How to make maximum use of the available pK_a data in non-aqueous solvents?

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26 HSKIKI Šibenik Apr 11, 2019

Overview

- Brønsted acidity and basicity in solution
  - pK_a values
- Influence of solvent
  - Polarity, acidity, basicity
- What non-aqueous pK_a data are available
- How to estimate pK_a of X on solvent S?

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Why do we need non-aqueous pK_a data?

- Most reactions and processes run **heterolytically**
  - Very often involving acid-base interactions
  - Very often in non-aqueous solutions
  - For understanding them pK_a values are necessary
- Design of **novel acids and bases**
- Development of **theoretical calculation methods**

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Acidity of molecules

- Brønsted acidity of a **molecule** refers to its ability to donate proton to other molecules
  - Usually defined in terms of equilibrium constants (K_a, pK_a) or deprotonation energies (GA or ΔG_{acid})

This is the main topic of this talk

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Acidity of media

- Brønsted acidity of a **medium** refers to its ability to donate proton to molecules in the medium
  - In aqueous solution: pH
  - Strongly acidic solutions: H_0
  - "Unified pH Scale" (pH_{abs})

A. Suu et al, *Anal. Chem.* 2015, *87*, 2623

D. Himmel et al, *Angew. Chem. Int. Ed.* 2010, *49*, 6885

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Acidity of molecules in solution

- Acidity of molecules in solution is defined in the framework of the **Brønsted** theory via the **pK_a values**

$$HA + S \underset{}{\overset{K_a}{\rightleftharpoons}} A^- + SH^+$$

$$pK_a = -\log K_a = -\log \frac{a(A^-) \cdot a(SH^+)}{a(HA)}$$

pK_a: the lower the value, the more acidic

Acidity of an acid is very different in different solvents!

Basicity of molecules in solution

- Basicity of a molecule B in solution is defined as the **acidity** of its **conjugate acid** (its **pK_a** value)

$$BH^+ + S \overset{K_a}{\rightleftharpoons} B + SH^+$$

$$pK_a = -\log K_a = -\log \frac{a(B) \cdot a(SH^+)}{a(BH^+)}$$

pK_a: the higher the value, the more basic

Basicity of a base is very different in different solvents!

Acidity and basicity of molecules in the gas phase

- Acidity/basicity of molecules in the gas phase is expressed via deprotnation **Gibbs' free energy**

