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# Computational investigations of NHC-backbone configurations for applications in organocatalytic umpolung reactions

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**ABSTRACT:** Density functional theory (DFT) and multiconfigurational self-consistent field theory (MCSCF) methods are employed to investigate variation of the electronic properties of various N-heterocyclic carbenes. Alterations to the backbone by increased or decreased conjugation, heteroatom substitution in the NHC ring, and electron-donating or -withdrawing backbone substituents are modeled. The MCSCF calculations show extensive delocalization of both the highest occupied and lowest unoccupied molecular orbitals for NHCs with polymerizable backbone substituents. The free energies of the intermediates and transition structures for benzoin condensation are also shown to be sensitive to substitution of the NHC backbone. Taken together, these results imply great sensitivity of the reactivity of poly(NHC) catalysts to backbone modification at this moiety. Implications with respect to enhancement of poly(NHC)s employed in umpolung catalysis are discussed.

## BACKGROUND

N-heterocyclic carbenes (NHCs) have emerged as an important class of compounds that mediate a variety of molecular transformations in catalysis such as benzoin condensation, trans-esterification, cyanosilylation, olefin metathesis, Stetter reactions, and so forth.[1-3] There exists a large variety of NHCs, thus synthesizing new variants is relatively facile. The substituents bound to the NHC contribute to both kinetic and electronic stability. The electron-withdrawing and π-electron-donating nitrogen atoms adjacent to the carbene C stabilize these structures both inductively by lowering the energy of the occupied s-orbital and mesomerically by donating electron density into the empty p-orbital. The C-based lone pair, situated in the plane of the heterocyclic ring of NHCs, renders these compounds nucleophilic. The NHC electronics are primarily governed by the class of heterocycle, with the substitution pattern of the ring backbone playing an important – if not always completely understood – role in their catalyses. Different backbone functionalities and classes of heterocycle introduced to the NHC motif allow for more independent variation of electronic parameters.[4] These advantages, when coupled with their unique electronic and steric properties, make NHCs an exceptional class of potential organocatalysts. As a result, in the past few decades, NHCs evolved from mere laboratory curiosities to molecules with growing practical application.

First studied by Cowley and Bielawski *et al.* in 2009, a class of polymeric NHCs were investigated as electro-conducting polymers, where the NHCs are integral to the main chain.[5, 6] Powell and coworkers investigated the electronic tunability of these polymeric NHCs (poly(NHC)s) and later went on to publish research covering the application of a different class of poly(NHCs) as recyclable, self-supported organocatalysts (**Figure 1**). Their experimental findings elucidated advantages in catalytic activity, high product yield and catalyst recyclability in the benzoin condensation reaction (67% yield of benzoin, 92% yield of recovered poly(NHC)).[7] The corresponding catalysts demonstrated improved catalytic activity upon incorporation into a polymeric framework. As such, their research could thus enable the use of other NHC-based catalysts that are conveniently regenerated and reused.
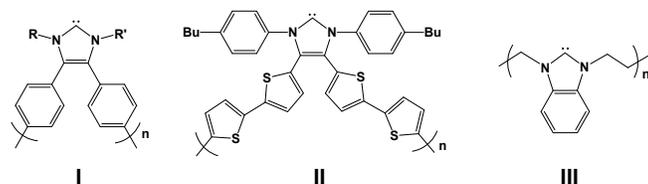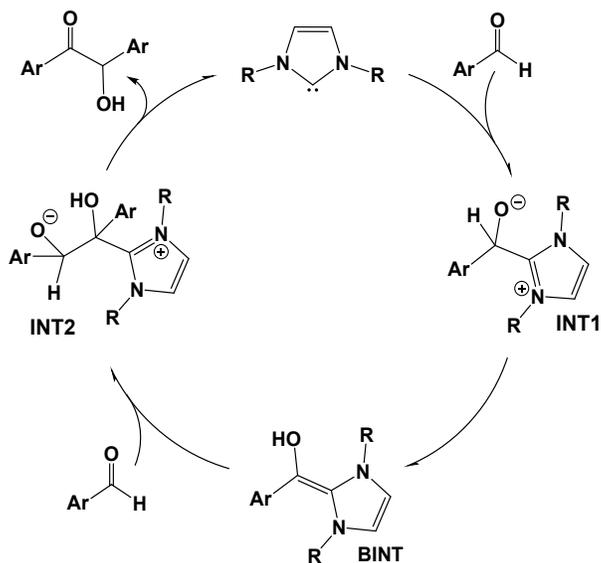
both monomeric and polymeric NHC derivatives hold promise as self-

supported catalysts. The latter possess advantages by placing the NHC orthogonal to the main chain, offering an efficient catalyst without the use of additional catalyst supports and linkers (**Figure 1**). As a result, the catalysts should be inexpensive, easily synthesized, and may be expected to persist even under a broad range of reaction conditions. Thus, such poly(NHC) catalysts are of interest for a range of "green catalysis" applications, particularly with greater understanding of the response of their electronic properties to backbone modification. To this end, the present modeling study was initiated.

Debate over NHC-catalyzed benzoin condensation has afforded different mechanistic models for the varying molecular transformations such as asymmetric benzoin condensations.[1, 2, 18, 19] The mechanism of the conversion from the zwitterionic state to the Breslow intermediate is not completely agreed upon for NHC-catalyzed benzoin reactions.[19, 20] The catalytic cycle in **Scheme 1** describing NHC-promoted benzoin condensation is based on previous investigations concerning the cyanide-catalyzed cycle proposed by Breslow in the 1950s. Breslow postulated that the active nucleophilic species was an enaminol-type intermediate (**BINT**, **Scheme 1**). Previous calculations assumed a direct 1,2-proton shift despite a high energy barrier in this process from the first zwitterionic intermediate (**INT1**) to the Breslow intermediate (**BINT**). The solvent has been proposed to play a significant role while others have proposed homolytic cleavage of a C–H bond resulting in a paramagnetic intermediate.[1, 19, 20] Recently, Hsieh and coworkers have proposed a radical-associated pathway to assist the tautomerization promoting the catalytic reaction. Thus, uncertainty remains in the mechanistic specifics of this important reaction upon modification of the carbene backbone, further motivating the current study.



