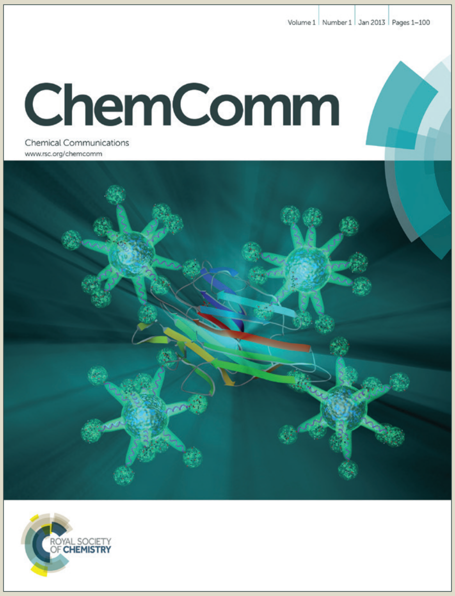
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Directionality of π-holes in nitro compounds.

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A statistical survey of the Cambridge Structural Database reveals that the interaction between the π-hole of nitro-groups and electron rich atoms is somewhat directional. High level *ab initio* computations indicate energies up to –6.6 kcal·mol^{-1}.

Intermolecular interactions determine how molecules interact with one another and are thus fundamental to inquiries in areas like supramolecular chemistry and molecular biology.[1] It is well-appreciated that even weak interactions (e.g. hydrogen bonding involving C–H) can bear functional relevance, especially when several such forces work in concert.[2] This begs the question what weak interactions can be identified as possibly functionally relevant.

Hydrogen (H) and halogen (Hlg) bonding are by far the best established intermolecular forces.[3] The regions of electropositive potential on R–H or R–Hlg (Fig. 1a and b, phenol and bromobenzene, respectively) can be described as an unpopulated σ^* antibonding orbital along the R–H/Hlg vector.[7b,c] These 'σ-holes' have also been identified on atoms that belong to the oxygen, nitrogen and carbon families, and their binding to electron rich entities is referred to as Chalcogen-,[4] Pnicogen-,[5] and Tetrel-bonding[6] respectively.

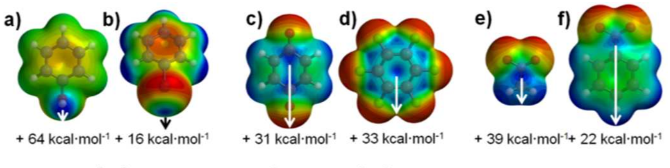

Fig. 1 Some σ-and π-holes with their electropositive potential (MP2/6-311+G**).

In analogy to the σ-hole, a π-hole can be seen as an electropositive potential located on an unpopulated π^*-orbital. The best-known π-hole interactions involve carbonyl compounds (e.g. Fig. 1c: *p*-quinone): Bürgi and Dunitz[7] uncovered the trajectory along which a nucleophile attacks the π-hole of a carbonyls' C-atom, and π-hole interactions involving amides are known to persist in protein structures.[8] Aromatic rings bearing electron withdrawing substituents such as hexafluorobenzene (Fig. 1d) can also function as a π-hole.[9] Interactions involving such π acidic aromatic rings are generally referred to as anion- or lone pair-π interactions.[10]

A recent theoretical study revealed that a π-hole can also be found on a nitro group.[11] Association of this π-hole with electron rich entities (ElR, e.g. H_2O, Cl^-) was estimated to vary in strength between –0.5 and –27.9 kcal·mol^{-1}. Fig. 1e and f illustrates the π-holes in nitromethane and nitrobenzene respectively. One might thus wonder if the '$NO_2^{\pi}\cdots$ElR' interaction bears any functional relevance. A first step in answering this question is to establish whether this intermolecular force actually is directional. Analysis of the data compiled within the Cambridge Structural Database (CSD)[12] has proven to be an exquisite tool in revealing the directional nature of traditional and non-canonical intermolecular forces. We thus set out to evaluate the CSD using a methodology that is particularly apt for ascertaining the directional character of weak intermolecular forces.[9]

Aliphatic and aromatic C–NO_2 compounds were considered that are abundant within the CSD: there are 900 Crystallographic Information Files (CIFs) containing nitromethane, and 14,227 CIFs containing an aromatic nitro compound where the NO_2 moiety is flanked by two *ortho*-H's (this allows the NO_2 and C_6H_2 moieties to be relatively coplanar). Illustrated in Fig. 2a is the query used to obtain initial datasets from the CSD.