$$HA \overset{K_a}{\rightleftharpoons} A^- + H^+$$

$$GA = \Delta G^{o}_{acid} = -RT \ln K_a$$

$$BH^+ \overset{K_a}{\rightleftharpoons} B + H^+$$

$$GB = \Delta G^{o}_{base} = -RT \ln K_a$$

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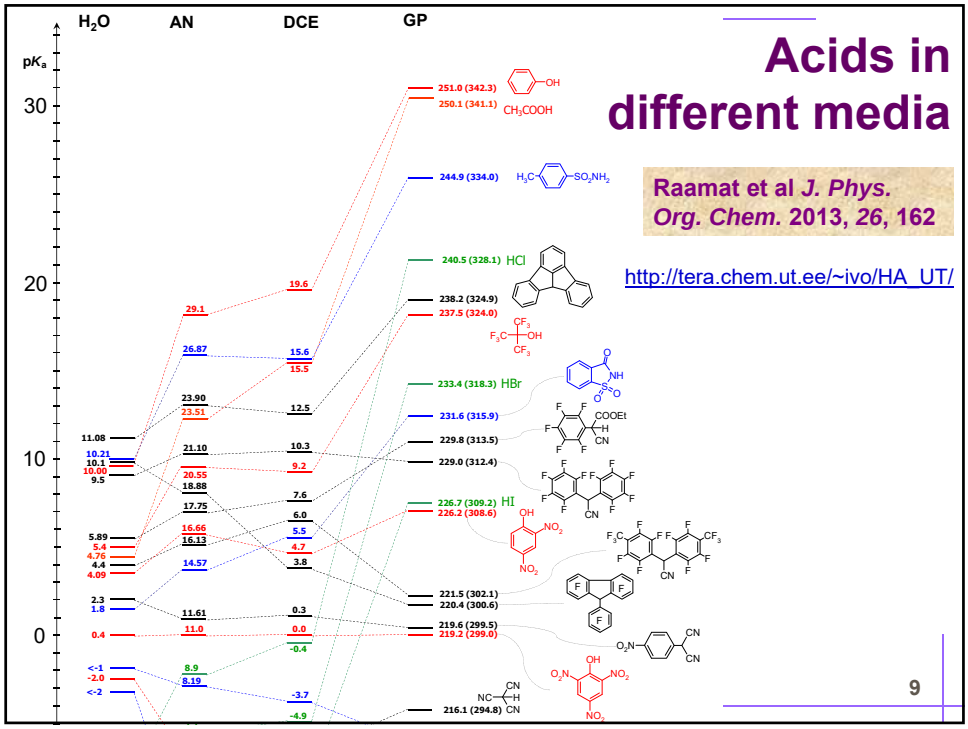
H2O
AN
DCE
GP
pKa
30
20
10
0
Acids in different media
Raamat et al J. Phys. Org. Chem. 2013, 26, 162
http://tera.chem.ut.ee/~ivo/HA_UT/
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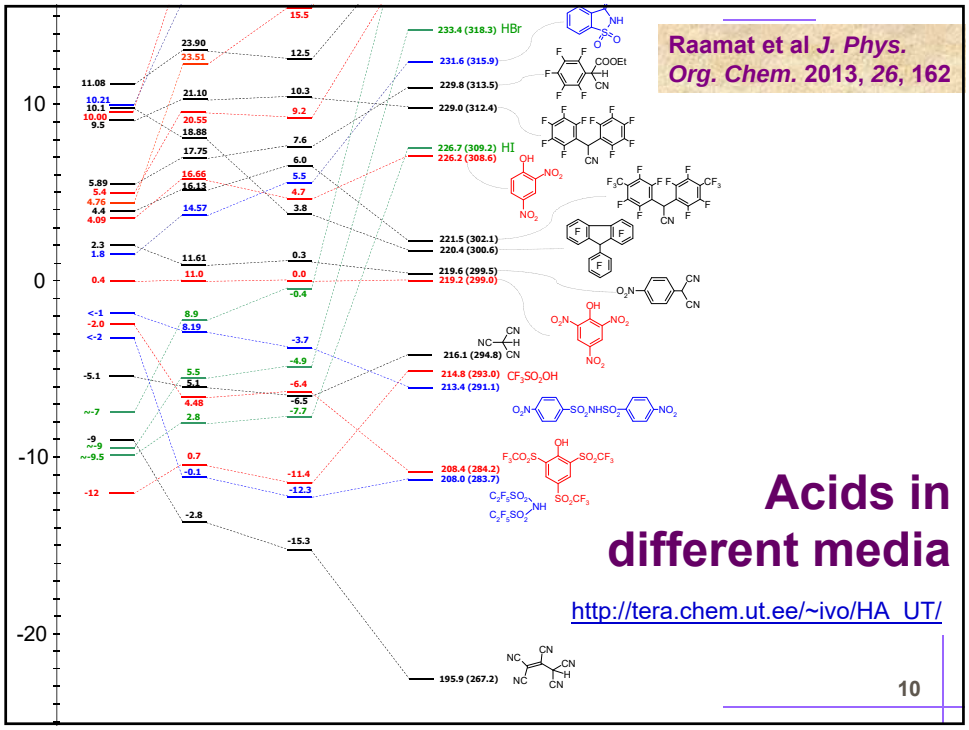
10
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-10
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Raamat et al J. Phys. Org. Chem. 2013, 26, 162
Acids in different media
http://tera.chem.ut.ee/~ivo/HA_UT/
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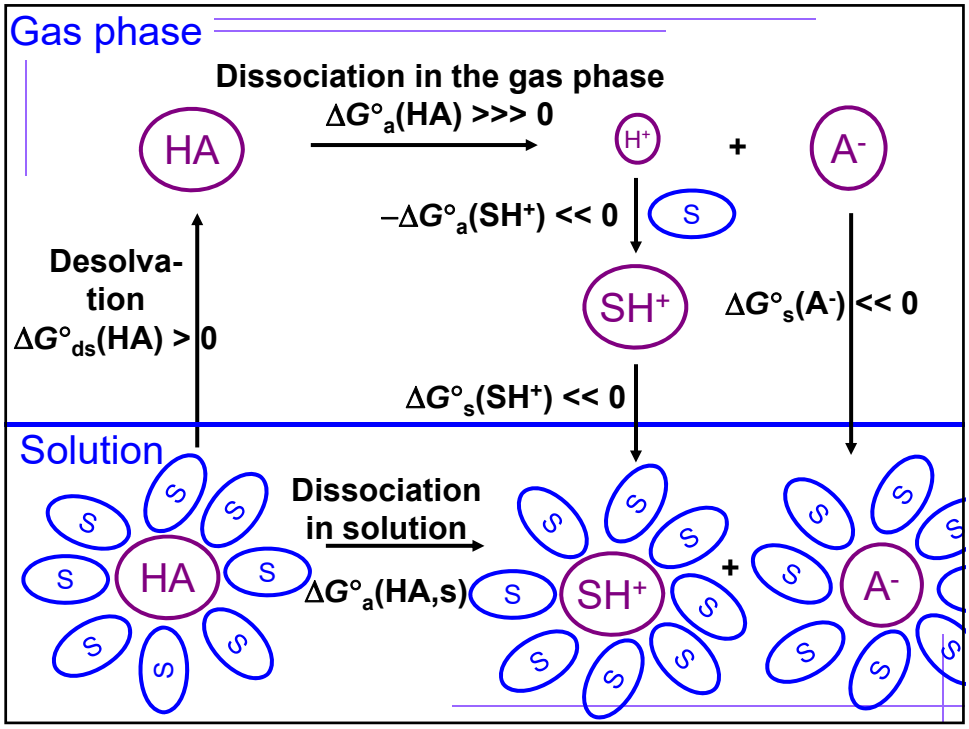
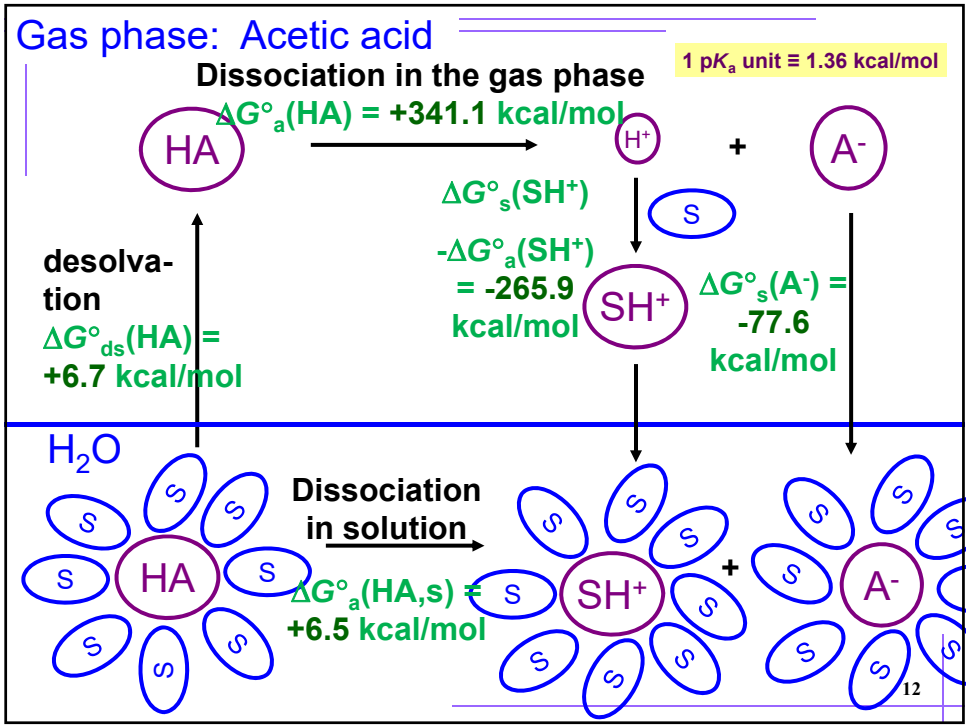

Gas phase
Dissociation in the gas phase
ΔG°a(HA) >>> 0
HA
H+
+
A-
–ΔG°a(SH+) << 0
S
Desolva-
tion
ΔG°ds(HA) > 0
SH+
ΔG°s(A-) << 0
ΔG°s(SH+) << 0
Solution
Dissociation
in solution
ΔG°a(HA,s)
HA
SH+
A-


Gas phase: Acetic acid
1 pKa unit ≡ 1.36 kcal/mol
Dissociation in the gas phase
ΔG°a(HA) = +341.1 kcal/mol
HA
H+
+
A-
ΔG°s(SH+)
S
-ΔG°a(SH+)
= -265.9
kcal/mol
SH+
ΔG°s(A-) =
-77.6
kcal/mol
desolva-
tion
ΔG°ds(HA) =
+6.7 kcal/mol
H2O
Dissociation
in solution
ΔG°a(HA,s) =
+6.5 kcal/mol
HA
SH+
A-
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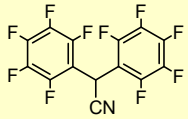
Acidity in solution and in the gas phase

