How to Study Molecular Recognition?

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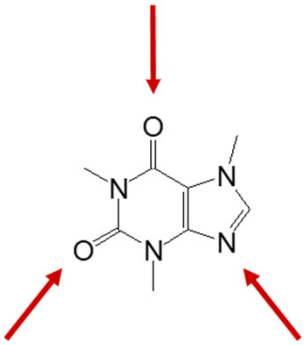
A Synthetic Receptor for Oxopurines Based on a Triphenylene Scaffold

Caffeine

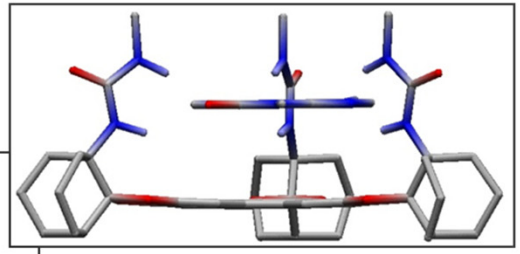
flat π-system suitable for π-π-interactions

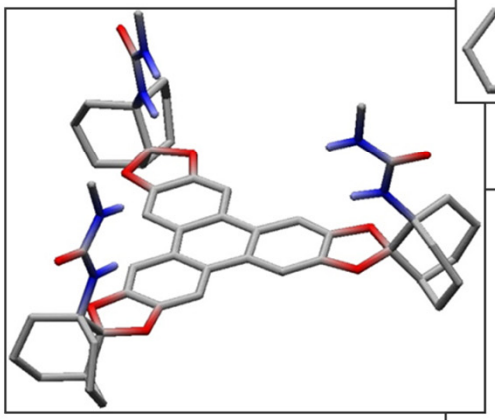


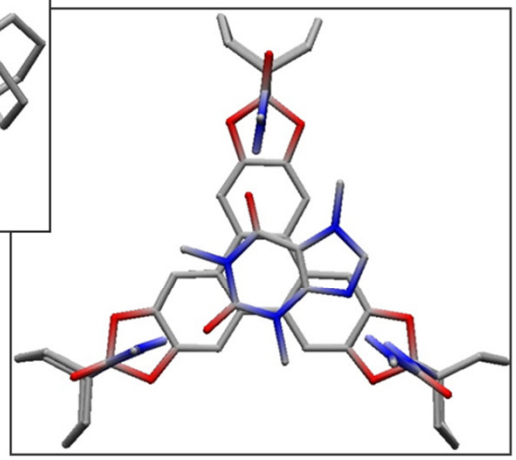
three hydrogen-bond acceptors with pseudo-C_3 symmetry

