



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

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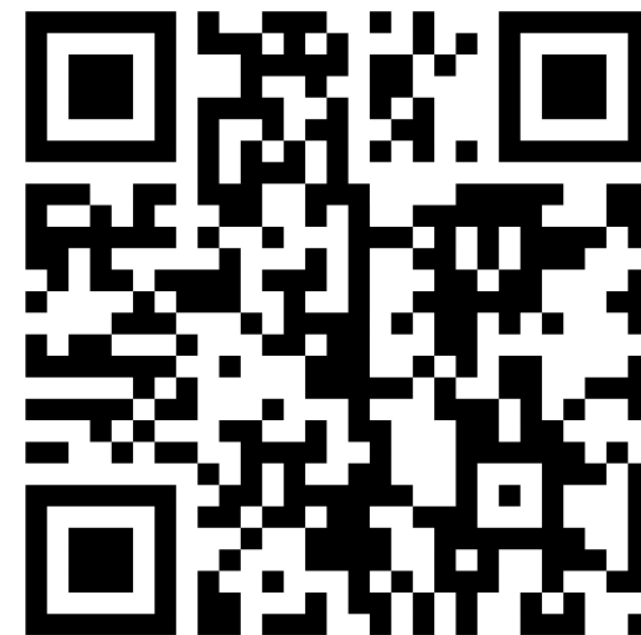
Slides: analytical.chem.ut.ee/bos2024/

University of Tartu

BOS 2024

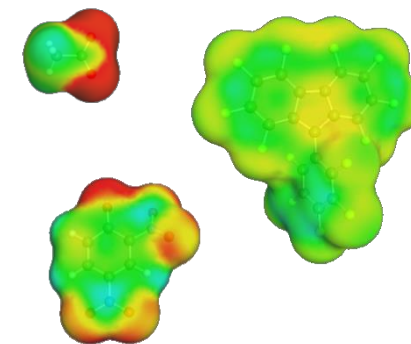
Riga

Jul 9, 2024



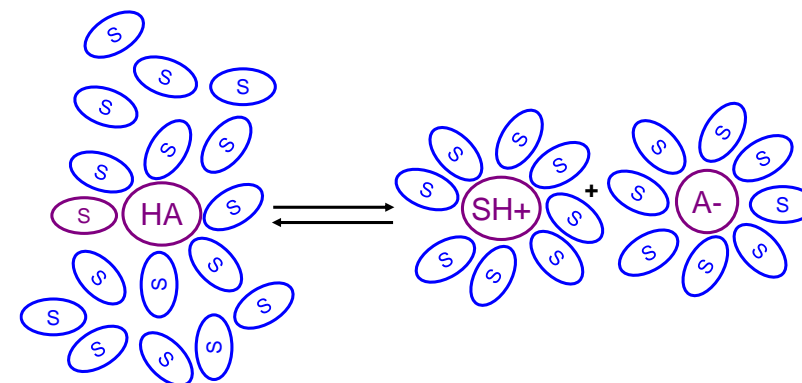
Overview

- **Brønsted acidity and basicity of molecules in solution**
 - What data exists (pK_a and pK_{aH} values, absolute and relative values)?



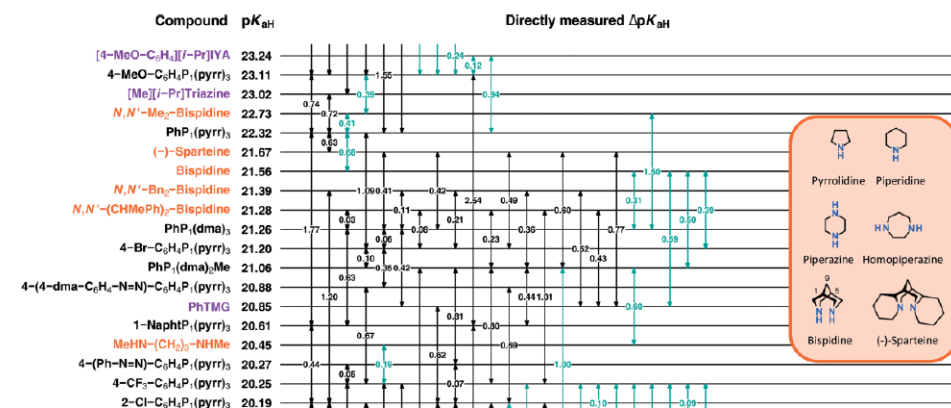
- **How and why does solvent influence pK_a values?**

- How do solvation energies, solvent properties (polarity, acidity, basicity), ion properties (charge localization) play a role?



- **What non-aqueous pK_a data are available?**

- How to estimate pK_a of compound X in solvent S?
- How good are the data?



Some notes

- We start with basics
- Only Brønsted acidity-basicity
- Big Picture is more important than nuances
 - A lot of explanations are simplified
 - A lot of data are approximate
- Slides: analytical.chem.ut.ee/bos2024/ and:
- **Ask questions at any time!**



Why do we need non-aqueous pK_a data?

- **Understanding and predicting** reactivity
 - Reactions often in **non-aqueous** solutions
 - Very often involving **protonation** and/or **deprotonation**
 - pK_a determines is a reactant neutral or ionized
 - Neutrals and ions have **very different polarity, solubility, distribution/partition, reactivity**
- Design of **novel acids and bases**
- Development of **theoretical calculation methods**
 - Increasingly: **machine learning, training AI**

Acidity of media

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

A. Heering et al, *Analyst* **2024**, 149, 1481

V. Radtke et al, *Pure Appl. Chem.* **2021**, 93, 1049

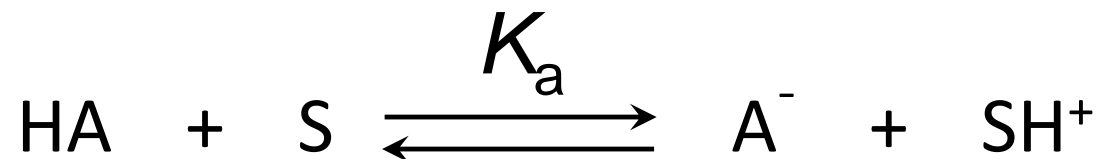
Acidity of molecules

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

This is the main topic of this talk


Acidity of molecules in solution

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



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

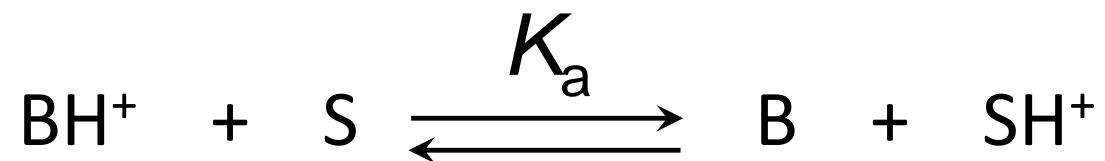
- S acts as a base
- Simplified scheme, valid in polar solvents
 - Ion-pairing is not considered



The lower the p*K_a* value
the stronger the acid


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)



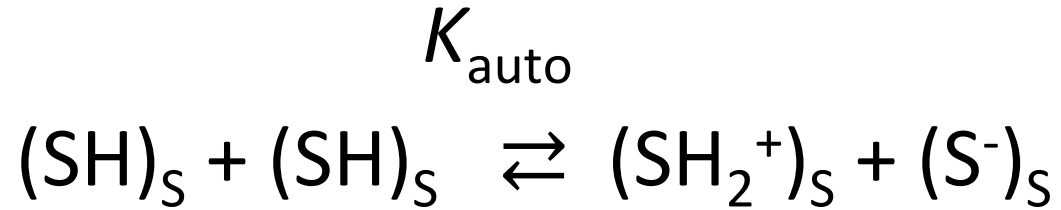
$$\begin{aligned} pK_a(\text{BH}^+) &\equiv pK_{aH}(\text{B}) \equiv pK_{\text{BH}^+}(\text{B}) = \\ &= -\log K_a(\text{BH}^+) = -\log \frac{a(\text{B}) \cdot a(\text{SH}^+)}{a(\text{BH}^+)} \end{aligned}$$

- S acts as a base
- Simplified scheme, valid in polar solvents
 - Ion-pairing is not considered



The higher the pK_{aH} value,
the stronger the base

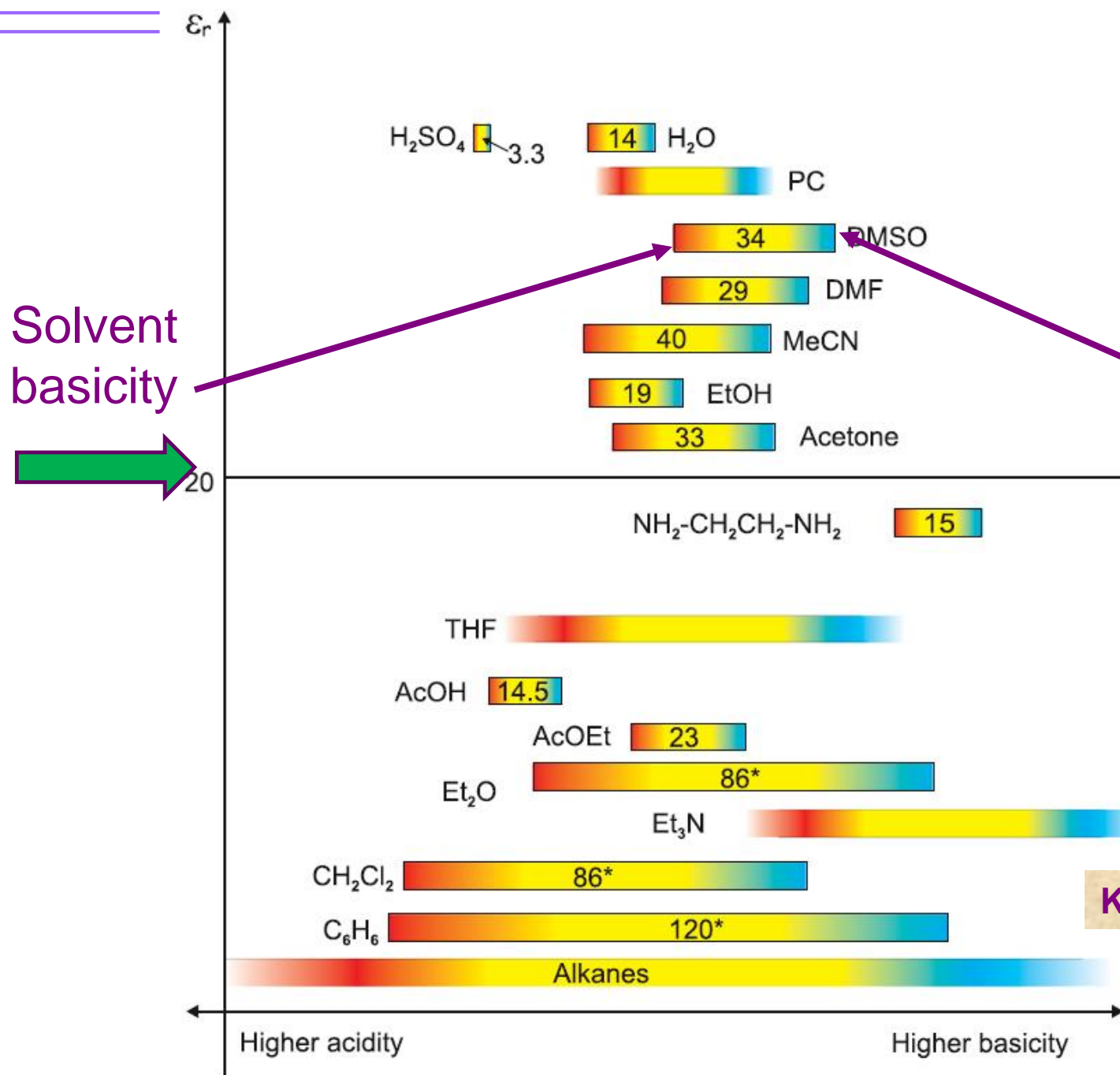
Acidity and basicity of solvent molecules: pK_{auto}



$$K_{\text{auto}} = a(\text{AH}_2^+) \cdot a(\text{S}^-) \quad pK_{\text{auto}} = -\log K_{\text{auto}}$$

- pK_{auto} defines the **span of pK_a scale**
 - Differentiating ability, related also to ion solvation ability
- **Low ion solvation** \rightarrow **High pK_{auto}** \rightarrow **wide pK_a span**

Solvent acidity, basicity and pK_{auto}

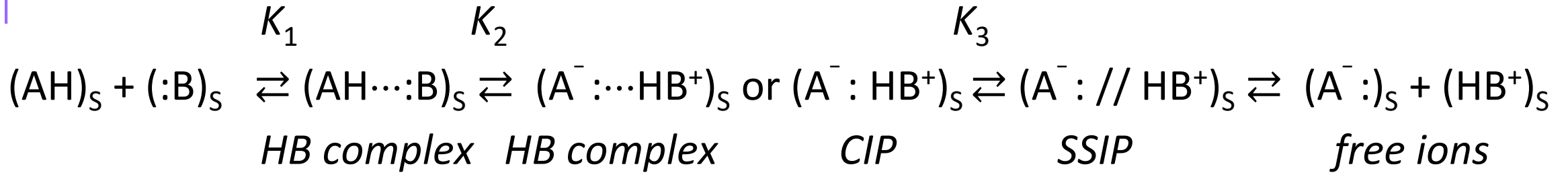


Values on the blocks are pK_{auto}
„Open ends“ mean unavailable data

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

* Computational estimates

Generalised acid-base reaction in a non-aqueous solvent



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

- Two typical situations:
 - Polar solvent and B = S then $\text{p}K_a = -\log(K_1 \cdot K_2 \cdot K_3 \cdot K_4)$ „free-ion $\text{p}K_a$ “ „normal $\text{p}K_a$ “
 - Nonpolar solvent B = strong base $\text{p}K_{\text{ip}} = -\log(K_1 \cdot K_2 \cdot K_3)$ or $-\log(K_1 \cdot K_2)$ „ion-pair $\text{p}K_a$ “
 - Can be recalculated into free-ion $\text{p}K_a$ values

We today speak mostly of free-ion $\text{p}K_a$ values

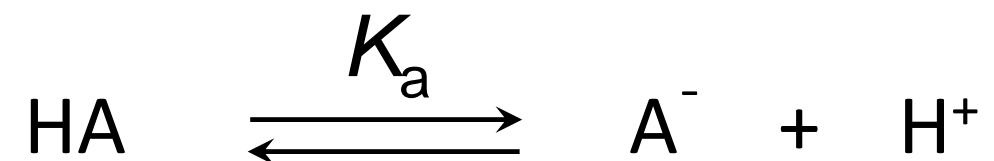
Some solvents

Solvent/ medium	E_T^N	ϵ	Basicity, HB acceptivity, B'	HB doni- city, α	pK_{auto}	Comments
Gas phase	–	1	–	–	–	
THF	0.207	7.47	287	0	Very high	Aprotic, ion-pair pK_a (free-ion pK_a values can be estimated)
1,2-Dichloro- Ethane	0.327	10.7	40	0	Very high	Aprotic, ion-pair pK_a (free-ion pK_a values can be estimated)
MeCN	0.460	35.9	160	0.19	ca 39	Aprotic, free-ion pK_a
DMSO	0.444	46.7	362	0	ca 33	Aprotic, free-ion pK_a
Methanol	0.762	33	High	0.98	18.9	Protic, free-ion pK_a
Water	1.000	81	High	1.17	14.0	Protic, free-ion pK_a

