

Acylthioureas as anion transporters: the effect of intramolecular hydrogen bonding

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Computational Details

The DFT, $V_{S,max}$ and E^2 interaction energies calculations were preceded by conformational analyses both on the free molecules and on the chloride complexes, which were performed with AMBER12 suite.¹ The receptors **5-8** and **10-12** were described with General Amber Force Field (GAFF)² parameters and AM1-BCC atomic charges.³ The anion was described with a net charge set to -1 and van der Waals parameters⁴ developed for the TIP3P water model.⁵ The Gaussian09⁶ package was used for all electronic structure calculations.

Conformational analysis

The molecular mechanics (MM) optimized structures of **5-8** and **10-12** molecules or chloride complexes were submitted to a 1 ns MD quenched run in the gas phase at 500 K. 10000 structures were saved and further full MM minimized until the convergence criterion of 0.0001 kcal mol⁻¹ was achieved. Afterwards, for each molecule, the conformations were energy sorted and the lowest energy structures were selected for subsequent DFT geometry optimizations. The lowest energy structure found for all free receptors exhibit an *anti* conformation stabilized by an intramolecular hydrogen bond; whereas the chloride complexes display to *syn* conformation with the two NH binding groups pointing to the anion.

DFT calculations

All structures of **5-8** and **10-12** (free receptors and complexes) previously optimized by MM, were re-optimized by DFT methods at B3LYP/6-311+G** level.

Calculated surface electrostatic potential maxima ($V_{S,max}$)

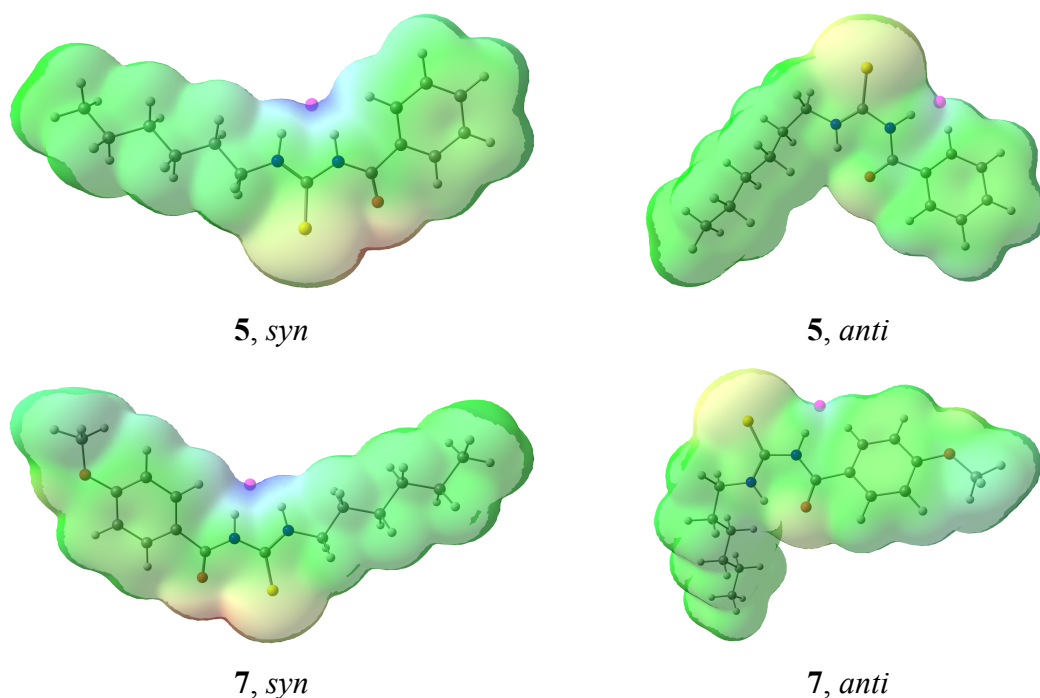
Single point energy calculations at the same level of theory were performed on the free receptors, for the *anti* and *syn* conformations, after removal of the chloride anion from the former. This calculation enabled the determination of the electrostatic potential

maxima on these molecules. The electrostatic potential at any point r created by the molecule's nuclei and electrons is given by

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r' - r|}$$

where Z_A is the charge of nucleus A located at R_A and $\rho(r')$ is the molecule's electronic density. In this work, the $V(r)$ was evaluated on the 0.001 electrons Bohr⁻³ contour of $\rho(r)$ and is henceforth labelled $V_s(r)$. The electrostatic potential surface maxima points, $V_{S,max}$, were computed using the Wavefunction Analysis Program, kindly provided by Bulat.⁷

The computed $V_{S,max}$ values for **5-8** and **10-12** are collected in Table 3 in the main text, while the electrostatic potential mapped on the molecular electron density surfaces are represented in Figure S1 for **5**, **7**, **8** and **10-12** together with the corresponding $V_{S,max}$ value represented, as pink dots. The $V_{S,max}$, the most positive region of the molecule, is located at the anion binding pocket for the *syn* conformations or near the NH_b group for the *anti* conformations.