flat, aromatic triphenylene π-system

three arms with urea units at distances of ca. 10 A

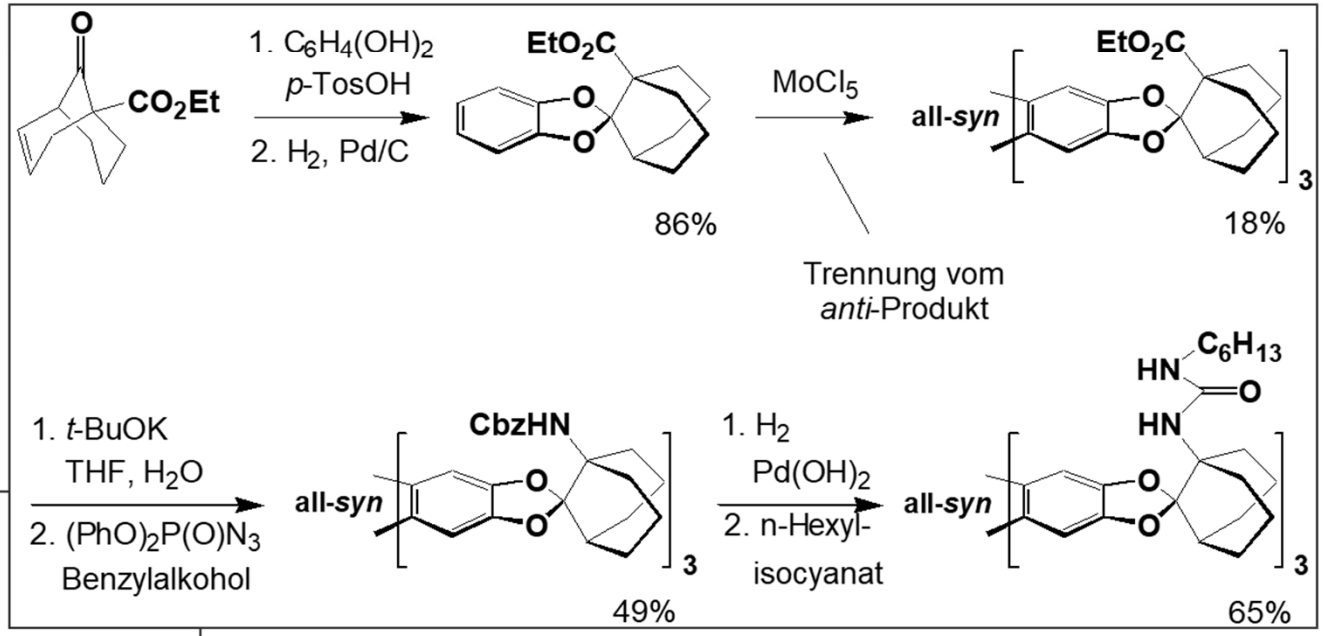


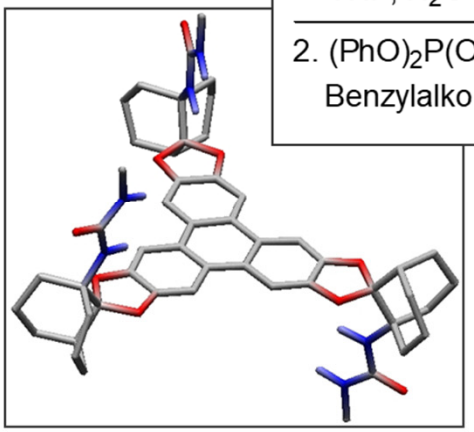




S. R. Waldvogel, R. Fröhlich, C. A. Schalley, *Angew. Chem.* **2000**, *112*, 2580
Angew. Chem. Int. Ed. **2000**, *39*, 2472

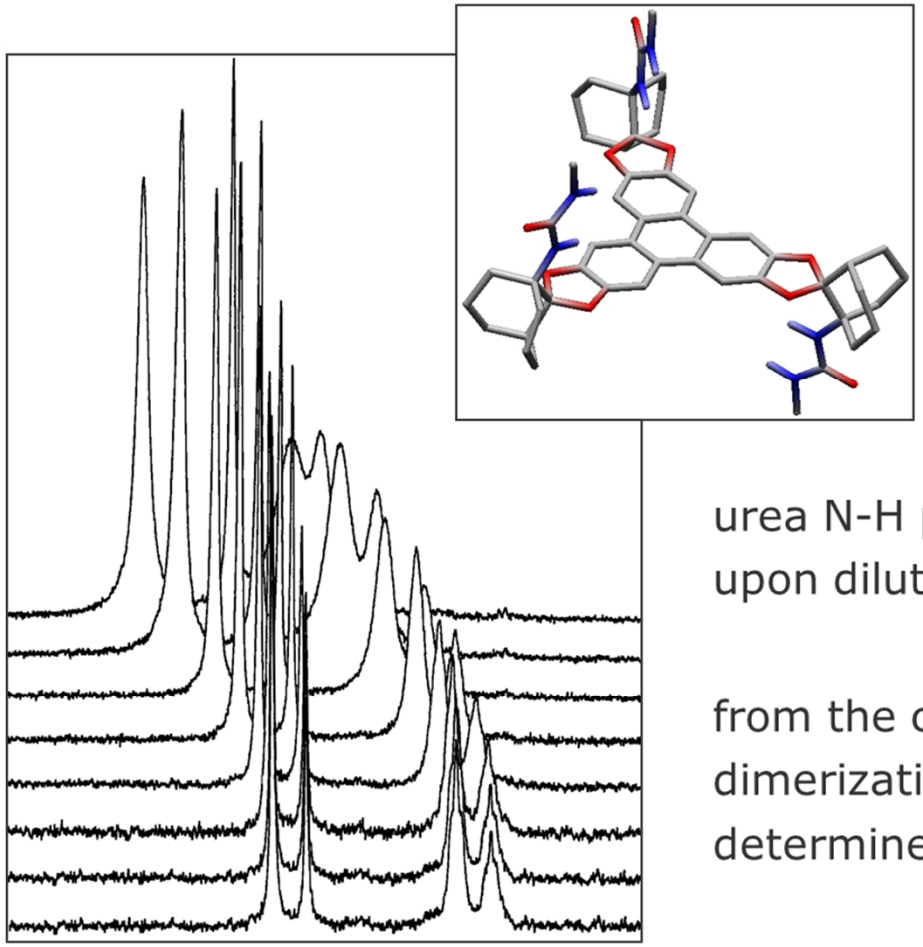
Synthesis of Receptors





side product: anti-receptor

Dimerization of Receptor?

