Towards discrimination of carboxylates
by hydrogen-bond donor anion receptors

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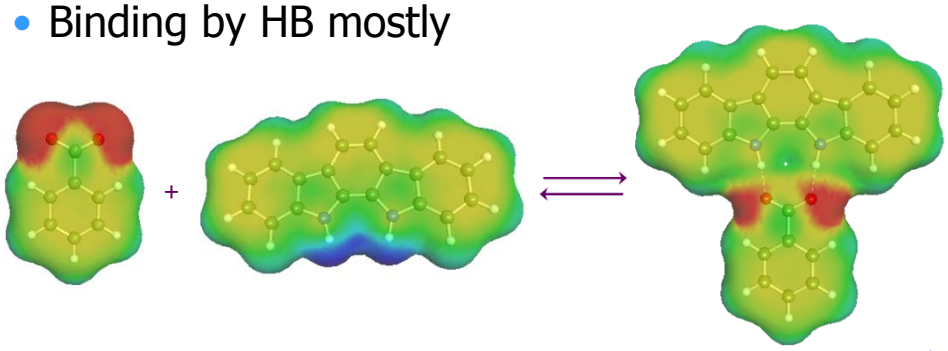
Background and aims

- Carboxylates are very common anions
- Large structural variety
- Yet, the -COO^- is fairly similar
- Binding by HB mostly



Not easy to *discriminate*!

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Aims

- Explore the possibilities of discriminating simple carboxylate anions with simple molecular receptors
  - Rather: building blocks
- Find relationships between binding affinity and structure
  - Useful for receptor array design

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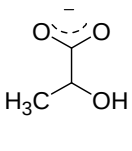
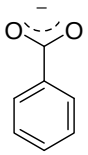
Anions in this work

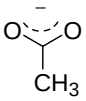
Simple but different:



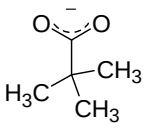
lactate



benzoate



acetate



trimethylacetate

	lactate	benzoate	acetate	trimethylacetate
pK_a	3.86	4.20	4.76	5.01
	Medium Hydrophilic	Bulky Hydrophobic Aromatic	Small	Bulky Hydrophobic Aliphatic

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Binding affinity

$$YH_n + X^- \underset{}{\overset{K_{ass}}{\rightleftharpoons}} YH_nX^- \qquad (1)$$

Receptor molecule — Anion — Receptor-anion complex

$$K_{ass} = \frac{a(YH_nX^-)}{a(YH_n)\cdot a(X^-)} \qquad (2)$$

Accurate measurement method needed!

Most important: *differences* of affinity

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How to achieve high accuracy?

Put *two* receptors *simultaneously* in a solution containing the anion X^-

$$Y_2H_n + Y_1H_nX^- \rightleftharpoons Y_2H_nX^- + Y_1H_n$$

Measure their *relative* binding affinity!

K. Haav *et al*, *J. Org. Chem.* 2013, *78*, 7796−7808

Relative binding affinity

$$Y_2H_n + Y_1H_nX^- \overset{K_{ass21}}{\rightleftharpoons} Y_2H_nX^- + Y_1H_n \quad (3)$$

$$K_{ass21} = \frac{K_{ass2}}{K_{ass1}} = \frac{a(Y_2H_nX^-)\cdot a(Y_1H_n)}{a(Y_1H_nX^-)\cdot a(Y_2H_n)} \quad (4)$$

$$\Delta \log K_{ass21} = \log K_{ass2} - \log K_{ass1} \quad (5)$$

a(X^-) has disappeared from the equations!

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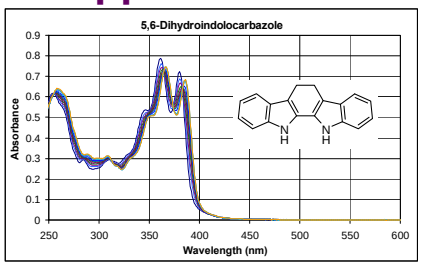
Advantages of relative measurement

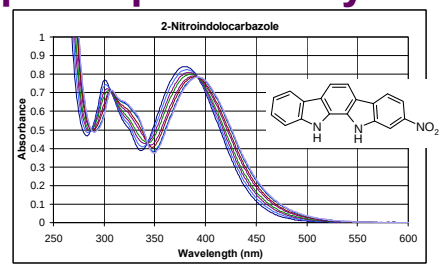
- Most experimental parameters (Water content, impurities, activity of X^-, …) are **automatically the same** for both receptors
- Ion association, homoconjugation, protonation, etc **cancel** to a large extent
- Activity coefficient ratios are similar:

