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Reactions of Carbenes with Ethers: The Role of Noncovalent Interactions[‡]

Jean-Luc Mieusset[a] and Udo H. Brinker*[a]

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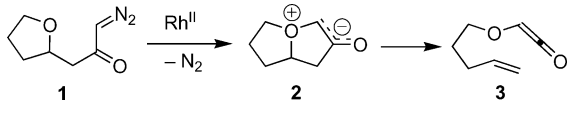
The influence of ethers upon carbenes has been investigated computationally by the B3LYP, MP2, and MPWB1K methods. Ylide formation is only obtained with reactive-electrophilic carbenes like cyclopentadienylidene, whereas more nucleophilic carbenes like cyclopent-2-enylidene associate by interactions of lone pairs of carbon and oxygen atoms with C–H bonds. Between the stabilized-electrophilic dichlorocarbene and the oxygen lone pairs, only weak complexes are formed. Furthermore, the mechanism of the C–H insertion of dichlorocarbene into bicyclic ethers containing a three-membered ring has been explored. The experimental data confirm the computational results. The insertion occurs easily into the α-position of the oxygen atom in secondary ethers but not into the methyl group of methyl ethers. In all cases, insertion into the α-position of a cyclopropane ring is not competitive.

Introduction

Singlet carbenes are species with a divalent carbon atom bearing a filled and an empty orbital. This raises the question whether they may be stabilized by compounds containing a heteroatom (P, O, N, S, etc.) with an electron lone pair.[1] This coordination leads to ylide formation; especially phosphonium ylides[2] and sulfur ylides[3] are widely used in organic synthesis. For ethers, in many cases, a preliminary formation of an oxonium ylide between the carbene and the ether oxygen atom has been assumed.[4,5] This assumption is primarily based on the observation of a formal carbene insertion into the C–O bond or ring expansion of strained cyclic ethers. These reactions are mainly noticed with vinylidenes[5e] or with highly reactive unstabilized carbenes,[5b,5g] i.e., methylene. Moreover, formation of a bicyclic ethereal oxonium ylide **2** followed by a [3+2] cycloreversion can be observed (Scheme 1).[6]



1 **2** **3**

Scheme 1.

The methylene/water interactions[7] have been already thoroughly investigated by Standard et al.[8] and Wiberg et al.[9] using HF, MP2, B3LYP, and QCISD studies in the gas phase and in solution.[10] It has been shown that an ylide-like methyleneoxonium species is formed as an intermediate with a relatively long C–O distance of 173.4 pm (MP2/6-311++G**) and 188.3 pm (QCISD/6-311++G**), respectively. This ylide possesses a relatively weak binding energy (15.3–9.6 kcal/mol at different MP2 and B3LYP levels). Accordingly, QCISD(T)/6-311++G**//QCISD/6-311++G** gives a lower value, 6.4 kcal/mol.

For the stabilized-electrophilic[11] carbene CCl_2, the chlorine atoms cause a decrease of the divalent carbon atom's reactivity and its propensity to interact with other molecules. Therefore, no oxonium ylide structures could be computed for CCl_2. An ab initio study of $CCl_2{\cdot}H_2O$ at the self-consistent field level using the Dunning DZP basis set led only to a complex held together by a hydrogen bond.[12] A weakly bound complex was found at the MP2/DZP level between two water molecules and a dichlorocarbene held together by two hydrogen bonds and one ylide-like interaction, where the lone pair of the oxygen atom is oriented toward the empty p-orbital of the carbene carbon atom.[13] However, even in this case, the C–O distance is still very long (279.8 pm), and the stabilization energy for this trimer adds up to 10.7 kcal/mol for all three interactions.[13] Similarly, only weak interactions were observed between carbene and ether by a laser flash photolysis study[14] of chloro(phenyl)carbene in THF and by the time-resolved IR spectra[15] of chloro(phenyl)carbene in a solution of 0.1 M THF in heptane. For dichlorocarbene, no kinetic evidence of specific solvation by an ethereal solvent was found.[16] In fact, dihalocarbenes are known to react with satisfying selectivity with activated C–H bonds, e.g., with C–H bonds in α-position to a heteroatom (O, N, S, etc.).[17]

[‡] Carbene Rearrangements. 71. Part 70: J.-L. Mieusset, U. H. Brinker, *J. Org. Chem.* **2008**, *73*, 1553.