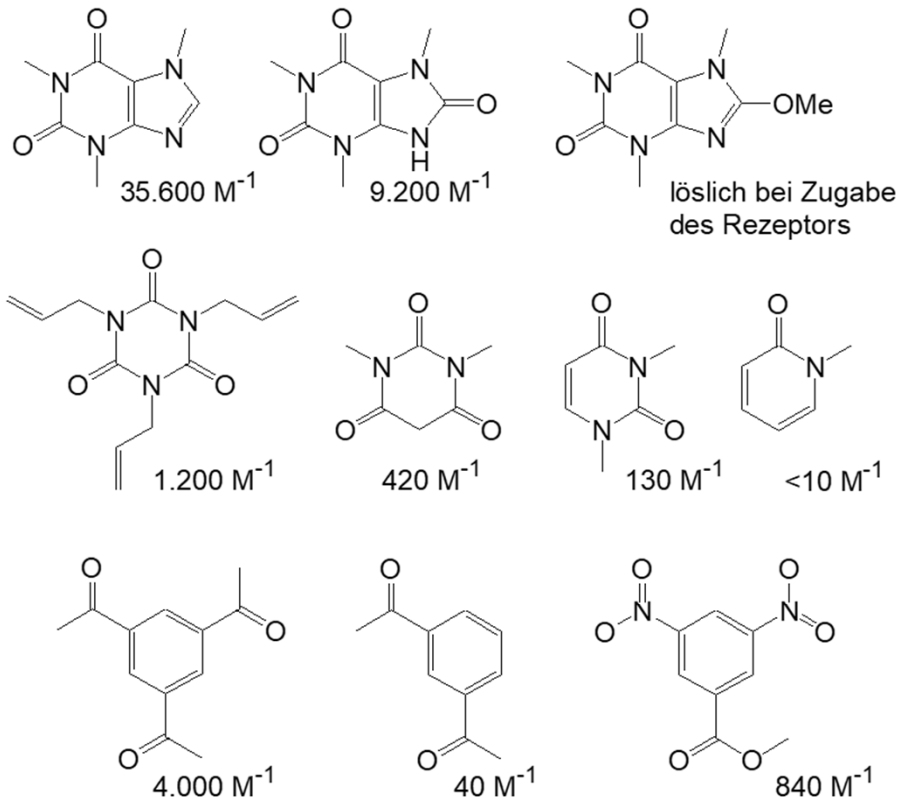


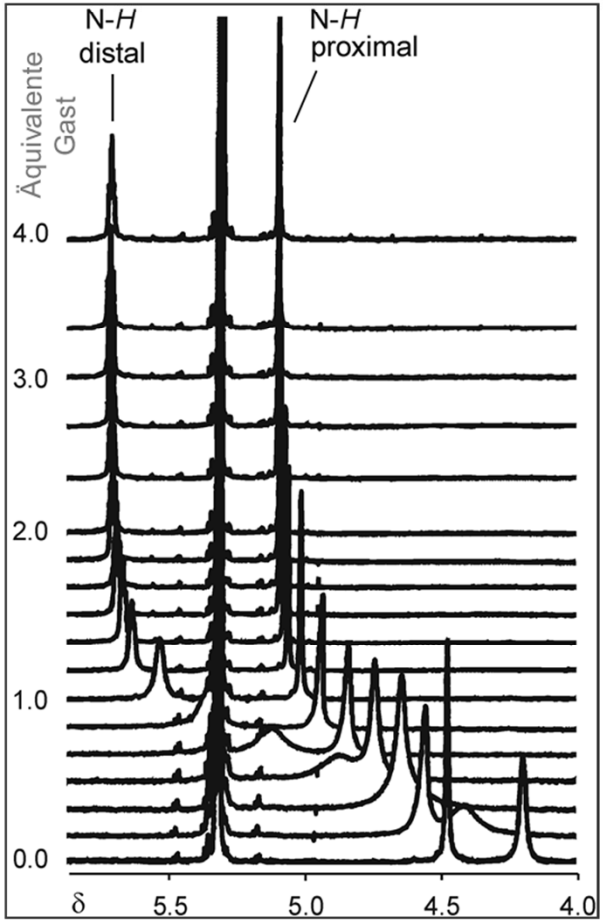
dilution experiment provides insight into dimerization of receptor

