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Exploring the Chemoselectivity of Reducing Reagents
--Manuscript Draft--

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REACTIVITY SCALES

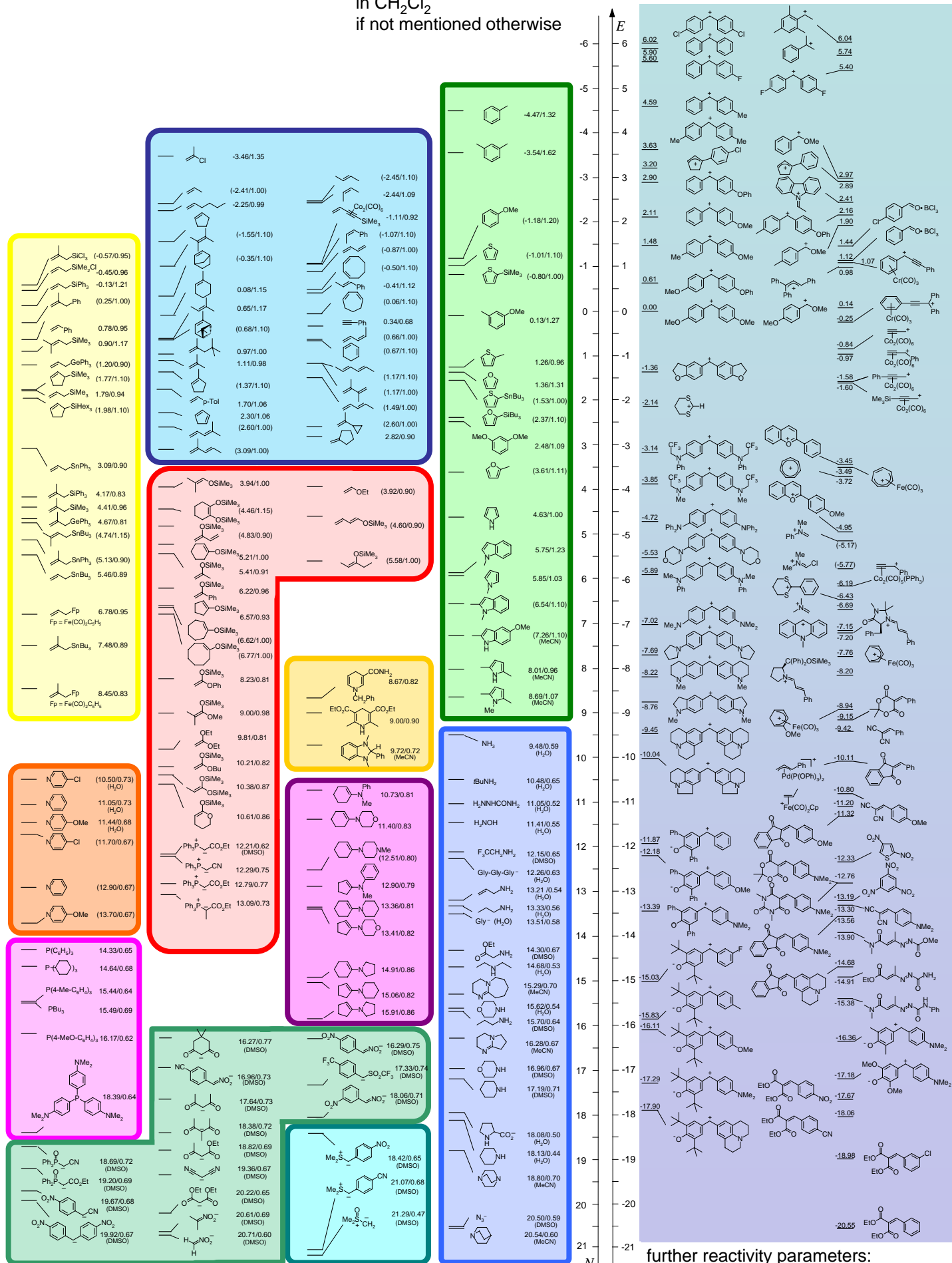
Nucleophilicity N / s_N

$\log k_{20^\circ\text{C}} = s_N(N + E)$

in CH_2Cl_2

if not mentioned otherwise

Electrophilicity E



further reactivity parameters:

www.cup.lmu.de/oc/mayr/DBintro.html

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Exploring the Chemoselectivity of Reducing Reagents

Overview

Controlling the reactivity and selectivity during the synthesis of a molecule is a very important criteria for chemists. This has led to the development of many reagents that allow chemists to pick and choose reagents suitable for a given task. Quite often, a balance between reactivity and selectivity needs to be achieved. This experiment will use IR spectroscopy as a way of monitoring the reaction and to understand the reactivity of carbonyl compounds as well as the reactivity of hydride-reducing reagents.

