

Nitrogen Heterocyclic Carbene (NHC) as a Versatile Oxygen Atom Acceptor that Abstracts Oxygen Atom from Aldehydes and CO₂ A Computational Research

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Abstract: The formal oxygen atom transfer (OAT) reaction with nitrogen heterocyclic carbenes (NHCs) as oxygen atom acceptor was designed and studied by density functional theory (DFT) calculations. Several properly designed NHCs were predicted to exhibit high reactivity towards the formal OAT reaction with aldehydes, in the presence of an intramolecular phosphine motif, which provides a new method to generate phosphorus ylide from aldehydes. Furthermore, the OAT reaction of NHCs with carbon dioxide (CO₂) was predicted to occur at room temperature to release carbon monoxide, aided by an intramolecular nucleophile. These results may give insights about new methodologies for ylide preparation and CO₂ reduction.

Introduction

The ("real" or formal) oxygen atom transfer (OAT) from a carbonyl group is connected to several topics of highest interest in current chemistry. The OAT from conventional carbonyl compounds, i.e. aldehydes or ketones, gives formally a carbene, or, upon the capture by a phosphine, a ylide, which is one of the most important reagents in organic synthesis^{1, 2}. Furthermore, once carbon dioxide (CO₂) is considered as a carbonyl compound, a readily available OAT process enables a pathway to transform CO₂ into CO, which provides a methodology that does not rely on transition metal-containing catalysts or nanocrystals³⁻⁶, or highly reactive main group species⁷⁻¹⁰. During the past decades, nitrogen heterocyclic carbenes (NHCs) have been developed as an adorable reagent due to their intriguing electronic structure, and widely used in organic catalysis^{11, 12}. However, the reactivity of NHCs as oxygen atom acceptor that abstracts oxygen atoms from carbonyl group to afford another carbene or carbene-equivalent, is relatively unexplored.

When preparing this paper, the author is delighted to see that Ayan Datta and Sabrata Kundu discovered a novel OAT reaction of NHC and nitrosoarene, affording formally a nitrene¹³. In this work, the author presents a computational research on the methodology in which NHCs undergo a formal OAT with aldehydes and CO₂ in the presence of nucleophiles, to give ylide and CO respectively. The results may be indicative for further experimental research.