urea N-H protons shift in the ^{1}H NMR upon dilution

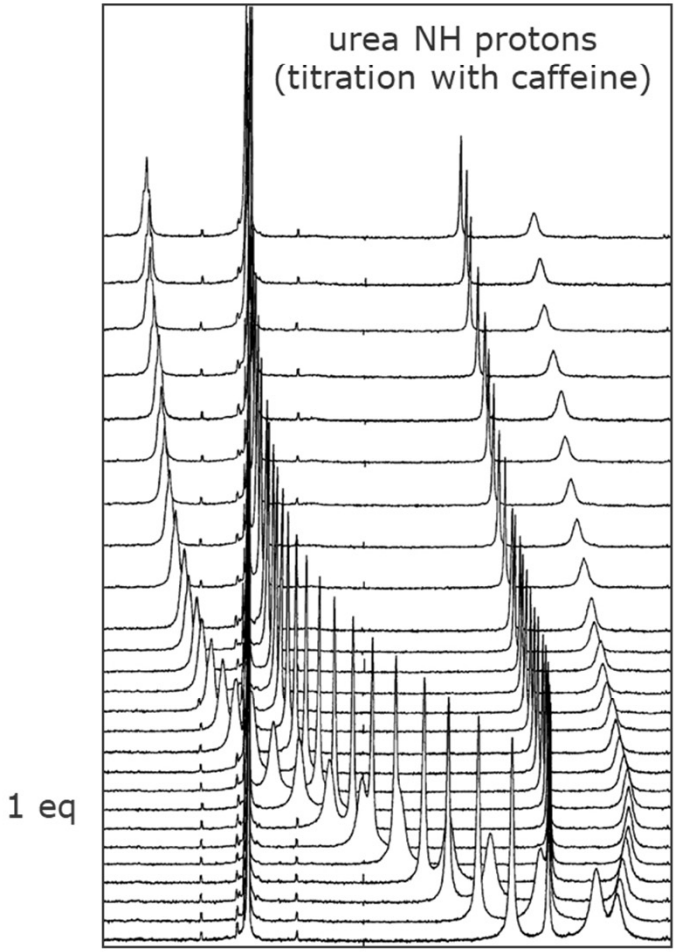
from the curvature of dilution curve, dimerization constant can be determined

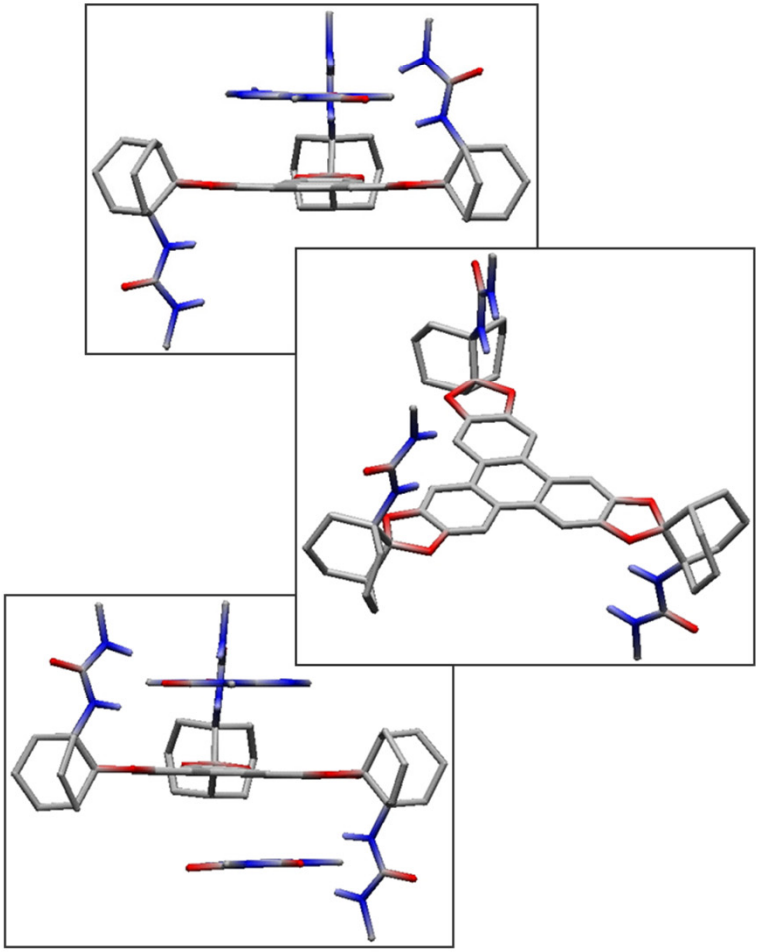
Binding Constants through ^{1}H NMR Titrations (CH_2Cl_2)



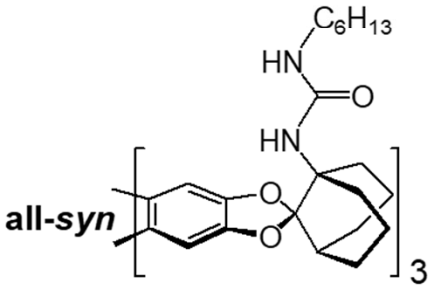


Control Experiments: How to?

