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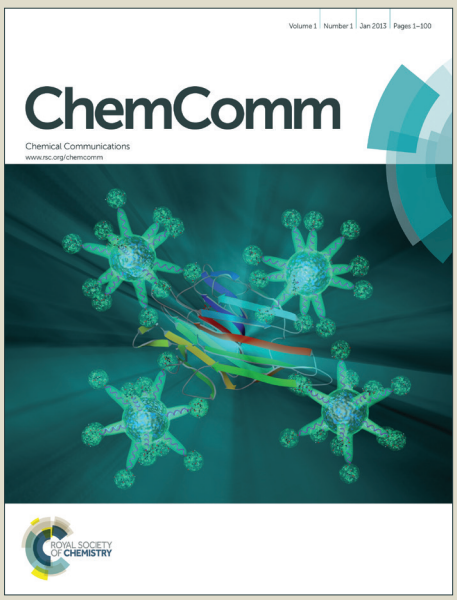

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ARTICLE

Unique Prototropy of *meso*-Alkylidenyl Carbaporphyrinoid Possessing one *meso*-Exocyclic Double Bond

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A generic synthesis, identification of structural identity, unique prototropy and spectroscopic properties of *meso*-alkylidenyl-thia(*m*-benzi)porphyrinoid containing one exocyclic double bond at the *meso*-position were presented.

In recent years, the chemistry of porphyrins and their congeners including isomeric porphyrins, aromatic and nonaromatic analogues, expanded porphyrins has drawn immense attention owing to their unique photophysical properties. Due to their unique structural and spectroscopic features, these macrocycles find potential applications in various areas including anion recognition,[1] photodynamic therapy (PDT)[2] and materials science.[3] The core modified congeners of porphyrins such as carbaporphyrinoids[4] and their metal complexes[5], pyridine containing porphyrinoids[6] and thia- or oxa-porphyrinoids[7] are of particular interest in the context of in-depth understanding of spectroscopic features and macroaromaticity. For instance, benziporphyrinoids or pyriporphyridoid[8,9] bearing a benzene or pyridine ring as a part of the core did not display porphyrin like macro-aromatic properties due to disruption of full macrocyclic conjugation pathway. However, it has been established empirically that the presence of tautomerizable functionality can enable these systems to be aromatic.[10] This type of tautomerism is unique and plays an important role in the electronic structures as well as the photophysical properties of these porphyrins. The NH tautomerism of porphyrin families have been well studied while the NH↔CH tautomerism has not been studied well. Thus, it would be important to develop related model systems for in-depth understanding of this tautomeric phenomenon. With these regards, we herein report synthesis and unique prototropy of a novel porphyrinoid system bearing only one exocyclic double bond at *meso*-position. This is the first example of *meso*-alkylidenyl porphyrin bearing single *meso*-exocyclic double bond reported thus far.[11-14] Recently, we reported the synthesis and spectroscopic properties of *meso*-alkylidene-porphyrins, including *meso*-alkylidenyl-thia(*m*-benzi)porphyrins and *meso*-alkylidenyl-thia(*p*-benzi)porphyrins, containing stable exocyclic C-C double bonds at multiple *meso*-positions and π-extension chemistry of those porphyrins.[15] The observations made with these studies revealed that these porphyrinoids are devoid of porphyrin-like global aromatic character. In addition to the presence of six membered ring(s), the exocyclic double bond at *meso*-positions interrupt the full macrocylic π-conjugation pathway. Moreover, in some cases different tautomeric forms were also isolated.[15a] The unusual features of these modified porphyrinoids inspired us to synthesize new *meso*-alkylidenyl porphyrinoids bearing only single exocyclic C-C double bond at a *meso*-position. Such system would constitute excellent model systems to probe the relationships between global aromaticity and stabilizing/destabilizing effect of the exocyclic double bond and peripheral substituents. Accordingly, herein we report, for the first time, a generic synthesis, unique prototropic and spectroscopic properties of *meso*-alkylidenyl-thia(*m*-benzi)porphyrin containing one exocyclic C-C double bond at the *meso*-position. The synthetic methodology adopted for the synthesis of **6** and **7** is depicted in Scheme 1. The Weinreb amide **1** was reduced to **2** with lithium aluminum hydride at -78°C followed by Knoevenagel type condensation with diethyl malonate giving compound **3** in moderate yield. The attempted conversion of the hydroxyl-vinyl derivative **3** to tripyrrane **5** in single step using either $BF_3.OEt_2$ or TFA was not successful. However, **5** was successfully synthesized in stepwise manner. Treatment of **3** with an excess of pyrrole in the presence of $InCl_3$ resulted in the formation of **4**, which on subsequent reaction with excess of pyrrole in the presence of $BF_3.OEt_2$ at 65°C afforded tripyrrane **5** in appreciable yield. Only a trace amount of **5** was formed, when the reaction was run at room temperature. The ^1H and ^{13}C NMR spectral analysis of **4** and **5** indicate the existence of diastereomers. Acid catalyzed, [3+1] type condensation of tripyrrane **5** and 2,5-bis-thiophene-dimethanol **12** followed by DDQ oxidation afforded the desired *meso*-alkylidenyl-thia(*m*-benzi)porphyrin **6** in 5% yield. The partially oxidized phlorin type compound **7** was also isolated in 2% yield. The phlorin type is a hybrid class of molecule having intermediate structural features between porphyrin and porphyrinogen.[16,17] In contrast to the other