Principles

Before understanding hydride-donor reagents, the reactivity of carbonyl compounds needs to be understood. Carbonyl compounds have a slight positive charge on the carbonyl-carbon giving it electrophilic-character (**Figure 1a**). Thus carbonyl compounds that have a positive charge are *more* reactive to different nucleophiles such as a hydride donor. Acyl chlorides have a good leaving group (Cl^-) making it also very electrophilic. Esters and amides are more stable because of the strong resonance structure from the second heteroatom on the carbonyl. A general range of reactivity is shown in **Figure 1b**.

Figure 1. The reactivity (electrophilicity) of different carbonyl carbons.

Most reductions of carbonyl compounds are done with reagents that transfer a hydride from boron or aluminum. Two common reagents of this type are sodium borohydride and lithium aluminum hydride (**Figure 2**). Sodium borohydride is a less reactive donor reagent but is efficient for reducing aldehydes and ketones to alcohols. Compared to lithium aluminum hydride, which is much more reactive and can reduce ketones and aldehydes to alcohols but also reduce esters, amides, and carboxylic acids.

Figure 2. Two common hydride-donating reagents.

A common table can be made to show the different combinations of reducing reagents (hydride donors) with a series of carbonyl compounds (**Figure 3**). It should be noted that some combinations produce no reaction. Other reactions only carry out a partial reduction.

Figure 3. Reactivity of hydride-donating reducing agents with electrophilic carbonyl compounds.

Commented [ASW1]: Above, and in Figure 4, you state/show that NaBH_4 can't reduce esters, but in this figure it can. Is it system-specific?








							
	<i>iminium ion</i>	<i>acid chloride</i>	<i>aldehyde</i>	<i>ketone</i>	<i>ester</i>	<i>amide</i>	<i>carboxylic acid</i>
LiAlH ₄	Amine	Alcohol	Alcohol	Alcohol	Alcohol	Amine	Alcohol
Red-Al		Alcohol	Alcohol	Alcohol	Alcohol	Amine	Alcohol
LiAlH(OtBu) ₃		Aldehyde	Alcohol	Alcohol	Alcohol	Aldehyde	
NaBH ₄	Amine		Alcohol	Alcohol			
NaBH ₃ CN	Amine						
B ₂ H ₆		Alcohol	Alcohol			Amine	Alcohol
AlH ₃			Alcohol	Alcohol	Alcohol	Amine	Alcohol
DIBAL-H			Alcohol	Aldehyde	Aldehyde	Aldehyde	Alcohol

Figure 3. Reactivity of hydride donor reducing agents with electrophilic carbonyl compounds

Commented [DK2]: Thanks for catching that mistake. You are correct. Here is an updated Figure3.

To demonstrate the varying degree in reactivity, a reaction with two carbonyl functional groups will be subjected to two sets of conditions with hydride-donating reducing reagents.

Figure 4. Chemoselective reduction of ethyl acetoacetate.

Procedure

1. Measuring Properties of Ethyl Acetoacetate

1. Take an IR of the starting material (ethyl acetoacetate).
2. Take a TLC using 40% ethyl acetate in 60% hexanes.

2. Reduction of Ethyl Acetoacetate with Sodium Borohydride

1. Add 1 mmol of ethyl acetoacetate to a round-bottom flask.
2. Add 5 mL of ethanol and swirl to mix completely.
3. Lower the beaker into an ice-water bath.
4. Weigh 1 mmol of sodium borohydride and slowly add to the stirred solution of ethyl acetoacetate.
 1. Add in small portions. The reaction is exothermic and bubbles vigorously.
5. Immediately after, monitor the reaction by TLC every few minutes until the reaction is complete.
6. Once complete, add 10 mL of water to the reaction mixture.
7. Transfer into a separatory funnel and extract with ethyl acetate (2x 30 mL).
8. Dry with DI water (1x 30 mL) and with brine (1x 30 mL).
9. Dry over sodium sulfate and filter into a round-bottom flask.
10. Evaporate solvent on the rotovap.
11. TLC and take IR of reduction product.

3. Reduction of Ethyl Acetoacetate with Lithium Aluminum Hydride

1. Add 1 mmol of lithium aluminum hydride into a dry round-bottom flask and cap it with a septum.
2. Purge flask with nitrogen gas using a nitrogen inlet line. Make sure to have an exit valve.

