

# Reversal of Diastereoselectivities in Intra- and Intermolecular Reactions of 2-Adamantanylidenes Primarily Caused by Electron-Donating and Electron-Withdrawing Substituents on C5<sup>†</sup>

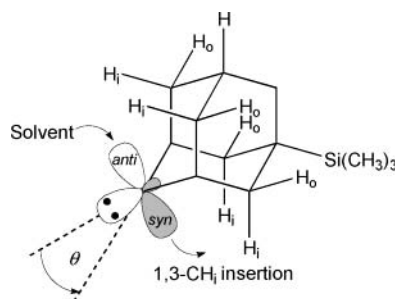
Wolfgang Knoll, Michael M. Bobek, Hermann Kalchhauser,<sup>‡</sup>  
Murray G. Rosenberg, and Udo H. Brinker\*

Institut für Organische Chemie, Universität Wien, Währinger Strasse 38,  
A-1090 Wien, Austria

udo.brinker@univie.ac.at

Received June 13, 2003

## ABSTRACT



A reversal of diastereoselectivity was observed for novel 5-(trimethylsilyl)adamantan-2-ylidene (1c) with regard to 5-hydroxyadamantan-2-ylidene (1a). Ostensibly in intermolecular reactions, 5-substituted 2-adamantanylidenes (1) are sterically unbiased. However, inductive effects originating from the pendant group *bend* the divalent carbon bridge of 1 either *toward* (ERG's, e.g.,  $-\text{Si}(\text{CH}_3)_3$ ) or *away from* (EWG's, e.g.,  $-\text{OH}$ ) the  $\gamma$ -position. Hence, the more exposed side is more susceptible to intermolecular reaction and the other side concomitantly undergoes intramolecular 1,3-CH insertions more readily.

To help account for the diastereoselectivities observed for the reactions of *alleged* sterically unbiased species,<sup>1</sup> 5-substituted 2-adamantanones have been widely employed. Still, this topic remains very controversial.<sup>1</sup> Of the many explanations offered for this phenomenon, Cieplak's has gained the most popularity.<sup>2</sup> His model invokes hyperconjugative electron donation of the more electron-rich C–C bonds into

the antibonding  $\sigma^*$ -orbital of the incipient bond during the transition state (Figure 1). This rationale has been criticized, because it appears to violate Frontier Molecular Orbital (FMO) theory.<sup>3</sup> Moreover, direct electrostatic interactions are neglected.<sup>4</sup> In contrast, quantum mechanical calculations of a substituted azaadamantane revealed a topological distortion of the adamantanyl framework (caused by the N atom) and were used to explain diastereoselectivities.<sup>5</sup> This distortion could have induced a *steric preference* during the

\* Address correspondence to this author. Phone: (43)-1-4277-52121.  
Fax: (43)-1-4277-52140.

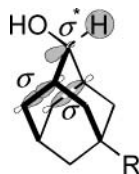
<sup>†</sup> Carbene Rearrangements. 58. For part 57, see: Rosenberg, M. G.; Brinker U. H. *J. Org. Chem.* **2003**, *68*, 4819–4832.

<sup>‡</sup> Deceased.

(1) See the special issue devoted entirely to this topic: le Noble, W. J., Gung, B. W., Eds. Diastereoselection. In *Chem. Rev.* **1999**, *99*, 1067–1480.

(2) (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Cieplak, A. S. *J. Am. Chem. Soc.* **1977**, *99*, 1265. (c) *Advanced Organic Chemistry*, 4th ed.; March, J., Ed.; Wiley: New York, 1992; p 754.

(3) Frenking, G.; Köhler, K. F.; Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1146.



**Figure 1.** Stabilizing interactions according to the Cieplak model.

reagent's attack. Indeed, Tomoda's recent B3LYP/6-31+G-(d,p) calculations, based on the Exterior Frontier Orbital Extension (EFOE),<sup>6</sup> show that the steric effect on the selectivity of reactions of 5-substituted 2-adamantanones *cannot be neglected*.<sup>6</sup> So, to demonstrate that alleged sterically unbiased species are actually biased, the reactive behavior of 5-substituted 2-adamantanylidenes (**1**) was investigated.