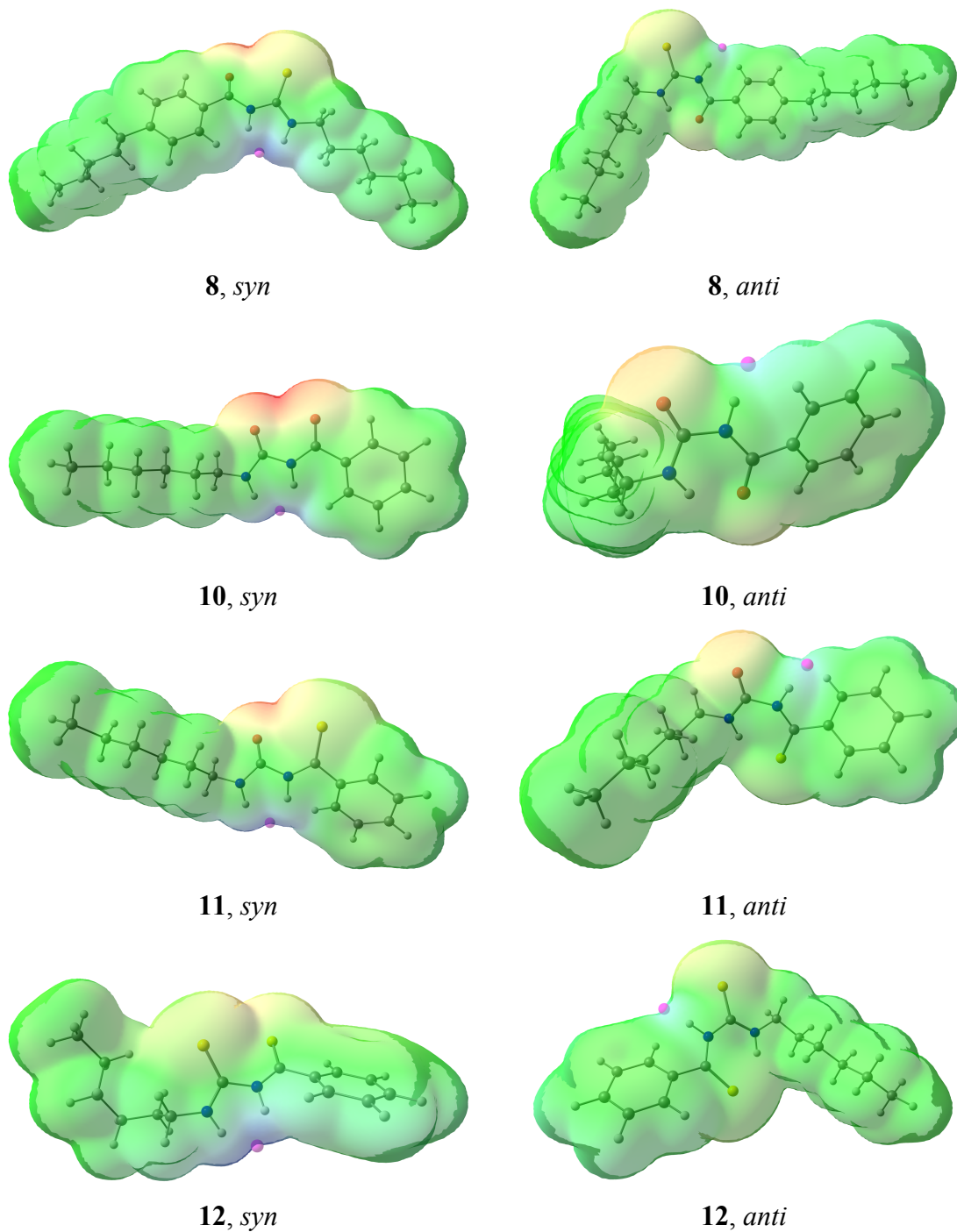


Figure SB1. Electrostatic potential mapped on the molecular electron density surface (0.001 electrons Bohr⁻³) for 5, 7, 8 and 10-12 *syn* and *anti* conformations. The colour scale ranges from blue (+0.11 a.u.) to red (-0.10 a.u.). The pink dots correspond to the location of the $V_{S,max}$.