**Figure 1**. Representative classes of (poly)NHCs.[5-10]

The benzoin condensation reaction has been widely studied for several decades, notably because of its importance in carbon-carbon bond formation through reverse polarity.[11-16] The process of attaching a catalyst to a solid support has often resulted in low yields, which thus creates synthetic challenges.[7, 17] In contrast to these difficulties,

**Scheme 1.** NHC-catalyzed benzoin condensation based on proposals by Breslow.[12, 13, 16]

investigations were compared with previously published work[5-7, 9, 15, 34-37] of the thoroughly investigated triazolylidene (**A**) and benzimidazolylidene (**B**) as well implementing more novel carbenes that possess either electron-withdrawing groups attached *para* on a ring to the carbene or electron-donating bithiophene groups, like **C** and **E**, respectively. Carbene **A** was selected based on previous research that indicated that increasing the nitrogen count in the heterocycle often leads to greater electron density on the nitrogens rather than being situated on the $p_z$ orbital of the carbene carbon. Thus, the negative charge in the Breslow intermediate (**BINT**) may be better stabilized by such a modification. The study of NHC catalyst models **B**, **C**, and **E** is given added import due to these being typical of polymerizable groups leading to poly(NHC) catalysts, see **Figure 1**. Additionally, a smaller and simpler NHC, the *N,N'*-dimethylimidazolylidene (**D**) was also investigated to quantify steric effects introduced by modifying the backbone.

It has been proposed[18, 24, 38] that a more electrophilic carbene carbon stabilizes the Breslow intermediate while with increased nucleophilicity, the carbene carbon atom becomes less inductive and less electron-withdrawing therefore increasing the tendency for addition of the first equivalent of the aldehyde. As such, important changes in the electronic structures of these umpolung catalysts require accurate descriptions of both occupied and unoccupied virtual
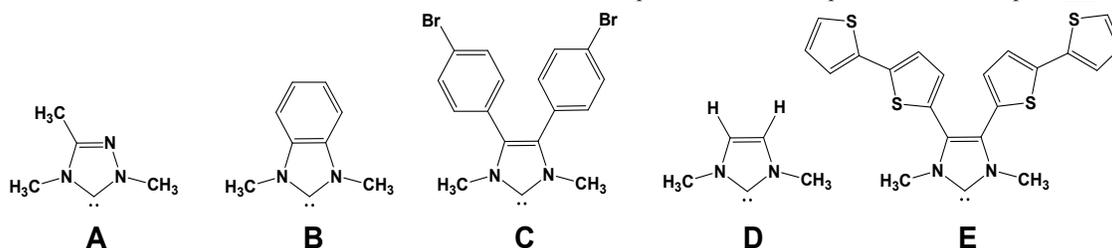


**Figure 2.** NHC variants investigated in the current study: 2,4,5-trimyethyl-1,2,4-triazolylidene (**A**), *N,N'*-dimethylbenzimidazolylidene (**B**), 4,5-bis(p-bromophenyl)-1,3-dimethylimidazolylidene (**C**), *N,N'*-dimethylimidazolyl-idene (**D**), 4,5-di(2,2'-bithiophene)-1,3-dimethylimidazolylidene (**E**).

orbitals,

To identify an efficient NHC-based umpolung catalyst for other C–C coupling reactions, an investigation was initiated of the carbenes **A – E** (**Figure 2**) in the elementary steps of benzoin condensation. The backbone substituents are varied to investigate the kinetic and thermodynamic outcomes of these modifications. To the best of our knowledge, neither a systematic computational study of polymerizable NHCs and their applications in organocatalysis, nor the impact of modification of the carbene backbone, has not been reported. We report herein a detailed investigation of NHC-catalyzed benzoin condensation. Additionally, both density functional and multi-configuration simulations are performed to correlate changes in reactivity for the benzoin condensation with changes to the frontier orbitals of the NHC catalysts.

A suitable umpolung catalyst for aldehydes in the benzoin condensation reaction requires both nucleophilicity and electrophilicity.[18, 21, 22] All five carbenes in **Figure 2** feature a five-membered unsaturated ring possessing two π-donating and σ-withdrawing nitrogen substituents adjacent to the carbene **C**. The presence of an unsaturated five-membered ring increases the population of the $p_z$ orbital at the carbene carbon.[23-28] The influence of delocalization of the π-electrons is associated with changing the number and the identity of the heteroatoms adjacent to the carbene center while increasing the number of nitrogen atoms within the rings would render the carbene less nucleophilic.[29, 30] Furthermore, the influence of the placement of phenyl rings on the backbone, fused or otherwise, plays a role in the stabilization of the intermediate and transition state species within the benzoin condensation catalytic cycle.[15, 22, 29, 31-33]

Several factors were taken into consideration when modifying the backbone of the N-heterocyclic carbenes in **Figure 2**. The current

it was deemed necessary to go beyond single-determinant DFT descriptions. Thus, the results of MCSCF (multi-configuration SCF) calculations are included here, which to our knowledge comprises the first such study of NHC-based umpolung organocatalysts.

**COMPUTATIONAL METHODOLOGY**

As the photophysical properties, coordination chemistry, and catalytic abilities of different classes of carbenes have been both experimentally and computationally investigated, preliminary calculations evaluated a set of functionals and basis sets to deduce appropriate models for the present research.[1, 20, 39-41] Density functional theory (DFT) has proven to be an effective and accurate tool for investigating the mechanisms of organocatalytic reactions.[21, 42-44] The B3LYP functional has been employed to a great extent in the past, particularly for modeling organic systems;[45] however, due to known limitations of B3LYP to adequately describe dispersion and long-range interactions, the results from this widely-used functional were compared to those of the M06-2X functional.[46-52] These functionals were employed in combination with the 6-31+G(d) and the 6-31G(d) basis sets as the standard methodology.[51, 53-57] The fine integration grid was used. For more detailed analyses of the impact of modeling specifics, see the Supplementary Information.