Acid	pK_a (water)	pK_a (MeOH)	pK_a (DMSO)	pK_a (MeCN)	ΔG_a (GP) kcal/mol
HBr	~ -9	~1	~ -7	5.5	318.3
2,4-Dinitrophenol	4.09	7.9	5.1	16.7	308.6
Acetic acid	4.76	9.6	12.3	23.51	341.1
	9.5		8.0	21.1	312.4

- Solvation energias are very different
- In water HBr is 10^{13} times **stronger** than 2,4-DNP
- In the gas phase HBr is 10^{7} times **weaker** than 2,4-DNP

1 pK_a unit ≡ 1.36 kcal/mol

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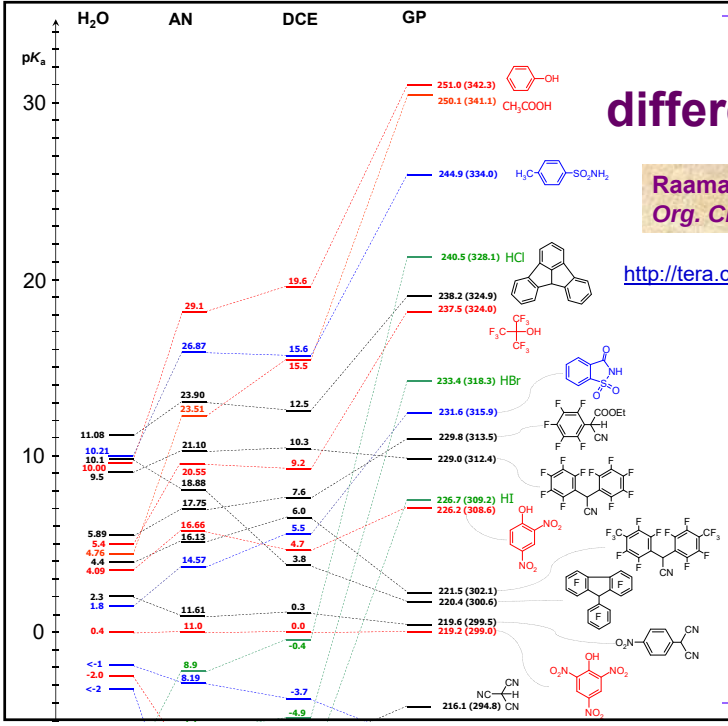
Acids in different media



Raamat et al *J. Phys. Org. Chem.* 2013, *26*, 162

http://tera.chem.ut.ee/~ivo/HA_UT/

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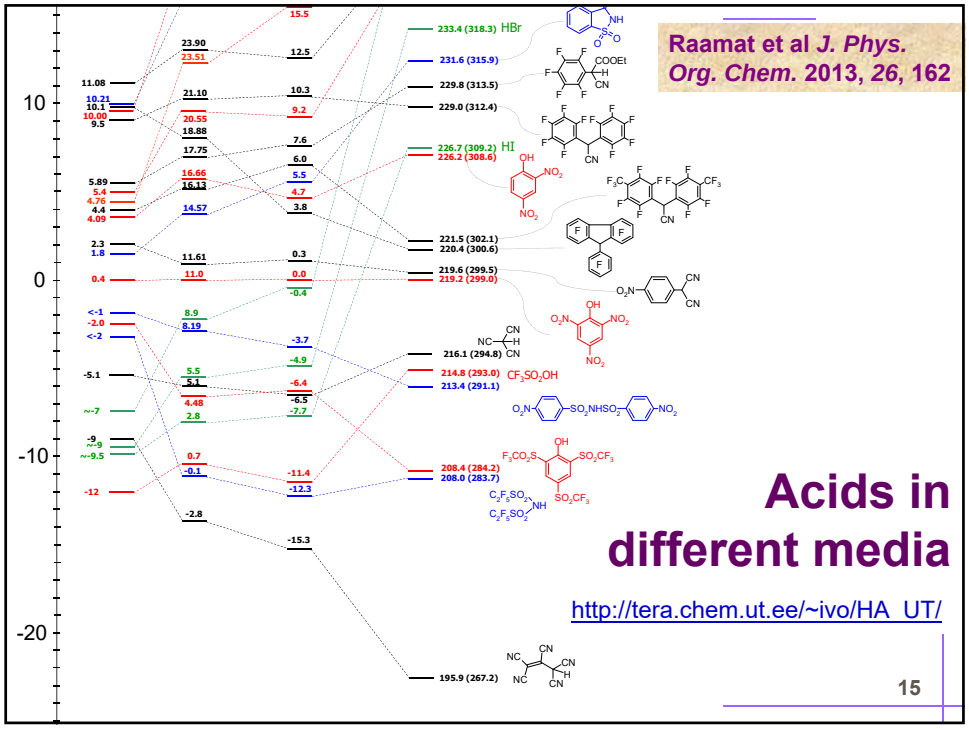
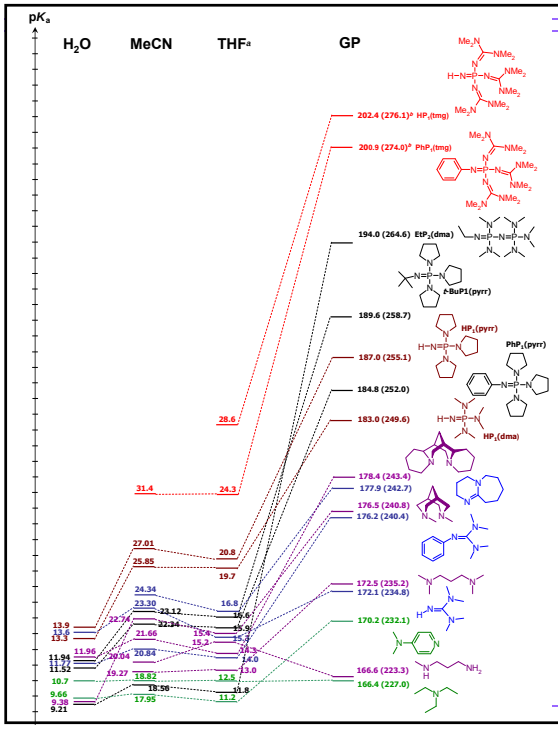


