_{IC} should increase the quantum yield, contrary to what has been obtained experimentally (Fig. 1). Thus, the observed viscosity dependence of the photodenitrogenation quantum yield stems mainly from the changes of the photodenitrogenation rate constant k_r in Eqn (4).

In analogy to Scheme 2 for the parent DBH (**1a**), the denitrogenation mechanism for the structurally elaborate azoalkane **3b** may be sketched as in Scheme 4. In this mechanism, the retardation of the photochemical denitrogenation (k_r) by the viscosity increase may be accounted for by depreciation of the pathway **A** through frictional impediments by the medium. This should enhance the lifetime of the photochemically generated *exo*-axial ^{1}**DZ** species and promote the conformational change to the *endo*-axial ^{1}**DZ** (pathway **C**) and subsequent reclosure to the starting azoalkane **3b** (pathway **D**).

For liquid-phase photodenitrogenations of azoalkanes, k_r decreases with viscosity (η); this decrease obeys the fractional-power dependence $k_r \sim \eta^{-\alpha}$, as expressed by Eqn (3) based on the free-volume model. With the neglect of k_f, Eqn (4) relates k_r to the experimental Φ data in the rearranged form of Eqn (5). Substitution of the viscosity relation of Eqn (3) into

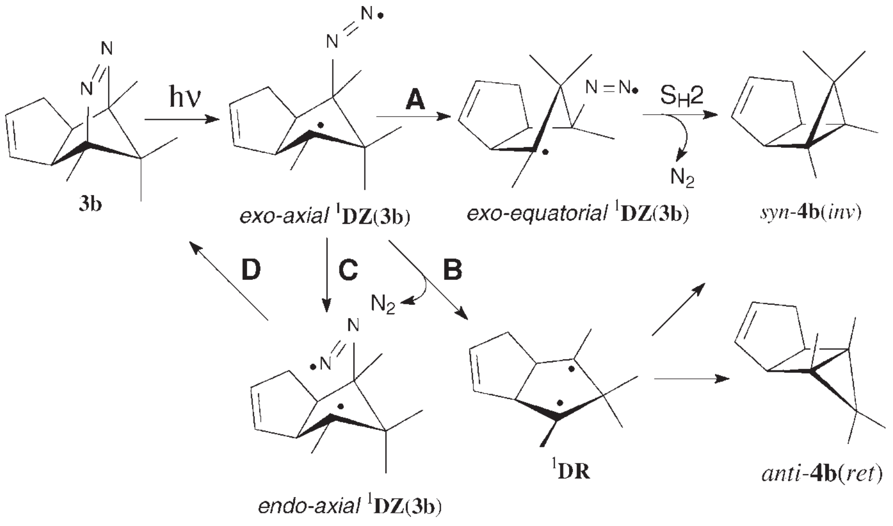
$$\Phi^{-1} - 1 = k_{IC}/k_r \tag{5}$$

and on taking logarithms leads to

$$\ln(\Phi^{-1} - 1) = \text{constant} - \alpha \ln\eta \tag{6}$$

in which k_{IC} = constant, as explained above. The double-logarithmic plot of the function $\Phi^{-1} - 1$ versus viscosity gives a straight line ($R^2 = 0.987$), the slope of which takes the value $\alpha = 0.140 \pm 0.007$ (cf. inset in Fig. 1).

Hence the choice of the structurally more elaborate azoalkane **3** for this study has been most fortunate in that a definite viscosity dependence of the photodenitrogenation quantum yield has become observable (Fig. 1).[26] Thereby, it has been experimentally confirmed that the *exo*-axial ^{1}**DZ** diradical is a *bona fide* intermediate in the photolysis, which may revert to the starting azoalkane (an energy-dissipating process), provided that the appropriate azoalkane is selected. For example, the parent DBH does not display such a viscosity behavior on its quantum yield of denitrogenation.[26]



Scheme 4

VISCOSITY DEPENDENCE OF DIASTEREOSELECTIVITY

Liquid-phase DBH photolysis: solvent dependence and polarity effects

The stepwise mechanism, with the unsymmetrical singlet diazenyl diradical ^{1}**DZ** as pivotal intermediate in the DBH photolysis, is also corroborated by the viscosity effects observed for the inversion (k_{inv}) and retention (k_{ret}) channels in the liquid-phase DBH photolysis.[27–30] In a more viscous solvent, the inversion process along the S_H2 trajectory is slowed owing to frictional impediments on the inversion motion (flap mode) of the methylene bridge, which is manifested by a decrease in the diastereoselectivity, i.e. the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio (cf. Fig. 2). In contrast, as explained in the Introduction, for the concerted denitrogenation process, no viscosity effect on the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio should operate.

As is evident from Fig. 2, the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio exhibits the same viscosity profiles in polar protic (alcohols and diols) and non-polar aprotic (isooctane–Nujol mixtures) media, but the two curves are shifted relative to one another by a constant factor of ca 1.3. This becomes especially apparent from the linear double-logarithmic plots of $\ln(k_{\mathrm{inv}}/k_{\mathrm{ret}})$ versus $\ln\eta$ (cf. inset in Fig. 2). In both cases, the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio depends on the viscosity to the same fractional power, i.e. α takes the value 0.050 ± 0.003 for both solvent series (cf. inset in Fig. 2).[28]

The fact that the same α values have been obtained for alcohols and isooctane–Nujol mixtures (Fig. 2) is mechanistically most significant, since it manifests that the same free volume is required for the inversion process in both sets of solvents. We conclude that it is the frictional (viscosity) imposition on the inversion process that controls the stereoselectivity ($k_{\mathrm{inv}}/k_{\mathrm{ret}}$) in the liquid-phase photochemical deazetation process within each solvent series.[28] If hydrogen bonding with the surrounding solvent molecules were significant, it would be difficult to conceive that the same frictional effects (same α values) would operate in the alcohol and in the hydrocarbon media.