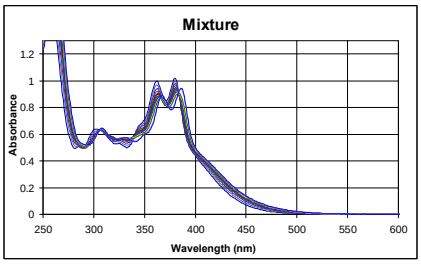
$$K_{ass21} = \frac{K_{ass2}}{K_{ass1}} = \frac{[Y_2H_nX^-]\cdot[Y_1H_n]}{[Y_1H_nX^-]\cdot[Y_2H_n]} \quad (6)$$

Extensively used for pK_a measurement: http://tera.chem.ut.ee/~ivo/HA_UT/

Applied for UV-Vis spectrophotometry







Anion: CH_3COO^-

K. Haav *et al*, *J. Org. Chem.* 2013, *78*, 7796−7808

$$\log K_{ass21} = \log \frac{K_{ass2}}{K_{ass1}} = \log \frac{[Y_2H_nX^-]\cdot[Y_1H_n]}{[Y_1H_nX^-]\cdot[Y_2H_n]} = 0.74$$

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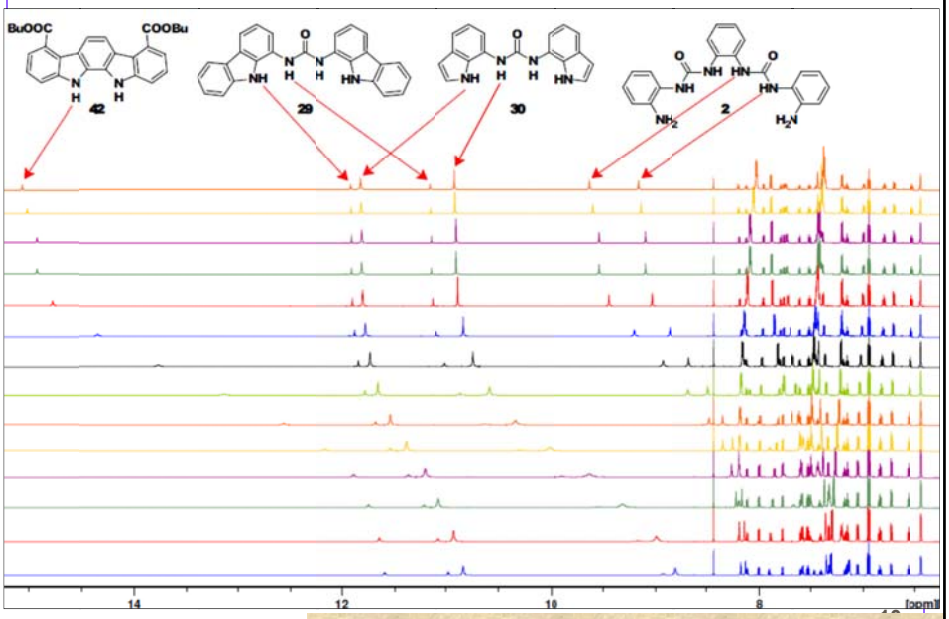
Applied for NMR spectroscopy

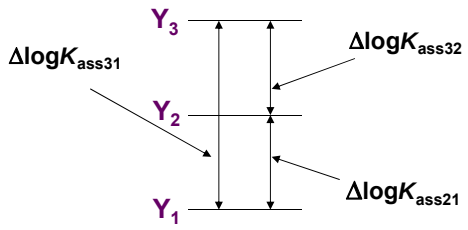


S. Kadam *et al*, *J. Org. Chem.* 2014, *79*, 2501−2513

QA of the results

- Every measurement is **"circularly validated"** by at least one additional "path":

$$\Delta \log K_{\text{ass31}} = \Delta \log K_{\text{ass32}} + \Delta \log K_{\text{ass21}}$$



