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Development of GSK's Acid and Base Selection Guides

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Further to the introduction of solvent and reagent guides at GSK, the reagent guide methodology has been adapted to score common acids and bases for use in situations where the chemistry is tolerant of a number of options. The pKa of each acid and base, and information as to whether they are generally recognised as safe are included to enhance the utility of such guides.

1. Introduction

Scientists at GSK have been consulting an internal base guide for over ten years to aid selection of bases as reagents. A more recent internal survey resulted in an expanded list of 63 bases, and an additional set of 18 acids. Two new guides were then compiled using methodology consistent with that applied to generate our reagent guide.[1]

Selecting the right acids or bases for a particular chemical transformation is influenced by a number of factors, including environmental, health and safety effects, reagent strength, solubility, boiling point, ease of removal and/or recovery, and ease of handling. These constraints may not always give rise to a variety of choices, but if there are multiple options, sustainability assessments can be consulted. Medicinal Chemistry timelines can sometimes hinder consideration of sustainability, but as projects progress, consulting these guides can be helpful before larger investments are made into the original Medicinal Chemistry routes and reagents.

2. Methodology

Assessments and calculations performed for the fifteen reagent guides published in early 2013[1] were followed to generate these acid and base guides (Tables 1 and 2). As before, the European Risk Phrases were used to assign an Environmental, Health and Safety Score for each reagent.[2] Additional concerns where acids and bases have large molecular weight, or generate gaseous, flammable or toxic by-products, or give rise to disposal issues such as incineration of halogenated acids were addressed through the Chemistry Scores. When generating the reagent guides, the most typical procedures utilizing the reagents were taken into account, and the Chemistry Scores were additionally weighted based on the amounts of reagents and co-reagents used. Clearly individual acids and bases might be employed in a variety of different stoichiometries depending on the reaction being considered, so for the purpose of ranking it was assumed that 1.1 equivalents of acids or bases were being used with no additional co-reagents. Within the acid guide separate entries were created for concentrated and dilute acid in cases where using a more dilute formulation has the benefit of reducing the risk of severe burns upon contact.

When acids or bases are used as solvents, other factors such as waste handling and life cycle assessment may need additional consideration. Solvent guides[3] published by various pharmaceutical companies can help evaluate the possible choices. Acids and bases as potential salt partners for *in vivo* experiments will have to undergo more rigorous health assessments, however the inclusion of information as to which acids and bases are generally recognized as safe (GRAS) by the US Food and Drug Administration as of March 2014 may assist in some decision making.

Individual pKa values are a key consideration when selecting acids and bases. Including pKa data in the acid/base guides increases utility and may help encourage chemists to consult these guides, and related reagent guides. Experimental pKa data were retrieved from ACD/pKa DB software.[4] Where a range of experimental pKa values were available in the literature, data obtained under aqueous conditions at 25 ºC with an ionic strength approaching 0 were used wherever possible.

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Table 1. Acid Selection Guide

