

Case Comparisons on the Basicity of Organic Nitrogen Compounds to Develop the Concepts of 'inductive effect' and 'mesomeric effect' in the Teaching Laboratory

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Abstract Inductive and resonance effects play an important role in understanding a variety of organic chemical reactions and their mechanisms. Most reactions are kinetic-controlled reactions, in which the effects take effect via the stabilization of reactive intermediates over shorter or longer reaction times. - To avoid this mental "detour", we have developed new learning opportunities on equilibrium reactions of organic bases with water for high school teacher education, with which inductive and resonance effects can be quickly worked out using conductivity and pH measurements. The learning opportunity has already been successfully tested in teacher education in Marburg.

Keywords: Basicity of Organic Compounds, Contrasting Cases, Inductive Effects, Resonance Effects, Teaching Lab

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1. Introduction







The majority of organic chemical reactions proceed under kinetic control: first- and second-order nucleophilic substitutions and eliminations, electrophilic additions to alkenes, electrophilic substitutions to aromatics, nucleophilic substitutions to carboxylic compounds, and radical substitutions exhibit more or less high activation energies. Most of these reactions also involve the passage of reactive intermediates, carbenium ions, carbanions or radicals. It's thermodynamic stability can be used to predict the relative kinetics of two reactions being compared, according to the BELL-EVANS-POLANYI theorem and HAMMOND'S postulate. These intermediates are typically stabilized by inductive effects (or by hyperconjugation), by conjugation, and by other electronic substituent effects exerted by groups containing heteroatoms. However, these effects also play an essential role in thermodynamically controlled reactions, of which Brønsted acid-base reactions are the most important class.

The aim of this work is to experimentally investigate the basicity of organic nitrogen bases in suitable near-by case comparisons and to correlate them with inductive effects and mesomeric effects, respectively. For learners, this provides an excellent opportunity to apply basic concept knowledge in a new subject context. In addition, due to the generally very low activation enthalpies, organic acid-base reactions have the experimental advantage that equilibria are established within seconds

and thus the experimental results can be observed or measured very quickly.

It should not go unmentioned that organic nitrogen bases play an important role also in synthetic chemistry. Due to the structural diversity of bases such as DABCO, DBU, DBN, HÜNIG'S base, TBD, TMG (Table 1.) and their generally good solubility in many organic solvents, a most suitable base or auxiliary base is available for almost every synthetic purpose.

Table 1. Synthetically significant organic bases

Name	Abbreviation	Structure
1,4-Diazabicyclo[2.2.2]octane	DABCO	
1,8-Diazabicyclo[5.4.0]undec-2-ene	DBU	
1,5-Diazabicyclo[4.3.0]non-5-ene	DBN	
N,N-Diisopropylethylamine	Hünig's base	
1,1,3,3-Tetramethylguanidine	TMG	
1,5,7-Triazabicyclo(4.4.0)dec-5-ene	TBD	

2. Subject Analysis

Reactions of organic bases and acids are basically subject to the same rules as inorganic acid-base reactions. Equilibrium constants and pK_a values are defined accordingly and, if the organic bases and acids are water-soluble, are determined with respect to water. Consequently, an organic acid such as acetic acid reacts with water in equilibrium to form acetate ions and oxonium ions, and an organic base such as triethylamine reacts to form triethylammonium ions and hydroxide ions, as shown in Figure 1. In both cases below, however, the equilibria are on the left side, since both acetic acid is a fairly weak acid compared to oxonium ions (H_3O^+), and triethylamine is a weak base compared to hydroxide ions (OH^-).