[a] Chair of Physical Organic and Structural Chemistry, Faculty of Chemistry, University of Vienna,
Währinger Str. 38, 1090 Vienna, Austria
Fax: 43-1-4277-52140
E-mail: udo.brinker@univie.ac.at

Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

Results and Discussion

Our calculations predict ylide formation with dimethyl ether only with reactive-electrophilic[11] carbenes, e.g., singlet cyclopentadienylidene (a carbene with a triplet ground state) and α-oxocarbenes (Figure 1). It is worth noticing that in both cases a resonance structure can be drawn, in which the negative charge is efficiently delocalized. The resulting ylides **4** and **2** are characterized by an almost normal C–O bond length (147.7 and 150.8 pm, respectively) and are about 20–25 kcal/mol more stable (24.4 and 19.9 kcal/mol, respectively) than the corresponding dissociated structures. Experimentally, many examples are given in the literature for α-oxocarbenes forming an oxonium ylide followed by a [1,2] insertion into the C–O bond (Stevens rearrangement) or by a [3,2] sigmatropic rearrangement in case of an allyl ether.[5i,6,18] Inspection of the interactions between dimethyl ether and 2-oxoethylidene reveals that the formation of ylide **2** is strongly affected by the fact that the formation has to occur intramolecularly. As a result, the oxygen atoms in **2** are forced into an (*E*) configuration. In fact, 2-oxoethylidene theoretically can give two different ylides with dimethyl ether: (*E*)- or (*Z*)-2-(dimethyloxonio)-ethenolate **5**. The arguments in favor of the description of ***Z*-5** as an enolate are provided by the NBO analysis for which it is the preferred Lewis structure, by the sp^2 hybridization of C(2), by the short C–C bond length (137.8 pm), and by the high rotation barrier (34 kcal/mol) around the C–C bond in ***Z*-5**. The destabilized ***E*-5** gives similar results but possesses already more characteristics of an α-oxo carbanion.[6] With a formation energy of 32.0 kcal/mol, ***Z*-5** is particularly stable, whereas the (*E*) isomer ***E*-5** is 11 kcal/mol higher in energy than ***Z*-5**. The main reason for this difference resides in the more favorable arrangement of the dipoles in ***Z*-5** resulting in a lowered dipole moment of 5.16 D (9.26 D for ***E*-5**).

Interestingly, the reactive-nucleophilic[11] cyclopent-2-enylidene also forms only weak complexes with dimethyl ether, but no ylides. For example, as revealed by an NBO analysis (see Supporting Information), complex **6** is mainly stabilized by interactions between the C(5)–H bond of the carbene and a lone pair on the oxygen atom and by electron donation from the filled orbital on the carbene center to two C–H bonds located on each methyl group. As a result of these three interactions, formation of **6** is exothermic by only 3.1 kcal/mol (2.4 and 4.9 kcal/mol with MPWB1K and MP2, respectively). Similarly, nucleophilic carbenes like alkylcarbenes and dimethoxycarbene have been found to form only loose complexes with oxirane with a complexation energy within a 0.8–5.5 kcal/mol range at the B3LYP/6-31G* level of theory.[19]

We were especially interested in the reaction between dichlorocarbene and ethers **7**, **8**, and **9** (Table 1).[20] The in silico results are in accordance with the experiments.[20] The lowest barrier is calculated for the insertion into the C–H bond of secondary ethers, the highest for the insertion into the C–H bonds of a methyl group. For these compounds, we have first examined whether DFT calculations are able

