On the Interaction between N-Heterocyclic Carbenes and Organic Acids: Structural Authentication of the First N–H ··· C Hydrogen Bond and Remarkably Short C–H ··· O Interactions**

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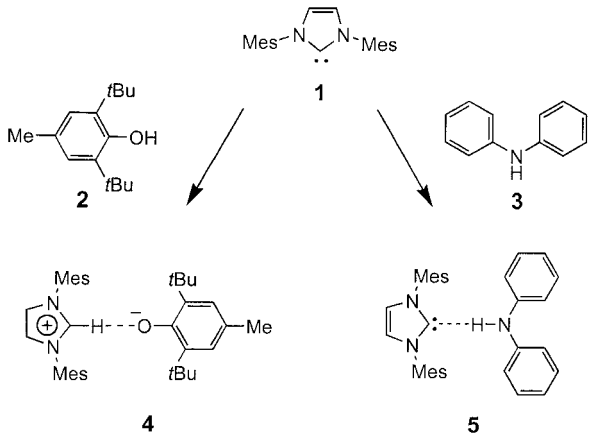
In memory of Ron Snaith

Recently we have shown that protonation of nonstabilized phosphorus ylides with organic acids such as phenols, secondary amines, or secondary phosphanes provides a facile route to hydrogen-bonded organic phosphonium salts.[1] Structural characterization of these salts has revealed extensive C–H ··· O, C–H ··· N, C–H ··· P, and C–H ··· π interactions and has yielded important structural information for the fundamental study of these weak hydrogen bonds. Given the considerable recent interest in the structure and chemistry of stable N-heterocyclic carbenes,[2] and their similar basicity to that of nonstabilized ylides, we felt it would be interesting to employ a similar route for the synthesis of hydrogen-bonded organic imidazolium salts. In particular, an isolated report[3] of a unique C–H ··· C interaction between a carbene and an imidazolium cation suggested the potential of using carbenes to promote unusual interactions in the solid state. Here we report a preliminary synthetic and structural study of the interactions between organic acids and carbenes. Our results include structures containing unprecedented geometries and types of interaction, and also offer a general insight into the interactions of imidazolium salts and stable carbenes with common organic substrates.

The N-heterocyclic carbene 1,3-dimesitylimidazol-2-ylidene (**1**) reacts with both 2,6-di-*tert*-butyl-4-methylphenol (**2**) and diphenylamine (**3**, Scheme 1). As expected, phenol **2** protonates the carbene to give an imidazolium aryloxide, **4**, which contains unusually short C–H ··· O interactions in the solid state. Unexpectedly, however, **1** and amine **3** cocrystallize as a neutral adduct **5**, which contains an unprecedented N–H ··· C interaction.



Scheme 1. Reactions of **1** with phenol **2** and amine **3**. Mes = C_6H_2-2,4,6-Me_3.

Crystals of **4** suitable for X-ray analysis were obtained from toluene solution (see Experimental Section). The crystal structure of **4**[4a] contains two cations and two anions in the asymmetric unit, together with toluene and hexane solvent molecules in the lattice (Figure 1). The structural parameters

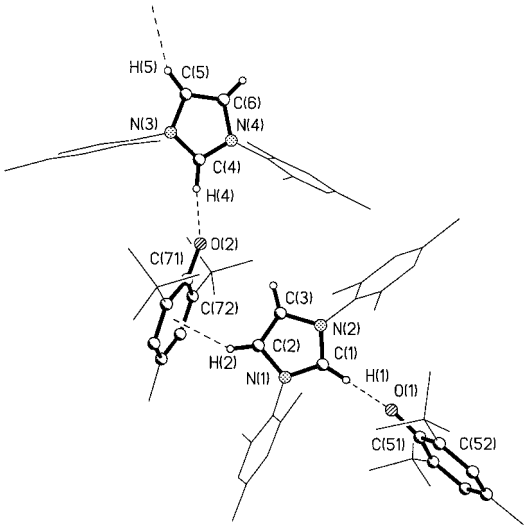


Figure 1. X-ray structure of **4**. For clarity, lattice solvent molecules and H atoms, except those of the imidazolium cation, are not shown whereas methyl, mesityl, and *tert*-butyl groups are shown in outline only. Selected bond lengths [Å] and angles [°]: C(1)-N(1) 1.330(3), C(1)-N(2) 1.342(2), C(2)-C(3) 1.337(3), C(2)-N(1) 1.390(3), C(3)-N(2) 1.390(3), C(51)-O(1) 1.309(2), C(4)-N(3) 1.334(3), C(4)-N(4) 1.339(3), C(5)-C(6) 1.347(3), C(5)-N(3) 1.387(3), C(6)-N(4) 1.393(3), C(71)-O(2) 1.306(2); N(1)-C(1)-N(2) 107.3(2), N(3)-C(4)-N(4) 107.3(2).