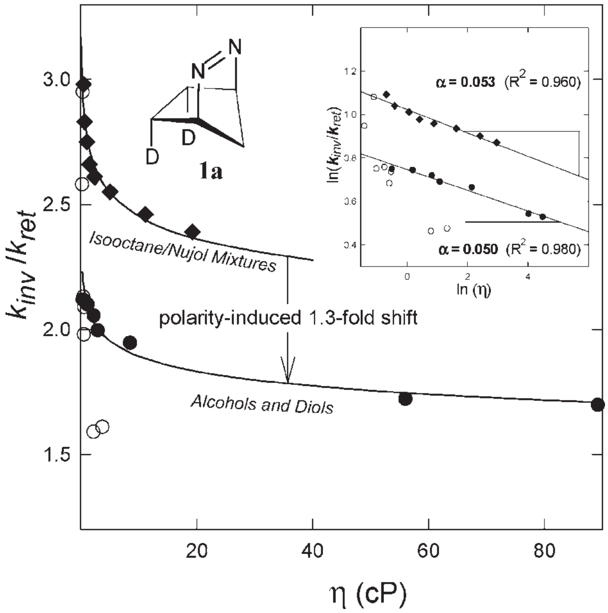


Figure 2. Viscosity dependence of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio in the DBH (**1a**) photolysis as a function of solvent for alcohols and diols (●), isooctane–Nujol mixtures (◆) and aprotic solvents of different polarity (○). The inset displays the double-logarithmic plots of the viscosity versus $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ data (η expressed in cP)

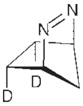
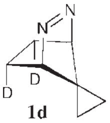
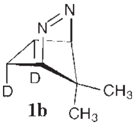
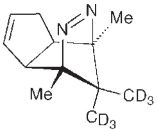
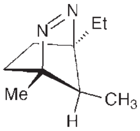
While the α values in aprotic isooctane–Nujol mixtures and alcohols match perfectly, the viscosity profile of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio in alcohols and diols is shifted downwards by a factor of ca 1.3. Clearly, the inversion process is obstructed more effectively (ca 30%) in the polar (alcohols) than in the non-polar (hydrocarbon) medium. The origin of this decrease of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio may be understood in terms of solvent polarity effects on the intermediary ^{1}**DZ** species. Such polarity effects of alcohols may result from specific (hydrogen bonding) and/or non-specific (bulk dielectric properties) solvent–solute interactions. Since hydrogen bonding is unlikely, we have suggested[28] that bulk polarity is responsible for the observed 1.3-fold shift of the viscosity profiles in the protic versus aprotic solvent series (Fig. 2). Presumably, the lower $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio in polar versus non-polar solvents manifests better stabilization of the dipole moment for the diazenyl diradical ^{1}**DZ** in a polar environment, which should retard the inversion process during the denitrogenation.[28]

To rationalize the observed polarity behavior of the stereoselectivity (Fig. 2), Onsager's reaction-field model[31] was helpful.[28] Indeed, with the help of this model, we have found a good correlation of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ data (normalized to a constant viscosity) with the Onsager polarity parameter $(\varepsilon - 1)/(2\varepsilon + 1)$. It is noteworthy that the observed polarity effect levels off at $\varepsilon > 10$, a behavior which agrees with the Onsager model.[28]

Structural dependence of stereoselectivity in viscosity-controlled denitrogenation

To convey how impressively the α parameter reflects structural effects on the denitrogenation coordinate through appropriate substitution of the DBH skeleton, in Table 2 are compiled the experimental α data for the photolysis of azoalkanes **1**. As expected, the lowest α value is observed for the parent DBH (**1a**), while dimethyl substitution in the methylene bridge (azoalkane **1b**) increases the α value by a factor of three. This is consistent with the inversion process (k_{inv}) along the S_H2 trajectory, which should be slowed owing to the frictional retardation of the methylene-bridge inversion motion. For the spirocyclic azoalkane **1d**, the α value is ca 1.4 times lower than for **1b**. This diminution of the α value may be

Table 2. The α values for the photochemical skeletal inversion[a]

Reactant	α
 **1a**	0.050 ± 0.003
 **1d**	0.105 ± 0.005
 **1b**	0.146 ± 0.005
 **3b**	0.20 ± 0.01
 **1c**	0.27 ± 0.01

[a] See Refs 27–30.

accounted for by a smaller substituent size of the methylene bridge in azoalkane **1d**.

The data in Table 2 reveal another mechanistically important fact: the bridgehead substitution in the azoalkane **1c** further increases the α parameter. Its value is about twice as high as that of the merely methylene bridge-substituted azoalkane **1b** and about five times higher than the parent DBH **1a**. This observation indicates that in addition to the flap motion of the methylene bridge, the displacement of the bridgehead substituents is also significant in the skeletal inversion during nitrogen extrusion.