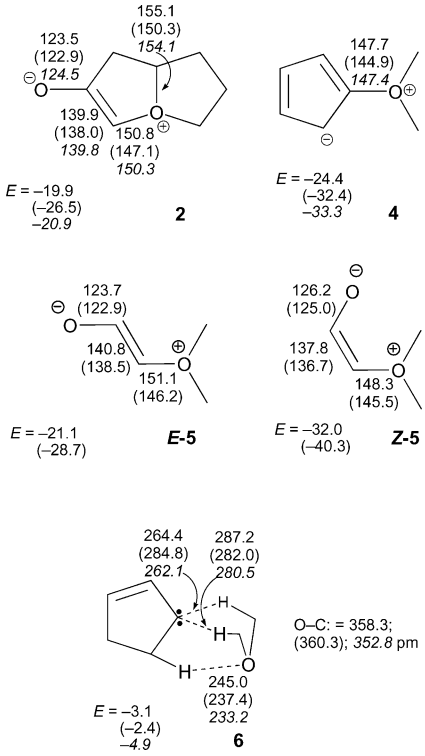
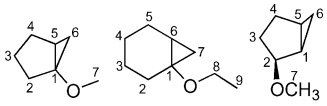


Figure 1. Structure and formation energies of oxonium ylides **2**, **4**, **5**, and of association complex **6**. Values correspond to B3LYP/6-31G(d) calculations, values given in parentheses result from MPWB1K/6-31+G(d,p) calculations, and values in italics correspond to MP2/6-31G(d) computations. Distances are given in pm and energies in kcal/mol.

to predict the outcome of the reaction, i.e., which product will be formed. In a second step, the strength of the interactions between the carbene and the oxygen atom was investigated.

First of all, the computations were performed on the most stable conformer of 1-methoxybicyclo[3.1.0]hexane (**7**) (Figure 2) as given by B3LYP/6-31G(d). At the beginning, the most reactive C–H bonds were determined by means of the calculation of their hydride transfer potential (HTP).[21] This methodology is particularly suitable to predict the regioselectivity of the C–H insertion of stabilized-electrophilic carbenes like dihalocarbenes. Indeed, these insertions proceed with a good selectivity due to a relatively high activation energy combined with a comparatively late transition state.[21] It has also been shown that these reactions take place efficiently only if the developing positive charge can be stabilized.[21,22] However, the reaction is concerted, and no fully developed carbocation is generated. Therefore, an analysis of the stability of the corresponding cation is misleading; instead, a better agreement is obtained by calculation of the HTP values. Using this methodology, it is found that the most likely insertion should take place into the methoxy group. H_C, the hydrogen atom *anti* to the C(1)–O bond is not activated, as reflected by its low HTP (46.1 kcal/mol). The reaction should occur either with H_A or H_B with the carbene placed in a synperiplanar arrange-

Table 1. Insertion reactions of dichlorocarbene into C–H bonds of ethers.[a]



7 **8** **9**

	TS	Bond	HTP[b]	E[c,d]	$E_{complex}$[d,e]	Yield[f]
7	**7A**	C(4)–H_{exo}	76.8 (67.7)	12.1 (11.3)	14.5 (14.6)	0
	7B	C(7)–H_A	68.3 (57.8)	10.7 (11.1)	13.1 (14.4)	
	7C	C(7)–H_B	72.0 (61.3)	10.5 (11.5)	12.9 (14.8)	
	7D	C(7)–H_C	46.1 (34.8)	–	–	
8	**8A**	C(8)–H_A	84.1 (74.1)	8.0 (9.4)	9.8 (13.2)	47
	8B	C(8)–H_b	88.5 (78.9)	7.8 (9.4)	9.6 (13.0)	
9	**9A**	C(2)–H	95.0 (86.1)	5.1 (6.1)	8.2 (9.7)	93
	9B[g]	C(2)–H	–	5.3 (6.8)	8.4 (10.4)	
	9C	C(2)–H	–	6.1 (8.0)	9.2 (11.6)	

[a] For the description of hydrogen atoms, see Figure 2. Activation energies in kcal/mol as given by B3LYP/6-31G(d); values in parentheses represent MPWB1K/6-31+G(d,p) computations. [b] The hydride transfer potential (HTP) is obtained from the isodesmic equation $CH_4 + R^+ \rightarrow CH_3^+ + RH$ by a single-point energy calculation with the cation obtained by removal of a hydride ion from the optimized structure of the parent hydrocarbon. [c] Energies relative to the reactants. [d] ZPEs calculated at the B3LYP/6-31G(d) level of theory. [e] Energies relative to the complex. [f] Taken from ref.[20] [g] See text for geometry.