For more accurate energetics, the 6-311++G(d,p) basis set was incorporated via single-point energy calculations at the previously optimized geometries. The integral equation formalism polarizable continuum model (IEF-PCM[58, 59]) was employed for the single points calculations to account for the effects of solvent. Reactants, products,

transition states, and intermediates were verified for the correct number of imaginary vibrational frequencies via calculation of the energy Hessian. All DFT calculations were carried out using the Gaussian 16 suite of programs.[60]

The GAMESS[61, 62] package was employed for multi-configurational self-consistent field (MCSCF) calculations to study the frontier orbitals of the NHC models with particular attention paid to polymerizable models such as **B**, **C** and **E** (**Figure 2**).[5-7, 63, 64] All MCSCF calculations employ the complete active space SCF (CASSCF) protocol. The structures optimized by DFT calculations were used for the CASSCF single point calculations. CASSCF calculations utilized small active spaces (electrons, orbitals – 2,2) and proceeded to larger (12,12) active space simulations, each exploring different RHF starting guess orbitals. The active space has been constructed from the carbene carbon σ lone pair and π/π* orbitals of the NHC ring, and the electrons that occupy these orbitals. Natural orbital occupation numbers (NOONs) and natural orbital (NO) plots were studied to deduce the suitability of various active space selections. As the MCSCF technique is variational, the active space initial guess orbitals of selected systems were reordered when performing the MCSCF calculations in order to identify potential lower energy active space solutions. The results and discussion herein focus on CAS(6,6)/6-31+G(d) calculations after careful analysis of NOs from among all the active spaces studied.

was determined to be **TS2**. B3LYP – on the other hand – in conjunction with the 6-31G(d) or 6-31+G(d) basis sets gave conflicting predictions, *e.g.*, different RDSs were predicted for the NHC modeled herein at these two levels of theory (**Figure 3** and **Figure 4**). Thus, in order to gain further insight into the catalytic pathway, the M06-2X/6-31+G(d)/IEF-PCM-DMSO combination was utilized for geometry optimizations and selected for further mechanistic investigations. It is reasonable to speculate that the conflicting results from prior modeling studies[11, 19, 24] is due to the basis set/functional sensitivity demonstrated in **Figure 3**. For more detailed analyses of the impact of modeling specifics, see the Supplementary Information.

## 2.   Modifying the carbene backbone

To investigate the influence of different carbene backbone substituents on the catalytic cycle (**Scheme 2**), N-heterocyclic carbene derivatives with increased heteroatoms in the ring core (**A**), a fused-ring backbone (**B**), electron-withdrawing *p*-bromophenyl groups (**C**), a smaller, less sterically hindered NHC with hydrogens on the backbone (**D**), and electron-donating bithiophene backbone substituents (**E**) are chosen (see **Figure 1**) for study. As noted above, NHC models **C** and **E** are particularly relevant to organocatalysis
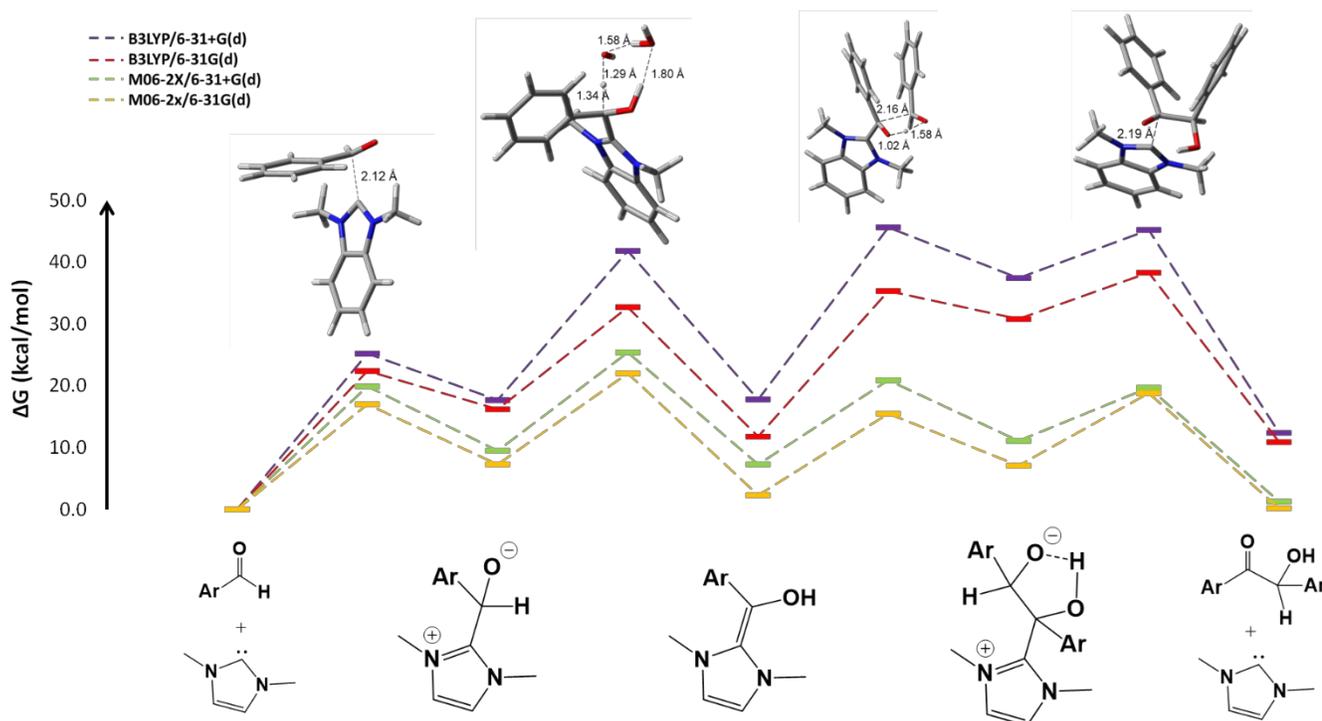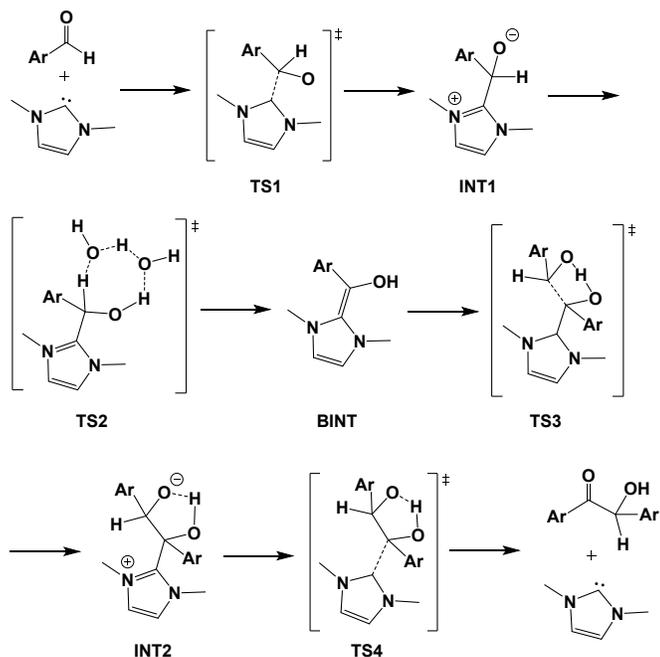