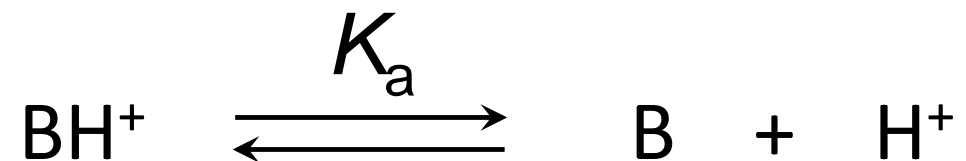
C. Reichardt, T. Welton *Solvents and Solvent Effects in Organic Chemistry*, 4th ed. VCH, 2011
 J.L.M. Abboud, R. Notario *Pure Appl. Chem.* 1999, 71, 645-718
 M. J. Kamlet et al. *J. Org. Chem.* 1983, 48, 2877-2887

Acidity and basicity of molecules in the gas phase

- **Intrinsic acidity/basicity** of molecules
- Expressed via deprotonation **Gibbs' free energy**

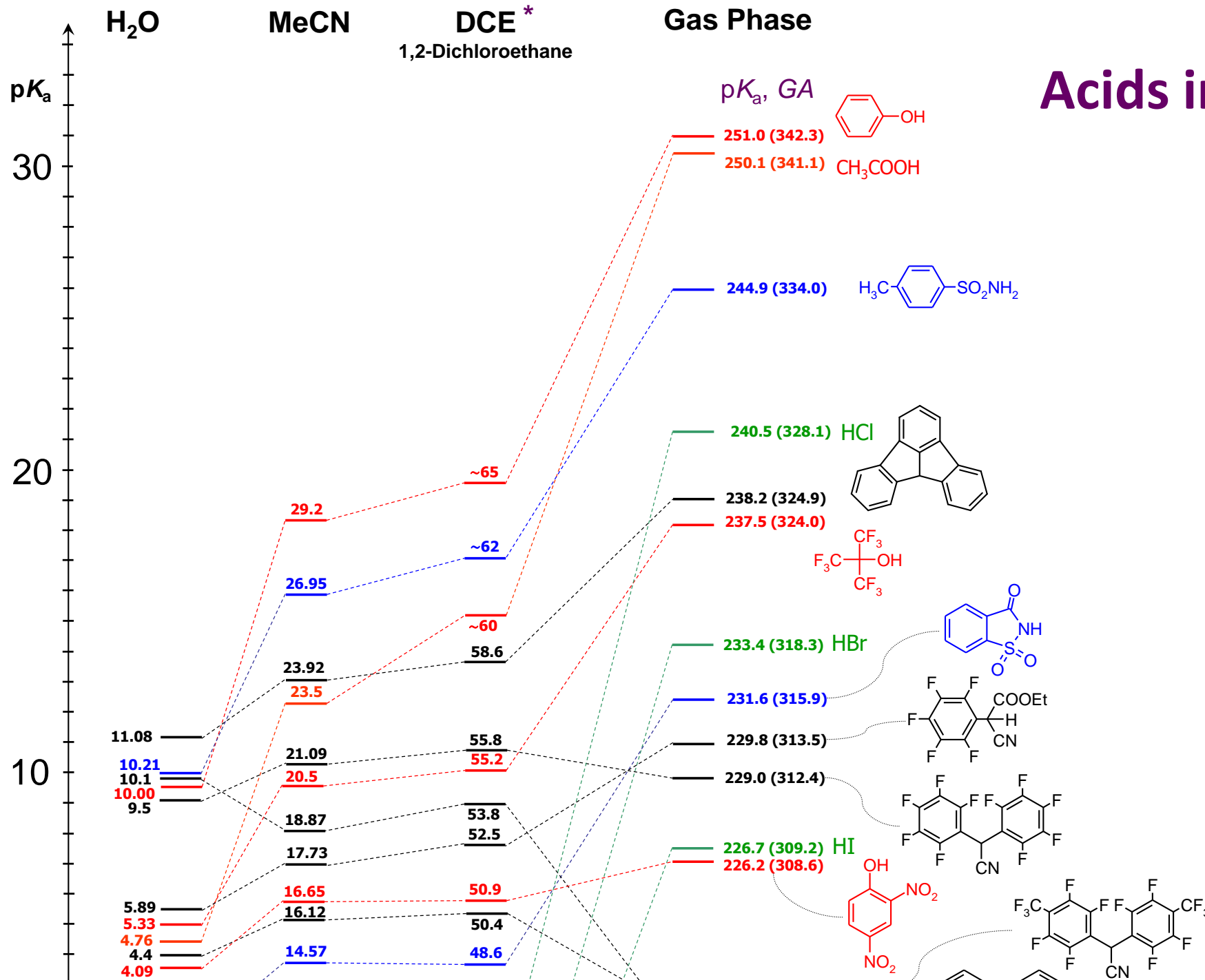


$$G_A = \Delta G_{\text{acid}}^0 = -RT \ln K_a$$



$$G_B = \Delta G_{\text{base}}^0 = -RT \ln K_a$$

1 pK_a unit ≡ 1.36 kcal/mol



Acids indifferent media

Data:

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

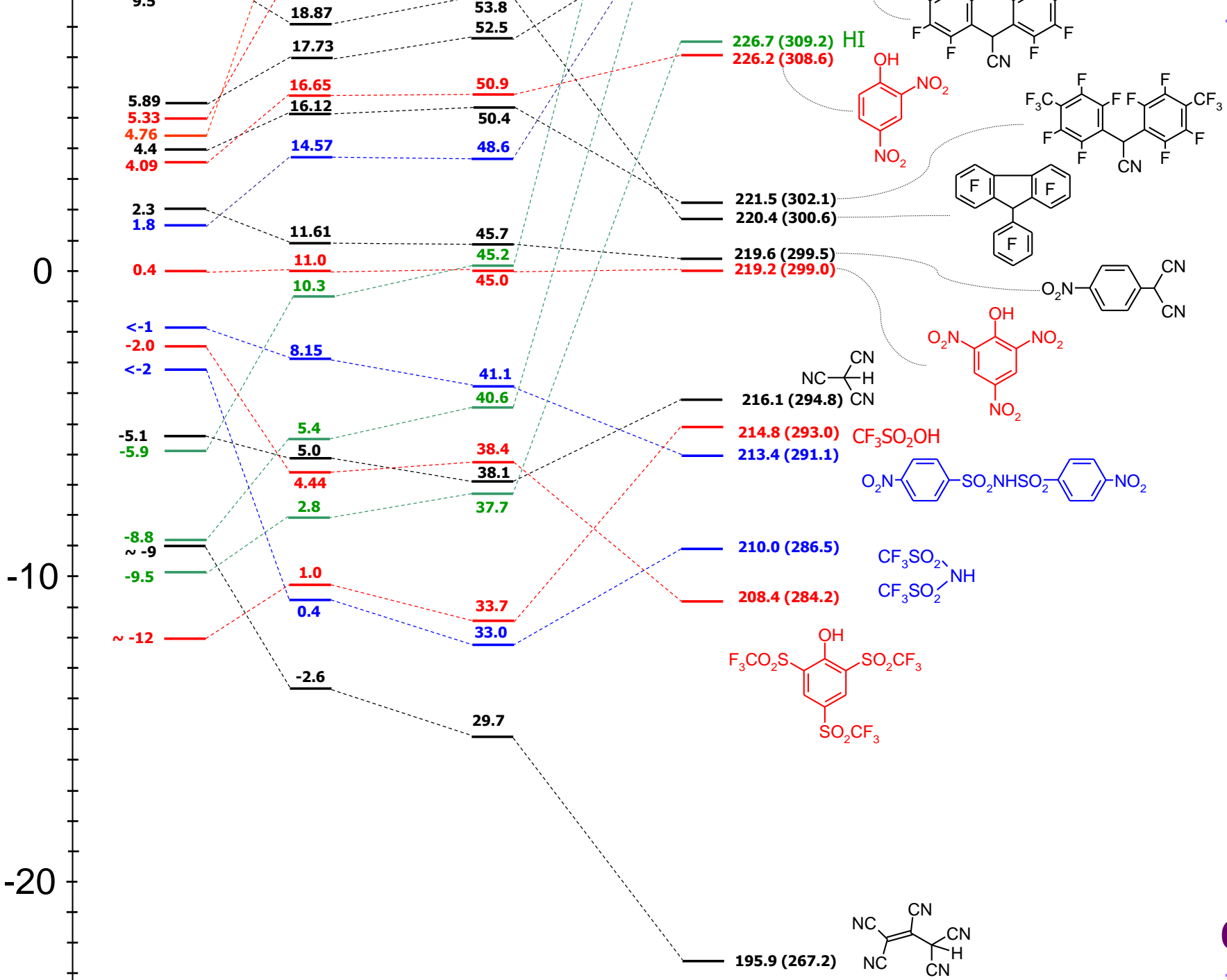
Trummal et al *J. Phys. Chem. A* **2016**, *120*, 3663

Paenurk et al *Chem. Sci.* **2017**, *8*, 6964–6973

Parman et al *J. Phys. Org. Chem.* **2019**, e3940

Kütt et al *Eur. J. Org. Chem.* **2021**, 1407

* Free-ion pK_a values calculated from experimental pK_{ip}.
Computationally anchored



Data:

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

Trummal et al *J. Phys. Chem. A* **2016**, *120*, 3663

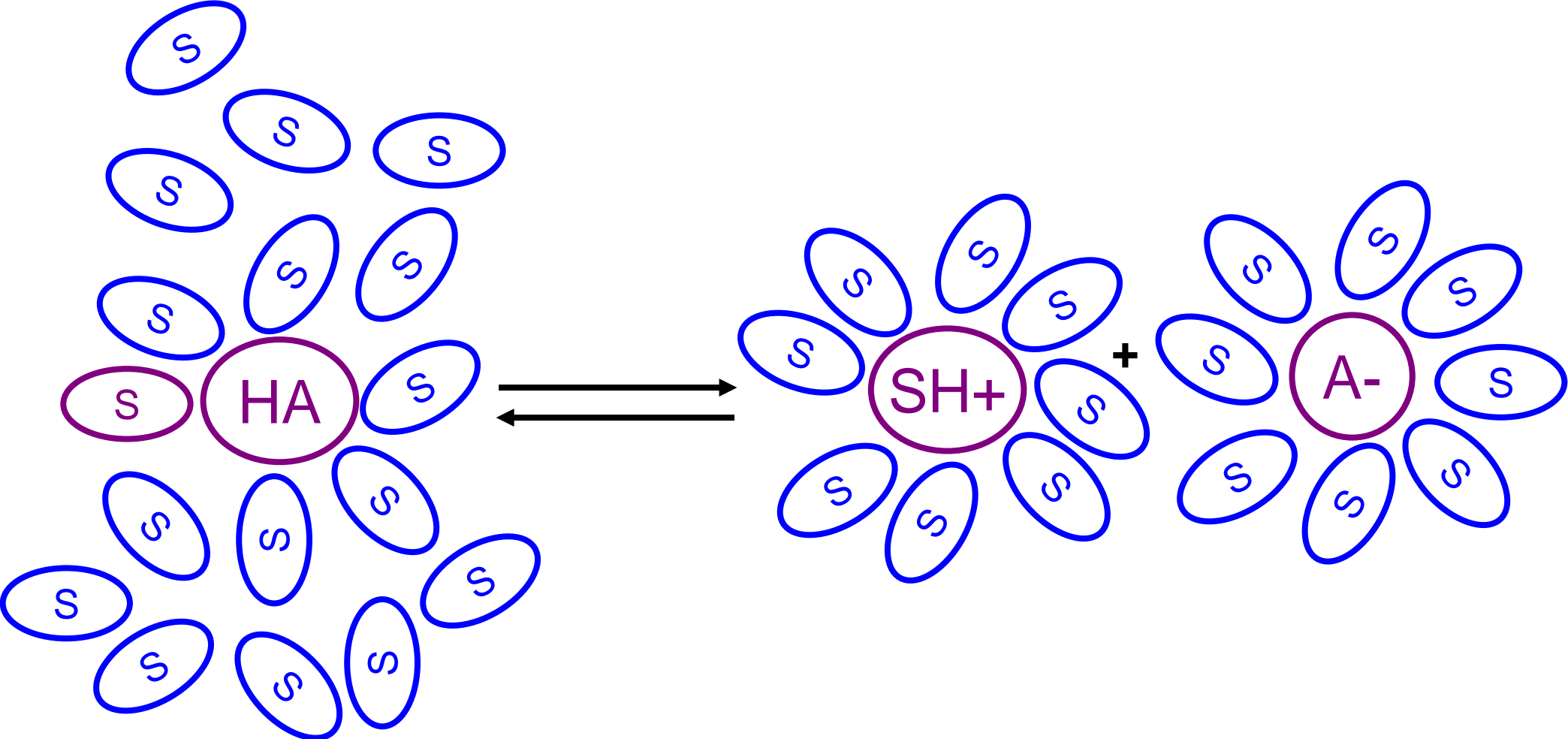
Paenurk et al *Chem. Sci.* **2017**, *8*, 6964–6973

Parman et al *J. Phys. Org. Chem.* **2019**, e3940

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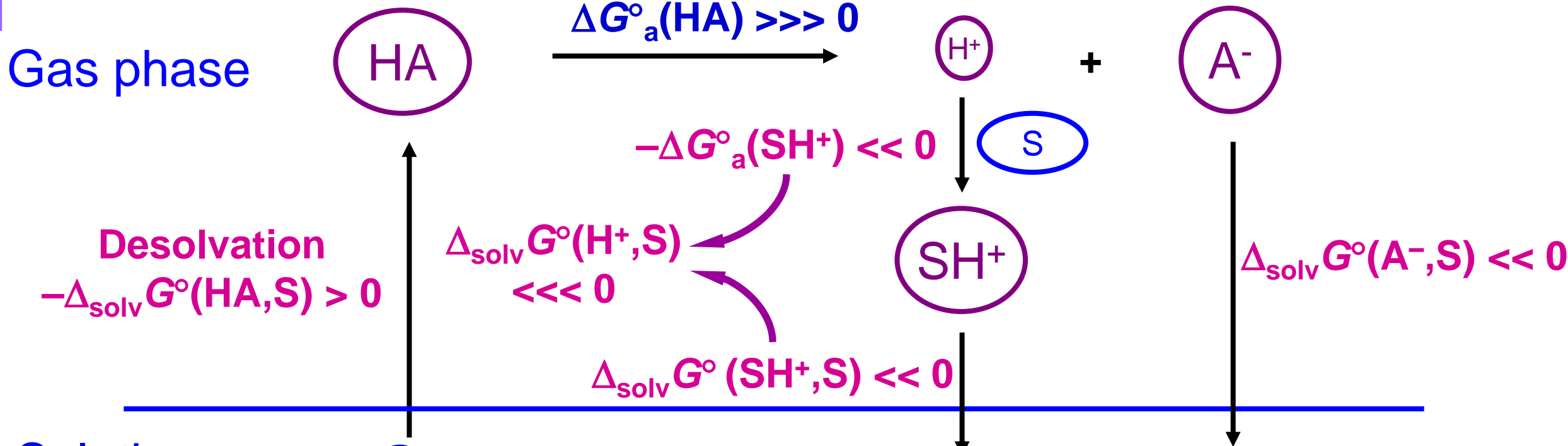
Acids in different media