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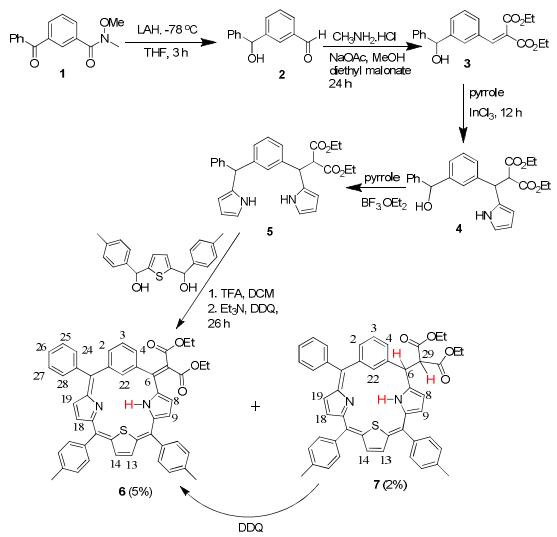
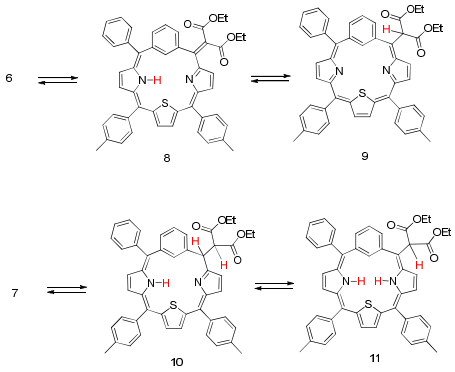
conventional porphyrinoids, phlorins usually exhibit multi-electron redox chemistry.[18] The presence of sp^3-carbon at *meso*-position disrupts the macrocyclic π-conjugation and as a result, the spectroscopic properties are different from those of porphyrins. Phlorin type **7** was easily reoxidized upon treatment with DDQ affording porphyrin **6**. However, attempted conversion of porphyrin **6** to phlorin **7** by simple reduction ($NaBH_4$) was not successful.

Scheme 1. Synthesis of compounds **6** and **7**



Compounds **6** and **7** are not expected to display macro-aromatic character. The presence of exocyclic double bond at *meso*-position is expected to be distorted due to the steric congestion between malonyl group and adjacent benzene ring. In order to reduce such steric hindrances, either the ester functionalities must be distorted or the benzene ring must be out of plane. The presence of tetrahedral *meso*-carbon in **7** interrupts the macrocyclic conjugation. In addition, both **6** and **7** can exist in several different tautomeric forms such as **8**/**9** and **10**/**11** as shown in scheme 2. However, only **6** and **7** were isolated under the conditions applied. These results indicate that the structures **6** and **7** are energetically favorable among the other possible tautomeric forms. Molecular mechanics calculations at M062X/6-31G (d,p) level revealed that the relative energies of **8** and **9** are 2.83 and 13.5 kcal/mol higher than that of **6**, while tautomer **7** was found to be 1.02 and 4.44 kcal/mol more stable than **10** and **11**, respectively (SI).[19] The structures of the macrocycles **6** and **7** were fully confirmed by spectroscopic methods. For example, MALDI-TOF mass spectra of compounds **6** and **7** showed different fragmentation pattern. Compound **6** shows molecular ion peak at 752.5 ($C_{49}H_{40}N_2O_4S$, M^+) and compound **7** shows 754.6 ($C_{49}H_{43}N_2O_4S$, M^++H). Noticeably, compound **6** showed a major fragment ion at m/z 708.5 corresponding to the loss of ethoxy group**,** while in the case of **7**, a fragmentation ion at 596.6 was observed corresponding to the loss of the diethylmalonyl group. ^{1}H NMR spectrum of compound **7** taken in DMSO-d_6 showed a single pyrrole N-H signal at 10.27 ppm indicating the existence of the intramolecular hydrogen bonding. The fact that all the resonance lines corresponding to four β-pyrrole-Hs and β-thiophene-Hs show separate signals indicates the asymmetric nature of the compound.