M. Oss *et al*, *Anal. Chem*. 2010, *82*, 2865–2872

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Experimental details

- Solvent: DMSO with 0.5% H_2O
- Counterion: tetrabutylammonium
- Concentrations:
  - Receptors:
    - UV-Vis: $n \cdot 10^{-5}$ M — K. Haav *et al*, *J. Org. Chem*. 2013, *78*, 7796−7808
    - NMR: $n \cdot 10^{-3}$ M — S. A. Kadam *et al*, *J. Org. Chem*. 2014, *79*, 2501−2513
  - Anion/titrant:
    - UV-Vis: $n \cdot 10^{-5}$ … $n \cdot 10^{-4}$ M
    - NMR: $n \cdot 10^{-2}$ … $n \cdot 10^{-1}$ M
- Every $\Delta \log K_{\text{assXY}}$ value is a mean from 5 to 16 titration points

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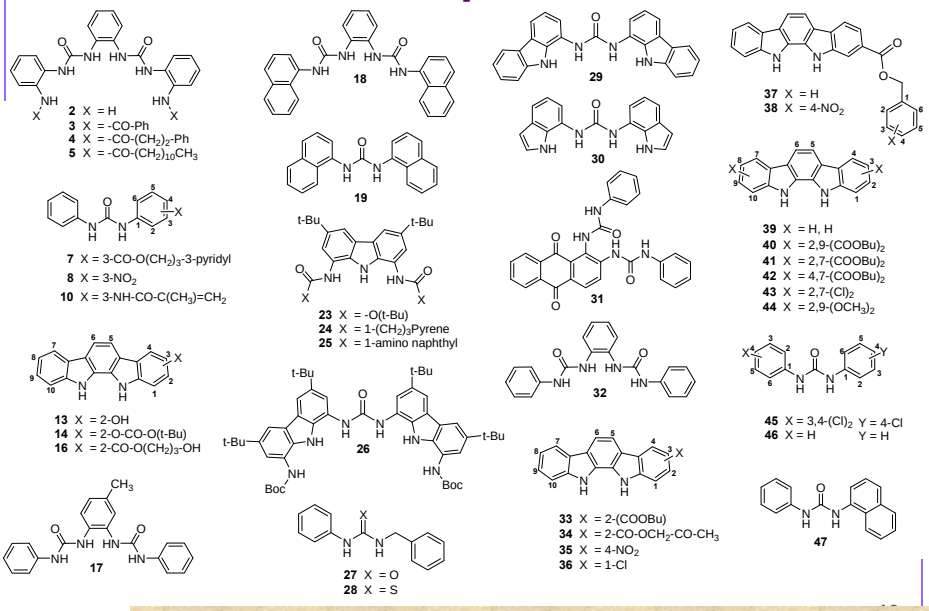
Receptors



S. A. Kadam *et al*, *Chem. Eur. J.* 2015, DOI: 10.1002/chem.201405858

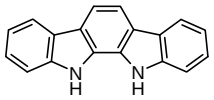
4 binding affinity ladders

Example: Acetate

No	Receptor number	logK_{ass}'	u_c^a	u_c^b	$\Delta\log K_{ass}$
26	Receptor **26**	4.94	0.01	0.09	
25	Receptor **25**	4.67	0.01	0.09	
30	1,3-diindolylurea **30**	4.63	0.01	0.09	
29	1,3-dicarbazolylurea **29**	4.56	0.01	0.09	
5	Receptor **5**	3.88	0.01	0.09	
4	Receptor **4**	3.85	0.01	0.09	
42	4,7-$(BuOCO)_2$ Indolocarbazole **42**	3.78	0.01	0.09	
18	Receptor **18**	3.74	0.01	0.09	
2	Receptor **2**	3.67	0.01	0.09	
17	Receptor **17**	3.64	0.01	0.09	
3	Receptor **3**	3.62	0.01	0.09	
7	Receptor **7**	3.58	0.01	0.09	
16	Receptor **16**	3.56	0.01	0.09	
24	Receptor **24**	3.38	0.01	0.09	
14	Receptor **14**	3.36	0.01	0.09	
39	**Indolocarbazole 39**	**3.27**	0.01	0.09	
10	Receptor **10**	3.24	0.01	0.09	
13	Receptor **13**	3.16	0.01	0.09	
31	Receptor **31**	3.09	0.01	0.09	
28	1-Benzyl-3-phenyl-thiourea **28**	2.80	0.01	0.09	
27	1-Benzyl-3-phenyl-urea **27**	2.51	0.01	0.09	
19	1,3-Di-naphthalen-1-yl-urea **19**	2.45	0.01	0.09	
23	Receptor **23**	2.41	0.01	0.09	

