



# Using the available $pK_a$ data in non-aqueous solvents

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Slides: [analytical.chem.ut.ee/ISSP21/](https://analytical.chem.ut.ee/ISSP21/)

University of Tartu

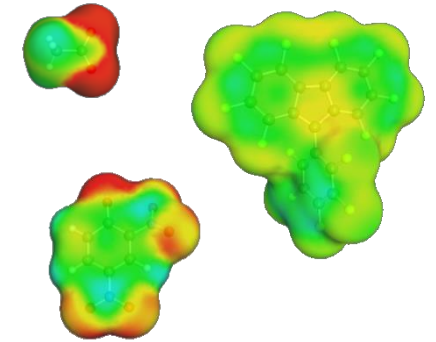


Novi Sad Sept 10, 2024

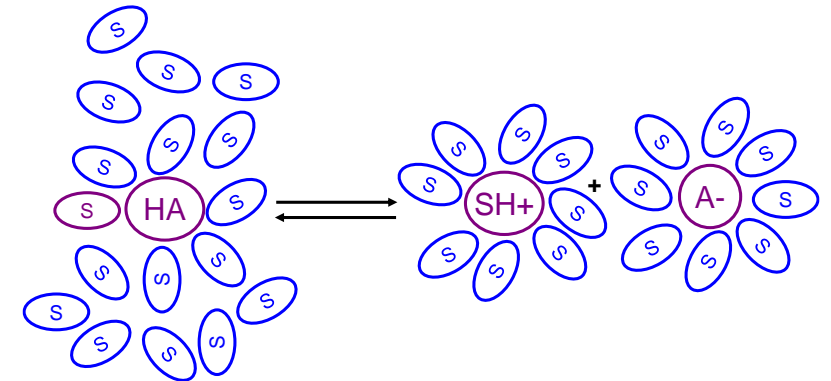


# Overview

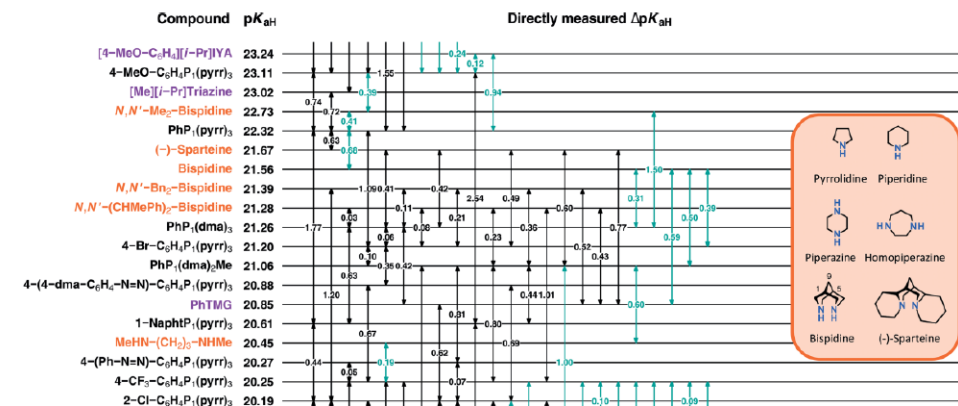
- **Brønsted acidity and basicity of molecules in solution**
  - What data exists ( $pK_a$  and  $pK_{aH}$  values, absolute and relative values)?



- **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
  - We leave ion-pairing out of discussion
    - In most considered solvents at low concentration ion-pairing can be neglected
    - In others free-ion  $pK_a$  values can be estimated
- Slides: [analytical.chem.ut.ee/ISSP21/](https://analytical.chem.ut.ee/ISSP21/) and:

Non-aqueous  $pK_a$  values:  
**rarely highly accurate**

Uncertainties ( $pK_a$  units,  $k=2$ ):  
 **$\leq \pm 0.1$** : the best data  
 **$\pm 0.3$** : almost always sufficient  
 **$\pm 1$** : often OK

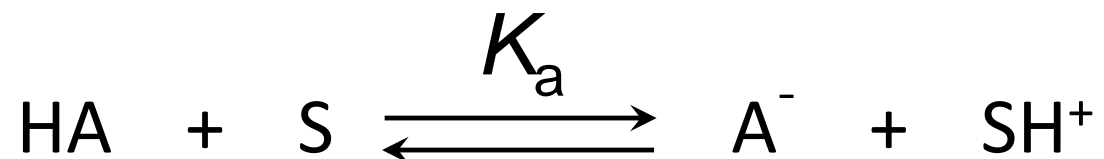


# Why do we need non-aqueous $pK_a$ data?

- **Understanding and predicting reactivity**
  - Reactions often in **non-aqueous** solutions
  - Very often involving **protonation** and/or **deprotonation**
  - $pK_a$  determines if a reactant is 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 molecules in solution

- Acidity of molecules in solution is defined in the framework of the **Brønsted** theory via the **p*K*<sub>a</sub> values**



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

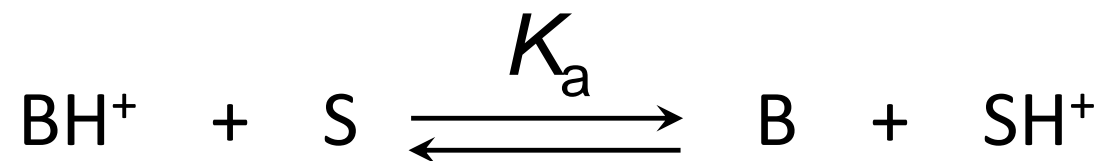
- Solvent S acts as a base
- Simplified scheme, valid in polar solvents
  - Ion-pairing is not considered



The lower the p*K*<sub>a</sub> 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)



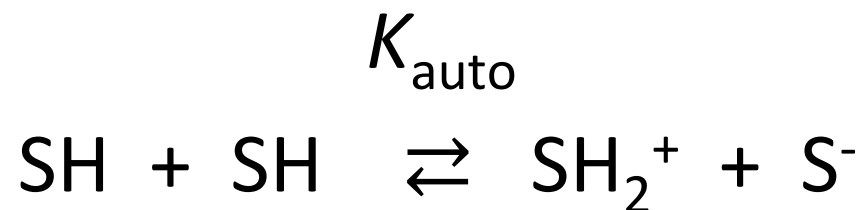
$$\begin{aligned} pK_a(\text{BH}^+) &\equiv pK_{aH}(\text{B}) \equiv pK_{\text{BH}^+}(\text{B}) = \\ &= -\log K_a(\text{BH}^+) = -\log \frac{a(\text{B}) \cdot a(\text{SH}^+)}{a(\text{BH}^+)} \end{aligned}$$

- Solvent 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

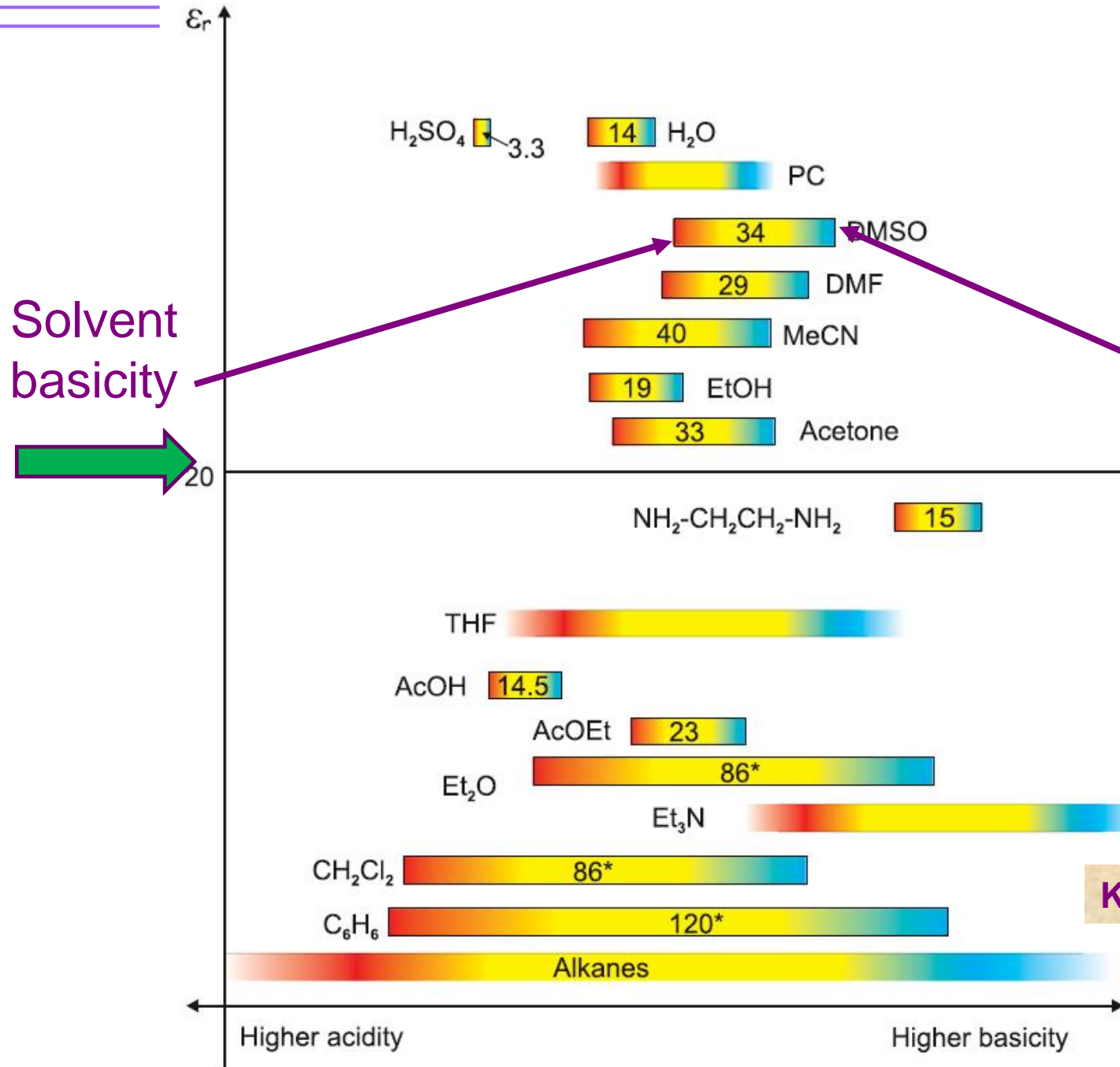
# Acidity and basicity of solvent molecules: $pK_{\text{auto}}$



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

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

# Solvent acidity, basicity and $pK_{\text{auto}}$



Solvent acidity

Values on the blocks are  $pK_{\text{auto}}$

„Open ends“ mean unavailable data

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

\* Computational estimates

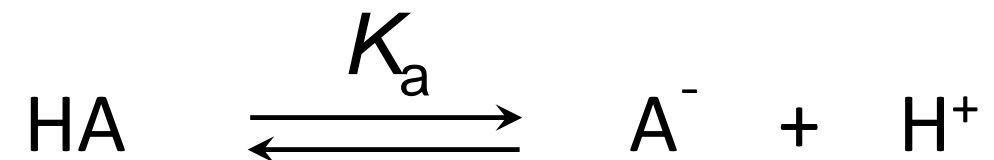
# Some solvents

Solvent/ medium	$E_T^N$	$\epsilon$	$\Delta_{\text{transfer}} G^\circ$ of $H^+$ from $H_2O$	HB doni- city, $\alpha$	$pK_{\text{auto}}$	Comments
Gas phase	–	1	–	–	–	
THF	0.207	7.47	NA	0	Very high	Aprotic, ion-pair $pK_a$ (free-ion $pK_a$ values can be estimated)
1,2-Dichloro- Ethane	0.327	10.7	NA	0	Very high	Aprotic, ion-pair $pK_a$ (free-ion $pK_a$ values can be estimated)
MeCN	0.460	35.9	+11.1	0.19	ca 39	Aprotic, free-ion $pK_a$
DMSO	0.444	46.7	-4.6	0	ca 33	Aprotic, free-ion $pK_a$
Methanol	0.762	33	+2.5	0.98	18.9	Protic, free-ion $pK_a$
Water	1.000	81	0	1.17	14.0	Protic, free-ion $pK_a$

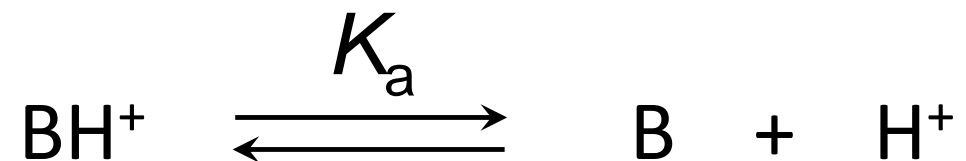
C. Reichardt, T. Welton *Solvents and Solvent Effects in Organic Chemistry*, 4th ed. VCH, 2011  
 J.L.M. Abboud, R. Notario *Pure Appl. Chem.* 1999, 71, 645-718  
 M. J. Kamlet et al. *J. Org. Chem.* 1983, 48, 2877-2887