Scheme 2. Possible tautomeric equilibrium of porphyrin **6** and its reduced form **7**.

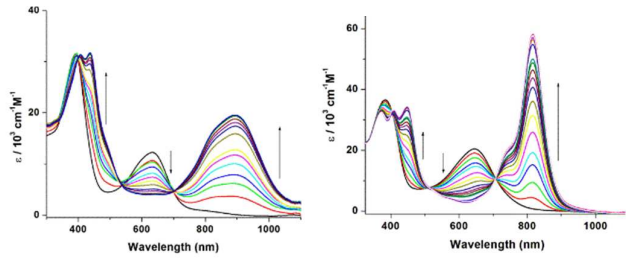


The unambiguous confirmation of the structural identity was obtained by 2D NMR spectroscopy including ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC and NOESY experiments (SI). For example, in compound **7**, two triplets appearing at 5.98 ppm (J = 3.2/2.7 Hz, 1H) and 6.53 ppm (J = 3.2/2.3 Hz, 1H) in ^{1}H NMR spectrum are assigned as β-pyrrole-Hs that hold the hydrogen. This was further confirmed by ^{1}H-^{1}H COSY spectra which displayed a cross peak correlation between β-pyrrole-Hs and core N-H. The cross-peak between malonyl-α-H resonance (δ 5.05 ppm, appearing as a doublet, J = 12.6 Hz) and *meso*-C-H resonance (δ 4.66 ppm, appeared as broad singlet), led us to conclude that later hydrogen must be attached to the *meso*-carbon adjacent to malonyl group (i.e, C-6). Based on 2D (^{1}H-^{13}C) HSQC experiment, the carbon signals at 53.8 and 44.6 ppm were assigned to α-malonyl carbon (C-29) and *meso*-carbon (C-6), respectively. In the 2D NOESY spectrum, the pyrolic N-H showed cross peak with both *meso*-C-H (H-6) and α-malonyl-C-H (H-29). The pyrrolic β-H at 6.53 ppm (H-8) also displayed cross peak correlation with malonyl C-H (H-29) resonance. The pyrrole N-H also displayed correlation with H-22. These results unambiguously confirmed the position of the core N-H as suggested in structure **7**. The compound having one exocyclic double bond and one core N-H may exist in two different tautomeric forms **6** and **8**. However, no evidence for the existence of the tautomeric forms such as **8**, **9**, **10** and **11** were observed even at low temperature (-60°C). Furthermore, oxidation of compound **7** with DDQ afforded the compound **6** quantitatively. The Uv-vis spectrum of compound **6** displayed a Soret-like band at 392 nm (ε = 3.2 x 10^4 $M^{-1}cm^{-1}$) and a Q-band at 636 nm (ε = 1.2 x 10^4 $M^{-1}cm^{-1}$) in CH_3CN. Dramatic changes in the UV-vis spectrum were observed upon incremental addition of acid (trifluoroacetic acid) to compound **6**. As shown in Figure 1(top), the Soret-like band becomes split with low energy shift appearing at 407 and 436 nm, while the intensity of Q-band decreased and finally disappeared with concomitant emergence of a new broad absorption band centered at ~895 nm. A vivid color change from green to yellow was observed. The absorption spectrum of compound **7** also contains two

absorption maxima, consisting of a Soret-like band at 385 nm (ε = 3.7 x 10^4 $M^{-1}cm^{-1}$) and a Q-band at 645 nm (ε = 2.0 x 10^4 $M^{-1}cm^{-1}$) in CH_3CN (Figure 1(bottom)). Analogous acid titration with TFA resulted in remarkable change in the spectrum. The Soret-like band transformed into three absorption bands at 371, 408 and 447 nm. The Q-band gradually disappeared with increasing concentration of the acid and a strong absorption band appeared at 816 nm with a clean isosbestic point at 707 nm. The original spectra were fully restored upon addition of excess base (triethylamine) in both cases, as would be expected for a reversible protonation–deprotonation process (SI).