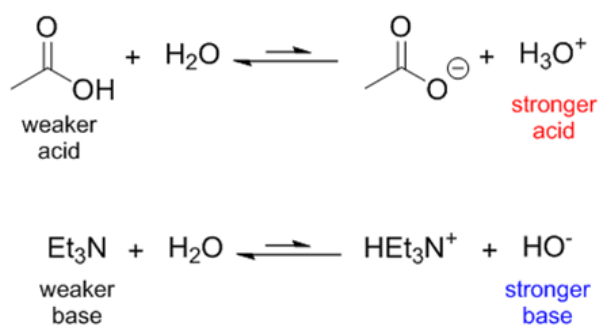


Figure 1. Reaction of acetic acid and of triethylamine with water

2.1. Substituents Influence the Position of the Equilibrium

The extent to which organic nitrogen compounds are nevertheless protonated at equilibrium in water depends on the substituent influences that thermodynamically stabilize or destabilize the respective base and its corresponding acid. If, for example, the nitrogen atom with its free electron pair is flanked by a carbonyl group, as in *N,N*-dimethylformamide (DMF), there is effectively no basicity at the nitrogen center, since the electron density at the nitrogen is greatly reduced by the strong $-M$ effect or resonance stabilization in the ground state (Figure 2, top). Amidines such as DBU, on the other hand, form well resonance stabilized amidinium ions after protonation (Figure 2, bottom). While DMF has a pK_a value of ~ -0.3 [1] and is thus not basic, that of DBU is consequently about 14 orders of magnitude higher at ~ 13.5 . [2].

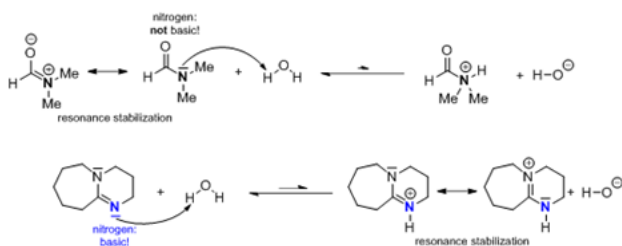


Figure 2. Reactions of organic nitrogen compounds with water. Upper example (DMF) with very well resonance stabilized neutral compound; lower example (DBU) with very well stabilized corresponding acid

Inductive effects also have a clear influence on the relative basicity of organic nitrogen compounds. For example, triethylamine ($pK_a \sim 10.75$ [3]) benefits from three $+I$ effects that increase the electron density at the N atom and thus its basicity. The formal replacement of a hydrogen atom by a chlorine atom as $-I$ substituent in (2-chloroethyl)-dimethylamine alone leads to a noticeably lower basicity ($pK_a \sim 9.4$ [4]). In order to investigate influences of substituents or structural features of organic nitrogen compounds in more detail, we have investigated the relative basicity of structurally similar pairs of bases that differ only in one structural feature.

2.2. Didactic Restructuring

This learning opportunity was developed by students as part of the subject didactics module ProfiWerk Chemie as part of the Marburg high school teacher training program. The objective was to create experimental learning opportunities based on near-by case comparisons that allow students to develop and apply robust organic chemistry concepts: the inductive and the mesomeric effect. It is intended for use in the organics teaching lab, where it has already been successfully tested. Against the background of subject-specific elementarization, we designed and experimentally investigated the contrasting cases (CCs) listed in Table 2 for the experimental learning opportunities to be developed. The structural features in which the compounds differ are marked in blue in each case. The compounds or chemicals used for this purpose meet the following criteria:

- structurally simple and distinguishable within a CC in only one structural feature,
- moderately different pK_a values within a CC,
- pK_a differences reproducibly measurable and clearly explainable by theoretical concepts,
- low volatility, highest possible purity of chemicals and good water solubility,
- acceptable price and good availability of substances,
- low to acceptable toxicity and thus suitability for student work in the laboratory.

Table 2. Possible near-by case comparisons

Case Comparisons		
+I effect	Case 1	
	Case 2	
-I effect	Case 3	
	Case 4	
+M effect	Case 5	

2.3. Learning Process Along the CPOE Cycle

Working with case comparisons is efficient and corresponds to the researcher's way of thinking

The didactic approach *Inventing with Contrasting Cases (ICC)* for learning to explain and transfer conceptual relations by means of contrasting cases has already proven effective in other disciplines [5]. ICC uses sets of contrasting cases (CCs) that reveal the "deep structure" [5] of the subject matter by varying a particular associated dimension. [6]. Since CCs show strong similarities to explanatory strategies of experts in organic chemistry, which have been assigned the term contrast classes [7], it is obvious to reflect on them in terms of subject didactics and to use them for different learning activities. - In a 2018 paper, the first attempt was made to describe a framework for concept-oriented task design in organic chemistry [8]. Referring to the epistemic practice of organic chemistry, the authors outline mechanistic problem-solving tasks consisting of groups of CCs, each differing in only one specific structural feature.