Natural bonding orbital analysis

Natural Bond Orbital (NBO) analysis was used to assess the intramolecular hydrogen bond strength in *anti* conformations of **5-8** and **10-12**. NBO Version 3.1 program⁸ at the B3LYP/6-311+G** level.

NBOs are transformed molecular orbitals, calculated to provide the ideal Lewis structure of a molecule. The NBO approach provides insights into the interaction between a filled (bonding or lone pair) Lewis type NBO (that act as a donor) and an empty (antibonding or Rydberg) non-Lewis NBO (that act as an acceptor). The donor-acceptor interaction energy in the NBOs was estimated *via* second-order perturbation theory analysis of the Fock matrix,⁹ and establishes the strength of that interaction. For each donor orbital (*i*) and acceptor orbital (*j*), the stabilization energy E^2 is associated with $i \rightarrow j$ delocalization, given by

$$E^2 = \Delta E_{ij} = q_i \frac{F_{(i,j)}^2}{\varepsilon_i - \varepsilon_j}$$

where q_i is the donor orbital occupancy, $F_{(i,j)}$ is the Fock matrix elements between the NBO *i* and *j*, and ε_i and ε_j are the orbital energies.

The NBO analysis shows that in the intramolecular hydrogen bonds of **5-8** and **10** the interaction is between the lone pair (LP₁ and LP₂) orbitals of the acyl oxygen atom and an empty antibonding (σ^*) N-H_a orbital, while in **11** and **12**, the interaction is between the lone pair orbitals (LP₁ and LP₂) of the thioacyl sulfur atom and the same antibonding orbital. Calculated E^2 energies between donor and acceptor orbitals in these hydrogen bonds are given in Table 4 in the main text. The donor-acceptor NBO interaction between oxygen or sulfur atoms LP orbitals and empty σ^* N-H_a orbitals are illustrated for receptor **5** in Figure S2.

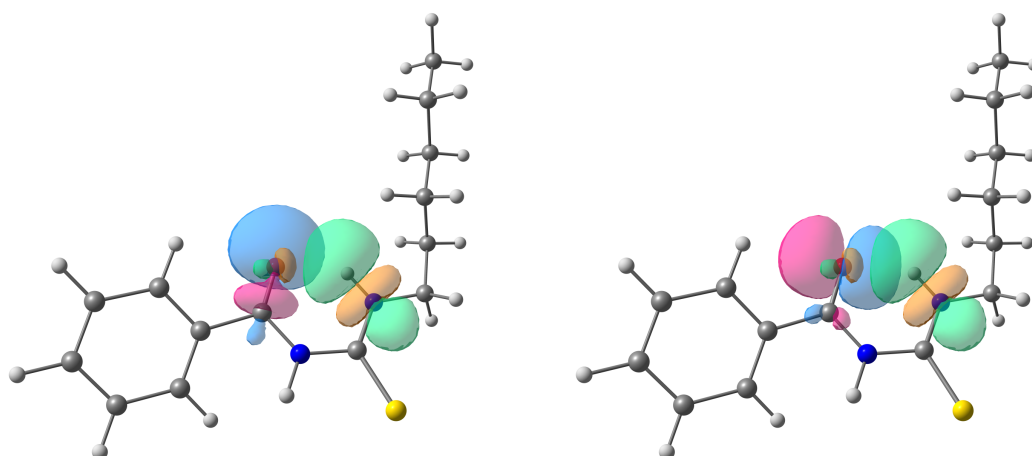


Figure SB2. Interaction between the oxygen LP₁ (left) or LP₂ (right) NBO (shown in pink and blue) and the corresponding N-H_a σ^* empty orbital (shown as orange and green) for **5**.