**Figure 3**. The Gibbs free energy (in kcal/mol) profile of the benzoin condensation catalyzed by *N,N'*-dimethylbenzimidazolylidene (**B**) at different levels of theory. All simulations employed the IEF-PCM-DMSO continuum solvation model. For further discussion of the impact of basis set and functional effects, see Supplementary Information.

given that they are polymerizable functionalities.

## RESULTS AND DISCUSSION

### 1.   Reaction free energy profile

Based on past research,[11, 15, 20, 22, 65] the rate determining step (RDS) of benzoin condensation is thought to be the assisted intermolecular proton transfer that occurs at **TS2**, see **Scheme 2**, leading to the formation of the Breslow intermediate (**BINT**). The present research demonstrates the sensitivity of the benzoin formation reaction coordinate to functional and basis set combinations. The M06-2X functional combined with the 6-31G(d) and 6-31+G(d) basis sets offer consistent predictions in that the RDS for all NHC catalysts

**Scheme 2**. Model benzoin condensation reaction catalyzed by an NHC.[18, 23]

For more accurate energetics, the larger 6-311++G(d,p) basis set was incorporated via single point calculations based on M06-2X/6-31+G(d)/IEF-PCM-DMSO-optimized geometries, **Table 1**. The energetic trends thus obtained are consistent with previous predictions.[1, 11, 19, 20, 22, 65, 66] The overall catalytic process was found to be thermoneutral when free energies were obtained at the M06-2X/6-311++G(d,p)/IEF-PCM-DMSO//M06-2X/6-31+G(d)/IEF-PCM-DMSO level of theory (**Figure 4**).

| $G$ | TS1 | INT1 | TS2 | BINT | TS3 | INT2 | TS4 |
|---|---|---|---|---|---|---|---|
| **A** | 20.0 | 11.7 | 29.2 | 11.8 | 21.8 | 11.1 | 25.1 |
| **B** | 20.0 | 10.4 | 28.6 | 5.1 | 18.8 | 10.4 | 19.1 |
| **C** | 20.5 | 8.9 | 25.6 | 8.1 | 19.4 | 14.5 | 21.4 |
| **D** | 18.3 | 7.4 | 25.3 | 9.9 | 18.0 | 11.6 | 19.2 |
| **E** | 21.0 | 10.2 | 28.2 | 9.0 | 20.3 | 15.0 | 21.6 |

**Table 1.** Relative free energies (kcal/mol) for the benzoin condensation reaction catalyzed by carbenes **A-E** calculated in DMSO with M06-2X/6-311++G(d,p)/IEF-PCM-DMSO//M06-2X/6-31+G(d)/IEF-PCM-DMSO. Separated reactants are defined as $G = 0$.
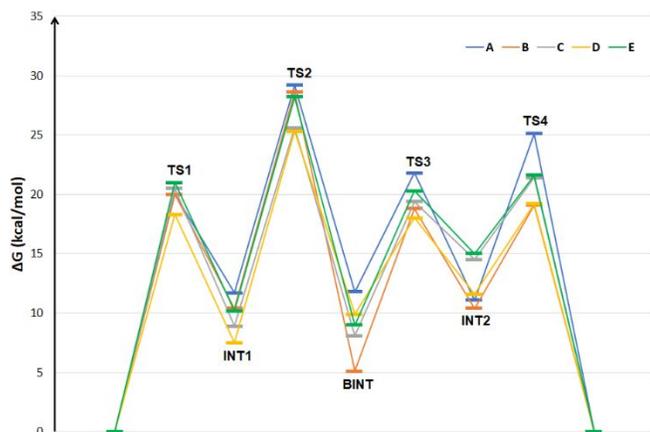


**Figure 4.** The Gibbs free energy (kcal/mol) profile of the benzoin condensation reaction at the M06-2X/6-311++G(d,p)/IEF-PCM-DMSO//M06-2X/6-31+G(d)/IEF-PCM-DMSO level of theory. Separated reactants are defined as $G = 0$.