Acid dissociation in a polar solvent

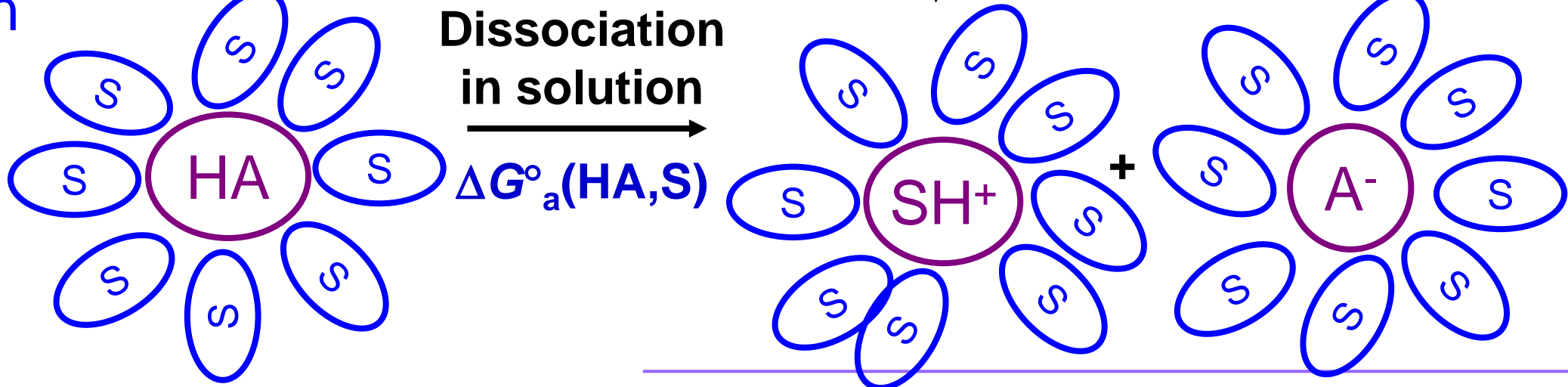


Thermodynamic cycle of acid dissociation

Dissociation in the gas phase



Solution

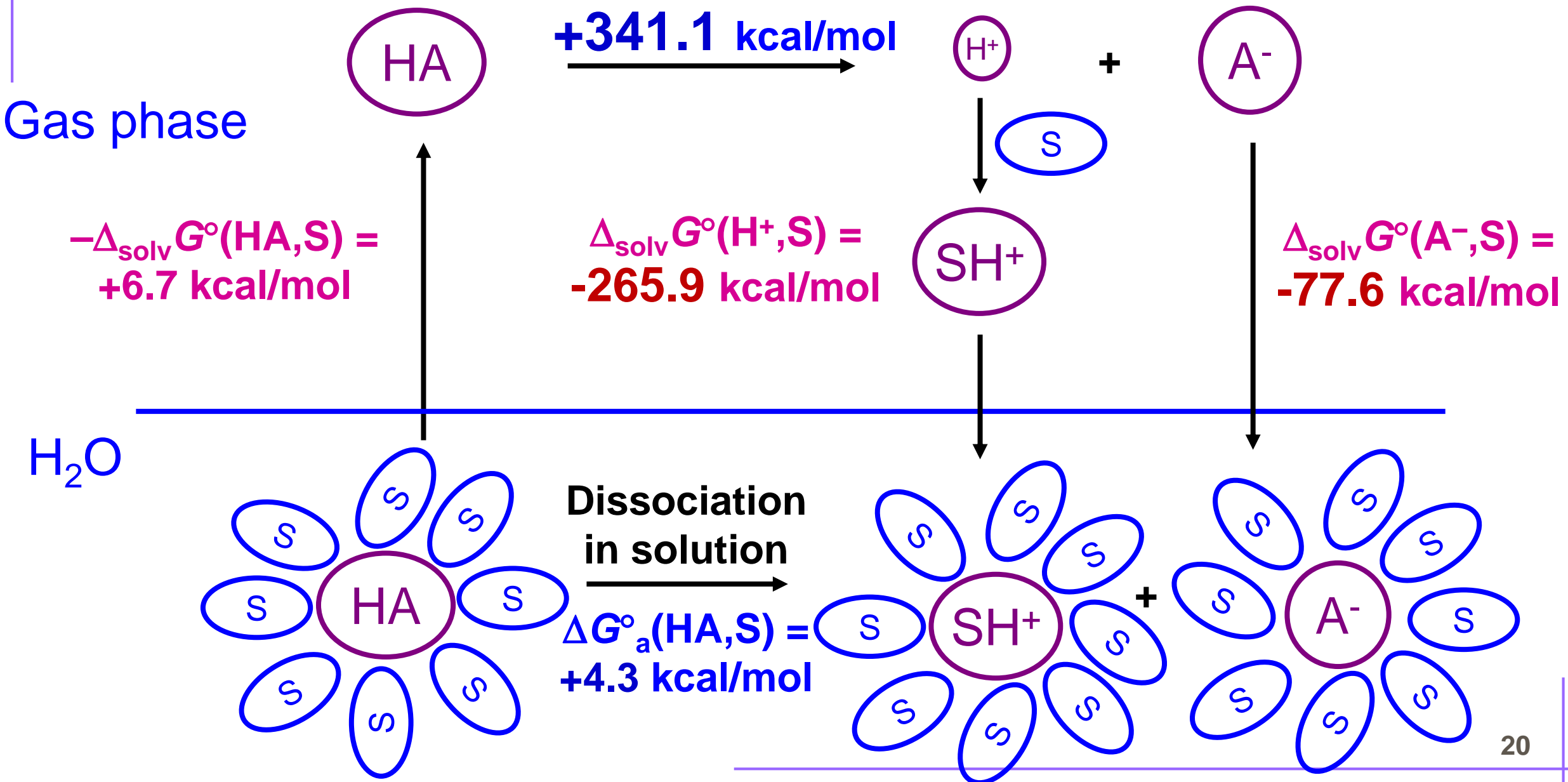


Different solvation energies → different pK_a values

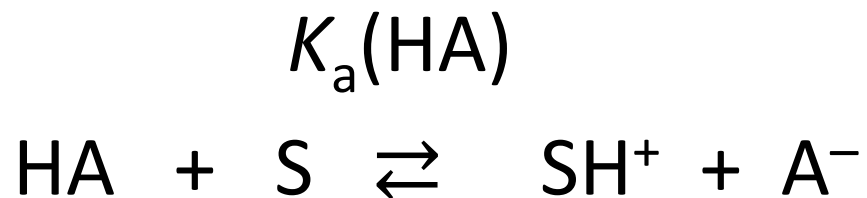
- The pK_a differences of a compound in different solvents are first of all due to differences in three solvation energies:
 - $\Delta_{\text{solv}}G^\circ(\text{H}^+, \text{S})$
 - $\Delta_{\text{solv}}G^\circ(\text{A}^-, \text{S})$
 - $\Delta_{\text{solv}}G^\circ(\text{HA}, \text{S})$
- These energies are influenced by the solvent properties
- Are solvation energies of all species equally important?

Example: Acetic acid

1 kcal = 4.184 kJ



Link between acidity in gas phase and solution (water)



$\Delta G^\circ_a(\text{HA}, \text{S}) =$	+4.3
$+ \Delta G^\circ_a(\text{HA})$	+341.1
$+ \Delta_{\text{solv}} G^\circ(\text{H}^+, \text{S})$	-265.9
$+ \Delta_{\text{solv}} G^\circ(\text{A}^-, \text{S})$	-77.6
$- \Delta_{\text{solv}} G^\circ(\text{HA}, \text{S})$	+6.7

Solvent: water
All values in kcal mol⁻¹

1 pK_a unit \equiv 1.36 kcal/mol

- Experimental: **+6.5 kcal mol⁻¹** (pK_a = 4.76)

pK_a values

Gas Phase

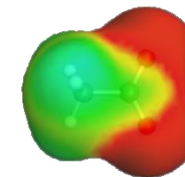
H₂O

DMSO

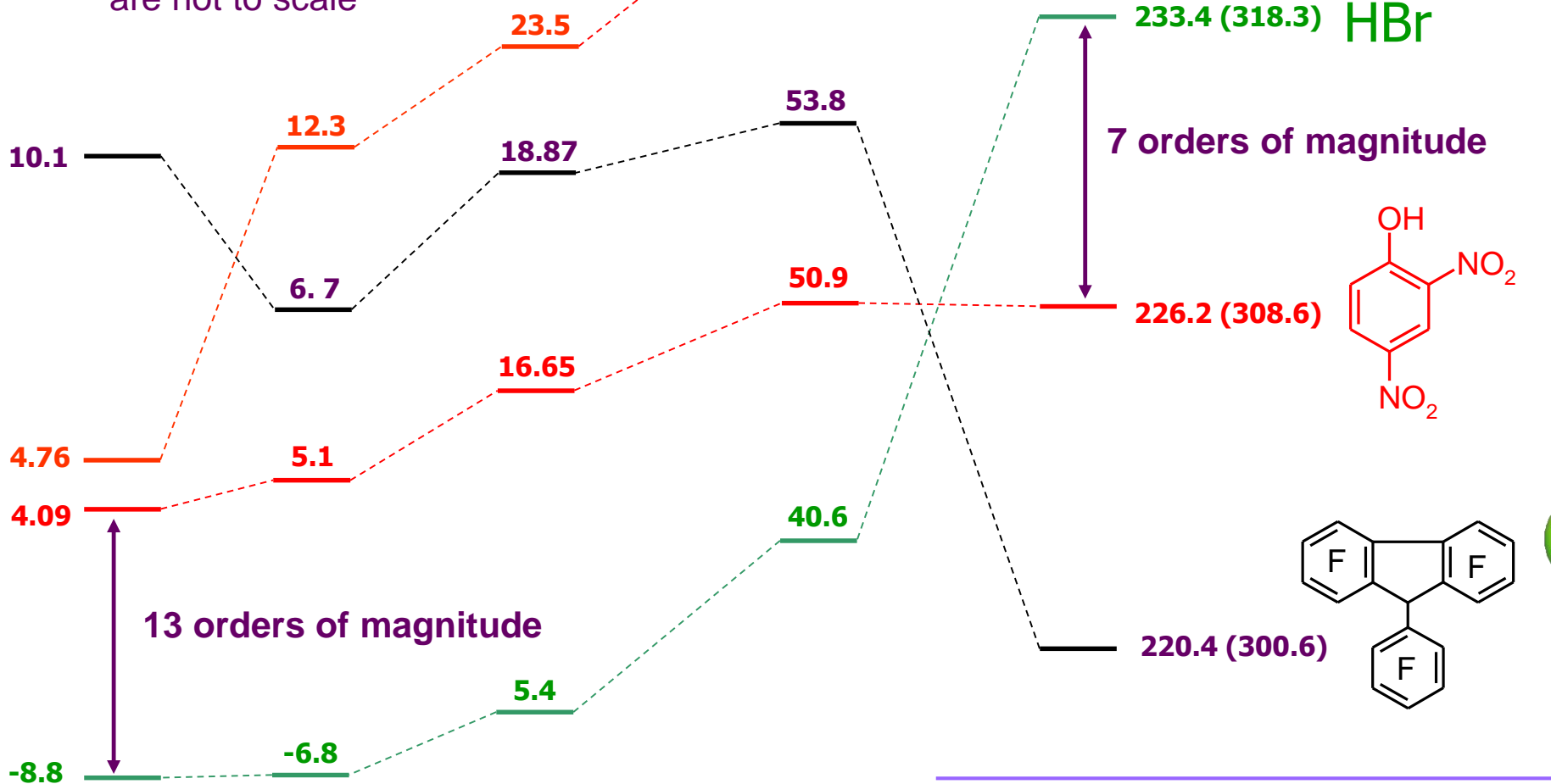
MeCN

DCE
1,2-Dichloroethane

250.1 (341.1) CH₃COOH



In this slide the positions of the „bars“ are not to scale

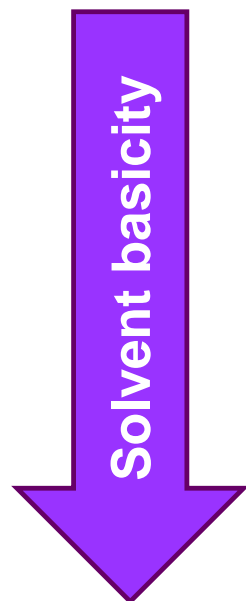


Charge localization in anions

The most important is the ability to solvate H⁺

- Differences of $\Delta_{\text{solv}} G^\circ$ of H⁺ from water to solvents:
(transfer free energies from H₂O to S)

1 pK_a unit \equiv 1.36 kcal/mol



Solvent, S	$\Delta_{\text{transfer}} G^\circ$ of H ⁺ from H ₂ O Difference of $\Delta_{\text{solv}} G^\circ$ of H ⁺ from H ₂ O (kcal/mol)
1,2-Dichloroethane	Highly positive
MeNO ₂	+23
MeCN	+11.1
MeOH	+2.5
<i>Water</i>	<i>0.0</i>
DMSO	-4.6
Pyridine	-6.7

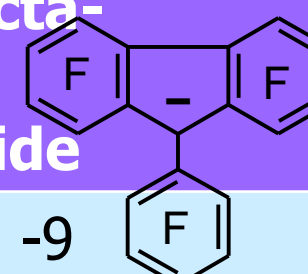
Just the **different solvation of H⁺** leads to pK_a difference of more than **11 pK_a units**

Next is the ability to solvate the anion A⁻

- Differences of $\Delta_{\text{solv}} G^\circ$ of anions from water to solvents: 1 pK_a unit \equiv 1.36 kcal/mol
(transfer free energies from H₂O to S)

Solvent, S	Protic?	Difference of $\Delta_{\text{solv}} G^\circ$ of A ⁻ from H ₂ O (kcal/mol)			
		CH ₃ COO ⁻	Br ⁻	2,4-Dinitrophenolate	C6F5-octafluorenyl
1,2-Dichloroethane	Aprotic	20	13	7	-9
MeCN	Aprotic	17	10	3	-13
DMSO	Aprotic	17	10	2	-15
MeOH	Protic	7	6	4	-10
<i>Water</i>	Protic	<i>0.0</i>	<i>0.0</i>	<i>0.0</i>	<i>0.0</i>