ment to the sterically least hindered C–H bond, i.e., C(7)–H_C. For these insertions, a barrier of 10.7 or 10.5 kcal/mol, respectively (**7B** and **7C**), has to be overcome. In comparison to parent bicyclo[3.1.0]hexane (**10**, Scheme 2), in **7**, the C–H bond in α-position to the cyclopropane ring, C(4)–H_{exo}, is slightly deactivated because of the inductive effect of the methoxy group. Indeed, the calculated barrier (**7A**: 12.1 kcal/mol) for this insertion is higher in energy than in **10** (11.4 kcal/mol).[21] However, this value is lower than the computed barrier for the formation of *endo*-2-dichloromethylbicyclo[3.1.0]hexane (**11**) (12.4 kcal/mol) or for the insertion into spiro[2.5]octane (**12**) (12.4 kcal/mol),[21] two reactions that were observed experimentally, albeit in low yield.[20]

In fact, no insertion into methyl ether **7** was found. These results suggest that the presence of the ether group slows down the insertion and permits other carbene reactions to dominate (e.g., dimerization). Indeed, many examples for the influence of ethers on the reactivity of carbenes are known.[10,23] We located several complexes between the ether oxygen atom and dichlorocarbene. **7E** is the complex lying in the deepest minimum that we found (Figure 2, see also Supporting Information). It is still very weak (ΔE_0 = –2.4, ΔG_{298} = +7.1 kcal/mol) and does not represent a bound minimum at ordinary temperatures. In usual cases, such weak interactions are mechanistically not relevant.[24] However, a difference in the calculated energy barrier of less than 2 kcal/mol is sufficient to distinguish between an activated bond into which the insertion of dichlorocarbene generated under PTC conditions[21] occurs in good yields and an unreactive C–H bond. From a synthetic point of view, these weak interactions are probably decisive.

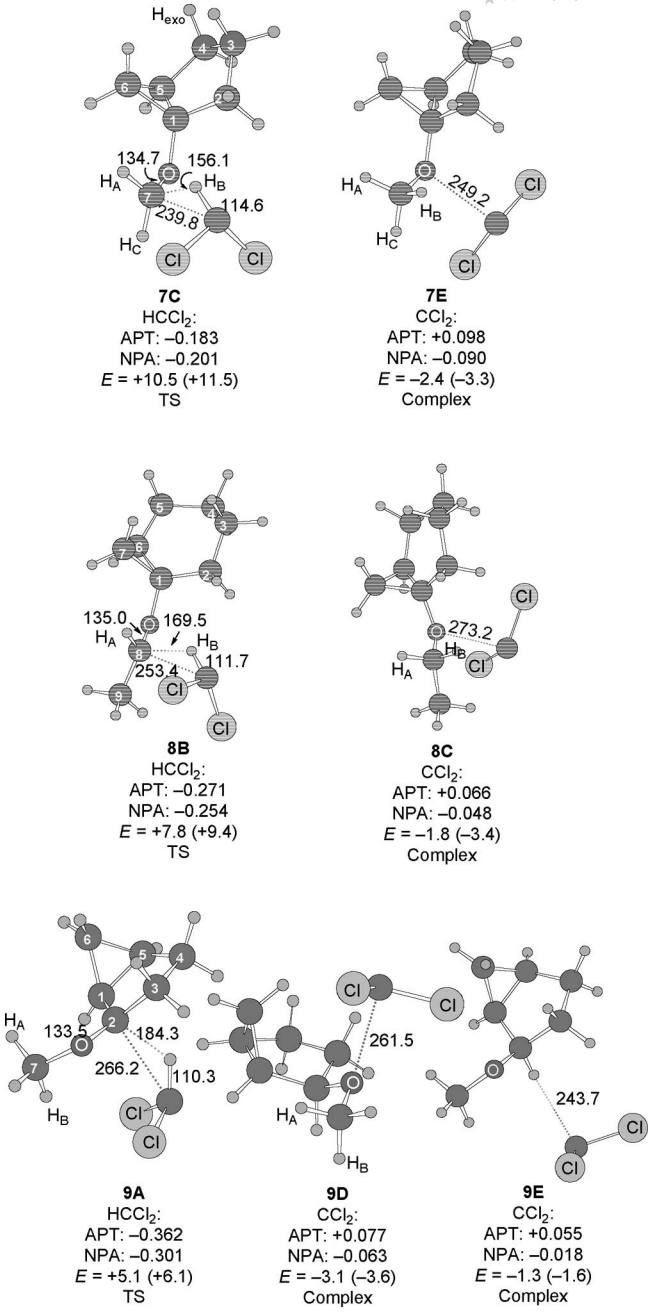
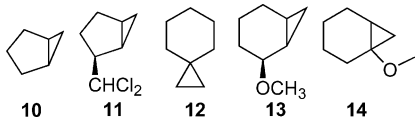