In contrast, the cyclopentene annelation in azoalkane **1e**, which is distant from the reaction site, does not cause a large effect, as the comparison of the α values with **1c** reveals (cf. Table 2). Hence our comparative analysis of the viscosity dependence as a function of the azoalkane structure (Table 2) reveals that not only the flap motion of the methylene bridge but also the bridgehead substitutents participate in the double-inversion process, as required for the S_H2 trajectory. This novel mechanistic feature, recognized through viscosity effects, is in accord with recent work in which the importance of bridgehead substitution has been demonstrated for the stereoselective inversion in the temperature-dependent photolysis of DBH-type azoalkanes;[15] later (see the section Substitution Effects) this mechanistic feature is addressed in more detail.

Temperature-controlled viscosity dependence in DBH photolysis

The variation of temperature may impose a composite effect on chemical transformations: besides altering the solvent viscosity and thereby modifying the external frictional effects on the molecular rearrangement in a condensed medium, the temperature change may also exert an internal influence on the chemical process, if the latter possesses a noticeable activation energy. The DBH photolysis definitively exemplifies such a case. Figure 3 displays the viscosity dependence of the stereoselectivity ($k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio) in the DBH photolysis as a function of temperature. Clearly, the temperature-controlled viscosity profile (Fig. 3) is steeper than that under isothermal conditions (Fig. 2);[27] this is particularly evident from the higher α value (0.14, cf. inset in Fig. 3). We have attributed the observed deviation in the solvent- and temperature-varied viscosity profiles of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio (Figs 2 and 3) for the parent DBH to the difference ($\Delta E^{\mathrm{i}} = E^{\mathrm{i}}_{\mathrm{inv}} - E^{\mathrm{i}}_{\mathrm{ret}}$) in the internal activation energies of the inversion ($E^{\mathrm{i}}_{\mathrm{inv}}$) and retention ($E^{\mathrm{i}}_{\mathrm{ret}}$) channels,[27] which is superimposed on the external energy difference (ΔE^{e}) due to the viscosity dependence. Hence the complete energy difference ($\Delta E = \Delta E^{\mathrm{i}} + \Delta E^{\mathrm{e}}$) is the sum of the internal (ΔE^{i}) and the external (ΔE^{e}) energy terms. Whereas the former term represents the inherent difference in the activation energies for the inversion and retention processes, the latter corresponds to the energy required to overcome the frictional impediment provided by the medium for the inversion mode.[27]

The ΔE^{e} term is linearly proportional to the activation energy (E_η) of the solvent fluidity (η^{-1}), i.e. $\Delta E^{\mathrm{e}} = \alpha E_\eta$ (cf. Ref. 27a). Thus, the difference in the total energy change is $\Delta E = \Delta E^{\mathrm{i}} + \alpha E_\eta$, for which the

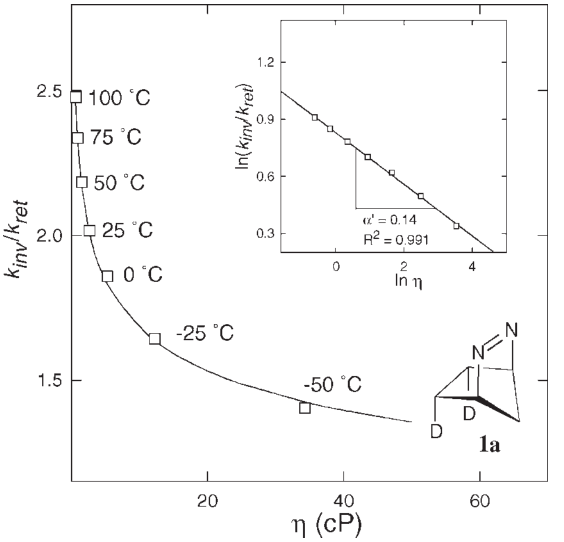


Figure 3. Viscosity dependence of the $k_{\mathrm{inv}}/k_{\mathrm{ret}}$ ratio in the DBH (**1a**) photolysis ($\lambda = 333$ nm) as a function of temperature in *n*-butanol (cf. Ref. 27). The inset displays the double-logarithmic plots (η in cP)

values $\Delta E = 0.62 \pm 0.03\,\text{kcal mol}^{-1}$ and $\alpha E_\eta = 0.23 \pm 0.01\,\text{kcal mol}^{-1}$ (1 kcal = 4.184 kJ) have been obtained from the Arrhenius plots of the $k_{\text{inv}}/k_{\text{ret}}$ ratio and *n*-butanol viscosity; from these data the internal contribution is calculated to be $\Delta E^{\text{i}} = 0.39 \pm 0.03\,\text{kcal mol}^{-1}$. Hence the superimposed internal temperature effect ($\Delta E^{\text{i}} = 0.39\,\text{kcal mol}^{-1}$) outweighs the external viscosity dependence ($\Delta E^{\text{e}} = 0.23 \pm \text{kcal mol}^{-1}$), but what should be stressed is that both energy terms may be assessed through such a composite temperature–viscosity study. Moreover, although the value $\Delta E^{\text{i}} = 0.39\,\text{kcal mol}^{-1}$ is small, it accounts adequately for the difference in the viscosity behavior of the $k_{\text{inv}}/k_{\text{ret}}$ ratio for the thermal (Fig. 3) and constant-temperature (Fig. 2) viscosity variations.