3. Add 10 mL of dry THF.
4. Place round-bottom flask into an ice bath.
5. Make a solution of 1 mmol of ethyl acetoacetate into 3 mL of dry THF and slowly add dropwise into the reaction flask.
6. The reaction will vigorously bubble until all of the reagent is added.
7. Immediately after, monitor the reaction by TLC every few minutes until the reaction is complete.
8. Once complete, add 1 M HCl dropwise. The reaction will bubble vigorously until all of the LiAlH_4 is consumed.
9. Once consumed (no more bubbling), the septum can be removed and diluted with ethyl acetate (40 mL) and 1 M HCl (20 mL).
10. Transfer to a separatory funnel.
11. Extract with ethyl acetate (3x 50 mL).
12. Dry with brine (1x 50 mL).
13. Dry over sodium sulfate and filter into a round-bottom flask.
14. Evaporate solvent on the rotovap.
15. TLC and take IR of reduction product.

Representative Results

Figure 5. Representative TLC reaction results.

Figure 6. Representative IR results for ethyl acetoacetate.

Figure 7. Representative IR results for ethyl 3-hydroxybutyrate.

Commented [ASW3]: Why is the spectrum different (absorbance vs. transmittance, grid lines)? Replace.

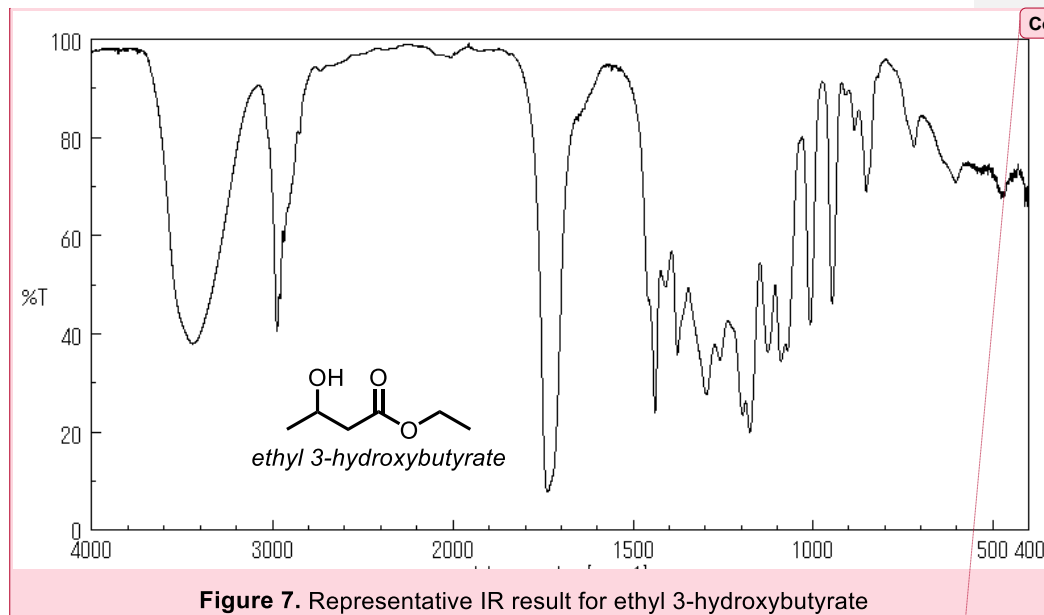


Figure 8. Representative IR results for 1,3-butanediol.

Summary

In summary, the trends of carbonyl reactivity and hydride donor ability have been reviewed and demonstrated. Hopefully the visual reactivity of the two commonly used reagents is apparent and can be appreciated.

Applications

The understanding of the reactivity of reagents and functional groups is of high importance when developing new methods for reductions or any other kind of reaction. Controlling the selectivity and reactivity of any reaction is an important factor to consider when deciding on the reagents used for a chemical step. This drives chemists to develop new reagents and new methods.

Figure 9. Example of reducing agent choice affecting stereochemistry.

The review of periodic trends is still important in organic chemistry. When adding potassium metal to water it is a more violent explosion than when sodium metal is added to water. For that reason, we could extend this analogy to the comparison and reasoning to why LiAlH_4 is more reactive than NaBH_4 .

On the entire spectrum of nucleophiles and electrophiles, reactivity matters. A weak nucleophile will not react with a weak electrophile. But a more reactive electrophile might

react with the same weak nucleophile. It all depends on their reactivity and the conditions. Professor Mayr has started a program where he and his students evaluate and quantify the reactivity of different reagents and functional groups. This chart helps for chemists to understand reactivity of different kinds of molecules which extend far beyond carbonyl chemistry.

Commented [ASW5]: Is this chart freely available?

I believe this chart is technically free. While this professor constantly publishes new results and increases further understanding of this chart. He has put up on his website a PDF for the chart. I have placed a link below and have attached a PDF version of these chart in the email.

<http://www.cup.lmu.de/oc/mayr/CDmayrPoster.html>