Figure 2. Geometries of the most stable complexes of **7**, **8**, and **9** with dichlorocarbene and of the lowest transition states for the insertion into the α-C–H bonds. All distances are in pm. Energies are in kcal/mol and correspond to B3LYP/6-31G(d) calculations, values in parentheses result from MPWB1K/6-31+G(d,p) calculations.



10 **11** **12** **13** **14**

Scheme 2.

Next, the most stable conformer of 1-ethoxybicyclo[4.1.0]heptane (**8**) was subjected to calculations. In order to minimize steric repulsion with the bicyclic skeleton, the

attack of CCl_2 occurs preferably in a specific orientation in which the chlorine atoms are close to the methyl group. The complex formed with CCl_2 is particularly weak (**8C**: –1.8 kcal/mol). The modest height of the barrier (**8B**: 7.8 kcal/mol) is compatible with the moderate yield obtained experimentally (47%).[20] With the MPWB1K functional, a slightly higher barrier (9.4 kcal/mol) is calculated, and complex **8C** is predicted to be slightly more stable (–3.4 kcal/mol). This trend can be found again at almost all stationary points which were located in this work.

In contrast, high yields (93%) are obtained by the reaction of *endo*-2-methoxybicyclo[3.1.0]hexane (**9**) with dichlorocarbene leading to C(2)–H insertion. Comparable results were observed from the insertion reactions into *endo*-2-methoxybicyclo[4.1.0]heptane (**13**) and 1-methoxybicyclo[4.1.0]heptane (**14**).[20] The most stable conformer of the secondary ether **9** is the one with the C–O bond antiperiplanar to C(2)–C(3). Dichlorocarbene approaches the C(2)–H bond in a synperiplanar arrangement to the C–O bond (**9A**: Figure 2). Since the corresponding carbocation being formed is tertiary and efficiently stabilized by the oxygen atom, the HTP of **9** is especially high (95.1 kcal/mol) and the barrier for the C–H insertion particularly low (**9A**: 5.1 kcal/mol in comparison to the reactants, 8.2 kcal/mol starting from the complex). Interestingly, the insertion into **9** is one of the rare examples in which the π-approach is favored over the σ-approach,[25] probably because the transition state is already highly polar and dipole–dipole interactions start to play a significant role. In fact, at the transition state, the chlorine atoms are in an eclipsed conformation upon C(3) and O(1) as in **9B**, and in a nearly eclipsed conformation upon C(1) and O(1) for **9A**, respectively. All other transition states described in this work result from a σ-approach.

An analysis of the charge partitioning for the transition states **7C**, **8B**, and **9A** reveals that the insertion into secondary ethers is significantly more polar than the reaction with methyl ether **7** (Figure 2). This difference can be directly related to the better ability of **9** to delocalize the positive charge build-up. At the transition states, the results from the Natural Population Analysis (NPA) and the Atomic Polar Tensor (APT)[26] model are in good agreement. However, for the complexes, the APT methodology predicts a positive charge on the carbene fragment, whereas NPA calculates a negative charge. The NPA result is in agreement with the interactions between occupied and virtual natural bond orbitals. Indeed, the stabilization results from electron donation from the oxygen lone pair into the LP* of the carbene. On the other hand, the APT result takes into account that the carbene starts to coordinate with a strongly electronegative heteroatom. Overall, whereas the APT model has proven to be very reliable for the description of molecules as long as electron-correlation effects are reproduced,[27] it has been shown to perform poorly for the estimation of charge transfer.[28]

