A GENERAL DESCRIPTION OF THE REACTIVITY OF HETEROAROMATIC COMPOUNDS BASED ON THE DONOR-ACCEPTOR CONCEPT

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Abstract- The reactivity of heteroaromatic ring- and exocyclic α-positions in ionic processes has been described in terms of 5 acceptor and 4 donor types, each in 5 levels of potency. The system is useful for prediction of reactivity and regioselectivity.

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This paper is dedicated to Dr. Masatomo Hamana on occasion of his 75th year anniversary.

1. Introduction

Many reactions are known in which azoles undergo electrophilic aromatic substitution of hydrogen or nucleophilic aromatic substitution of leaving groups. The positions of attack in these reactions can be predicted roughly from the charge distribution resulting from delocalization of enamine and imine fragments in the nuclei.[1] Alternatively, the resonance stabilization of the possible intermediates can be compared. In 1-substituted pyrazoles enamine delocalization accounts for increased charge density at the three ring carbon atoms and imine delocalization accounts for the decreased charge density at C-3 and C-5. These considerations explain why C-3, C-4, and C-5 of 1-substituted pyrazoles are attacked by electrophiles while C-3 and C-5 are susceptible to nucleophilic attack.[2] However, these considerations do not explain more subtle differences in reactivity, like the regioselectivity between electrophilic attack at C-3, C-4, and C-5 or the regioselectivity by nucleophilic attack at C-3 and C-5. In addition to such limitations, azoles can undergo a series of reactions, like metalation followed by reaction with an electrophile, in which reactivity can not be explained solely by inspection of resonance structures. Such reactions are becoming increasingly important giving access to many new substituent patterns. These reactions frequently take place in activated azoles, like azolium ions, azole-N-oxides, and N-alkoxy-substituted azoles.* Furthermore the latter species may undergo a unique nucleophilic substitution reaction.

When synthesizing substituted heteroaromatics, α-side chain positions offer interesting points of chemical attack. Some facets of the reactivity of these positions are revealed by evaluation of charge delocalization through resonance.[1] Not all reaction types, however, can be rationalized in

* The compounds studied have been named according to the IUPAC nomenclature. From this follows that numbering of ring positions starts at oxygen substituted nitrogen atoms.

this way. Again, N-alkoxy, N-acyloxy, and N-siloxy-substituted azoles display two unique side chain reactions.

An attempt has now been made to give a more general description of the reactivity of heteroaromatic ring- and exocyclic α-positions in ionic processes. The principle applies to neutral, dipolar, as well as charged heteroaromatics with fixed structures. The new approach is based on the donor-acceptor concept.[3] All reaction types involve a donor or an acceptor center in the heteroaromatic compound. The donor and acceptor centers are characterized by a number which refers to the reaction type. Bars underneath the donor and acceptor symbols are used to describe the relative reactivity in the individual reaction types. In this way each ring carbon atom and exocyclic α-carbon atom is marked with symbols that describe all the ionic reactions it can take part in and with which reactivity. Even regioselectivity in a given reaction can frequently be predicted.

In the following the different reaction types are described and the donor or acceptor characterization is shown. Next, the ranking of the relative potency of the individual centers is made. The result is shown using N-substituted 1,2-diazoles, 1,3-diazoles, and 1,2,3-triazoles as examples. The characterization of isoxazoles and isothiazoles is the same as that of 1,2-diazoles, the characterization of oxazole and thiazole is the same as that of 1,3-diazoles, and the characterization of oxadiazole and thiadiazole is the same as that of 1,2,3-triazoles. The principle of characterization can easily be extended to encompass other 5- and 6-membered heterocycles. In all cases functional group substituents contribute to the over-all reactivity in the usual manner.

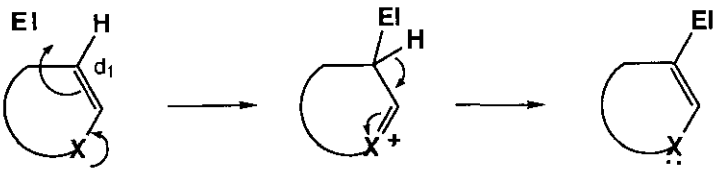
2. Reactions at ring carbon atoms

Most ionic processes of ring carbon atoms of neutral, dipolar, and charged heteroaromatics belong to the following types: (i) electrophilic aromatic substitution, (ii) nucleophilic addition-elimination, or (iii) reaction of carbanionic centers with electrophiles.