Inorganic acids	CAS number	EHS	Clean chemistry	Greenness	pKa[a]	GRAS[b]	Comment
Hydrochloric acid	7647-01-0	7	7	7.3	*-8*[5]	YES	Waste disposal issues upon incineration. Halogenated waste.
Hydrobromic acid	10035-10-6	7	7	7.3	*-9*[5]	NO	Waste disposal issues upon incineration. Halogenated waste.
Phosphoric acid, dilute	7664-38-2	7	7	7.3	1.90, 6.74, 11.74[6]	YES	Waste disposal issues upon incineration.
Sulfuric acid, dilute	7664-93-9	7	7	7.3	*-3.19*, 1.98[7]	NO	Waste disposal issues upon incineration.
Hydroiodic acid	10034-85-2	7	5	6.4	*-9.9*[8]	NO	Causes severe burns (R35). Waste disposal issues upon incineration. Halogenated waste.
Phosphoric acid	7664-38-2	7	5	6.4	1.90, 6.74, 11.74[6]	YES	Waste disposal issues upon incineration.
Sulfuric acid	7664-93-9	7	5	6.4	*-3.19* 1.98[7]	NO	Causes severe burns (R35). Waste disposal issues upon incineration.
Nitric acid	7697-37-2	5	3	4.3	-1.37[9]	NO	Strong oxidant (R8). Causes severe burns (R35).
Hydrogen fluoride	7664-39-3	3	5	4.2	*3.2*[8]	NO	Toxic (R26/27/28). Causes severe burns (R35). Special vessel necessary. Waste disposal issues upon incineration. Halogenated waste.
Perchloric acid	7601-90-3	3	3	3.0	*~-5*[10]	NO	Strong oxidant (R8). Causes severe burns (R35). Waste disposal issues upon incineration. Halogenated waste.
Organic acids	**CAS number**	**EHS**	**Clean chemistry**	**Greenness**	**pKa[a]**	**GRAS[b]**	**Comment**
Glutaric acid	110-94-1	10	9	9.3	4.41, 5.52[11]	NO	
Citric acid	77-92-9	10	7	8.5	*2.93*[12]	YES	
Ascorbic acid	50-81-7	10	7	8.5	*4.09*[12]	YES	
p-TsOH (monohydrate)	6192-52-5	10	7	8.5	-6.57[13]	NO	
Benzoic acid	65-85-0	7	9	8.0	4.20[14]	YES	
Oxalic acid	144-62-7	7	9	8.0	1.25, 4.23[11]	NO	
Pivalic acid	75-98-9	7	9	8.0	*4.94*[12]	NO	
Succinic acid	110-15-6	7	9	8.0	*4.24*[12]	YES	
Acetic acid	64-19-7	7	9	7.5	4.76[15]	YES	Causes severe burns (R35).
Propionic acid	79-09-4	7	9	7.5	*4.79*[12]	YES	
Formic acid, dilute	64-18-6	7	9	7.5	3.75 [16]	YES	
Methanesulfonic acid	75-75-2	7	7	7.3	-1.92**Error! Bookmark**	NO	

					not defined.		
Formic acid	64-18-6	7	7	6.9	3.75[16]	YES	Causes severe burns (R35).
Trifluoromethanesulfonic acid	1493-13-6	7	5	6.1	-12**Error! Bookmark not defined.**	NO	Causes severe burns (R35). Halogenated waste.
Trifluoroacetic acid	76-05-1	7	5	6.0	0.50**Error! Bookmark not defined.**	NO	Causes severe burns (R35). Waste disposal issues upon incineration. Halogenated waste.
Trichloroacetic acid	76-03-9	3	5	3.6	0.52**Error! Bookmark not defined.**	NO	Causes severe burns (R35). Waste disposal issues upon incineration. Halogenated waste.

[a] pKa numbers in italics are not experimentally obtained data.
[b] GRAS (Generally Recognized as Safe) is an FDA designation that a chemical or substance added to food is considered safe by experts. http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm

Table 2. Base Selection Guide

Carbonates	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
Sodium bicarbonate	144-55-8	10	9	9.3	5.95[17]	YES	
Potassium bicarbonate	298-14-6	10	9	9.3	5.95[17]	YES	
Sodium carbonate	497-19-8	10	9	9.3	9.1[17]	YES	
Potassium carbonate	584-08-7	9	9	8.8	9.1[17]	NO	
Cesium carbonate	534-17-8	10	5	7.4	9.1[17]	NO	
Phosphates	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
Trisodium phosphate (anh.)	7601-54-9	10	8	9.0	11.74[18]	YES	
Tripotassium phosphate (anh.)	7778-53-2	7	7	7.3	11.74[18]	YES	
Hydroxides	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
Potassium hydroxide	1310-58-3	7	9	8.0	15.74[19]	YES	Causes severe burns (R35).
Sodium hydroxide	1310-73-2	7	9	8.0	15.74[19]	YES	Causes severe burns (R35).
Calcium hydroxide	1305-62-0	7	9	8.0	15.74[19]	YES	
Barium hydroxide	17194-00-2	7	8	7.7	15.74[19]	NO	
Lithium hydroxide	1310-65-2	4	8	5.7	15.74[19]	NO	
Hydrides	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
Sodium hydride	7646-69-7	5	5	5.0	*35.0*[20]	NO	May cause runaway reaction with certain solvents, such as DMF, DMA. Highly flammable gaseous by-product (hydrogen) needs abating. Use of mineral oil dispersions greatly reduce fire hazard.
Potassium hydride	7693-26-7	5	5	5.0	*35.0*[20]	NO	May cause runaway reaction with certain solvents, such as DMF, DMA. Highly flammable gaseous by-product (hydrogen)

