Mapping of N–C Bond Formation from a Series of Crystalline Peri-Substituted Naphthalenes by Charge Density and Solid-State NMR Methodologies

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Abstract: A combination of charge density studies and solid state nuclear magnetic resonance (NMR) $^{13}J_{NC}$ coupling measurements supported by periodic density functional theory (DFT) calculations is used to characterise the transition from an n–π* interaction to bond formation between a nucleophilic nitrogen atom and an electrophilic sp$^2$ carbon atom in a series of crystalline peri-substituted naphthalenes. As the N–C distance reduces there is a sharp decrease in the Laplacian derived from increasing charge density between the two groups. At N–C = 1.8 Å, with the periodic DFT calculations predicting, and heteronuclear spin-echo NMR measurements confirming, the $^{13}J_{NC}$ couplings of $\geq 3$–6 Hz for long C–N bonds (1.60–1.65 Å), and $^{13}J_{NC}$ couplings of $< 1$ Hz for N–C $> 2.1$ Å.

Introduction

The concept of structure in chemistry implies the existence of bonds that can persist over a range of inter-nuclear distances until a point is reached where the bond is considered broken.[1] The formation of bonds is central to our understanding of all chemical processes. In this study, we measure the degree of covalent bond formation in a series of crystalline organic compounds using two complementary solid-state methods. X-ray crystallography and NMR which are both supported by density functional theory (DFT) calculations.

Interactions between electrophilic and nucleophilic functional groups separated by a range of interatomic distances, measured by single-crystal X-ray diffraction, can be considered to represent discrete stages in the reaction between such groups.[2] The concept was first developed using transannular amine-carbonyl interactions (with interatomic distances ranging from 1.64 to 2.58 Å) in a series of pyrrolizidine alkaloids, such as senkirkine and clivorine (ESI Scheme S1, structures S1 and S2).[3] It was extended to through-space interactions in peri-disubstituted naphthalenes between dimethylamino or methoxy groups and a ketone, ester or carboxamide electrophile, where small pyramidalizations of the carbonyl carbons were observed.[4] These peri-naphthalene systems can alternatively contain methylthio or naphtholato moieties as electron-rich groups, and alkynes, polarized alkenes or aldehydes as the electron-deficient centre.[5,6] For peri-naphthalenes bearing a dimethylamino (-NMe$_2$) group adjacent to an electrophilic group containing a multiple bond (such as C=O, C=O, or C=N), the naphthalene skeleton can hold the groups close to the optimal orientation for orbital overlap, often referred to as the Bürgi–Dunitz angle, inducing an n–π* interaction which can modify the chemistry of the groups.[4] If the electrophile is sufficiently reactive an intramolecular bond is formed.[7] The inter-group separation can be controlled by adjusting the substituents at the opposing peri positions.[8] n–π* Interactions are particularly important in chemistry, e.g., O–C=O interactions between the carbonyl groups is critical in determining conformations of proteins (such as collagen), and the role of n–π* interactions in enzymatic processes is only just being recognised.[9] X-ray crystallography of model compounds based on peri-naphthalenes andacenaphthenes have been used to probe the mechanism of nucleophilic attack on silicon and unconventional hydrogen bonding to an amide nitrogen atom.[10]

To study the progression from n–π* interaction to initial bond formation we designed a series of six peri-naphthalenes with a -NMe$_2$ group situated next either to an aldehyde or various alkene functionalized with two terminal electron-attracting groups, outlined in Figure 1, 1–6. X-ray crystallog-
raphy shows the \( \text{Me}_2\text{N} \cdots \text{C} \) distances decrease as the electrophilic strength of the alkene series increases, with the longest for two benzoyl groups terminating the alkene (1; 2.695 Å), then for two nitriles (3; 2.413 Å), and finally three with a cyclic link between the terminal groups: a diester (4; 1.651 Å), a diamide (5; 1.624 Å) and a diketone (6; 1.612 and 1.626 Å).[7,11] The aldehyde has the second-longest interatomic distance in the series (2; 2.481 Å).[12] Notably, for 4–6 the separations correspond to the formation of a particularly long \( \text{N} \cdots \text{C} \) bond (1.612–1.651 Å) which completes a doubly-fused five-membered ring in a zwitterionic structure (cf. a \( \text{Me}_2\text{N} \cdots \text{CHRCO}_2^- \) bond: 1.536 Å, and a typical \( \text{N} \cdots \text{C} \) bond between neutral atoms: 1.47 Å).[13] We have probed the development of \( \text{N} \cdots \text{C} \) peri-bonding in this series of crystals using two complementary solid-state methods:

1. by determination and topological analysis of the charge densities for the six molecules in this series using

\[ \text{Me}_2\text{N} \cdots \text{C} \]

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accurate, high-resolution single crystal X-ray diffraction measurements, which are supported by DFT calculations.

