



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?

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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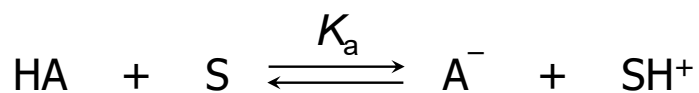
Acidity of media

- 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**



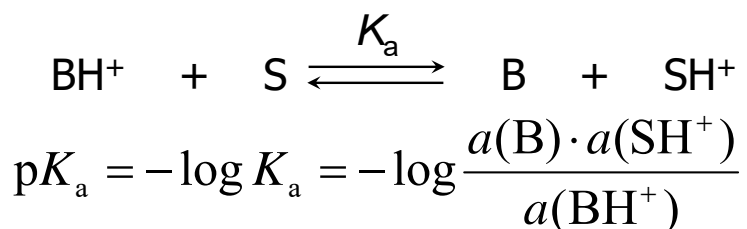
$$\text{p}K_a = -\log K_a = -\log \frac{a(\text{A}^-) \cdot a(\text{SH}^+)}{a(\text{HA})}$$

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)

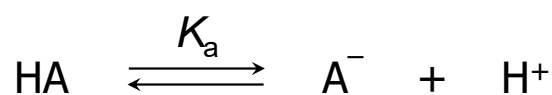


pK_a: the higher the value, the more basic

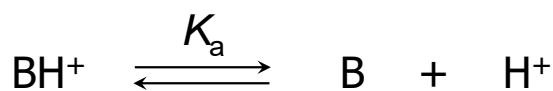
Basicity of a base is very different in different solvents!

Acidity and basicity of molecules in the gas phase

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

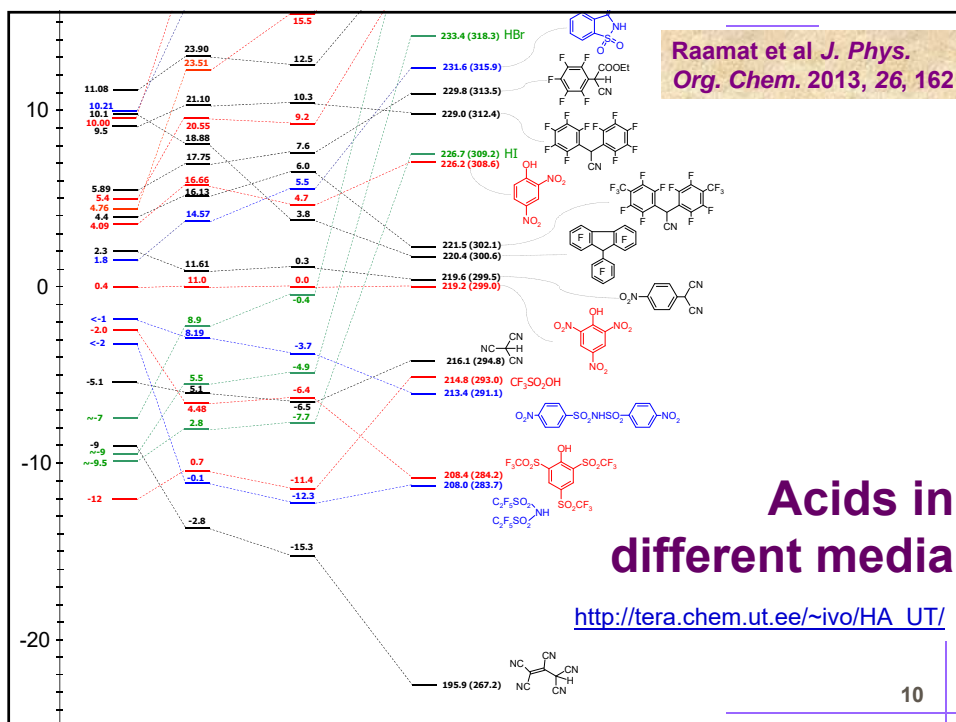
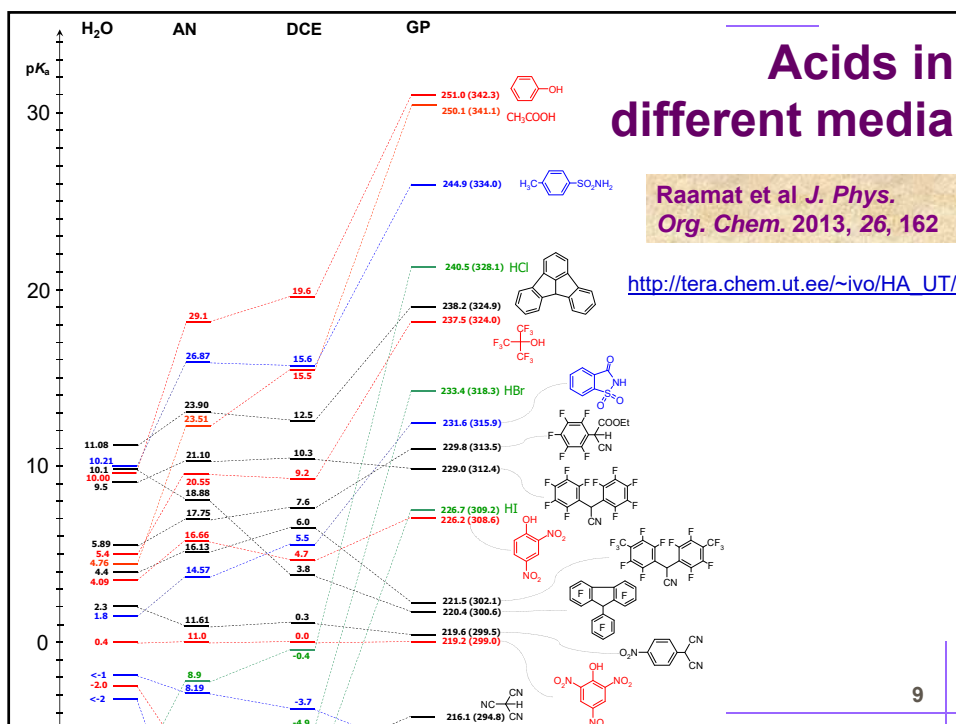