Surprisingly, little is known about these potentially versatile carbenes.<sup>7</sup> So recently, we reported the intra- and intermolecular insertion reactions of 5-hydroxyadamantan-2-ylidene (**1a**)<sup>8</sup> and 5-aminoadamantan-2-ylidene (**1b**).<sup>9</sup> Each carbene, which has a  $\sigma$ -electron-withdrawing group (EWG) on C5, was generated from its corresponding 3*H*-diazirine in the gas-phase reaction ( $\Delta$ ) and in solution ( $h\nu$ ). The thermally induced gas-phase reaction of the diazirine 4-aziadamantan-1-ol afforded a 90:10 ratio of 2,4-didehydroadamantanol diastereomers (Table 1).<sup>8</sup> Similarly, 4-aziadamantan-

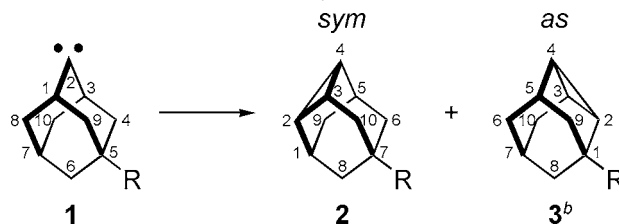
**Table 1.** Ratios of Diastereomeric Products Obtained from 5-Substituted 2-Adamantanylidenes (**1**)

carbene	reaction conditions	ratio <sup>a</sup>	
		<b>2a-c</b>	<b>3a-c</b>
<b>1a<sup>b</sup></b>	$\Delta$ , 250 °C	90	10
<b>1b<sup>c</sup></b>	$\Delta$ , 250 °C	80	20
<b>1c</b>	$\Delta$ , 260 °C	26	74
		<b>4a-c</b>	<b>5a-c</b>
<b>1a<sup>b</sup></b>	$h\nu$ , MeOH (FN) <sup>d</sup>	15	85
<b>1b</b>	$h\nu$ , MeOH (FN) <sup>d</sup>	15	85
<b>1c</b>	$h\nu$ , MeOH (FN) <sup>d</sup>	69	31
		<b>6a-c</b>	<b>7a-c</b>
<b>1a<sup>b</sup></b>	$h\nu$ , <i>c</i> -C <sub>6</sub> H <sub>12</sub>	11	89
<b>1b</b>	$h\nu$ , <i>c</i> -C <sub>6</sub> H <sub>12</sub>	22	78
<b>1c</b>	$h\nu$ , <i>c</i> -C <sub>6</sub> H <sub>12</sub>	63	37

<sup>a</sup> Error =  $\pm 2\%$  (determined by GC and NMR). <sup>b</sup> See refs 8 and 10. <sup>c</sup> See ref 9. <sup>d</sup> 0.5 M fumaronitrile.

1-amine gave 2,4-didehydroadamantanamines in a ratio of 80:20 (Table 1).<sup>9</sup> Thus, carbenes **1a,b** predominantly formed the *symmetrical* insertion products (**2a,b**) (Scheme 1), which

**Scheme 1.** Intramolecular Reactions of 5-Substituted 2-Adamantanylidenes (**1**)<sup>a</sup>

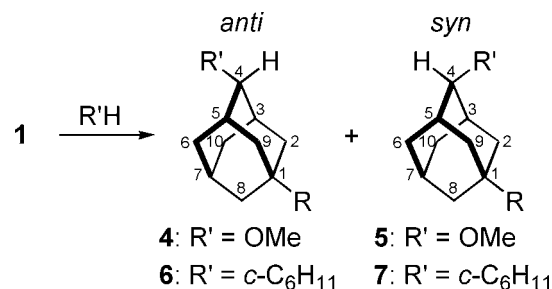


<sup>a</sup> R = (a) OH, (b) NH<sub>2</sub>, (c) Si(CH<sub>3</sub>)<sub>3</sub>. <sup>b</sup> Only one enantiomer shown.

are formed from intramolecular 1,3-CH insertions by the *distal* sides of the carbenes.

To discover whether electrostatic control is involved in intermolecular reactions, the diazirine precursors of **1a** and **1b** each were photolyzed in *polar* methyl alcohol (MeOH) and *nonpolar* cyclohexane (*c*-C<sub>6</sub>H<sub>12</sub>) (Scheme 2). Remark-

**Scheme 2.** Intermolecular Reactions of 5-Substituted 2-Adamantanylidenes (**1**) with MeOH and *c*-C<sub>6</sub>H<sub>12</sub><sup>a</sup>



<sup>a</sup> R = (a) OH, (b) NH<sub>2</sub>, (c) Si(CH<sub>3</sub>)<sub>3</sub>.