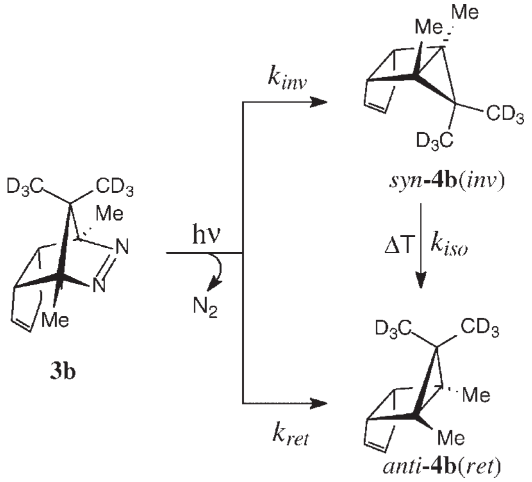
The featured example demonstrates how sensitive the viscosity probe is for determining experimentally small energy differences in the activation barriers for competitive processes. This constitutes an additional advantage of harnessing viscosity as a powerful mechanistic tool. It should be mentioned, however, that on substitution of the DBH molecule, the external frictional effects begin to dominate the internal contributions, and it becomes difficult to acquire the internal energy (ΔE^{i}) term through the viscosity assay. Indeed, for the substituted derivative **1c**, the isothermal and thermally controlled viscosity profiles coincide,[5] which implies that the ΔE^{i} term is negligible compared with ΔE^{e}.

Viscosity dependence of azoalkane photolysis versus thermal *syn*-to-*anti* housane isomerization

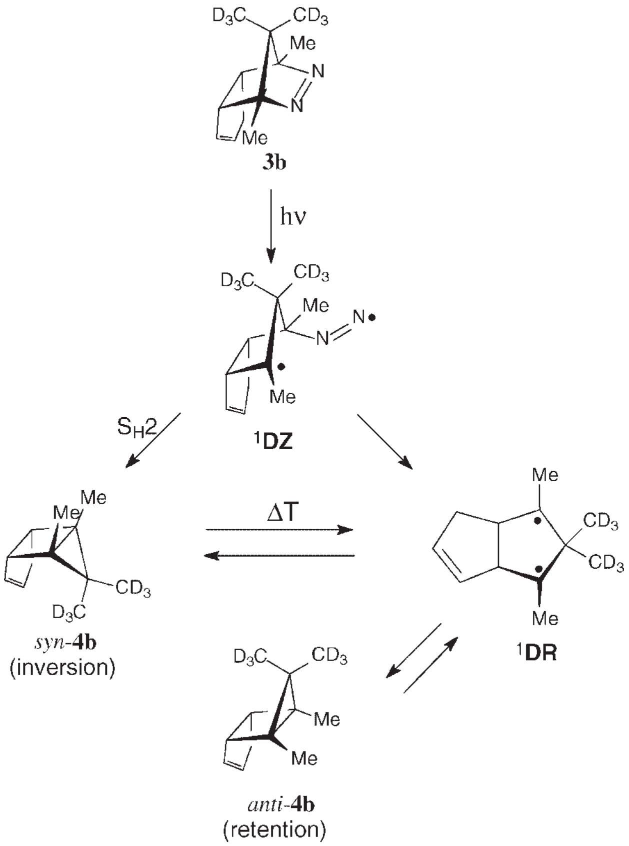
To validate the viscosity control in the azoalkane photolysis, the thermal *syn*-to-*anti* isomerization of the corresponding housane was examined, since both molecular rearrangements involve a similar spatial transposition of the dimethyl-substituted methano bridge during the inversion process. For this purpose, the tricyclic azoalkane **3b** and its housane product **4b** were chosen (Scheme 5).[29] The reason for having selected the structurally more elaborate housane *syn*-**4b** to probe viscosity effects in the thermal isomerization rests on the practical fact that for the parent housane **2a** too high temperatures (>200 °C) are required and the rate constants (k_{iso}) are not sufficiently accurate.[29]

The viscosity profiles for the $k_{\text{inv}}/k_{\text{ret}}$ ratio in the azoalkane **3b** photolysis and the isomerization rate constant k_{iso} were found to superimpose reasonably well and both quantities depend on viscosity to a similar fractional power. For the azoalkane photolysis we obtained $\alpha = 0.20 \pm 0.01$ and for the housane isomerization $\alpha = 0.16 \pm 0.03$; within the experimental error, these are about the same.

The mechanistically significant feature of the photolysis[27] of the azoalkanes and the thermal isomerization[32] of their housane products resides in the intermediacy of the nitrogen-free cyclopentanediyl ^{1}**DR** species, common to both processes (Scheme 6). As is evident from the composite mechanism in Scheme 6, the substituted methylene bridge in the inversion processes ^{1}**DZ** → *syn*-**4b** and *syn*-**4b** → *anti*-**4b** experiences flap motions of similar amplitudes. Hence one may expect the same viscosity effects for these reactions, as is manifested by the nearly equal α values for the photolysis of the