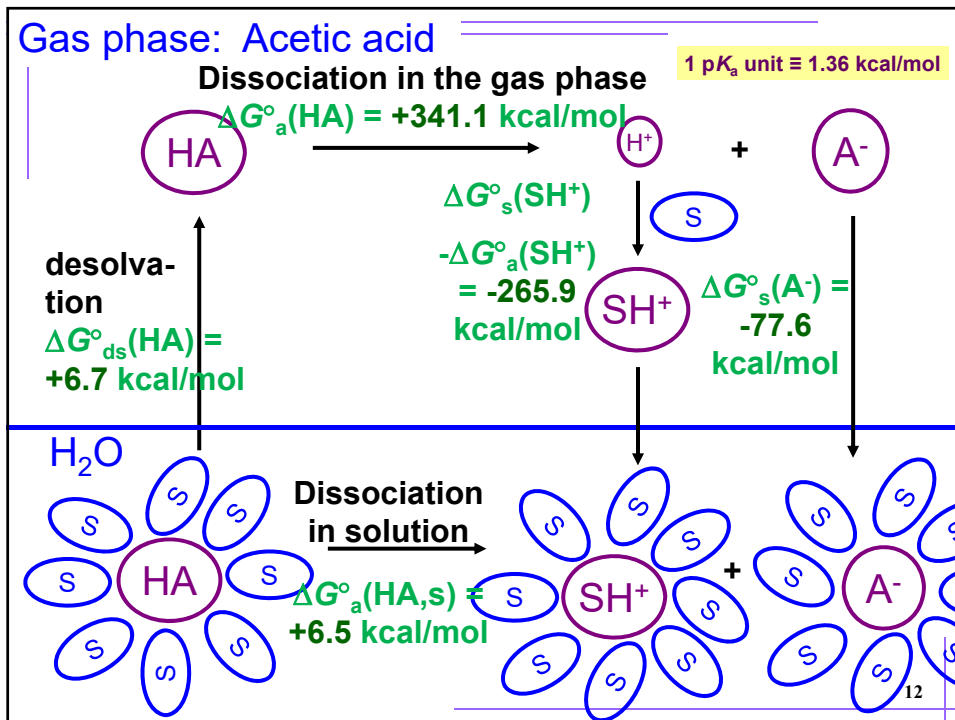
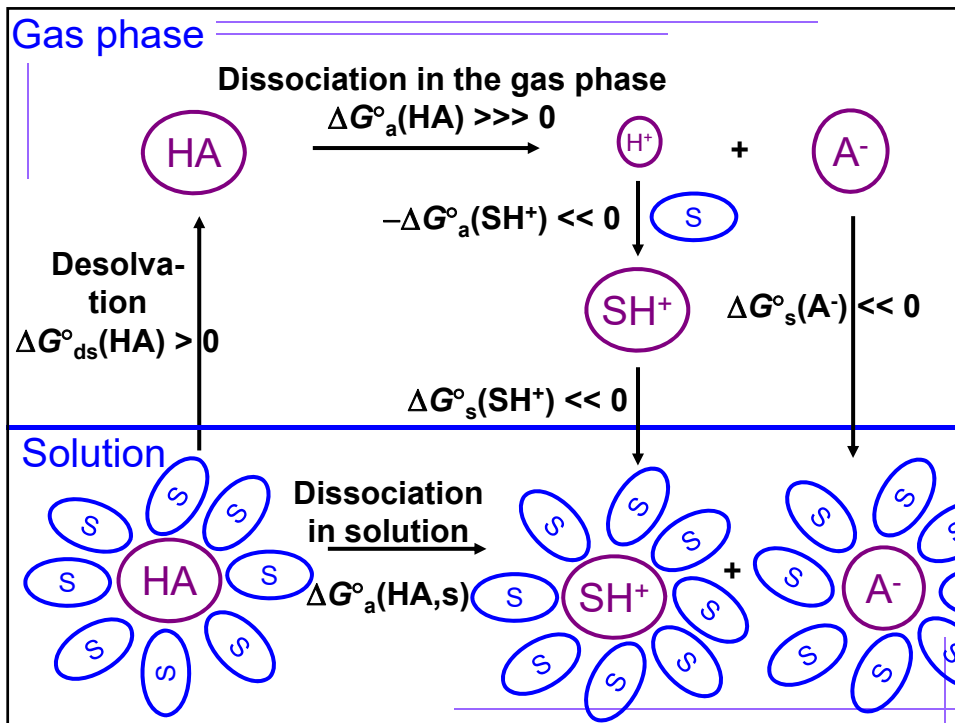
$$G_A = \Delta G_{\text{acid}}^{\circ} = -RT \ln K_a$$



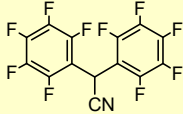
$$G_B = \Delta G_{\text{base}}^{\circ} = -RT \ln K_a$$

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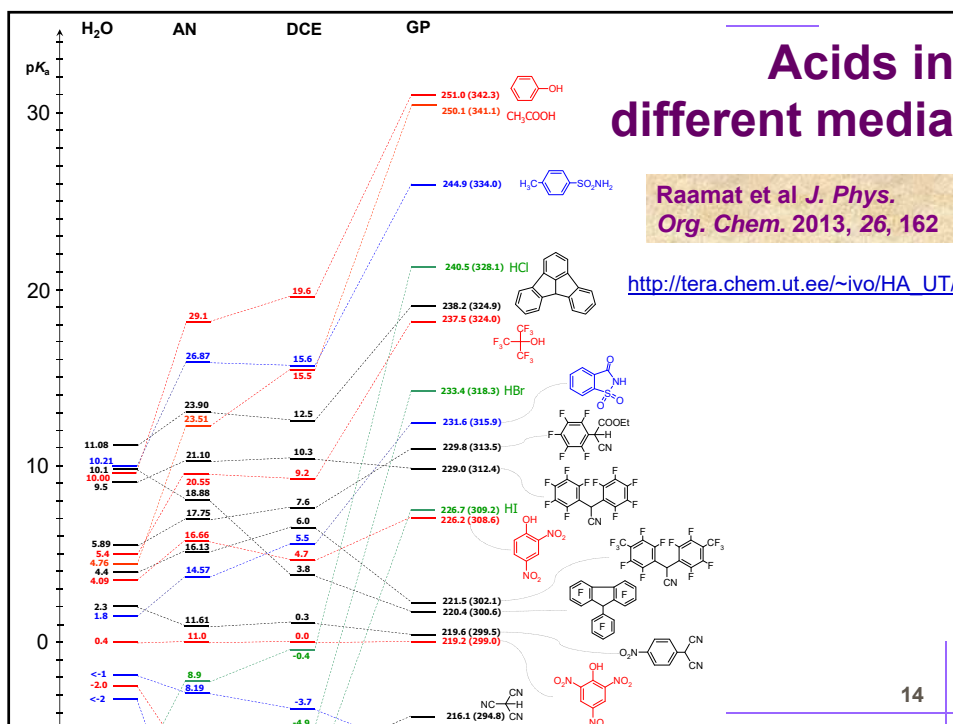


