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Quantitative Index of the Relative Ease of Formation and σ-Bonding Strength of N-Heterocyclic Carbenes

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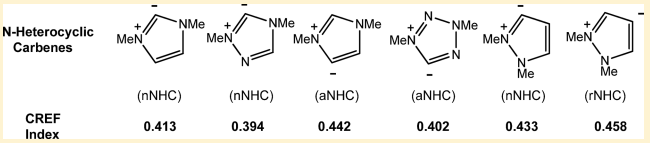
Supporting Information

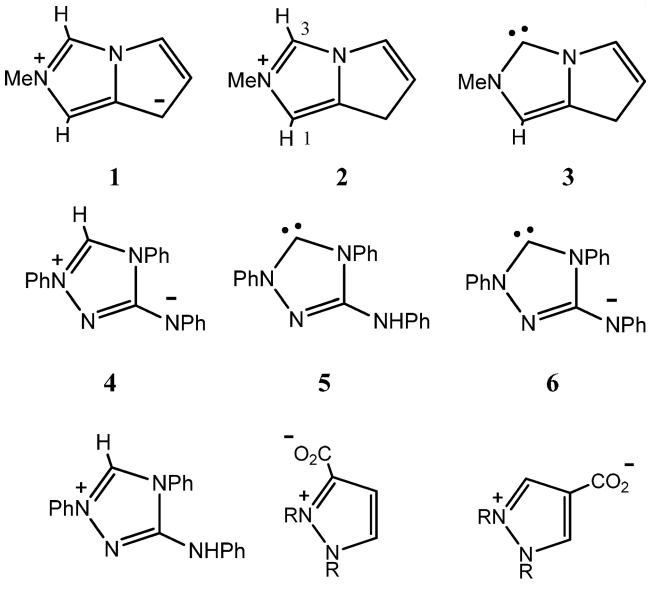
ABSTRACT: An energy-based index of the ease of N-heterocyclic carbene (NHC) formation either by deprotonation of precursor salts to give neutral NHCs or deprotonation of heterocyclic mesomeric betaines to give anionic NHCs is described. This index (CREF; Carbene Relative Energy of Formation), which is easily calculated using DFT methods, also gives a quantitative measure of the relative σ-donor strength of NHCs. CREF index values for a wide range of known and unknown NHC ring systems are reported and their significance discussed.



1. INTRODUCTION

We describe a simple quantitative index of the relative ease of formation of neutral and anionic N-heterocyclic carbenes (NHCs)[1−3] by heterolytic cleavage of σ-bonds and conversely a measure of the σ-donor strength of NHCs (excluding steric effects).

In 1989, we described a study of the mesomeric betaine **1** and proposed that base-catalyzed deuterium exchange at position 3 of the precursor salt **2** occurs via the NHC **3**, which we described as a σ-ylide.[4] No exchange was observed at position 1. We now describe a quantitative measure of the relative ease of exchange at these positions allowing direct comparison with other species. Similarly, a recent study has shown that under mild conditions the mesoionic heterocycle Nitron **4** gives products attributed to the tautomeric NHC **5**,[5] but the mechanism is not yet clear. We now describe a direct comparison of the relative ease of formation of the anionic NHC **6** formed by deprotonation of Nitron **4** and that of the neutral NHC **5** formed via initial catalytic protonation to give the cation **7**. Finally, we illustrate the use of the index for assessment of the relative ease of decarboxylation of heterocyclic carboxylates. For example, derivatives of the pyrazolium-3-carboxylates **8** decarboxylate to the corresponding NHC under mild conditions, whereas the isomers **9** require much harsher conditions.[6]



A number of molecular properties have been used to compare closely related NHCs,[1] often with special reference to binding to metals. These include the molecular electrostatic potential (MESP),[7] the computationally derived ligand electronic parameter (CEP),[8] the Tolman electronic parameter (TEP),[9] HOMO energies,[10,11] and calculated proton affinities.[10,12] However, any comparison of the energetics of diverse species needs to consider both the NHC and its precursor since their structure/substituent effects may differ.