## Acidity and basicity of molecules in the gas phase

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



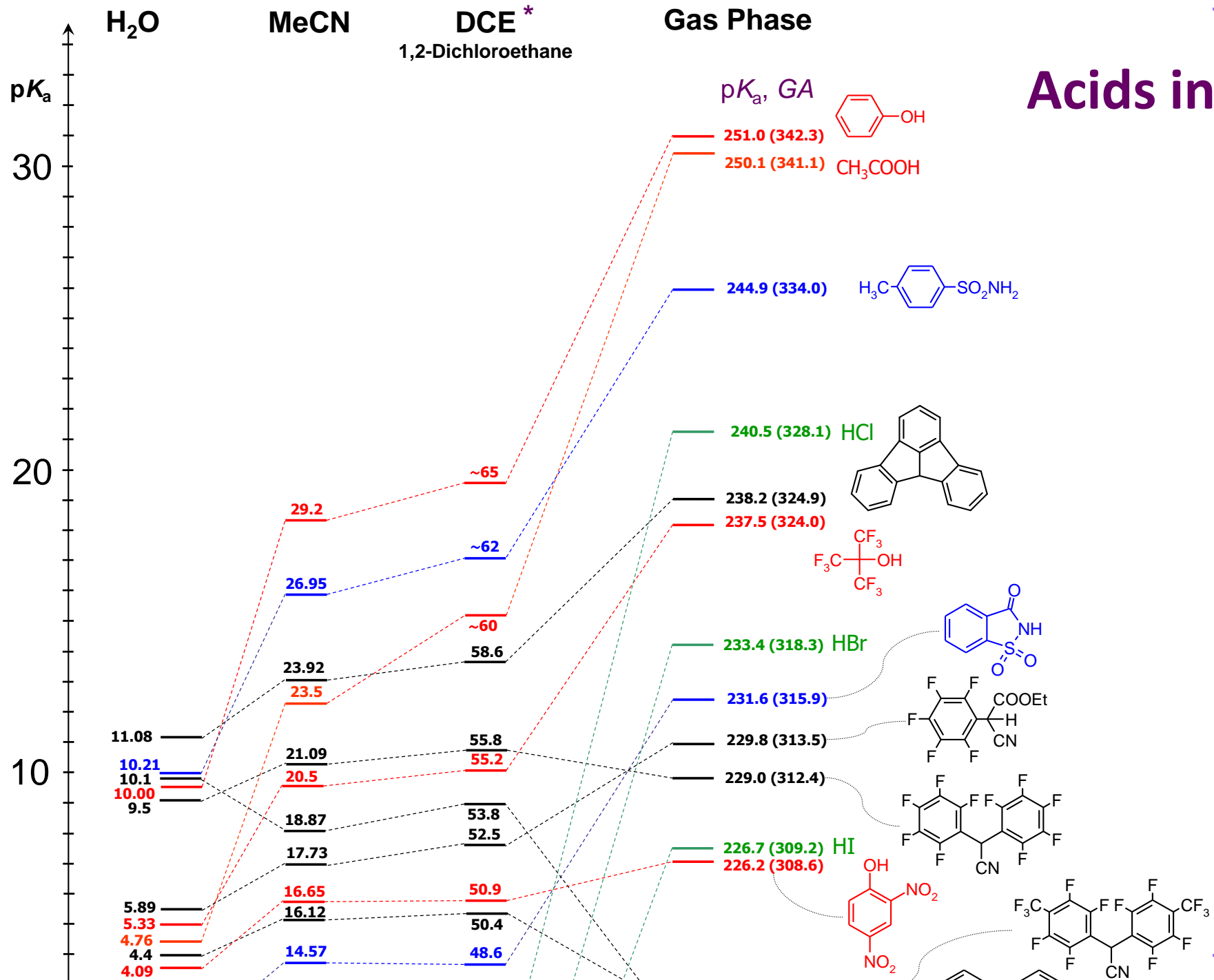
$$G_A = \Delta G_{\text{acid}}^0 = -RT \ln K_a$$



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

1 pK<sub>a</sub> unit ≡ 1.36 kcal/mol





# Acids in different media

Data:

Ramat 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

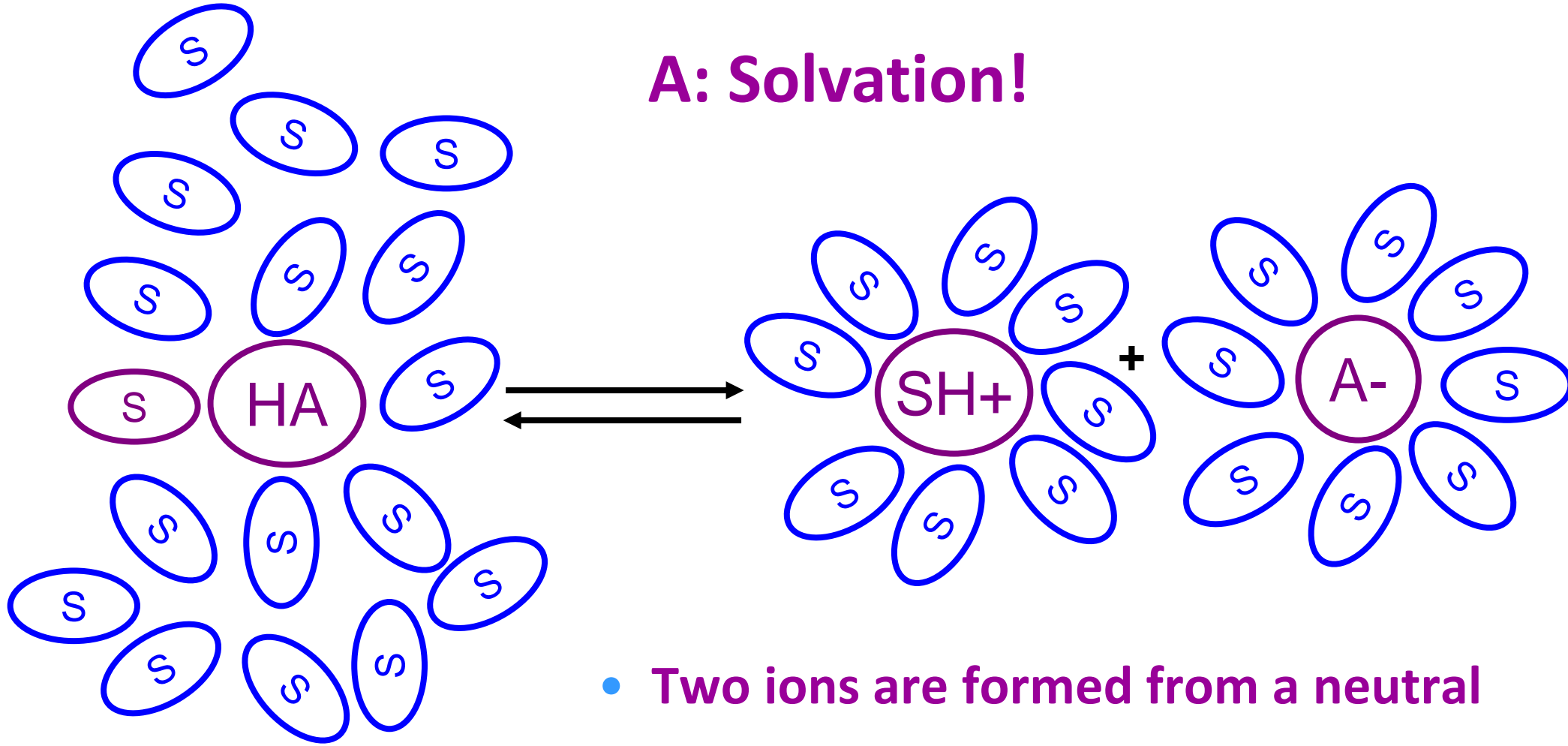
Free-ion pK<sub>a</sub> values calculated from experimental pK<sub>ip</sub>.  
Computationally anchored

GA in kcal mol<sup>-1</sup>



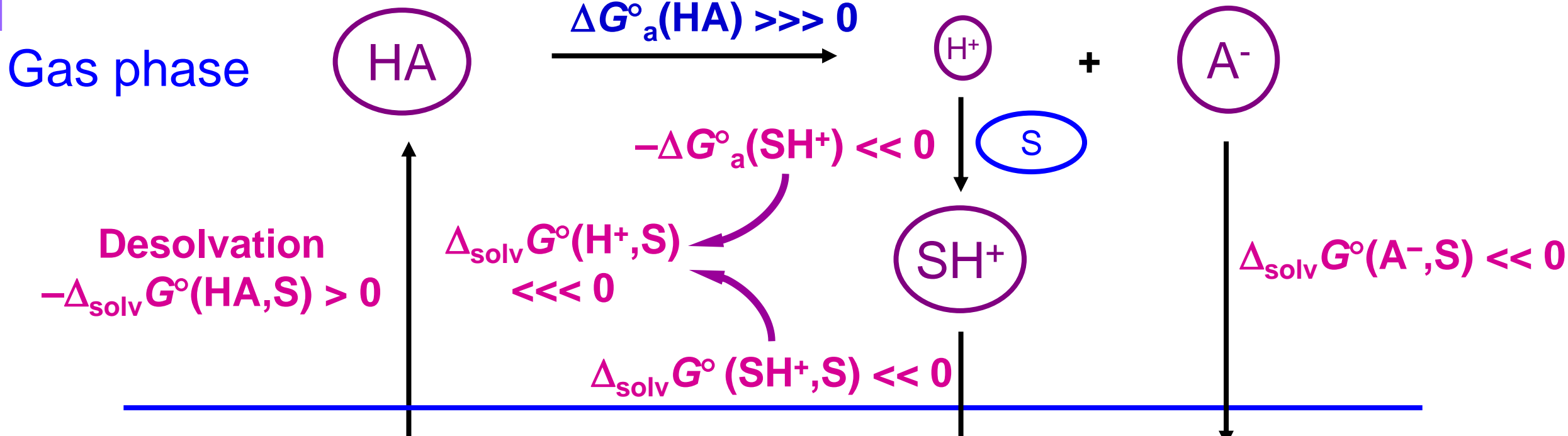
# Acid (uncharged) dissociation in a polar solvent