Acidity in solution and in the gas phase

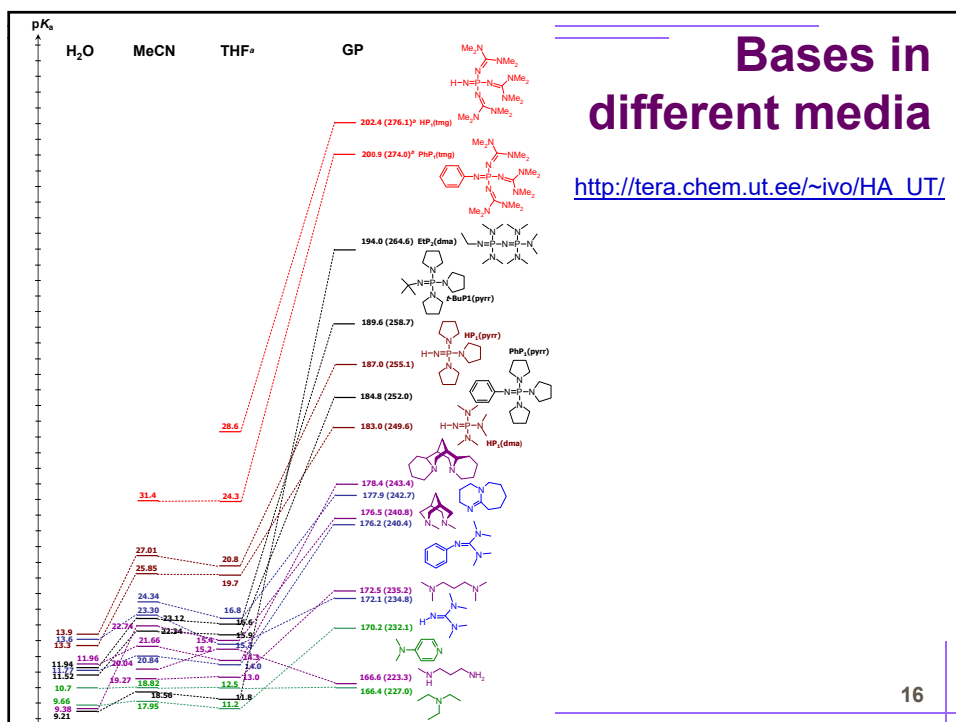
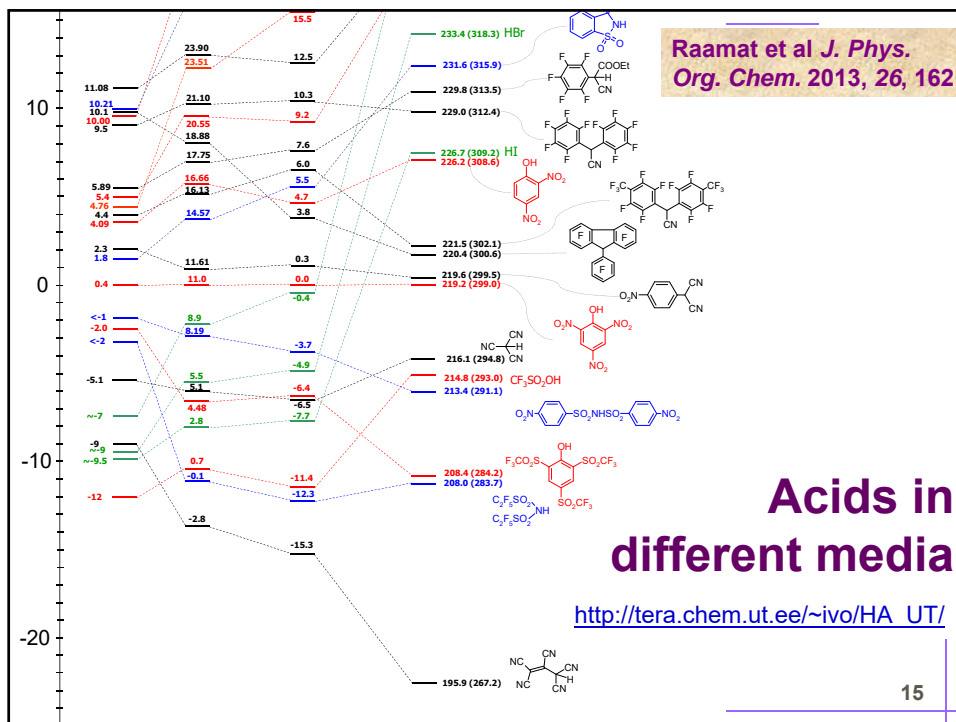
Acid	pK _a (water)	pK _a (MeOH)	pK _a (DMSO)	pK _a (MeCN)	ΔG _a (GP) kcal/mol
HBr	~ -9	~1	~ -7	5.5	318.3
2,4-Dinitrophenol	4.09	7.9	5.1	16.7	308.6
Acetic acid	4.76	9.6	12.3	23.51	341.1
	9.5		8.0	21.1	312.4

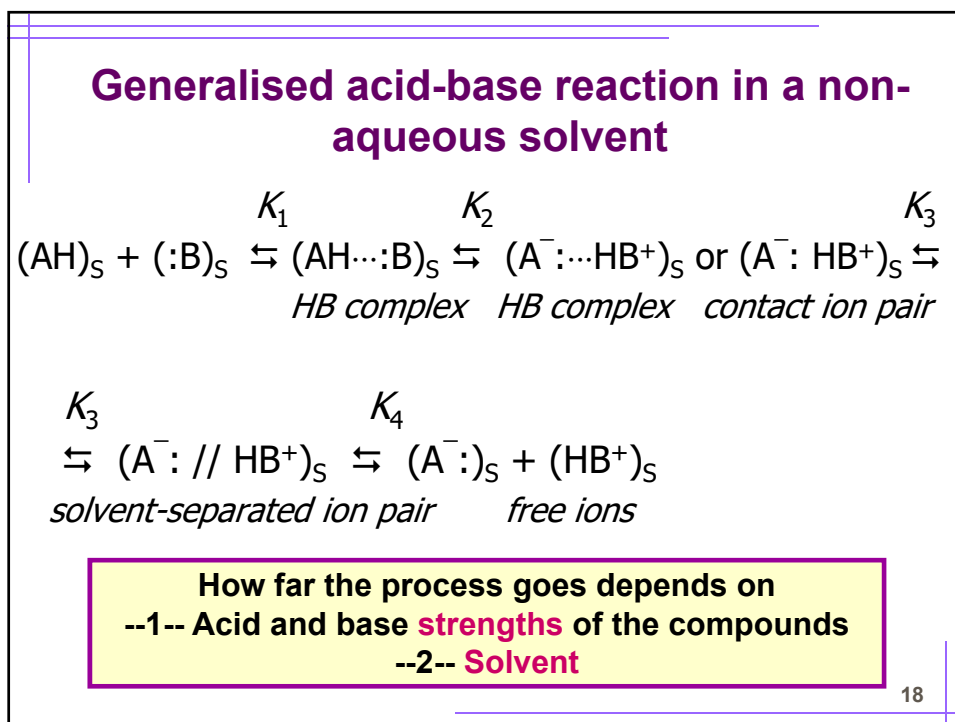
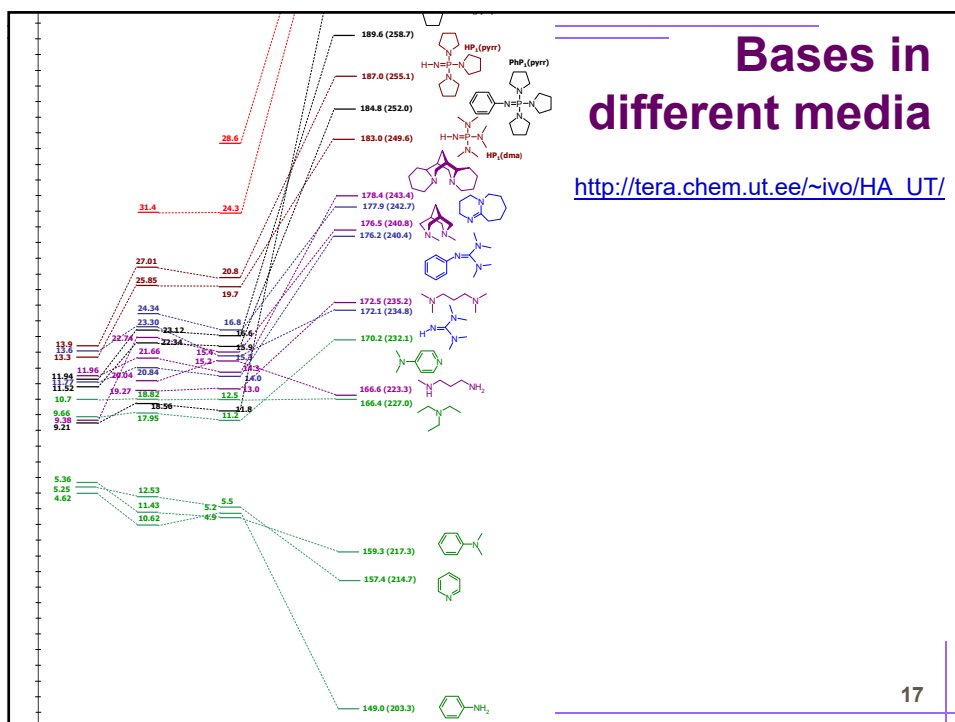
- Solvation energies are very different
- In water HBr is 10¹³ times **stronger** than 2,4-DNP
- In the gas phase HBr is 10⁷ times **weaker** than 2,4-DNP