Results and Discussions

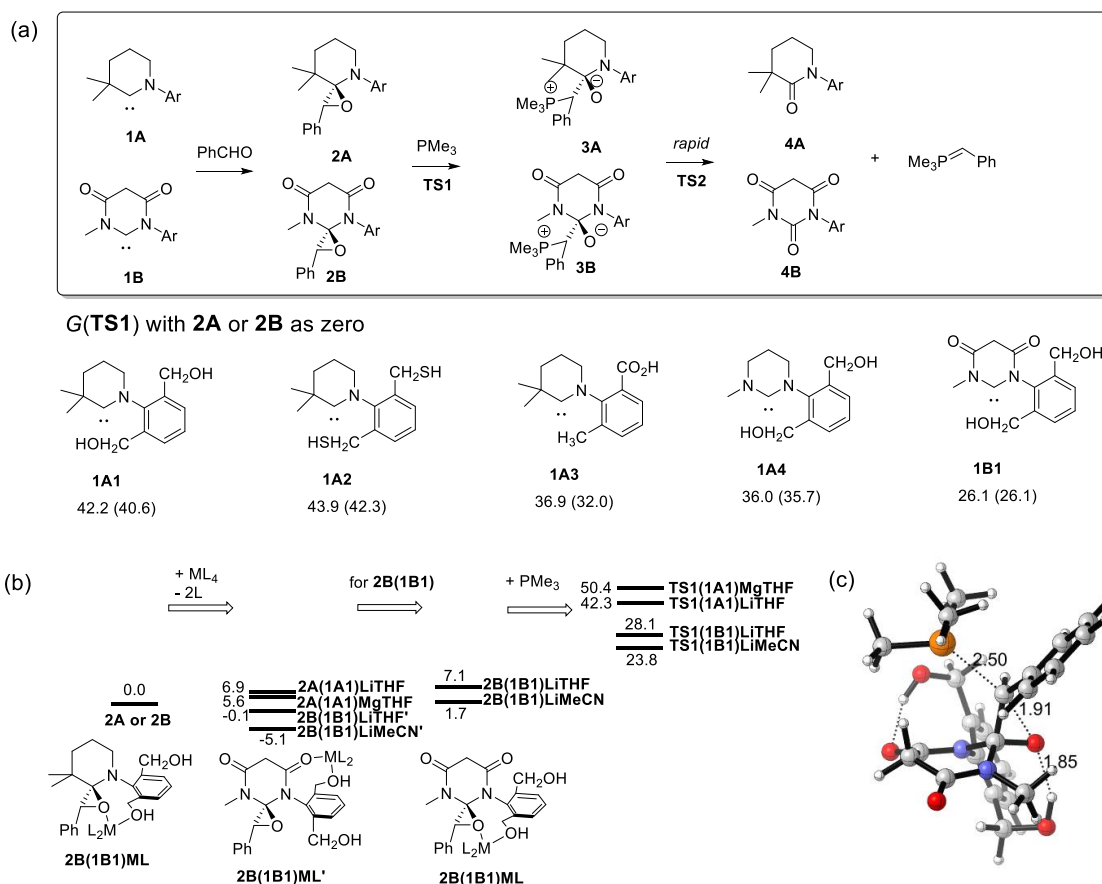


Figure 1. (a) The mechanism of the expected formal OAT from benzaldehyde, and the NHCs examined along with the corresponding Gibbs free energy of TS1 with **2A** or **2B** as zero point. Values inside and outside brackets are under THF and MeCN solvation, respectively. (b) Free energetics of some key intermediates and TS1 for **1B1** in the presence of solvated metal ions. Energies are in kcal/mol. (c) The geometry of TS1(**1B1**).

This work commenced from the computational design of a formal OAT from benzaldehyde, which is previously known to reversibly form an isolable epoxy adduct **2B** (Figure 1) with NHCs¹⁴. Since a bare phenylcarbene (singlet) as product is thermodynamically inaccessible (+22.6 kcal/mol in THF for **1A1**), this study makes use of an external phosphine to generate a ylide, one of the most useful compounds in organic chemistry. NHC-benzaldehyde adduct undergoes a rate-determining nucleophilic attack by incoming phosphine, followed by a rapid elimination to give the ylide product. The full free energy surface (FES) of **1B1** is shown in Figure S1. In the design of the four NHCs (**1A1** to **1A4**, **1B1**), weakly acidic protons were introduced by hydroxyl, carboxyl or thiol groups to stabilize the developing negative charge on the oxygen atom in TS1. All the four NHCs exhibit high barrier, which is not reduced by coordination of Lewis acidic Li⁺ or Mg²⁺. The superior reactivity of **1B** over **1A** could be explained by its lower $\sigma^*(\text{C}-\text{O})$ antibonding orbital energy (Figure S2). As a result, an intramolecular strategy was employed to reduce the overall barrier.