(2) using NMR to directly measure the $^{13}C$ coupling between the two nuclei involved in the interaction in the solid state for isotopically enriched molecules 2, 3, 4 and 6.

For the NMR study, the molecules were prepared with $^{15}N$ (60%) and $^{13}C$ (99%) isotopic labels at the peri positions (ESI). The crystallographically determined couplings are related to the experimentally determined $^{13}C$ couplings using periodic DFT calculations to derive the theoretical coupling constants, thus providing a joint solid-state charge density/NMR approach. The closely-related charge density studies on peri-systems relate to proton sponges and alon along hypervalent bonding in S···S and S···Se situations have also been completed.[14,15] Solid-state $^{13}C$ coupling studies between peri halogenide elements have also been made.[16] However, no combined charge density/$^{13}C$ coupling studies on crystalline peri-naphthalenes have been reported.

**Results and Discussion**

Charge density determinations were made from X-ray diffraction data on high-quality crystals of 1–6 at 100 K, with data for 6 collected using a synchrotron source (Diamond Light Source) on account of small crystal size. Parameters derived from the topological analysis of the charge densities using QTAIM are given in Table 1.[17] Laplacian maps through the molecular plane are shown in Figure 1 with further details, e.g., molecular graphs showing bond paths, and bond and ring critical points, given in the ESI. All structures have a bond (3, −1) critical point between the interacting peri N and C atoms, that is a point where the electron density gradient is zero and is a maximum in two and a minimum in one of three orthogonal directions. As the Me$_2$N—C distance decreases from 2.6758(4) to 1.6070(6) Å, the charge density at this critical point increases dramatically from 0.13 e Å$^{-3}$ in 1, to 1.29 and 1.35 e Å$^{-3}$ in the two distinct crystallographic environments for the cyclic dione 6, which is ca. 80% of the charge density for a typical N—C bond, as observed in the N—Me bonds in 6 (1.55–1.62 e Å$^{-3}$) or seen in tetramethylammonium cations (1.54–1.65 e Å$^{-3}$).[18]

The Laplacian $\nabla^2 \rho$, the second derivative of the charge density with respect to distance, highlights areas of charge concentration and depletion, and thus reveals the fine details of the electronic distribution. The Laplacian maps show an increasing spread of charge concentration between the interacting N and C atoms as their separation distance decreases (Figure 1). For 1–3, the charge concentration on the N atom is representative of the lone pair, but for 4–6, there is contact between the charge concentrations on the N and C atoms. The Laplacian values at the bond critical point (BCP) for 1–3 are small and positive, indicating closed-shell interactions, and increase slightly from 1 to 3 (1.69 to 2.20 e Å$^{-3}$), but decrease strongly from 4 to 6 (−2.92 to −6.73 e Å$^{-3}$), indicating the shared nature of these interactions. However, they do not reach the Laplacian values for typical N—C bonds, as seen in the N—Me moieties in 6 (−8.49 to −9.60 e Å$^{-3}$). Together with charge density data, this suggests that even in 6 the N—C bond in the five-membered ring between peri groups is not fully formed. We note that although in the structural formulae of 4–6 the peri N atom is assigned a charge of +1, the Hirshfeld and QTAIM charges derived from the CD study are much smaller (Hirshfeld: 0.00 to +0.12; QTAIM: −0.18 to −0.98), and the Hirshfeld charges contrast with those for 1–3, which are negative (−0.04 to −0.11), due to the more localized electron lone pair.