**A: Solvation!**

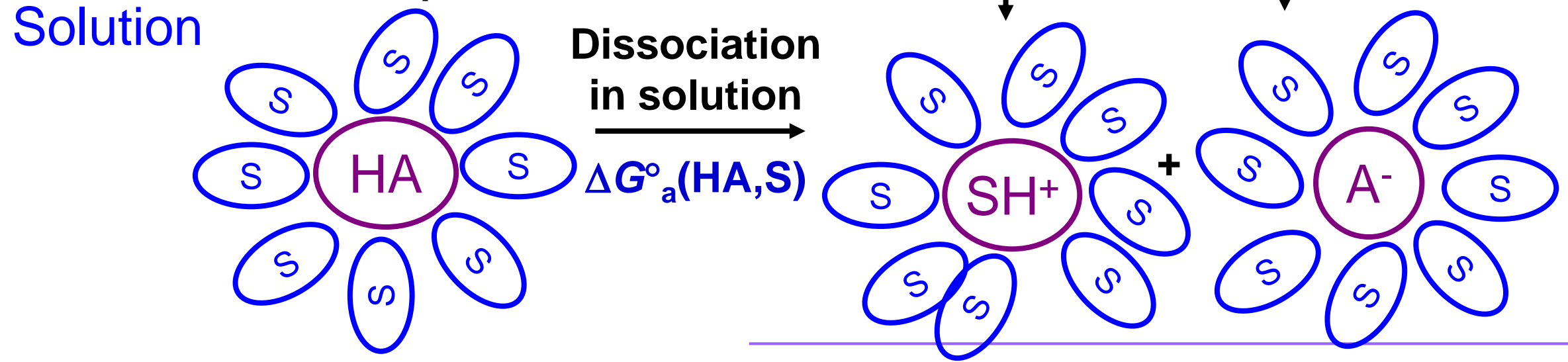


- Two ions are formed from a neutral
- Very solvent-sensitive

### Dissociation in the gas phase



### Thermodynamic cycle of acid dissociation

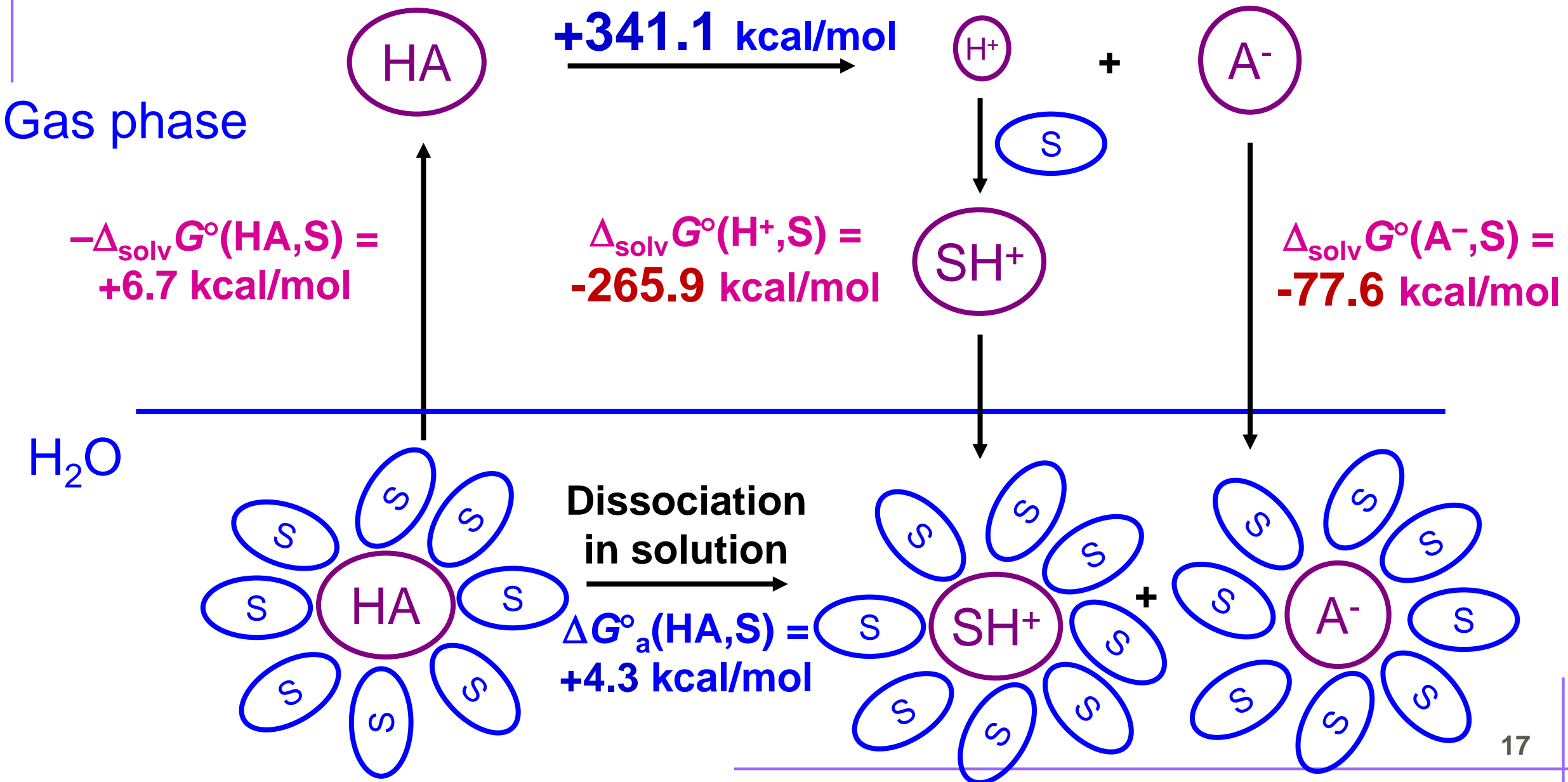


## Different solvation energies → different $pK_a$ values

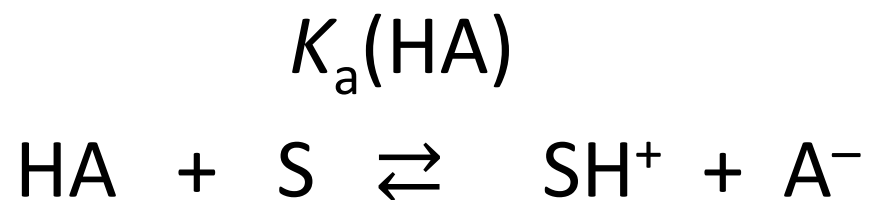
- The  $pK_a$  differences of a compound in different solvents are first of all due to differences in three solvation energies:
  - $\Delta_{\text{solv}}G^\circ(\text{H}^+, \text{S})$
  - $\Delta_{\text{solv}}G^\circ(\text{A}^-, \text{S})$
  - $\Delta_{\text{solv}}G^\circ(\text{HA}, \text{S})$
- These 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 the gas phase and solution (water)



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

Solvent: water  
All values in kcal mol<sup>-1</sup>

1 pK<sub>a</sub> unit  $\equiv$  1.36 kcal/mol

- Experimental: **+6.5 kcal mol<sup>-1</sup>** (pK<sub>a</sub> = 4.76)

$pK_a$  values

Gas Phase

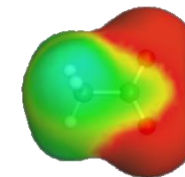
H<sub>2</sub>O

DMSO

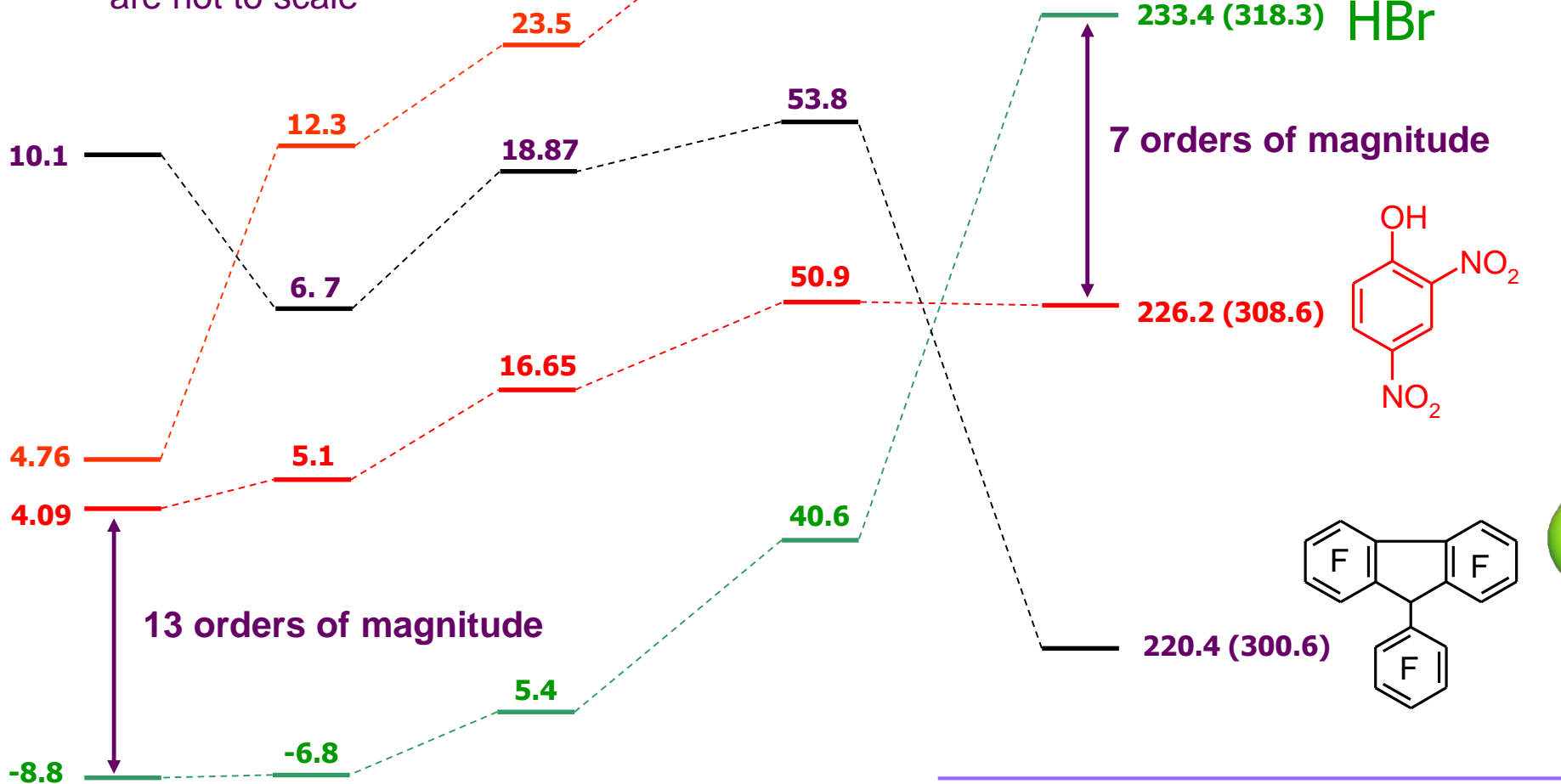
MeCN

DCE  
1,2-Dichloroethane

250.1 (341.1) CH<sub>3</sub>COOH



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

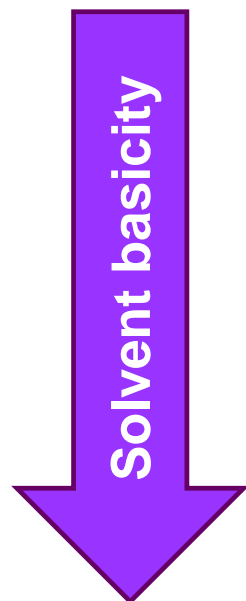


Charge localization in anions

# The most important is the ability to solvate H<sup>+</sup>

- Differences of  $\Delta_{\text{solv}} G^\circ$  of H<sup>+</sup> from water to solvents:  
(transfer free energies from H<sub>2</sub>O to S)

1 pK<sub>a</sub> unit  $\equiv$  1.36 kcal/mol



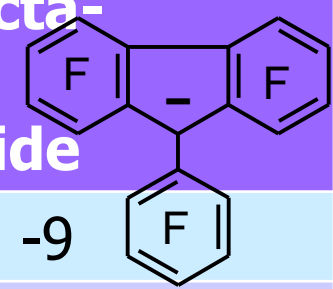
Solvent, S	$\Delta_{\text{transfer}} G^\circ$ of H <sup>+</sup> from H <sub>2</sub> O Difference of $\Delta_{\text{solv}} G^\circ$ of H <sup>+</sup> from H <sub>2</sub> O (kcal/mol)
1,2-Dichloroethane	Highly positive
MeNO <sub>2</sub>	+23
MeCN	<b>+11.1</b>
MeOH	+2.5
<i>Water</i>	<i>0.0</i>
DMSO	<b>-4.6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

Just the **different solvation of H<sup>+</sup>** leads to pK<sub>a</sub> difference of more than **11 pK<sub>a</sub> units**

## Next is the ability to solvate the anion A<sup>-</sup>

- Differences of  $\Delta_{\text{solv}} G^\circ$  of anions from water to solvents: 1 pK<sub>a</sub> unit  $\equiv$  1.36 kcal/mol  
(transfer free energies from H<sub>2</sub>O to S)

Solvent, S	Protic?	Difference of $\Delta_{\text{solv}} G^\circ$ of A <sup>-</sup> from H <sub>2</sub> O (kcal/mol)			
		CH <sub>3</sub> COO <sup>-</sup>	Br <sup>-</sup>	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>

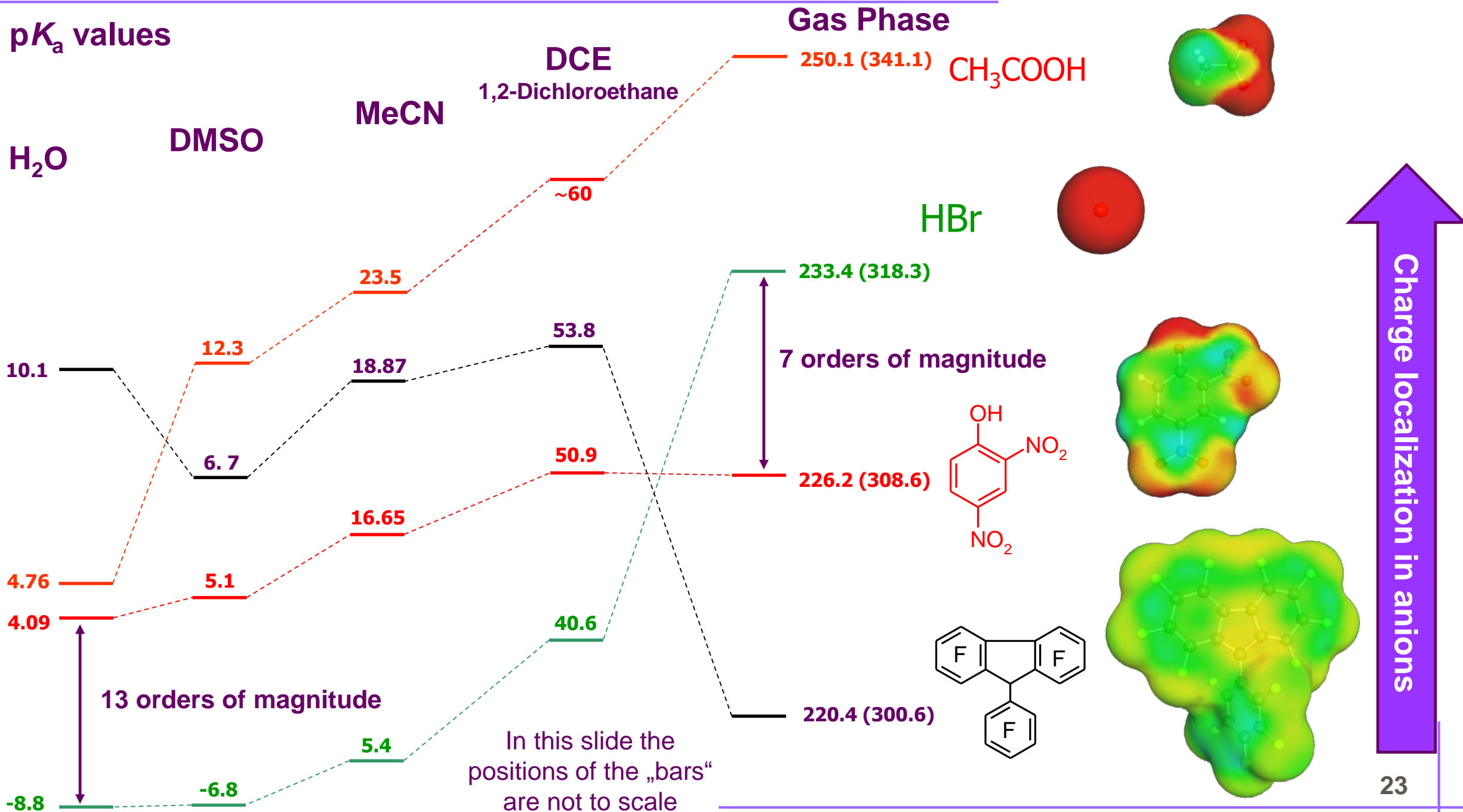


Solvent HB donicity

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



# $pK_a$ of acids: some 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  $pK_a$
- **„Acidity order reversals“ are due to differences in anion solvation**
  - Constant differences  $\rightarrow$  constant  $pK_a$  differences
  - Varied differences  $\rightarrow$  „acidity order reversals“
- $pK_{auto}$  determines the span of the  $pK_a$  values