Solvent HB donicity



Charge localization in anions

Solvation free energies of neutrals are typically small, compared to ions

- If aiming at the big picture then we can ignore them

pK_a values

H₂O

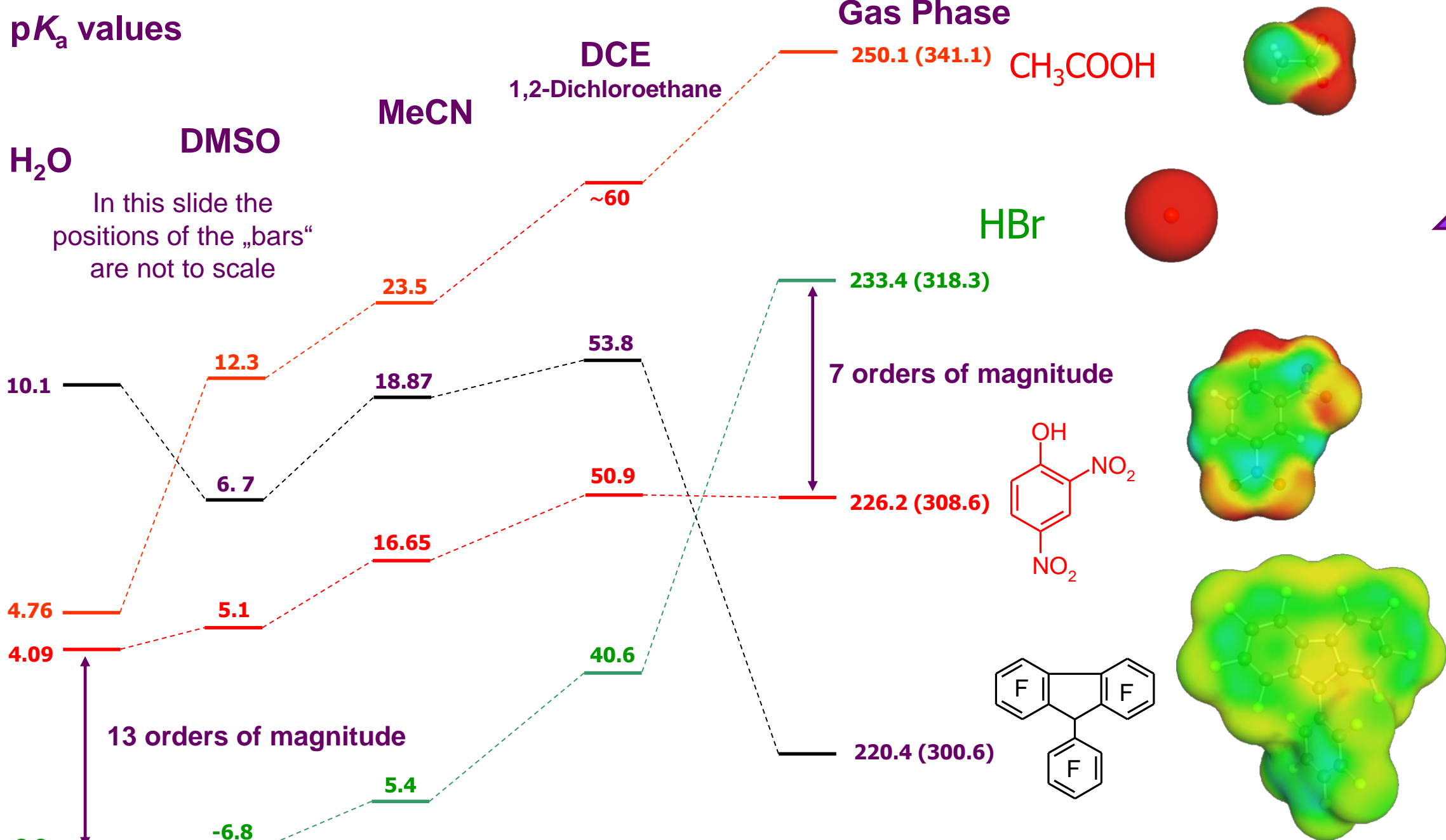
DMSO

MeCN

DCE
1,2-Dichloroethane

Gas Phase

In this slide the positions of the „bars“ are not to scale



pK_a of acids: observations, generalisations

- Mostly **ion** solvation matters
 - Especially **small ions** and/or with **localized charge**
- **Solvation of H^+ shifts the whole scale**
 - More basic solvent \rightarrow lower the pK_a
- **„Crossing points“ are due to differences in anion solvation**
 - Constant differences \rightarrow constant pK_a differences
 - Varied differences \rightarrow „crossing points“
- pK_{auto} determines the span of the pK_a values

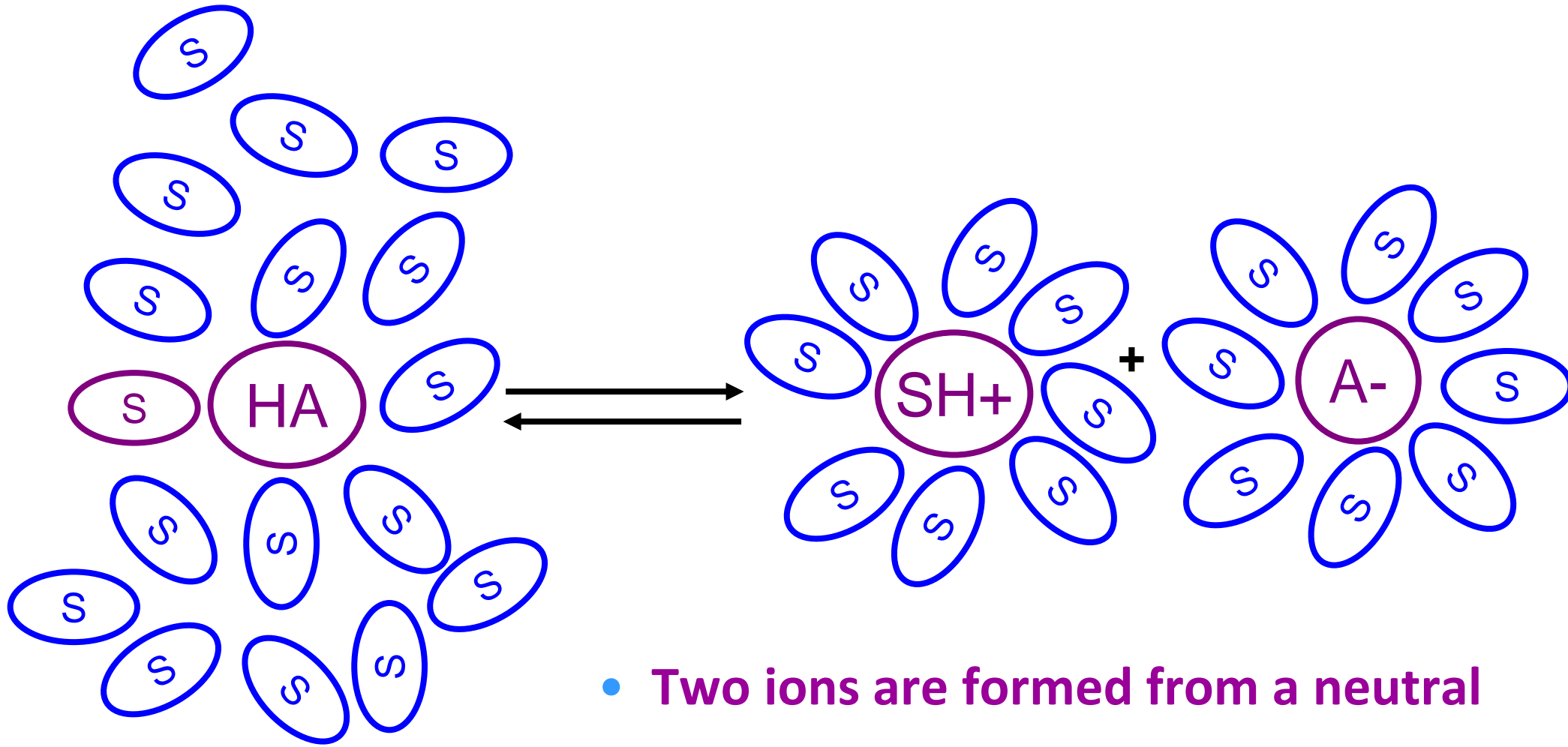
You will not find an acid which has lower pK_a in MeCN than in Water or DMSO

pK_a differences between MeCN and DMSO are 11 .. 14 units

pK_a order of a carboxylic acid and a CH acid often changes between water and DMSO

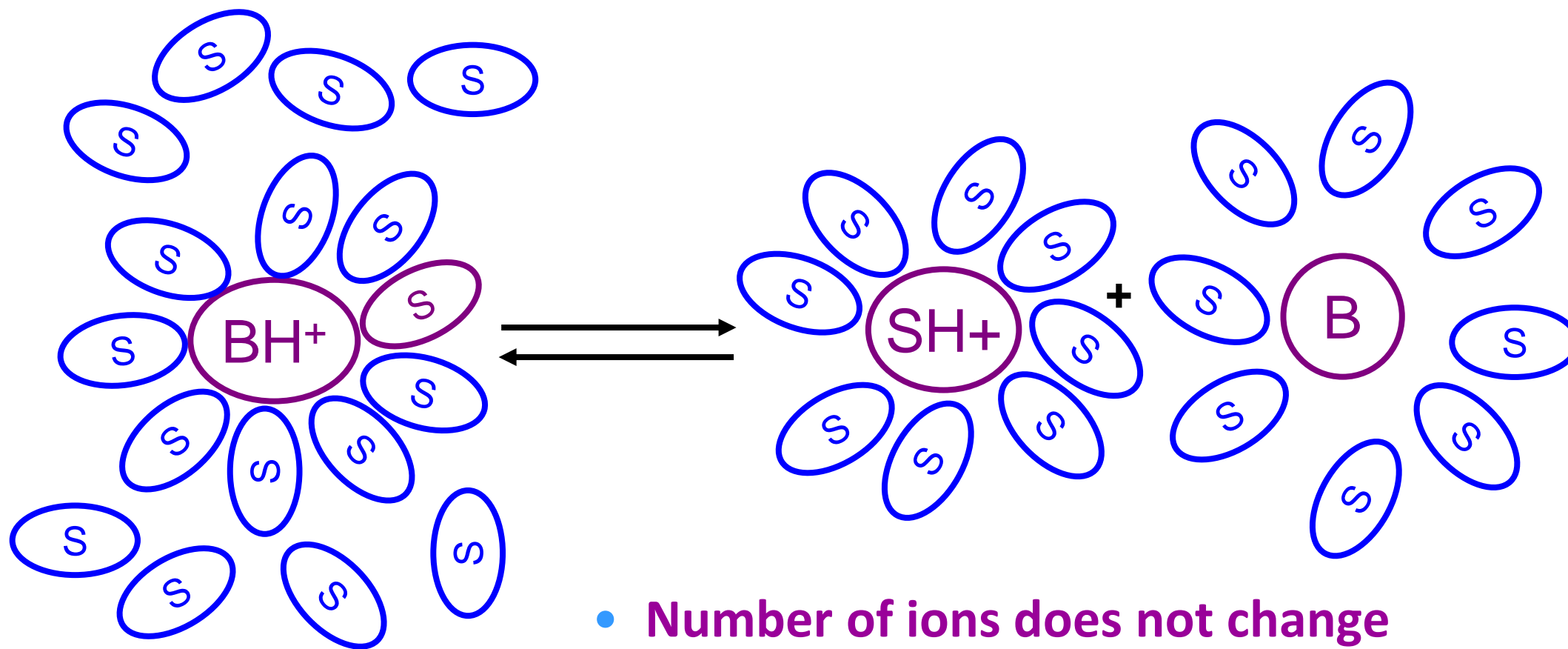
pK_a span in water is 14 pK_a units, in DMSO and MeCN it is more than 30 pK_a units

Acid (uncharged) dissociation in a polar solvent



- Two ions are formed from a neutral
- Very solvent-sensitive

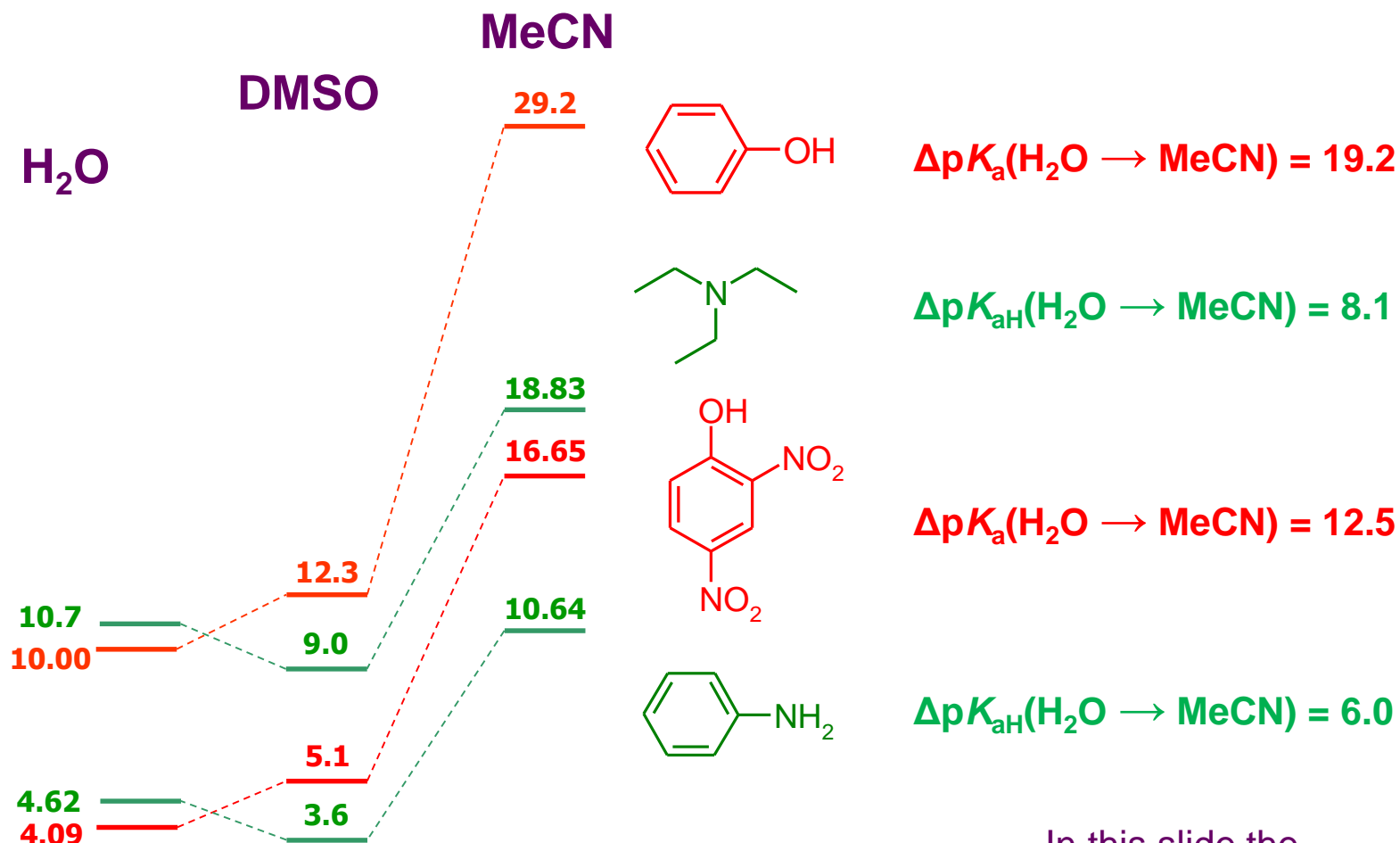
Base (cationic acid) in a polar solvent



- Number of ions does not change
- Somewhat less solvent-sensitive

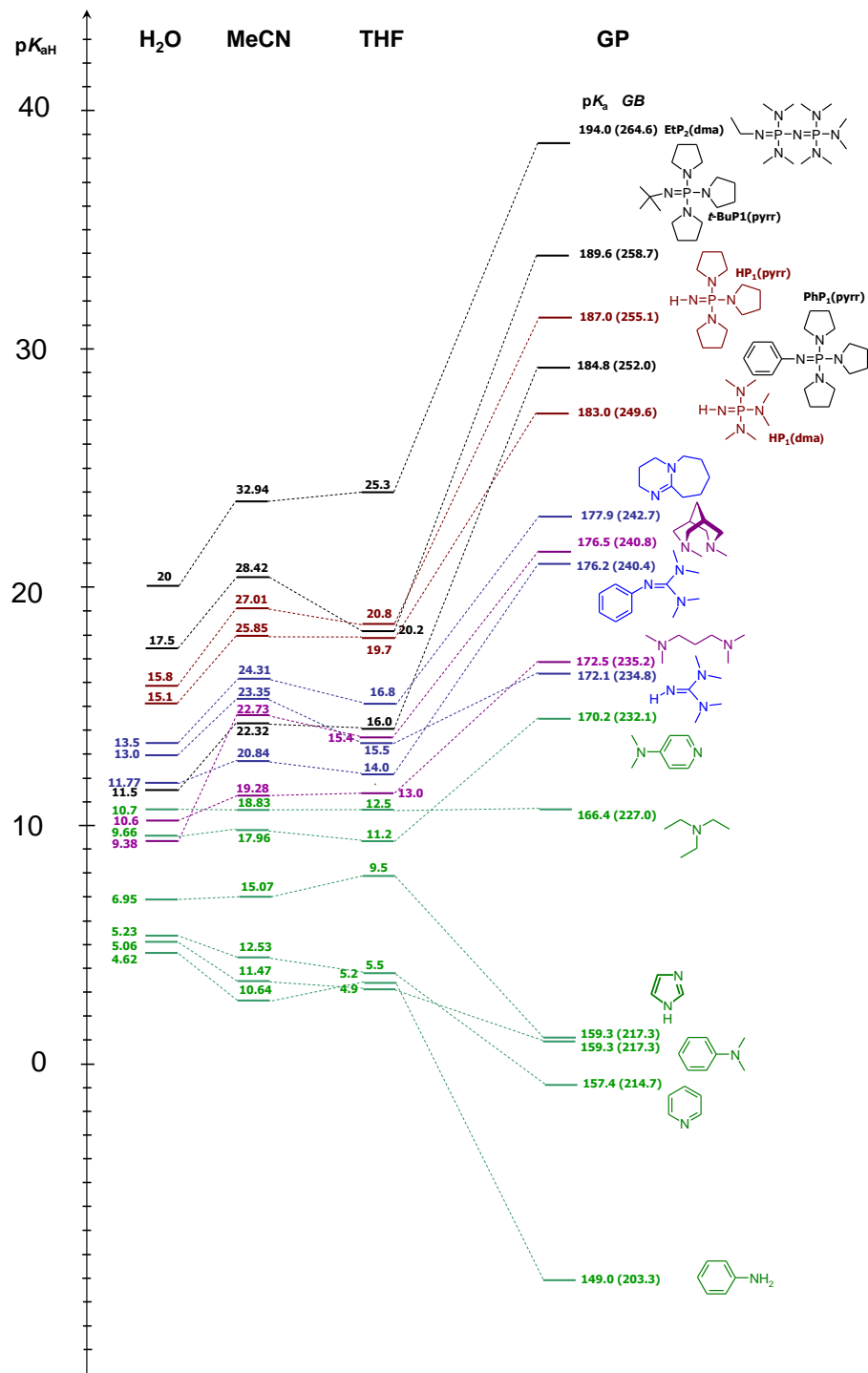
Solvent effects on bases are different from acids!