The alkene bond under attack from the dimethylamino group extends its length by ca. 0.12 Å from 1.3509(3) and 1.3659(2) Å in 1 and 3 to 1.4687(6) and 1.4737(6) Å in the two crystallographically independent molecules of 6, with a decrease in the charge density at the BCP, from 2.28 and 2.25 e Å$^{-3}$ in 1 and 3 to 1.84 and 1.85 e Å$^{-3}$ in 6. Furthermore, there is a change in the Laplacian from −19.87 and −20.10 e Å$^{-3}$ in 1 and 3 to −14.76 and −14.77 e Å$^{-3}$ in 6. Given that the typical charge density and Laplacian values for a single C—C bond are ca. 1.6 e Å$^{-3}$ and −10 to −12 e Å$^{-3}$, this

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Table 1: The C—N bond distances for 1–6 and S1–S3 in order of decreasing Me$_2$N—C separation, with parameters from the charge density determinations, experimental solid-state NMR $^{15}N$ and $^{13}C$ isotropic chemical shifts, and the GIPAW-DFT calculated $^{13}C$ couplings and isotropic shifts. The DFT isotropic shifts were determined using $\delta_{iso} = -[\delta_{ref} - \delta_{cal}]$, where $\delta_{ref} = 170$ ppm for $^{13}C$ and −153 ppm for $^{15}N$.[17]
suggests that the double bond in 6 has not been fully transformed into a single (σ) bond. There is also a change in the ellipticity of this bond, derived from the CD determination (Section 2, ESI), from 0.29–0.32 for 1 and 3, to 0.13–0.17 for 4–6 which could be interpreted as a reduction in the π component of the bonding, though this approach has been questioned since there is no direct connection between the topological analysis and an orbital based description of bonding.

To provide data for intermediate N···C separations, the charge densities for the alkaloids senkirkine and clivorine, S1 and S2, were determined using B3LYP functionals, a 6–311 + +G** basis set, and atomic coordinates from their reported crystal structures. At the BCPs for their transannular N···C interactions there are small charge concentrations (0.33 and 0.56 e Å⁻³) increasing with decreasing N···C separation, and their Laplacian values (2.26 and 2.13 e Å⁻⁵) are similar to those of the dinitrile 3. Further calculations were completed for 1–6 and reproduced the experimental charge densities at the N···C BCP to within 0.2 e Å⁻³ for 1–5, while for 6 the values were within 0.7 e Å⁻³, though the diffraction dataset for 6 is slightly less extensive and complete than for 1–5. The trend of the Laplacians was also reproduced, though with greater divergence (more negative) for 4–6 (ESI, Figure S27).

The variation of Laplacian with the N···C separation for 1–6 and S1 and S2 (Figure 3), shows a trend which can be fitted with a Morse-like function, which shows a small rise in Laplacian as the N···C distance contracts to ca. 2.1 Å and then

**Figure 2.** The ¹⁵N–¹³C heteronuclear spin-echo intensities (black circles) of the ¹⁵N resonance with an increasing tau (τ) delay for the naphthalenes a) 2, b) 3, c) 4 and d) 6 at 11.75 T (¹H = 500.1, ¹³C = 125.76 and ¹⁵N = 50.69 MHz) and a MAS frequency of (νr) 11 kHz. On each graph the GIPAW-DFT determined Simpson simulated JNC couplings (cyan), T₂ determined from spin-echo experiments (green), and their product (red) are given. The decays follow a cos(τ/τ₂)exp(−τ/τ₂) function. (i, ii, iii and iv) The respective ¹⁵N MAS NMR spectra of structures 2, 3, 4, and 6, those without a bond give a low-frequency resonance (blue) and after a bond has formed a ≈ 50 ppm shift to high frequency (red) is observed.
couplings even when inhomogeneous broadening (Figure 2a and b) both show very shallow exponential decays which are indicative of narrow resonances that are not broadened by $J_{NC}$ coupling contributions. A green simulated fit is given for the $T_2$ decays, with the blue SIMPSON simulation of the periodic DFT determined $J_{NC}$ coupling, and their product is given in red. The observed decay can be reliably fitted to both the $T_2$ decays.

The heteronuclear $^{15}$N-$^{13}$C spin-echo decay for the aldehyde 2 and dimitrile 3 (Figure 2a and b) both show very shallow exponential decays which are indicative of narrow resonances that are not broadened by $J_{NC}$ coupling contributions. A green simulated fit is given for the $T_2$ decays, with the blue SIMPSON simulation of the periodic DFT determined $J_{NC}$ coupling, and their product is given in red. The observed decay can be reliably fitted to both the $T_2$ decays.
component (determined from a homonuclear spin-echo) and $T_2$ with the minor 0.48 or 0.45 Hz $1J_{NC}$ coupling. The origin of these small $1J_{NC}$ couplings is attributed to the weak bonding interaction between the two nuclei.