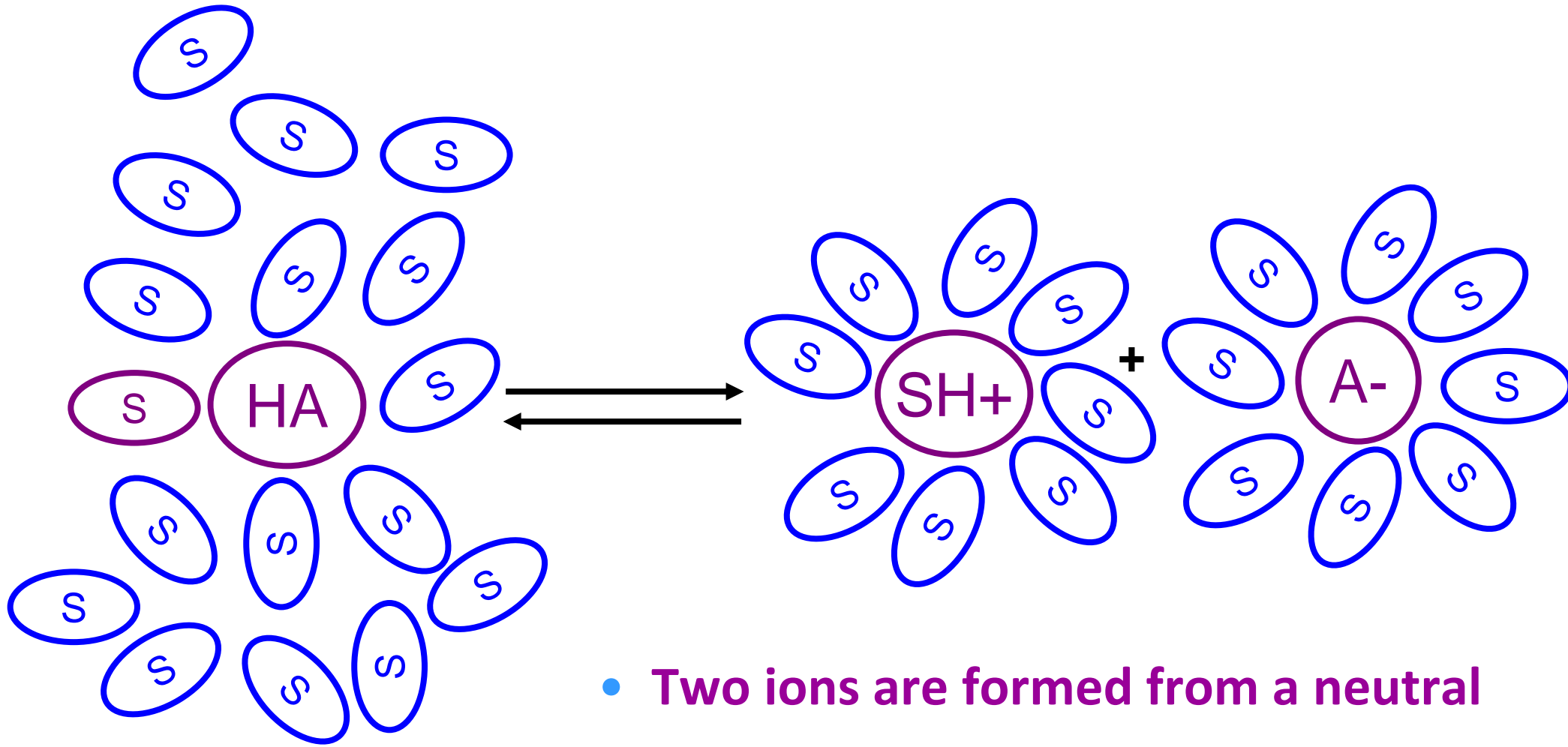
You will not find an acid which has lower  $pK_a$  in MeCN than in Water or DMSO

$pK_a$  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

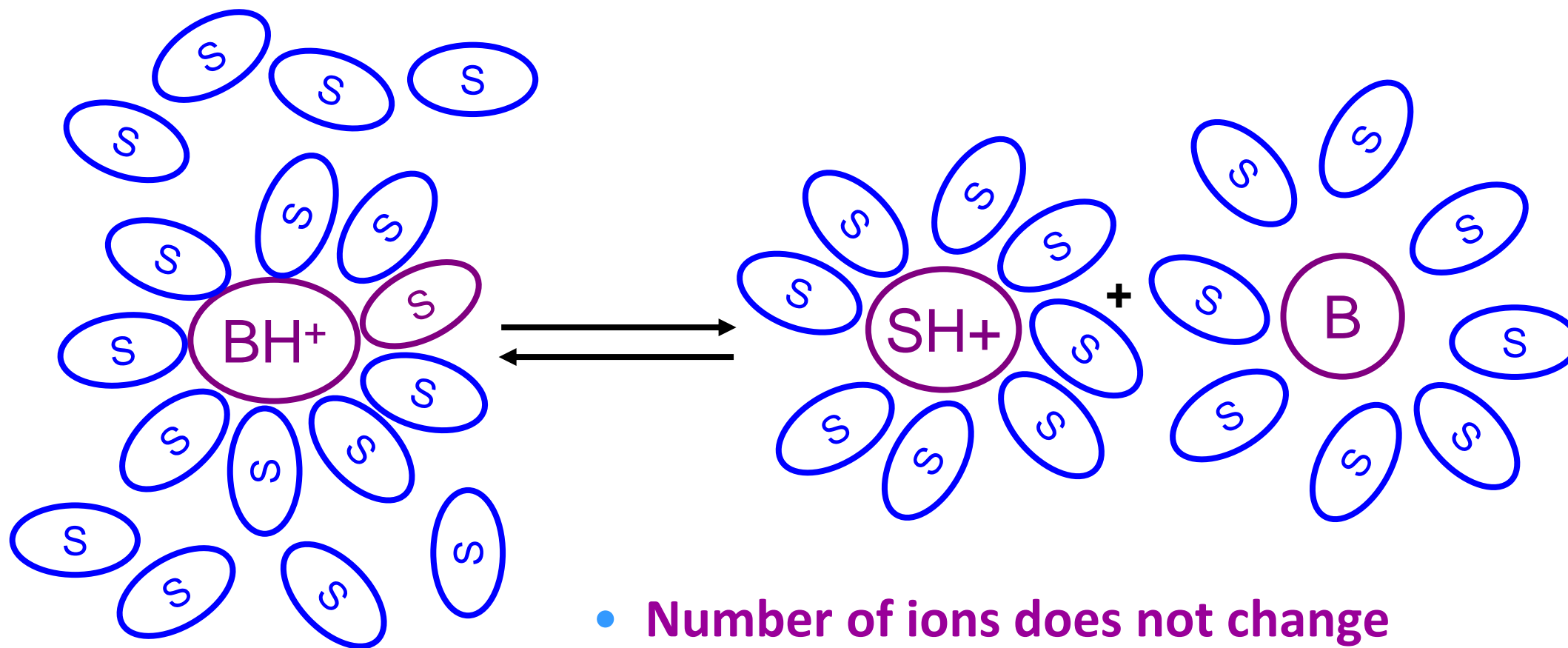
$pK_a$  span in water is 14  $pK_a$  units, in DMSO and MeCN it is more than 30  $pK_a$  units

## Acid (uncharged) dissociation in a polar solvent



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

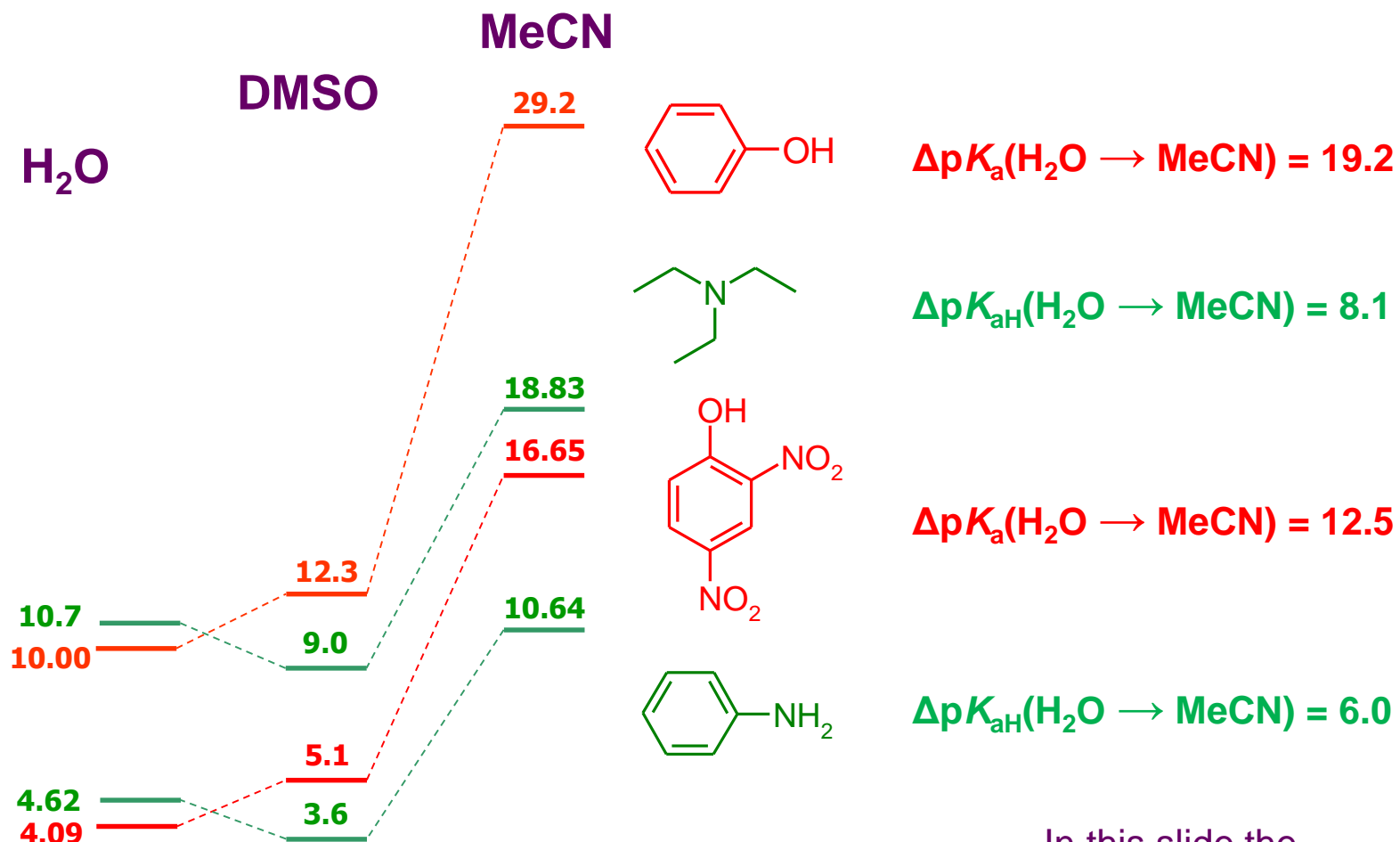
## Base in a polar solvent (Handled as acidity of a cationic acid)



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

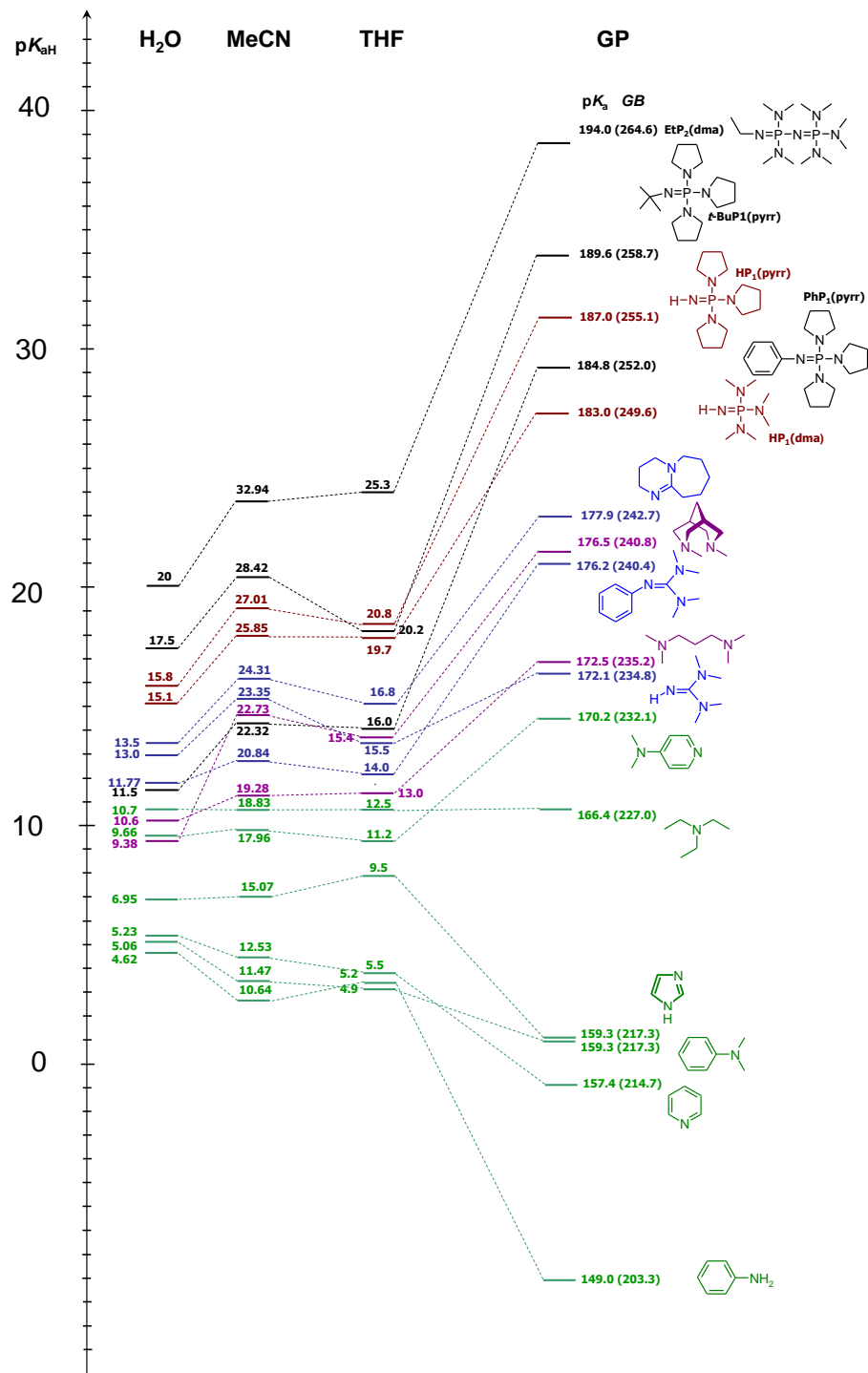
# Solvent effects on bases are different from acids!

