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Thermodynamics of N-Heterocyclic Carbene Dimerization: The Balance of Sterics and Electronics

Albert Poater,[†] Francesco Ragone,[†] Simona Giudice,[†] Chiara Costabile,[†] Reto Dorta,[‡]
Steven P. Nolan,[§] and Luigi Cavallo*,[†]

Dipartimento di Chimica, Università di Salerno, Fisciano (SA), I-84084, Italy, Department of Organic Chemistry, University of Zurich, Zurich, Switzerland, and Institute of Chemical Research of Catalonia (ICIQ), Tarragona, Spain

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Summary: The past decade has seen N-heterocyclic carbenes (NHC) emerging as a credible alternative to ubiquitous tertiary phosphines as ligands in organic and organometallic chemistry. In many cases NHC ligands have proven more effective than phosphines as ancillary ligands in catalysis, while in some cases they also enable unexpected and welcomed chemical routes to new products.[1] These initial discoveries have paved the way to a continued search for new NHCs able to promote more effective and/or unprecedented catalysis. Nevertheless, the search for new and useful NHCs remains an arduous task, because, to date, useful NHCs have to be synthesized as monomeric species, while some monomeric NHCs have the disappointing tendency to easily dimerize as shown in eq 1.

$$2\ \mathrm{NHC}: \Leftrightarrow \mathrm{NHC}{=}\mathrm{CHN} + -E_{\mathrm{dim}} \qquad (1)$$

Several studies have offered insights into the mechanism of NHCs dimerization[2] and clearly evidenced that the thermodynamic tendency of a given NHC to dimerize can be linked to its steric and electronic properties. For example, the stronger tendency to dimerize of saturated NHCs (**1** in Chart 1) with respect to their unsaturated analogues (**3** in Chart 1) was correlated to an electronic effect.[3] This electronic effect can be specifically associated with the singlet−triplet splitting, $E_{\mathrm{S-T}}$, which is the energy required to promote one of the electrons of the σ-HOMO carbenic lone pair to the π^*-LUMO centered on the carbenic C atom.[2b,c] Similarly, it was shown that an appropriate increase of the steric bulk of the R substituent on the N atoms is key in achieving stable saturated or aromatic (**2** in Chart 1) monomeric NHCs. Nevertheless, the exact balance between these two effects is not clearly understood. In this contribution, we propose a model addressing factors determining the stability of NHCs, aiming, in the end, to provide a model to quantify these effects for different NHC families.

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* Corresponding author. E-mail: lcavallo@unisa.it.

[†] Università di Salerno.

[‡] University of Zurich.

[§] ICIQ.

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(2) (a) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, L.; Paolini, F.; Schütz, J. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 5896. (b) Carter, E. A.; Goddard, W. A., III *J. Phys. Chem.* **1986**, *90*, 998. (c) Heinemann, C.; Thiel, W. *Chem. Phys. Lett.* **1994**, *217*, 11. (d) Cheng, M.-J.; Hu, C.-H. *Chem. Phys. Lett.* **2000**, *322*, 83. (e) Cheng, M.-J.; Hu, C.-H. *Chem. Phys. Lett.* **2001**, *349*, 477. (f) Nyulászi, L.; Veszprémi, T.; Forró, A. *Phys. Chem. Chem. Phys.* **2000**, *2*, 3127. (g) Graham, D. C.; Cavell, K. J.; Yates, B. F. *J. Phys. Org. Chem.* **2005**, *18*, 298. (h) Denk, M. K.; Hezarkhani, A.; Zheng, F.-L. *Eur. J. Inorg. Chem.* **2007**, 3527. (i) Luan, X.; Mariz, R.; Gatti, M.; Costabile, C.; Poater, A.; Cavallo, L., Linden, A.; Dorta, R. *J. Am. Chem. Soc.*, published online April 29, 2008 http://dx.doi.org/10.1021/ja800861p.