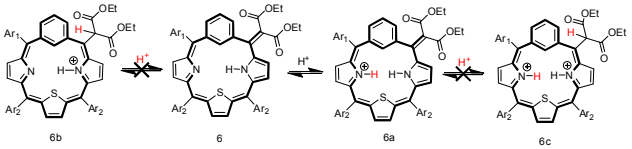
In order to determine the putative protonation site, ^{1}H NMR spectroscopic changes were followed upon addition of TFA in $CDCl_3$/ CD_2Cl_2. Protonation of **6** resulted in dramatic change in the chemical shift of all (pyrrolic and thiophene) β-protons including aromatic protons. Upon the addition of 2.0 equivalent of TFA, all the β-pyrrolic protons shifted to low fields, while the thiophene-Hs (originally appeared as a singlet at 6.8 ppm) became a broad singlet and a doublet appearing at 6.75 and 7.14 ppm (J = 5.3 Hz) respectively. Two N-H signals were also observed at 10.39 and 9.83 ppm.

Figure 1. UV-vis absorption spectral changes of **6** (2.39 x 10^{-5} M) (top trace) and **7** (2.65 x 10^{-5} M) (bottom trace) in CH_3CN observed upon titration with TFA (0 -10 equivalents).



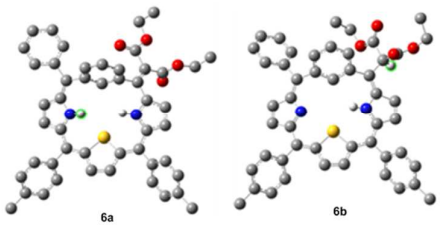
The proton NMR spectral changes upon addition of TFA clearly indicates that the protonation occurs exclusively in the core nitrogen (Scheme 3). No evidence for the protonation at the α-carbon of the malonyl group was observed even after addition of 15.0 equivalent of TFA. ^{1}H NMR spectroscopic analysis of the protonated **7** (TFA/CD_2Cl_2) also indicated that protonation occurs in the macrocyclic core. In the presence of 5.0 equivalents of TFA, two β-pyrrole-Hs originally appearing as two broad singlets at 6.62 and 6.50 ppm, respectively, were shifted to 6.61 and 6.03 ppm, while the other two β-pyrrole-Hs and the thiophene-Hs including aromatic protons was shifted to low field (SI). The fact that the protonation of **6** occurred exclusively in the core but not at the α-position of the diethylmalonyl group stands in marked contrast to what was seen in the *meso*-alkylidenyl-thia(*m*-benzi)porphyrins bearing two exocyclic C-C double bonds reported previously.[15] This observation could be interpreted in terms of a situation where the instability may arise due to the formation of endocyclic double bond (and hence weak anti-aromatic character is expected) upon protonation at the malonyl α-position. These were further rationalized by electronic structure calculations (Figure 2).[19] Electronic energy calculations revealed that the core protonated isomer (**6a**) is more stable by 11.34 kcal/mol than the α-protonated form (**6b**). The origin of the energetic preference for **6a** over **6b** was examined using the NBO analysis.[20]

Scheme 3. Possible protonation sites in porphyrin **6**.



The calculated and localized (or Lewis) energy difference, $\Delta E_L = E_L$(**6a**) - E_L(**6b**) = 283.99 kcal/mol, favors the α-protonated form (**6b**). The steric strain arising between tetrahedral malonyl functionality upon protonation and adjacent aromatic rings may be part of the reason.

Figure 2. Optimized structures of **6a** and **6b** in the gas phase. All hydrogen atoms except for the one originally bound to the nitrogen atom and the newly added one (highlighted in green color) were omitted for clarity.

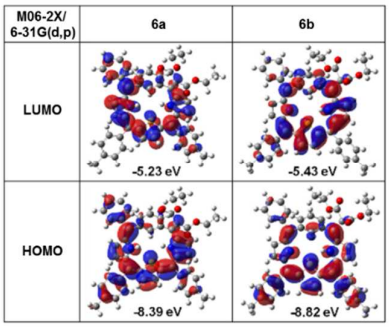


However, the delocalized (or non-Lewis) energy difference, $\Delta E_{NL} = E_{NL}$(**6a**) - E_{NL}(**6b**) = -295.33 kcal/mol, strongly favors the core-protonated form (**6a**), eventually making **6a** more stable than **6b**. This delocalization contribution to the total energy difference between **6a** and **6b** is also confirmed by the frontier molecular orbital (MO) energies and molecular electrostatic potential (MEP) maps for the both compounds. As shown in Figure 3, the HOMO-LUMO energy gap for **6a** (3.16 eV), which is smaller than that for **6b** (3.39 eV), indirectly demonstrates that the electrons in **6a** are more delocalized because electronic delocalization reduces the energy gap between HOMO and LUMO. The MEP maps for **6a** and **6b** also indicate that the electrons of **6a** are more delocalized than that of **6b** (SI).