$pK_a$  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:

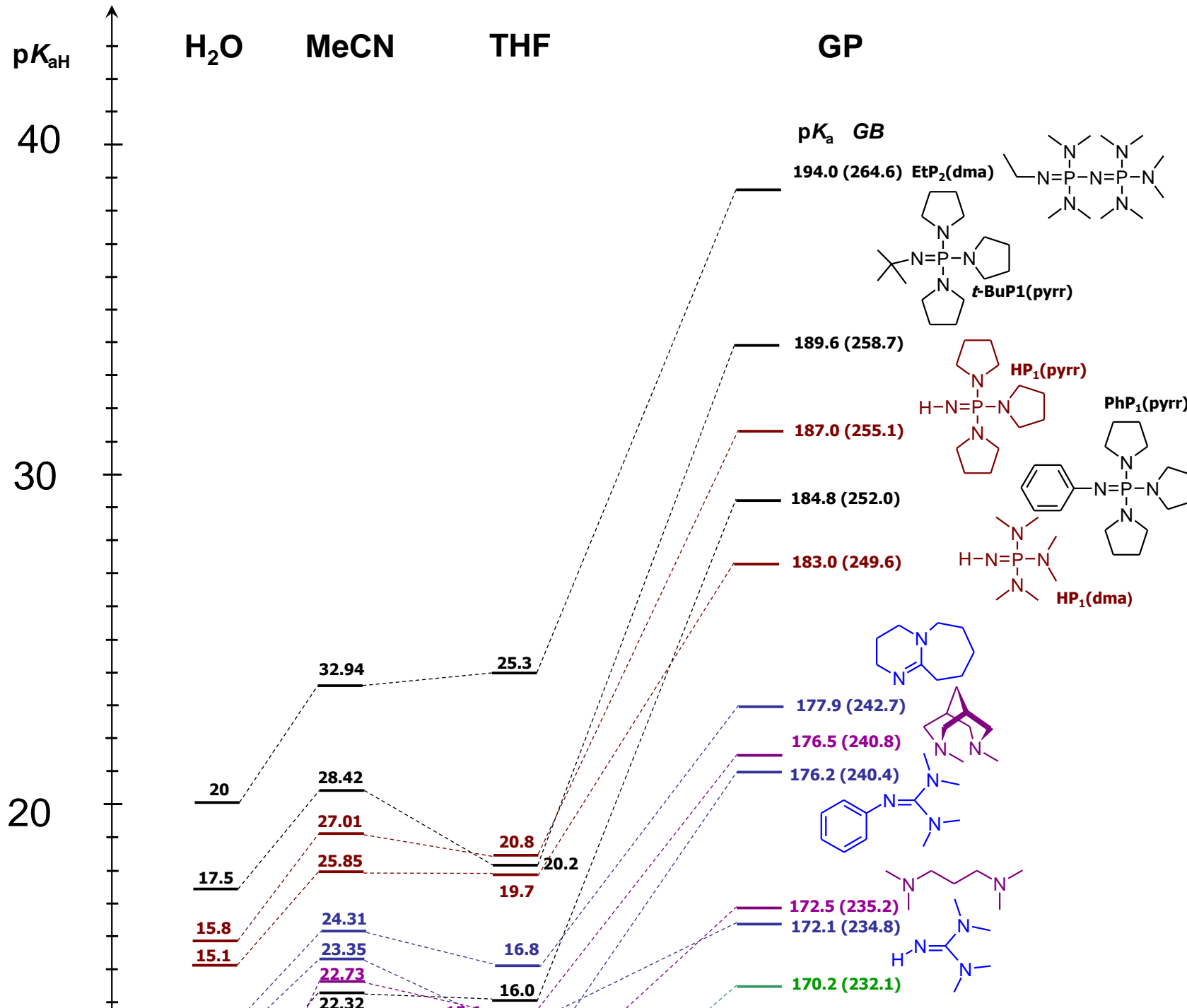
Kaupmees et al  
*Croat. Chem. Acta*  
**2014**, 87, 385

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:

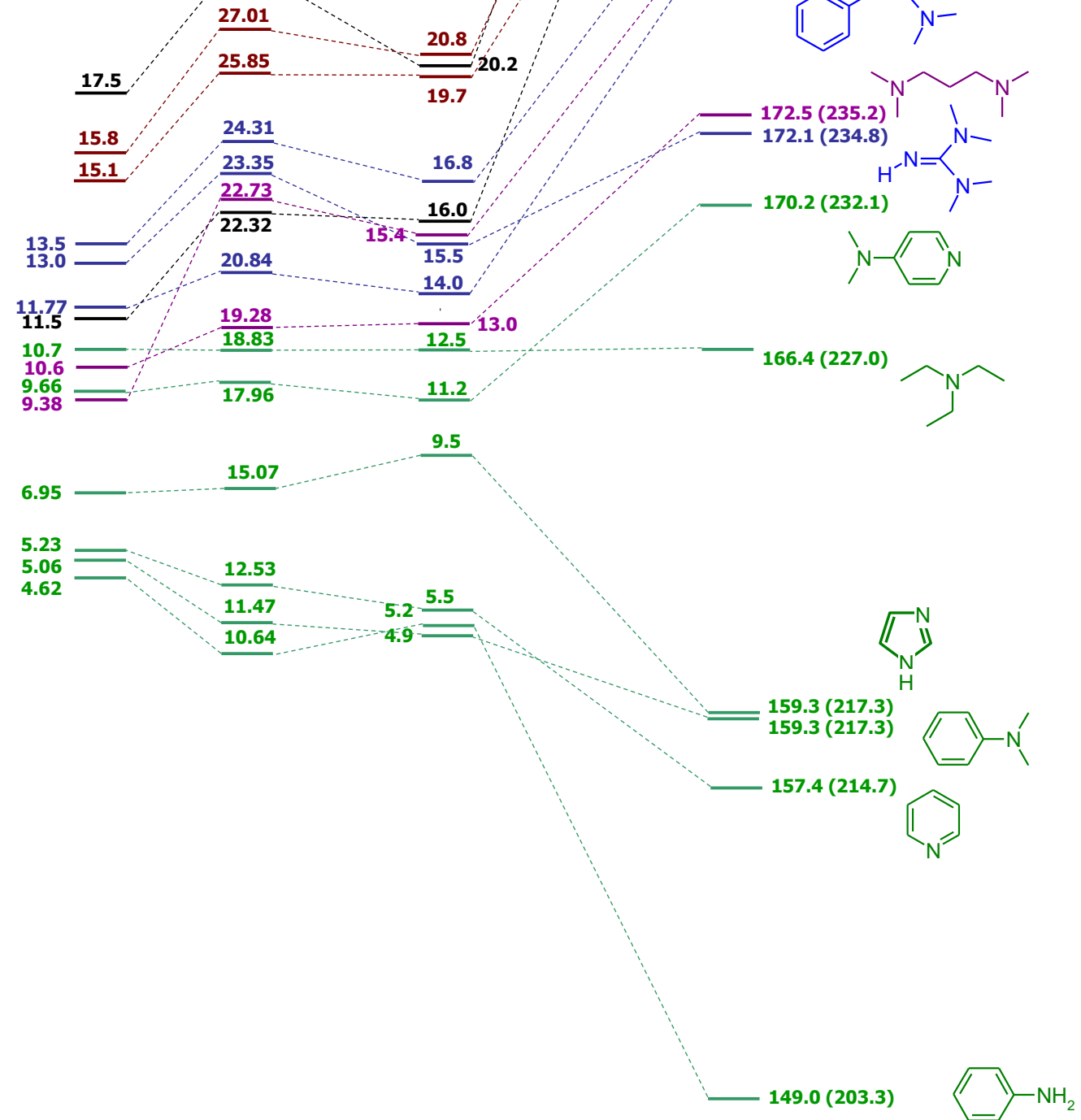
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# Bases in different media



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*J. Phys. Org. Chem.* **2019**, 6735

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

iBond database

# Sources of non-aqueous $pK_a$ values?

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

## Acid-Base Dissociation Constants in Dipolar Aprotic Solvents

KOSUKE IZUTSU

456

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

## Equilibrium Acidities in Dimethyl Sulfoxide Solution

FREDERICK G. BORDWELL

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

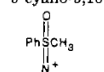
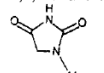
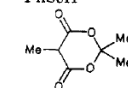
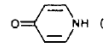
Received May 6, 1988 (Revised Manuscript Received August 10, 1988)