Considering the mechanism, the reactive centers in these processes can be described by using a simple notation comprising two acceptor types and two donor types as follows:

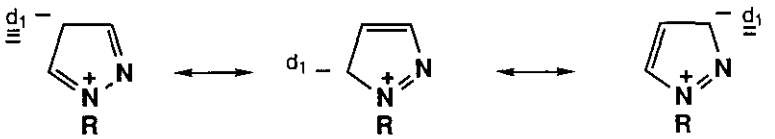
2.1 Electrophilic aromatic substitution

In azoles electrophilic substitution takes place at the β-position of enamine fragments. These positions get their negative properties through mesomeric delocalization and their donor character is designated d_1.*



Scheme 1

In order to describe the regioselectivity in such reactions, bars are used to indicate enhanced reactivity while a parenthesis indicates low reactivity. The relative reactivity of individual positions in individual types of compounds is rated by evaluating to which extent the negative charge is stabilized in dipolar resonance structures with the positive charge situated on nitrogen. Three such resonance structures can be envisaged for 1-substituted pyrazoles:

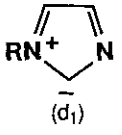


Scheme 2

The negative charge at C-5 is inductively stabilized by an adjacent positive nitrogen atom, that at C-3 is stabilized by a neutral nitrogen atom, while that at C-4 is not stabilized inductively. Thus the stabilization of the negative charge of the three donor centers decreases in the order C-5>C-3>C-4. If it is assumed that a donor center is more potent and susceptible to electrophilic attack the less the

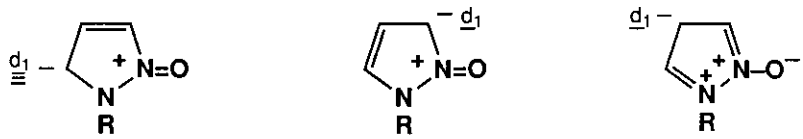
* In the general reaction Schemes 1, 6, 12, 15, 16, 17, 20, 26, and 27 El signifies an electrophile, Nu a nucleophile, and X a nitrogen, oxygen or sulphur atom. The nature of Z is discussed in the individual cases. OR stands for an alkoxy, acyloxy, or siloxy group. The other atoms of the nuclei in these schemes may be carbon or heteroatoms to make up a 5-membered heteroaromatic ring.

stabilization of the negative charge, the reactivity is expected to increase in the order C-5<C-3<C-4. This is denoted placing no, two, or three bars underneath the d_1 symbol. Experiments confirm this order as described below. Using these terms, C-4 of 1-substituted imidazoles as well as C-4 of 1- and 2-substituted 1,2,3-triazoles are denoted with double bar since these positions exhibit the same kind of stabilization as C-3 of 1-substituted pyrazoles. The 5-position of 1-substituted imidazoles and 1,2,3-triazoles exhibits the same stabilization as C-5 of 1-substituted pyrazoles and is denoted without a bar. The negative charge at the 2-position of 1-substituted imidazoles is stabilized both by an adjacent positive and a neutral nitrogen atom. Consequently, the expected low reactivity is denoted by putting the d_1 symbol in a parenthesis.



Scheme 3

Following these lines other ring carbon atoms in neutral azoles and their N-oxides can be characterized. If the N-oxide function is part of an enolate like fragment the negative charge at the carbon atom next to the oxygen-substituted nitrogen atom is augmented as illustrated by dipolar resonance structures. The resulting increase of reactivity is denoted by adding a bar. For example, the 3-position of 2-substituted pyrazole 1-oxides is upgraded from a double to a triple bar. The double bar is acquired since a negative charge at C-3 is stabilized by an adjacent neutral nitrogen atom. Likewise, the 5-position is upgraded with one bar from no bar which it acquires since a negative charge at this position is stabilized by a positive nitrogen atom. In 2-substituted pyrazole 1-oxides the resonance structure with a negative charge at C-4 is less likely since it possesses a positive nitrogen atom next to another one, although the charge of the second is reduced by its negative oxygen atom (see Scheme 4). The resonance structure, and hence the stabilization, can not be compared with the previous cases. The reactivity has been set arbitrarily to $\underline{d}_1$, reflecting the experimental finding that C-4 and C-5 of these species are of similar reactivity in halogenation reactions.[4]



Scheme 4

Apparently, N-oxidation reduces the reactivity of this position in terms of two bars. Accordingly, the reactivity of the analogous 4-position of 2-substituted 1,2,3-triazole-1-oxides, is expected to be reduced in terms of two bars as compared to the parent 2-substituted triazole. The 5-position of 3-substituted imidazole-1-oxides is stabilized by an adjacent nitrogen atom which is only partly positive since its charge is being reduced by its negative oxygen atom. Therefore, C-5 is more reactive than C-4 where the negative charge is stabilized by an adjacent, ordinarily positive nitrogen atom. The expected enhanced reactivity of C-5 is denoted with a bar.*

Scheme 5

Similar reasoning applies to C-4 and C-5 of 3-substituted 1,2,3-triazole-1-oxides.

In mesoionic anhydro pyrazolium hydroxides and triazolium hydroxides an enolate fragment is added enhancing the reactivity of the β-positions which are denoted with a triple bar.