Raamat et al *J. Phys. Org. Chem.* 2013, *26*, 162

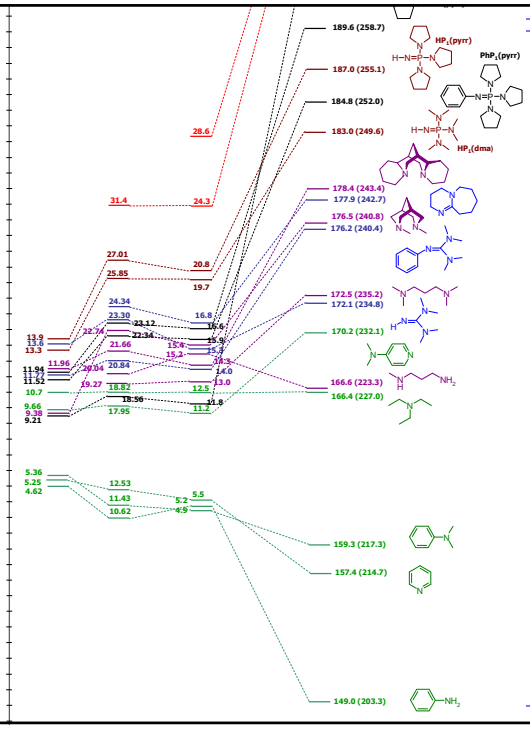
Acids in different media

http://tera.chem.ut.ee/~ivo/HA_UT/



Bases in different media

http://tera.chem.ut.ee/~ivo/HA_UT/



Bases in different media

http://tera.chem.ut.ee/~ivo/HA_UT/

Generalised acid-base reaction in a non-aqueous solvent

$$(AH)_S + (:B)_S \underset{}{\overset{K_1}{\leftrightarrows}} (AH\cdots:B)_S \overset{K_2}{\leftrightarrows} (A^-:\cdots HB^+)_S \text{ or } (A^-:HB^+)_S \overset{K_3}{\leftrightarrows}$$

HB complex *HB complex* *contact ion pair*

$$\overset{K_3}{\leftrightarrows} (A^-:\,//\,HB^+)_S \overset{K_4}{\leftrightarrows} (A^-:)_S + (HB^+)_S$$

solvent-separated ion pair *free ions*

How far the process goes depends on
--1-- Acid and base strengths of the compounds
--2-- Solvent

How does solvent influence pK_a?

- By solvating the species
  - Ions are much solvated **much stronger**
    - First approximation: neglect neutrals
  - Especially **small ions** and/or with **localized charge**
- HB acceptor properties / basicity
  - Solvation of H^+ , HA, BH^+
- HB donor properties / acidity
  - Solvation of A^-, B:
- Dielectric constant
  - Promotes dissociation

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Solvent acidity and basicity: pK_{auto}

$$(SH)_S + (SH)_S \overset{K_{auto}}{\leftrightarrows} (SH_2^+)_S + (S^-)_S$$

$$K_{auto} = a(AH_2^+) \cdot a(S^-) \qquad pK_{auto} = -\log K_{auto}$$

- pK_{auto} defines the **span of pKa scale**
  - Differentiating ability
- **High pK_{auto}** is preferable

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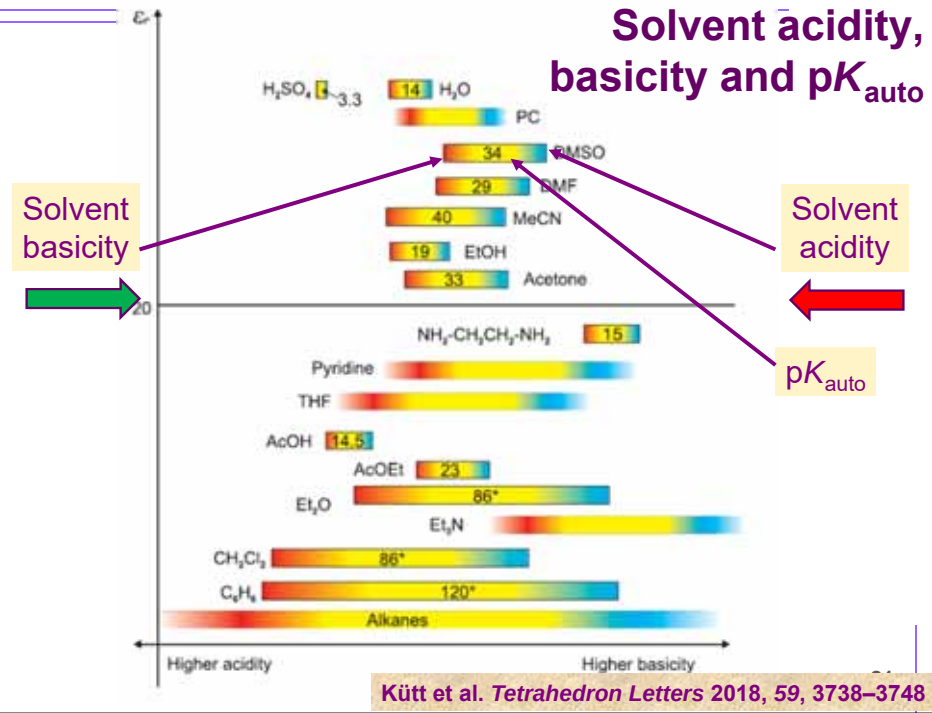
Solvent acidity, basicity and pK_{auto}



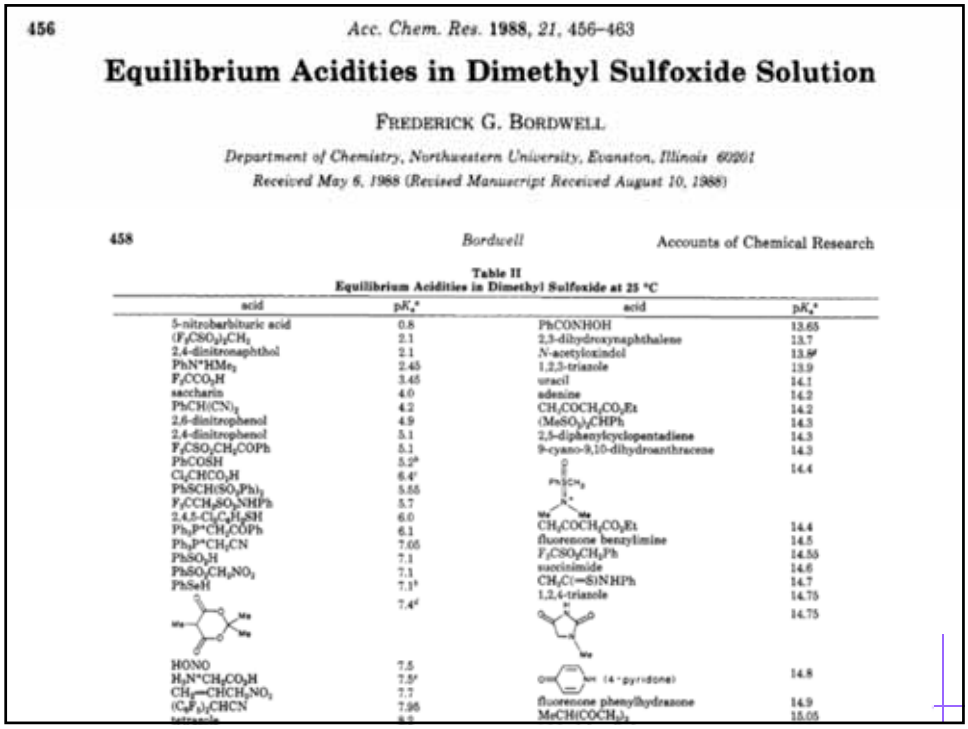
Kütt et al. *Tetrahedron Letters* 2018, *59*, 3738–3748