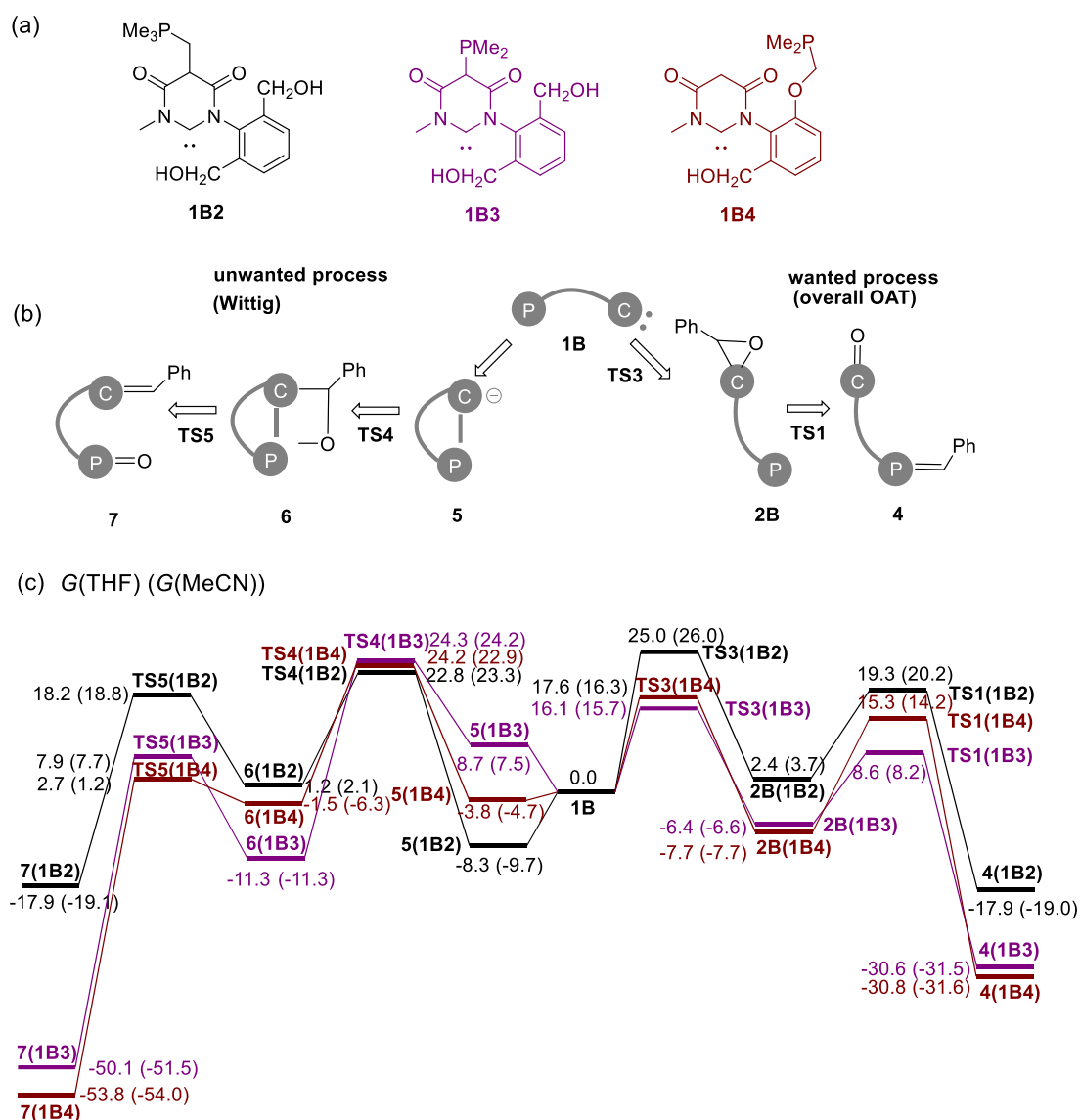
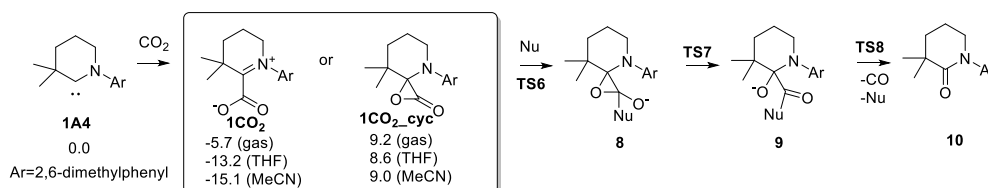


Figure 2. (a) NHCs with intramolecular phosphine studied in this section. (b) Conceptual scheme of the wanted process and potential competing side-reactions. (c) FES (in kcal/mol) of the formal OAT reaction with benzaldehyde. Numbers inside and outside brackets show energies with THF and acetonitrile as solvent, respectively.

