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Carbenes in Constrained Systems. 4.[§] Encapsulation of an Asymmetric Diazirine: Reactivity of 2-Methylcyclohexanylidene

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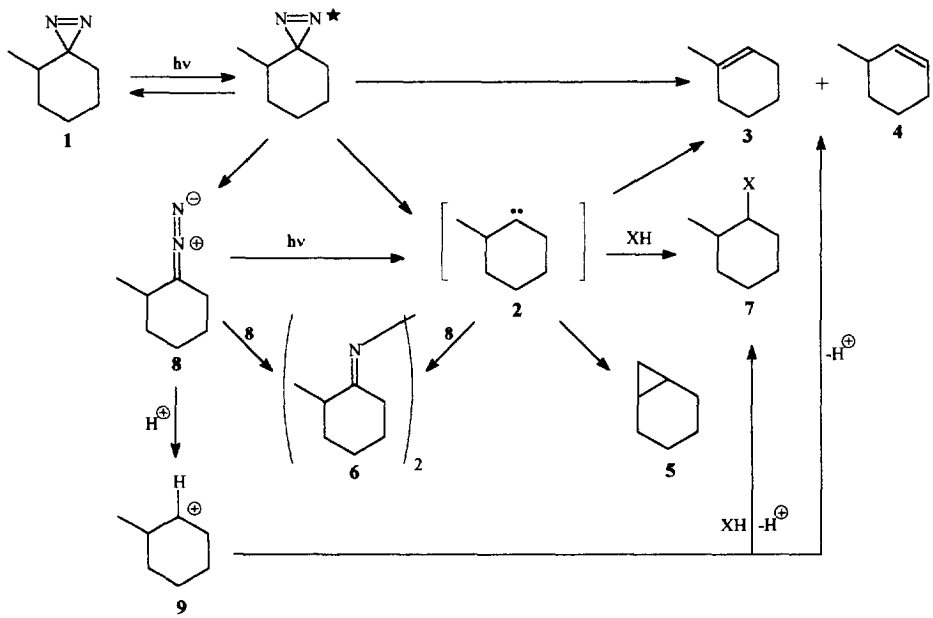
Abstract: 2-Methylcyclohexanylidene was generated from the corresponding diazirine within the cavities of α-, β- and γ-cyclodextrin by photolysis in the solid state. To surmise how these constrained systems affect the residing carbene's selectivity, a comparison with conventional reaction methods was made.

Carbenes are highly reactive intermediates that often frustrate efforts to steer which reaction pathway they follow. Thus, it is difficult to control which intramolecularly-derived isomer the carbene will prefer to rearrange to.[1] Furthermore, azine formation is always a pertinent option for a freely diffusing carbene or azi-/diazo-precursor.[2]



Scheme 1. Some intra- and intermolecular reactions of 2-methylcyclohexanylidene (**2**).

We have shown,[3] however, the ability of molecular host media to alter the selectivity of carbenes. Not only can intermolecular azine formation be suppressed but certain intramolecular C-H insertions can be enhanced by

factors up to 900 times.[3b]

We now extend our pursuit and attempt to control the intramolecular 1,2-hydride shift in carbenes. This might seem improbable, considering recent evidence for a quantum mechanical (QM) tunneling mechanism for this process.[4] However, we hypothesized that a misalignment of the involved molecular orbitals (MOs) in the rearrangements, effected by cyclodextrin (CD) hosts, might reduce orbital overlap and lead to altered selectivities.

Scheme 1 shows[5] the transformations that asymmetric 2-methylcyclohexanylidene (**2**) can undergo. Most noteworthy is the choice between formation of 1-methylcyclohexene (**3**) and 3-methylcyclohexene (**4**).