Some solvents

Solvent/ medium	ε	HBA: DN, B'	HBD α	pK_{auto}	Useful for
Gas phase	1	–	–	–	Any acid or base
Heptane	1.94	0.0	0	–	(Any acid or base)*
THF	7.47	20, 287	0	Very high	Weak acids, strong bases**
1,2-Dichloro-Ethane	10.7	0.1, 40		Very high	Strong acids, weak bases**
MeCN	35.9	14.1, 160	0.19	ca 39	Strong acids, weak bases
DMSO	46.7	29.8, 362	0	ca 33	Weak acids, strong bases
Methanol	33	High	0.98	18.9	Medium acids and bases
Vesi	81	High	1.17	14.0	Medium acids and bases

*** Solubility issues**

**** Ion-pair acidities and basicities**



456 Acc. Chem. Res. 1988, 21, 456–463

Equilibrium Acidities in Dimethyl Sulfoxide Solution

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Received May 6, 1988 (Revised Manuscript Received August 10, 1988)

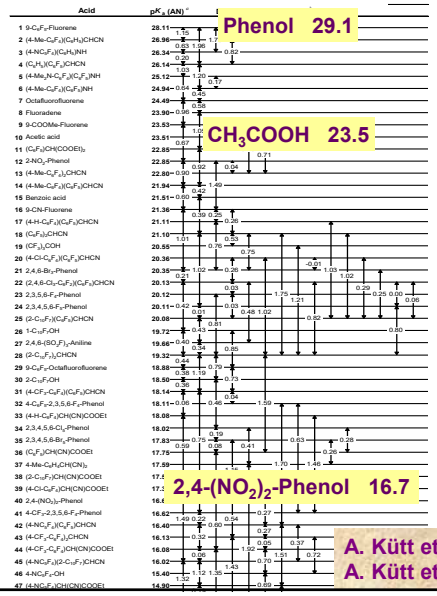
458 Bordwell Accounts of Chemical Research

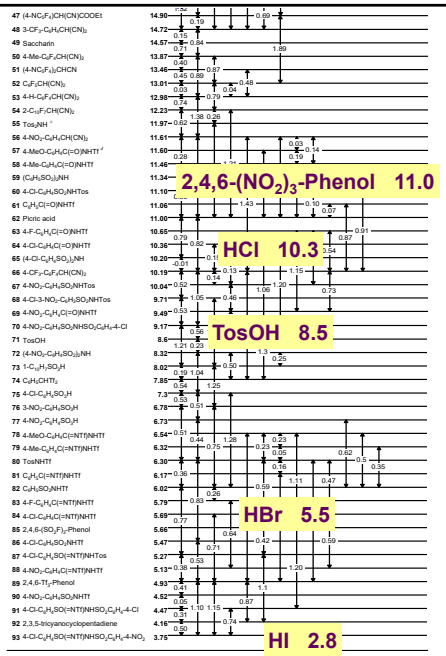
Table II
Equilibrium Acidities in Dimethyl Sulfoxide at 25 °C

acid	pK_a*	acid	pK_a*
5-nitrobarbituric acid	0.8	PhCONHOH	13.65
$(F_3CSO_2)_2CH_2$	2.1	2,3-dihydroxynaphthalene	13.7
2,4-dinitronaphthol	2.1	*N*-acetyloxindol	13.8[g]
PhN^+HMe_2	2.45	1,2,3-triazole	13.9
F_3CCO_2H	3.45	uracil	14.1
saccharin	4.0	adenine	14.2
$PhCH(CN)_2$	4.2	$CH_3COCH_2CO_2Et$	14.2
2,6-dinitrophenol	4.9	$(MeSO_2)_2CHPh$	14.3
2,4-dinitrophenol	5.1	2,5-diphenylcyclopentadiene	14.3
$F_3CSO_2CH_2COPh$	5.1	9-cyano-9,10-dihydroanthracene	14.3
PhCOSH	5.2[b]		14.4
Cl_3CHCO_2H	6.4[c]		
$PhSCH(SO_2Ph)_2$	5.55		
$F_3CCH_2SO_2NHPh$	5.7		
2,4,5-$Cl_3C_6H_2SH$	6.0		
$Ph_3P^+CH_2COPh$	6.1	$CH_3COCH_2CO_2Et$	14.4
$Ph_3P^+CH_2CN$	7.05	fluorenone benzylimine	14.5
$PhSO_2H$	7.1	$F_3CSO_2CH_2Ph$	14.55
$PhSO_2CH_2NO_2$	7.1	succinimide	14.6
PhSeH	7.1[b]	$CH_3C(=SiNHPh$	14.7
	7.4[d]	1,2,4-triazole	14.75
			14.75
HONO	7.5	(4-pyridone)	14.8
$H_3N^+CH_2CO_2H$	7.5[b]		
$CH_2{=}CHCH_2NO_2$	7.7	fluorenone phenylhydrazone	14.9
$(C_6F_5)_2CHCN$	7.95	$MeCH(COCH_3)_2$	15.05
tetrazole	8.2		

Self-consistent acidity scale (pK_a scale) in MeCN

http://tera.chem.ut.ee/~ivo/HA_UT/





A. Kütt et al, *J. Org. Chem.* 2006, *71*, 2829
A. Kütt et al *J. Org. Chem.* 2011, *76*, 391

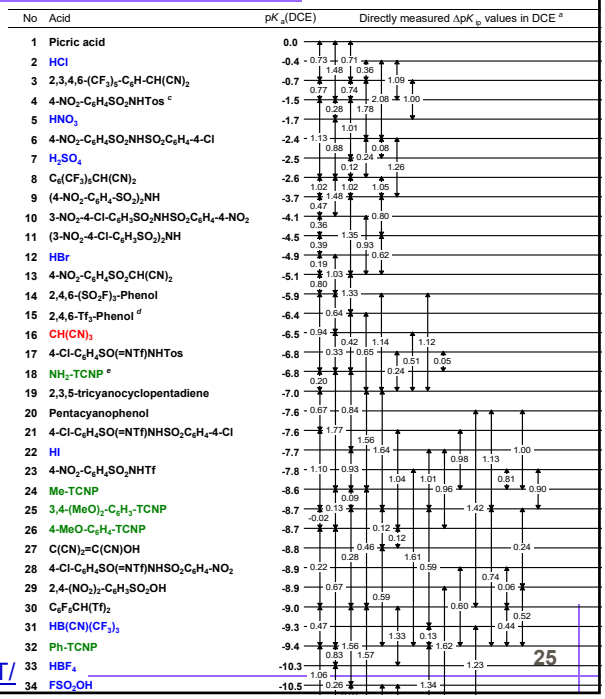
1,2-DCE acidity scale

- **The most acidic equilibrium acidity scale in a constant-composition medium**

- Relative acidities
  - Not easy to anchor
  - Some values available in literature, but are very doubtful