458

Bordwell

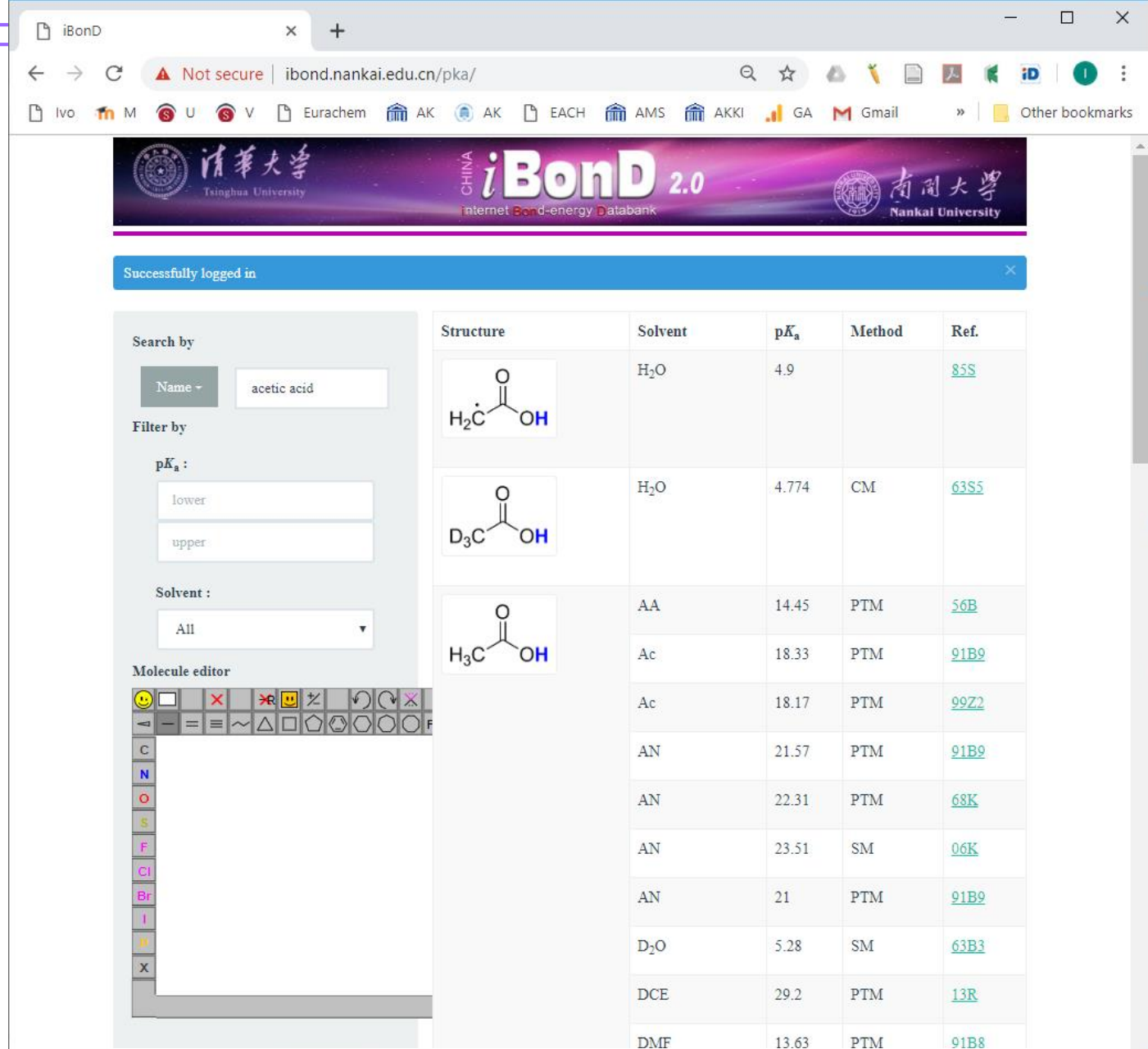
Accounts of Chemical Research

Table II  
Equilibrium Acidities in Dimethyl Sulfoxide at 25 °C

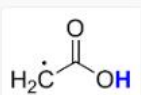
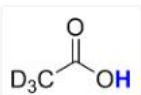
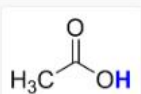
acid	$pK_a^a$	acid	$pK_a^a$
5-nitrobarbituric acid	0.8	PhCONHOH	13.65
(F <sub>3</sub> CSO <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>	2.1	2,3-dihydroxynaphthalene	13.7
2,4-dinitronaphthol	2.1	N-acetyloxindol	13.8 <sup>f</sup>
PhN <sup>+</sup> HMe <sub>2</sub>	2.45	1,2,3-triazole	13.9
F <sub>3</sub> CCO <sub>2</sub> H	3.45	uracil	14.1
saccharin	4.0	adenine	14.2
PhCH(CN) <sub>2</sub>	4.2	CH <sub>3</sub> COCH <sub>2</sub> CO <sub>2</sub> Et	14.2
2,6-dinitrophenol	4.9	(MeSO <sub>2</sub> ) <sub>2</sub> CHPh	14.3
2,4-dinitrophenol	5.1	2,5-diphenylcyclopentadiene	14.3
F <sub>3</sub> CSO <sub>2</sub> CH <sub>2</sub> COPh	5.1	9-cyano-9,10-dihydroanthracene	14.3
PhCOSH	5.2 <sup>b</sup>		14.4
Cl <sub>2</sub> CHCO <sub>2</sub> H	6.4 <sup>f</sup>		
PhSCH(SO <sub>2</sub> Ph) <sub>2</sub>	5.55	CH <sub>3</sub> COCH <sub>2</sub> CO <sub>2</sub> Et	14.4
F <sub>3</sub> CCH <sub>2</sub> SO <sub>2</sub> NHPh	5.7	fluorenone benzylimine	14.5
2,4,5-Cl <sub>3</sub> C <sub>6</sub> H <sub>2</sub> SH	6.0	F <sub>3</sub> CSO <sub>2</sub> CH <sub>2</sub> Ph	14.55
Ph <sub>3</sub> P <sup>+</sup> CH <sub>2</sub> COPh	6.1	succinimide	14.6
Ph <sub>3</sub> P <sup>+</sup> CH <sub>2</sub> CN	7.05	CH <sub>3</sub> C(=S)NHPh	14.7
PhSO <sub>2</sub> H	7.1	1,2,4-triazole	14.75
PhSO <sub>2</sub> CH <sub>2</sub> NO <sub>2</sub>	7.1		14.75
PhSeH	7.1 <sup>b</sup>		
	7.4 <sup>d</sup>		14.8
HONO	7.5	fluorenone phenylhydrazone	14.9
H <sub>3</sub> N <sup>+</sup> CH <sub>2</sub> CO <sub>2</sub> H	7.5 <sup>e</sup>	MeCH(COCH <sub>3</sub> ) <sub>2</sub>	15.05
CH <sub>2</sub> =CHCH <sub>2</sub> NO <sub>2</sub>	7.7		
(C <sub>6</sub> F <sub>5</sub> ) <sub>2</sub> CHCN	7.95		
tetrazole	8.2		

# 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 <sub>2</sub> O	4.9		<a href="#">85S</a>
	H <sub>2</sub> O	4.774	CM	<a href="#">63S5</a>
	AA	14.45	PTM	<a href="#">56B</a>
	Ac	18.33	PTM	<a href="#">91B9</a>
	Ac	18.17	PTM	<a href="#">99Z2</a>
	AN	21.57	PTM	<a href="#">91B9</a>
	AN	22.31	PTM	<a href="#">68K</a>
	AN	23.51	SM	<a href="#">06K</a>
	AN	21	PTM	<a href="#">91B9</a>
	D <sub>2</sub> O	5.28	SM	<a href="#">63B3</a>
	DCE	29.2	PTM	<a href="#">13R</a>
DMF	13.63	PTM	<a href="#">91B8</a>	

[ibond.nankai.edu.cn/pka/](http://ibond.nankai.edu.cn/pka/)

## Acidity-Basicity Data (pK<sub>a</sub> 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!

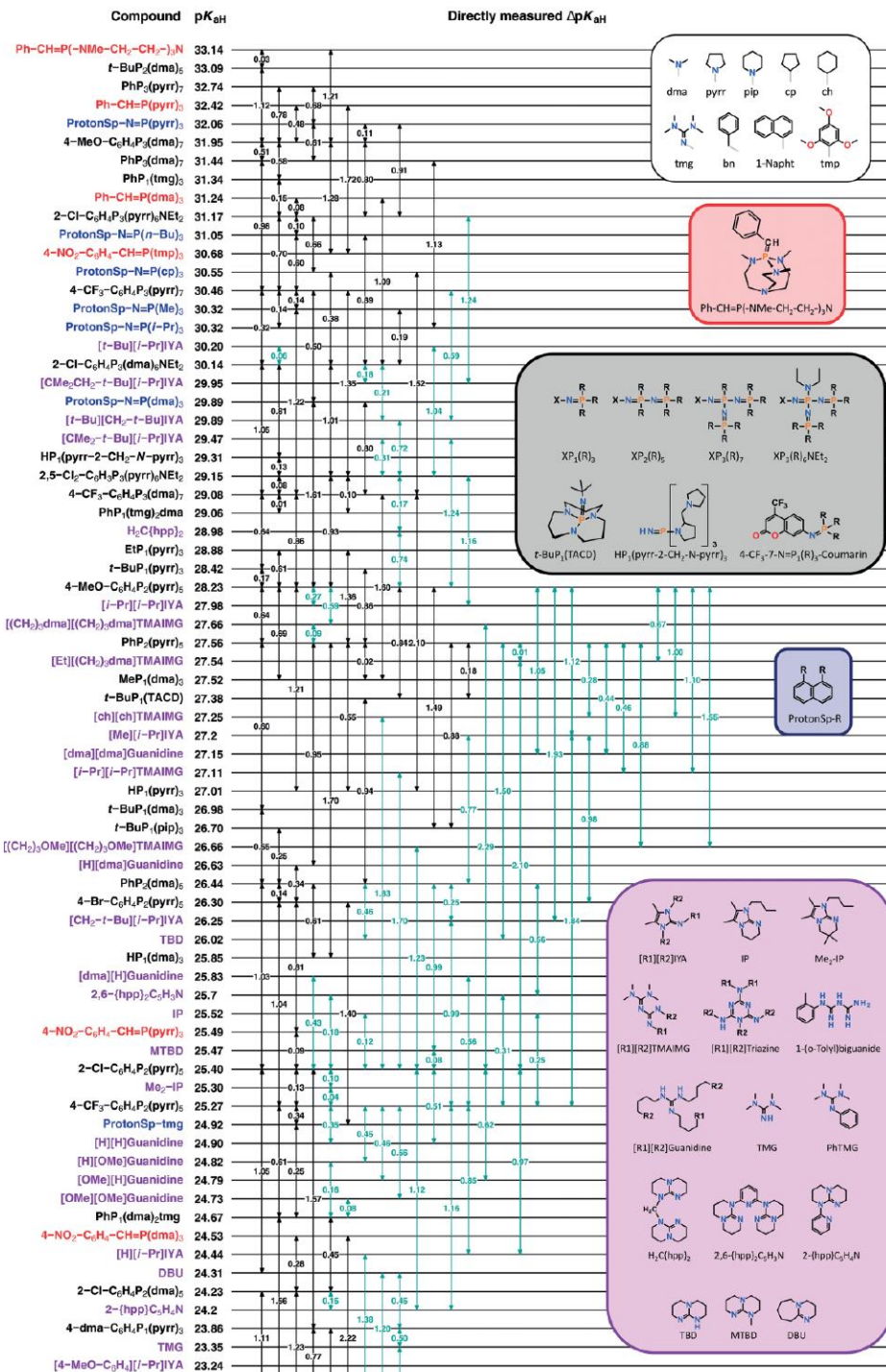
The highlighted papers contain large amounts of pK<sub>a</sub> data (or other information): acids – red, bases – blue, both acids and bases – purple.

Publication	Data	Medium	Method	Description	Available files
<a href="#">Dalton Trans. 2024, 53, 14226</a>	pK <sub>aH</sub> and GB values	Acetonitrile, gas phase	UV-Vis spectrometry, Computations	Basicity (pK <sub>aH</sub> values in MeCN and GB values) of a number of <b>phosphane (posphine) bases</b> , including several seminal phosphanes, such as trimethylphosphane, triphenylphosphine, tripyrrolidinophosphane, tris-pentafluorophenylphosphane, etc.	<a href="#">pK<sub>aH</sub> values of phosphanes in MeCN and GB values</a> (PDF)
<a href="#">Eur. J. Org. Chem. 2023, 26, e202300453</a>	pK <sub>aH</sub> and GB values	Acetonitrile, THF, gas phase	UV-Vis spectrometry, Computations	Basicity values in MeCN and THF (pK <sub>aH</sub> values) of a number of <b>phosphane (posphine) bases</b> containing the benzophenoneimine (bpi) moiety.	<a href="#">pK<sub>aH</sub> values of phosphanes in MeCN and THF</a> (PDF)
<a href="#">Bioorgan. Med. Chem. 2023, 81, 117203</a>	pK <sub>a</sub> values	MeCN and MeCN : water mixtures	UV-Vis spectrometry	pK <sub>a</sub> and pK <sub>aH</sub> values, of different <b>drugs, bioactive and related compounds</b> 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.	<a href="#">pK<sub>a</sub> and pK<sub>aH</sub> values of different drugs, bioactive and related compounds in acetonitrile-water mixtures and acetonitrile</a> (PDF)
<a href="#">Chem. Eur. J. 2022, 29, e202202953</a>	pK <sub>a</sub> values	Acetonitrile	UV-Vis spectrometry, <sup>31</sup> P NMR	pK <sub>a</sub> values of <b>Singly-linked and Macrocyclic Bisphosphoric Acid catalysts for Asymmetric Phase-transfer and Brønsted-acid Catalysis</b> . It turns out that the linker length has large influence on enantioselectivity but does not influence much the pK <sub>a</sub> value.	<a href="#">pK<sub>a</sub> values of Singly-linked and Macrocyclic Bisphosphoric Acid catalysts in MeCN</a> (PDF)
<a href="#">Anal. Chem. 2022, 94, 4059-4064</a>	Biphasic pK <sub>a</sub> values (pK <sub>a</sub> <sup>ow</sup> values)	Octanol:Water	UV-Vis spectrometry, <sup>1</sup> H NMR, <sup>13</sup> C NMR, <sup>31</sup> P NMR	<b>Biphasic pK<sub>a</sub> values (pK<sub>a</sub><sup>ow</sup> values) of 35 acids</b> 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 <sub>a</sub> value (pK <sub>a</sub> <sup>o</sup> non-miscible phase (where directly obtained). Concentration-independent values were obtained by extrapolating the apparent values to zero concentration using a Debye–Hückel model.	<a href="#">Octanol:water biphasic pK<sub>a</sub> values (pK<sub>a</sub><sup>ow</sup> values) of 35 acids and extrapolation plot</a> (PDF)
<a href="#">Acc. Chem. Res. 2021, 54, 3108-3123</a>	pK <sub>a</sub> values (pK <sub>aH</sub> 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 <b>pK<sub>a</sub> (pK<sub>aH</sub>) values in MeCN and THF, as well as gas-phase basicities of around 30 important superbases</b> (amidines, guanidines, proton sponges, phosphazenes, phosphanes, phosphorus ylides, carbodiphosphoranes) are presented.	<a href="#">pK<sub>a</sub> (pK<sub>aH</sub>) values in MeCN and THF, as well as gas-phase basicities of around 30 important superbases</a> (PDF)
<a href="#">Eur. J. Org. Chem. 2021, 1407-1419</a>	pK <sub>a</sub> values	Acetonitrile	UV-Vis spectrometry	<b>pK<sub>a</sub> values of 231 acids</b> 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 <sub>a</sub> 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.	<a href="#">Acidity pK<sub>a</sub> values of 231 acids in acetonitrile</a> (PDF)
<a href="#">J. Am. Chem. Soc. 2020, 142, 15252-15258</a>	pK <sub>a</sub> values	Acetonitrile	UV-Vis spectrometry	<b>Chiral benzoic acid catalysts</b> 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 <sub>a</sub> values of the acids compared benzoic acids with similar substitution.	<a href="#">Acidities (pK<sub>a</sub> in MeCN) of the enantioselective carboxylic acid catalysts</a> (PDF)