							needs abating. Use of mineral oil dispersions greatly reduce fire hazard.
Acetates	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
Potassium acetate	127-08-2	10	9	9.3	4.76[21]	NO	
Sodium acetate	127-09-3	10	9	9.3	4.76[21]	YES	
Alkoxides	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
Sodium methoxide	124-41-4	5	9	6.9	15.1[22]	NO	Highly flammable (R11). Toxic (R23/24/25).
Sodium ethoxide	141-52-6	5	9	6.9	15.93[22]	NO	Highly flammable (R11).
Sodium *tert*-butoxide	865-48-5	5	9	6.9	19.2[22]	NO	Highly flammable (R11). Causes severe burns (R35).
Potassium *tert*-butoxide	865-47-4	5	9	6.9	19.2[22]	NO	Highly flammable (R11). Causes severe burns (R35).
Lithium methoxide	865-34-9	4	8	5.7	15.1[22]	NO	Highly flammable (R11). Toxic (R23/24/25).
Lithium ethoxide	2388-07-0	4	8	5.7	15.93[22]	NO	Highly flammable (R11).
Lithium tert-butoxide	1907-33-1	4	8	5.7	19.2[22]	NO	Highly flammable (R11).
Phosphazanes	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
Phosphazane BEMP	98015-45-3	7	5	6.0	27.58[23]	NO	
Phosphazane P2-Et	165535-45-5	7	5	6.0	32.66[23]	NO	
Amines	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
2-Methylpyridine	109-06-8	8	9	8.3	5.97[24]	NO	
2,6-Lutidine	108-48-5	8	9	8.3	6.75[24]	NO	
DBN	3001-72-7	7	9	8.0	*13.5*[25]	NO	
Pyridine	110-86-1	7	9	7.5	5.17[24]	NO	Highly flammable (R11).
4-Methylpyridine	108-89-4	7	9	7.5	6.02[24]	NO	Toxic (R24).
Morpholine	110-91-8	7	9	7.5	8.49[26]	NO	
Diethylaminopropylamine	104-78-9	7	9	7.5	*10.48*[27]	NO	
Tetramethylguanidine	80-70-6	7	9	7.5	13.6[28]	NO	
DBU	6674-22-2	7	8	7.3	*12.5*[25]	NO	Causes severe burns (R35).
2,2,6,6-Tetramethylpiperidine	768-66-1	7	8	7.3	11.1[29]	NO	
Triethylamine	121-44-8	5	9	6.9	10.77[30]	NO	Highly flammable (R11). Toxic (R23/24). Causes severe burns (R35).
Diisopropylamine	108-18-9	5	9	6.9	11.05[36]	NO	Highly flammable (R11).
Piperidine	110-89-4	5	9	6.9	11.22[31]	NO	Highly flammable (R11). Toxic (R23/24).
Dimethylethylamine	598-56-1	5	9	6.9	10.16[32]	NO	Highly flammable (R11).
Dipropylamine	142-84-7	5	9	6.9	10.91[29]	NO	Highly flammable (R11). Causes severe burns (R35).
N-Methylmorpholine	109-02-4	5	9	6.9	7.41[29]	NO	Highly flammable (R11).
n-Butylamine	109-73-9	5	9	6.9	10.61[33]	NO	Highly flammable (R11). Causes severe burns (R35).
Diethylamine	109-89-7	5	9	6.9	10.98[36]	NO	Highly flammable (R11). Causes severe burns (R35).
Ammonia	7664-41-7	5	9	6.5	9.21[34]	NO	Toxic (R23).
Diisopropylethylamine	7087-68-5	5	9	6.5	*10.75*[35]	NO	Highly flammable (R11).
tert–Butylamine	75-64-9	5	9	6.5	10.63[30]	NO	Highly flammable (R11). Toxic (R25). Causes severe burns (R35).
DABCO®	280-57-9	5	9	6.5	*8.4*[25]	NO	Highly flammable (R11).
Cyclohexylamine	108-91-8	5	9	6.5	10.62[36]	NO	
Tributylamine	102-82-9	5	7	6.3	9.93[37]	NO	Toxic (R23/24/25).