The proton transfer pathway that occurs via **TS2** leading to the formation of the Breslow intermediate is assisted by two molecules of $H_2O$ (**Scheme 2**) The rate-determining step, **TS2**, is most favored by **D** ($G^{\ddagger}_{TS2} = 25.3$ kcal/mol) and **C** ($G^{\ddagger}_{TS2} = 25.6$ kcal/mol) with the most destabilized transition state resulting from carbene **A** ($G^{\ddagger}_{TS2} = 28.2$ kcal/mol). The umpolung of benzaldehyde that occurs at **TS2** is thus most stabilized by imidazolylidene (**D**) and 4,5-bis(p-bromophenyl)-1,3-dimethylimidazolylidene (**C**), which implies that this catalysis can be quite sensitive to sterics (**D**), backbone (**C**) substitution, as well as the number of heteroatoms in the heterocycle (**A**). There does not appear to be obvious correlation between the free energy of the Breslow intermediate and the free energy of the transition state that precedes it.

The Breslow intermediate, **BINT**, is most energetically favored by *N,N'*-dimethylbenzimidazolylidene, **B**, resulting in the shortest C=C bond (1.373 Å, **Figure 5**) where the higher energy **BINT** stationary points are characterized by slightly longer (*ca.* ranging 0.01 - 0.02 Å) C=C bonds. The Breslow intermediate is most stabilized for carbene **B** ($G_{BINT} = 5.1$ kcal/mol), followed by carbenes **C** ($G_{BINT} = 8.1$ kcal/mol), **E** ($G_{BINT} = 9.0$ kcal/mol), **D** ($G_{BINT} = 9.9$ kcal/mol), and finally **A** ($G_{BINT} = 11.8$ kcal/mol). The additional nitrogen atom in the triazolylidene **A** causes a decrease in $p_{\pi}$-orbital-donation from the nitrogen atoms, thereby increasing the electrophilicity of the carbene carbon and resulting in a destabilized **BINT** state (**Table 1**). The second benzaldehyde addition is most favored for **D** ($G^{\ddagger}_{TS3} = 18.0$ kcal/mol), **B** ($G^{\ddagger}_{TS3} = 18.8$ kcal/mol), and **C** ($G^{\ddagger}_{TS3} = 19.4$ kcal/mol), where the most destabilized energy transition states result from carbenes **A** and **E** ($G^{\ddagger}_{TS3} = 21.8$ kcal/mol and $G_{TS3} = 20.3$ kcal/mol, respectively).
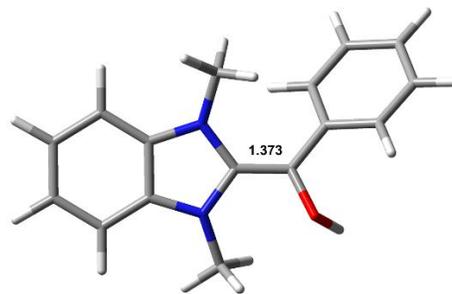


**Figure 5.** Breslow intermediate **BINT** resulting from the first addition of benzaldehyde to *N,N'*-dimethylbenzimidazolylidene, **B**. Bond length in Angstrom units.

Polymerizable N-heterocyclic carbene **C** possesses the lowest activation free energy for the important transition from **INT1** to **TS2** ($\Delta G = 16.7$ kcal/mol). The proton-transfer RDS, **TS2**, is slightly more stabilized versus the other known polymerizable carbenes, **B** and **E**, by -3.0 kcal/mol and -2.6 kcal/mol respectively. The imidazolylidene (**D**) maintains the lowest overall RDS, however, polymerizing such a species would likely prove more experimentally challenging than carbenes such as **B**, **C** or **E**. Based on the results discussed above and previous experimental investigations,[7] 4,5-bis(*p*-bromophenyl)-1,3-dimethylimidazolylidene (**C**) holds promise as a polymerizable and self-supported catalyst for organocatalytic umpolung reactions. This combined with our overall analysis indicates that carbene **C** possesses appropriate kinetic and structural properties to be considered as the basis for further investigation.

### 3.    Influence of *para*-substituents on the catalytic cycle

The addition of phenyl rings to the backbone of a modified carbene has received little attention in previous research on benzoin condensation. As such, it was decided to investigate both the position of the phenyl ring and modification of the *para* substituents. In an effort to identify better catalyst leads for the condensation of benzaldehydes, where the catalysts are both polymerizable and self-supported, the *para* substituents were changed from bromine (**C**) to chloro- (**C–Cl**), amino- (**C–NH₂**), and cyano-, CN, (**C–CN**) (**Figure 6**).
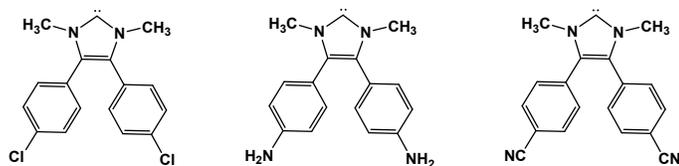
**Figure 6**. Modification of carbene **C**, 4,5-bis(*p*-bromophenyl)-1,3-dimethylimidazolylidene, where the *para* substituents are changed from bromo- to chloro-, amino-, and cyano- groups.