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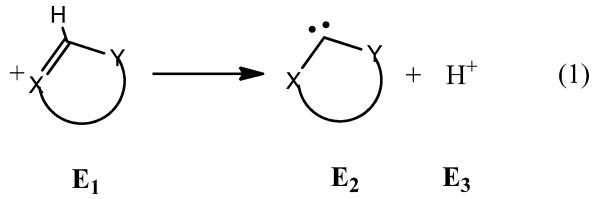
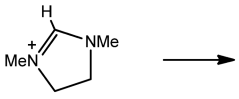
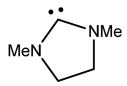
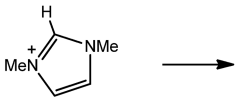
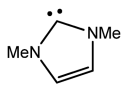
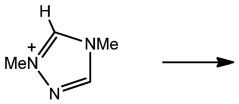
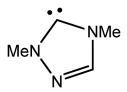
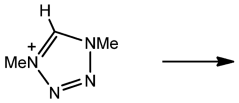
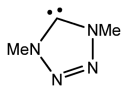
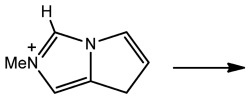
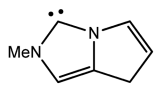
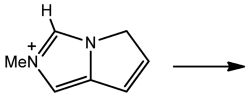
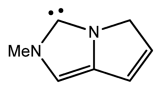
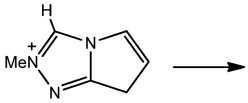
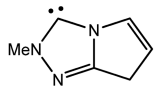
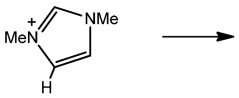
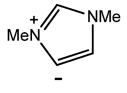
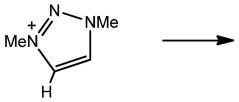
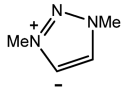
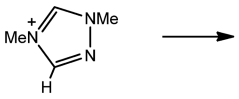
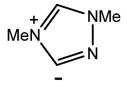
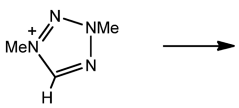
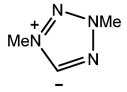
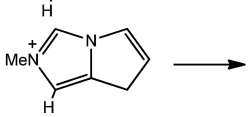
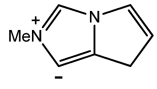
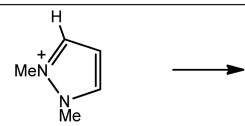
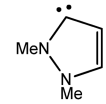
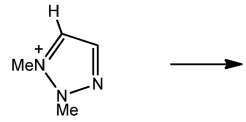
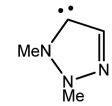
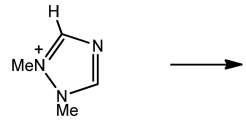
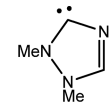
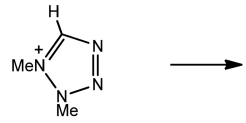
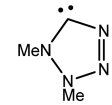
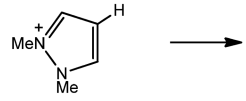
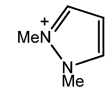
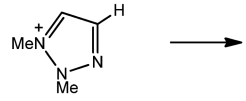
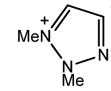
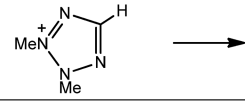
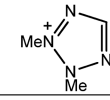
The most common route to NHCs is deprotonation of a suitable heterocyclic precursor. Consider the general reaction shown in eq 1. In a localized bond view, heterolytic cleavage



of the C−H bond requires transfer of the two electrons of a C−H bond to a σ lone pair. Effectively, one electron is transferred from the proton environment to carbon. If the energies of the σ orbitals are lowered, deprotonation should be facilitated. There will also be π effects that influence the carbene energy, especially from electron-donating substituents. However, both these effects will also influence the energy of the precursor and will not necessarily be similar. A universal index of reactivity must therefore take into account all of these effects in both precursor and product. In eq 1, the energies of the precursor and products are E_1, E_2, and E_3,

Table 1. Neutral Five-Membered NHCs

Entry	PRECURSOR	NHC	E + ZPE[a,b]	CREF
A.	Imidazol-ylidenes and aza analogues			
	(i) Classical Normal NHCs (nNHCs)			
1			-306.351788 -305.937653	0.414
2			-305.167859 -304.754800	0.413
3			-321.201501 -320.807395	0.394
4			-337.209851 -336.837376	0.372
5			-381.362781 -380.946856	0.416
6			-381.365703 -380.949829	0.416
7			-397.397356 -396.999116	0.398
	(ii) Abnormal NHCs (aNHCs)			
8			-305.167859 -304.725728	0.442
9			-321.182172 -320.761779	0.420
10			-321.201501 -320.778003	0.424
11			-337.213337 -336.811439	0.402
12			-381.362781 -380.919099	0.444