ably, the *anti:syn* ratios for EWG-substituted carbenes **1a** and **1b** were similar (Table 1). So, although a detailed mechanism for these insertion reactions is not yet known, the comparable selectivities observed in a polar and a nonpolar solvent discount direct electrostatic control of the reagent's orientation. And, complementary to the *intramolecular* insertions, the ratios for both *intermolecular* reactions are in favor of the insertion products, i.e., **5a,b** and **7a,b**, that are formed from attack of the *proximal* side of the carbene. Moreover, the effect is temperature independent, because photolysis of 4-aziadamantan-1-amine in MeOH for 2.5 h gave the same ratio of **4b** to **5b** (15:85) at  $-70$  and  $15$  °C. Note that photolysis of cyclic diazirines sometimes yields

(6) (a) Tomoda, S.; Senju, T. *Tetrahedron* **1999**, *55*, 5303. (b) Tomoda, S. *Chem. Rev.* **1999**, *99*, 1243.

(7) Majerski employed the Bamford-Stevens reaction to generate 5-methyladamantan-2-ylidene and 5-chloroadamantan-2-ylidene by thermolysis (180 °C) of the corresponding, dry *p*-tosylhydrazones sodium salts. See: HirsI-Starcevic, S.; Majerski, Z. *J. Org. Chem.* **1982**, *47*, 2520.

(8) (a) Bobek, M. M.; Brinker, U. H. *J. Am. Chem. Soc.* **2000**, *122*, 7430. (b) Teager, T. S.; Murray, R. K., Jr. *J. Org. Chem.* **1993**, *58*, 5548.

(9) Knoll, W.; Bobek, M. M.; Giester, G.; Brinker, U. H. *Tetrahedron Lett.* **2001**, *42*, 9161.

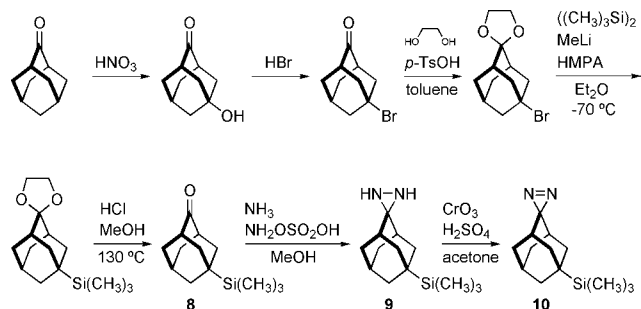
(4) (a) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (b) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638. (c) Adcock, W.; Cotton, J.; Trout, N. A. *J. Org. Chem.* **1994**, *59*, 1867.

(5) (a) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 232. (b) Gung, B. W.; Wolf, M. A.; Mareska, D. A.; Karipides, A. *J. Org. Chem.* **1994**, *59*, 4899.

the corresponding linear diazo compounds, which can be protonated by MeOH to give carbocations.<sup>10</sup> Of course, the interference of a carbocation from a diazo compound can be inhibited if fumaronitrile (FN) is added prior to the photolysis in MeOH, because FN scavenges diazo compounds.<sup>8,10</sup>

Naturally, the need for a  $\sigma$ -electron-donating (ERG) substituent arose. Since computations for the trimethylsilyl group were most promising, 4-azi-1-(trimethylsilyl)adamantane (**10**) was synthesized (Scheme 3). The required 5-(tri-

**Scheme 3.** Synthesis of 4-Azi-1-(trimethylsilyl)adamantane (**10**)



methylsilyl)adamantan-2-one (**8**) was prepared according to the literature with only slight modification.<sup>11</sup> For the standard synthesis of the corresponding diazirine **10**, the standard method was applied.<sup>12</sup> The reaction sequence **8** → **9** → **10** afforded the diazirine in an unoptimized yield of 43%.

To obtain the intramolecular insertion products, diazirine **10** was decomposed in the injector of a preparative GC, and then the product effluent was directly separated on its column (SE-30).<sup>13a</sup> The structural assignments for the two products were simple, because 2,4-didehydro-7-(trimethylsilyl)adamantane (**2c**) contains a plane of symmetry that reduces the number of <sup>13</sup>C signals to eight whereas 2,4-didehydro-1-(trimethylsilyl)adamantane (**3c**) is asymmetric (*as*) and should exhibit eleven <sup>13</sup>C signals.<sup>14</sup> When compared with the –OH group results (Table 1), the 26:74 ratio found for

–Si(CH<sub>3</sub>)<sub>3</sub> compounds **2c:3c** represents a *reversal* of the insertion ratios. To wit, the major product **3c** is formed from intramolecular 1,3-CH insertion by the *proximal* side of the carbene.