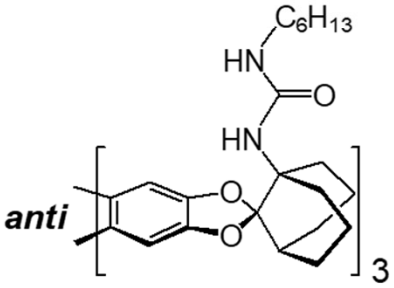




Control Experiments: Conclusions

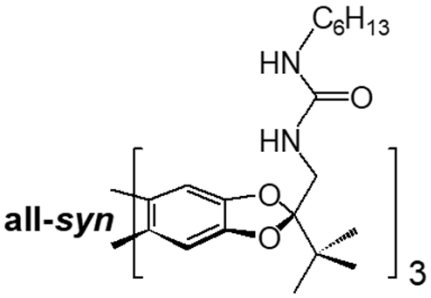


35.600 M^{-1}

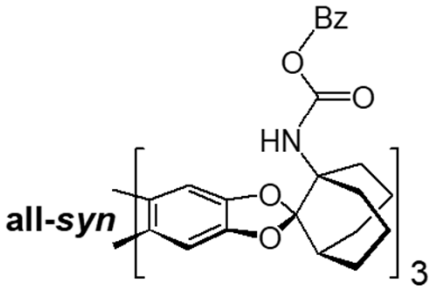


1:1 1.000 M^{-1}

2:1 20 M^{-1}



170 M^{-1}



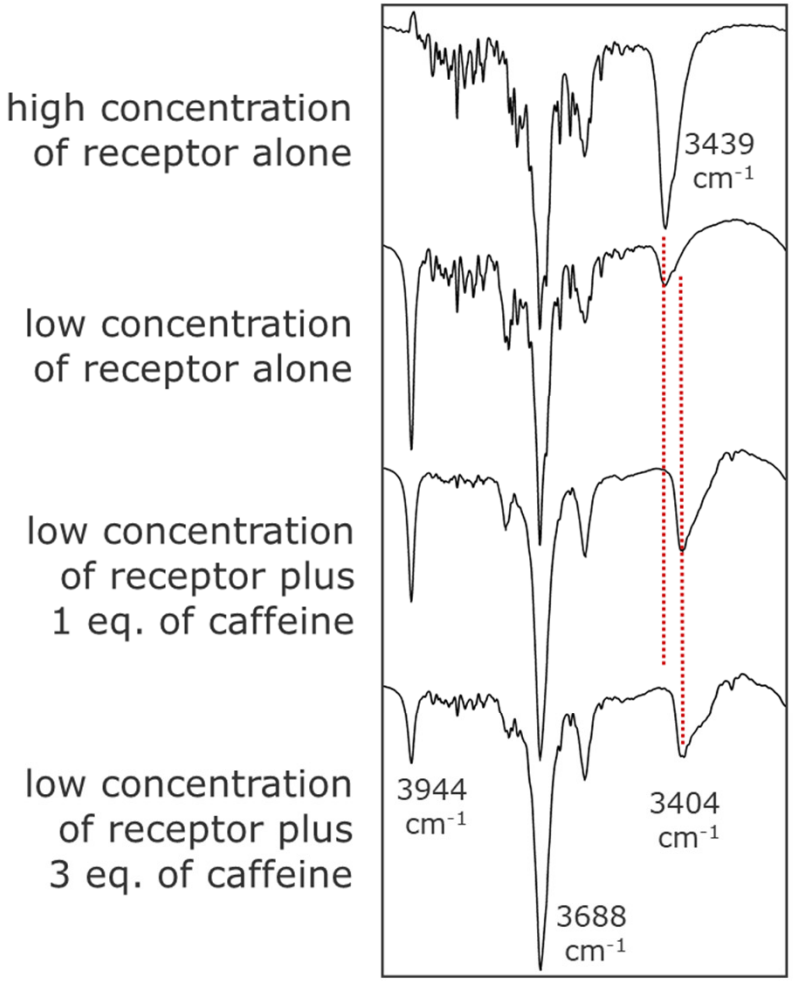
< 10 M^{-1}

Evidence for Binding from Other Methods: IR Spectroscopy

N-H/O-H stretch vibrations change their wavenumbers when hydrogen bonding occurs or changes with concentration

receptor dimerizes (new IR band upon dilution)