Entry	PRECURSOR	NHC	E + ZPE[a,b]	CREF
B.	Pyrazol-ylidenes and aza analogues			
	(i) Non-Classical Normal NHCs (nNHCs)			
13			-305.136545 -304.703725	0.433
14			-321.164682 -320.750402	0.414
15			-321.187045 -320.765640	0.421
16			-337.187492 -336.788107	0.399
	(ii) Remote NHCs (rNHCs)			
17			-305.136545 -304.678400	0.458
18			-321.164682 -320.717060	0.448
19			-337.194018 -336.763929	0.430

[a]Hartrees. [b]The first value relates to the reactant and the second to the product.

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respectively. The energy required to deprotonate the precursor (ΔE) is $E_2 + E_3 - E_1$. However, the energy of the proton (E_3) in the gas phase is zero, and for similar reaction conditions in a solvent, it will have a constant value. For NHC formation under similar reaction conditions, solvent and reagent effects on the proton can therefore be incorporated into a constant k. Thus, the energy required for NHC formation is given by $\Delta E = E_2 - E_1 + k$.

The energy of deprotonation ΔE to form a NHC is therefore directly related to $E_2 - E_1$, and using DFT calculated energy values (E + ZPE) in the gas phase for precursor and NHC product, this can be used as an easily derived index for comparison of the ease of formation, and conversely the σ -bonding potential, of a diverse range of NHCs. The index is a measure of the energy required to break heterolytically a C−H bond. For closely related heterocycles with similar solvation, it is a quantitative indicator of the relative ease of NHC formation. It shows the dependence of the carbene−precursor energy gap on the electronic structure of the precursor and is an indicator of the trends in ease of NHC formation by C−H (or C−C) bond cleavage and of NHC σ-donor strength. We refer to this index as the Carbene Relative Energy of Formation (CREF) index: CREF = $E_2 - E_1$. The unit of this quantity is 1 hartree or 1 au of energy. In the following section, we discuss the variation of the CREF index with structure and substituents of a representative selection of neutral and anion NHCs.

2. RESULTS AND DISCUSSION

2.1. Neutral N-Heterocyclic Carbenes. *2.1.1. Five-Membered Rings (Table 1).* Table 1 shows calculated CREF values for NHC structures derived from imidazolium (entries 1−12) and pyrazolium (entries 13−19) precursors. Normal NHCs (nNHC) can be represented by sextet structures; those with two α-heteroatoms are described as classical nNHCs (Table 1, A(i)) and those with one α-heteroatom are described as nonclassical nNHCs (Table 1, B(i)). Abnormal NHCs (aNHC) can only be represented by dipolar resonance forms (Table 1, A(ii)). Remote NHCs (rNHC) describe NHCs with no heteroatom adjacent to the carbene center (Table 1, B(ii)).[3] It is well established that aza substitution stabilizes NHCs and that this also weakens their σ-donating properties.[10,12,13] This is reflected in the CREF values of the classical normal NHCs (nNHCs) (entries 1−7) where each aza substitution reduces the CREF values by ca. 0.02 units. In the same series, the abnormal NHCs (aNHCs) (entries 8−12) are more difficult to form with CREF values in the order of 0.03 units higher (cf. entries 1 and 8), but the effect of aza substitution is similar to that in nNHCs, i.e., ca. 0.02 units per nitrogen. It is noteworthy that aromaticity has little effect on CREF values (cf., Table 1, entries 1 and 2) since this is common to both reactant and product.