(3) There is ample experimental evidence that NHCs derived from benzimidazolium and imidazolinium salts dimerize upon deprotonation. Dimerization of deprotonated imidazolidium salts seems more difficult. For a rare example, see: Taton, T. A.; Chen, P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1011.

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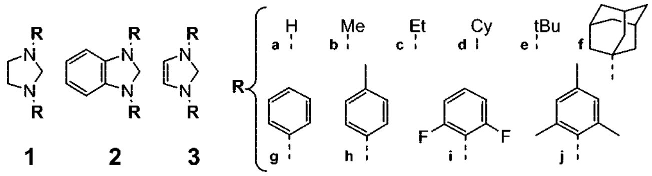
Chart 1



To this end, we argue that the dimerization enthalpy of a given NHC, E_{dim}, can be decomposed as shown in eq 2,

$$E_{\mathrm{dim}} = (A \times \mathrm{NHC}_{\mathrm{Steric}}) + (B \times \mathrm{NHC}_{\mathrm{Electronic}}) + C \qquad (2)$$

where $\mathrm{NHC}_{\mathrm{Steric}}$ and $\mathrm{NHC}_{\mathrm{Electronic}}$ are molecular descriptors able to capture the steric and electronic properties of a given NHC, respectively, while A, B, and C are empirical parameters fitted to reproduce a set of E_{dim} values. Within this approach it is natural to set $\mathrm{NHC}_{\mathrm{Electronic}} = E_{\mathrm{S-T}}$. Sterically we assume $\mathrm{NHC}_{\mathrm{Steric}} = \%V_{\mathrm{Bur}}$, where $\%V_{\mathrm{Bur}}$ is the buried volume, a molecular descriptor that can be considered an analogue of Tolman's cone angle for tertiary phosphines. We have already shown that $\%V_{\mathrm{Bur}}$ can be successfully used to classify the steric properties of NHC ligands.[4] Finally, due to the paucity of experimental data,[5] the E_{dim} we fitted are DFT dimerization energies, $E_{\mathrm{dim}}^{\mathrm{DFT}}$.[6] The $E_{\mathrm{S-T}}$ values and the geometries used for the calculation of the $\%V_{\mathrm{Bur}}$ were also obtained from DFT calculations.[8,9] The set of NHC ligands we considered is reported in Chart 1 and were selected to cover a large portion of the steric and electronic space.

Minimization of χ^2 of eq 3 with respect to the A, B, and C parameters of eq 2 resulted in the following parameters: $A = 3.28$ (3.22) kcal/mol, $B = 2.08$ (1.99), and $C = -233.25$ (-220.34) kcal/mol. Values in parentheses refer to calculations that include solvent effects, THF in this case.

$$\chi^2 = \sum_{\mathrm{NHCsofChart1}} (E_{\mathrm{dim}}^{\mathrm{DFT}} - E_{\mathrm{dim}}^{\mathrm{Fit}})^2 \qquad (3)$$

A plot of the fitted versus the DFT dimerization energies calculated in the gas phase is presented in Figure 1. Together with a correlation parameter $R^2 = 0.93$, the plot indicates that using $E_{\mathrm{S-T}}$ and $\%V_{\mathrm{Bur}}$ as molecular descriptors for electronic and steric effects and appropriately fitting the A, B, and C parameters of eq 2 allow to reproduce the DFT dimerization energies of all NHCs in Chart 1 with remarkable accuracy. Very similar results are obtained if the parameters of eq 2 are optimized to reproduce the DFT dimerization energies in THF ($R^2 = 0.88$). It is noteworthy that the dimerization energies span a remarkably large window from -40.3 to $+33.5$ kcal/mol in the gas phase and from -28.6 to $+36.2$ kcal/mol in THF.