In addition to the high barrier, a competing pathway in which the phosphine binds NHCs to give an unwanted ylide and undergoes Wittig reaction with the aldehyde, should be avoided. Three NHCs with intramolecular phosphine, **1B2** to **1B4**, were designed and both the pathways were examined. For **1B**, the NHC-phosphine intramolecular complex **5** is more stable than the bare NHC, and the following Wittig process outcompeted the wanted formal OAT. On the contrary, due to the high strain caused by the rigid bicyclo[2.2.1] skeleton, the addition of **5(1B3)** to benzaldehyde is inaccessible, and the wanted formal OAT is expected to occur smoothly with a barrier of 16.1 kcal/mol in THF, determined by the NHC-benzaldehyde adduct formation step. Once **2B(1B3)** is formed, it is expected to give the expected ylide product **4** with a low barrier of 15.0 kcal/mol. Similarly, the formal OAT also outcompetes the Wittig side-reaction for **1B4**, although with a higher

barrier of 23.0 kcal/mol with the intramolecular ring-opening as the rate-determining step. Overall, in this section two candidates for the generation of ylide from aldehydes were suggested by DFT calculations.



Entry	Nucleophile	G(gas)	G(THF)	G(MeCN)
1	Pyridine	43.4	49.7	51.7
2	DMAP	35.9	41.5	43.3
3	2-hydroxypyridine	14.5	24.5	27.5
4	2-thiopyridine	26.8	36.4	39.1
5	Imidazolate	-4.3	25.9	30.2
6	Trimethylimidazolate (Im ⁻)	7.2	34.3	38.9
7	2,6-dimethylphenolate (OAr ⁻)	6.2	27.0	30.2
8	2,6-dimethylphenthioanion (SAr ⁻)	12.6	32.9	35.6
9	2-hydroxypyridin-4-olate	-4.3	19.6	24.5
10	HF2 ⁻	3.9	38.7	43.3
11	KOAr(THF) ₃	4.0	17.7	-
12	KIm(THF) ₃	7.4	21.4	-

Table 1. Gibbs free energetics of **9** with various nucleophiles (kcal/mol), using **1A4** as model molecule. **1CO2** is taken as the zero point for values in the table.

After finding out candidates for ylide generation from an aldehyde, the author turned to the transformation of CO₂, a small molecule that can be considered as a special carbonyl group compound. NHCs are known to form two types of CO₂-adducts, namely the zwitterion **1CO2** and the cyclic **1CO2_cyc**, according to both theoretical and crystallographic evidence^{15, 16}. Upon addition of an extra nucleophile, **1CO2_cyc** is expected to give a quaternary alkoxide anion and eliminate carbon monoxide while regenerating the nucleophile. With **1A4** as the model molecule, the nucleophile-effect was examined by considering the Gibbs free energy of the key intermediate **9**, which provides a lower-limit of the overall barrier¹⁷. Although the formation of **9** is favored in gas phase, it comes rather endothermic even in solvent with moderate dipole (THF). Among the results, anionic N- or O- nucleophiles behave optimally. Although stabilization to the negatively charged oxygen atom in **9** is provided by hydrogen bonding (entry 3, 4) or potassium cation (entry 11, 12), the magnitude is inadequate to give a molecule that works at room temperature.