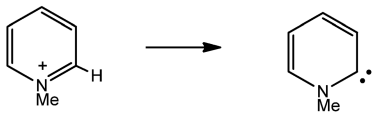
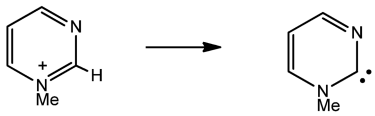
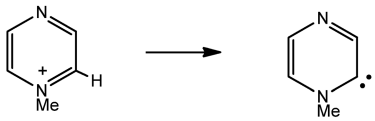
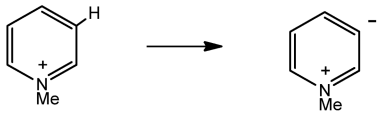
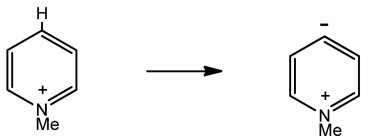
The pyrazolinium series is restricted to nonclassical nNHCs (entries 13−16) and remote NHCs (rNHCs) (entries 17−19). Again, aza substitution facilitates formation of the NHCs, but the effect is smaller when the pyridine-type nitrogen is adjacent to the carbene center (cf. entries 14 and 15). This effect has been previously recognized, notably by Bernhammer and co-workers[12] in their detailed computational study of 14 five-membered NHCs and is attributable to a destabilizing interaction between adjacent nitrogen and carbene lone pairs.

Comparison of CREF values of pairs of isomers in Table 1 reveals that nonclassical NHCs are significantly more difficult to generate than their classical isomers (cf. entries 1 and 13). However, they are easier to generate than aNHCs (cf. entries 8 and 13). Remote NHCs are particularly unstable (entries 17−19) but will be good σ-donors.

On the basis of these results (Table 1), we conclude that the easily calculated CREF index provides a convenient and reliable measure of the ease of formation and σ-donating properties of five-membered NHCs and that the results are in accord with detailed computational studies of selected systems.[10,12,13]

2.1.2. Six-Membered Rings (Table 2). Extension of the study to six-membered rings reveals that generation of a nonclassical nNHC at the 2-position of a pyridinium ring (CREF 0.429; Table 2, entry 1) is comparable in energy to the formation of a five-membered nonclassical nNHC (CREF 0.433; Table 1, entry 13). This is consistent with the experimental observation of pyridine-2-ylidenes as reactive intermediates.[14] The results in Table 1 suggest that a CREF value of ≤0.414 is necessary for isolation and that this may also require steric effects. In a similar manner as noted for five-membered rings (Table 1), aza substitution adjacent to the carbene center lowers the CREF value by 0.007 but not by as much as a remote nitrogen (0.018) (cf. Table 2, entries 2 and 3). The pyridine-3-ylidene and −4-ylidene (entries 4 and 5) are less stable than the pyridine-2-ylidene (entry 1) by ∼0.0235 CREF units. Since each 0.01 CREF unit corresponds to 0.01 hartree or 6.2 kcal mol^{-1}, this corresponds to an energy difference of ∼14.6 kcal mol^{-1}, which is in good agreement with previously reported values of ∼15 kcal mol^{-1}.[14]

Table 2. Neutral Six-membered NHCs

Entry	PRECURSOR	NHC	E + ZPE[a,b]	CREF
	Pyridinium NHCs			
	(i) Non-Classical Normal NHCs (nNHCs)			
1			-287.914638 -287.485596	0.429
2			-303.954187 -303.531961	0.422
3			-303.944385 -303.533061	0.411
	(ii) Remote NHCs (rNHCs)			
4			-287.914638 -287.463219	0.451
5			-287.914638 -287.460234	0.454

[a]Hartrees. [b]The first value relates to the reactant and the second to the product.

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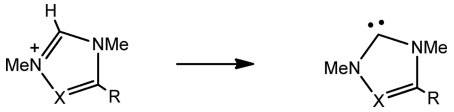
2.1.3. Substituent Effects (Table 3). The influence of ring substituents on NHCs is of some interest. Table 3 shows

Table 3. Substituent Effects on Imidazol-2-ylidenes



entry	R	X	E + ZPE[a,b]	CREF
1	H	CH	−305.167859	0.413
			−304.754800	
2	OH	CH	−380.407772	0.418
			−379.990174	
3	F	CH	−404.426261	0.404
			−404.021778	
4	CF_3	CH	−642.294862	0.397
			−641.897708	
5	NO_2	CH	−509.696948	0.387
			−509.309591	
6	NHPh	CH	−591.552957	0.419
			−591.133850	
7	NHPh	N	−607.596634	0.405
			−607.191884	
8	F	CF	−503.679730	0.396
			−503.284024	
9	benzo[*d*]		−458.807782	0.412
			−458.395628	
10	pyrimidino[4,5-*d*]		−490.900933	0.395
			−490.506133	