For the intermolecular reactions, diazirine **10** was dissolved in MeOH and *c*-C<sub>6</sub>H<sub>12</sub>, respectively, and then photolyzed for 3 h.<sup>15</sup> The insertion products were separated via preparative GC.<sup>13b,c</sup> Structural correlation of the major and minor products was difficult. Yet, the configurations at C4 of **4c** (MeOH-insertion) and **6c** (*c*-C<sub>6</sub>H<sub>12</sub>-insertion) could be assigned with use of 2-D NOESY experiments.<sup>16</sup>

As briefly mentioned earlier<sup>8</sup> and discussed in more detail in another paper,<sup>17</sup> the  $\sigma$ -electron-withdrawing –OH group can diminish electron density from the C1–C9 and C3–C4 bonds.<sup>18</sup> Hyperconjugation with the antibonding  $\sigma^*$ -MO of the C–O bond and the –*I* effect of the hydroxy group may cause this depletion, which leads to an interaction of the empty p-orbital on C2 with the more electron-rich C1–C8 and C3–C10 bonds. We assert that this compensatory orbital interaction physically *distorts* the ground-state carbene, causing it to become sterically biased. Indeed, calculations of parent 2-adamantanylidene,<sup>19,20</sup> as well as single-crystal X-ray structures of 2-adamantanyl cations,<sup>21</sup> support this notion. Moreover, the observed selectivity of **1a** cannot be attributed to its corresponding carbene precursor, since the C1–C2–C3 bridge of the diazirine shows no significant distortion.<sup>22</sup>

Since the C1–C2–C3 carbene bridge in **1a**—in its most stable conformation—is bent *away* from the substituent (*distal*-carbene),<sup>17</sup> the major product should result from intramolecular 1,3-CH insertion by the *distal* side of the carbene. In *distal-1a*, the C<sub>8,10</sub>–H bonds are more accessible than the C<sub>4,9</sub>–H bonds. In other words, the ratios observed for the intramolecular 1,3-CH insertion reactions in **1a** can be explained by applying the principle of least motion,<sup>23</sup> which would therefore favor production of symmetrical (*sym*) **2a**. Indeed, that is what was observed.

The rapid equilibrium between *distal-1a* and *proximal-1a* lies on the side of the former carbene conformer, because the latter one is higher in energy ( $\Delta E = 1.54$  kcal/mol), according to calculations.<sup>17</sup> Since more space is available for incoming reagents, such as MeOH and *c*-C<sub>6</sub>H<sub>12</sub>, on the *proximal* side of *distal-1a*, intermolecular insertions will

(10) Kirmse, W.; Meinert, T. *J. Chem. Soc., J. Chem. Commun.* **1994**, 1065. Kirmse, W.; Meinert, T.; Modarelli, D. A.; Platz, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 8918.

(11) (a) Geluk, H. W. *Synthesis* **1972**, 374. (b) Geluk, H. W.; Schlattmann, J. L. M. A. *Tetrahedron* **1968**, *24*, 5361. (c) Geluk, H. W.; Schlattmann, J. L. M. A. *Tetrahedron* **1968**, *24*, 5369. (d) Xie, M.; le Noble, W. J. *J. Org. Chem.* **1989**, *54*, 3836.

(12) (a) Schmitz, E. In *Chemistry of Diazirines*; Liu, M. T. H., Ed.; CRC: Boca Raton, FL, 1987; Vol. 1, Chapter 3. (b) Isaev, S. D.; Yurchenko, A. G.; Stepanov, F. N.; Kolyada, G. G.; Novikov, S. S.; Karpenko, N. F. *Russ. J. Org. Chem.* **1973**, *9*, 745 (translation of *Zh. Org. Khim.*). (c) Schmitz, E.; Ohme, R. *Chem. Ber.* **1962**, *95*, 795.

(13) Preparative GC column with 30% poly(dimethylsiloxane): (a) pyrolysis:  $T_{\text{oven}} = 140$  °C,  $T_{\text{injector}} = 260$  °C. (b) MeOH insertion products:  $T_{\text{oven}} = 180$  °C,  $T_{\text{injector}} = 220$  °C. (c) *c*-C<sub>6</sub>H<sub>12</sub> insertion products:  $T_{\text{oven}} = 250$  °C,  $T_{\text{injector}} = 220$  °C.