1 pK_a unit ≡ 1.36 kcal/mol 13



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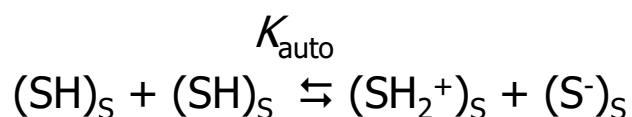


How does solvent influence pK_a ?

- 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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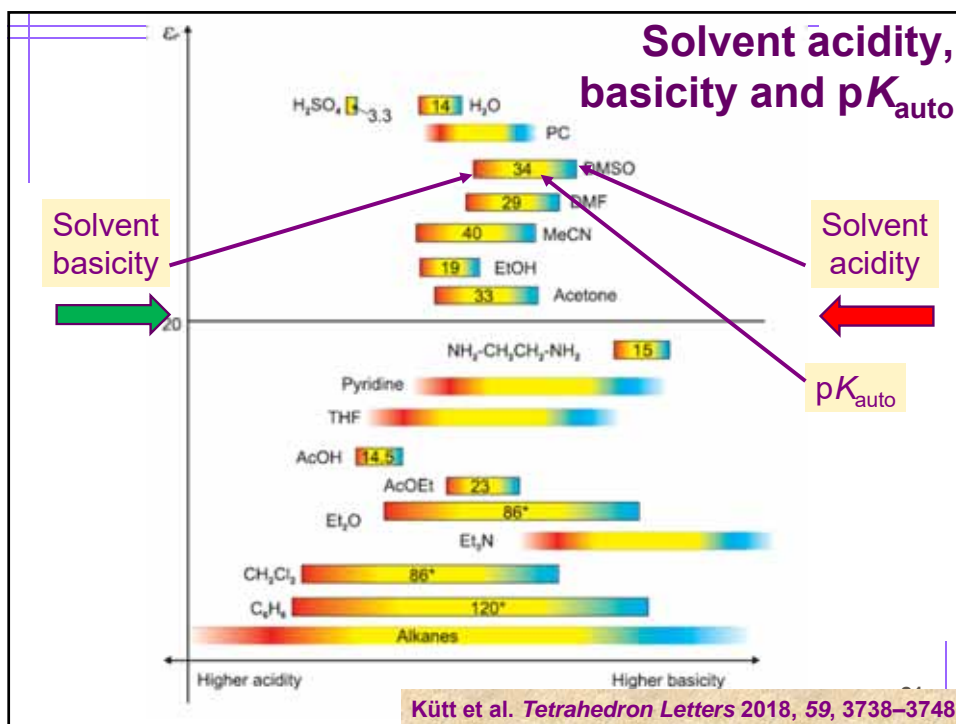
Solvent acidity and basicity: pK_{auto}



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

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

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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

Equilibrium Acidities in Dimethyl Sulfoxide Solution

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


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

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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 ₂ CSO ₂) ₂ CH ₂	2.1	2,3-dihydroxynaphthalene	13.7
2,4-dinitrophenol	2.1	N-acetylindol	13.8 ^a
Ph ⁺ NHM ₂	2.45	1,2,3-triazole	13.9
F ₂ CCO ₂ H	3.45	uracil	14.1
saccharin	4.0	adenine	14.2
PhCH(CN) ₂	4.2	CH ₃ COCH ₂ CO ₂ Et	14.2
2,6-dinitrophenol	4.9	(MeSO ₂) ₂ CHPh	14.3
2,4-dinitrophenol	5.1	2,3-diphenylcyclopentadiene	14.3
F ₂ CSO ₂ CH ₂ COPh	5.1	9-cyano-9,10-dihydroanthracene	14.3
PhCO ₂ H	5.2 ^a		
Cl ₂ CHCO ₂ H	6.4 ^a		14.4
PhSCH(SO ₂ Ph) ₂	5.55		
F ₂ CCH(SO ₂ NHPh) ₂	5.7	CH ₃ COCH ₂ CO ₂ Et	14.4
2,4,5-Cl ₃ C ₆ H ₃ SH	6.0	fluorenone benzylimine	14.5
Ph ₂ P ⁺ CH ₂ COPh	6.1	F ₂ CSO ₂ CH ₂ Ph	14.55
Ph ₂ P ⁺ CH ₂ CN	7.05	succinimide	14.6
PhSO ₂ H	7.1	CH ₂ (=Si)NHPh	14.7
PhSO ₂ CH ₂ NO ₂	7.1	1,2,4-triazole	14.75
PhSeH	7.1 ^a		
	7.4 ^a		
HONO	7.5		14.8
H ₂ N ⁺ CH ₂ CO ₂ H	7.5 ^a	fluorenone phenylhydrazone	14.9
CH ₂ =CHCH ₂ NO ₂	7.7	MeCH(COCH ₃) ₂	15.05
(C ₆ F ₅) ₂ CHCN	7.95		
toluene	8.5		