Anchoring and consistency

- Anchored to **Indolocarbazole**:



- Consistency standard deviation: $s = \sqrt{\frac{SS}{n_m - n_c}}$
- For all four scales: **s = 0.01 log units**
  - Shows the "average" mismatch between the relative values

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Usefulness of the scales

- Accurate binding strength comparison is possible
- Structure-binding relationships for designing new receptors and receptor arrays

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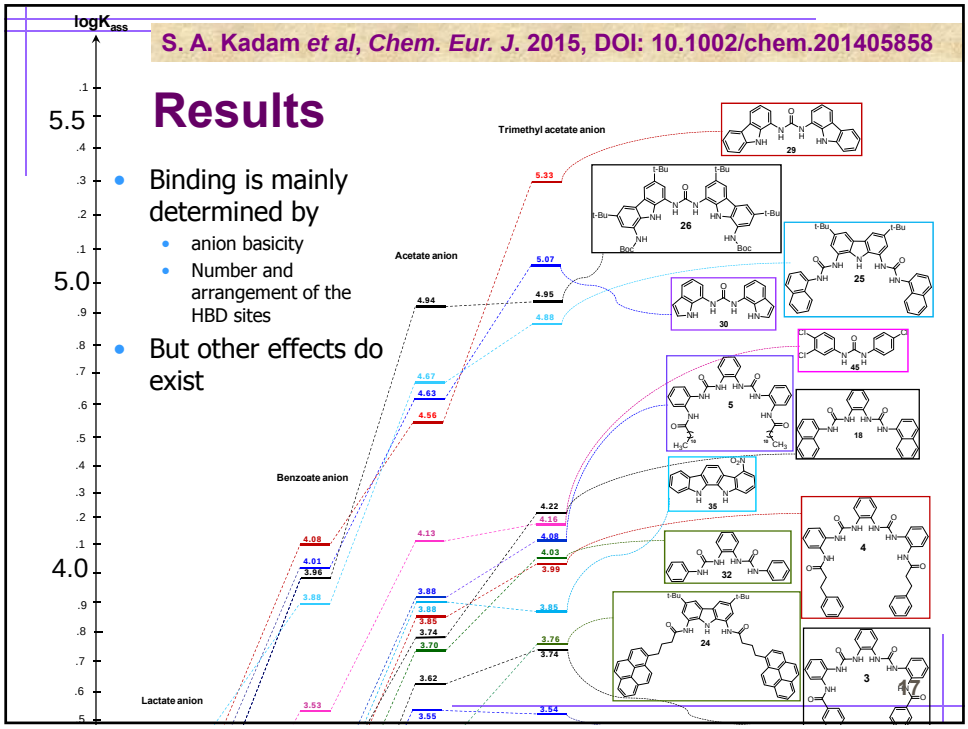
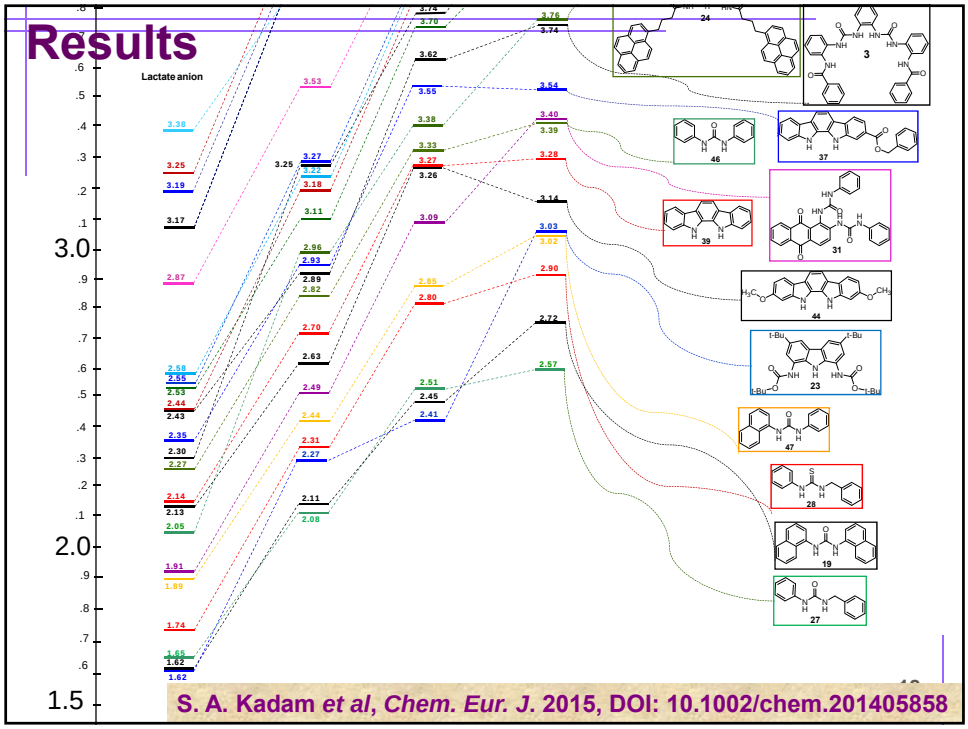
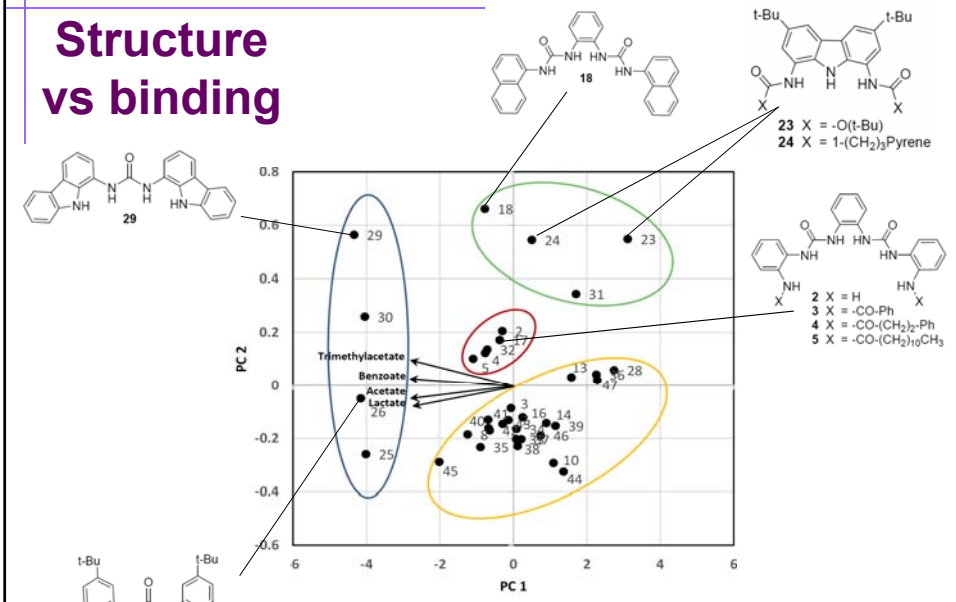