A. Kütt et al *J. Org. Chem.* 2011, *76*, 391

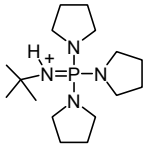
http://tera.chem.ut.ee/~ivo/HA_UT/



1,2-DCE acidity scale

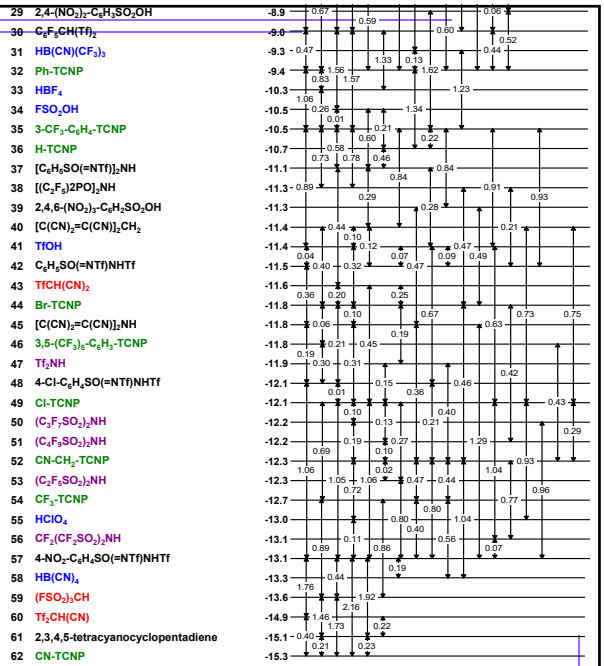
- Ion pair acidities
- Counter-ion:

t-BuP$_1$(pyrr)H+



- Aqueous pK_a (H_0) values down to -10 .. -15
- In pipeline:
  - Weaker acids
  - Weak bases

A. Kütt et al *J. Org. Chem.* 2011, *76*, 391



Self-consistent basicity scale in MeCN (1)

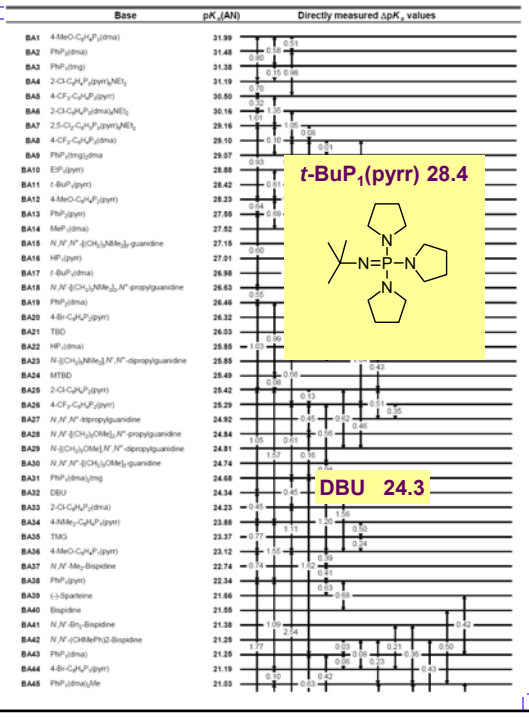
- Anchor: Pyridine
- Free ions
- Titrants:
  - TfOH
  - *t*-BuP$_1$(pyrr)

I. Kaljurand et al *J. Org. Chem.* 2005, *70*, 1019

A. Kütt, PhD thesis

… and other works

http://tera.chem.ut.ee/~ivo/HA_UT/



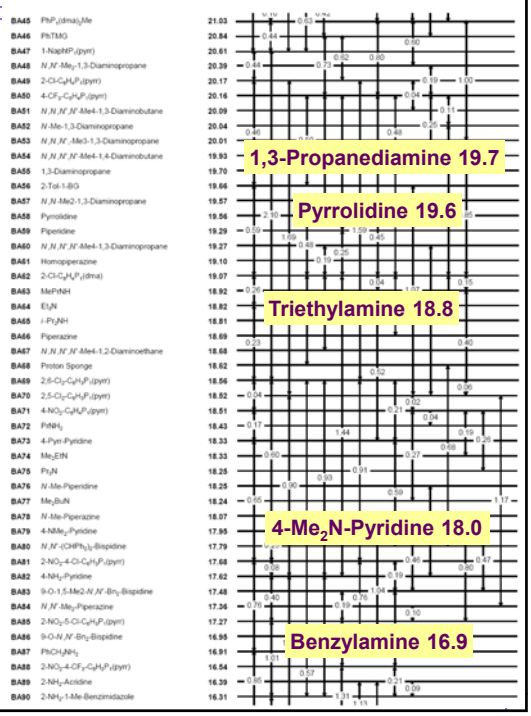
Self-consistent basicity scale in MeCN (2)

I. Kaljurand et al *J. Org. Chem.* 2005, *70*, 1019

A. Kütt, PhD thesis

… and other works

http://tera.chem.ut.ee/~ivo/HA_UT/



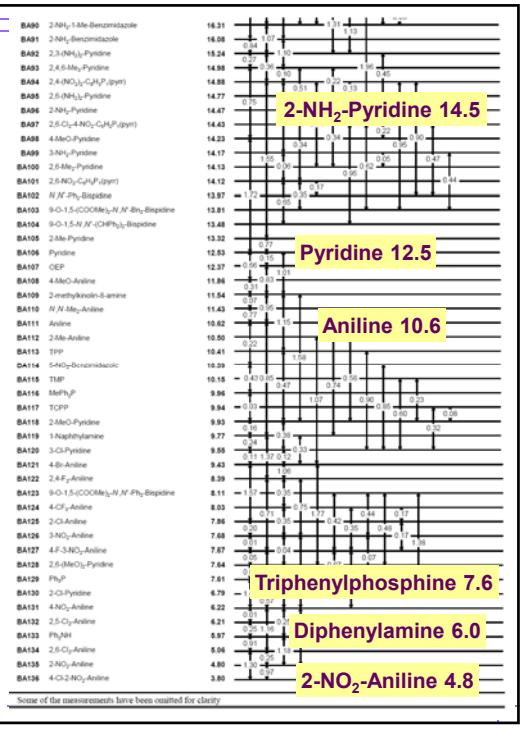
Self-consis-tent basicity scale in MeCN (3)