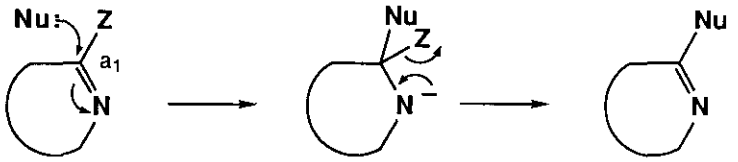
The result of the complete d_1 analysis is shown in Scheme 30. The results are in keeping with the experimental findings of regioselectivity. Thus bromination of 1-methylpyrazole in the presence of excess base -the base preventing protonation which will produce a pyrazolium ion with a different reactivity profile- produces the 4-bromo derivative. Under forced conditions further bromination takes place at the 3- and then at the 5-position.[4] In 1-substituted imidazoles the order of reactivity in bromination is C-4>C-5>>C-2.[5] In 1-substituted 1,2,3-triazoles, the 4-position is more reactive than

* The denotation is based on the assumption that the stabilizing effect of an oxygen substituted nitrogen atoms is midrange between that of a positive and a neutral nitrogen atom. However, the reactivity of the 5-position of 3-benzyltriazole-1-oxide in the bromination reaction described below indicates that an oxygen substituted nitrogen atom is more like a neutral one. Future experiments may therefore be in favor of the use of a double bar.

the 5-position.[6] This also pertains in 3-substituted 1,2,3-triazole 1-oxides.[7] In 2-substituted pyrazole 1-oxides the 3-position is more reactive than the 5-position.[4] In 2-substituted 1,2,3-triazole 1-oxides the 5-position is more reactive than the 4-position.[8] Anhydro 1,2,3-triazolium hydroxides are brominated under mild conditions.[9]

In most cases the denotations reflect the relative reactivity of the neutral, dipolar or charged azole. For example, the 4-position of 1-substituted pyrazoles and the 5-position of 2-substituted pyrazole 1-oxides, both denoted with a triple bar, are brominated at the same rate as demonstrated by competition experiments.[4] However, exceptions exist. Thus in competition experiments, the 5-position of 3-benzyl-1,2,3-triazole-1-oxide denoted with one bar is brominated faster than the 4-position of the parent 1-benzyltriazole denoted with a double bar.[7] The reason for such discrepancies is that only five levels of reactivity are used to describe both regioselectivity and relative reactivity of different species with emphasis on the former aspect. A better discrimination of reactivities will require more levels of denotation.

2.2 Nucleophilic addition elimination

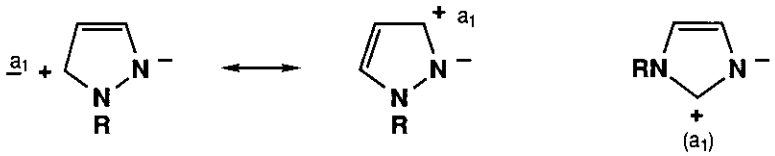


Scheme 6

The group to be eliminated may be a leaving group, like halogen, or it may be a hydride ion as in the Chichibabin reaction, the Ziegler alkylation, or related processes.[10,11]

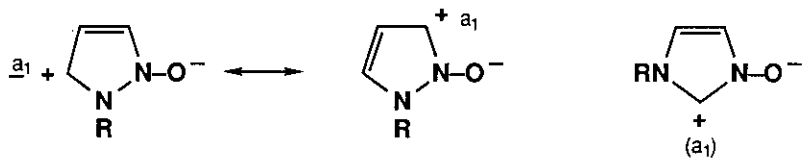
Nucleophilic addition elimination reactions occur at imine carbon atoms, which become positively charged through resonance. These acceptor centers are characterized a_1. The analysis of relative acceptor potential is performed parallel to the donor analysis above by evaluating the inductive stabilization of the positive charge effected by adjacent nitrogen atoms.

In neutral azoles, a positive charge at a ring carbon atom may be stabilized increasingly by a neutral, a negative, or a neutral plus a negative nitrogen atom. The reactivity is expected to decrease in that order. This is denoted with a bar, no bar, or a parenthesis as exemplified in Scheme 7.



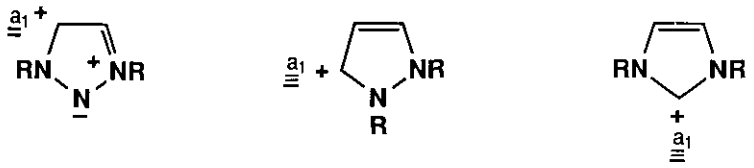
Scheme 7

In azole-N-oxides, a positive charge at a ring carbon atom may be stabilized increasingly by a neutral nitrogen atom, a nitrogen which is partly negative due to oxygen-substitution, or both. The expected decreasing reactivity is denoted with a bar, no bar, or a parenthesis as exemplified in Scheme 8.



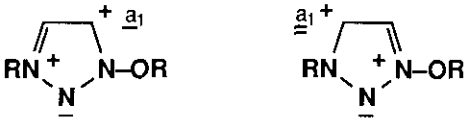
Scheme 8

In azolium ions the resonance structures with positively charged ring carbon atoms may be with or without a negative charge. The latter structures are expected to be more susceptible to nucleophilic attack. The positive charge at ring carbon atoms of the former structures may be stabilized by a neutral nitrogen atom, while in the latter structures one or two neutral nitrogen atoms may be stabilizing. The expected increasing reactivity is denoted with a double bar, a triple bar and -in order to limit the number of bars- again a triple bar, as exemplified in Scheme 9.