4-Methyl-1,2-diazaspiro[2.5]oct-1-ene (**1**)[6] was prepared from the corresponding ketone *via* the Schmitz reaction[7] and subsequent oxidation with a Ag_2O/ether suspension. Photolyses of **1** in solution or in the solid state, with a 450-W Hg-arc lamp, were performed for an average of 3h. Typical solution photolyses were conducted by vortexing a 2.5-mL argon-purged solution in a test tube equipped with a rubber septum and a syringe. The results of solution photolyses are shown in Table 1 (see entries 3-6). The solutions turned peach-colored for a few hours during photolysis. We ascribe this to the formation of the linear diazo compound **8** (IR: (n-C_5H_{12}) $\bar{\nu}$=2025cm^{-1} (C=N=N); UV: (n-C_5H_{12}) λ= 492 nm), a valence isomer of **1**.

Carbene **2** can also be generated from the corresponding tosylhydrazone sodium salt *via* the Bamford-Stevens reaction.[8] The gas phase results are also included in the Table (see entry 2) as are the results of Wilt and Wagner[8b] (see entry 1).

Table 1. Effect of Reaction Medium on Selectivity of 4-Methyl-1,2-diazaspiro[2.5]oct-1-ene (**1**).[a]

Relative % of: Methods:	**3**	**4**	**3:4**	**5**	**6**	**7**
1)[b] 180°C (NMP)[8b]	63	27	2.3	trace	-	-
2)[b] 250°C (5 torr)	78	22	3.6	-	-	-
3) 0.1M n-C_5H_{12}	45	21	2.1	-	34	-
4) 0.5M n-C_5H_{12}	25	11	2.2	-	64	-
5) 0.1M MeOH	43	24	1.8	-	-	33[c]
6) 0.5M MeOH	42	23	1.8	-	-	35[c]
7) α-CD	72	28	2.6	-	-	-
8) β-CD	66	34	1.9	-	-	-
9) γ-CD	62	30	2.1	-	8	-

[a] error= ±3%
[b] tosylhydrazone sodium salt
[c] 1-methoxy-2-methylcyclohexane

Typical procedure for the preparation of **1**@CDs: a 1.5-mmol aliquot of **1** from a known (by ^{1}H NMR) concentrated pentane solution was injected into a rapidly stirring 90% saturated aqueous solution of the appropriate CD (1.5 mmol). The white precipitate was vacuum-filtered and washed with small amounts of water, dried overnight in a desiccator and then weighed. Guest:host ratios were determined by ^{1}H NMR spectroscopy (DMSO-d_6) and were used to calculate absolute yields.[9] These were 50% (**1**@α-CD), 57% (**1**@β-CD) and 69% (**1**@γ-CD) and may reflect the increasing cavity sizes of the hosts. Solid state photolyses were carried out by vortexing 200 mg of **1**@CD in an argon-purged 10-mL Erlenmeyer flask (Pyrex) equipped with a rubber septum and a syringe. After 2h no more **1** was present by NMR nor by GC analysis. The complexes were dissolved in *ca.* 1 mL of DMSO (or DMSO-d_6) and the products were then extracted with *ca.* 0.5 mL of pentane and dried over

$(NH_4)_2SO_4$. GC proved to be more accurate for analysis than ^1H NMR.

In contrast to all other reaction conditions, trace amounts of norcarane **5** are produced only by the thermal Bamford-Stevens method in solution.[8b] Formation of 2-methylcyclohexanone azine (**6**) is inhibited in MeOH, due to the diazo compound's **8** short lifetime in protic media.[5a] This same inhibition is seen with α- and β-CD and can be attributed either to their hydroxy moieties and/or their supramolecular capabilities. Note that small amounts of **6** were formed in γ-CD since two molecules of **1** could be associated with the larger γ-CD.