Scheme 5



Scheme 6

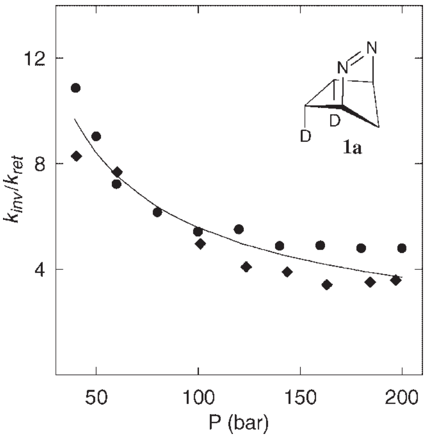


Figure 4. Pressure dependence of the k_{inv}/k_{ret} ratio (data taken from Ref. 33) for the photolysis ($\lambda = 333$ nm) of DBH (**1a**) in supercritical carbon dioxide (◆) and ethane (●) at 50 °C

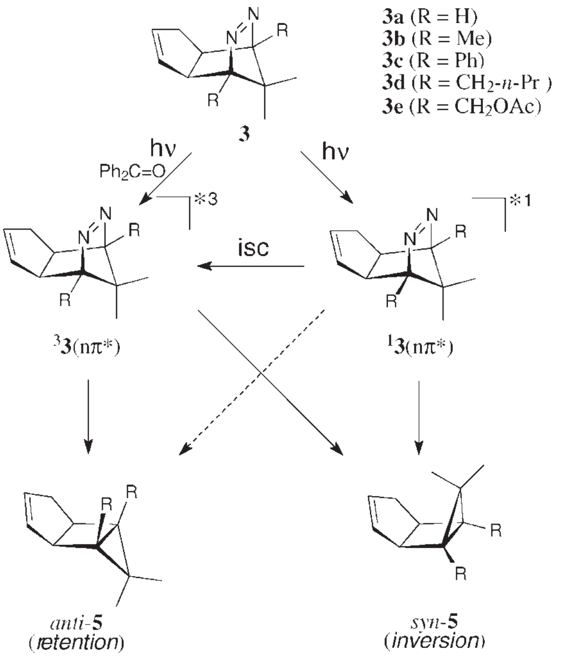
azoalkane **3b** and the thermolysis of the housane *syn*-**4b**. The inverted housane is formed from the azoalkane through the intramolecular homolytic displacement of the nitrogen molecule by backside attack (S_H2 process) in the diazenyl diradical ^{1}**DZ**, whereas loss of the inversion selectivity derives from the common ^{1}**DR** species, experimentally assessed for the first time through the facile thermal *syn*-to-*anti* isomerization of the housane **4b**.

DBH photolysis in supercritical fluids: pressure dependence of diastereoselectivity

As seen from Fig. 4, the diastereoselectivity in the DBH photolysis in supercritical fluids (sc-CO_2 and sc-C_2H_6) depends on pressure.[33] An increase in pressure up to 200 bar leads to a ca 2.3-fold decrease of the stereoselectivity (k_{inv}/k_{ret} ratio) in sc-CO_2 and sc-C_2H_6. Analysis of the observed pressure dependence in terms of collisional (self-diffusion coefficient) and frictional (viscosity) effects discloses that frictional impositions by the fluid medium account best for the experimental observations. Hence the supercritical-phase results are consistent with the already presented experimental data on the liquid-phase DBH photolysis.[27]

SUBSTITUENT EFFECTS

The dependence of the diastereoselectivity on substituents in the azoalkanes **3** has helped to consolidate the photochemical denitrogenation mechanism in Scheme 4, and has provided valuable details on the reaction coordinate for the inversion versus retention processes. Whereas the *syn/anti* ratios stayed relatively constant in the triplet photodenitrogenation for the medium effects presented in the previous sections, it will now be seen that also for the triplet mode profound changes in the diastereoselectivity are caused by the type of substituent that is placed at the bridgehead positions. For this reason, we shall view the substituent effects also as a function of spin multiplicity and gain further mechanistic insight into the intermediates involved in the photodeazetation.

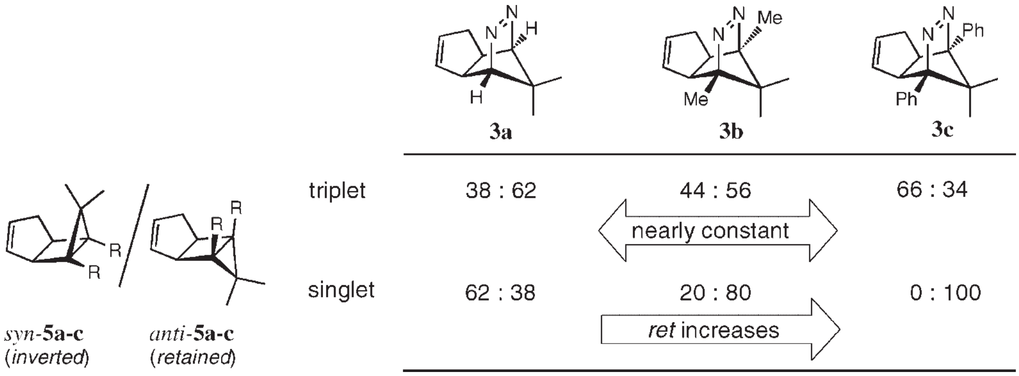


Scheme 7

To understand the substituent effects, it is necessary to classify them as rotationally symmetric (azoalkanes **3a**–**c**) and rotationally unsymmetric (azoalkanes **3d**,**e**) at the bridgehead positions (Scheme 7).[15,34,35] The bridgehead substituents in the azoalkanes **3a**–**c** are rotationally symmetric in the sense that both sides of the incipient 1,3-cyclopentanediyl ring are equally sterically shielded on rotation of the substituents about the bridgehead position and, therefore, no side preference is expressed. In contrast, the rotationally unsymmetric *n*-propyl and the acetoxymethyl groups in the azoalkanes **3d** and **3e** act like a windshield wiper, in that their respective ethyl and acetoxy rests encounter distinct steric interactions with the *gem*-dimethyl-substituted methylene bridge or the annelated cyclopentene ring as they sweep across the two sides of the incipient cyclopentanediyl ring during their rotation about the bridgehead position. Clearly, for these substituents both sides are sterically differentiated and preferred conformations may be acquired. Additionally, we shall see that the long-range steric interactions between the annellated ring and the *gem*-dimethyl-substituted methylene bridge affect the diastereoselectivity for both the singlet and triplet photodenitrogenation.[34,35]