The case comparisons in Table 2 fit precisely into this scheme due to the fact that different inductive or mesomeric effects (as "deep structure") have direct effects on the basicity of organic nitrogen compounds due to different structural features.

Design experiments and implement them in CPOE cycles

In line with epistemological and cognitive psychological perspectives, the design of such learning opportunities should not only be theoretical, but must also be reflected in appropriate laboratory experiments [6]. To this end, the authors of the above paper propose to embed new experiments in a compare-predict-observe-explain (CPOE) cycle [8] that links theoretical reflections with experiments. Adapted to the question and solutions of this paper, the learning opportunity would be staged in the following way (Figure 3.):

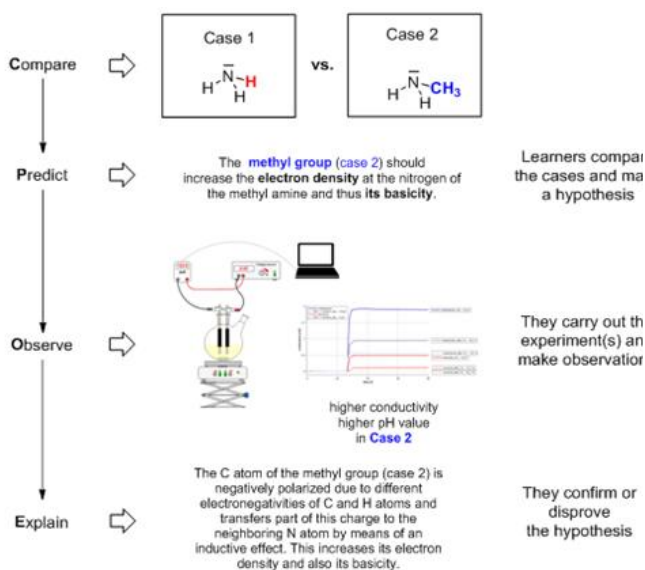


Figure 3. CPOE cycle of the reaction of organic bases with water

At the beginning, the learners would have to reflect theoretically on the case comparisons (Compare), which would lead to a hypothesis on the expected differences (Predict). Subsequently, the case comparisons would be carried out experimentally and measurement results would be recorded (Observe). The final step would be the interpretation of the measurement results against the background of the different structural features with the deepening of the concepts inductive effect and mesomeric effect (Explain). A didactic "cycle" is created by the fact that the learners encounter case comparisons of inductive and mesomeric effects in other contexts, e.g. in reaction mechanisms, which they can process with the same approach.

3. Experimental Realization

In order to plan experiments for the determination of the relative basicity of organic nitrogen compounds with explanatory potential for teaching purposes in the laboratory, it is indispensable to link up with the basal analytical prior knowledge of the students and to use proven measurement methods. These include the fact that ionic solutions conduct electricity and, in this respect, the formation of hydroxide ions in the course of protolysis reactions of organic bases with water (Figure 1, bottom) is accompanied by an easily measurable increase in the electrical conductance of the reaction solution. In addition, the pH of such solutions increases due to the formation of hydroxide ions. Electrical conductance and pH values are higher when comparing two or three bases of a CC (according to Table 2), the stronger the respective base is. In addition, since the activation energies of Brønsted base-acid reactions are very low, the adjustment of the equilibria should take place very quickly.

3.1. Conductivity and pH Measurements, Experimental Setup

The experimental setup is shown here schematically only for the conductivity measurement with a multimeter (Figure 4, top left); the apparatus for measuring pH values (with pH meter instead of multimeter) is set up analogously. For the measurement, a flask with at least two openings is required, in which a magnetic stir bar is located. Two steel electrodes are immersed in the reaction solution. For comparative measurements, the cross-sections and distances between the electrodes must be constant. For this purpose, it is recommended to insulate the middle part of the electrodes evenly with a non-conductive material [9] and to fix the electrodes. The electrodes are connected to a voltage source and a multimeter, which is connected to a computer to record and evaluate the measured current. Alternating voltage is applied for the measurement.