pK_a and pK_{aH} values



In this slide the positions of the „bars“ are to scale

- The interpretation logic is the same but the **trends are different**
- In a broad approximation the pK_{aH} trends are governed by differences in solvation of H^+
 - Cation solvation ability does not differ between solvents as much as anion solvation ability



Bases in different media

Data:

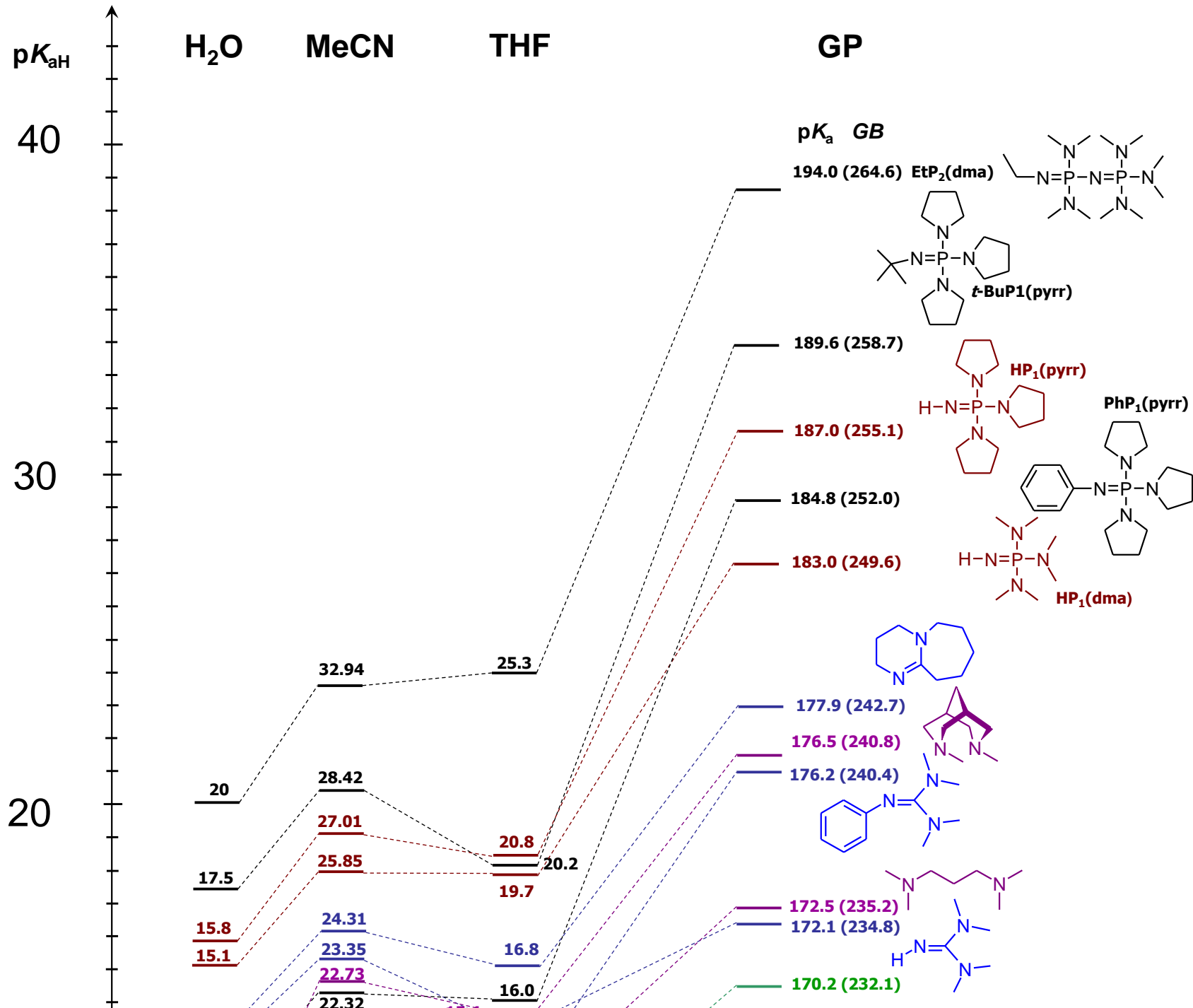
Kaupmees et al
Croat. Chem. Acta
2014, 87, 385

Tshepelevitsh et al
J. Phys. Org. Chem. **2019**, 6735

Vazdar et al *Acc. Chem. Res.* **2021**, 54, 3108

iBond database

Bases in different media



Data:

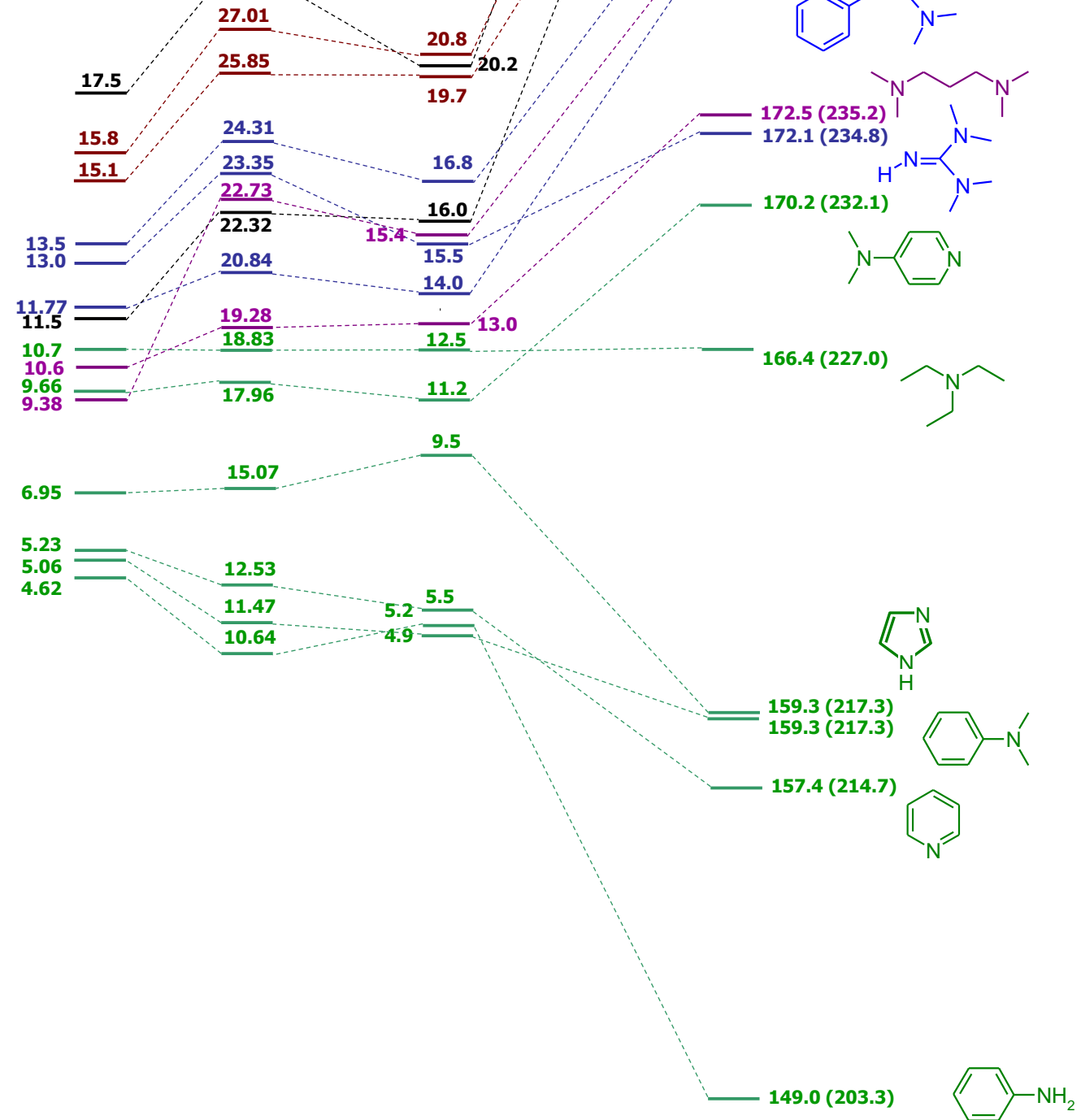
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Vazdar et al *Acc. Chem. Res.* **2021**, 54, 3108

iBond database

Sources of non-aqueous pKa values?

456

Acc. Chem. Res. 1988, 21, 456-463

Equilibrium Acidities in Dimethyl Sulfoxide Solution

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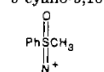
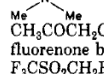
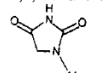
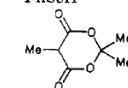
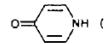
Received May 6, 1988 (Revised Manuscript Received August 10, 1988)

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Bordwell

Accounts of Chemical Research

Table II
Equilibrium Acidities in Dimethyl Sulfoxide at 25 °C

acid	pK _a ^a	acid	pK _a ^a
5-nitrobarbituric acid	0.8	PhCONHOH	13.65
(F ₃ CSO ₂) ₂ CH ₂	2.1	2,3-dihydroxynaphthalene	13.7
2,4-dinitronaphthol	2.1	N-acetyloxindol	13.8 ^f
PhN ⁺ HMe ₂	2.45	1,2,3-triazole	13.9
F ₃ 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	2,5-diphenylcyclopentadiene	14.3
F ₃ CSO ₂ CH ₂ COPh	5.1	9-cyano-9,10-dihydroanthracene	14.3
PhCOSH	5.2 ^b		14.4
Cl ₂ CHCO ₂ H	6.4 ^c		
PhSCH(SO ₂ Ph) ₂	5.55		
F ₃ CCH ₂ SO ₂ NHPh	5.7	CH ₃ COCH ₂ CO ₂ Et	14.4
2,4,5-Cl ₃ C ₆ H ₂ SH	6.0	fluorenone benzylimine	14.5
Ph ₃ P ⁺ CH ₂ COPh	6.1	F ₃ CSO ₂ CH ₂ Ph	14.55
Ph ₃ P ⁺ CH ₂ CN	7.05	succinimide	14.6
PhSO ₂ H	7.1	CH ₃ C(=S)NHPh	14.7
PhSO ₂ CH ₂ NO ₂	7.1	1,2,4-triazole	14.75
PhSeH	7.1 ^b		14.75
	7.4 ^d		
HONO	7.5		14.8
H ₃ N ⁺ CH ₂ CO ₂ H	7.5 ^e	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		
tetrazole	8.2		

International Union of Pure and Applied Chemistry
Chemical Data Series No 35

Acid-Base Dissociation Constants in Dipolar Aprotic Solvents

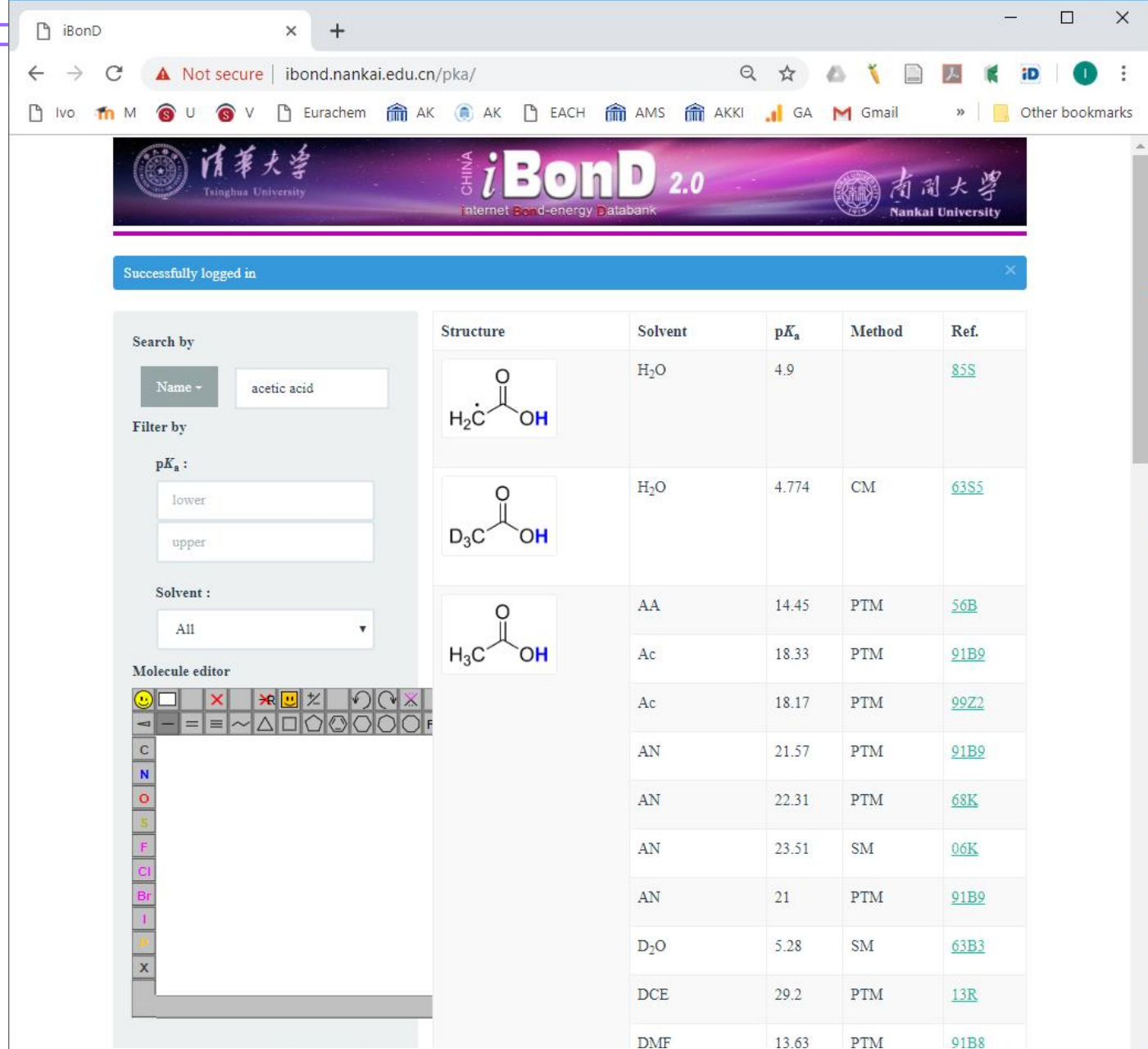
KOSUKE IZUTSU

Solvent	Density g cm ⁻³ (25°C)	Relative permittivity (25°C)	Donor number	Acceptor number
Acetone	0.7844	20.56	17.0	12.5
	0.7765	35.94	14.1	18.9
	0.8363	37.76	27.8	13.6
	0.9439	36.71	26.6	16.0
	1.0954	46.45	29.8	19.3
	1.0202	29.30(20°)	38.8	10.6
		13.11(20°)		13.3

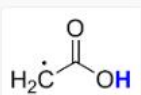
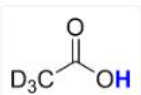
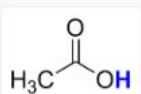
Additional tables and notes are visible in the background, including 'Solvent: Acetone' and 'Acid(A) or Base(B)' columns.