Self-consistent acidity scale (pK_a scale) in MeCN

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

Acid	pK_a (AN)	f
1 9-CF ₃ -Fluorene	28.11	1.55
2 14-Me-CF ₃ (CF ₃) ₂ CHCN	28.96	0.23
3 14-NO ₂ -CF ₃ (CF ₃) ₂ CHCN	28.54	0.25
4 CF ₃ (CF ₃) ₂ CHCN	28.14	0.27
5 14-Me-CF ₃ (CF ₃) ₂ NH	28.12	1.20
6 14-NO ₂ -CF ₃ (CF ₃) ₂ NH	24.94	0.26
7 Octahydrofluorene	24.49	0.26
8 Fluorenone	23.90	0.26
9 9-COOMe-Fluorene	23.53	0.26
10 Acetic acid	23.51	0.27
11 CF ₃ (CH ₂ COOEt) ₂	22.95	0.27
12 2-NO ₂ -Phenol	22.85	0.27
13 14-Me-CF ₃ (CF ₃) ₂ CHCN	22.80	0.27
14 14-NO ₂ -CF ₃ (CF ₃) ₂ CHCN	21.94	0.27
15 Benzoic acid	21.51	0.27
16 9-CN-Fluorene	21.36	0.27
17 14-H-CF ₃ (CF ₃) ₂ CHCN	21.11	0.27
18 CF ₃ (CF ₃) ₂ CHCN	21.10	1.21
19 CF ₃ (CF ₃) ₂ NH	20.99	0.27
20 14-CF ₃ (CF ₃) ₂ CHCN	20.35	0.27
21 2,4,6-Br ₃ -Phenol	20.35	1.22
22 2,4,6-Cl ₃ -CF ₃ (CF ₃) ₂ CHCN	20.13	0.27
23 2,3,5-F ₃ -Phenol	20.12	0.27
24 2,3,5,6-F ₄ -Phenol	20.11	0.27
25 2-(CF ₃) ₂ CF ₃ CHCN	20.08	0.27
26 1-C ₆ F ₅ OH	19.72	0.27
27 2,4,6-(SO ₂ F) ₃ -Phenol	19.60	0.27
28 2-CF ₃ (CF ₃) ₂ CHCN	19.32	0.27
29 9-CF ₃ -Octahydrofluorene	18.88	0.27
30 2-C ₆ F ₅ OH	18.50	0.27
31 14-CF ₃ (CF ₃) ₂ CHCN	18.14	0.27
32 14-CF ₃ (CF ₃) ₂ Phenol	18.10	0.27
33 14-H-CF ₃ (CF ₃) ₂ CHCN	18.02	0.27
34 2,3,5,6-Cl ₄ -Phenol	17.83	0.27
35 CF ₃ (CH ₂ COOEt) ₂	17.76	0.27
36 14-CF ₃ (CF ₃) ₂ CHCN	17.59	0.27
37 4-Me-C ₆ H ₄ (CN) ₂	17.59	0.27
38 2-(CF ₃) ₂ CHCN	17.1	0.27
39 14-CF ₃ (CF ₃) ₂ CHCN	17.1	0.27
40 2,4,6-(NO ₂) ₃ -Phenol	16.4	0.27
41 4-CF ₃ (CF ₃) ₂ CHCN	16.2	0.27
42 14-NO ₂ -CF ₃ (CF ₃) ₂ CHCN	16.40	0.27
43 14-CF ₃ (CF ₃) ₂ CHCN	16.13	0.27
44 14-CF ₃ (CF ₃) ₂ CHCN	16.08	0.27
45 14-CF ₃ (CF ₃) ₂ CHCN	16.02	0.27
46 4-NO ₂ -CF ₃ (CF ₃) ₂ CHCN	15.40	1.21
47 14-NO ₂ -CF ₃ (CF ₃) ₂ CHCN	14.90	1.21

Phenol 29.1

CH₃COOH 23.5

2,4-(NO₂)₂-Phenol 16.7

47 14-NO ₂ -CF ₃ (CF ₃) ₂ CHCN	14.90	1.21
48 3-CF ₃ -C ₆ H ₄ (CN) ₂	14.72	0.26
49 Saccharin	14.57	0.26
50 14-Me-CF ₃ (CF ₃) ₂ CHCN	13.87	0.26
51 14-NO ₂ -CF ₃ (CF ₃) ₂ CHCN	13.46	0.26
52 CF ₃ (CF ₃) ₂ CHCN	13.01	0.26
53 4-H-CF ₃ (CF ₃) ₂ CHCN	12.98	0.26
54 2-CF ₃ (CF ₃) ₂ CHCN	12.23	1.20
55 TosNH ₂ ⁺	11.97	0.26
56 4-NO ₂ -C ₆ H ₄ (CN) ₂	11.81	0.26
57 4-Me-C ₆ H ₄ (CF ₃) ₂ NH ⁺	11.60	0.26
58 4-Me-C ₆ H ₄ (CF ₃) ₂ NH	11.46	0.26
59 (CF ₃) ₂ SO ₂ NH	11.34	1.19
60 4-CO-C ₆ H ₄ (SO ₂) ₂ NH	11.10	0.26
61 CF ₃ (CF ₃) ₂ NH	11.06	0.26
62 Nitro acid	11.00	0.26
63 4-F-C ₆ H ₄ (CF ₃) ₂ NH	10.85	0.26
64 4-CO-C ₆ H ₄ (CF ₃) ₂ NH	10.36	0.26
65 4-CO-C ₆ H ₄ (SO ₂) ₂ NH	10.26	0.26
66 4-CF ₃ (CF ₃) ₂ CHCN	10.19	0.26
67 4-NO ₂ -C ₆ H ₄ (SO ₂) ₂ NH	10.04	0.26
68 4,5,6-(NO ₂) ₃ -C ₆ H ₂ (SO ₂) ₂ NH	9.71	0.26
69 4-NO ₂ -C ₆ H ₄ (CF ₃) ₂ NH	9.47	0.26
70 4-NO ₂ -C ₆ H ₄ (SO ₂) ₂ NH	9.17	0.26
71 TosOH	8.6	1.20
72 4-NO ₂ -C ₆ H ₄ (SO ₂) ₂ NH	8.32	1.20
73 1-C ₆ H ₄ (SO ₂) ₂ NH	8.02	0.26
74 C ₆ H ₅ (NTf ₂)	7.85	0.26
75 4-CO-C ₆ H ₄ (SO ₂) ₂ NH	7.25	0.26
76 3-NO ₂ -C ₆ H ₄ (SO ₂) ₂ NH	6.79	0.26
77 4-NO ₂ -C ₆ H ₄ (SO ₂) ₂ NH	6.73	0.26
78 4-Me-C ₆ H ₄ (CF ₃) ₂ NH	6.54	0.26
79 4-Me-C ₆ H ₄ (CF ₃) ₂ NH	6.32	0.26
80 TosNH ₂	6.30	0.26
81 C ₆ H ₅ (NTf ₂)	6.17	0.26
82 C ₆ H ₅ (NTf ₂)	6.02	0.26
83 4-F-C ₆ H ₄ (CF ₃) ₂ NH	5.79	0.26
84 4-CO-C ₆ H ₄ (NTf ₂) ₂ NH	5.69	0.26
85 2,4,6-(SO ₂ F) ₃ -Phenol	5.66	0.26
86 4-CO-C ₆ H ₄ (NTf ₂) ₂ NH	5.47	0.26
87 4-CO-C ₆ H ₄ (SO ₂) ₂ NTf ₂	5.37	0.26
88 4-NO ₂ -C ₆ H ₄ (CF ₃) ₂ NH	5.17	0.26
89 2,4,6-T ₃ -Phenol	4.93	0.26
90 4-NO ₂ -C ₆ H ₄ (SO ₂) ₂ NH	4.82	0.26
91 4-CO-C ₆ H ₄ (SO ₂) ₂ NTf ₂ (HSO ₂ CF ₃) ₂ -Cl	4.47	0.26
92 2,3,5-Trioxanocyclopentadiene	4.16	0.26
93 4-CO-C ₆ H ₄ (SO ₂) ₂ NTf ₂ (HSO ₂ CF ₃) ₂ -NO ₂	3.75	0.26

