

June 3, 2014

## Mechanistic insight into benzenethiol catalyzed amide bond formations from thioesters and primary amines

Nicolai Stuhr-Hansen,<sup>1,2</sup> Nicolai Bork,<sup>3,4\*</sup> Kristian Strømgaard<sup>1</sup>

1. Department of Drug Design and Pharmacology, University of Copenhagen, DK-2100 Copenhagen, Denmark
2. Department of Chemistry, Faculty of Sciences, University of Copenhagen, Thorvaldsensvej 40, 1871 Frederiksberg C, Denmark.
3. Department of Chemistry, University of Copenhagen, DK-2100 Copenhagen Ø, Denmark
4. Division of Atmospheric Sciences and Geophysics, Department of Physics, University of Helsinki, FI-00014 Helsinki, Finland

\* Correspondence to: nicolai.bork@helsinki.fi

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## S1 Main reactions

We consider the following reactions: The uncatayzed reaction



where R is  $-\text{COCH}_3$  and R' is  $-\text{CH}_3$ , and the catalyzed reaction via trans-thioesterfication,



whereafter the catalyst is regenerated,



For future convenience, we will here include (2)+(4),



## S2 Assumptions

We assume that all reaction rates are first order in both reactants

$$r = k[\text{R}_1][\text{R}_2], \quad (6)$$

where  $\text{R}_1$  and  $\text{R}_2$  denote the reactants, and that all species are thermally equilibrated at all times, i.e. that their concentrations are governed by the law of mass action. Further, the reaction rates are assumed to follow Arrhenius type expressions, i.e.

$$r = [\text{R}_1][\text{R}_2] \times A \times \exp\left(-\frac{E_A}{k_B T}\right) \quad (7)$$

where A is a pre-exponential factor,  $E_A$  is the Gibbs free activation energy,  $k_B$  is Boltzmanns constant and T is the absolute temperature.

## S3 The catalytic speed-up

Considering the high exothermicity of the second step of the catalysed reaction, it is clear that reaction (3) is practically irreversible and hence that

$$r_{cat} = r_3 \quad (8)$$

$$= [\text{RSPH}][\text{R}'\text{NH}_2] \times A_3 \times \exp\left(-\frac{E_{A3}}{k_B T}\right) \quad (9)$$

where  $r_{cat}$  denotes the overall catalyzed reaction rate.

We are interested in the catalytic speed-up, i.e. the ratio

$$\frac{r_{cat}}{r_1} = \frac{[\text{RSPH}]}{[\text{RSEt}]} \frac{A_3}{A_1} \exp\left(-\frac{E_{A3} - E_{A1}}{k_B T}\right) \quad (10)$$

Due to the equilibrium of reac. (5) we have that

$$\frac{[\text{RSPH}]}{[\text{RSEt}]} = \frac{[\text{PhSH}]}{[\text{EtSH}]} \exp\left(-\frac{\Delta G_5}{k_B T}\right) \quad (11)$$

where  $\Delta G_5$  is the Gibbs free energy difference between reactants and products.

Inserting (11) in (10) we obtain

$$\frac{r_{cat}}{r_1} = \frac{[\text{PhSH}]}{[\text{EtSH}]} \frac{A_3}{A_1} \exp\left(-\frac{\Delta G_5 + E_{A3} - E_{A1}}{k_B T}\right). \quad (12)$$

Assuming that  $[RSPH]$  is small implies that  $[EtSH]=[RNHR']$ . Further, the only net reaction consuming PhSH is (4) and we thus have and that

$$[PhSH] = [PhSH]_0 - [EtSH] \quad (13)$$

$$= [PhSH]_0 - [RNHR'] \quad (14)$$

(12) can thus be written as

$$\frac{r_{cat}}{r_1} = \frac{[PhSH]_0 - [RNHR']}{[RNHR']} \times \frac{A_3}{A_1} \exp\left(-\frac{\Delta G_5 + E_{A3} - E_{A1}}{k_B T}\right). \quad (15)$$

Determination of the pre-exponentials is often attempted based on a solvent cage forming around the reactants and remains non-trivial and associated with significant uncertainties. However, since reactions (1) and (3) are so similar it is reasonable to assume that  $A_1 \sim A_3$ .