The iBond database

- Lots of data
- Many solvents
- Search by structure, substructure, ...
- But no critical revision of the pK_a values



The screenshot shows the iBond database interface. The search results table is as follows:

Structure	Solvent	pK_a	Method	Ref.
	H ₂ O	4.9		85S
	H ₂ O	4.774	CM	63S5
	AA	14.45	PTM	56B
	Ac	18.33	PTM	91B9
	Ac	18.17	PTM	99Z2
	AN	21.57	PTM	91B9
	AN	22.31	PTM	68K
	AN	23.51	SM	06K
	AN	21	PTM	91B9
	D ₂ O	5.28	SM	63B3
	DCE	29.2	PTM	13R
DMF	13.63	PTM	91B8	

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

Acidity-Basicity Data (pK_a Values) in Nonaqueous Solvents (and some in water as well)

If you cannot find the data that you need, please contact [ivo.leito\[at\]ut.ee](mailto:ivo.leito[at]ut.ee). We may be able to help!

The highlighted papers contain large amounts of pK_a data (or other information): **acids – red**, **bases – blue**, **both acids and bases – purple**.

Publication	Data	Medium	Method	Description	Available files
Eur. J. Org. Chem. 2023, 26, e202300453	pK_{aH} and GB values	Acetonitrile, THF, gas phase	UV-Vis spectrometry, Computations	Basicity values in MeCN and THF (pK_{aH} values) of a number of phosphane (posphine) bases containing the benzophenoneimine (bpi) moiety.	pK_{aH} values of phosphanes in MeCN and THF (PDF)
Bioorgan. Med. Chem. 2023, 81, 117203	pK_a values	MeCN and MeCN : water mixtures	UV-Vis spectrometry	pK_a and pK_{aH} values, of different drugs, bioactive and related compounds in acetonitrile-water mixtures and acetonitrile: Hydrochlorthiazide, Ibuprofen, Valsartan, Atenolol, Lidocaine, Mepivacaine, Propranolol, Scopolamine, Nalidixic acid, 3-aminophenol, benzoic acid. The used water-acetonitrile mixtures were meant to be nonpolar media mimicking the cell membrane interior.	pK_a and pK_{aH} values of different drugs, bioactive and related compounds in acetonitrile-water mixtures and acetonitrile (PDF)
Chem. Eur. J. 2022, 29, e202202953	pK_a values	Acetonitrile	UV-Vis spectrometry, ^{31}P NMR	pK_a values of Singly-linked and Macrocylic Bisphosphoric Acid catalysts for Asymmetric Phase-transfer and Brønsted-acid Catalysis . It turns out that the linker length has large influence on enantioselectivity but does not influence much the pK_a value.	pK_a values of Singly-linked and Macrocylic Bisphosphoric Acid catalysts in MeCN (PDF)
Anal. Chem. 2022, 94, 4059-4064	Biphasic pK_a values (pK_a^{ow} values)	Octanol:Water	UV-Vis spectrometry, 1H NMR, ^{13}C NMR, ^{31}P NMR	Biphasic pK_a values (pK_a^{ow} values) of 35 acids of various structures and chemical properties (mostly lipophilic) – carboxylic acids (benzoic acid, sorbic acid, cinnamic acid, ibuprofen, stearic acid, etc), phenols (pentachlorophenol, pentabromophenol, etc), sulfonamides and sulfonimides, as well as different CH acids – were determined in the 1-octanol:water solvent system. Biphasic pK_a value (pK_a^{ow} value) is measured in biphasic systems of water in equilibrium with a non-miscible organic solvent, in such a way that $a(H^+)$ is measured in aqueous phase (where most of H^+ ions reside) and the anion/neutral ratio in the organic phase (where most of the neutrals and anions reside, the latter as ion pairs). The directly obtained (apparent) pK_a^{ow} values depend on concentration. Concentration-independent values were obtained by extrapolating the apparent values to zero concentration using a Debye–Hückel model.	Octanol:water biphasic pK_a values (pK_a^{ow} values) of 35 acids and extrapolation plot (PDF)
Acc. Chem. Res. 2021, 54, 3108-3123	pK_a values (pK_{aH} values), gas-phase basicities	MeCN, THF, gas phase	UV-Vis spectrometry, NMR, Computations	An overview is given on design and synthesis of neutral (uncharged) superbasic molecules that besides high basicity have other desirable properties. Important structural features of superbases are discussed and pK_a (pK_{aH}) values in MeCN and THF, as well as gas-phase basicities of around 30 important superbases (amidines, guanidines, proton sponges, phosphazenes, phosphanes, phosphorus ylides, carbodiphosphoranes) are presented.	pK_a (pK_{aH}) values in MeCN and THF, as well as gas-phase basicities of around 30 important superbases (PDF)
Eur. J. Org. Chem. 2021, 1407-1419	pK_a values	Acetonitrile	UV-Vis spectrometry	pK_a values of 231 acids in acetonitrile, ranging from hydrogen iodide (2.8) and indole (32.57) and covering almost 30 orders of magnitude. This is the revised and significantly extended version of our pK_a scale of acids in MeCN. The acids have wide structural variety, ranging from common families (phenols, carboxylic acids, sulfonic acids, hydrogen halides) to highly special molecules (chiral BINOL catalysts, bis(benzoxazole-2-yl)methanes, polyfluorinated compounds) and superacids.	Acidity pK_a values of 231 acids in acetonitrile (PDF)
J. Am. Chem. Soc. 2020, 142, 15252-15258	pK_a values	Acetonitrile	UV-Vis spectrometry	Chiral benzoic acid catalysts are reported that efficiently catalyse enantioselective [4+2] cycloadditions of acetals. The peculiar structure of the acids features covalently linked thiourea sites that stabilize the carboxylate conjugate bases via intramolecular hydrogen bond to the anionic site. This leads to the low pK_a values of the acids compared benzoic acid.	Acidities (pK_a in MeCN) of the enantioselective carboxylic acid catalysts (PDF)
Angew. Chem. Int. Edit. 2020, 59, 2028-2032	pK_a values	Acetonitrile	UV-Vis spectrometry	Chiral superacids are reported that efficiently catalyse enantioselective [4+2] cycloadditions of acetals. The peculiar structure of the acids features covalently linked thiourea sites that stabilize the carboxylate conjugate bases via intramolecular hydrogen bond to the anionic site. This leads to the low pK_a values of the acids compared benzoic acid.	Chiral superacids catalyzing [4+2] cycloadditions of acetals (PDF)
Rapid Commun. Mass. Sp. 2020	Gas-phase acidity values	Gas phase	FT-ICR mass spectrometry	This scale of gas-phase acidities was compiled. The scale ranges from 295.4 to 277.1 kcal mol ⁻¹ and extends the previously reported scale towards higher acidities. Gas-phase acidities for several important superacids (e.g. triflic acid) were significantly revised.	Gas-phase acidities of superacids (PDF)
Eur. J. Org. Chem. 2019, 6735-6748	pK_a values (pK_{aH} values)	Acetonitrile, DMSO, THF, Water	UV-Vis spectrophotometry	pK_a values (pK_{aH} values) in MeCN, DMSO, THF and water (altogether close to 400 values) for a large number of organic bases representing all main classes (amines, diamines, anilines, pyridines, imidazoles, amidines, phosphazenes, etc). Simple equations	Basicity pK_a (pK_{aH}) values of 279 bases in acetonitrile (PDF)

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

[d catalysts](#)

[eracids \(PDF\)](#)

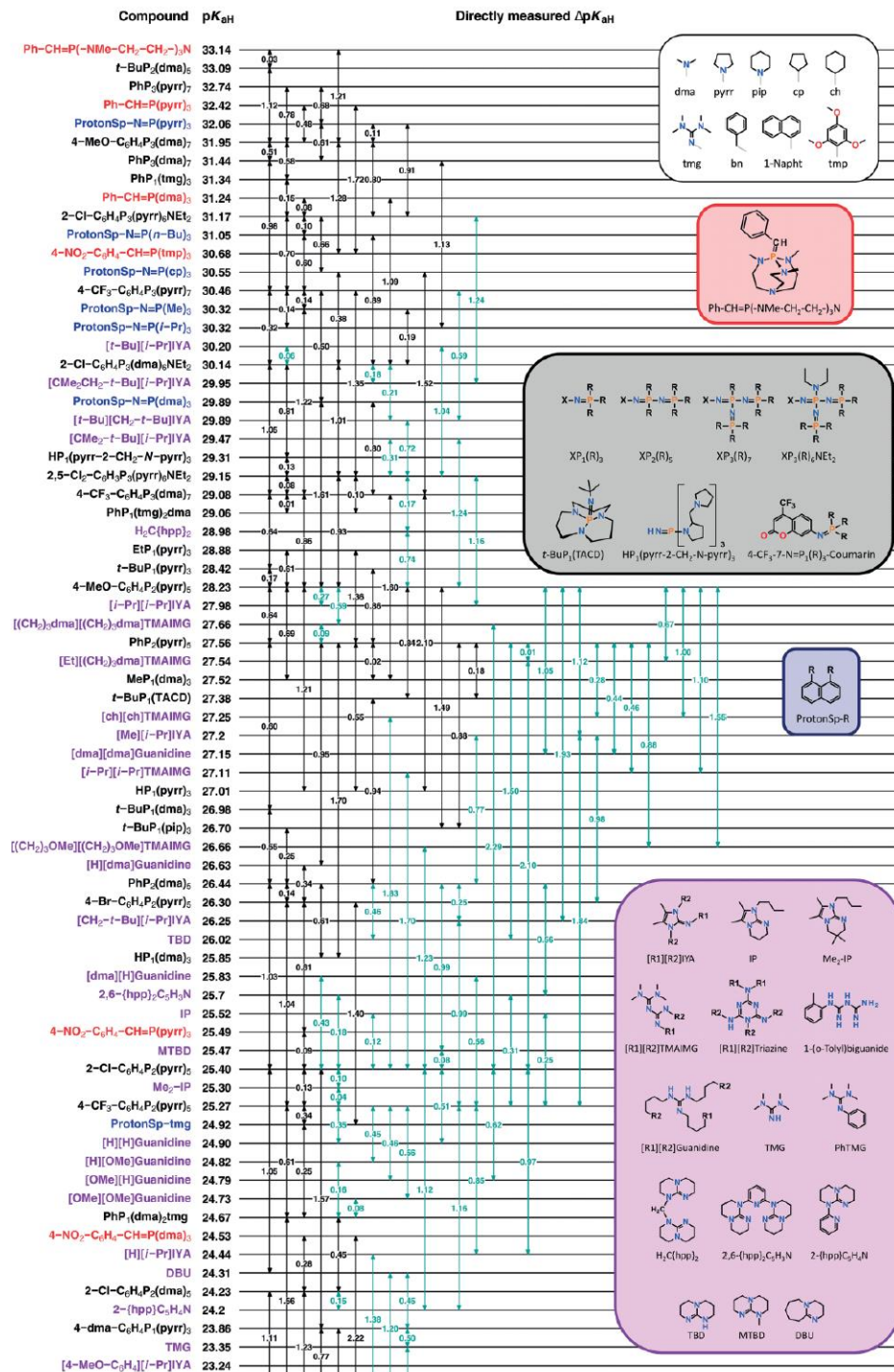
[Basicity pK_a \(pK_{aH}\) values of 279 bases in acetonitrile \(PDF\)](#)

[Basicity pK_a \(pK_{aH}\) values of selected](#)

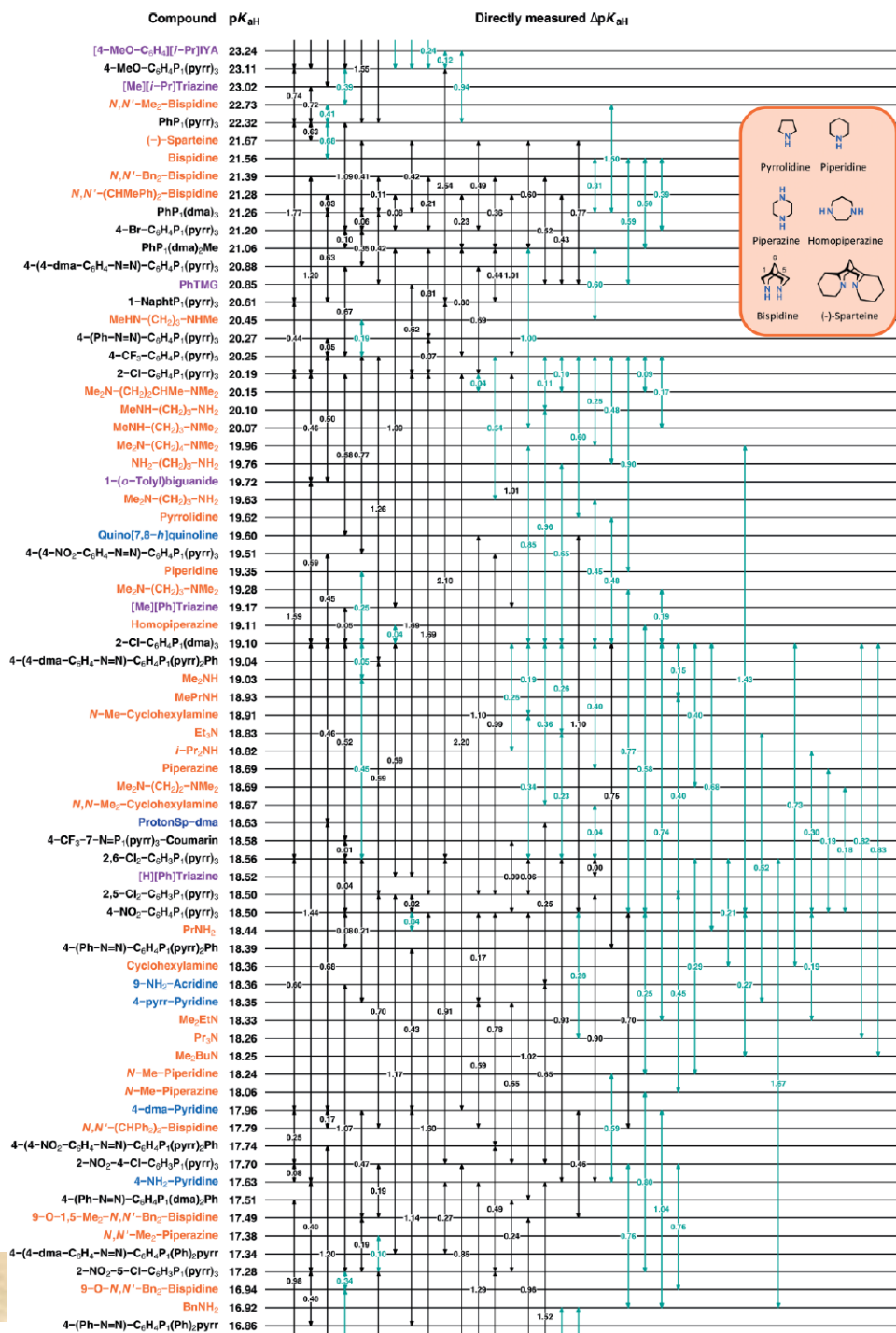
Example: Self consistent basicity scale in MeCN