within both cation and anion are unremarkable and consistent with those observed previously in other salts,[1a, 3] although **4** is, to our knowledge, the first structurally characterized example of an imidazolium aryloxide. Of more interest are the close contacts between the ions—ion pairs are associated through C–H ··· O interactions:[*] C(1)-H(1) ··· O(1): $D = 2.801(4)$,

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[*] Throughout this paper, geometrical parameters of an interaction D–H ··· A are described with the notation D = D ··· A distance, d = H ··· A distance, and θ = D-H-A angle (in Å and °). Where the acceptor is an aryl ring, A represents the centroid of that ring.

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$d = 1.87(3)$, $\theta = 175(2)$; C(4)-H(4)···O(2): $D = 2.842(4)$, $d = 1.88(3)$, $\theta = 169(2)$. To our knowledge, these interactions are significantly shorter than any previously reported hydrogen bonds between C–H donors and O acceptors.[5] For example, very short and approximately linear C–H···O interactions have been noted in $[(NO_2)_3CH]_2 \cdot$dioxane,[6] ($Ph_3SiC{\equiv}CH \cdot OPPh_3$),[7] and $[(Ph_3PCH_3)^+(2,6\text{-}Ph_2C_6H_3O)^-]$[1a] for which the minimum C···O separations are 2.94, 3.02, and 3.02 Å, respectively. Secondary C–H···π interactions, involving alkenyl C–H groups of cations and the aryl rings of anions, complete the polymeric supramolecular structure of **4** (C(2)-H(2)···X: $D = 3.041$, $d = 2.21$, $\theta = 146$; C(5)-H(5)···X: $D = 3.184$, $d = 2.30$, $\theta = 149$; where X = centroid of C(71)-C(76) and C(51)-C(56), respectively). Similar but longer-range C–H···π interactions have been observed previously for the cation, with a cyclopentadienyl counteranion,[8] and for the anion, with a phosphonium countercation.[1a]

Crystals of **5** suitable for X-ray analysis were obtained by cocrystallization of **1** and **3** from toluene solution (see Experimental Section). In contrast to the salt described above, the X-ray structure of **5**[4b] is unequivocally that of a neutral carbene–amine adduct rather than an imidazolium amide (Figure 2). The H atom was located unambiguously in a difference electron density map derived from the low-temperature X-ray data (Figure 3), and further confirmation comes from observation of an acute N-C-N angle within the C_3N_2 ring which is characteristic of a neutral carbene rather than an imidazolium cation (N(1)-C(1)-N(2) angle, 101.7(1)°; cf. 101.4(2)° in the free carbene[9] and 107.3(2)° in **4**). Thus, the key feature in the structure of **5** is an unprecedented interaction consistent with a N–H···C hydrogen bond (N(3)–H(1)···C(1): $D = 3.196(2)$, $d = 2.30(1)$, $\theta = 179(2)$). Although reminiscent of the C–H···C interaction in a cationic imidazolium–carbene adduct,[3] this is, to our knowledge, the first interaction of its type and also unique in that it involves a classically strong hydrogen bond donor group (that is, D–H contains an electronegative atom) in a "σ" hydrogen bond, together with a carbon-based acceptor.

Taken together, the characterization of **4** and **5** can be viewed as a structural model for the proton transfer from an acidic X–H group to a basic C atom which is significant in relation to the use of stable carbenes as strong bases.[10] The very short, linear interactions observed in **4** and **5** are close in geometry to the expected linear transition state $[X \cdot\cdot H \cdot\cdot C]^{\ddagger}$ for proton transfer in these systems. This correlates well with the fast (on the NMR timescale) proton transfer observed between a carbene related to **1** and its conjugate acid.[10]