We insert  $[PhSH]_0=0.1$  M,  $[RNHR']=0.05$ M (end concentration),  $T=298$  K,  $\Delta G_5= 2.66$  kJ/mol,  $E_{A3}=103.11$  kJ/mol,  $E_{A1}=142.52$  kJ/mol, and obtain

$$\frac{r_{cat}}{r_1} = 2.8 \times 10^5 \quad (16)$$

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Time(min)	0 Eq	0.2 Eq	0.5 Eq	1 Eq	2 Eq
0	0	0	0	0	0
5	0	4	13	23	43
10	0	8	18	32	62
20	0	10	29	45	80
30	0	14	34	54	87
45	0	19	42	58	91
60	0	23	48	67	95
90	0	28	53	72	100
120	0	34	57	78	100

Table S1: Conversion of thioester to amide (in %) as function of time and added PhSH.

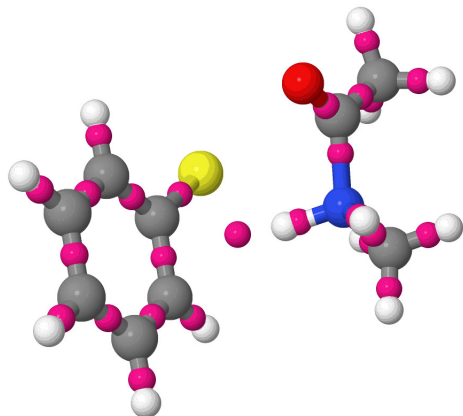


Figure S1: Atoms-In-Molecules analysis of the bond critical points in the transition state structure of reaction 3, confirming the presence of a bond from an amine proton to the  $\pi$ -electrons of the aromatic ring. The bond critical points are purple spheres.

## S4 Thermodynamics

Species	$E_{B3LYP}$	$G_{B3LYP}$	$E_{CCSD(T)}$	$G_{corrected}$
EtS <sup>-</sup>	-477.5490	-477.5095	-476.7115	-476.6720
PhS <sup>-</sup>	-629.9907	-629.9303	-628.7378	-628.6775
RSEt	-630.6859	-630.6056	-629.4400	-629.3597
RSPH	-783.1115	-783.0103	-781.4510	-781.3497
PhSH	-630.4495	-630.3804	-629.1972	-629.1280
EtSH	-478.0208	-477.9727	-477.1851	-477.1370
R'NH <sub>2</sub>	-95.8666	-95.8252	-95.5562	-95.5148
RNHR'	-248.5454	-248.4743	-247.8199	-247.7488