I. Kaljurand et al *J. Org. Chem.* 2005, *70*, 1019

A. Kütt, PhD thesis

… and other works

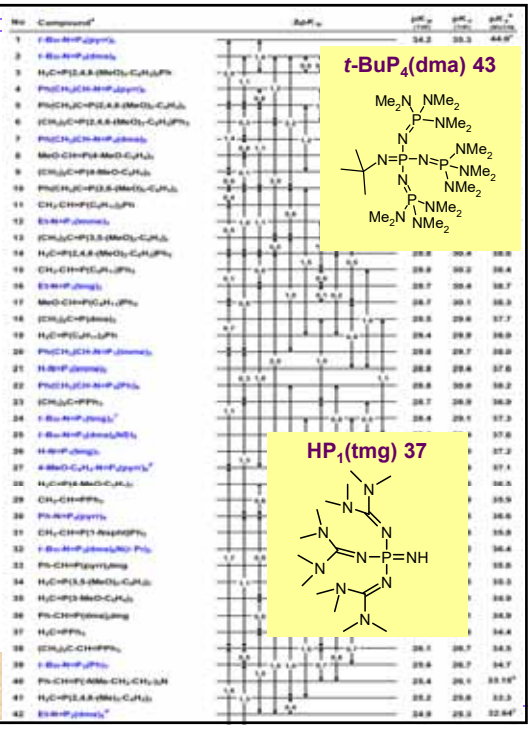
http://tera.chem.ut.ee/~ivo/HA_UT/

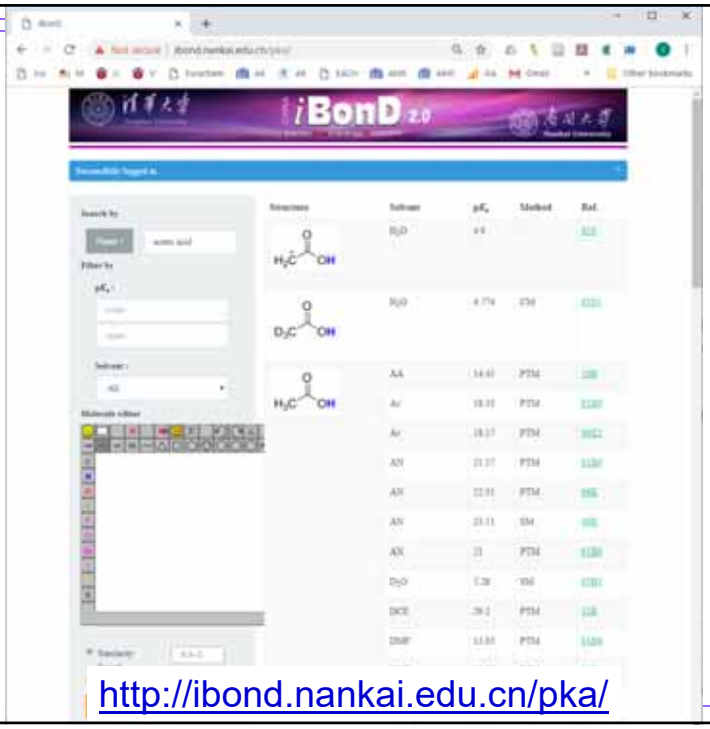


Self-consistent basicity scale in THF

- Anchor: Triethylamine
- Ion pairs
  - Counterion $MeSO_3^-$
- Titrants:
  - $MeSO_3H$
  - *t*-BuP_4(pyrr)
  - Liberation of bases: KH

J. Saame et al *J. Org. Chem.* 2016, *81*, 7349





http://ibond.nankai.edu.cn/pka/

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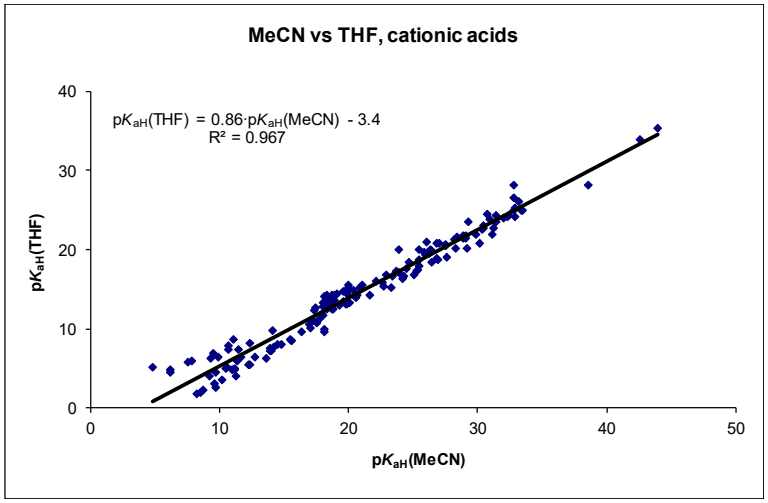
Typical issue: no pKa data for X in solvent S

- Possible solutions:
  - **Measure**
  - **Compute**
    - Usually correlations are needed for corrections
  - **Correlate between solvents**
    - Reliable data of **similar compounds** are needed in **both solvents**
      - Best if large span
    - Works best within a **homogeneous compound series**
    - Not between any solvents
  - **Cross-use between solvents**
    - Only suitable for **„stronger-weaker"** statements

Kütt et al. *Tetrahedron Letters* 2018, *59*, 3738–3748

Sometimes correlations are good …



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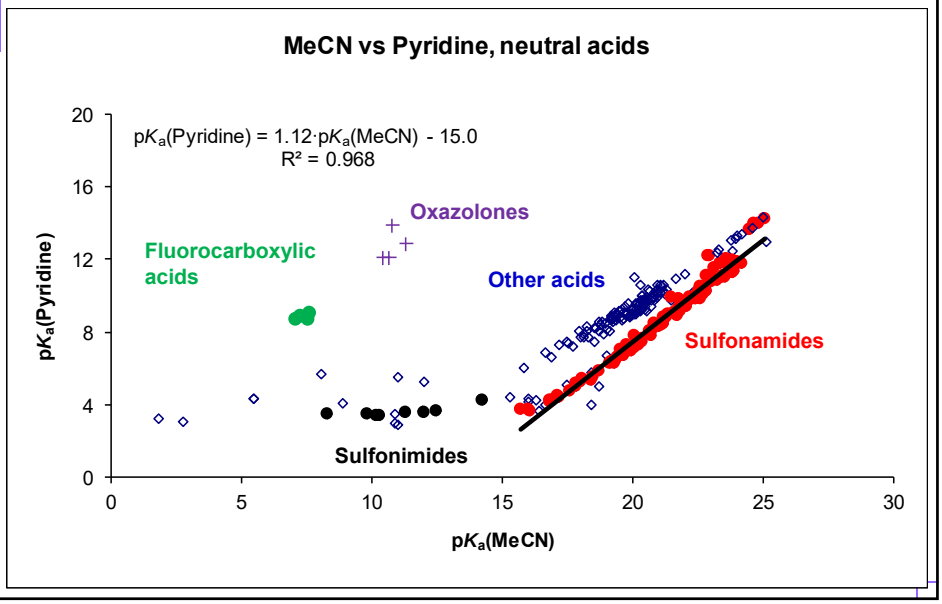
… Sometimes tricky