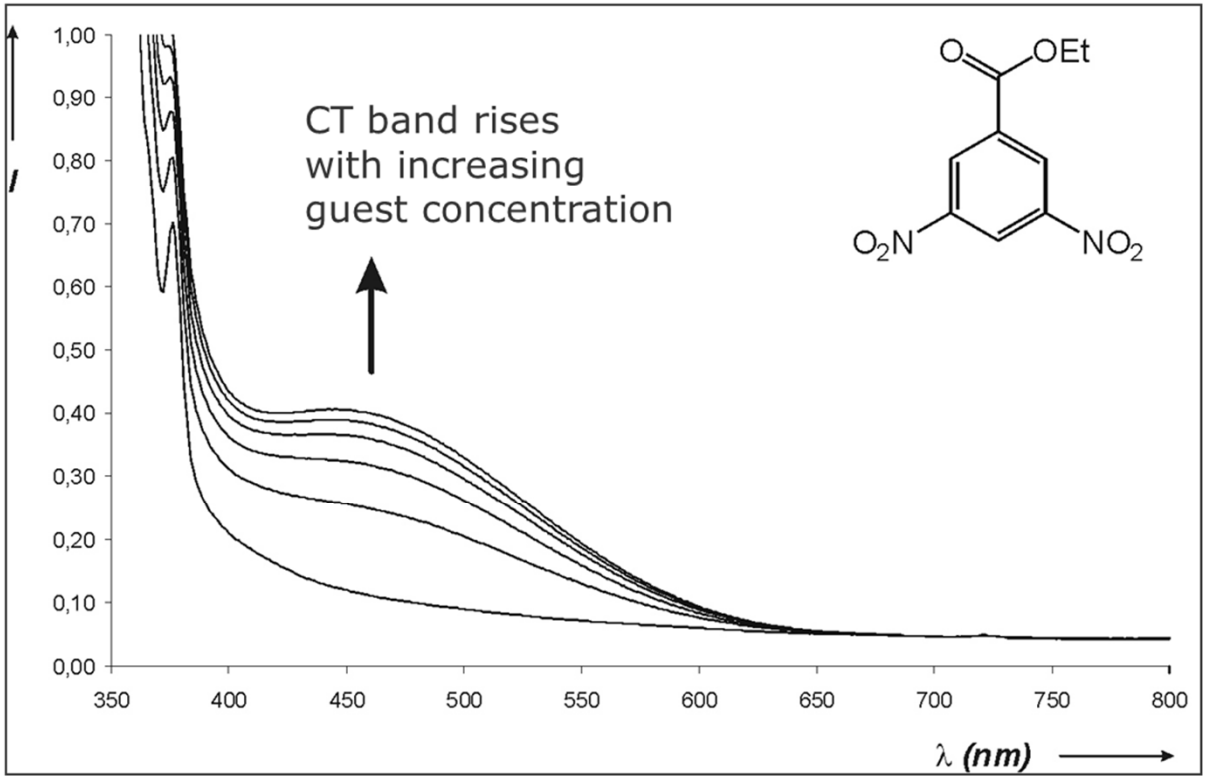
caffeine forms hydrogen bonds at a different position from those of the receptor dimer