[a]Hartrees. [b]The first value relates to the reactant and the second to the product.

calculated CREF index values for a series of substituted imidazole-2-ylidenes. Relative to the parent system (entry 1), rings with σ-electron-withdrawing substituents (F, CF_3, and NO_2) lower the CREF index, presumably due to an inductive effect lowering the energies of the σ orbitals. In contrast, π-donating substituents (OH and NHPh) have a small but adverse effect. The F substituent possessing strong σ-electron-withdrawing and weak π-donating properties shows a moderate CREF-lowering effect. It might be expected that the resonance effect due to an amino substituent would contribute to the stabilization of the π-deficient carbene center, but a similar effect will also stabilize the cationic precursor. The net effect is therefore small but negative (Table 3, entries 1 and 6). A benzo substituent has no effect, and benzimidazolylidene (entry 9) has the same CREF index as imidazolylidene (entry 1). Although remote, the two extra ring nitrogens in the purine analogue (entry 10) significantly lower the CREF value.

2.2. Anionic N-Heterocyclic Carbenes (Table 4). In addition to neutral NHCs (Tables 1-3), anionic NHCs are of current interest. They are generated by deprotonation of heterocyclic mesomeric betaines (HMBs),[15] and CREF values for representative examples are reported in Table 4. HMBs can be divided into three fundamentally different classes; these are conjugated, cross-conjugated, and semiconjugated HMBs.[16,17] The examples shown in Table 4 are divided into the three classes and then subdivided according to NHC type.

A direct comparison between CREF index values for neutral and anionic NHCs must be treated with caution since the solvation profile for precursors and products will differ significantly. In addition, some anionic NHCs are in association with a metal ion (e.g., Li^+), and this will modify the properties. In general, the calculated CREF values for anionic NHCs are considerably higher (Table 4) than those for neutral NHCs (Tables 1−3). This increase is related to the energetic cost of charge separation when the proton and anionic carbene are separated. Nevertheless, the same structural trends are observed as for neutral NHCs.

2.2.1. Conjugated Heterocyclic Mesomeric Betaines (Table 4A). For conjugated HMBs, the classical nNHCs (Table 4, entries 1−7) are formed more easily than nonclassical nNHCs (entries 8−11). For both types, the effect of aza substitution is slightly smaller than for neutral systems. Since examples of anionic imidazole-2-ylidene-4-olates (entry 1) have been generated quantitatively (using lithium bis(trimethylsilyl)amide at 0 °C) and trapped,[18,19] the CREF value (0.576) is a marker for accessible anionic carbenes. In this context, in addition to other type A[20] mesoionic precursors (entries 2−4),[21] the bicyclic classical nNHC (CREF value (0.573) shown in entry 5 (and its aza analogues) may be of some interest; as far as we are aware, the type D[22] heteropentalene HMB precursor and its salts are unknown.[4,22]

The corresponding nonclassical anionic nNHCs (Table 4, entries 9−11), like their neutral analogues (Table 1) are less stable with CREF values >0.6, and the aNHCs and rNHCs (Table 4, entries 12−14) have similarly high values.

2.2.2. Cross-Conjugated Heterocyclic Mesomeric Betaines (Table 4B). The anionic NHCs derived from cross-conjugated HMBs (Table 4, entries 15−18) are of particular interest for two reasons: (i) the CREF index values are among the lowest of the anionic NHCs studied, and (ii) 1,3-dimesityl analogues of the NHCs shown in entries 15 and 16 have been prepared and their ligand binding studied.[23−25] The reason for the relatively low CREF values (0.525−0.550) in these systems may be related to the fact that the charges are cross-conjugated and that the negative charge is restricted to a structural fragment remote from the carbene center. In this context, it is interesting to note that in the bicyclic anionic nNHC shown in Table 4, entry 5, in which the negative charge is not cross-conjugated, the CREF value (0.573) is significantly higher. The lower CREF value for the aza derivative (entry 16) relative to the deaza derivative (entry 15) is consistent with experimental observation of "reduced donicity" of the dimesityl derivative.[25] The anionic systems shown in entries 17 and 18 have not been reported, as far as we are aware, and may be of potential interest as ligands.