pK_a Correlation possibilities

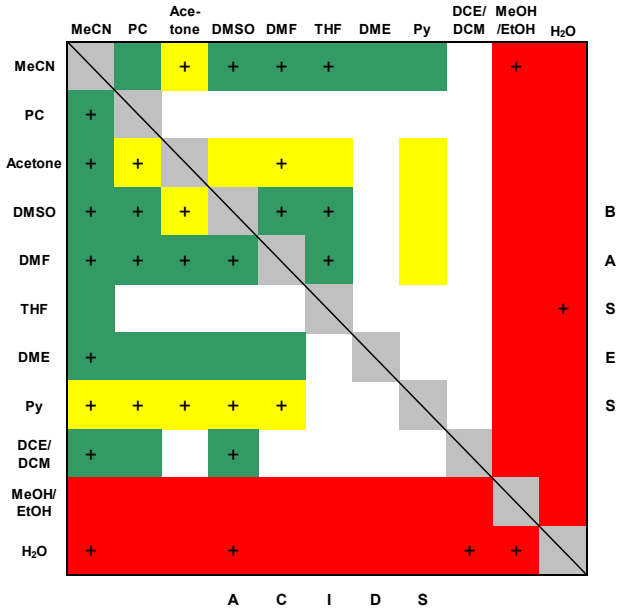
Legend:

Reliable

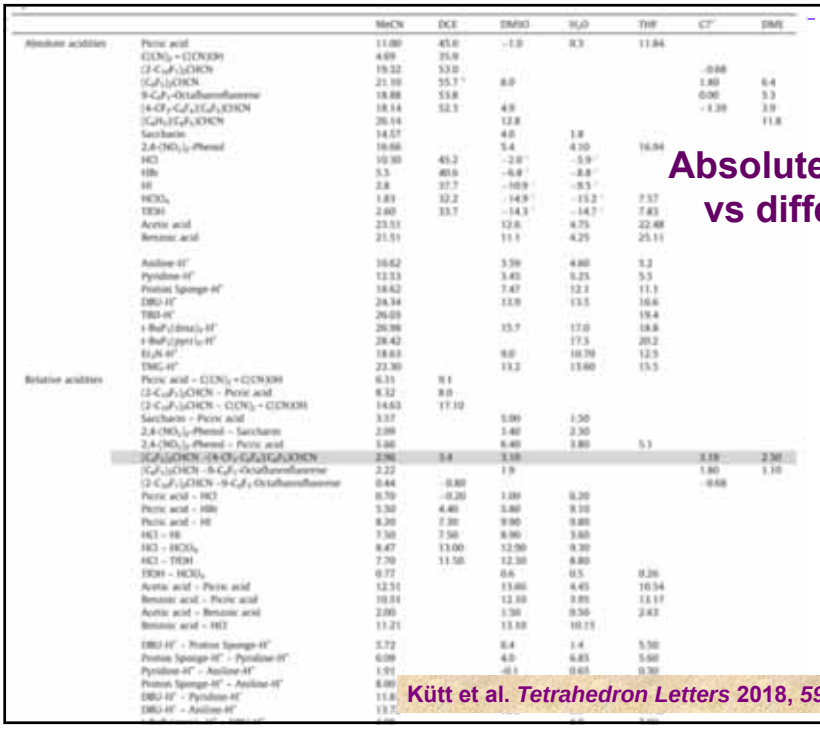
Lower reliability

Not reliable

„+": real data available

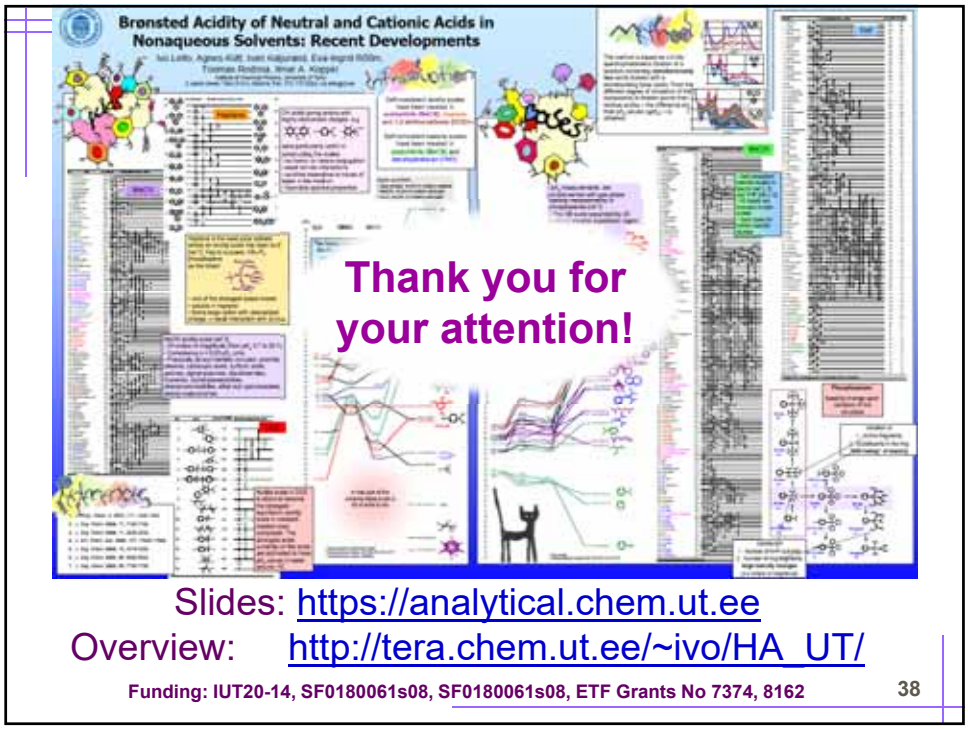


Kütt et al. *Tetrahedron Letters* 2018, *59*, 3738–3748



Absolute values vs differences

Kütt et al. *Tetrahedron Letters* 2018, *59*, 3738–3748



Slides: https://analytical.chem.ut.ee

Overview: http://tera.chem.ut.ee/~ivo/HA_UT/

Funding: IUT20-14, SF0180061s08, SF0180061s08, ETF Grants No 7374, 8162

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