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Intra- and Intermolecular Diastereoselectivity of 5-Hydroxy-2-adamantylidene†

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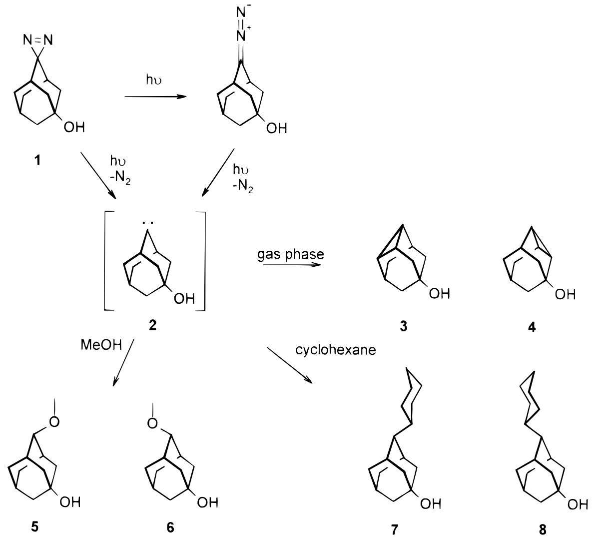
The rationale of the diastereoselectivity in the reactions of alleged sterically unbiased molecules has been reviewed extensively, but remains a controversial issue.[1] An explanation of this phenomenon was brought forth by Cieplak[2] who invoked hyperconjugative donation of electrons into the σ*-orbital of the incipient bond formed. Other authors criticized this approach[3] because of its neglect of direct electrostatic interactions.[4] Another explanation is based on the distortion of the geometry of the precursor that could induce a steric preference for the reagent's attack.[5] Although various types of reactions with substituted adamantanes have been studied,[6] virtually nothing is known about the behavior of the corresponding carbenes.[7] The geometry of these highly reactive intermediates should closely resemble the activated complexes of their reactions.[8] Therefore, the investigation of carbene reactions should allow general conclusions about the nature of the observed diastereoselectivity.

To this end, the intra- and intermolecular insertion reactions of 5-hydroxy-2-adamantylidene (**2**) were studied in the gas phase and in solution. **2** appears to be an ideal system for the following reasons. Direct steric interactions with the approaching reagent should be negligible, because the substituent at C-5 is located practically opposite of the divalent carbon. Moreover, the rigidity of the adamantane skeleton prohibits conformational changes that would influence the course of the reaction.

Carbene **2** was generated thermally and photochemically from 2-azi-5-hydroxyadamantane **1**,[9] which was prepared from the corresponding ketone.[10] In general, carbenes can be generated by photolysis of diazirines via two competing pathways.[11] They can be formed by the extrusion of nitrogen either directly from the excited state diazirine or indirectly from the linear diazo compound.[12] Calculations[13] and experimental results[14] suggest a singlet ground state for adamantylidene.

In polar protic solvents such as methanol, however, the diazo compound is readily protonated leading to the corresponding carbocation.[15] This carbeniumion reacts with methanol to yield methyl ethers. The possible formation of an interfering carbocation from the diazo compound must be inhibited, if only carbene reactions are to be studied.[15]

Scheme 1: Reactions of 5-Hydroxyadamantylidene (**2**)



The intramolecular 1,3 C−H insertion products **3** and **4** (Scheme 1) were formed quantitatively by vacuum pyrolysis in a 90:10 ratio in favor of the *anti* insertion product **3** (Table I).[16,17] Diazirine **1** was photolyzed[18] in cyclohexane to yield products **7** and **8**. For the intermolecular C−H insertion reaction, the ratio was reversed to 89:11 in favor of the *syn*-substituted (Figure 1) product **7**. The photolysis of **1** in methanol was carried out without fumaronitrile (FN) and in the presence of at least a one 100-fold excess of FN. In pure methanol, the O−H insertion occurs in high yields with a ratio of 74:26 in favor of the *syn*-substituted product **5**.[19] However, in the presence of FN, a potent 1,3-dipolarophile, this ratio is increased to 85:15. The combined yield of O−H insertion products **5** and **6** dropped from 89 to 58%,[20] independent of the concentration of FN chosen. Since the diazo compound is completely scavenged in a 0.5 M FN solution, the higher ratio of **5** to **6** (85:15) can be exclusively attributed to carbene insertions.

In addition, an ab initio geometry optimization of the singlet ground state of **2** was performed.[21] The calculated structure shows a deviation of 7.4° away from the O−H group of the carbene carbon from the $H_1-C_1-C_3-H_3$ plane. Even when choosing a starting geometry with C_2 bent toward the O−H substituent by about 20°, the carbene carbon passes the $H_1-C_1-C_3-H_3$ plane and settles in the described conformation.

Analysis of the orbitals of this conformation reveals that the unoccupied p-orbital (LUMO) of the singlet carbene participates in the C_1-C_8 and C_3-C_{10} bonds (Figure 2).

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† Carbene Rearrangements. 54. For Part 53, see: Wagner, R. A.; Weber, J.; Brinker, U. H. *Chem. Lett.* **2000**, 246.

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(17) An analogous behavior was found for 5-chloroadamantylidene and 5-methyladamantylidene. See: Hirsl-Starcevic, S.; Majerski, Z. *J. Org. Chem.* **1982**, *47*, 2520.

(18) Hanovia 700-W medium-pressure mercury arc lamp doped with FeI_2; Pyrex filter; 2 h photolysis time at 12−15 °C.