In summary, we have demonstrated that *meso*-alkylidenyl-thia-(*m*-benzi) porphyrin **6** containing single exocyclic C-C double bond and its reduced form, a phlorin type **7** are readily prepared in one-pot reaction. The spectroscopic properties of these phorphyrinoids are consistent with the predicted non-aromatic character and partially conjugated electronic structure. The non-aromatic character of **6** is attributed to the steric repulsion between malonyl group and benzene ring. Resulting tilted disposition of benzene ring prevents complete planarity of the system. Also, the presence of electron withdrawing bulky malonyl function at the bridging *meso*-position results in stabilization of the tautomer containing exocyclic C-C double bond. On the other hand, core-modified phlorin type **7** containing one sp^3*meso*-carbon bears disrupted macrocyclic conjugation pathway. When treated with acid, both compounds showed exclusive core protonation accompanying a dramatic color

change from green/bluish green to yellow, which could be reversed by the addition of Et_3N. Moreover, the synthetic methodology developed in this study would enable to synthesize the similar porphyrinoid systems with different spectroscopic properties and thus could facilitate the in-depth understanding of the relationship between macro-aromaticity and the porphyrin ring distortion.

Figure 3. Isodensity surfaces of HOMO and LUMO for **6a** and **6b** and their energy values.



It is also noteworthy to mention that the phlorin type **7** has one stereogenic center. Therefore, the synthetic approach adopted in this study could also find application in the synthesis of chiral calixphyrins that have potential application in the recognition of chiral anionic substrates.[24]

Acknowledgements

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Notes and references

1 J. L. Sessler, P. A. Gale, W. S. Cho, *Synthetic Anion Receptor Chemistry*; Royal Society of Chemistry: Cambridge, 2006; pp 131.

2 (a) B. G. Maiya, A. Harriman, J. L. Sessler, G. Hemmi, T. Murai, T. E. Mallouk, *J. Phys. Chem*., 1989, **93**, 8111. (b) J. L. Sessler, G. Hemmi, T. D. Mody, T. Murai, A. Burrell, S. W. Young, *Acc. Chem. Res.,* 1994, **27**, 43. (c) J. L. Sessler, R. A. Miller, *Biochem. Pharmacol.* 2000, **59**, 733.

3 (a) J. L. Sessler, T. D. Mody, G. W. Hemmi, V. M. Lynch, S. W. Young, R. A. Miller, *J. Am. Chem. Soc.,* 1993, **115**, 10368. (b) J. M. Lim, Z. S. Yoon, J.-Y. Shin, K. S. Kim, M.-C. Yoon, D. Kim, *Chem. Commun.,* 2009, 261. (c) J.-Y. Shin, K. S. Kim, M.-C.Yoon, J. M. Lim, Z. S. Yoon, A. Osuka, D. Kim, *Chem. Soc. Rev.,* 2010, **39**, 2751.

4 (a) T. D. Lash, *Synlett.,* 2000, 279. (b) T. D. Lash, *The Porphyrin Handbook,* ed. K. Kadish, K. M. Smith, R. Guilard, Academic Press, 2000, vol. 2, pp. 125; (c) H. Furuta, T. Asano, T. Ogawa, *J. Am. Chem. Soc.*, 1994, **116**, 767. (d) P. Chmielewski, L. Latos-Grazynski, K. Rachlewicz, T. Glowiak, *Angew. Chem., Int. Ed. Engl*., 1994, **33**, 779.

5 (a) S. Venkatraman, V. G. Anand, S. K. Pushpan, J. Sankar, T. K. Chandrashekar, *Chem. Commun.,* 2002, 462. (b) M. Stepien, L. Latos-Grazynski, T. D. Lash, L. Szterenberg, *Inorg. Chem.*, 2001, **40**, 6892. (c) T. D. Lash, K. Miyake, *Chem. Commun.*, 2004, 178.