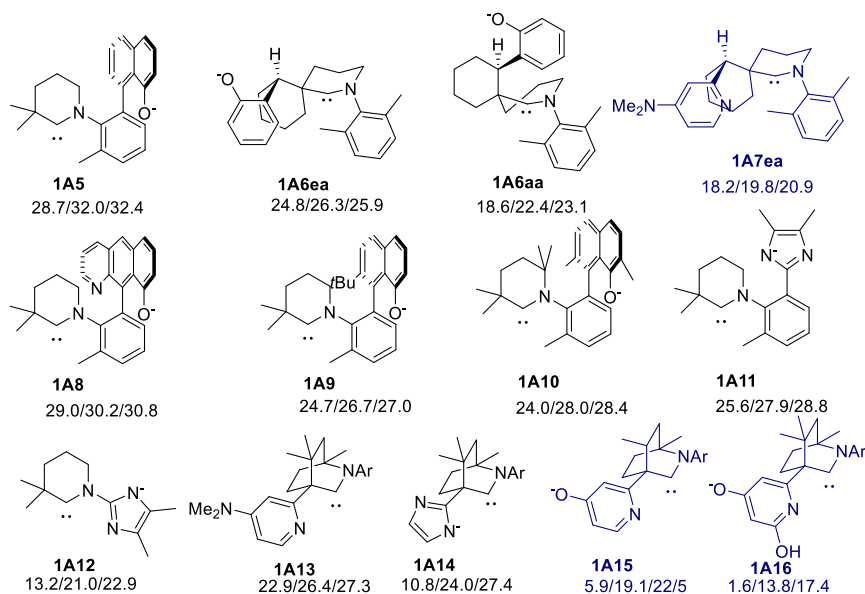


Figure 3. Structures and the relative Gibbs free energies (kcal/mol, with **1CO₂** as zero point) of intermediate **8** for the NHCs studied. The data follows the following format: gas phase/in THF/in acetonitrile.

The intramolecular strategy was again employed to reduce the overall barrier. NHCs with intramolecular nucleophiles (**1A5** to **1A16**) were designed and the relative Gibbs free energies of the tetrahedron intermediate **8** were studied. Unfortunately, **8s** are still high-energetics even in the presence of intramolecular nucleophiles, which is in part due to the strong repulsion between the negatively charged nucleophile and the carboxyl oxygen in **1CO₂** (see Supporting Information for details). Attempts to distribute negative charges on the nucleophile, or to fix the conformation by bulky groups, led to the design of **1A8** and **1A9**, which are still inefficient. Notably, solvation strongly increases the energy of **8**, by stabilizing the zwitterionic **1CO₂**. According to the results, **1A7ea**, **1A15** and **1A16** were selected for further exploration.

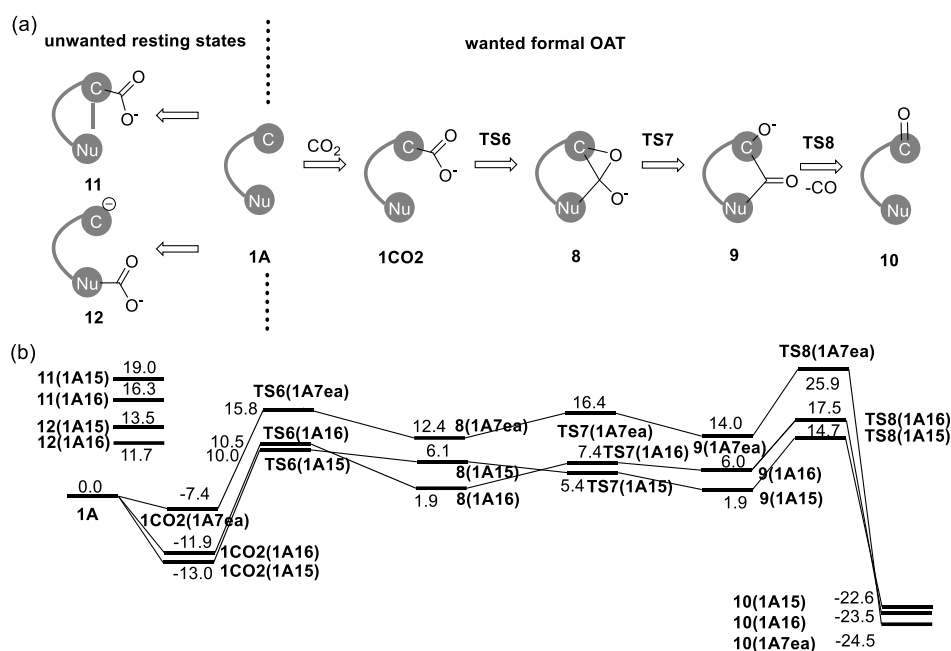


Figure 4. Conceptual representation of the formal OAT with CO₂ and possible resting states. (b) The FES (kcal/mol) in THF for the three candidates.