The energetic trends in **Figure 7** follow those discussed in the preceding sections with the exception of the electron-donating para substituent, **–NH₂**, whereby **BINT** is destabilized compared to **INT1** by +0.8 kcal/mol (**Table 2**). The presence of an electron-donating amino group situated para to the backbone of the carbene thus destabilizes **BINT** ($G_{BINT}$ = 8.1 kcal/mol) as well as the rate determining proton-transfer step, **TS2** ($G^{\ddagger}_{TS2}$ = 29.5 kcal/mol), implying that this NHC is less suitable as an umpolung catalyst for benzoin condensation (**Figure 7**). However, the addition of the electron-withdrawing groups stabilize **TS2** and **BINT**. The barrier to the proton-transfer step defined by **TS2** is lowest for the *p*-chlorophenyl substituent, ($G^{\ddagger}_{TS2}$ = 24.1 kcal/mol), followed by the *p*-bromophenyl ($G^{\ddagger}_{TS2}$ = 25.6 kcal/mol), and then the *p*-cyanophenyl ($G^{\ddagger}_{TS2}$ = 26.6 kcal/mol). The **BINT** state is most energetically favored for the *p*-cyanophenyl ($\Delta G_{BINT}$ = 7.5 kcal/mol) and then the *p*-chlorophenyl species ($G_{BINT}$ = 7.6 kcal/mol). Hence, there is a substantial influence upon benzoin condensation by the *para* substituent on the phenyl rings of the carbene catalyst, which may constitute a profitable avenue for experimental exploration.

| $G$ | TS1 | INT1 | TS2 | BINT | TS3 | INT2 | TS4 |
|---|---|---|---|---|---|---|---|
| **C-Br** | 19.8 | 8.9 | 25.6 | 8.1 | 19.0 | 14.5 | 21.1 |
| **C-Cl** | 19.4 | 8.5 | 24.1 | 7.6 | 18.5 | 14.4 | 20.9 |
| **C-NH₂** | 18.6 | 7.3 | 29.5 | 8.1 | 16.8 | 13.1 | 20.1 |
| **C-CN** | 20.4 | 9.5 | 26.6 | 7.5 | 19.9 | 15.2 | 21.4 |

**Table 2.** Relative free energies (kcal/mol) calculated at the M06-2X/6-311++G(d,p)/IEF-PCM-DMSO//M06-2X/6-31+G(d)/IEF-PCM-DMSO level for benzoin condensation catalyzed by modifying carbene **C**, where Br is replaced with Cl in **C–C l**, NH₂ in **C-NH₂**, and CN in **C–C N**.
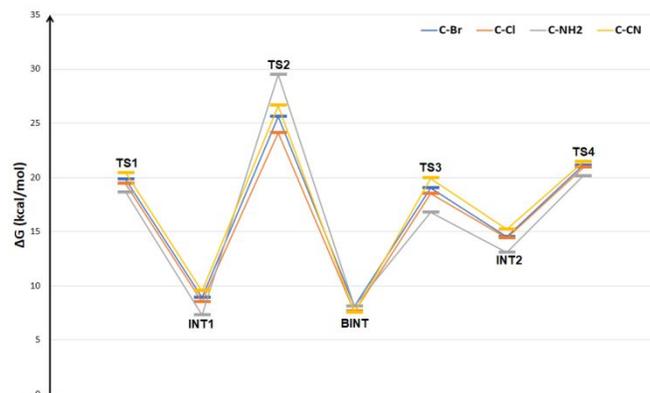


**Figure 7**. The Gibbs free energy (kcal/mol) profile after modifying the *para*-substituents – see **Figure 6** – on the backbone of carbene **C** optimized at the M06-2X/6-311++G(d,p)/IEF-PCM-DMSO//M06-2X/6-31+G(d)/IEF-PCM-DMSO level of theory. Separated reactants are defined as $G = 0$.

## 4. MCSCF Natural Orbital Analysis

Extensive experimental studies have been conducted on a wide selection of heterocyclic carbenes with different N-substituents and varying backbone substituents.[24, 67, 68] In order for a carbene to be a suitable umpolung catalyst it must feature nucleophilic reactivity towards the aldehyde and electrophilic properties to stabilize the negative charge in the umpolung step. In orbital terms, this implies that a high-energy HOMO and a low-lying LUMO are desired. Given the importance of the virtual orbitals, and the limitations in DFT methods in describing these, we undertook multi-configuration SCF calculations at DFT-optimized geometries.

Natural orbitals of carbenes **A - E** are obtained from the MCSCF calculations and the relevant natural orbital occupation numbers NOONs) were computed. In general, the NOON for active space orbitals can vary between 0 and 2 $e^-$, with lower/higher energy natural orbitals having higher/lower NOONs. The key frontier orbitals of carbenes **A - E** are shown in **Figure 8**. What is especially striking in the context of polymerizable NHC systems such as **B** and **C** is that there is significant delocalization of the frontier NOs between the N-heterocycle core and the backbone substituents. Based on these initial results, models **B** and **C** merit further orbital analysis (see Supplementary Information for more detailed analyses of **A**, **D**, and **E**).

MCSCF calculations shows that the HOMO, which is defined as the occupied natural orbital with a NOON furthest from 2.00 $e^-$, of **A** and **D** is a π orbital of the N–C–N moiety as well as the π orbital of the unsaturated C–C bond in the carbene backbone (1.93 $e^-$ for **A** and **D**). The HOMO – 1 of both **A** and **D** (1.96 $e^-$ for **A** and 1.97 $e^-$ for **D**) is the π orbital of the N–C heterocycle bond. The LUMO and LUMO + 1 of **A** and **D** are the π* orbitals of heterocycle. In both **C** and **E**, the HOMO and HOMO – 1 are the π orbitals of the respective backbone substituents where the orbitals are located on the bromobenzene and bithiophene substituents, respectively. The LUMO and LUMO + 1 are similar in constitution in that they are located on the backbone substituents. The HOMO and HOMO – 1 of **B** are the π orbitals of the benzene backbone. The LUMO and the LUMO + 1 are the π* orbitals of the benzene backbone.