Rotationally symmetric bridgehead substitution

For the rotationally symmetric derivatives **3a**–**c**, the temperature dependence of the diastereoselectivity

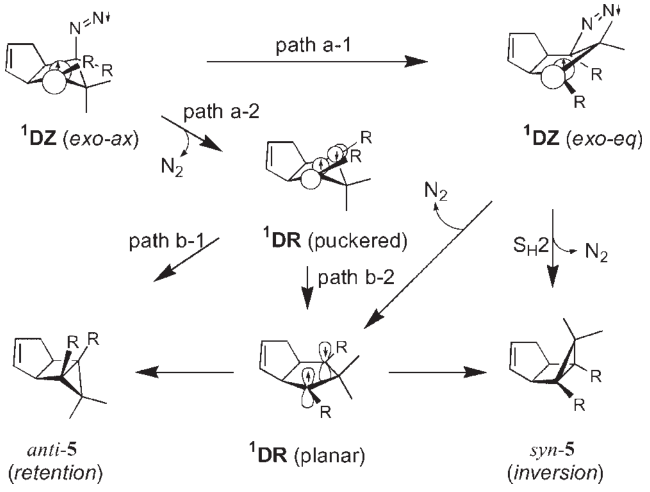


Scheme 8

(*syn*/*anti* ratio) in their photodenitrogenation (cf. Scheme 7) manifests a competition between the singlet (high-temperature) and triplet (low-temperature) reaction channels in the direct photolysis.[15] More explicitly, the observed change-over in the reaction path with temperature stems from the temperature dependence of the α-CN bond cleavage in the singlet-excited azoalkanes **3**: at higher temperatures (20–40 °C) the α scission is efficient, whereas at lower temperatures (-20 to -75 °C) it no longer competes effectively with the essentially temperature-independent (barrierless) intersystem crossing (Scheme 7).[15,34,35] The triplet pathway of the photodenitrogenation at low temperatures is evidenced by the same product distribution for the direct and benzophenone-sensitized photolysis under the same temperature conditions.[15,34,35]

Scheme 8 summarizes the results on the product distribution for the triplet and singlet photolysis channels of the azoalkanes **3a–c**. For the triplet reaction path, two characteristic features are evident from Scheme 8, namely the low diastereoselectivity and the small substituent effect on the latter; thus, for **3a** merely a small preference for the retained product has been found, whereas for **3c** an inverted housane is slightly favored (Scheme 8). The low stereoselectivity suggests the intervention of a thermally equilibrated planar diradical **DR** in the triplet process, which affords similar amounts of the inverted (*syn*) and retained (*anti*) housanes **5** upon ring closure.[15,34,35] As expected, for the planar **DR** intermediate the substituent effects on the inversion and retention channels are similar. In contrast, the singlet reaction channel exhibits a pronounced dependence on bridgehead substitution. In the latter case, the amount of the *anti* diastereomer (retention) follows the order Ph > Me > H (Scheme 8), i.e. the larger the substituent, the more retained housane is formed. This increased retention is interpreted in terms of the inertia (mass) effect of the substituents and steric interaction (size) between the substituents at the bridgehead and the methylene bridge during the deazetation step of the *exo*-axial conformation [^{1}**DZ**(*exo*-ax)] of the diazenyl diradical **DZ** (Scheme 9).[15,34,35] The larger mass imparts a drag (inertia) on the bridgehead substituent during the inversion, whereas the larger size imposes a higher steric barrier in moving the bridgehead substituents past the *gem*-dimethyl bridge. Both as expected slow the conformational changes and promote nitrogen loss from the initial geometry.

To rationalize qualitatively the bridgehead-substituent effect, it suffices to consider the two extreme cases, the unsubstituted derivative **3a**(H/H) and the diphenyl case **3c**(Ph/Ph). Scheme 9 displays two bifurcation steps, namely paths a-1/a-2 and paths b-1/b-2. For **3a**(H/H), both the mass drag and the steric hindrance are minimal on the conformational change along path a-1 and most of the singlet-state denitrogenation proceeds by the S_H2 mechanism to afford mainly inverted housane *syn*-**5a**(*inv*). Since substantial amounts of retained housane *anti*-**5a**(*ret*) are produced, denitrogenation along path a-2 must compete, but beyond this point it is difficult to assess even qualitatively what happens stereochemically, because no information is available on the relative importance of the path b-1 versus path b-2 in the subsequent bifurcation step.



Scheme 9

If one assumes, however, that all of the ^{1}**DR**(puckered) relaxes to ^{1}**DR**(planar) along path b-2, on the basis of the observed product ratios,[15] about one-third of the direct photolysis goes through the S_H2 process and the remaining two-thirds through the thermally equilibrated ^{1}**DR**(planar) diradical.