The zwitterions 4 and 6 both show a more dramatic exponential decay, which cannot solely be attributed to the measured $T_2$ relaxation. The GIPAW-DFT $1J_{NC}$ calculations predict more substantial couplings of 5.88 Hz for 4 and an average of 4.15 Hz for 6. When the cosine of these couplings is multiplied by the exponent of the $T_2$ decay, the red projections (Figure 2c and d) are observed, which are in good agreement with the spin-echo data. The dione 6 has two crystallographically distinct molecules, with Me$_2$N--C distances of 1.607 and 1.625 Å, resulting in $1J_{NC}$ couplings of 3.57 and 4.73 Hz, respectively. It is presumed both sites will give an equal contribution to the spin echo, thus a $1J_{NC}$ coupling of 4.15 Hz was utilised in the simulation. Unfortunately, the summation of the two offset $1J_{NC}$ components dampens the cosine feature of the decay, giving a less accurate fit. Concurrent periodic-DFT calculations were performed on two structures arising from variable temperature studies on a substituted derivative of 3 (S3, ESI), which have been very recently reported, to provide $1J_{NC}$ couplings in the Me$_2$N--C: 1.7–2.4 Å region. In this unique case the Me$_2$N--C separation at 200 K is 2.167(4) Å, but contracts, in a reversible process, to 1.749(3) Å at 100 K giving calculated $1J_{NC}$ values of 1.94 and 7.04 Hz, respectively.

In Figure 3, the N--C distance ($R_{NC}$) is plotted against both the second derivative of the charge density and the periodic DFT-derived, NMR confirmed, $1J_{NC}$ coupling constants (Hz) for 1–6 and S1–S3. A negative second derivative of the electron density is representative of a shared shell covalent bond which is observed below 1.8 Å. Between 1.8 and 2.45 Å a positive second derivative of the electron density is observed, which is still covalent in nature but is defined as regular closed-shell, and at longer bonds lengths (> 2.45 Å) no covalency is observed and a pure closed-shell bond arrangement dominates. The corresponding $1J_{NC}$ coupling results can be tentatively fitted to an inverse Morse function (Figure 3, red dashed line), in contrast to the Morse-like dependence outlined by charge density. It is interesting to note that though the $1J_{NC}$ values are larger for 4–6 with high delocalization indices for the peri N--C bond, and very small for 1–3, there is a maximum in the value of $1J_{NC}$ (ca. 7.4 Hz) which occurs at an N--C separation of ca. 1.79 Å. Indeed, the maximum coincides with the point where the Laplacian of the charge density in the bond begins to strongly decrease as the N--C distance closes. Above an N--C separation of 2.45 Å, corresponding to a calculated energy density of zero at the bond critical point, the coupling remains constant at a minimum value of 0.5 Hz, consistent with no significant covalency between the two atoms.

**Conclusion**

We have presented an advanced NMR crystallography methodology that allows DFT-driven observables and experimental charge density measurements to be utilised to determine the conditions required for bond formation in a series of model compounds containing a Me$_2$N--C(sp$^2$) interaction or partially formed bond. For this model system, as confirmed by DFT corroborated charge density and NMR observations, the variation of Laplacians and $1J_{NC}$ coupling constants suggest that at an N--C separation of ca. 1.8 Å, the system starts to form a covalent shared shell bond, with an increasing degree of formation as the atomic separation reduces further. This approach opens up the possibility of identifying the transition state for bond formation, of importance, for example, for understanding enzyme catalyzed conjugate additions.[31]

For additional bond formation studies, a more computational approach could be taken. Models for different reaction stages could be obtained using calculations on various substituted peri-naphthalene compounds, with the N--C interaction distance constrained to desirable distances in the 1.5–2.5 Å range but allowing full relaxation of the rest of the structure. From each such structure QTAIM parameters and $1J$-couplings could be derived. Modelling of crystal structures may also assist, for example, the tolerance of a N--C interaction within the 1.7–2.3 Å range, for example, in S3, may be partly due to other attractive interactions such as the hydrogen bonding in the crystal packing.[32] Furthermore, computational methodologies, such as random structure searching, can identify new synthetic targets with desired N--C distances.[32] To summarise, we have illustrated here that charge density, NMR and DFT methods can be used together to characterize bond formation, a process which is at the heart of chemistry.

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**Conflict of Interest**

The authors declare no conflict of interest.
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