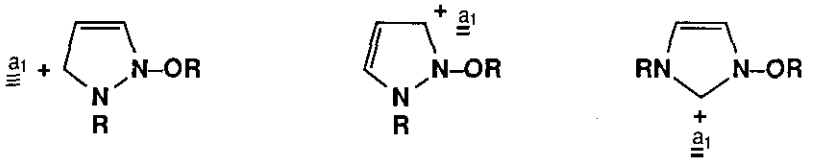
Scheme 9

In N-OR-substituted azolium ions, positively charged ring carbon atoms in resonance structures with a negative charge may be stabilized by an OR-substituted or a neutral nitrogen atom. The OR-substituted nitrogen atom is considered to be weakly negative reducing the reactivity as compared to the corresponding positions in R-substituted azolium ions. Therefore, positions adjacent to N-OR fragments are denoted with only one bar.



Scheme 10

Positively charged ring carbon atoms in resonance structures devoid of negative charge may be stabilized by a neutral, a weakly negative OR-substituted nitrogen atom, or both. The expected reactivity in this series is denoted with a triple bar, a double bar, and a double bar as exemplified in Scheme 11.



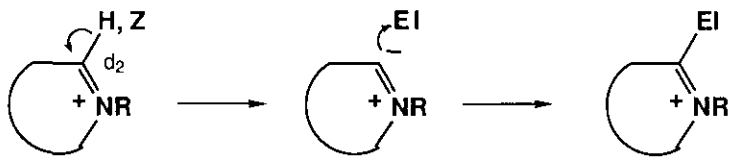
Scheme 11

The ring carbon atoms of mesoionic anhydro pyrazolium hydroxides and triazolium hydroxides are denoted with a single bar according to the rules described above.

The resulting denotation summarized in Scheme 30 is accordant with a series of experimental observations on reactivity and regioselectivity. Thus, halogen at C-5 of 1-substituted 1,2,3-triazoles is subject to nucleophilic substitution with strong nucleophiles at elevated temperatures. In contrast, halogen at C-4 of 1- or 2-substituted 1,2,3-triazoles remains unchanged under similar conditions.[6] The denotation also agrees with the fact that a hydroxy group at C-5 of 1-substituted pyrazoles is more readily displaced by chlorine upon treatment with phosphorous oxychloride than a hydroxy group at C-3. This reaction is initiated by phosphorylation and followed by a rate limiting nucleophilic displacement reaction of the phosphoryl group with chloride ions.[12]

In 2-substituted pyrazole 1-oxides, halogen at the 3-position is more readily displaced by nucleophiles than halogen at the 5-position.[13] In 3-substituted 1,2,3-triazole-1-oxides, halogen at C-4 is more readily displaced than halogen at C-5.[7] In 2-substituted 1,2,3-triazole-1-oxides and 1-methoxy-2-substituted 1,2,3-triazolium ions, halogen at C-5 is more readily displaced than halogen at C-4.[8,14] The activated positions of azolium salts exhibit enhanced reactivity as compared to the neutral azoles as seen in the pyrazole, imidazole and triazole series.[15] Halogen at C-3 and C-5 of pyrazolium ions is readily displaced with nucleophiles while halogen at C-4 first react under extreme conditions and then by a different mechanism.[16] Halogen at C-2 of imidazolium ions is readily displaced with nucleophiles while displacement of halogen at C-4 and C-5 requires extreme conditions.[17] Halogen at C-4 and C-5 of 1,3-disubstituted 1,2,3-triazolium ions reacts with displacement under mild conditions.[18] So does halogen at C-5 of 1,2-disubstituted triazolium ions while halogen at C-5 of these salts is far less reactive.[19] In N-methoxypyrazolium salts, halogen at C-3 is more reactive than halogen at C-5 in nucleophilic displacement reactions.[13] The reactivity of anhydro pyrazolium and triazolium hydroxides in this reaction has not yet been studied.

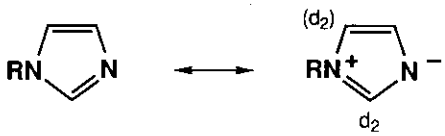
2.3 Reaction of carbanionic centers with electrophiles



Scheme 12

The carbanionic centers may be generated by metalation of halogen-substituted azoles or by deprotonation. Alternatively, the centers may arise by debromination, demethylthiolation, demethylsulfonylation, desilylation, or similar reactions under expulsion of a positively charged leaving group, like a bromonium ion.[15]

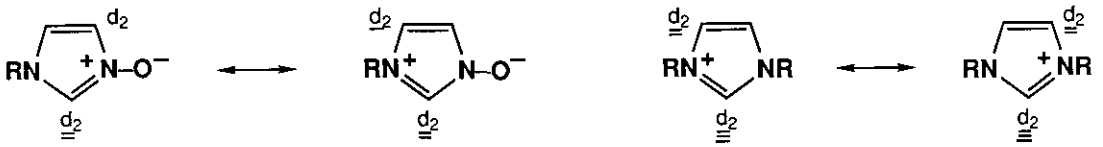
The negative charge at the aromatic nucleus adopts an sp^2-orbital which is coplanar with the ring, therefore the carbanionic center can only be inductively stabilized. In reactions with such anions, their formation is the rate limiting step. Therefore stability of the anions runs parallel with reactivity. The negative charge is better stabilized at imonium than at ammonium carbon atoms. In neutral azoles imonium and ammonium carbon positions of dipolar resonance forms are designated d_2 and (d_2) respectively.