2.2.3. Semiconjugated Heterocyclic Mesomeric Betaines (Table 4C). The CREF values for anionic NHCs derived from semiconjugated HMBs (Table 4, entries 19−22) are relatively high, and carbenes derived from these systems have not been studied. The examples shown in entries 19 and 20 are formed from type B[20] mesoionic rings. They have CREF values ∼0.015 units higher than analogous derivatives of type A mesoionic rings (Table 4, entries 1 and 3). This is in accord with the previously noted difference between CREF values for classical and nonclassical nHMBs (e.g., Table 1, entries 1 and 13).

The results described in Tables 1−4 show consistent trends and allow a direct quantitative comparison of the ease of formation of related NHC products. In the light of these CREF values, it is instructive to consider the experimental examples described in the introduction. For the salt **2**, the

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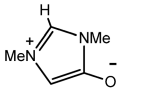
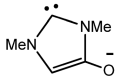
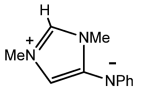
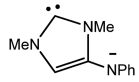
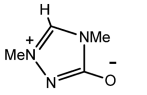
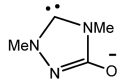
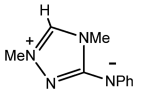
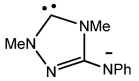
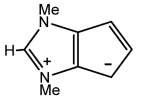
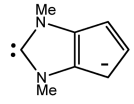
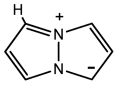
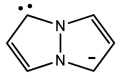
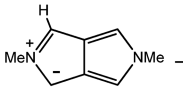
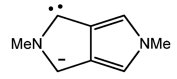
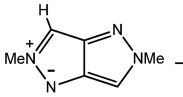
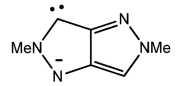
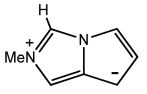
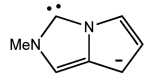
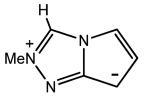
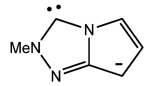
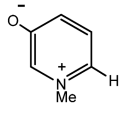
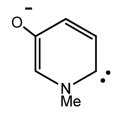
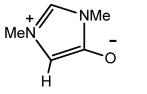
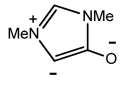
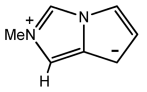
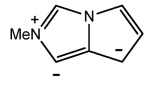
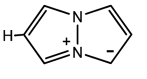
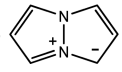
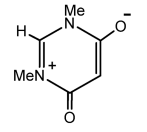
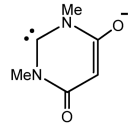
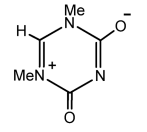
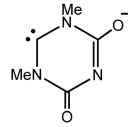
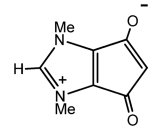
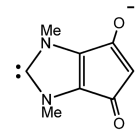
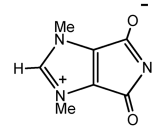
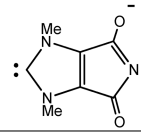
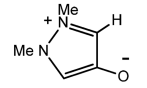
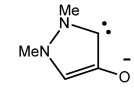
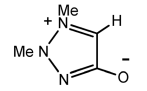
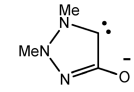
Table 4. Anionic NHCs

Entry	PRECURSOR	NHC	E + ZPE[a,b]	CREF
A	**Conjugated HMBs**			
	(i) Normal NHCs (nNHCs)			
1			-380.031212 -379.455354	0.576
2			-591.144114 -590.587129	0.557
3			-396.086832 -395.525576	0.561
4			-607.199918 -606.655000	0.545
5			-420.252178 -419.679517	0.573
6			-341.649633 -341.040059	0.610
7			-420.262979 -419.639794	0.623
8			-452.362596 -451.760589	0.602
9			-380.965021 -380.379741	0.585
10			-397.015825 -396.446608	0.569
11			-362.777677 -362.187415	0.590
	(ii) Abnormal and Remote NHCs			
12			-380.031212 -379.412162	0.619
13			-380.965021 -380.359028	0.606
14			-341.649633 -341.026813	0.623
B	**Cross-Conjugated HMBs**			
15			-493.409989 -492.862803	0.547
16			-509.475309 -508.937309	0.538
17			-569.564356 -569.028128	0.536
18			-585.634974 -585.108588	0.526
C	**Semi-Conjugated HMBs**			
19			-379.968398 -379.374961	0.593
20			-396.019791 -395.444815	0.575
21			-493.382770 -492.804968	0.578
22			-509.417466 -508.861155	0.556

[a]Hartrees. [b]The first value relates to the reactant and the second to the product.