2,4,6-(NO₂)₃-Phenol 11.0

HCl 10.3

TosOH 8.5

HBr 5.5

HI 2.8

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

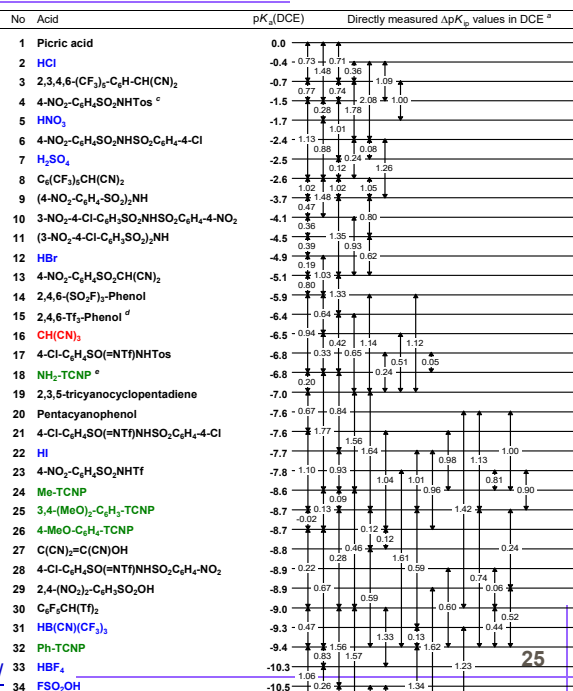
1,2-DCE acidity scale

- 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

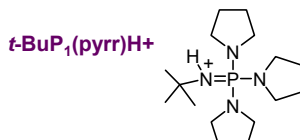
http://tera.chem.ut.ee/~ivo/HA_UT/



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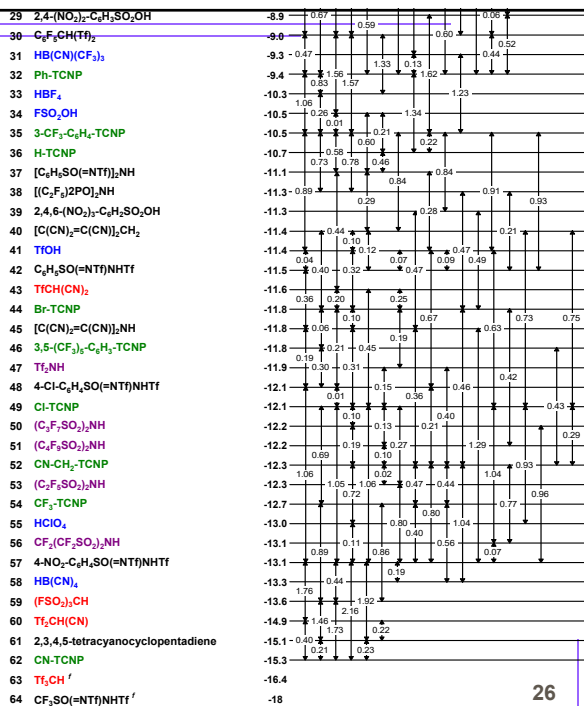
1,2-DCE acidity scale

- Ion pair acidities
- Counter-ion:



- Aqueous pK_a (H₀) values down to -10 .. -15
- In pipeline:
 - Weaker acids
 - Weak bases

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



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Self-consistent basicity scale in MeCN (1)

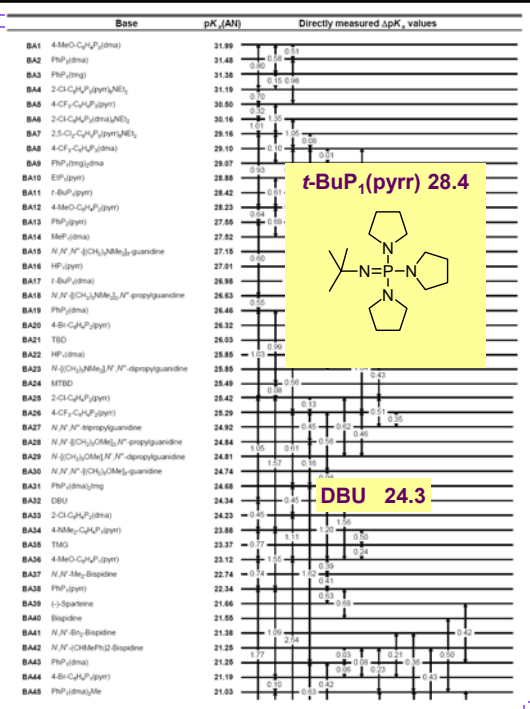
- Anchor: Pyridine
- Free ions
- Titrants:
 - TfOH
 - *t*-BuP₁(pyrr)

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/



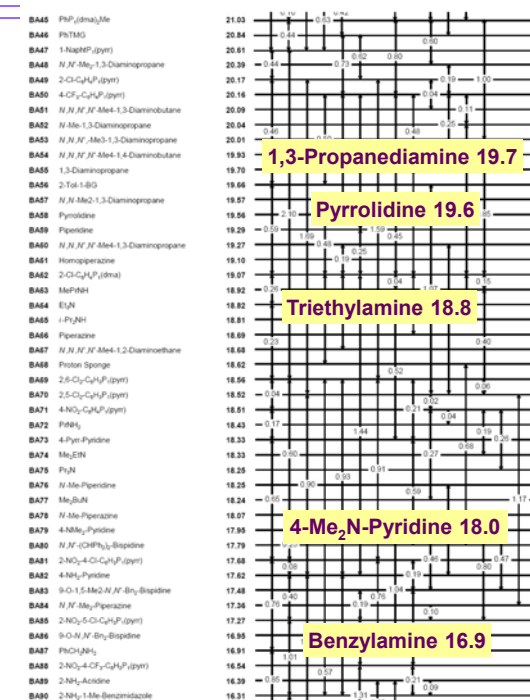
Self-consistent basicity scale in MeCN (2)