- 270 bases
- pK_{aH} span: 1.3 .. 33.1
- 682 relative basicity (ΔpK_{aH}) measurements
- Internal consistency
 - 0.03 „normal“ compounds
 - 0.06 „difficult“ compounds

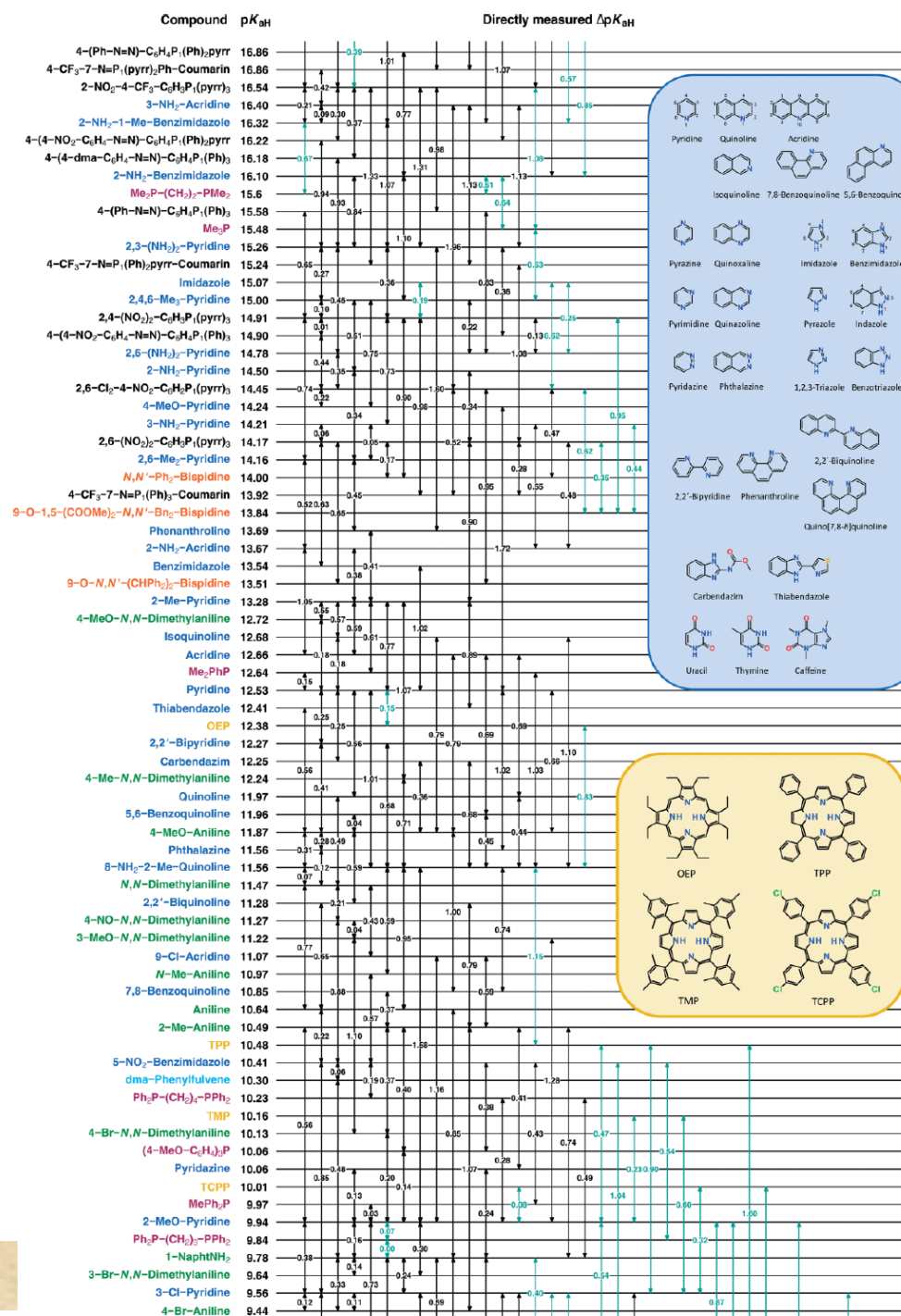
Tshepelevitsh et al. *Eur. J. Org. Chem.* 2019, 6735–6748



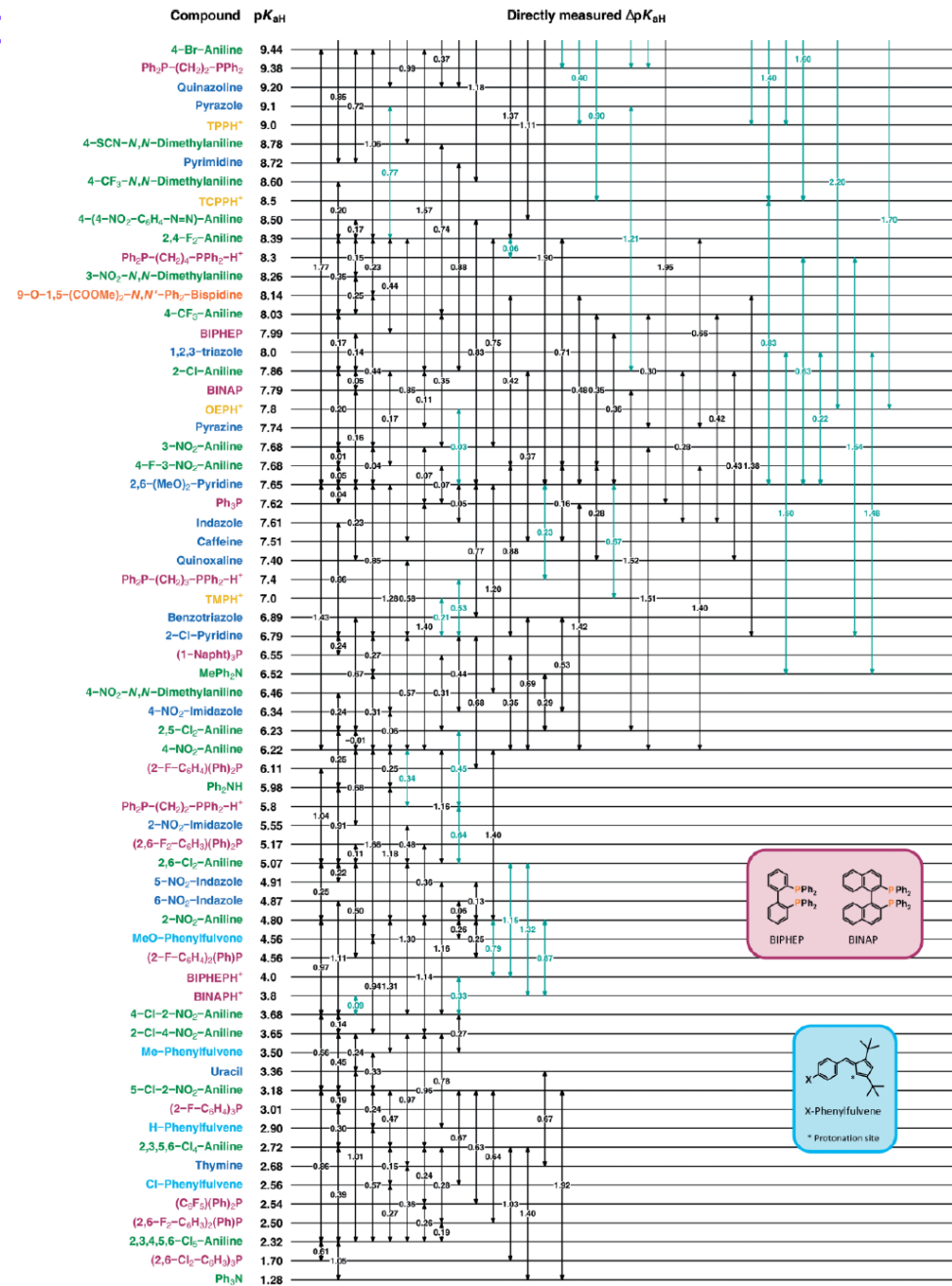
Example: Self consistent basicity scale in MeCN



Example: Self consistent basicity scale in MeCN



Example: Self consistent basicity scale in MeCN



Typical issue: no pK_a data for X in solvent S

- Possible solutions:

- **Measure**

- **Compute**

- Increasingly useful and used

- Usually **correlations with experimental data** are needed for good accuracy

- **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

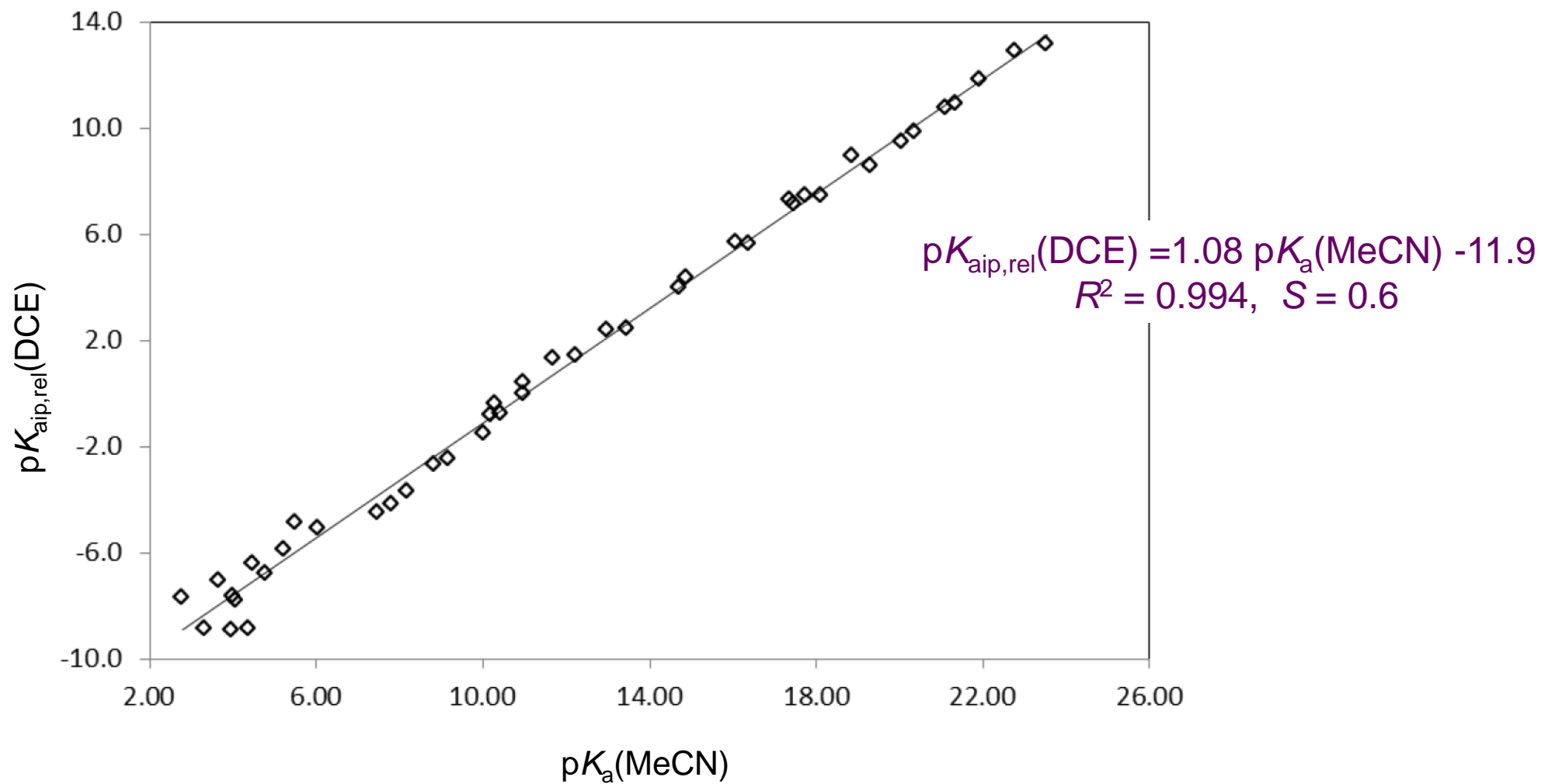
- **Cross-use between solvents**

- **Only with structurally similar compounds!**

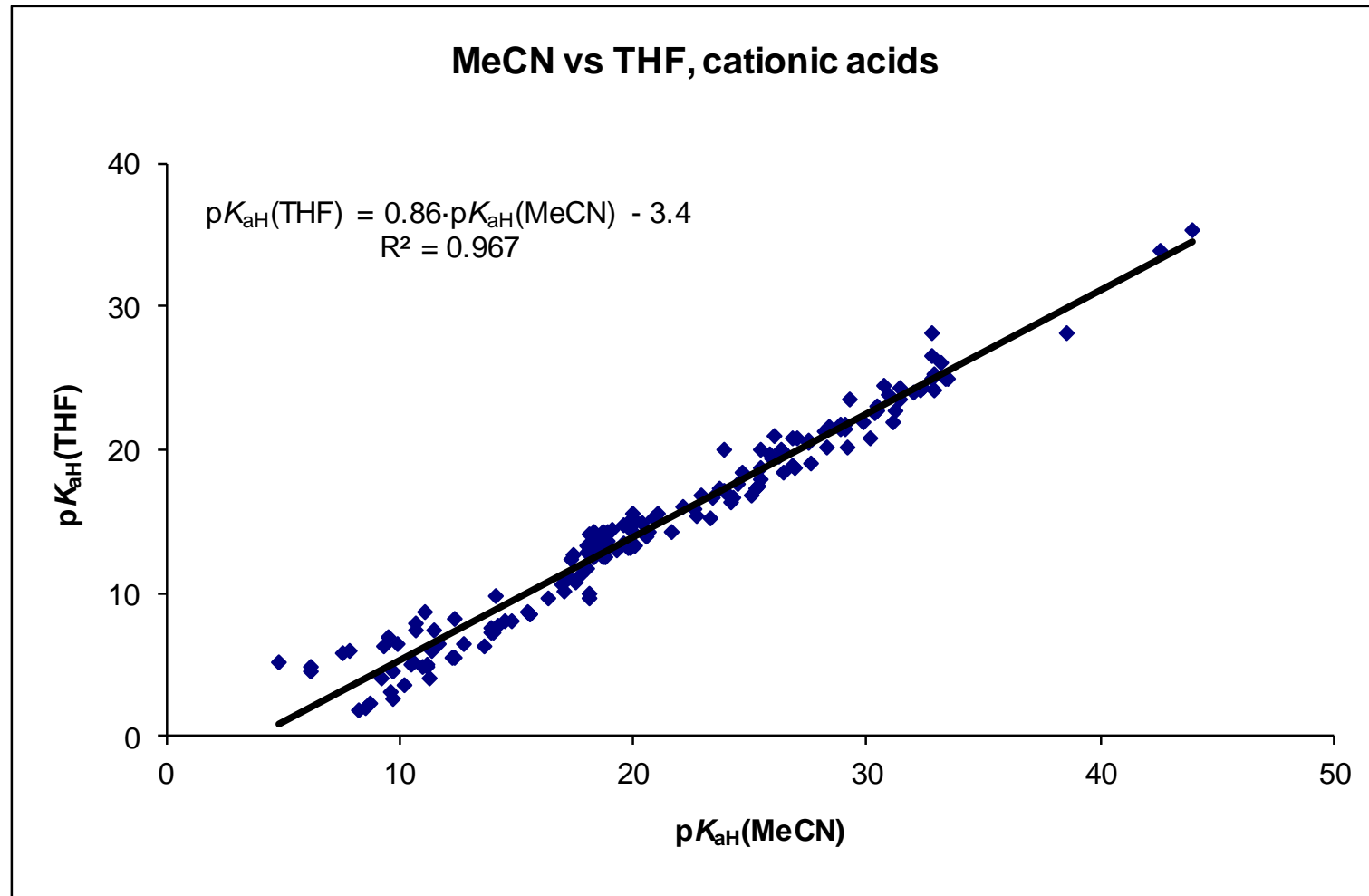
- In many cases **acidity/basicity order** remains the same