(19) **5** and **6** are also formed by solvolysis of the corresponding tosylates. Grob, C. A.; Wang, G.; Yang, C. *Tetrahedron Lett.* **1987**, *28*, 1247.

(20) Fumaronitrile traps the diazo compound in a 1,3-dipolar cycloaddition, preventing the formation of a carbocation via the diazonium ion route (also see ref 15). In addition to **5** and **6**, several products probably stemming from the 1,3-dipolar addition to the diazo compound and decomposition products thereof could be detected. For the photochemical decomposition of 1,3-dipolar addition products see: Sander, W.; Wrobel, R.; Komnick, P.; Rademacher, P.; Muchall, H. M.; Quast, H. *Eur. J. Org. Chem.* **2000**, 91.

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10.1021/ja001123m CCC: $19.00

Table 1: Ratios of Diastereomeric Products Formed from **1**

reaction conditions	yield[a] %	product distribution[b]	
pyrolysis			
		3	**4**
gas phase (neat)	>99	90	10
photolysis			
		7	**8**
5 mM in cyclohexane	92	89	11
photolysis			
		5	**6**
5 mM in MeOH	89[c]	74	26
5 mM in MeOH (0.5 M fumaronitrile)	57	85	15
5 mM in MeOH (1.0 M fumaronitrile)	58	83	17

[a] Combined yield of insertion products, determined by GC. [b] Error: ±2%, determined by GC and NMR spectroscopy. [c] 1-Hydroxyadamantane, **3** and **4** are formed in small amounts.

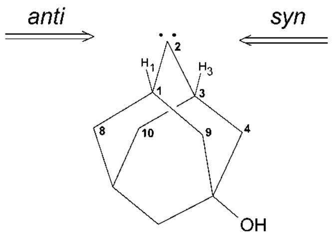

Figure 1. Possible sides for the attack on **2**.

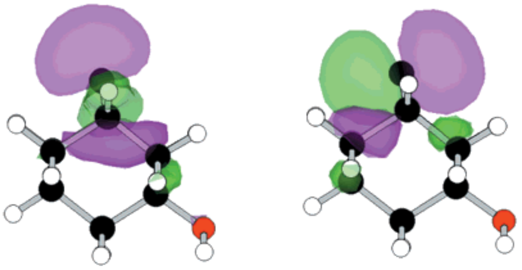

Figure 2. HOMO (left) and LUMO (right) of **2**.

It is generally accepted that an electron-withdrawing substituent in the 5-position of the adamantane skeleton can reduce the electron density from the C_1-C_9 and the C_3-C_4 bonds.[6] This is due to hyperconjugation with the antibonding σ^*-orbital of the C−O bond and the −I effect of the O−H group. As a consequence, the empty p-orbital of C_2 preferentially interacts with the more electron rich C_1-C_8 and C_3-C_{10} bonds. This hyperconjugative interaction can account for the observed deviation of the geometry of the divalent carbon at C_2. This conclusion is corroborated by calculations of unsubstituted adamantylidene[13] and low-temperature single-crystal X-ray structures of 2-adamantyl cations.[22] These electronically related compounds show a similar geometrical distortion caused by hyperconjugation.[22] Single-crystal X-ray analysis of carbene precursor **1** reveals no significant distortion of C_2 and the diazirine ring.[23] Therefore, the observed selectivity cannot be attributed to **1**.

Now one can begin to answer the question about the cause of the observed diastereoselectivity. In the intermolecular reactions, direct electrostatic interactions through space with the approaching reactant seem very unlikely. The insertion of a carbene into C−H bonds is a concerted reaction of the singlet state.[24] This is in contrast to the polar mechanism O−H insertion.[25] One would expect a higher selectivity for the charged intermediate involved in the O−H insertion. The comparable diastereoselectivity observed in the O−H (85:15) and C−H (89:11) insertion reactions strongly argues against direct electrostatic control of the reagent's orientation. Although a hyperconjugative stabilization of the σ^*-orbital of the new C−C or C−O bonds formed in the transition state cannot be ruled out, it is not necessary to invoke Cieplak's concept[2] to explain the results of the intermolecular reactions. It is not clear, however, whether the Cieplak approach is applicable also for the intramolecular case. If hyperconjugation with the newly formed C−H bond is considered, the experimental results are in agreement with Cieplak's model. On the other hand, consideration of the C−C bond formed contradicts the experimental findings.

The calculations show the singlet ground state of carbene **2** to be most stabilized when bent 7.4° away from the O−H substituent. According to the principle of least motion,[26] the intramolecular C−H insertion should preferentially occur into the C−H bonds proximal to the reactive center. This agrees well with the experimental findings; the major product **3** stems from an insertion into the C_8-H or $C_{10}-H$ bond. The predominant intermolecular O−H and C−H insertion products **5** and **7** result from an approach of the reagent via the more exposed *syn* face of adamantylidene **2**. The bulkier part of the reacting molecule can be better accommodated there. Both, the intra- and intermolecular selectivity can, therefore, best be explained by the distortion of the geometry of carbene **2**. EFOE analysis of **2** shows, that the plane-divided accessible space (PDAS) of 266.5 au^3 of the *syn*-side is much larger than the PDAS of 196.2 au^3 of the *anti*-side of the molecule.[27] These results emphasize that the observed diastereoselectivity is caused by changes of the diastereofacial accessibility already present in the ground state. Therefore, in the adamantylidene system, the outcome of a reaction is much more governed by steric factors than expected so far.[6] More calculations and experiments including electron-donating substituents, are in progress to fully address these questions.

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Supporting Information Available: Analytical data (NMR, MS, IR) of compounds **3** to **8** and structural data of **2** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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