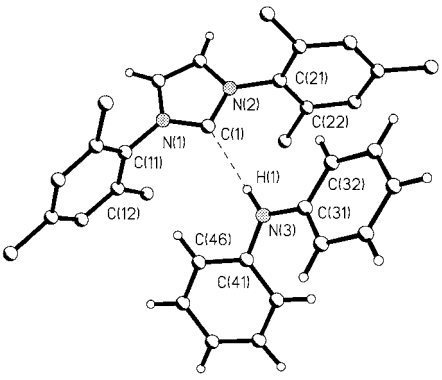

Figure 2. X-ray structure of **5**. For clarity, mesityl group H atoms and C–H···π interactions between phenyl and mesityl groups are not shown. Selected bond lengths [Å] and angles [°]: C(1)-N(1) 1.370(2), C(1)-N(2) 1.373(2), C(2)-C(3) 1.345(2), C(2)-N(1) 1.395(2), C(3)-N(2) 1.394(2), C(31)-N(3) 1.401(2), C(41)-N(3) 1.399(2), C(46)···centroid of C(11)–C(16) 3.808(4), C(32)···centroid of C(21)–C(26) 3.437(4); N(1)-C(1)-N(2) 101.7(1), C(31)-N(3)-C(41) 126.0(1).

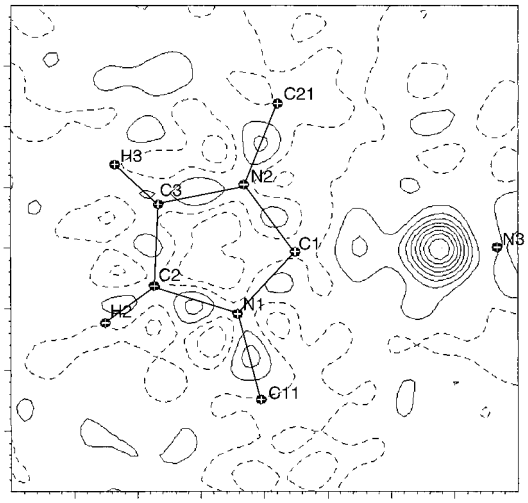

Figure 3. Difference electron density map for the hydrogen-bond region of **5**, in the plane of the carbene ring, showing location of H(1). Contours shown at intervals of 0.1 Å^3 (dashed lines represent negative electron density; min. –0.2, max. 0.92 Å^3).

Our results also have implications for reactions in imidazolium-based ionic liquids.[11] The existence of hydrogen bonds between the cation and the anionic component (e.g., Cl^-, $AlCl_4^-$) of ionic liquids has been recognized.[12] However, the abnormally short interactions between an imidizolium cation and a phenoxide anion found in **4** highlights that basic O- and N-containing species present in ionic liquids will also be in intimate contact with the imidazolium cation through short (and presumably strong) C–H···X interactions. This may have a significant influence on the reactivity of basic reagents and catalysts in ionic liquids.

The carbene character of **5** appears to be retained in hydrocarbon solution (^{13}C NMR in C_6D_6: C(1), $\delta = 215.2$; cf. $\delta = 219.7$ for the carbene centre of **1** in [D_8]THF). This suggests that such adducts may find use as a means of stabilizing carbenes prior to metal complexation. Furthermore, organic imidazolium salts such as **4** are also attractive precursors for the generation of novel carbene-complexed organometallic species. We are currently investigating these and other aspects of the chemistry and structure of organic imidazolium salts and hydrogen-bonded carbene adducts.

Experimental Section

All reactions and manipulations were performed under an atmosphere of dry argon by using standard Schlenk and glovebox techniques. Solvents were distilled over appropriate drying agents and degassed prior to use. **1** was prepared as described in the literature;[9] **2** and **3** were purchased from Aldrich.

4: **1** (0.58 g, 1.9 mmol) and **2** (0.42 g, 1.9 mmol) were dissolved in warm toluene (5 mL). Overnight and at room temperature the resulting solution yielded a crop of yellow needles. First batch yield 0.91 g (91 %), mp. 197–

199 °C. Elemental analysis (%) calcd for $C_{36}H_{48}N_2O$: C 82.39, H 9.22, N 5.34; found: C 80.43, H 9.37, N 5.12; ^{1}H NMR (C_6D_6, 300 MHz, 25 °C, TMS): $\delta = 1.50$ (s, *t*Bu, 18H), 2.23 (s, Me, 18H), 2.36 (s, Me, 3H), 6.49 (s, C=CH, 2H), 6.63 (br s, NCHN, 1H), 6.88 (s, *m*-ArH, 4H), 7.17 (s, ArH, 2H) ppm.