Scheme 13

The resulting notification shown in Scheme 30 is in keeping with the regioselectivity observed by deprotonation of N-substituted azoles and metalation of their halogeno-substituted derivatives. Thus 1-substituted pyrazoles have been deprotonated at the 5- but not at the 4-position.[20] In 1-substituted imidazoles H-2 is more readily abstracted than H-5 while H-4 is resistant to deprotonation.[21] In 1-substituted 1,2,3-triazoles H-5 is more readily abstracted than H-4.[22] 1-Substituted 5-bromopyrazoles are metalated easier than the 4- and 3-bromo-substituted isomers.[23,24] Extensive studies have revealed that in metalation of 1-substituted halogenoimidazoles the reactivity decreases in the order C-2>>C-5>C-4. [25-27]

In N-oxides the negative charge is delocalized at an exocyclic oxygen atom. This increases the polarization and the positive charge at the R-substituted nitrogen atom. Therefore, two bars are added to the designations of the adjacent positions corresponding to those of the neutral azoles. The oxygen-substituted nitrogen atom is less positive. Therefore, only one bar is added at the adjacent positions.



Scheme 14

In azolium ions the positive charge at the nitrogen atoms is further increased. This is denoted by adding three bars to the designations of the neutral azoles.

The positive charges at nitrogen atoms increases in N-oxides and even more in azolium ions. Therefore, imonium and ammonium carbon positions are denoted with a bar and a double bar in N-oxides and with a double bar and a triple bar in azolium ions.

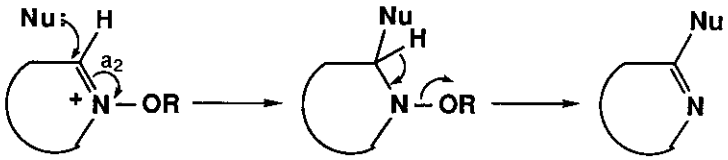
In anhydro pyrazolium and 1,2,3-triazolium hydroxides the negative charge at nitrogen is stabilized by an adjacent positive nitrogen atom. The corresponding expected reactivity is denoted with a bar as above.

The resulting notification shown in Scheme 30 is in keeping with the observation that pyrazole- and triazole-N-oxides are deprotonated more readily than the parent azoles.[7,28] Even the low regioselectivity between the 3- and 5-positions of pyrazole-N-oxides [28] and between the 4- and 5-positions of the two types of triazole-N-oxides [7,29] corresponds to the denotations. Again, the use of only five levels of denotation may lead to discrepancies when comparing reactivity of different species. Thus, the 4-position of 3-substituted triazole 1-oxides, denoted with one bar is more readily deprotonated than the 3-position of the 2-substituted pyrazole 1-oxides, denoted with a double bar.[7,29] On the other hand the denotations of the azolium ions reflect very well the relative acidity of the different positions as determined by deuterium exchange experiments.[15] Generation of carbanionic centers has not yet been reported in the anhydro pyrazolium or triazolium hydroxide series.

N-Alkoxy-, N-acyloxy-, and N-siloxy-substituted azolium ions may undergo a unique nucleophilic addition with elimination of methanol. The acceptor centers in this reaction are identified and characterized as follows:

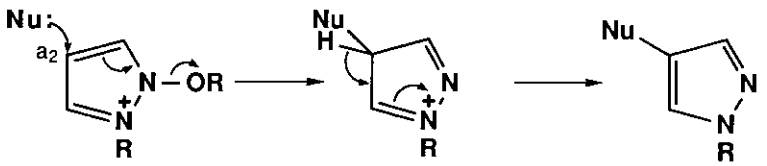
2.4 Nucleophilic addition with elimination of methanol

The centers in this reaction are designated a_2. The sequence may be nucleophilic addition elimination of HOR.



Scheme 15

Alternatively, the mechanism can be envisaged as a 1,3 or 1,5 nucleophilic displacement with $^-$OR as the leaving group, followed by loss of a proton. An example of the 1,3 displacement is shown in Scheme 16.*



Scheme 16

In this process the quaternary nitrogen atom may adopt any ring position.

In practice, it will be difficult to make a distinction between the different order of events. However, the second sequence seems best suited for an analysis of acceptor potential since the initial step is nucleophilic addition and the analysis therefore becomes closely related to that of a_1-centers of N-OR-substituted azolium ions. Thus, a positive charge at the 3- and 5-positions of the pyrazolium ion is inductively stabilized by a neutral or a weakly negative, OR-substituted nitrogen atom. The expected decreasing reactivity is denoted with a triple and a double bar as shown in Scheme 11. There are four exceptions to the analogy between a_1 and a_2 centers, namely the 4-position of pyrazolium ions, the 4- and 5-positions of imidazolium ions, and the 4-position of 1,2-disubstituted 1,2,3-triazolium ions. These positions do not have a_1 character since a positive charge at these

* Conjugation may extend the reactivity to remote positions like the β-position of vinylic substituents or to ortho and para positions of aryl substituents.[13]

positions does not exhibit the necessary stabilization. However, the positions do have a_2 acceptor potential since the nucleophilic displacement of $^-$OR shown in Scheme 16 may be a concerted reaction. The reactivity of these centers has been denoted arbitrarily with a bar. This choice is based on the observation that the 4-position in the N-OR-substituted pyrazolium [13] and the 1,2-disubstituted 1,2,3-triazolium ions [8,14] is less reactive than the remaining positions.