As an alternative to a measurement with the multimeter, it is also possible to measure with the chemophone, which emits an acoustic signal whose frequency correlates with the level of conductance. The chemophone is connected directly to the electrodes of the apparatus without a voltage source and computer.

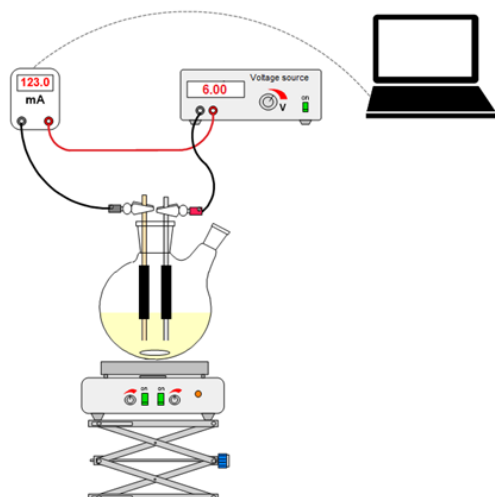


Figure 4. Measurement of electrical conductivity values of solutions of organic bases in water with the multimeter

3.2. Inductive Effects

+I effects increase the basity!

3.2.1. Comparison of Ammonia with Methylamine (Table 2, Case 1)

From a didactic perspective, the simplest example of the effect of a positive inductive effect on base strength is given in the CC pair ammonia and methylamine, in that these very simple structures differ by exactly one methyl group. To measure their relative basicity, 10 mL of distilled water is introduced into a 100-mL two-neck flask. After switching on the conductance measurement, 0.30 mL (~ 3.5 mmol) of a 40% aqueous methylamine solution is added after 20 s with the magnetic stirrer switched on. After about 60 s of measurement time, this is terminated. After disposing of the reaction solution, a second measurement is carried out analogously with 0.26 mL (~ 3.5 mmol) of a 25% aqueous ammonia solution.

As expected, the methylamine solution showed both higher electric conductance and pH (Figure 5):

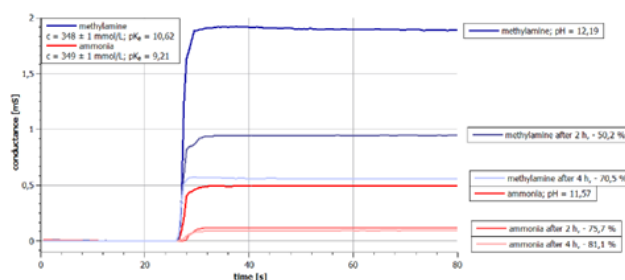


Figure 5. Comparison of conductance and pH values of solutions of ammonia and methylamine

It should be noted in this comparison that the conductance values and pH values of both solutions decrease over time as a result of the evaporation of the bases (see conductance values after 4 h in each case). From a didactic perspective, it should be mentioned that a comparison of an inorganic base with an organic base is made here, thus creating a conceptual link.

3.2.2. Comparison of Pyridine, 3-methylpyridine and 3,4-dimethylpyridine (Table 2, Case 2)

The electron density of the nitrogen center of the heteroaromatic pyridine, and thus its basicity, also benefits from the +I effects of one or two methyl groups. For learners, this case is interesting in that the effect of the inductive effects can be seen from looking at the resonance formulas of the conjugate acid, the pyridinium ion. Especially the third resonance formula with the positive charge in ipso position contributes to the understanding of the stabilization.