According to the full FES (Figure 4), the overall barrier is determined by the C–C bond cleavage transition state **TS8** and **1CO₂**. Among the three candidates, **1A15** exhibits the lowest barrier of 27.7 kcal/mol in THF. Although an extremely sluggish reaction at room temperature is indicated, it is noted that the overall barrier decreases dramatically to 14.3 kcal/mol in gas (Table S1). The dependency of overall barrier on solvent was examined and it is shown that the reaction has a room-temperature accessible overall barrier of 21.8 kcal/mol in toluene (Figure S3), indicating that solvents with low dipole are required for efficient CO₂ transformation, and **1A15** is the optimal candidate for this reaction.

In a summary, the reactivity of NHCs towards stepwise formal OAT with aldehydes and CO₂ was studied computationally. By properly design of intramolecular bifunctional NHCs (**1B3** or **1B4**), the OAT from benzaldehyde to NHCs was shown to exhibit a low barrier of 16.1 kcal/mol in THF, and outcompetes the potential unwanted process. Then the reaction is extended to CO₂ as substrate: in the presence of an intramolecular nucleophile (**1A15**), CO₂ is expected to transfer its oxygen to NHC, affording CO as product. These results shed light on new methods to generate ylides from aldehydes, or reduce CO₂ to CO, which may give insights for experimentalists to realize such reactions actually in a flask.

Methods

The Gaussian 16 program¹⁸ was employed for all DFT calculations, with Gaussian 09 default integral grids. Geometry optimization and frequency calculation was carried out at M06-2X/def2-SVP level¹⁹⁻²¹ in gas phase, and the transition states were verified by the intrinsic reaction coordinate (IRC). Then single point energy calculations were performed with an enlarged basis set ma-def2-TZVP at gas phase²². The solvation effect was introduced by the SMD model²³, and the final Gibbs free energy with solvation is derived as: G(solvent)=thermal correction (M06-2X/def2-

SVP) + single point (M06-2X/ma-def2-TZVP) + single point (M05-2X/6-31G(d)/SMD(solvent))^{20, 23-26} – single point (M05-2X/6-31G(d)/gas) + 1.89 kcal/mol, as recommended by Coote et al²⁸. The analysis of CM5 atomic charge²⁹ was performed with Multiwfn³⁰. The orbitals were visualized by VMD³¹.

Acknowledgement

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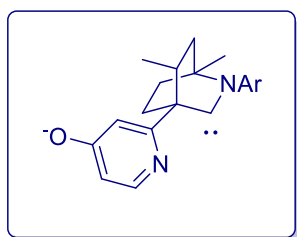
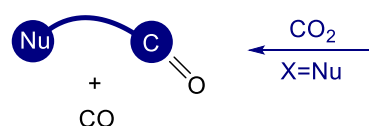
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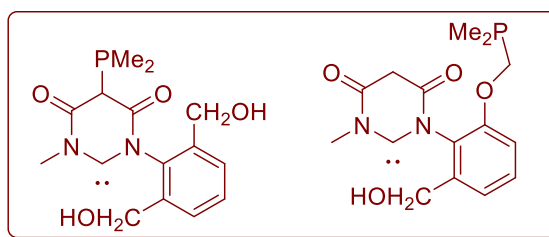
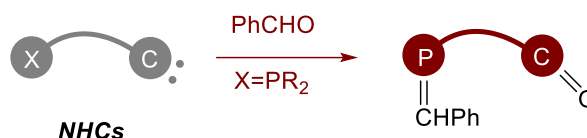
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Generation of CO from CO₂



Generation of ylide from aldehyde



TOC