CREF index values for deprotonation at positions 1 and 3 are 0.444 and 0.416, respectively (Table 1, entries 5 and 12). This corresponds to an energy difference of 0.028 hartree or 17.4 kcal mol^{-1}. Under the conditions of the experiment (MeO^-Na^+/MeOD), these CREF values are entirely consistent with the observation of deuterium exchange in salt **2** at position 3 and no exchange at position 1. The position of protonation of the precursor salt makes no difference to the conclusion (Table 1, entries 5 and 6).

The formation of NHC products by the type A mesoionic molecule Nitron **4**[5] and related systems[26] under mild conditions (THF, room temperature) is of some interest. On the basis of ring substituent effects, we have tentatively suggested that this may occur via the anionic nNHC **6**.[27] However, this did not take into account related substituent effects in the precursor **4**, which are inherent in the CREF index. On the basis of the CREF value for the dimethyl analogue (0.545) (Table 4, entry 4), this value seems rather

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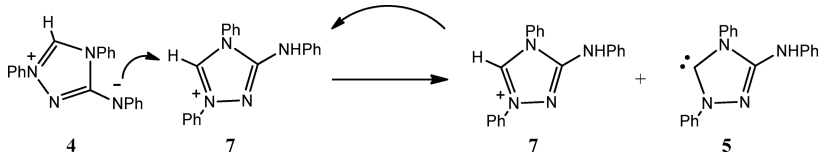
Scheme 1



high to account for anion carbene formation under the mild experimental conditions: formation of anionic NHCs usually requires a strong inorganic base. Nitron is a base (pK_{aH} 10.34),[28] and its use as an analytical reagent involves formation of a nitrate salt. A more plausible mechanism requires the presence of a trace of Nitron salt. The CREF value for the triazolium cation **7** (0.405)(Table 3, Entry 7) is sufficiently low for it to be feasible that Nitron **4** may itself deprotonate the cation **7** to form the transient NHC **5** (Scheme 1), which is rapidly trapped. This transformation regenerates cation **7** perpetuating the reaction until all of the Nitron **4** has been consumed.

Although the CREF indexes relate to the cleavage of C−H bonds, they are also relevant to heterolytic cleavage of other σ bonds leading to NHC formation, e.g., decarboxylative cleavage of C−CO_2^- bonds. In this context, it is informative to consider the CREF values related to decarboxylation of the pyrazolium carboxylates **8** and **9**. The corresponding values are **8** (0.433) (Table 1, entry 13) and **9** (0.458) (Table 1, entry 17). The difference in CREF values is entirely consistent with their relative ease of decarboxylation.

3. CONCLUSIONS

We have described an easily calculated, energy-based index (CREF) that facilitates a quantitative comparison of the ease of formation and σ-donor strength (excluding steric effects and metal to ligand π bonding) of a diverse set of NHCs. We believe that this index has merit for (i) comparing and rationalizing the properties of NHCs, (ii) directing attention to new heterocyclic systems of potential interest and tuning the properties of known systems, and (iii) may also be useful as a teaching aid.

4. COMPUTATIONAL DETAILS

The DFT calculations were carried out by using the Gaussian 09 program,[29] and the hybrid B3LYP functional[30,31] accompanied by the 6-311++G(d,p) basis set[32] was employed. All geometry optimizations were performed as the gas phase calculations and were followed by frequency calculations to ensure that the stationary points obtained were true minima on the potential energy surface and to calculate the zero-point vibrational corrections (ZPE) to energy. These ZPE-corrected values were subsequently used for calculation of the CREF index. As this index is based on energy, it depends on the theoretical method employed. However, the use of relative energy effectively minimizes this dependence.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01304.

Atom coordinates and absolute energies of calculated structures (PDF)

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Notes

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