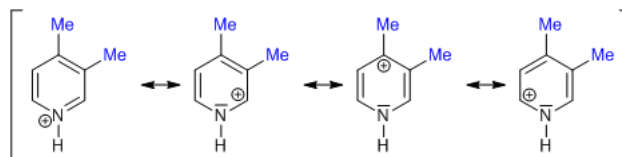


Figure 6. resonance formulas of the 3,4-dimethylpyridinium ion

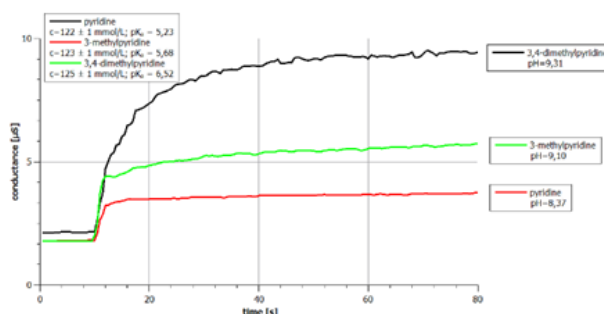


Figure 7. Comparison of the conductance and pH values of the aqueous solutions of pyridine, 3-methylpyridine and 3,4-dimethylpyridine

To investigate this, 10 mL of distilled water is placed in a 100-mL two-neck flask. After turning on the measurement, 0.10 mL (~ 1.24 mmol) of pyridine is added after 20 s with the magnetic stirrer on. After about 60 s measurement time is terminated. After disposing of the reaction solution, a second measurement is carried out analogously with 0.12 mL (~ 1.23 mmol) of 3-methylpyridine and a third measurement with 0.12 mL (~ 1.07 mmol) of 3,4-dimethylpyridine.

Again, conductance and pH measurements correlate excellently with the expectations that methyl groups as substituents of the heteroaromatic increase its basicity (Figure 7). It is also interesting to note here that the equilibration takes about 30 s, especially for the 3,4-dimethylpyridine, which may be due to the poorer water solubility of this compound.

-I effects lower the basity!

3.2.3. Comparison of *N*-methylpiperidine with *N,N'*-Dimethylpiperazine (Table 2, Case 3)

Provided that there is a (further electronegative) heteroatom in α -, β - or γ -position to the basic center, which can exert an inductive but not a mesomeric effect, the electron pull of this atom decreases the electron density at the basic center and thus also its basicity. To observe this phenomenon, the comparison of *N*-methylpiperidine with *N,N'*-dimethylpiperazine is best suited for many reasons. For this purpose, 10 mL of distilled water is placed in a 100-mL two-neck flask. After

turning on the measurement, 0.20 mL (~1.65 mmol) of *N*-methylpiperidine is added after 20 s with the magnetic stirrer on. After about 60 s measurement time is terminated. After disposal of the reaction solution, a second measurement is carried out analogously with 0.22 mL (~1.64 mmol) of *N,N'*-dimethylpiperazine.

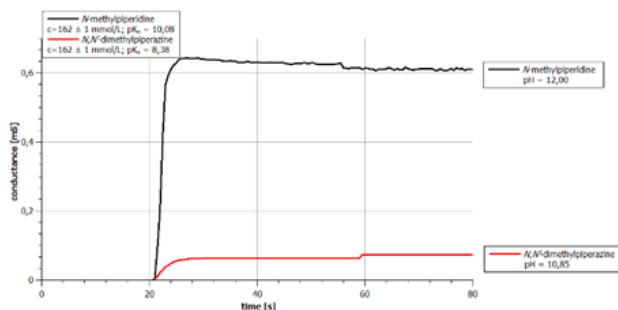


Figure 8. Comparison of the conductance and pH values of *N*-methylpiperidine with *N,N'*-dimethylpiperazine in water

Conductance and pH values of the two compounds differ significantly in each case because of the -I effect of piperazine (Figure 8).

3.2.4. Comparison of *N,N,N',N'*-tetramethyldiaminoethane with *N,N,N',N'*-tetramethyldiaminobutane (Table 2, Case 4)

To investigate the dependence of the -I effect on the distance between the centers, it is convenient to compare *N,N,N',N'*-tetramethyldiaminoethane with *N,N,N',N'*-tetramethyldiaminobutane. For this purpose, 10 mL of distilled water is introduced into a 100-mL two-neck flask. After switching on the measurement, 0.15 mL (~ 1,0 mmol) of *N,N,N',N'*-tetramethyldiaminoethane is added after 20 s with the magnetic stirrer switched on. After about 60 s measurement time is terminated. After disposing of the reaction solution, a second measurement is carried out analogously with 0.18 mL (~ 0.98 mmol) *N,N,N',N'*-tetramethyldiaminobutane.