Evidence for Binding from Other Methods: UV/Vis Spectroscopy

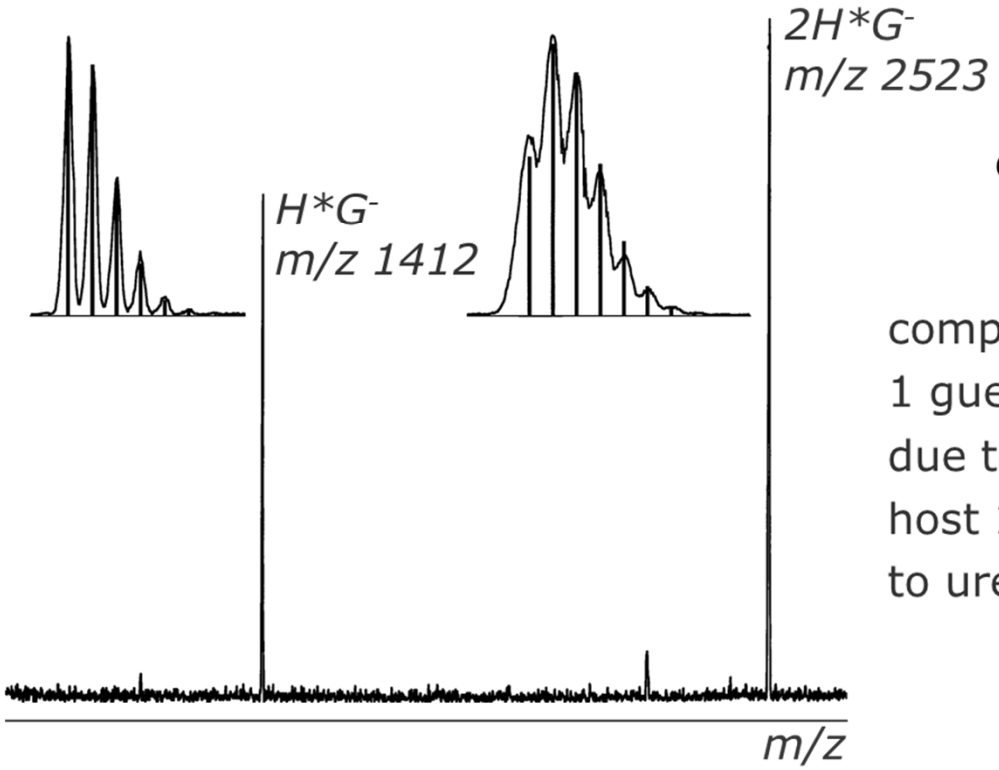
caffeine: no charge transfer band in the UV/Vis spectra

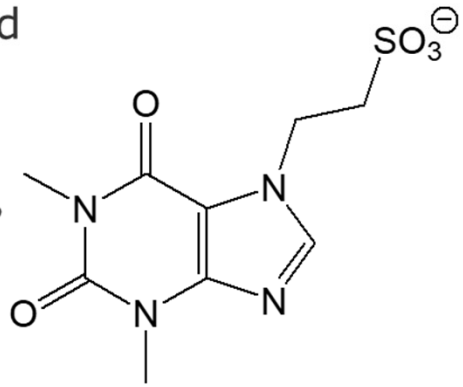
with nitro compounds (incl. TNT) complex forms with red color



Evidence for Binding from Other Methods: Mass Spectrometry

for mass spectrometry, a charge, and thus a charged analog of caffeine is needed





complexes of 2 hosts and 1 guest anion observed due to caffeine binding of host 1 and anion binding to urea protons of host 2

Temperature-Dependent NMR Experiments

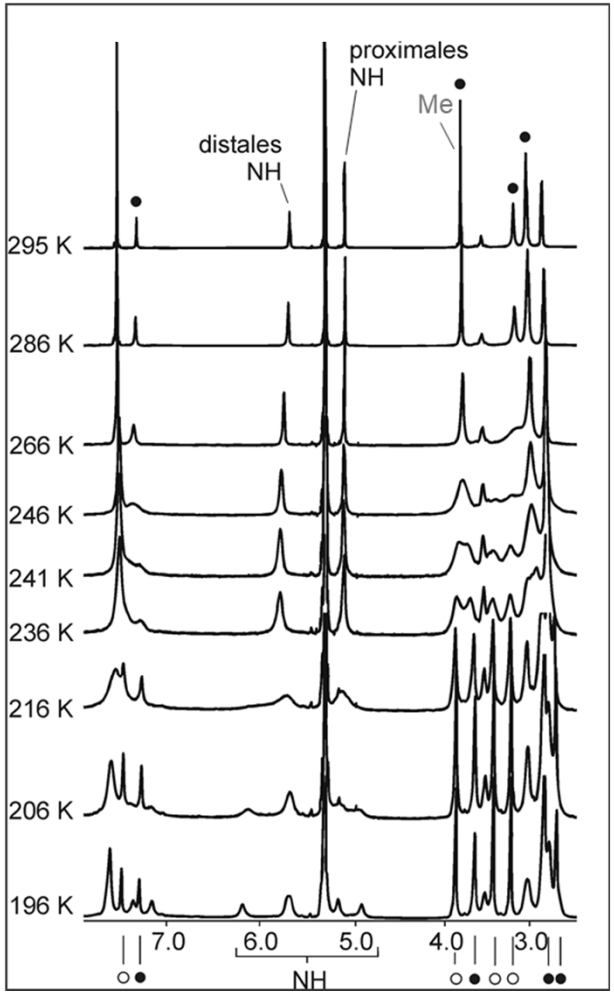
$$\Delta G^{\neq} = RT_c \cdot \ln \frac{RT_c\sqrt{2}}{\pi \cdot N_A \cdot h \cdot |\nu_A - \nu_B|}$$