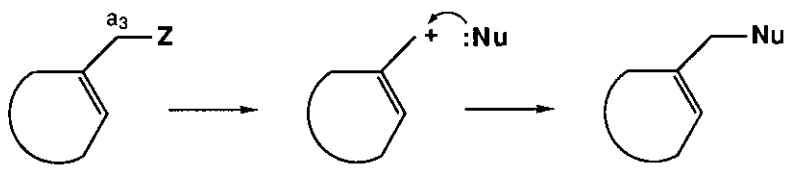
The result of the characterization presented in Scheme 30 agrees with the fact that the 3-position of 1-OR-substituted 2-benzylpyrazolium salts is more reactive than the 5-position.[13] More examples of confirmation of predicted regioselectivity wait for experimental testing.

3. Reactivity at the α–position of side chains *

The α–position of side chains in heteroaromatics may take part in (i) S_N1 type nucleophilic aliphatic substitution and (ii) generation of a carbanionic center which react with an electrophile. Quaternary azolium ions may also react by (iii) N-dealkylation. If N-OR-substituted they furthermore may react by (iv) elimination of HOR followed by nucleophilic addition, and (v) loss of a proton from the α-position of the N-OR alkyl group followed by elimination of a carbonyl compound. The reactive centers in these processes can be characterized by a notation including three acceptor types and two donor types.

3.1 S_N1 type nucleophilic aliphatic substitution

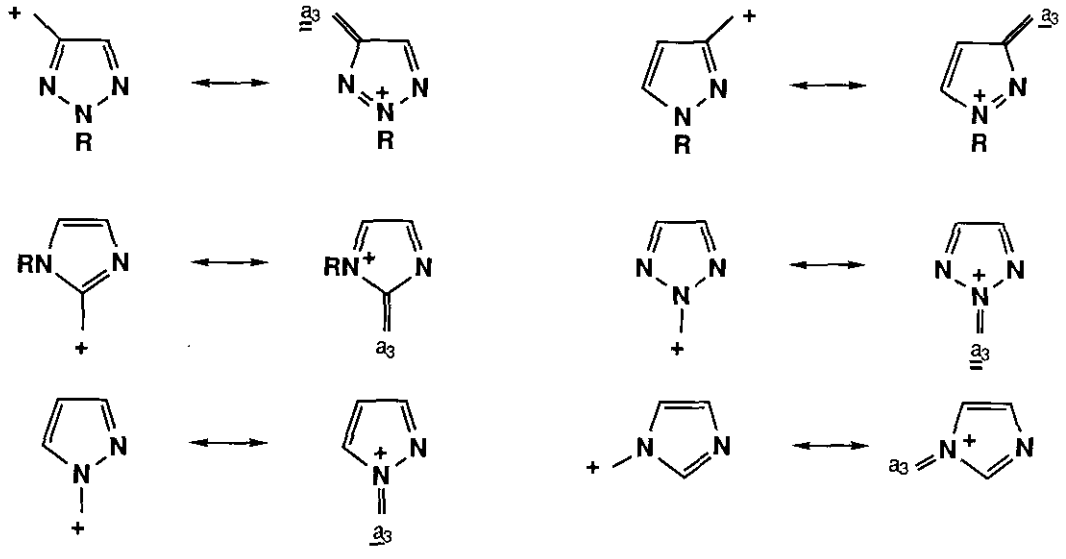
In S_N1 type nucleophilic aliphatic substitution the reactive center is designated a_3.



Scheme 17

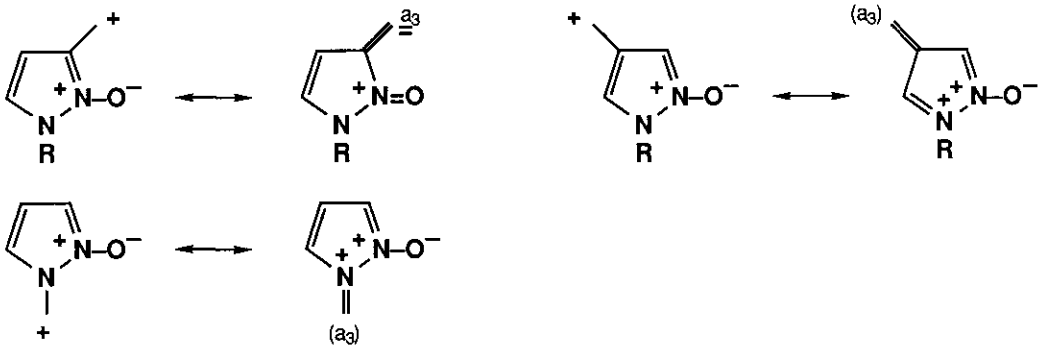
* For reasons of simplicity only α-positions are discussed. However conjugation may extend the reactivity to remote side chain positions.