The insertion reactions of dihalocarbene into benzyl methyl ether,[29a] ethyl methyl ether,[29b] dimethyl ether,[29c] and methyl isopropyl ether[29d] were already studied at the MP2/6-31G(d) level of theory. The obtained results confirm our findings with a very low barrier found for the insertion of dichlorocarbene into the isopropyl group (4.9 kcal/mol), low barriers for the insertion into the benzyl group and the α-C–H bond of the ethyl group (9.0 and 7.8 kcal/mol, respectively). However, we disagree on the very high barriers computed previously for the insertion into methyl groups (28.7–31.6 kcal/mol).[29a–29d] For the C–H insertion into dimethyl ether, we calculated a barrier of only 11.2 kcal/mol at the B3LYP/6-31G(d) level of theory and 10.5 kcal/mol at the MP2/6-31G(d) level.

Conclusions

The B3LYP/6-31G(d) level of theory is suitable for the prediction of the reactivity of bicyclic ethers toward the insertion of dichlorocarbene into their C–H bonds. Experimentally, the insertion is very efficient into secondary ethers. In contrast, insertion into methoxy C–H bonds still has never been observed, even though the calculated barrier for this reaction is not excessively high (10.5–11.2 kcal/mol), because the partial positive charge that has to be built up during the insertion cannot be stabilized efficiently by this primary substituent. Moreover, partly because of the inductive effect of the electronegative oxygen atom, no insertion into the C(2)–H and C(4)–H bonds of methyl ether **7** is obtained, although these bonds have proven to be efficiently activated by the cyclopropane ring.[21] Our results speak for synthetically significant interactions between dichlorocarbene and the ether group, although only weak stabilizations (1.3–3.1 kcal/mol) are computed for the complexes of **7**–**9** with dichlorocarbene, a stabilized-electrophilic[11] carbene. Since these complexes are higher in energy than the reactants on the free-energy surface at the standard state, they cannot be considered as a first step in the insertion reaction. Strong interactions between ethers and carbenes leading to ylide formation were only found for reactive-electrophilic[11] carbenes like cyclopentadienylidene or acylcarbenes. In the case of predominantly nucleophilic carbenes (e.g., cyclopent-2-enylidene), the weak association obtained between carbene and ether takes place mainly between C–H bonds and the lone pairs of the divalent carbon atom and the oxygen atom.

Computational Methods

The Gaussian 03 program[30] was used for density functional theory calculations, employing Becke's[31] three-parameter hybrid method, and the exchange functional of Lee, Yang, and Parr (B3LYP).[32] Geometries were optimized at the B3LYP/6-31G(d) level of theory. The stationary points were characterized by vibrational analysis. All reported energies include zero-point corrections. The results obtained were confirmed by geometry optimizations with two other methods. The geometry optimization was repeated using ab initio calculations at the MP2(FC)/6-31G(d) level of theory and the newly developed hybrid meta density functional theory model for kinetic MPWB1K[33] in association with the 6-31+G(d,p) basis set. MPWB1K is based on the modified Perdew and Wang 1991 ex-

change functional[34] (mPW) and Becke's 1995 meta correlation functional[35] (B95). MPWB1K has been shown to be one of the most accurate recent DFT methods, significantly better than B3LYP.[36] It is recommended for general-purpose applications in thermochemistry and kinetics.[37,38] It is also recommended for noncovalent interactions involving nonmetals and performs better without counterpoise correction for the basis set superposition error (BSSE).[37,39] The zero point vibrational energies (ZPE) were scaled by a factor of 0.9806 for B3LYP/6-31G(d),[40] 0.967 for MP2(FC)/6-31G(d),[40] and 0.9537 for MPWB1K/6-31+G(d,p).[33] The hydride transfer potential (HTP) was obtained from the isodesmic equation $CH_4 + R^+ \rightarrow CH_3^+ + RH$ by a single-point energy calculation for the cation obtained by removal of a hydride ion from the optimized structure of the parent hydrocarbon. Unless otherwise stated, all values in the text refer to B3LYP calculations. Quantification of donor/acceptor interactions has been made by second-order perturbation analysis as incorporated in the Natural Bond Orbital (NBO) method.[41]

Supporting Information (see footnote on the first page of this article): Cartesian coordinates and energies for all relevant stationary points.

Acknowledgments

Calculations were performed on the Schrödinger III cluster at the University of Vienna.

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