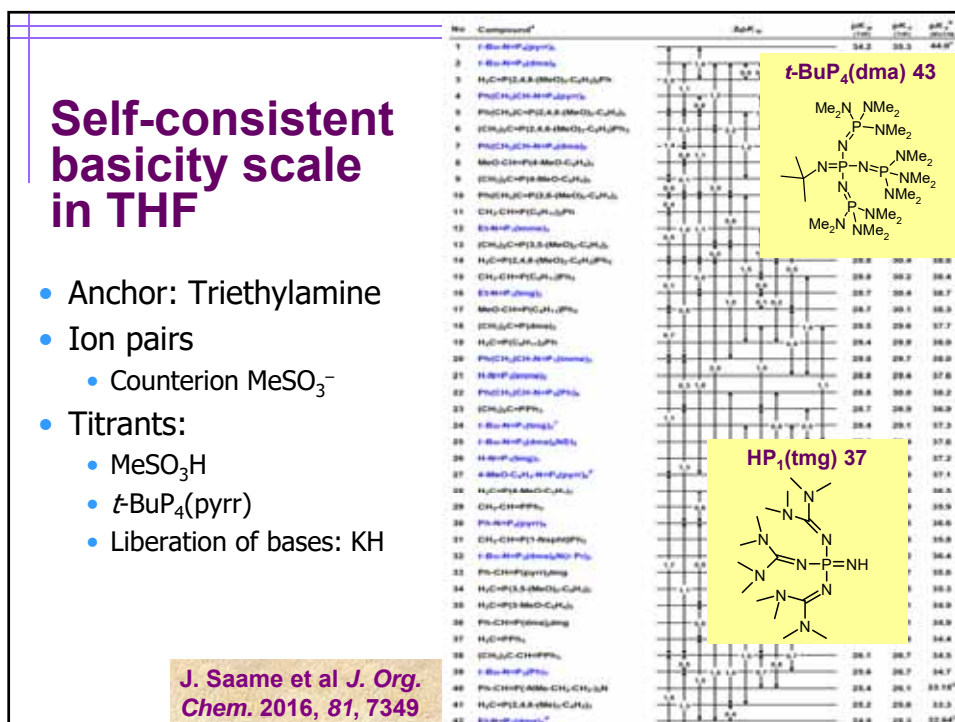
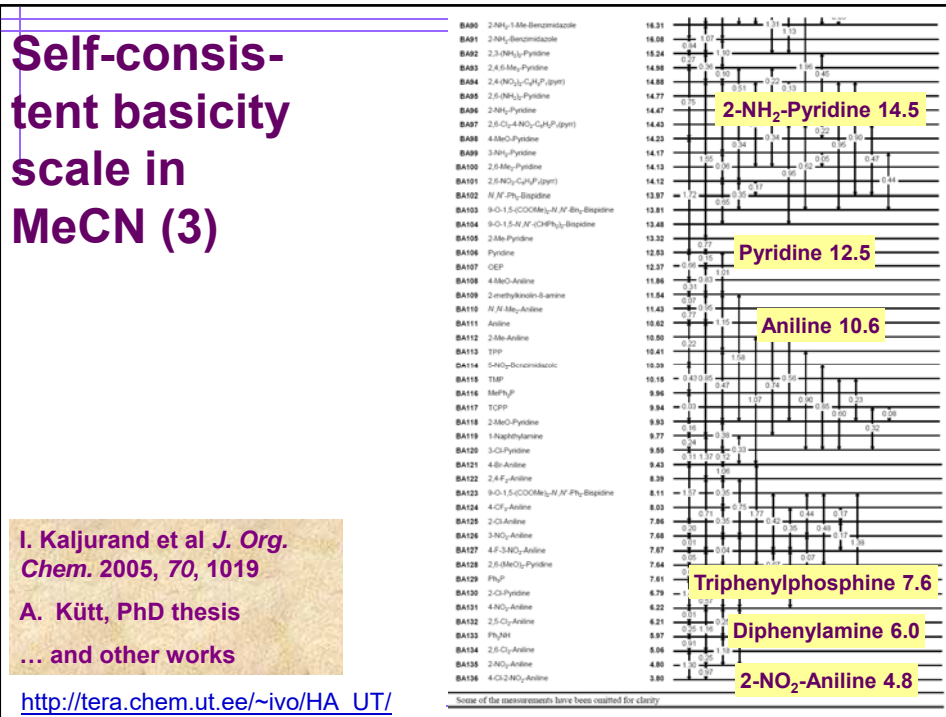
I. Kaljurand et al *J. Org. Chem.* 2005, 70, 1019

A. Kütt, PhD thesis

... and other works

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





Search for: acetic acid

Structure	Solvent	pKa	Method	Ref.
<chem>CC(=O)O</chem>	H ₂ O	4.75	PTM	122
<chem>CC(=O)O</chem>	H ₂ O	4.75	PTM	122
<chem>CC(=O)O</chem>	AA	14.41	PTM	128
<chem>CC(=O)O</chem>	Ac	18.11	PTM	128
<chem>CC(=O)O</chem>	Ac	18.11	PTM	128
<chem>CC(=O)O</chem>	AN	21.17	PTM	128
<chem>CC(=O)O</chem>	AN	21.17	PTM	128
<chem>CC(=O)O</chem>	AN	21.11	SM	128
<chem>CC(=O)O</chem>	AN	21.11	SM	128
<chem>CC(=O)O</chem>	D ₂ O	4.78	SM	128
<chem>CC(=O)O</chem>	DMS	28.2	PTM	128
<chem>CC(=O)O</chem>	DMS	11.55	PTM	128

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

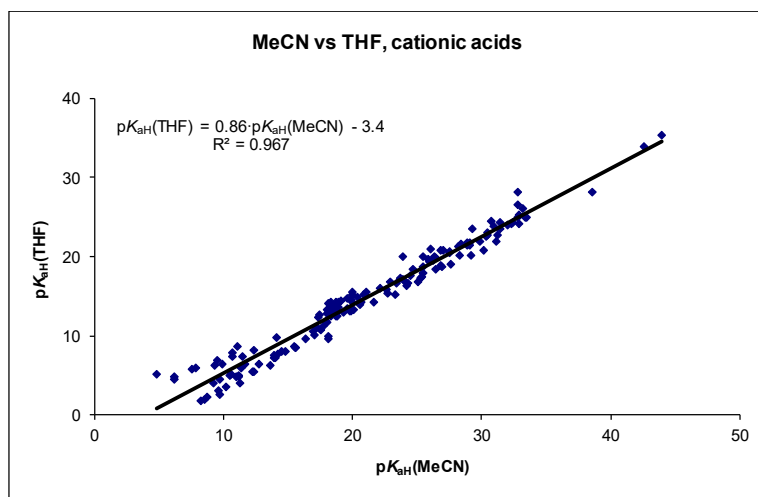
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Typical issue: no pKa data for X in solvent S