4-(Dimethylamino)pyridine	1122-58-3	3	9	5.2	9.60[38]	NO	Toxic (R25/27).
Dicyclohexylamine	101-83-7	3	7	4.3	11.25[39]	NO	Toxic (R24/25).
Imidazole	288-32-4	2	9	3.9	6.99[39]	NO	Toxic (R61).
Disilazides	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
KHMDS	40949-94-8	5	7	5.9	29.5[40]	NO	Highly flammable (R11).
NaHMDS	1070-89-9	5	7	5.9	29.5[40]	NO	Highly flammable (R11).
LiHMDS	4039-32-1	4	8	5.5	29.5[40]	NO	Highly flammable (R11).
Amides	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
LiTMP	38227-87-1	4	8	5.5	37.3[40]	NO	
LDA	4111-54-0	3	8	4.5	35.7[40]	NO	Highly flammable (R11).
Sodium amide	7782-92-5	4	3	3.7	*35.0*[20]	NO	Forms peroxide. Toxic and flammable gaseous by-product (ammonia) needs abating.
Lithium amide	7782-89-0	4	3	3.7	*35.0*[20]	NO	Forms peroxide. Toxic and flammable gaseous by-product (ammonia) needs abating.
Alkyllithiums	CAS number	EHS	Clean Chemistry	Greenness	pKa[a] (BH^+)	GRAS[b]	Comment
n-Hexyllithium	21369-64-2	2	8	4.0	*40.0*[41]	NO	Highly flammable (R11). Causes severe burns (R35).
n-Butyllithium	109-72-8	1	7	3.1	*50.0*[41]	NO	Highly flammable (R11). Highly flammable gaseous by-product (butane) needs abating.
sec-Butyllithium	598-30-1	1	7	3.1	*51.0*[41]	NO	Highly flammable (R11). Causes severe burns (R35). Highly flammable gaseous by-product (butane) needs abating.
tert-Butyllithium	594-19-4	1	7	3.1	*53.0*[41]	NO	Highly flammable (R11). Highly flammable gaseous by-product (butane) needs abating.

[a] pKa numbers in italics are not experimentally obtained data.
[b] GRAS (Generally Recognized as Safe) is an FDA designation that a chemical or substance added to food is considered safe by experts. http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm

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3. The benefits of selecting more sustainable conditions

In addition to their sustainability advantages, greener acids and bases often have additional benefits. Commonly used reactions found in the Medicinal Chemistry literature may have significant issues when employed on large scale. One such example is the use of NaH in DMF. Exposure of solid NaH to air and the release of highly flammable hydrogen gas on large scale have significant safety risks, and the combination of NaH and DMF has been implicated in runaway reactions.[42] Using alkoxides such as potassium *tert*-butoxide instead can alleviate these concerns.

When it is not feasible to replace a class of acids or bases with significantly more sustainable counterparts, the guides can still point out differences within the available choices. For example, transformation requiring the use of alkyllithiums will likely proceed as well with hexyllithium as with its short-chain analogs, and the by-product will be liquid hexane instead of flammable alkane gases. Even this is not ideal as hexane has neurotoxicity concerns.[43] Currently there is still a need for new commercially available organolithium reagents to address these safety issues.

Reactions such as BOC-deprotections are generally carried out using strong acids. Replacing TFA in dichloromethane with HCl in cyclopentyl methyl ether (CPME),[44] minimizes the safety hazard of severe skin damage, and reduces the amounts of chlorinated materials.

Choosing more sustainable conditions by first intent in Medicinal Chemistry can result in safer reaction conditions, less hazardous waste, and significant time savings during subsequent scale up campaigns.

4. Conclusion and further work

Not all acids or bases are interchangeable for every purpose, but these guides can help examine multiple choices, and can also facilitate changing a culture, encouraging people to consider sustainability as one of many criteria when planning a reaction.

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Notes and references

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