5: **1** (0.30 g, 1.0 mmol) and **3** (0.17 g, 1.0 mmol) were dissolved in toluene (5 mL) by gentle warming. Overnight and at room temperature the resulting solution yielded a crop of orange crystals. First batch yield 0.18 g (38%), mp. 158–162 °C. Elemental analysis (%) calcd for $C_{33}H_{35}N_3$: C 83.68, H 7.45, N 8.87; found: C 82.85, H 7.37, N 8.92; ^{1}H NMR (C_6D_6, 300 MHz, 25 °C, TMS): $\delta = 2.25$ (s, *o*-Me, 12H), 2.26 (s, *p*-Me, 6H), 5.92 (br s, NH, 1H), 6.55 (s, C=CH, 2H), 6.90 (s, *m*-MesH, 4H), 6.96, 7.18, 7.26 (m, ArH, 10H) ppm.

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[4] a) Crystal data for **4**: $C_{167}H_{229}N_8O_4$, colorless block of dimensions $0.2 \times 0.2 \times 0.1$ mm^3, trigonal, $P\bar{3}$, $a = 27.008(9)$, $c = 17.684(9)$ Å, $V = 11171(8)$ Å^3, $Z = 3$, $\rho_{calcd} = 1.076$ g cm^{-3}. Data collected on a Bruker Smart diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) and ω scans at $T = 100(2)$ K, $2\theta_{max} = 54.96°$, 121949 reflections measured, of which 17075 independent ($R_{int} = 0.0557$), $\mu = 0.063$ mm^{-1} (no absorption correction). Structure solved by direct methods (SHELXS-97)[13] and refined on F^2 by full-matrix least-squares (SHELXL-97),[13] 867 parameters, $R_1 = 0.0597$ (11562 data $I > 2\sigma(I)$), $wR_2 = 0.1852$ (all data). H atoms were placed in calculated positions with a riding refinement, except those involved in hydrogen bonding which were refined freely and isotropically. Site occupancy of lattice hexane solvent was estimated to be 0.75 and fixed at that value. b) Crystal data for **5**: $C_{33}H_{35}N_3$, yellow needle of dimensions $0.5 \times 0.3 \times 0.2$ mm^3, triclinic, $P\bar{1}$, $a = 9.663(2)$, $b = 10.578(2)$, $c = 14.967(3)$ Å, $\alpha = 80.60(3)$, $\beta = 71.68(3)$, $\gamma = 67.72(3)°$, $V = 1342.3(5)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.172$ g cm^{-3}. Data collected on a Bruker Smart diffractometer with $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å) and ω scans at $T = 30(2)$ K, $2\theta_{max} = 54.34°$, 11025 reflections measured, of which 5307 independent ($R_{int} = 0.0285$), $\mu = 0.069$ mm^{-1} (no absorption correction). Structure solved by direct methods (SHELXS-97)[13] and refined on F^2 by full-matrix least-squares (SHELXL-97),[13] 465 parameters, $R_1 = 0.0376$ (4412 data $I > 2\sigma(I)$), $wR_2 = 0.0991$ (all data). All H atoms were refined freely and isotropically. CCDC-161117 and CCDC-161118 (**4** and **5**, respectively) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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An Efficient Stereoselective Total Synthesis of DL-Sesquicillin, a Glucocorticoid Antagonist**

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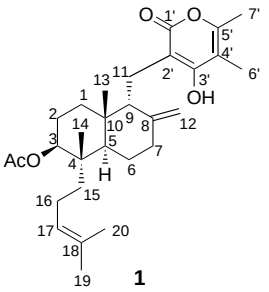
Sesquicillin is a C29 isoprenoid-related fermentation product isolated from *Acremonium* sp., strain 132-94.[1] The compound was first identified through screenings directed at the discovery of new agents that inhibit glucocorticoid-induced gene expression in suitably engineered COS-7 cells ($IC_{50} = 0.1–0.5$ μg). In principle, sesquicillin could function as a glucocorticoid antagonist.[2] Also, antihypertensive and bronchospasmolytic properties have been ascribed to sesquicillin in patent disclosures.[3] It is only relatively recently that the gross structure and stereochemistry of sesquicillin have been assigned to be **1**, largely on the basis of detailed NMR spectroscopic measurements. As such, sesquicillin bears a striking resemblance to subglutinols A and B.[4] We hoped that a total synthesis of sesquicillin would allow access to the natural product and its analogues. In this way, we could begin to evaluate the potential of this particular type of glucocorticoid antagonist in projected applications.



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