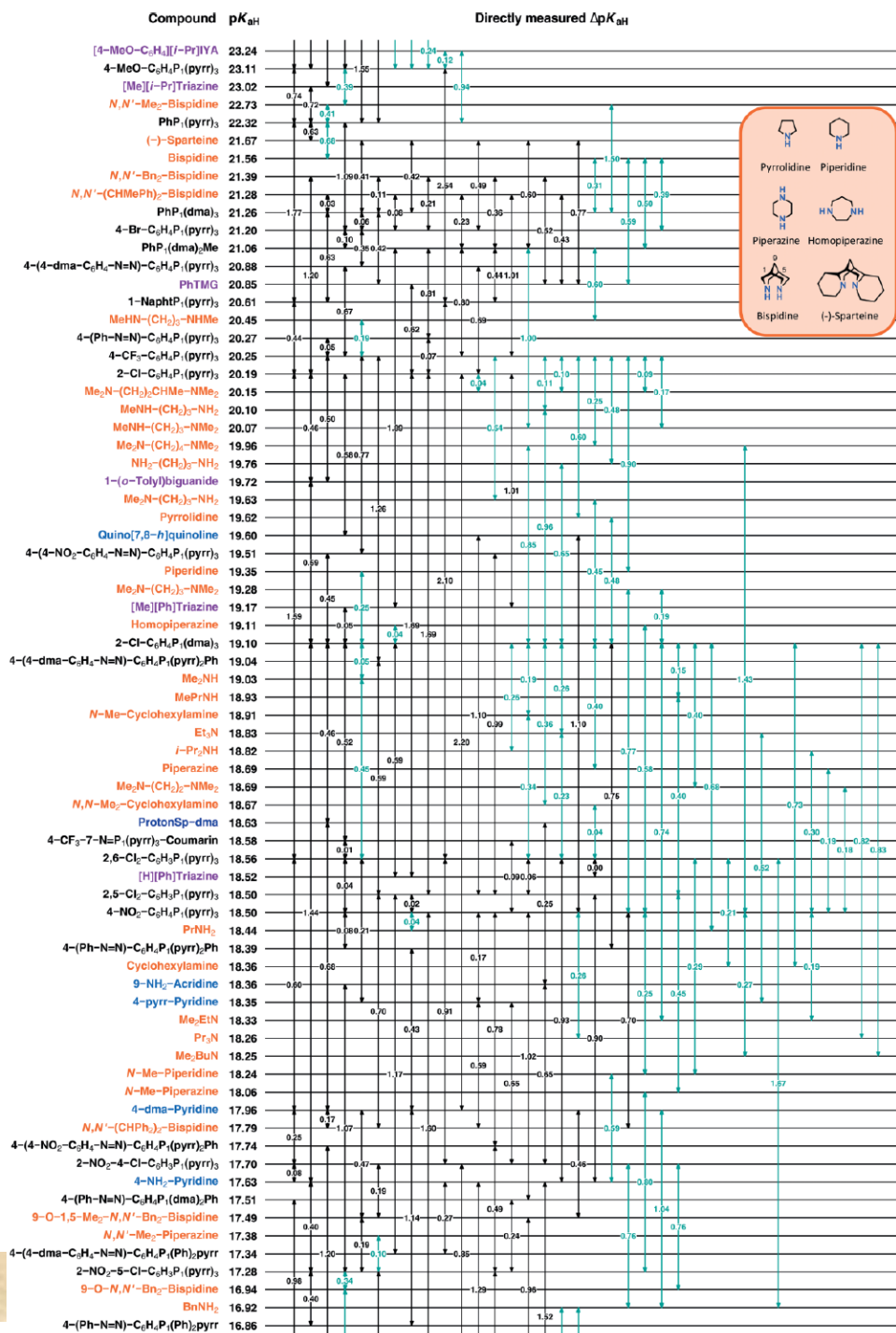
[analytical.chem.ut.ee/HA\\_UT/](http://analytical.chem.ut.ee/HA_UT/)

# Example: Self-consistent basicity scale in MeCN

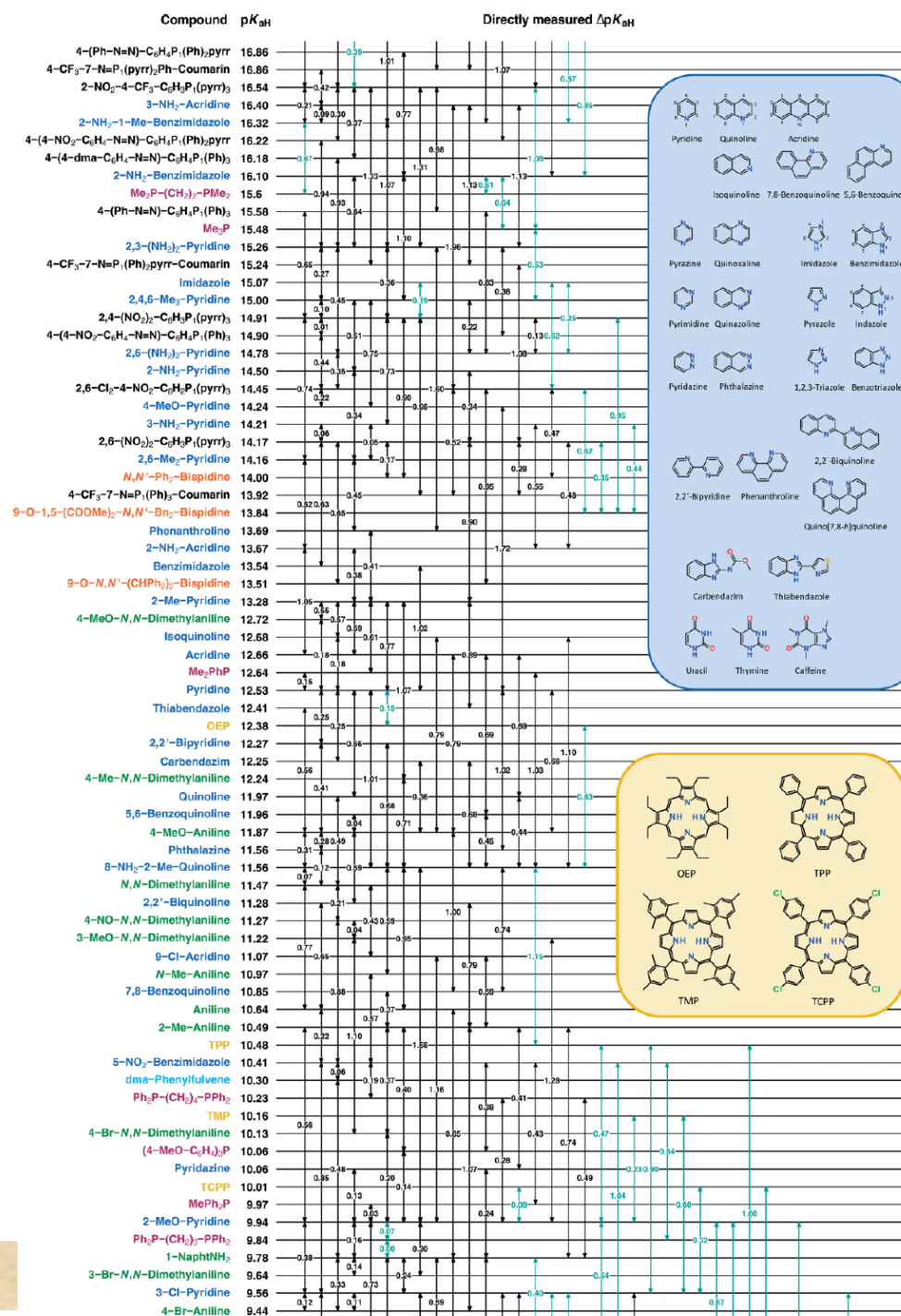
- 270 bases
- $pK_{aH}$  span: 1.3 .. 33.1
- 682 relative basicity ( $\Delta pK_{aH}$ ) measurements
- Consistency std dev:
  - 0.03  $pK_a$  units „normal“ compounds
  - 0.06  $pK_a$  units „difficult“ compounds
    - Accounts for random effects



# Example: Self-consistent basicity scale in MeCN

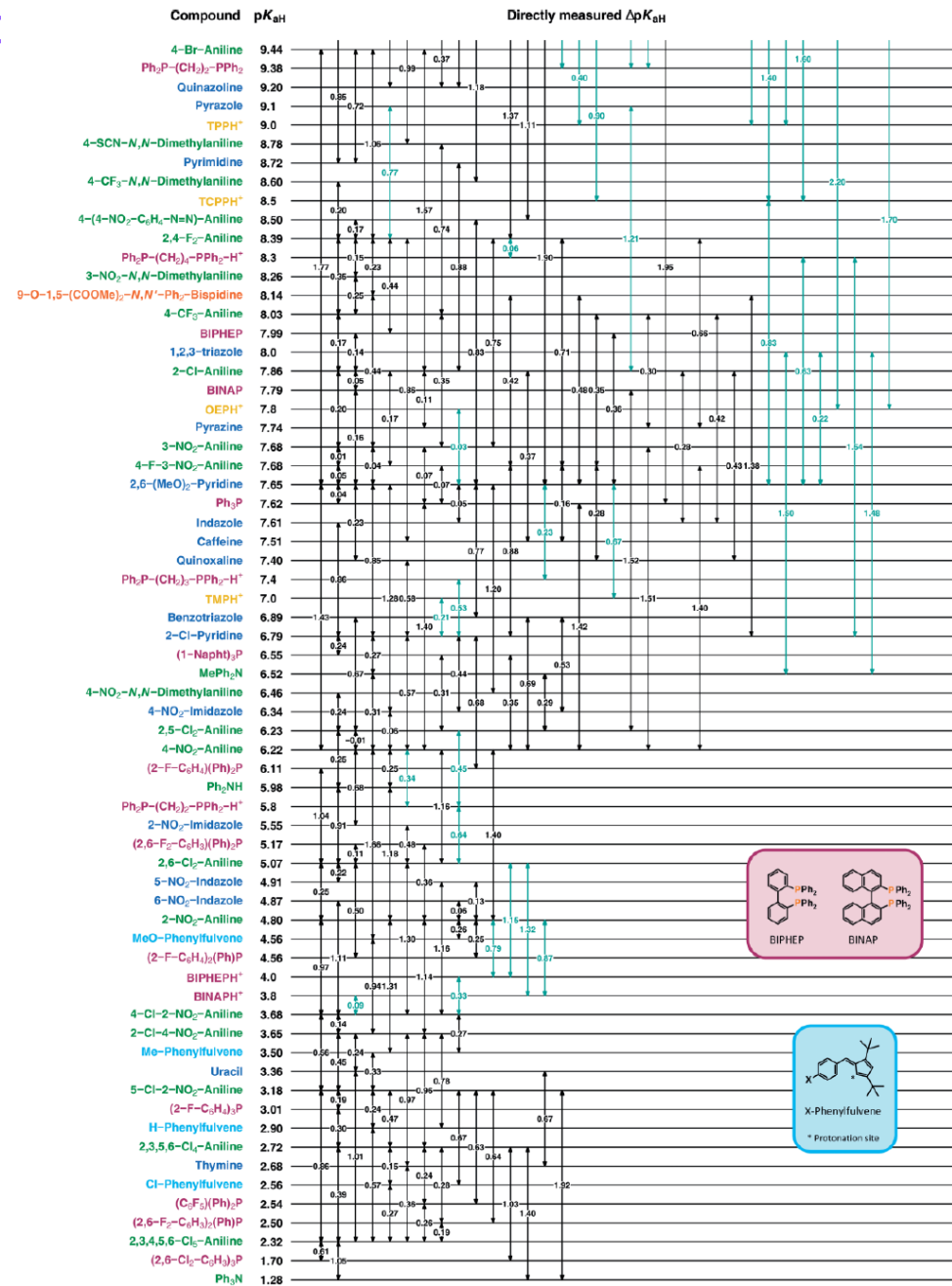


# Example: Self-consistent basicity scale in MeCN



# Example: Self-consistent basicity scale in MeCN

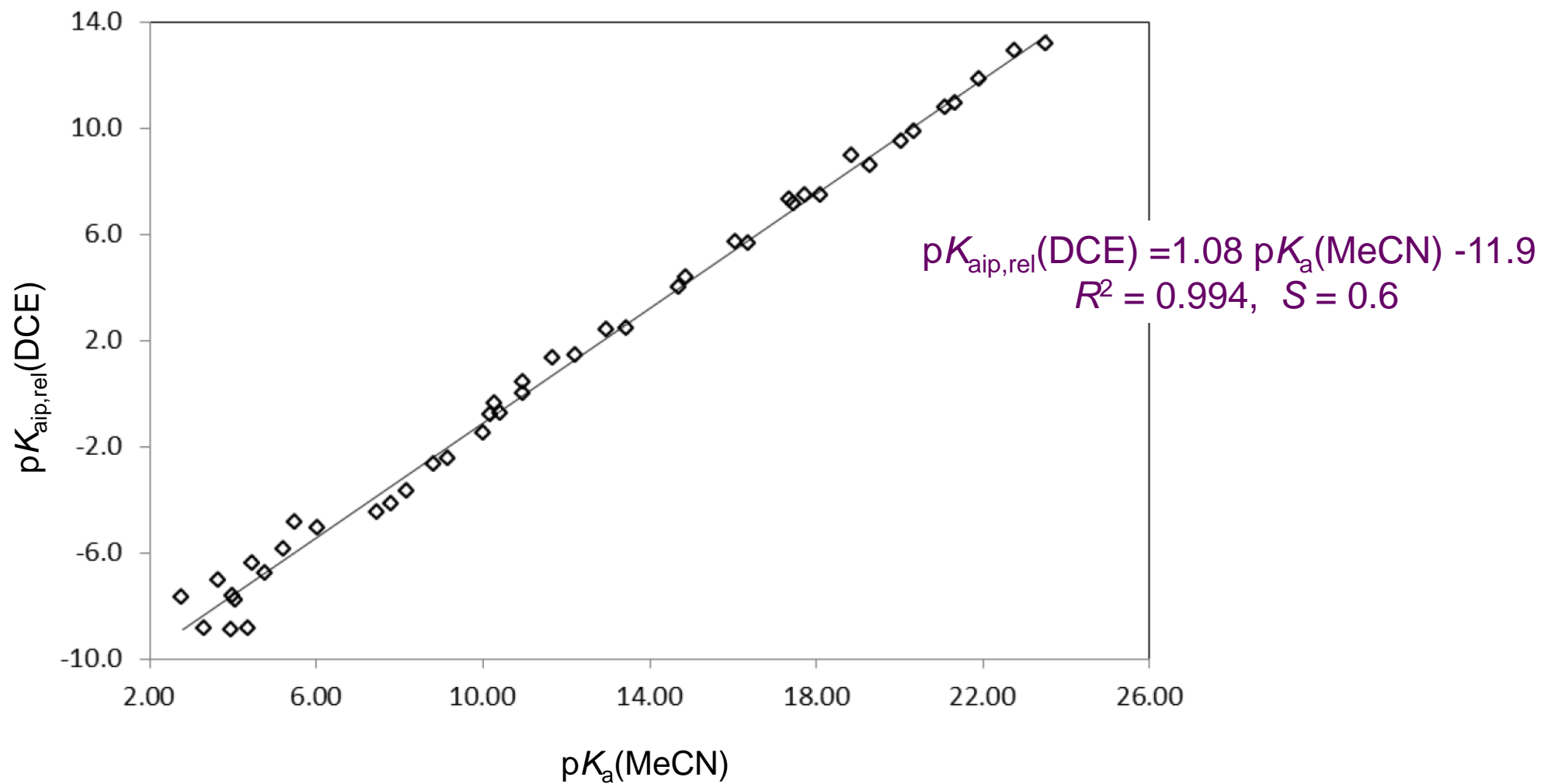
„Ladder“ available from:  
[analytical.chem.ut.ee/HA\\_UT/](http://analytical.chem.ut.ee/HA_UT/)