The LUMOs of **B**, **C**, and **D** are delocalized on the backbone substituents of the carbene, whereas **B** shows some density still situated within the heterocycle core. Carbenes **B**, **C** and **E** exhibit significant conjugation between backbone substituents with the heterocycle core. Most importantly, the MCSCF calculations make it apparent that there is significant delocalization between the backbone and heterocycle evident at both the top of the valence band as well as

the bottom of the conduction band, which has important implications or the use of these and related polymeric NHCs as the basis of novel organocatalysts.
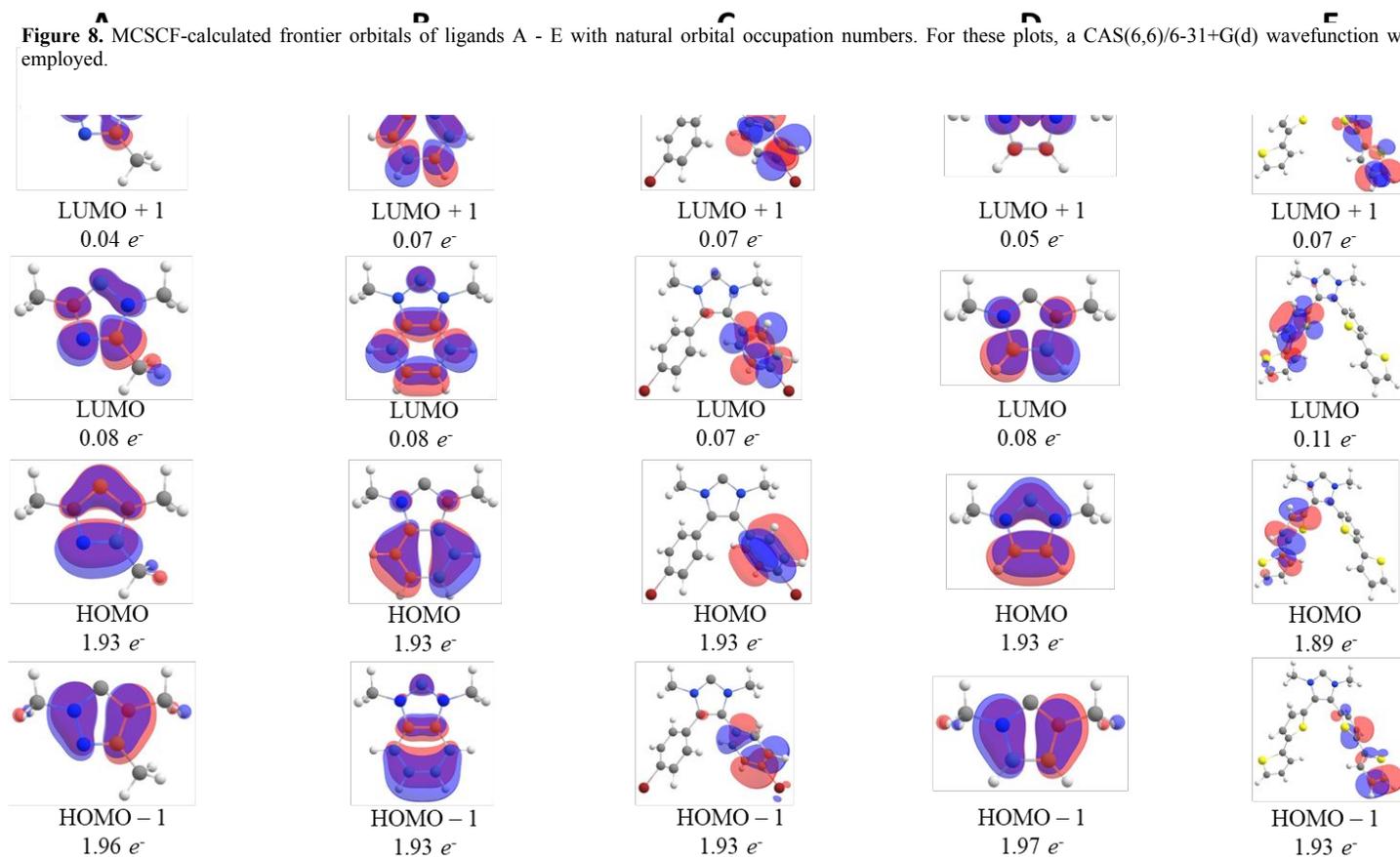
## SUMMARY AND CONCLUSIONS

N-heterocyclic carbenes (NHCs) are an important class of molecules used in a vast array of molecular transformations. Polymeric NHCs are an emerging family of promising "green catalysts" for several organic transformations, including benzoin condensation. Modification of the backbone, introduction of heterocycle aromaticity, backbone NHC substitution, or substitution of substituents on the phenyl groups of the backbone are shown in this research to result in both significant changes to the electronic structure as well as the catalytic cycle for benzoin condensation. The most important specific conclusions from this research are summarized here.

DFT calculations reveal that to accurately describe benzoin condensation, solvent effects must be taken into consideration while employing a basis set with both polarization and diffuse functions, *e.g.*, 6-31+G(d), and a functional that includes dispersion corrections, *e.g.*, the meta-GGA-based M06-2X functional. It is hypothesized that conflicting results from previous studies[11, 19, 24] of benzoin condensation vis-à-vis the rate-determining step and stability of the Breslow intermediate arise from this sensitivity of the computed free energies to the level of theory. Recently, a radical mechanism has also been proposed for this transformation,[19, 20] whose study by the computational recipes developed here would be a worthy direction for future research.

Relative to the reactants, benzoin and benzaldehyde, the free energies for the rate-determining step, **TS2** (solvent assisted proton transfer), **Figure 9**, is destabilized as the number of nitrogen atoms in the NHC ring is increased. Among the carbenes studied, lower activation free energies for the rate determining step result from carbenes **C** and **D** ($G^{\ddagger}_{TS2}$ = 25.6 kcal/mol and $G^{\ddagger}_{TS2}$ = 25.3 kcal/mol, respectively). However, considering the orbital energies and characteristics, relative balance between nucleophilicity and electrophilicity, thermodynamic stability, and laboratory viability, carbene **C** would appear to be a more suitable monomer for an umpolung poly(NHC) catalyst. Furthermore, substituting *para*-bromo for *para*-chloro on the backbone phenyl further lowers the activation energy ($G^{\ddagger}_{TS2}$ = 24.1 kcal/mol) of the resulting NHC catalyst. The present analysis thus indicates that poly(carbene) catalysts possessing electron-withdrawing groups on the phenyl rings of the carbene backbone as suitable lead candidates for benzoin condensation and related organic transformations. Future research to investigate *meta*- or poly-substituted phenyl substituted NHC catalysts would be of great interest.