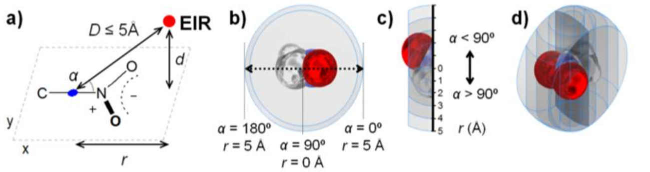

Fig. 2 Illustrations of the method used to analyse directionality of intermolecular interactions between an electron rich atom (El.R., N, P, As, O, S, Se, Te, F, Cl, Br, I or At) and a nitro group (in this illustration nitromethane).

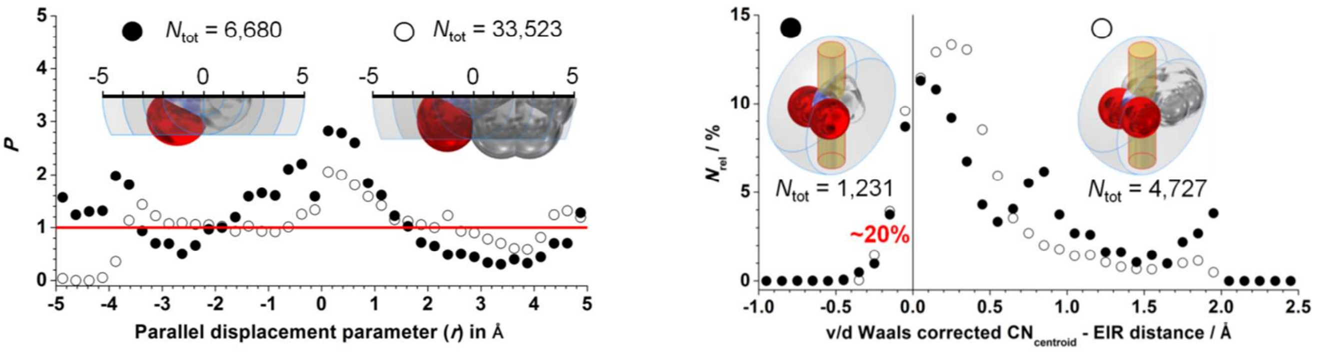

Fig. 3 Analysis of the directional nature of CNO_2 π-holes. Left: directionality plots of P *vs.* r for $CH_3NO_2\cdots ElR$ (●, N_{tot} = 6,680) and $C_6H_2NO_2\cdots ElR$ (○, N_{tot} = 33,523) of the data characterized by $D \le 5$ Å and $y \pm 2$ Å; Right: $N_{relative}$ *vs.* v/d Waals corrected $CN_{centroid}$–ELR distance (assuming $({}^{vdW}C+{}^{vdW}N)/2$ = 1.625 Å) for $CH_3NO_2\cdots ElR$ (●, N_{tot} = 1,231) and $C_6H_2NO_2\cdots ElR$ (○, N_{tot} = 4,727) of the data characterized by $D \le 5$ Å and $r \pm 1$ Å.

An entry was considered a hit when the *inter*molecular distance (D) between the C–N centroid (blue) and any electron rich atom (red, ElR = N, P, As, O, S, Se, Te, F, Cl, Br, I or At) was ≤ 5 Å. The initial dataset is thus confined within a sphere with a radius of 5Å, centred on the C–N centroid. The spatial separation (d) between ElR and the CNO_2 plane was also retrieved from the CSD. The xy coordinates relative to this plane were determined as describes elsewhere.[13] By virtue of Pythagoras's theorem, the parallel displacement parameter r could be derived from D and d. The $CN^{centroid}$–N–ElR angle (α) was measured as well.