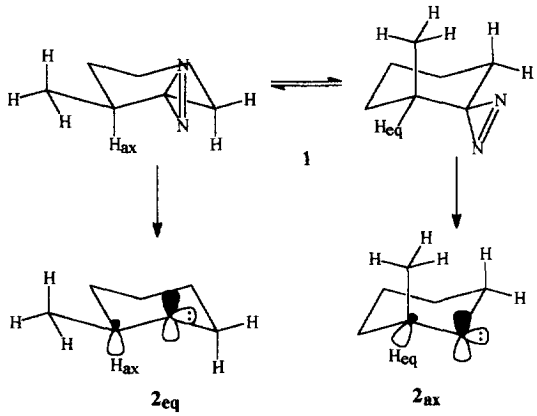
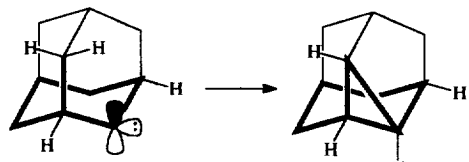


Figure 1. Generation of two conformeric isomers of carbene **2** from an equilibrated **1**.

Statistically, the rate of formation of alkene **4** should be twice that of alkene **3**. This, however, is not the case, due to unequal reactivities of the migrating hydrides. For the corresponding carbocation **9**, Saytzeff's rule predominates, leading to a ratio of **3**:**4** of about 5.4.[10] This rule is less stringent for the intractable carbene **2** and ratios of about 1.8-3.6 were observed (see Table 1). In methanol (see entries 5,6), however, considerable amounts of ether **7** (X= OCH_3) are formed. This may derive either from protonation of **1** and/or **8** to give carbocation **9**, which picks up methanol, or from insertion of carbene **2** into the O-H bond of methanol.[11] Because of this additional complication, the ratios of **3**:**4** are obscured. The tight fit of a cyclodextrin cavity might disfavor the equatorial preference of the methyl group in **1**. As depicted in Fig. 1, should the methyl group in **1** be forced to adopt an axial conformation, the hydrogen at C-2 would assume an equatorial position. The misalignment of the filled MO of the C-H bond (HOMO) with the empty orbital (LUMO) at the carbene center would necessarily reduce orbital overlap and concomitantly suppress the formation of **3**. Of course, the conformation of **2**@CD must resemble that of **1**@CD, and also the classical energy barrier to a 1,2-hydride shift cannot be undermined by ultrafast QM tunneling. This is important because it has been shown for a divalent carbon in a rigid molecule [12] that the photolytic H_{ax}/H_{eq} migration preference is 1.2, assuming no QM tunneling.

It should be noted, from Figs. 1 and 2, that an axially positioned methyl group would be more susceptible to a 1,3-C-H insertion. This axial conformer mimics that of the scaffolded adamantanylidene (**10**) which cannot undergo the competing 1,2-hydride migration to afford adamantene. Instead, **10** has been shown to have an up to 900 times enhanced 1,3-C-H insertion capability to afford 2,4-dehydroadamantane (**11**) within supramolecular complexes.[3a,b] Thus, should conformational control over **1** inside CD cavities be achieved, not only would production of the less-substituted alkene **4** be enhanced, but also the product of 1,3-C-H insertion, norcarane **5**, should proliferate.

Table 1 also shows that the ratio of **3**:**4** is only slightly affected by solid state supramolecular photolysis



10 11

Figure 2. Analogy of 1,3-C-H insertion for adamantanylidene.

of **1**@CDs, compared to conventional methods. This is either because 1) the conformation of **1** inside the CDs is the same as in conventional media or 2) that the ring flipped axial methyl conformer $\mathbf{2}_{ax}$ is predominant but the reaction coordinate for the QM tunneling process is independent of the torsion angle of the involved MOs in the rearrangement. However, the absence of norcarane **5** rules out the second conclusion in favor of the first one, according to the aforementioned analogy. Finally, the lack of enhanced production of **5** is another testimony for the crucial need for optimal orbital alignment in carbene insertion reactions.

CAS Registry Number®: 4-Methyl-1,2-diazaspiro[2.5]oct-1-ene *[14359-89-8]*

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§ Carbene Rearrangements, 45 (Carbene Rearrangements in Constrained Systems, 4); for part 44 (part 3) see ref.[3c]

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