**Figure 8.** MCSCF-calculated frontier orbitals of ligands A - E with natural orbital occupation numbers. For these plots, a CAS(6,6)/6-31+G(d) wavefunction was employed.

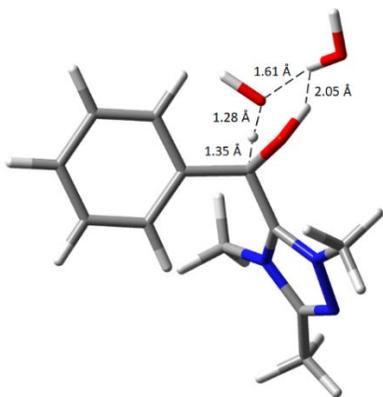| A | B | C | D | E |
|---|---|---|---|---|
| LUMO + 1<br>0.04 $e^-$ | LUMO + 1<br>0.07 $e^-$ | LUMO + 1<br>0.07 $e^-$ | LUMO + 1<br>0.05 $e^-$ | LUMO + 1<br>0.07 $e^-$ |
| LUMO<br>0.08 $e^-$ | LUMO<br>0.08 $e^-$ | LUMO<br>0.07 $e^-$ | LUMO<br>0.08 $e^-$ | LUMO<br>0.11 $e^-$ |
| HOMO<br>1.93 $e^-$ | HOMO<br>1.93 $e^-$ | HOMO<br>1.93 $e^-$ | HOMO<br>1.93 $e^-$ | HOMO<br>1.89 $e^-$ |
| HOMO − 1<br>1.96 $e^-$ | HOMO − 1<br>1.93 $e^-$ | HOMO − 1<br>1.93 $e^-$ | HOMO − 1<br>1.97 $e^-$ | HOMO − 1<br>1.93 $e^-$ |

**Figure 9**. Rate-determining step, **TS2** of 2,4,5-trimyethyl-1,2,4-triazolylidene, **A**. Bond lengths in Angstrom units.

In the current investigation, it was observed that backbone substituents have a significant effect on the computed catalytic cycle. To determine which carbene would be a suitable umpolung catalyst for the benzoin condensation reaction, the carbene must feature both nucleophilic reactivity as well as electrophilic properties for the stabilization of zwitterionic and Breslow intermediates; see, for example, the molecular electrostatic potential plot of **TS2** for the *para*-chloro-phenyl decorated NHC catalyst model in **Figure 10**. More importantly, in the context of identifying novel poly(NHC) catalysts, MCSCF simulations of NHC monomers that possess polymerizable backbone substituents indicate significant delocalization between the NHC core and the substituent orbitals for both occupied and unoccupied orbitals near the Fermi level, **Figure 8**. Taken together, this work demonstrates that backbone modifications can significantly impact the electronic structure of the NHCs, which in turn significantly impact the free energy profile of the catalytic cycle for benzoin condensation. Extension of this research to other umpolung catalysis would be of great interest.
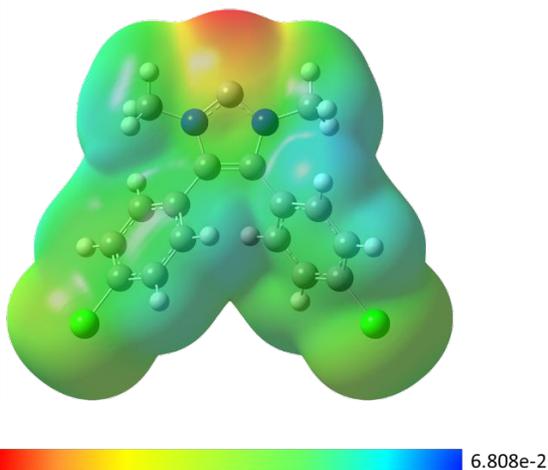


**Figure 10.** Molecular electrostatic potential for the *para*-chloro modification of umpolung organocatalyst **C** (see **Figure 6**). In this case, the colors have been chosen such that regions of attractive potential appear in red and those of repulsive potential appear in blue.

These noteworthy results are significant for the design of various types of carbenes for use in syntheses requiring umpolung catalysts. The electronic character of cyclic carbenes is complicated and further probing of their electronic character by going beyond their simple π-donating abilities is of great interest – especially in organocatalysis. It would be interesting to investigate potential radical-associated pathways for NHC-catalyzed benzoin condensation employing the various carbenes discussed in this

research. Moreover, reducing the number of or simply changing the identity of heteroatoms as well as the increasing the distance of the heteroatoms from the carbene center could impose a drastic change upon the donating abilities of NHCs. Applying these findings to other umpolung reactions involving activated or un-activated C–C bonds[69-71], various carbonyl compounds[18, 38, 65], or possibly *α,β*-unsaturated aldehydes may reveal more interesting information about reactivity.[40, 72, 73] Finally, carbenes inspired by nature such as those derived from the coenzyme thiamine are also promising candidates for future research.[12, 20]

## ASSOCIATED CONTENT

**Supporting Information.** Additional computational details.

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"Computational modeling and orbital analyses reveal enhanced catalytic properties based on N-heterocyclic carbene backbone modifications."
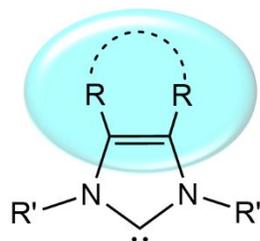
**Backbone Substituents**

- Provide electronic stabilization
- Substituents affect carbene electronics
- Significant electron delocalization

**Green Catalysis**

- Poly(NHCs)
- Potentially self-supported, recyclable organocatalysts