Z may be a leaving group, like halogen. If the positive charge is mesomerically delocalized only on carbon atoms the reactivity is expected to be similar to that of a benzyl carbocation. Only positions at which the positive charge is further stabilized by delocalization to a nitrogen atom are designated a_3. Substituents at both carbon and nitrogen may possess a_3 character. In neutral azoles the positive charge at nitrogen may be decreasingly stabilized by two, one or no adjacent neutral nitrogen atom. The reactivity is expected to decrease in the same order since in S_N1 type nucleophilic substitution stability of the intermediate carbocation runs parallel with reaction rate. The three levels of the a_3 center are denotated with a a double, a single, and no bar.



Scheme 18

In azole-N-oxides the positive charge at certain exocyclic α-positions may be stabilized by delocalization to the N-oxygen atom. This is expected to enhance stability and hence reactivity. Therefore, a bar is added to such positions. The positive charge at certain exocyclic α-positions may be delocalized to nitrogen atoms adjacent to the weakly positive, oxygen-substituted nitrogen atom. The low stabilization and low expected reactivity is denotated with a parenthesis.

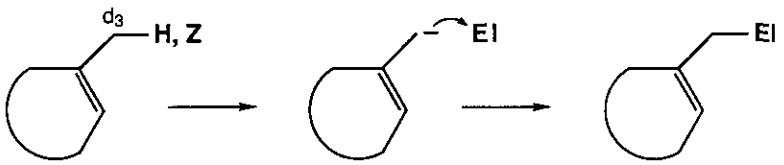


Scheme 19

It is anticipated that azolium ions do not possess a_3 centers since this would give rise to a double positively charged species. The resulting notification is shown in Scheme 31. The reported S_N1 type nucleophilic substitution reactions of azoles seems too scarce to allow a trustworthy comparison between predicted and observed reactivity.

3.2 Reaction of α-situated exocyclic carbanionic centers with electrophiles

The reactive center in these processes is denotated d_3.



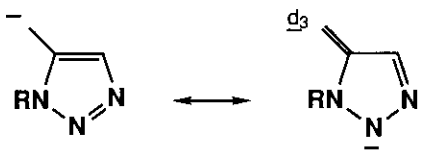
Scheme 20

The centers may be generated in the same way as d_2-centers. Another analogy with the d_2-centers is that stability and reactivity run parallel. If the negative charge is mesomerically delocalized only on carbon atoms the reactivity is expected to be similar to that of a benzyl carbanion. Positions are only accepted as d_3-centers if their negative charge is further stabilized by delocalization to a nitrogen atom. Substituents at both carbon and nitrogen may possess d_3 character.

The most stable anions are derived from azolium ions in which the negative charge is cancelled by the positive with formation of a neutral species. Such d_3-centers are denoted with a triple bar. Positions of N-oxides in which the negative charge is adopted by a weakly positive oxygen-substituted nitrogen atom are denoted with a double bar.

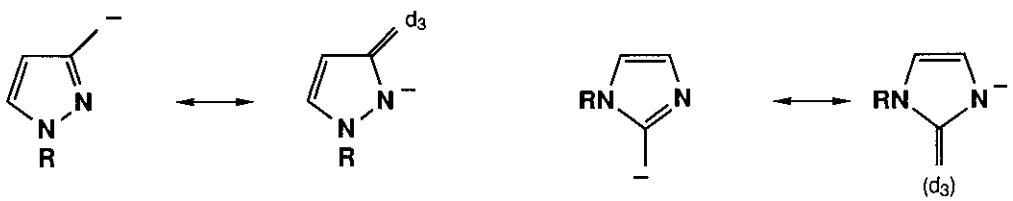
Scheme 21

If the negative charge at nitrogen is inductively stabilized by two nitrogen atoms the position is denoted with a single bar. One of the stabilizing nitrogen atoms is neutral while the second may be positive, oxygen-substituted, or neutral.



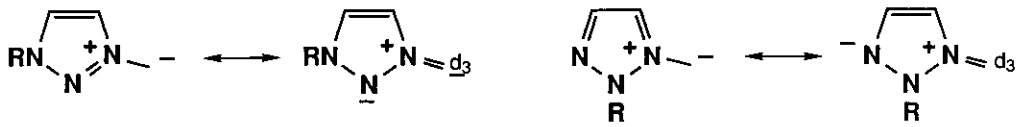
Scheme 22

When the negative charge at nitrogen is stabilized by one or no neutral nitrogen atoms, no bar or a parenthesis is used.



Scheme 23

A negative charge at the α-position of N-substituents may be delocalized to a nitrogen atom where it may be stabilized by a positive or an adjacent neutral nitrogen atom. This is denoted with a single or no bar.



Scheme 24

The complete assignment of d_3-centers is shown in Scheme 31. A contradiction between prediction and experimental evidence pertains for 1,5-dimethylpyrazole which is deprotonated at the N-methyl group not predicted as a d_3 center and apparently not at the 5-methyl group, denoted d_3.[21] However, reported data suitable for checking the correspondence between predicted and observed reactivity are still too scarce to be conclusive.