For this study, only the data characterized by $y = \pm 2$ Å was considered, which are therefore located within the 4 Å wide spherical segment illustrated in Fig. 2b-d. The data can thus be characterized by the parallel displacement (r) within this spherical segment, either towards the NO_2 group ($\alpha < 90°$) or towards the atoms attached to C ($\alpha > 90°$). To analyse directionality, we applied a method described in detail elsewhere.[9,13,14] This method entails computing the parameter $P(r)$,[‡] which signifies the distribution of the data along r that has been corrected for the volume occupied by the host and for a random scattering of data. When $P \neq 1$, a *non-accidental clustering* of data is established and $P > 1$ is indicative of an attractive interaction.

The P versus r plots for CH_3NO_2 (black circles) and $C_6H_2NO_2$ (open circles) are shown in the left hand side of Fig. 3. For both 'hosts', $P > 1$ around $r = 0$, indicating some directionality of the π-hole. The P-values of 2–3 are similarly to those observed for $C\text{–}H\cdots\pi^{phenyl}$ hydrogen bonding.[15] In the case of CH_3NO_2, the observed clustering is spread out over the region ranging from $r = -1$ to $+1$ Å. It is likely that CH···ElR hydrogen bonding also contributes to the observed distribution. The clustering observed for aromatic NO_2 is spread out over the region $r = 0$ to $+1$ Å, and hydrogen bonding cannot contribute in this case. It was further assessed how exactly the data is distributed within the data characterized by $-1 > r < 1$Å. Thus, the relative hit fraction was plotted as a function of the van der Waals corrected $CN^{centroid}\cdots ElR$ distance, as is shown in the right hand side of Fig. 3. For both central groups roughly 20% van der Waals overlap is present. These two plots together indeed show that a nitro moiety can be a directional π-hole donor.

We have analysed theoretically (see ESI for details) several representative complexes between electron rich moieties and nitrobenzene (Fig. 4a; a similar study with nitromethane is reported elsewhere).[11]

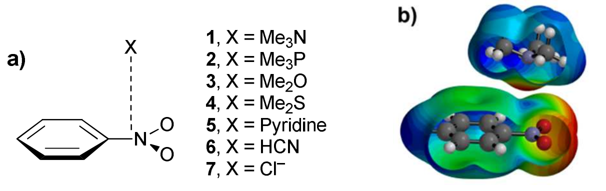

Fig. 4 a) Complexes **1**-**7** studied in this work. B) Pictorial representation of the complementarity of the MEP surfaces of nitrobenzene and trimethylamine.

The interaction energies and some geometric features of the complexes are gathered in Table 1.

Table 1. BSSE corrected interaction energies (E, kcal/mol) and equilibrium distances from the electron rich atom to the N (D_N) and C (D_C) atoms of the C–NO_2 moiety (in Å) of complexes **1**–**7** at the MP2/6-311+G**//PB86-D3/def2-TZVPD level of theory.

Complex	E	D_N	D_C
1	–6.2	2.770	2.932
2	–4.3	3.636	3.547
3	–4.4	2.825	2.931
4	–4.7	3.416	3.448
5	–4.7	2.956	3.001
6	–2.3	3.181	3.191
7	–6.6	3.204	3.047

The interaction energies are similar for nearly all complexes ranging from –2.3 to –6.6 kcal/mol and the most favourable one corresponds to chloride complex **7**. The π-hole in nitrobenzene is located along the C–N bond and close to the nitrogen atom (see Fig 1f and 4b). We have included both ElR···N and ElR···C distances (denoted as D_N and D_C respectively) in Table 1. All complexes exhibit similar D_N and D_C distances and in all cases the electron rich atom is located over the C–N bond, in agreement with the MEP analysis. The interaction energy is modest in complex **6** due to the low basicity of the sp-hybridized nitrogen atom of the HCN molecule.