logK ass
S. A. Kadam et al, Chem. Eur. J. 2015, DOI: 10.1002/chem.201405858
Results
Binding is mainly determined by
anion basicity
Number and arrangement of the HBD sites
But other effects do exist
Trimethyl acetate anion
Acetate anion
Benzoate anion
Lactate anion
5.5
5.0
4.0


Results
Lactate anion
3.0
2.0
1.5
S. A. Kadam et al, Chem. Eur. J. 2015, DOI: 10.1002/chem.201405858

Structure vs binding



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Work in progress

- Scales with different anions
- More different receptors on the same scales

Different receptors to include in the scale are most welcome!

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Thanks to these people!

Kristjan

Sandip

Kerli

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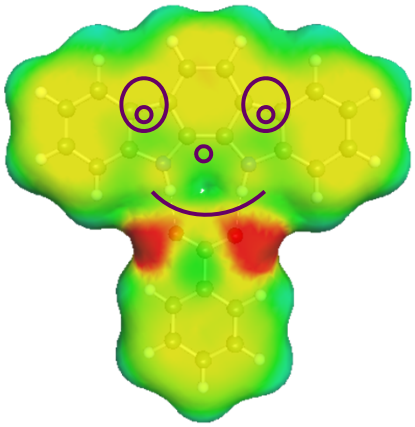

Thank you for your attention!

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