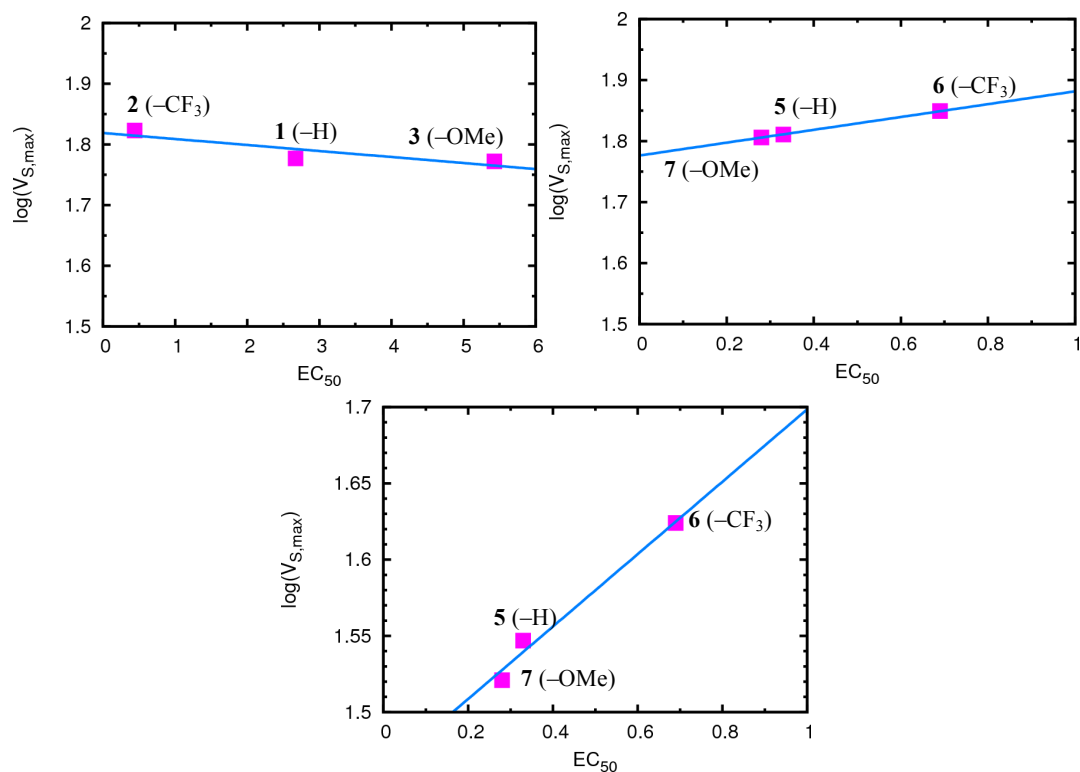


Figure SB3. Graphical representation of the correlations between the transport ability (EC_{50}) and the electrostatic potential surface maxima ($\log(V_{s,max})$) for mono-thioureas 1-3 (plot **a**), *syn* conformation of acylthioureas 4-7 (plot **b**) and *anti* conformation of acylthioureas 4-7 (plot **c**). Linear regression equation and R^2 for each plot: (**a**) $\log(V_{s,max}) = -0.0101EC_{50} + 1.8193$, $R^2 = 0.7743$; (**b**) $\log(V_{s,max}) = 0.1043EC_{50} + 1.7767$, $R^2 = 0.9999$; (**c**) $\log(V_{s,max}) = 0.2352EC_{50} + 1.4621$, $R^2 = 0.9820$.

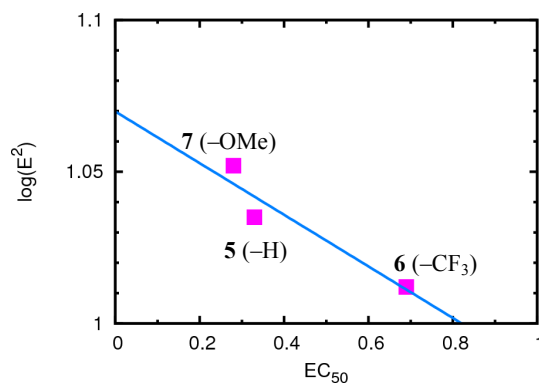


Figure SB4. Graphical representation of the correlation between EC_{50} and the intramolecular hydrogen bond strength ($\log(E^2)$) for the *anti* conformation of acylthioureas 4-7. Linear regression equation and R^2 : $\log(E^2) = -0.0861EC_{50} + 1.0701$, $R^2 = 0.9023$.

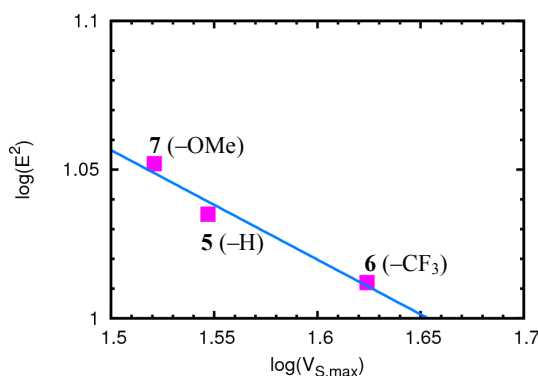


Figure SB5. Graphical representation of the correlation between $\log(V_{s,max})$ and $\log(E^2)$ for the *anti* conformation of acylthioureas **4-7**. Linear regression equation and R^2 : $\log(E^2) = -0.3753\log(V_{s,max}) + 1.6198$, $R^2 = 0.9668$.

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