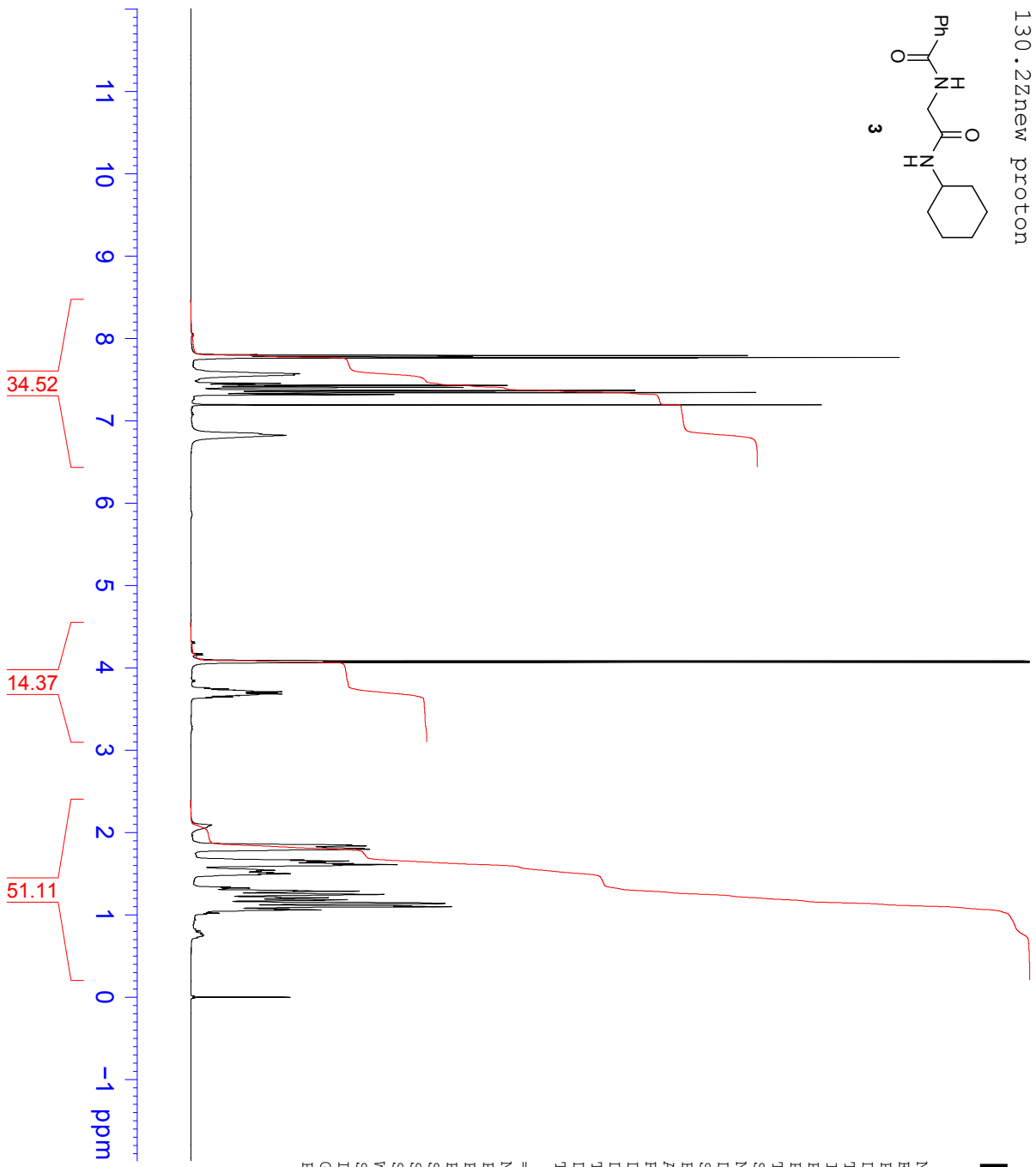
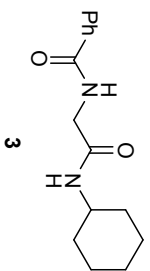
Table S2: Electronic and Gibbs free energies of the most important species. All calculations are using the 6-31+G\* basis set. Unites are Hartree. R is -COCH<sub>3</sub> and R' is -CH<sub>3</sub>.

Energy	$E_{B3LYP}$	$G_{B3LYP}$	$E_{CCSD(T)}$	$G_{corrected}$
$E_{A1}$	87.77	148.58	81.71	142.52
$E_{A2}$	87.95	139.91	55.31	107.26
$E_{A3}$	61.40	123.34	41.17	103.11
$\Delta G_2$	42.07	42.40	40.2515	40.58
$\Delta G_4$	-34.00	-34.50	-37.41	-37.41
$\Delta G_5$	8.07	7.90	2.83	2.66

Table S3: Electronic and Gibbs free energies of the main reactions. All calculations are using the 6-31+G\* basis set. Unites are kJ/mol.

## S5 <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra of *N*-cyclohexyl hippuramide (3)

Email= nsh@chem.ku.dk  
 130.22new proton

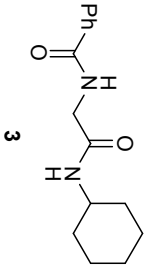


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RG 128
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DE 6.50 usec
TE 297.2 K
D1 1.50000000 sec
TD0 1

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SF 300.1300252 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
  
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Email= nsh@chem.ku.dk  
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 44.02

32.84  
 25.49  
 24.74



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PL13 20.00 dB
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PL12W 0.26924726 W
PL13W 0.15071319 W
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