The optimized geometries of some complexes are shown in Fig. 5, including the "atoms-in-molecules"[16] distribution of critical points computed for complexes **1** (lone pair donor ElR) and **5** (anionic ElR). The optimized geometries and critical point distribution for the rest of complexes are included in the ESI. It can be clearly observed in Figs. 5 and S1 that the position of the ElR atom of the interacting molecule coincides with the location of the π-hole in all complexes, indicating that the interaction is basically electrostatic in nature. The AIM analysis of **1** is complicated since it shows five bond critical points symmetrically distributed. One bond critical point (ρ = 1.54×10^2 a.u.) connects both nitrogen atoms characterizing and confirming the π-hole interaction. In addition, two bond critical points (ρ = 0.62×10^2 a.u.), which connect two hydrogen atoms of trimethylamine to two carbon atoms of the ring, reveal the presence of two C–H/π interactions. Moreover, two additional bond critical points (ρ = 0.70×10^2 a.u.) connecting two hydrogen atoms to the oxygen atoms of the nitro group, reveal the presence of two C–H···O interactions. The charge density computed at the bond critical point that connects both nitrogen atoms is considerably greater than the ones measured at the other bond critical points (1.54×10^2 *vs.* ~0.66×10^2). Therefore, the complexation is dominated by the π-hole interaction with some contribution of the other two. In complex **7** the distribution shows a single bond critical point that connects the Cl^- to the carbon atom, instead of the nitrogen atom, confirming the interaction.

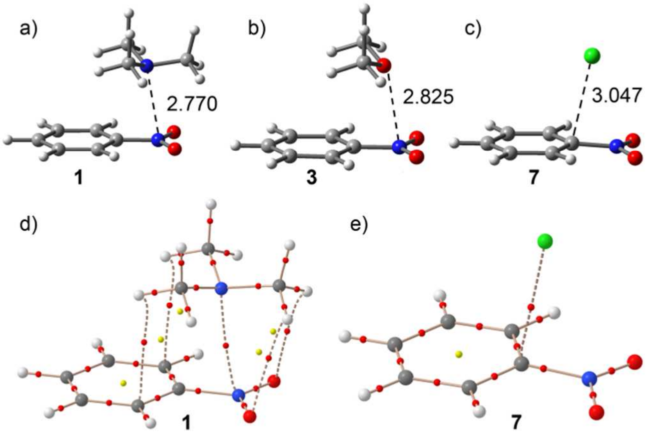

Fig. 5 a-c) Optimized π-hole complexes **1**, **3** and **7** studied in this work. d,e) Distribution of critical points in complexes **1** and **7** (bond and ring critical points are represented by red and yellow spheres, respectively). Bond paths connecting bond critical points are represented.

In conclusion, we have demonstrated that the nitro group in nitromethane and nitrobenzene is able to interact favourably with electron rich molecules by means of the π-hole that is located above and below the C–N bond. The interaction is characterized by the presence of a bond critical point that connects the ElR atom to the C–N bond. More importantly, the statistical survey of the CSD study reveals that the interaction between the π-hole of nitro-groups and electron rich atoms is directional. Nitro groups are widespread amongst small organic molecules and (at date) the Protein Data Bank (PDB) contains 380 ligands that bear an $-NO_2$ moiety. It is thus reasonable to anticipate an experimental study unveiling the functional relevant on this novel π-hole interaction.

Notes and references

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‡ $$P(r) = \frac{N_r}{N_{total}} \div \frac{V_r^{free}}{V_{total}^{free}}$$

N_r = the number of hits in between two *r*-values; N_{total} = the total number of hits; V_r^{free} = the volume in between two *r*-values minus the volume of the host in between these two *r*-values (hence the free volume), as found within a 4 Å wide symmetrical spherical segment of a sphere with 5 Å radius; V_{total}^{free} is the volume of a 4 Å wide symmetrical spherical segment of a sphere with 5 Å radius minus the volume of the host in that body. Models of the central groups were constructed using averages of interatomic distances and angles and assuming generally accepted van der Waals radii. All volumes were computed using Autodesk® Inventor® Professional.

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