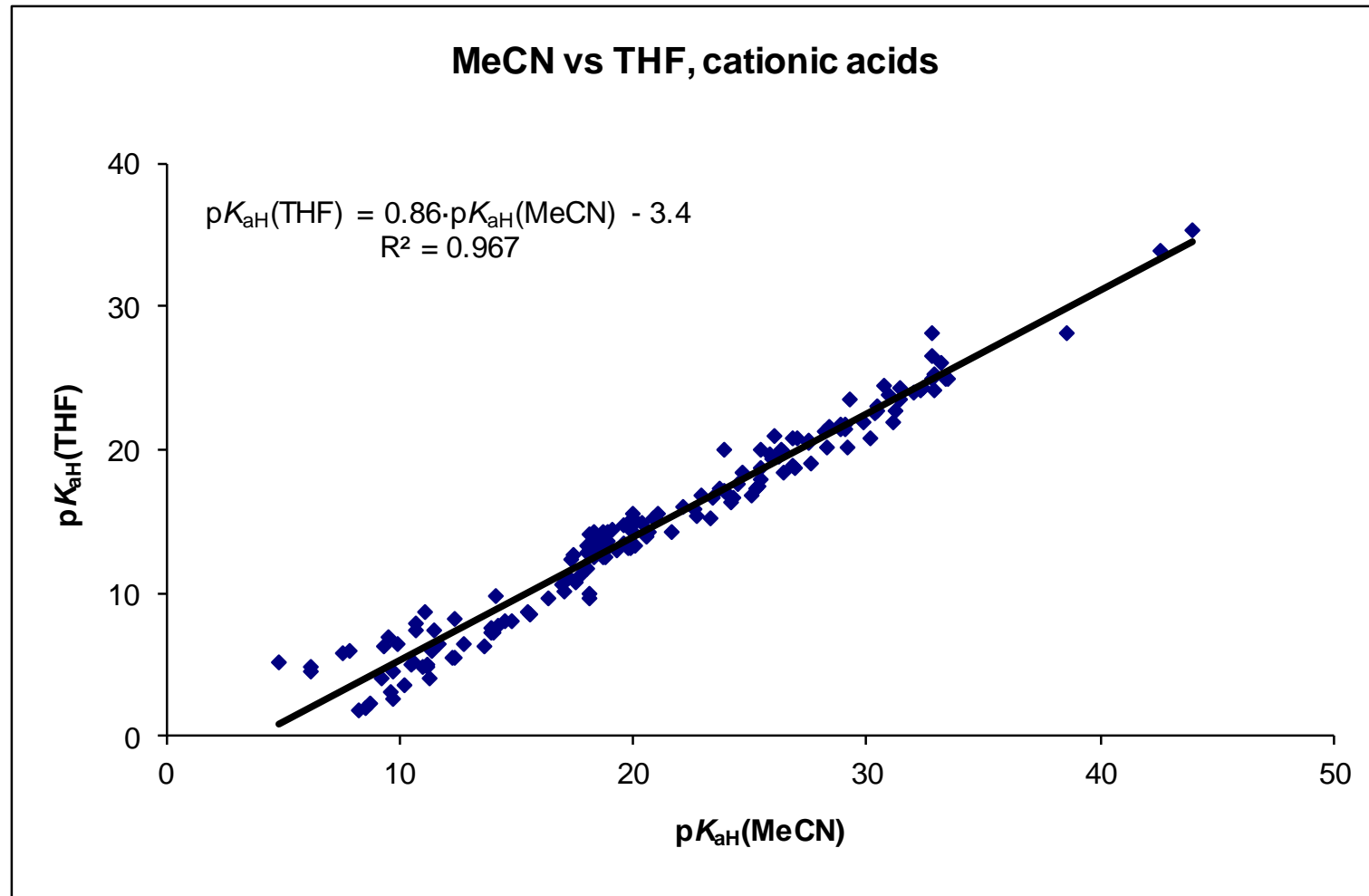
## Typical issue: no $pK_a$ data for X in solvent S

- 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

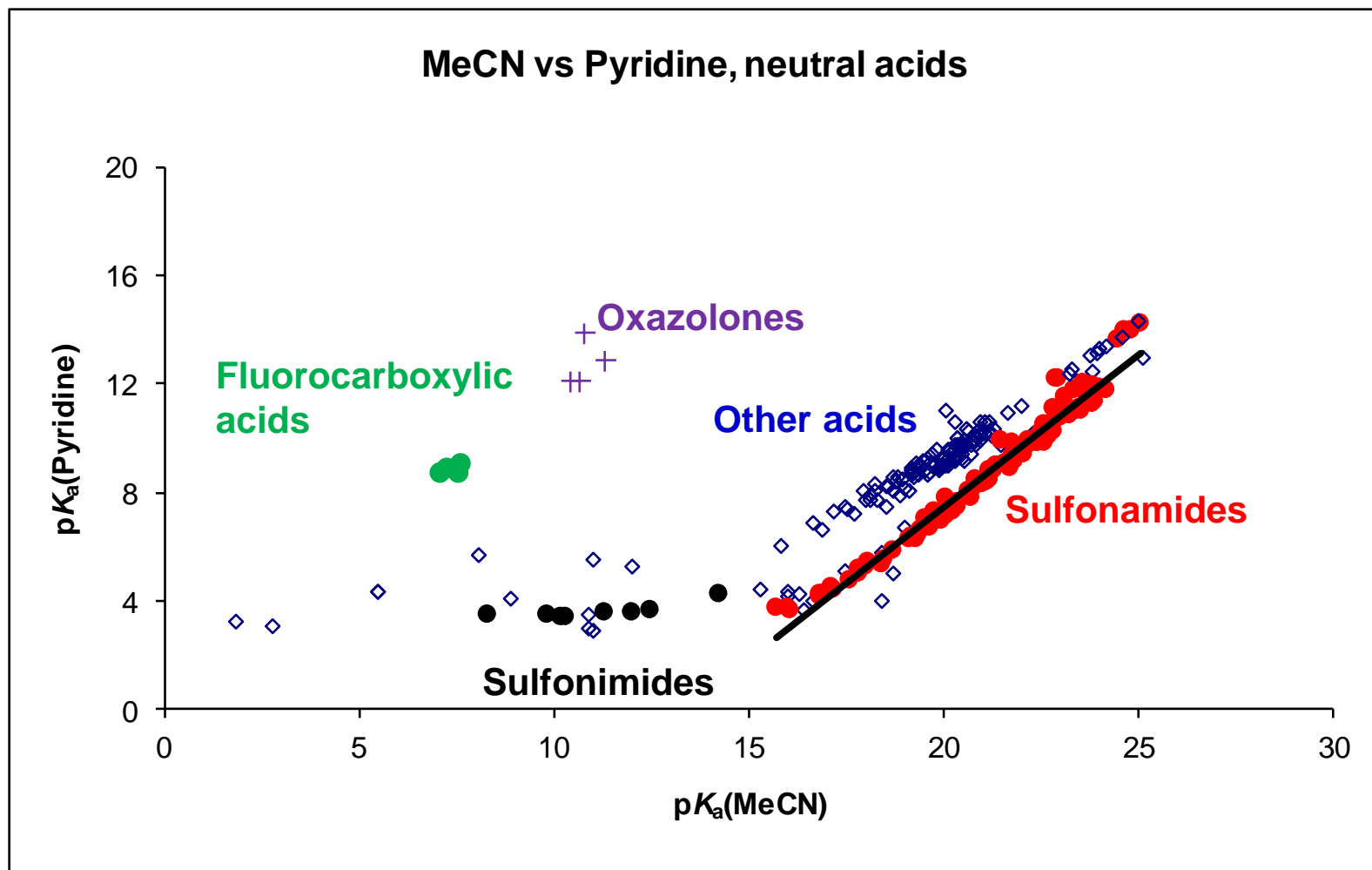
## Sometimes correlations are very good



# Sometimes correlations are satisfactory



# Sometimes correlations are tricky or do not work



# pK<sub>a</sub> correlation possibilities

Legend:

Reliable

Mediocre reliability

Tricky

„+“: real data available

	MeCN	PC	Acetone	DMSO	DMF	THF	DME	Py	DCE/DCM	MeOH/EtOH	H <sub>2</sub> O	
MeCN			+	+	+	+					+	
PC	+											
Acetone	+	+			+							
DMSO	+	+	+		+	+						B
DMF	+	+	+	+		+						A
THF											+	S
DME	+											E
Py	+	+	+	+	+							S
DCE/DCM	+			+								
MeOH/EtOH												
H <sub>2</sub> 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 <sup>[a]</sup>	<i>S</i>	<i>R</i> <sup>2</sup>	<i>u</i> <sup>[b]</sup>	p <i>K</i> <sub>s</sub> (MeCN) range
<b>Water</b>							
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
<b>DMSO</b>							
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
<b>DMF</b>							
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
<b>DCE</b>							
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 <sup>f</sup>	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<sub>a</sub> values in polar aprotic solvents

- More than **9000** pK<sub>a</sub> 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 autumn 2024
- Huge XLSX file will be deposited
- To be continued with pK<sub>aH</sub> of bases

The screenshot shows the IUPAC website project details page. The browser address bar shows the URL [iupac.org/project/2015-020-2-500/](http://iupac.org/project/2015-020-2-500/). The page header includes the IUPAC logo and the text 'INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY'. Navigation links include 'Contact', 'Login', 'Join', 'IYPT 2019', and 'Shop'. A search icon is also present. The main navigation bar has tabs for 'WHO WE ARE', 'WHAT WE DO', 'EVENTS', 'PROJECTS', and 'NEWS'. The 'PROJECTS' tab is active, displaying the project title 'Critical compilation of acid pKa values in polar aprotic solvents'. Below the title, a table provides project details: Project No.: 2015-020-2-500, Start Date: 1 May 2016, End Date: (blank), Cite: <https://iupac.org/project/2015-020-2-500>, and Division: Analytical Chemistry Division. On the right side, there is a sidebar with 'Chair' Ivo Leito and a list of 'Members' including Jean-François Gal, Ivári Kaljurand, Vilve Nummert, Mare Piirsalu, Martí Rosés Pascual, Reinhard Schwesinger, Sofja Tshepelevitsh, Jonathan Wenyan, and Zheng. The left sidebar contains a list of links: 'PROJECTS', 'WHAT IS AN IUPAC PROJECT', 'FAQS ON THE PROJECT', 'SUBMISSION AND APPROVAL PROCESS', 'PROJECT SUBMISSION FORM AND GUIDELINES', 'ADVICE FOR PROJECT REVIEWERS', 'PROJECT REVIEW PROCEDURE', and 'INFORMATION FOR TASK GROUP CHAIRS'. At the bottom, there are tabs for 'Objective', 'Description', and 'Progress', with 'Objective' selected. The 'Objective' section begins with the text: 'The objective is to summarize and critically evaluate the data on ionization constants of acids (pK<sub>a</sub> data) available in a selection of polar aprotic solvents, which are either (1) the most popular solvents for pK<sub>a</sub> determination or (2) have properties specifically suitable for determination of pK<sub>a</sub> values'.

# 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 <sub>a</sub>	DMSO_Ref	DMSO_Comments	MeCN_pK <sub>a</sub>	MeCN_Ref	MeCN_Comments	DMF_pK <sub>a</sub>	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 „ $pK_{\text{auto}}$  range“ in the solvent
- **Unsure? Confused? Write me: [ivo.leito@ut.ee](mailto:ivo.leito@ut.ee)**
  - Or talk to me here at ISSP21





Thanks  
to all these  
people!

Funding: Uniphied  
([www.uniphied.eu](http://www.uniphied.eu))  
IUPAC project 2015-020-2-500,  
Estonian Ministry of Education  
and Research (TK210), Estonian  
Research Council grants IUT20-  
14 and PRG690, Estonian Center  
of Analytical Chemistry  
([www.akki.ee](http://www.akki.ee))