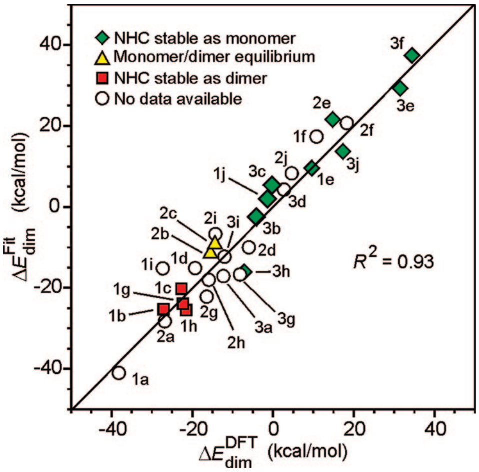


Figure 1. Plot of $E_{\mathrm{dim}}^{\mathrm{Fit}}$ versus $E_{\mathrm{dim}}^{\mathrm{DFT}}$ for the NHCs of Chart 1. The diagonal line is plotted to guide the eye. The color scheme indicates the experimental behavior. More details can be found in the Supporting Information.

The good agreement we obtained quantifies the relative role of steric and electronic effects on the dimerization of NHCs and unifies NHCs with different architectural skeletons (saturated, aromatic, or unsaturated) and different R groups (from alkyls to aromatics) into a single model. Indeed, both $E_{\mathrm{dim}}^{\mathrm{DFT}}$ and $E_{\mathrm{dim}}^{\mathrm{Fit}}$ reproduce the well-known fact that unsaturated NHCs show a much higher tendency to be stable as free monomers (green diamonds in Figure 1). This also highlights the fact that saturated NHCs with small R groups normally dimerize (red squares in Figure 1), although they are not so far from being stable as monomers, and that there exists a small section of the NHC space where the monomer−dimer equilibrium is established (yellow triangles in Figure 1). Considering that NHCs **3b**[10] and **1c**[11] are known to be stable as monomers and dimers, respectively, an energy window separating NHCs that will be stable as monomers ($E_{\mathrm{dim}}^{\mathrm{Fit}} > -2.6$ (3.3 in THF) kcal/mol) and NHCs that will dimerize ($E_{\mathrm{dim}}^{\mathrm{Fit}} < -18.9$ (-9.4 in THF) kcal/mol) can be tentatively proposed; see Figure 1.[12,13]

Nevertheless, some words of cautions are needed. First, this kind of calculation predicts the thermodynamic stability of a given NHC and says nothing on its possible kinetic stability. Second, an extremely bulky NHC might be stable as a monomer, but sterically too demanding to be accommodated in the coordination sphere of a given metal complex. Third, if the dimerization energy of a given NHC is low, a dimer−monomer equilibrium might be established that enables the formation of NHC−metal compounds with certain transition metal precursors. Thus, knowledge of how much the dimer is lower in energy than the monomer can be very useful.

With respect to the straightforward calculation of the E_{dim} from optimization of the dimeric and monomeric species, the

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(5) Liu, Y.; Lindner, P. E.; Lemal, D. M. *J. Am. Chem. Soc.* **1999**, *121*, 10626.

(6) The $E_{\mathrm{dim}}^{\mathrm{DFT}}$ have been calculated as the energy difference between the optimized geometries of the dimer NHC═CHN and of two monomers NHC. See ref 7 and the Supporting Information for details.

(7) The DFT calculations were performed with the Gaussian03 package, using the GGA BP86 functional, with the TZVP basis set of Ahlrichs on main group atoms, and the relativistic Stuttgart ECP basis set on Ir. Calculations were performed in the gas phase and in solution (the PCM solvation model has been used to simulate THF as the solvent). See the Supporting Information. This approach results in a dimerization enthalpy of−8.8 kcal/mol for **2c**, versus an experimental value of−13.7 ± 0.6 kcal/mol; see ref 5.

(8) The $E_{\mathrm{S-T}}$ has been calculated as the energy difference between the DFT-optimized geometries of the monomer NHC in the triplet and singlet electronic states, respectively. See ref 7 and the Supporting Information.