In contrast, the stereochemical analysis of the **3c**(Ph/Ph) case is straightforward, since only the retained housane *anti*-**5c**(*ret*) is obtained, i.e. complete retention is observed for the first time in the singlet photodenitrogenation. In this case, both the mass and steric factors operate so efficiently that only the a-2 and b-1 paths are pursued by the respective diradicals ^{1}**DZ**(*exo*-ax) and ^{1}**DR**(puckered); the conformational changes in the a-1 and b-2 steps are too slow to compete with the a-2 and b-1 paths and no inverted housane is formed.

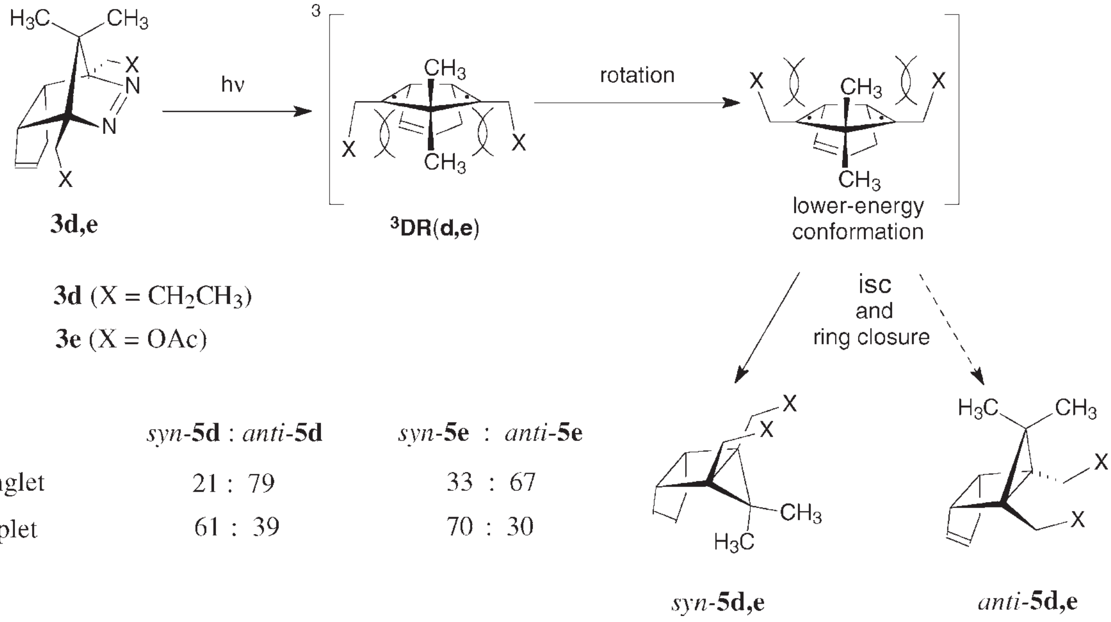
Rotationally unsymmetric bridgehead substitution

In contrast to the rotationally symmetric bridgehead substituents (azoalkanes **3a**–**c**), which engage an unselective triplet reaction channel and selective formation of *anti*-configured (retained) housanes in the singlet process (Scheme 8), the rotationally unsymmetric bridgehead-substituted azoalkanes **3d**,**e** are moderately diastereoselective for both the singlet and triplet modes of photolysis (Scheme 10), as evidenced by the *syn*/*anti* (inversion/retention) ratio.[34,35] Thus, the photolysis of **3d**,**e** affords under singlet conditions (high-temperature direct photolysis) predominantly the retained housanes *anti*-**5d**,**e** (*syn*/*anti* 21:79 for housane **5d** and 33:67 for **5e**), whereas under triplet conditions (low-temperature direct or benzophenone-sensitized photolysis) the inverted diastereomer *syn*-**5d**,**e** is favored (*syn*/*anti* 61:39 for **5d** and 70:30 **5e**).

This unprecedented inversion for the triplet pathway is rationalized in terms of the unsymmetric nature of the *n*-propyl and acetoxymethyl substituents in regard to rotation about the bridgehead position of the planar cyclopentane-1,3-diyl triplet diradicals ^{3}**DR**(**d**,**e**), cf. Scheme 10. For the lower-energy conformation of the ^{3}**DR**(**d**,**e**) diradical, the X fragments (CH_3CH_2, OAc) of the bridgehead substituents point for steric reasons away from the annellated cyclopentene ring and are preferably located on the upper side of the diyl ring. After intersystem crossing (isc) of the triplet diradicals ^{3}**DR**(**d**,**e**) to the singlet diradicals ^{1}**DR**(**d**,**e**), the *gem*-dimethyl-substituted methylene bridge may tilt either downward or upward, to close to the respective *syn* and *anti* housanes (Scheme 10). The preference for the *syn* housane comes from the steric interactions of the upper methyl group on the methylene bridge with the two bridgehead substituents in their lower energy conformation (located above the diyl plane), which directs the tilting motion of the methylene bridge downwards in favor of the *syn* housane.