- 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

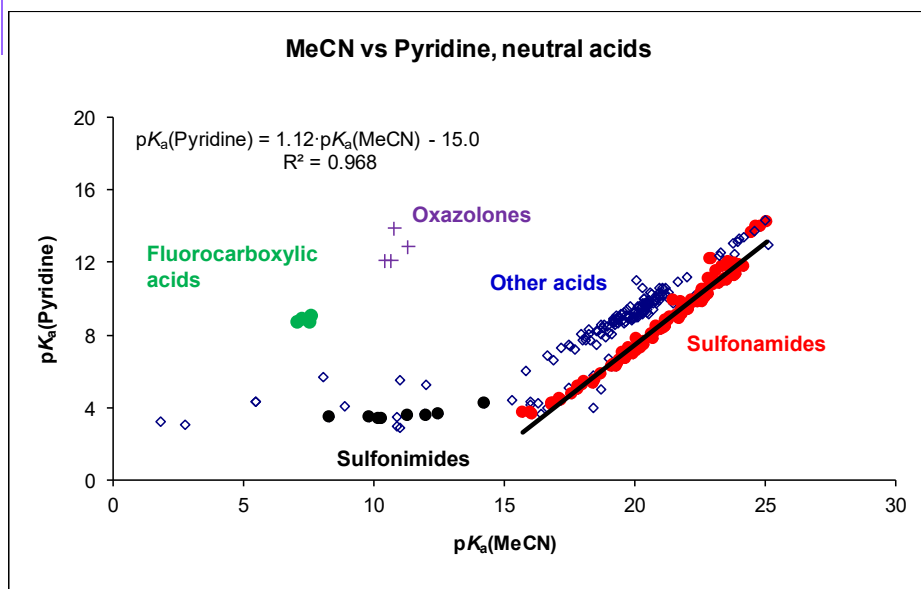
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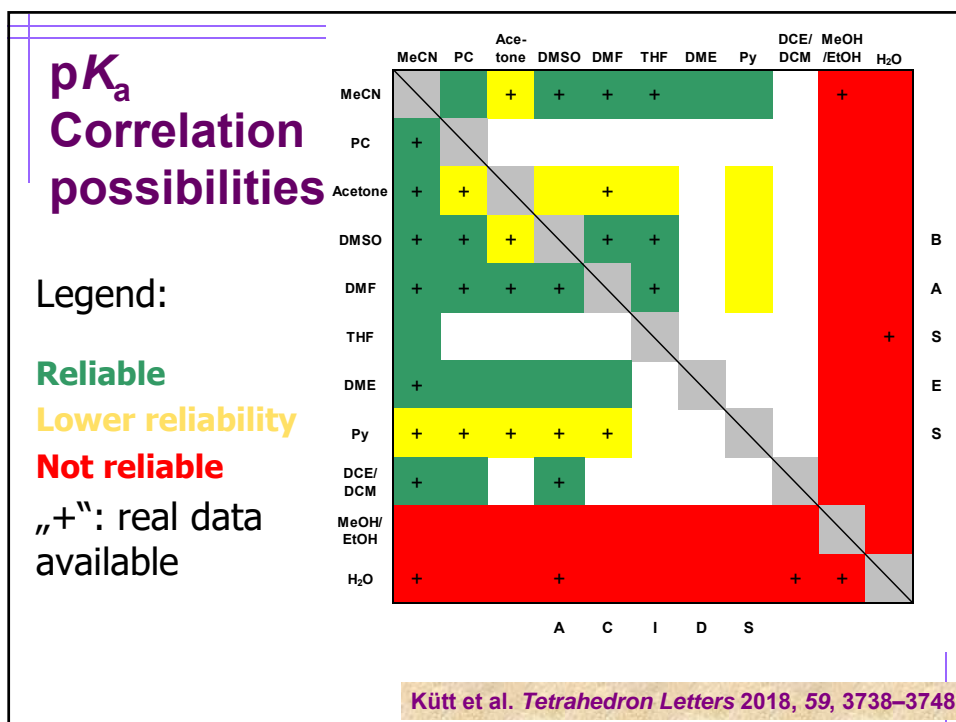
Sometimes correlations are good ...



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... Sometimes tricky





Absolute values vs differences

	MeCN	DCE	DMSO	H ₂ O	THF	Cl ⁻	DMS
Absolute acidities							
Peric acid	11.80	45.0	-1.0	9.3	11.84		
Cl ₂ N ₂ +Cl ₂ NH	4.89	35.8					
(2-C ₆ F ₅) ₂ CHCN	19.32	53.0				-0.88	
(C ₆ F ₅) ₂ CHCN	21.10	55.3 [†]	8.0			1.80	6.4
9-C ₄ F ₇ -Octabromfluorene	18.88	55.8				0.00	3.3
(4-Cl) ₂ -C ₆ F ₃ (C ₆ F ₅) ₂ CHCN	18.14	52.1	4.9			-1.30	3.0
(C ₆ F ₅) ₂ C ₆ H ₄ CHCN	38.14		12.8				11.8
Saccharin	14.57		4.0	1.8			
2,4-(NO ₂) ₂ -Phenol	10.66		3.4	4.70	16.94		
HCl	19.30	45.2	-2.0 [†]	-5.9 [†]			
HBr	5.5	40.6	-6.0 [†]	-8.8 [†]			
HI	2.8	37.7	-10.9 [†]	-8.3 [†]			
HNO ₃	1.83	32.2	-14.9 [†]	-13.2 [†]	7.57		
TEOH	2.40	33.7	-14.1 [†]	-14.7 [†]	7.83		
Acetic acid	23.51		12.6	4.75	22.68		
Benzoic acid	25.51		11.1	4.25	25.11		
Relative acidities							
Aniline-H ⁺	10.62		5.59	4.80	5.2		
Pyridine-H ⁺	12.53		3.45	3.25	5.5		
Protos Sponge-H ⁺	18.62		7.47	12.1	11.1		
DBU-H ⁺	28.34		13.0	13.5	16.6		
TBD-H ⁺	26.05				19.4		
1-Bu ⁺ (dme) ₂ -H ⁺	26.98		15.7	17.0	18.8		
1-Bu ⁺ (prr) ₂ -H ⁺	28.42			17.5	20.2		
Et ₃ N-H ⁺	18.83		9.0	10.70	12.5		
DMG-H ⁺	23.30		13.2	13.60	15.5		
Peric acid - Cl ₂ N ₂ +Cl ₂ NH	6.91	8.1					
(2-C ₆ F ₅) ₂ CHCN - Peric acid	8.32	8.0					
(2-C ₆ F ₅) ₂ CHCN - Cl ₂ N ₂ +Cl ₂ NH	14.63	17.10					
Saccharin - Peric acid	3.37		5.06	1.50			
2,4-(NO ₂) ₂ -Phenol - Saccharin	2.89		1.40	2.30			
2,4-(NO ₂) ₂ -Phenol - Peric acid	5.80		6.40	6.80	5.3		
(C ₆ F ₅) ₂ CHCN - (9-Cl) ₂ -C ₆ F ₃ (C ₆ F ₅) ₂ CHCN	2.96	8.4	3.98			3.18	2.30
(C ₆ F ₅) ₂ CHCN - 9-C ₄ F ₇ -Octabromfluorene	2.22	1.9				1.80	1.10
(2-C ₆ F ₅) ₂ CHCN - 9-C ₄ F ₇ -Octabromfluorene	0.44	-0.80				-0.88	
Peric acid - HCl	8.70	-0.20	1.00	0.20			
Peric acid - HBr	5.30	4.40	3.00	9.10			
Peric acid - HI	8.30	7.50	9.00	9.80			
HCl - HBr	5.30	7.50	6.00	3.00			
HCl - HNO ₃	8.47	13.00	12.00	9.30			
HCl - TEOH	7.70	11.50	12.30	8.80			
TEOH - HNO ₃	0.77		0.6	0.5	0.20		
Acetic acid - Peric acid	12.51		13.60	4.65	10.34		
Benzoic acid - Peric acid	10.01		12.10	3.95	11.17		
Acetic acid - Benzoic acid	2.80		1.50	0.50	2.83		
Benzoic acid - HCl	11.21		13.10	10.15			
DBU-H ⁺ - Protos Sponge-H ⁺	5.72		8.4	1.4	5.50		
Protos Sponge-H ⁺ - Pyridine-H ⁺	6.09		4.0	4.85	5.60		
Pyridine-H ⁺ - Aniline-H ⁺	1.91		-0.1	0.05	0.70		
Protos Sponge-H ⁺ - Aniline-H ⁺	8.80						
DBU-H ⁺ - Pyridine-H ⁺	11.9						
DBU-H ⁺ - Aniline-H ⁺	13.7						

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