- Often **acidity/basicity differences** remain similar

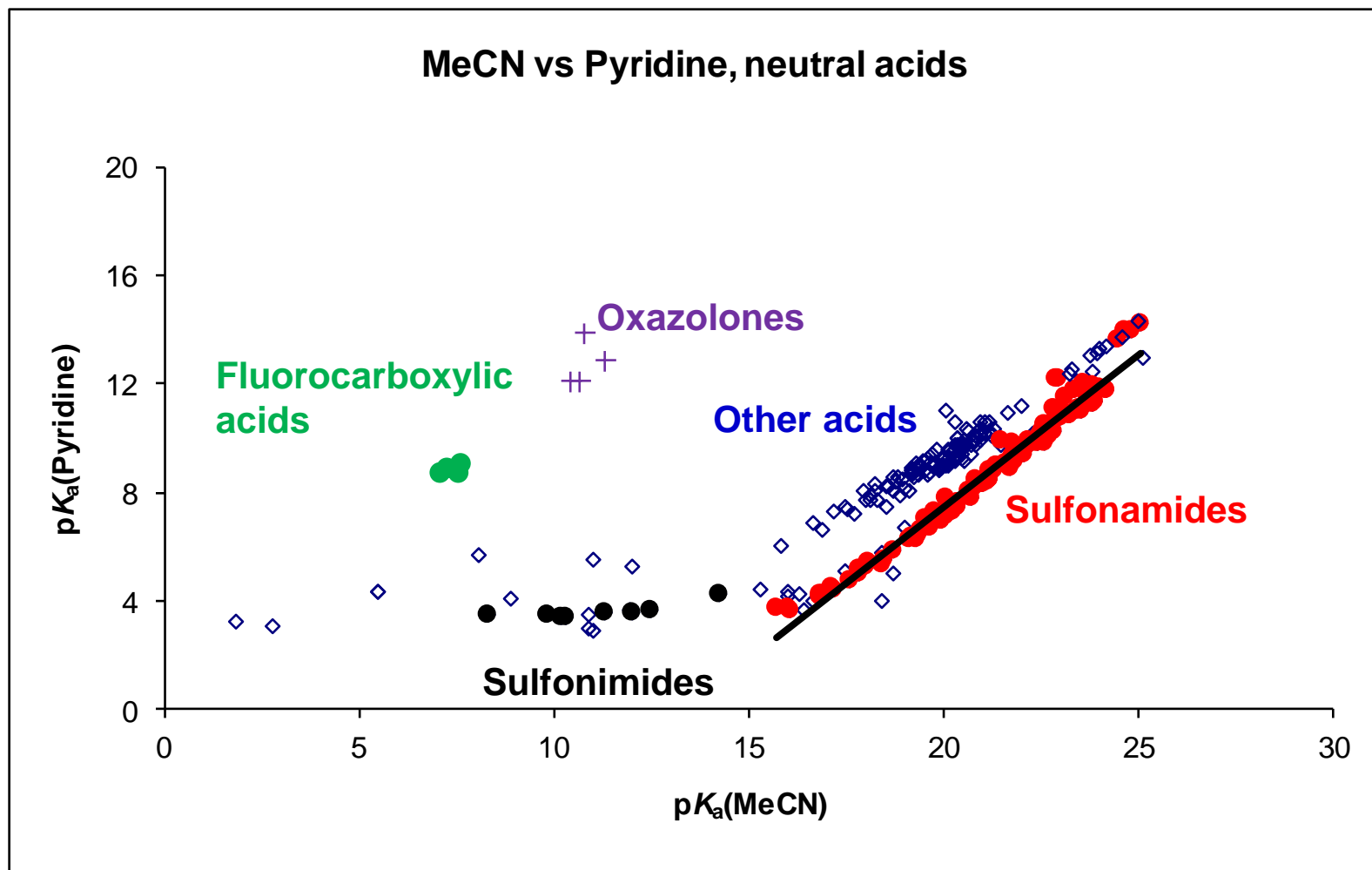
Sometimes correlations are very good



Sometimes correlations are good



Sometimes correlations are tricky or do not work



pK_a correlation possibilities

Legend:

Reliable

Mediocre reliability

Tricky

„+“: real data available

	MeCN	PC	Acetone	DMSO	DMF	THF	DME	Py	DCE/DCM	MeOH/EtOH	H ₂ O	
MeCN			+	+	+	+					+	
PC	+											
Acetone	+	+			+							
DMSO	+	+	+		+	+						B
DMF	+	+	+	+		+						A
THF											+	S
DME	+											E
Py	+	+	+	+	+							S
DCE/DCM	+			+								
MeOH/EtOH												
H ₂ O	+			+					+	+		

A C I D S

... Sometimes published correlation equations are available

- Correlations within families work better!
 - But only for compounds belonging to the families!

Table 2. Equations for conversion of acidity data from acetonitrile to other media. Standard errors are given in parentheses. *N* – number of compounds used in regression; *S* – standard error of regression.

Eq. No	Compounds included	<i>N</i>	Equation ^[a]	<i>S</i>	<i>R</i> ²	<i>u</i> ^[b]	<i>pK</i> _s (MeCN) range
Water							
1.1	All available	47	$pK_s(\text{H}_2\text{O}) = pK_s(\text{MeCN}) \cdot 0.72(0.03) + nC \cdot 0.45(0.05) + nON \cdot 0.19(0.05) - X\text{-CO} \cdot 1.6(0.5) - 12.0(0.6)$	1.2	0.961	1.4	2.8...32.6
1.2	OH acids (18 phenols, 3 carboxylic acids, 1 alcohol)	22	$pK_s(\text{H}_2\text{O}) = pK_s(\text{MeCN}) \cdot 0.55(0.01) - X\text{-CO} \cdot 2.2(0.2) + nC \cdot 0.13(0.04) + MW \cdot 0.0017(0.0007) - 6.5(0.5)$	0.3	0.994	0.3	4.4...29.2
1.3	NH acids	15	$pK_s(\text{H}_2\text{O}) = pK_s(\text{MeCN}) \cdot 0.70(0.02) - nS \cdot 2.9(0.2) - nH \cdot 0.24(0.06) - 3.9(0.4)$	0.3	0.995	0.4	10.5...32.6
DMSO							
2.1	All available	75	$pK_s(\text{DMSO}) = pK_s(\text{MeCN}) \cdot 0.94(0.02) + n\text{HBD} \cdot 1.1(0.2) + X\text{-SO}_2 \cdot 1.8(0.3) - X\text{-H} \cdot 0.8(0.3) - 10.7(0.5)$	1.1	0.969	1.2	2.8...32.6
2.2	CH acids	27	$pK_s(\text{DMSO}) = pK_s(\text{MeCN}) \cdot 0.78(0.03) + nS \cdot 1.4(0.3) - X\text{-CN} \cdot 0.6(0.3) - 8.0(0.7)$	0.7	0.979	0.9	7.7...28.8
2.3	NH acids (mainly diarylamines and sulfonamides)	24	$pK_s(\text{DMSO}) = pK_s(\text{MeCN}) \cdot 1.00(0.02) + X\text{-SO}_2 \cdot 2.0(0.2) + nN \cdot 0.3(0.1) - 12.6(0.6)$	0.4	0.991	0.5	14.6...32.6
2.4	OH acids (16 phenols/naphthols, 5 other acids)	21	$pK_s(\text{DMSO}) = pK_s(\text{MeCN}) \cdot 0.87(0.02) - n\text{NO}_2 \cdot 1.0(0.1) + n\text{CF}_3 \cdot 0.37(0.09) - 8.0(0.6)$	0.5	0.992	0.6	10.5...29.2
DMF							
3.1	All available	22	$pK_s(\text{DMF}) = pK_s(\text{MeCN}) \cdot 0.91(0.03) - 7.6(0.6)$	0.9	0.982	0.9	10.2...32.6
3.2	Phenols	7	$pK_s(\text{DMF}) = pK_s(\text{MeCN}) \cdot 0.95(0.01) - 9.5(0.3)$	0.2	0.999	0.2	11.0...29.2
3.3	Aromatic sulfonamides	7	$pK_s(\text{DMF}) = pK_s(\text{MeCN}) \cdot 0.77(0.02) - 3.5(0.6)$	0.05	0.995	0.06	24.6...27.0
DCE							
4.1	All available	47	$pK_s(\text{DCE}) = pK_s(\text{MeCN}) \cdot 1.10(0.03) + 32.6(0.4)$	1.2	0.973	1.2	2.8...23.5
4.2	CH acids, excl TCNP acids ^f	27	$pK_s(\text{DCE}) = pK_s(\text{MeCN}) \cdot 1.05(0.01) + 33.5(0.2)$	0.3	0.997	0.3	3.6...23.5
4.3	Aromatic sulfonimides	9	$pK_s(\text{DCE}) = pK_s(\text{MeCN}) \cdot 1.03(0.03) + 32.8(0.2)$	0.2	0.995	0.2	3.3...10.0

To be submitted soon: Critical compilation of acid pK_a values in polar aprotic solvents

- More than **9000** pK_a values
- Close to **5000** acids
- In **DMSO, MeCN, DMF, pyridine, acetone, propylene carbonate, THF**
- **Critical evaluation**
 - Flagging as „preferred“ or „doubtful“
 - Correcting, where possible
- To be submitted to *Pure Appl. Chem.* during summer 2024
- Huge XLSX file will be deposited
- To be continued with pK_{aH} of bases

The screenshot shows the IUPAC website interface for a specific project. The browser address bar indicates the URL is iupac.org/project/2015-020-2-500/. The page features a navigation menu with categories: WHO WE ARE, WHAT WE DO, EVENTS, PROJECTS, and NEWS. The main content area is titled 'Critical compilation of acid pKa values in polar aprotic solvents'. Below the title, there is a table of project details:

Project No.:	2015-020-2-500
Start Date:	1 May 2016
End Date:	
Cite:	https://iupac.org/project/2015-020-2-500
Division:	Analytical Chemistry Division

Below the table, there are tabs for 'Objective', 'Description', and 'Progress'. The 'Objective' tab is selected, showing the following text:

Objective

The objective is to summarize and critically evaluate the data on ionization constants of acids (pK_a data) available in a selection of polar aprotic solvents, which are either (1) the most popular solvents for pK_a determination or (2) have properties specifically suitable for determination of pK_a values

On the right side of the page, there is a sidebar with the following information:

Chair
Ivo Leito

Members
Jean-François Gal
Ivari Kaljurand
Vilve Nummert
Mare Piirsalu
Martí Rosés Pascual
Reinhard Schwesinger
Sofja Tshepelevitsh
Jonathan Wen Yuan
Zheng

Excerpt of data table

- Results of critical evaluation:
- Out of **9713** values:
 - Doubtful **1932**
 - Unreliable **811**
 - Corrected **2376**

The screenshot shows an Excel spreadsheet titled "pKa_Data_Table.xlsx" with the following data table:

	E	S	T	U	V	W	X	Y	Z	AA
1	Compound	DMSO_pK _a	DMSO_Ref	DMSO_Comments	MeCN_pK _a	MeCN_Ref	MeCN_Comments	DMF_pK _a	DMF_Ref	DMF_Comments
28	Butanoic acid (Butyric acid)	12.9	C1	Pt, 3 mM	24.0	C1	Pt, 4 mM; 22.73 corrected by +1.3	12.5	B109	Pt, ND; 10.0 corrected by +2.5, doubtful
29	Butanoic acid (Butyric acid)	11.0	B109	Pt, ND; doubtful						
30	2-Methyl-propanoic acid (Isobutyric acid)	12.8	B101	Pt, ND	23.4	B101	Pt, ND; 22.20 corrected by +1.2, doubtful	14.05	B101	Pt, ND
31	2-Methyl-propanoic acid (Isobutyric acid)	10.5	B109	Pt, ND; unreliable				13.4	B109	Pt, ND; 10.6 corrected by +2.8, doubtful
32	2-Methyl-propanoic acid (Isobutyric acid)							4.28	P44	C, ND; unreliable
33	Pentanoic acid (Valeric acid)	12.2	B109	Pt, ND; doubtful				13.9	B109	Pt, ND; 10.9 corrected by +3.0, doubtful
34	2,2-Dimethyl-propanoic acid (Pivalic acid)	12.9	K18	Pt	23.6	B101	Pt, ND; 22.28 corrected by +1.3, doubtful	14.27	B101	Pt, ND
35	2,2-Dimethyl-propanoic acid (Pivalic acid)	12.9	B101	Pt, ND						
36	2,2-Dimethyl-propanoic acid (Pivalic acid)	13.3	F6,S1	UV, ND; 12.4 corrected by +0.9, doubtful						
37	Cyclohexanecarboxylic acid				24.7	C17	Pt, 23.3 corrected by +1.4			
38	Heptanoic acid (Enanthic acid)	11.1	B109	Pt, ND; doubtful				13.9	B109	Pt, ND; 10.9 corrected by +3.0, doubtful
39	Cyclohexyl-acetic acid	12.6	B101	Pt, ND	23.3	B101	Pt, ND; 22.06 corrected by +1.2, doubtful	13.17	B101	Pt, ND
40	7-Methyl-decanoic acid							13.3	E6	Pt, ND; unreliable
41	Bicyclo[2.2.2]octane-1-carboxylic acid	12.9	K16,K18	Pt						
42	Bicyclo[2.2.2]octane-1-carboxylic acid	12.8	K17	Pt, ND						
43	Bicyclo[2.2.2]octane-1-carboxylic acid	12.5	R4	Pt, 0.6 mM, I ~ 1 mM						
44	Cubanecarboxylic acid	12.2	K16,K18	Pt						
45	Phenyl-acetic acid	11.7	B101	Pt, ND	21.8	B101	Pt, ND; 20.73 corrected by +1.05, doubtful	13.5	D1	Pt, no temp., 10-100 mM
46	Phenyl-acetic acid	11.6	C4	Pt, 10-20 mM, I = 100 mM				12.93	B101	Pt, ND
47	Phenyl-acetic acid	11.6	K18	Pt						
48	Phenyl-acetic acid	10.6	P1	Pt, ND, I → 0; doubtful						
49	α-Methyl-4-(2-methylpropyl)benzeneacetic acid (Ibuprofen)				22.77	V23	UV			
50	Diphenyl-acetic acid	10.9	R7	UV, ~ 0.4 mM	21.3	B101	Pt, ND; 20.3 corrected by +1.0, doubtful	12.19	B101	Pt, ND
51	Diphenyl-acetic acid	10.9	B101	Pt, ND						

Warning signs for potentially low reliability pK_a data

- **Molecular structure**
 - Strongly outlying pK_a from a good correlation within a series
 - Substituents behave unexpectedly
- **Solvent effects**
 - Unexpected differences between pK_a values in different solvents
 - Values outside the „ pK_{auto} range“ in the solvent
- **Unsure? Confused? Write me: ivo.leito@ut.ee**
 - Or talk to me here at BOS 2024



Thanks
to all these
people!

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(www.uniphied.eu)
EU Regional Development Fund
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and high-technology devices for
energy recuperation systems"),
Estonian Research Council
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of Analytical Chemistry
(www.akki.ee)