Long-range steric effects

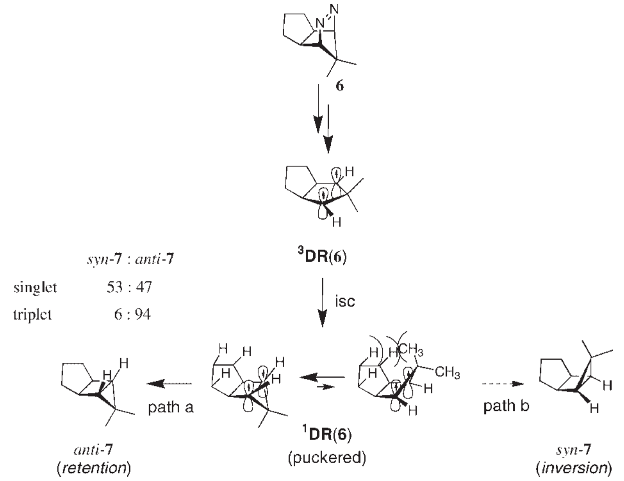
Usually the triplet photolysis of azoalkanes **3a**–**c** displays a low diastereoselectivity, with a slight preference for the retained housane *anti*-**5a** (H/H at the bridgehead positions), for which the *syn*/*anti* ratio is 38:62. This slight preference for retention has recently[31] been mechanistically attributed to the steric interactions between the annellated cyclopentene ring and the *gem*-dimethyl-substituted methylene bridge during the ring closure of the planar nitrogen-free triplet diradical ^{3}**DR**. It may be



3d (X = CH_2CH_3)
3e (X = OAc)

	syn-**5d** : *anti*-**5d**	*syn*-**5e** : *anti*-**5e**
singlet	21 : 79	33 : 67
triplet	61 : 39	70 : 30

Scheme 10



Scheme 11

anticipated that an increase in the steric interactions between the remote annellated ring and the *gem*-dimethyl-substituted methylene bridge should raise the energy barrier of the ^{3}**DR** → *syn*-**5a** cyclization and, consequently, the formation of *anti* housane should be enhanced. That this is actually the case, has been demonstrated[34,35] for the photodenitrogenation of the azoalkane derivative **6** with the annelated cyclopentane ring (Scheme 11). Whereas in the direct photolysis (singlet process) the *syn/anti*-**7** housane ratio (*syn/anti* 53:47 for **7**[34,35] versus 62:38 for **5a**[15]) is nominally affected by this structural change, for the benzophenone-sensitized photolysis (triplet-excited process) essentially exclusively (*syn/anti* 6:94 for **7**[34,35] versus 38:62 for **5a**[15]) the *anti*-**7** housane is observed.

Scheme 11 provides a pictorial rationale for the essentially exclusive *anti* stereoselectivity in the photolysis of azoalkane **6** under triplet conditions. After intersystem crossing (isc) to the singlet diradical ^{1}**DR**, the direction of the ring closure to the diastereomeric housanes **7** is controlled by the remote steric effects between the *gem*-dimethyl-substituted methylene bridge with the cyclopentane-annellated ring. This steric interaction is more effective for the bulkier annellated cyclopentane versus cyclopentene rings during the puckering motion of the ring closure in the resulting ^{1}**DR**(**6**) diradical, such that the *anti*-**7** (path a) rather than *syn*-**7** (path b) is produced in high preference (Scheme 11).

CONCLUSIONS

The present review reveals that the puzzling phenomenon of double inversion in the denitrogenation of azoalkanes, discovered by Roth and Martin in 1967,[2] still attracts much attention of mechanistic and physical organic chemists, most prominently during the last 5 years. The lion's share of recent experimental material refers to the photochemical nitrogen-extrusion process. This is because the thermal denitrogenation usually requires high temperatures, which restricts severely the variation of experimental conditions, i.e. the choice of temperature and solvent, to examine medium effects such as those of viscosity and polarity. Unfortunately, the use of more readily thermolyzed azoalkanes through appropriate substitution also enhances the ease of housane isomerization during their generation, such that the stereochemical information is erased and mechanistic conclusions are obviated. These disadvantages are avoided in the photodenitrogenation, for which a wide range of temperature and a large number of solvents of varying viscosity and polarity may be employed. Through these studies, especially the viscosity effects on the inversion versus retention of stereoselectivity, a detailed mechanistic picture on the photochemical deazetation was acquired. Thus, the diazenyl diradical **DZ** figures as a pivotal intermediate in the singlet photolysis, to account for the high degree of inversion, whereas the nitrogen-free cyclopentanediyl species **DR** serves as precursor for the essentially isomerized mixture of housanes in the triplet process of the parent DBH and simply substituted derivatives. Valuable fine structure on the denitrogenation coordinate was assessed through substituent effects, which have helped to consolidate this complex mechanism. Although inversion usually prevails in the singlet-state photodenitrogenation, through appropriate bridgehead substitution the process may be steered entirely towards retention. Similarly, the unselective triplet-state mode may be channeled exclusively along retention by means of long-range steric effects through proper substitution. On the basis of the combined experimental and computational efforts during the last few years, the mechanism of the perplexing photochemical denitrogenation of DBH-type azoalkanes is now well understood.

Acknowledgements

We express our sincere gratitude to all our colleagues who participated in the experimental and theoretical work on this fascinating mechanistic problem; their names are cited in the original publications. The generous financial support of the Deutsche Forschungsgemeinschaft, the Volkswagen-Stiftung the Fonds der Chemischen Industrie, the Russian Foundation for Basic Research and the Division of Chemistry and Material Science of the Russian Academy of Sciences is gratefully appreciated.

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