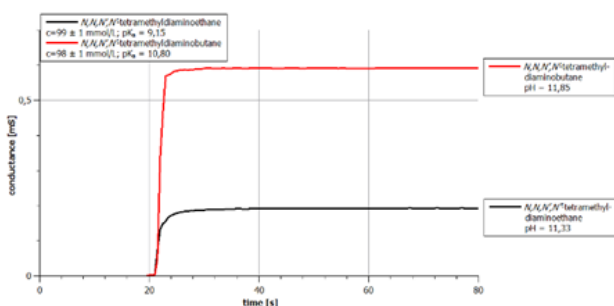


Figure 9. Comparison of the conductance and pH values of *N,N,N',N'*-tetramethyldiaminoethane with *N,N,N',N'*-tetramethyldiaminobutane in water

In agreement with the theory, the comparative measurements (Figure 9) show that the -I effect of the heteroatom nitrogen on the basicity of the compound decreases with increasing distance. The aqueous solution of *N,N,N',N'*-tetramethyldiaminobutane (with ϵ -standing N atom) exhibits a measurably higher conductance and also a higher pH than *N,N,N',N'*-tetramethyldiaminoethane, (with γ -standing N atom) although the differences are not as large as in the piperidine-pyrazine comparison.

3.3. Mesomeric Effects: Comparison of 'DBU' with 'TBD' (Table 2, Case 5)

To study the effect of mesomeric effects, the most suitable case comparison is to compare 1,8-diazabicyclo[5.4.0]undec-2-ene (DBU) with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). For this purpose, 10 mL of distilled water is placed in a 100-mL two-neck flask. After turning on the measurement, 0.10 mL (~ 0.67 mmol) of DBU is added after 20 s with the magnetic stirrer on. After about 60 s measurement time is terminated. After disposal of the reaction solution, a second measurement is performed analogously with 1.00 mL of a 10 % aqueous TBD (~ 0.71 mmol) solution in 9 mL distilled water (Figure 10):

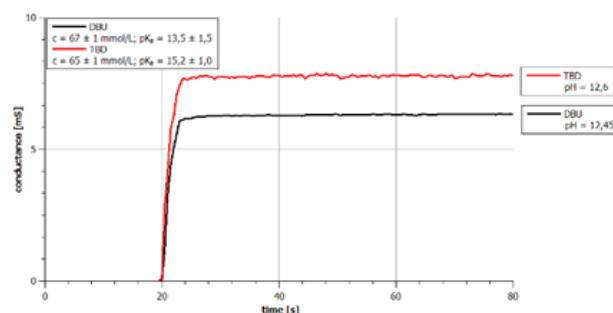


Figure 10. Comparison of the conductance and pH values of 1,8-diazabicyclo[5.4.0]undec-2-ene (DBU) with 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)

From the perspective of learners, what is particularly interesting about this comparison is that the -I effect of an additional heteroatom is far overcompensated by its simultaneous +M effect. Thus, this measurement result of a +M effect of the additional amino group dominating over a -I effect correlates with the electronic substituent effect of amino substituents also observed in other subject contexts such as electrophilic aromatic substitution. The +M effect is most simply expressed in the possibility to formulate one more resonance formula for the corresponding acid of TBD than for the corresponding acid of DBU.

4. Conclusion

The experimental case comparisons presented here offer an excellent opportunity to transfer knowledge about substituent effects acquired in reaction mechanistic contexts to the field of organic base-acid equilibrium reactions with students of grammar school teaching or - with appropriate prior knowledge - also with pupils of grammar school upper grades. For the practical implementation of the experiments in the laboratory, we recommend the CPOE cycles model [8], the core of which is that learners develop concept-based explanations based on observations of their own experimental case comparisons. As mentioned earlier, the learning opportunity was successfully tested in the organics teaching lab. In addition, the experiments have since been supplemented by a series of structurally analogous case comparisons to organic acids.

Acknowledgements

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