6 (a) T. D. Lash, K. Pokharel, J. M. Serling, V. R. Yant, G. M. Ferrence, *Org. Lett.*, 2007, **9**, 2863. (b) R. Mysliborski, L. Latos-Grazynski, *Eur. J. Org. Chem.*, 2005, 5039.

7 (a) C. H. Hung, C. Y. Lin, P. Y. Lin, Y. J. Chen, *Tetrahedron Lett.*, 2004, **45**, 129. (b) P.-Y. Heo, K. Shin, C.-H. Lee, *Tetrahedron Lett.*, 1996, **37**, 197. (c) C.-H. Lee, H.-J. Kim, *Tetrahedron Lett.*, 1997, **38**, 3935. (d) S. K. Pushpan, A. Srinivasan, V. R. G. Anand, T. K. Chandrashekar, A. Subramanian, R. Roy, K.-I. Sugiura, Y. Sakata, *J. Org. Chem.*, 2001, **66**, 153.

8 (a) K. Berlin, E. Breitmaier, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1246. (b) T. D. Lash, S. T. Chaney, D. T. Richter, *J. Org. Chem.*, 1998, **63**, 9076.

9 A. N. Kozyrev, J. L. Alderfer, T. J. Dougherty, R. K. Pandey, *Angew. Chem., Int. Ed.*, 1999, **38**, 126.

10 (a) T. D. Lash, *Angew. Chem., Int. Ed. Engl*., 1995, **34**, 2533. (b) T. D. Lash, S. T. Chaney, *Chem.Eur. J.*, 1996, **2,** 944.

11 W. S. Sheldrick, *J. Chem. Soc., Perkin Trans. 2*, 1976, 453.

12 N. Y. Nelson, C. J. Medforth, R. G. Khoury, D. J. Nurco, K. M. Smith, *Chem. Commun.*, 1998, 1687.

13 L. R. Milgrom, J. P. Hill, G. Yahioglu, *J. Heterocycl. Chem.*, 1995, **32**, 97.

14 C. Otto, E. Breitmaier, *Liebigs Ann. Chem.*, 1991, 1347.

15 (a) E.-K. Sim, S.-D. Jeong, D.-W. Yoon, S.-J. Hong, Y. Kang, C.-H. Lee, *Org. Lett.*, 2006, **8**, 3355. (b) S.-D. Jeong, S.-J. Hong, K.-J. Park, S. Ham, J. L. Sessler, V. M. Lynch, C.-H. Lee, *J. Org. Chem.*, 2007, **72**, 6232. (c) S.-D. Jeong, K. J. Park, H.-J. Kim, C.-H. Lee, *Chem. Commun.*, 2009, 5877.

16 J. L. Sessler, R. S. Zimmerman, C. Bucher, V. Kral, B. Andrioletti, *Pure and Appl. Chem*., 2001, **73**, 1041.

17 W. Dehaen, *Top. Heterocycl. Chem.,* 2010, **24**, 75.

18 (a) A. J. Pistner, G. P. A. Yap, J. Rosenthal, *J. Phys. Chem*. C, 2012, **116**, 16918. (b) A. J. Pistner, D. A. Lutterman, M. J. Ghidiu, Y.-Z. Ma, J. Rosenthal, *J. Am. Chem. Soc.,* 2013, **135**, 6601.

19 For the conformational analysis for **6a** and **6b**, 50 initial structures for each molecule were generated using the MMFF force field as implemented in the Spartan 14 package.[20]. These structures were then optimized with the semi-empirical AM1 method. The 10 lowest energy structures out of 50 structures were selected and further optimized at the M06-2X/3-21G level of theory. On the basis of the calculated results, the 5 lowest energy structures among the 10 structures were chosen and optimized again at the M06-2X/6-31G(d,p). The final lowest energy structure for each molecule was selected and frequency analysis was performed to verify the optimized structure as a minimum. All calculations for the compounds in the gas phase were performed using the Gaussian 09 software package,[23] and visualizations were made by Gauss View 5.[24]

20 Y. Shao et al., *Phys. Chem. Chem. Phys*., 2006, **8**, 3172.

21 M.J. Frisch et al., Gaussian 09 Revision D.01, Gaussian, Inc., Wallingford, CT, 2013.

22 GaussView 5, Gaussian, Inc., Pittsburgh, PA, 2009.

23 NBO 6.0, E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, C. R. Landis, F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison, **2013**.

24 M. Bernatkova, B. Andrioletti, V. Kral, E. Rose, J. Vaissermann, *J. Org. Chem.*, 2004, **69**, 8140.

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