(14) 2,4-Didehydro-7-(trimethylsilyl)adamantane (**2c**):  $\delta_c$ /ppm (62.9 MHz, CDCl<sub>3</sub>) –5.7 (–Si(CH<sub>3</sub>)<sub>3</sub>), 18, 19.5, 23.5, 28.1, 31.2, 32.8, 52.4. 2,4-Didehydro-1-(trimethylsilyl)adamantane (**3c**):  $\delta_c$ /ppm (62.9 MHz, CDCl<sub>3</sub>) –4.2 (–Si(CH<sub>3</sub>)<sub>3</sub>), 21.3, 25.3, 25.6, 26.7, 28.7, 33.1, 33.3, 33.6, 53.6.

(15) Heraeus TQ 718 Z4 700-W medium-pressure Hg-arc lamp doped with FeI<sub>2</sub> ( $\lambda_{\text{max}} = 370$  nm, borosilicate glass filter) at  $T_{\text{sample}} = 12$ – $15$  °C.

(16) The H atoms on C2, C9, and C8 of the products *anti*-4-methoxy-1-(trimethylsilyl)adamantane (**4c**) and *anti*-4-cyclohexyl-1-(trimethylsilyl)adamantane (**6c**) exhibit NOE's with the –Si(CH<sub>3</sub>)<sub>3</sub> group. The geminate H atoms on C2 and C9 have NOE's with the H atoms on C3 and C5 and, most importantly, with the H atom on C4. This proves that **4c** and **6c** are the anti stereoisomers.

(17) Kaneno, D.; Tomoda, S. *Org. Lett.* **2003**, *5*, 2947.

(18) Kasej, M.; Chang, W.-S.; le Noble, W. J. *Chem. Rev.* **1999**, *99*, 1387.

(19) Shustov, G. V.; Liu, M. T. H. *Can. J. Chem.* **1998**, *76*, 851.

(20) (a) Brinker, U. H.; Buchkremer, R.; Kolodziejczyk, M.; Kupfer, R.; Rosenberg, M.; Poliks, M. D.; Orlando, M.; Gross, M. L. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1344. (b) Bally, T.; Matzinger, S.; Truttman, L.; Platz, M. S.; Morgan, S. *Angew. Chem., Int., Ed. Engl.* **1994**, *33*, 1964.

(21) Laube, T. *Acc. Chem. Res.* **1995**, *28*, 399.

(22) Bobek, M. M.; Giester, G.; Kählig, H.; Brinker, U. H. *Tetrahedron Lett.* **2000**, *41*, 5663.

(23) Hine, J. *J. Org. Chem.* **1966**, *31*, 1236.

preferentially take place there, affording the *syn*-disubstituted adamantanes **5a** and **7a**.

The general arguments listed above for the  $\sigma$ -electron-withdrawing  $-\text{OH}$  group are valid in a *reverse* fashion for a  $\sigma$ -electron-donating group, such as  $-\text{Si}(\text{CH}_3)_3$ . With this C5-substituent, the energetically more stable species is *proximal-1c* ( $\Delta E = -0.40$  kcal/mol).<sup>17</sup> This conformation should favor *intramolecular* 1,3-CH insertions by the *proximal* side of the carbene and *intermolecular* insertion reactions from the *distal* side, which is more exposed. Indeed, that is what was also observed.

In conclusion, a 5-substituted 2-adamantanylidene **1** with a  $\sigma$ -electron-withdrawing substituent (EWG), such as  $-\text{OH}$ , is *distal* and preferentially yields *intermolecular* products having *syn* stereochemistry and *intramolecular* products having *syn* stereochemistry. With a  $\sigma$ -electron-rich group (ERG), such as  $-\text{Si}(\text{CH}_3)_3$ , the carbene is *proximal* and preferentially yields *intermolecular* products having *anti* stereochemistry and *intramolecular* products having *as* stereochemistry, i.e., the diastereoselectivities are *reversed*.

Indeed, the “to and fro” bending model advocated herein fully predicts which intra- and intermolecular products will be favored. It also explains why the facial selectivity is mutually exclusive, i.e., the more exposed side is more susceptible to intermolecular reaction and the more sheltered side concomitantly undergoes intramolecular 1,3-CH insertions more readily. Hence, the use of carbenes to explore the diastereoselectivities of adamantane derivatives is advantageous, because unlike with ketones, *exo*-methylene alicyclics, and carbocations, only the carbenes afford *intramolecular* products in addition to intermolecular ones.

**Acknowledgment.** Dedicated to Professor Emanuel Vogel on the occasion of his 75th birthday. This work was supported by the Fonds zur Förderung der wissenschaftlichen Forschung in Österreich (Project P12533-CHE). We also thank Professor S. Tomoda, University of Tokyo, for discussions and for communicating his results to us prior to publication.<sup>17</sup>

OL0350700