T_c **= 243 K** (600 MHz) for Me protons of caffeine

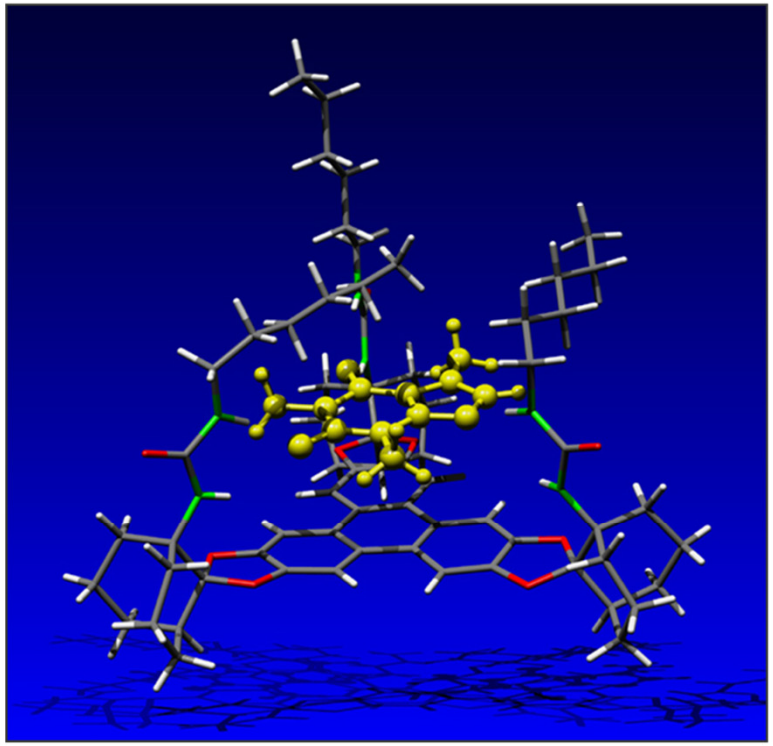
T_c **= 216 K** (600 MHz) for NH protons of receptor

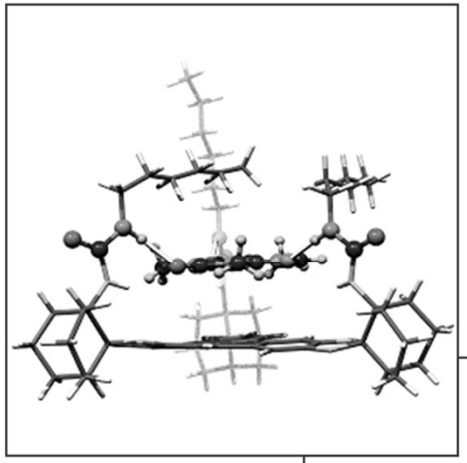
barrier for caffeine exchange: 11,4 kcal/mol

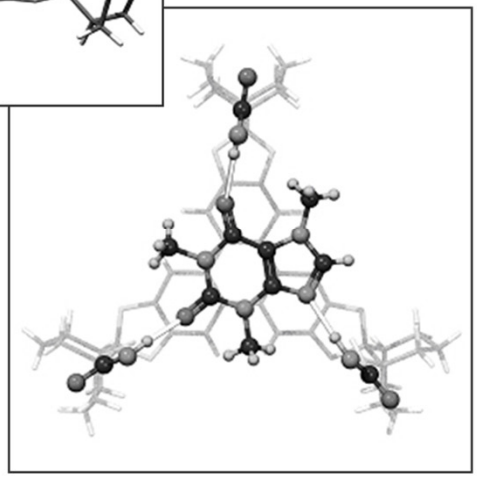
barrier for rotation of caffeine inside receptor: 9,7 kcal/mol



Crystal Structure of Caffeine-Receptor Complex







Conclusions: Binding Mode of Caffeine

- *caffein binds preferentially through three hydrogen bonds to distal urea protons (NMR shifts, one constant IR band, smaller distances in crystal structure)*
- *proximal urea protons are not well preorganized and only form weak, non-linear hydrogen bonds (crystal structure)*
- *charge transfer interactions do not play an important role for caffeine, but support binding of other aromatic guests (UV/Vis spectra)*
- *rigid, well preorganized urea arms necessary (control experiments with flexible receptors)*
- *two dynamic processes can be distinguished in solution (VT-NMR experiments)*
- *binding mode in solution is analogous to that in the crystal*