(9) The $\%V_{\mathrm{Bur}}$ has been calculated using the geometry of the NHC ligand from the DFT-optimized geometry of the (NHC)Ir(CO)$_2$Cl complex. See ref 7 and the Supporting Information for details.

(10) Herrmann, W. A.; Köcher, C.; Goosen, L. J.; Artus, J. G. R. *Chem.− Eur. J.* **1996**, *2*, 1627.

(11) Wiberg, N. *Angew. Chem., Int. Ed. Engl.* **1968**, *10*, 766.

(12) Sometimes, the alkali-metal base used for deprotonation is not innocent and can coordinate to the nascent carbene; see:Alder, R. W.; Blake, M. E.; Bortolotti, C.; Bufali, S.; Butts, C. P.; Linehan, E.; Oliva, J. M.; Orpen, A. G.; Quayle, M. J. *Chem. Commun.* **1999**, 241.

(13) If the tendency for dimerization is more pronounced, NHC−M compounds can sometimes be obtained through a carbene transfer agent (Ag$_2$O). For a recent example with NHC salt **1i**, see:Ritter, T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 11768.

energy decomposition scheme we presented replaces the dimer calculation by two new monomer calculations for each NHC to be examined, i.e., optimization of the NHC in the triplet electronic state to evaluate the E_{S-T}, and optimization of the (NHC)Ir(CO)$_2$Cl complex to evaluate the $\%V_{Bur}$. Besides the advantage of an easy decomposition of E_{dim} into steric and electronic contributions, there is the additional advantage that E_{dim} from eq 2 could be used to check results from the straightforward E_{dim} calculation, due to the difficulties in locating the best geometry for the dimer. Indeed, for bulky R, the groups on both halves of the dimer have a tendency to interlock in various ways, and finding the most stable conformation of the dimer can become nontrivial (this is not an issue for the monomer). Further, saturated NHCs have the additional complication of a very flexible ring. Thus, the added simplicity of the monomer-only approach could be a distinct advantage.

To quantify the predictive ability of eq 2, we followed a leave-one-out cross-validation resampling procedure. In turn, sequentially one NHC value was excluded by the training set of 30 NHCs of Chart 1, and the A, B, and C parameters were fitted to a training set composed by the 29 remaining NHCs. The fitted parameters were used to predict the dimerization energy of the omitted NHC, and the corresponding cross-validation absolute prediction error $e = |E_{dim}^{DFT} - E_{dim}^{Fit}|$. This procedure was repeated for all the 30 NHCs considered, each time leaving out one NHC. The corresponding average cross-validation absolute prediction error, e_{av}, is the average of the single e values and amounts to only 4.4 and 4.9 kcal/mol in the gas phase and in THF, respectively. These e_{av} give an estimate of the error that can be expected if the dimerization energy of a new NHC is calculated using eq 2.

In conclusion, we rationalized the dimerization behavior of a large number of NHCs with different steric and electronic properties within a single model. Our approach can have a strong practical impact in the rational design of new NHCs with *ad hoc* tuned steric and electronic properties. In fact, the natural strategy to design a new NHC is to introduce bulky R groups to avoid dimerization. Unfortunately, sterically too demanding NHC ligands often have a detrimental effect in catalysis.[14] At the same time, even small electronic differences can result in rather varied catalytic behavior.[15] Thus eq 2 could assist in an appropriate calibration of these steric and electronic effects.

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Supporting Information Available: Computational details, energies, and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) As an example, too bulky NHC ligands are detrimental in the case of the ring-closing metathesis of tri- and tetrasubstituted substrates See: (a) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y *Org. Lett.* **2007**, *9*, 1589. (b) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339, as well as in the case of ring-opening metathesis polymerizationSee: (c) Ledoux, N.; Linden, A.; Allaert, B.; Mierde, H. V.; Verpoort, F. *Adv. Synth. Catal.* **2007**, *349*, 1692.

(15) Getty, K.; Delgado-Jaime, M. U.; Kennepohl, P. *J. Am. Chem. Soc.* **2007**, *129*, 15774.