3.3 N-Dealkylation

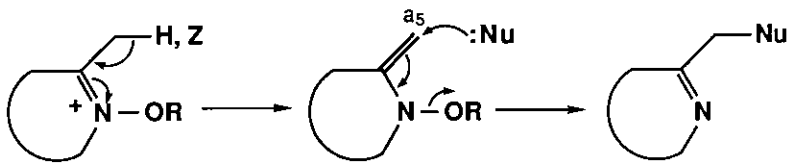
The reactive center in dealkylation of quaternary salts is denotated a_4.

Scheme 25

The relative reactivity in dealkylation reactions is expected to depend on the stability or the basicity of the leaving group, i. e. the neutral N-substituted azole. An analysis of the relative stability of the N-substituted azoles has not been invoked here since a quantitative measure for their basicity is readily accessible.[30] Apparently, no systematic study of the dealkylation of azolium salts has yet been carried out.

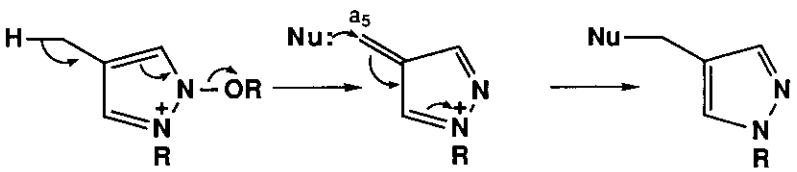
3.4 Elimination of HOR followed by nucleophilic addition

The sequence may be generation of an N-OR-substituted enamine fragment followed by nucleophilic addition and elimination of $^{-}$OR. The reactive centers are denoted a_5 since the azole serves as an acceptor in the product determining step.



Scheme 26

Alternatively, the mechanism can be envisaged as a 1,4 or 1,6 elimination of HOR followed by nucleophilic addition. An example of the 1,4 elimination is shown in Scheme 27.



Scheme 27

This sequence is feasible with the quaternary nitrogen atom situated at any position in the ring.
In practice, it will be difficult to discriminate between the different order of events. However, the latter sequence seems best suited for the analysis of relative reactivity. While the center reacts as an acceptor it is created as a carbanionic donor. Assuming that generation of the anion is the rate limiting step * the analysis of reactivity becomes closely related to the analysis of d_3-centers.
The d_3 properties of 4- and 5-substituents of 1,3-disubstituted 1,2,3-triazolium ions are identical. In the N-OR-substituted triazolium ions, a negative charge at the α-position of a 4-substituent is stabi-

* The intermediate methylene compounds have never been detected when following this kind of reactions by nmr-spectroscopy.[29]

lized by a neutral and a weakly positive, OR-substituted nitrogen atom. A negative charge at the α-position of a 5-substituent is better stabilized, namely by a positive and a weakly negative, OR-substituted nitrogen atom. The expected regioselectivity between the two positions is denoted with a bar and a double bar.

Scheme 28

The 4-position of pyrazolium ions, the 4- and 5-positions of imidazolium ions, or the α-position of substituents at ring nitrogen atoms do not have d_3 character since a negative charge at these positions can not be delocalized to a ring nitrogen atom. However, the positions have a_5 character since the elimination of $^-$OR shown in Scheme 27 may be a concerted reaction. The reactivity of these centers has been denoted arbitrarily with a bar.

The result of the complete a_5 analysis presented in Scheme 31 is in harmony with experiments demonstrating that in 2-substituted 1-acetoxy- or 1-siloxypyrazolium salts methyl groups both at C-3 and C-5 are susceptible to attack in this reaction.[29] The reactivity of a 4-methyl group is unknown. In 2-substituted 1-methoxy-1,2,3-triazolium salts a methyl group at C-5 is more reactive than one at C-4.[14] The 1-acetoxy-2-methyltriazolium ion is attacked by chloride and acetate ion at both C-5 (an a_2 reaction) and at the N-methyl group (an a_5 reaction).[31]

3.5 Deprotonation followed by elimination of a carbonyl compound

The reactive center is denotated d_4 since deprotonation most likely is the rate limiting step.

Scheme 29

The result of the designation of exocyclic α-positions is shown in Scheme 31. No ranking has been made since the process is regioselective by nature. Furthermore, the deprotonation rate is not expected to be significantly influenced by the remote heteroaromatic ring. The reaction has been verified in 2-substituted 1-methoxypyrazolium salts [13] and 1-methoxy-1,2,3-triazolium salts.[8,14]

4. Conclusion

The reactivity in ionic processes of the ring carbon atoms of heteroaromatics with fixed structure can be described in a simple and versatile way in terms of two acceptor and two donor types, ranked in five levels. The characterization shown in Scheme 30 makes a basis for prediction of regioselectivity in the individual species. The characterization allows a good estimate of relative reactivity between different species and even assessment of the outcome when different reaction types compete. Analogously, the reactivity of exocyclic α-positions can be delineated in terms of four acceptor and two donor types, ranked in five levels as seen in Scheme 31. The characterization is confirmed by many experiments.

ACKNOWLEDGEMENT

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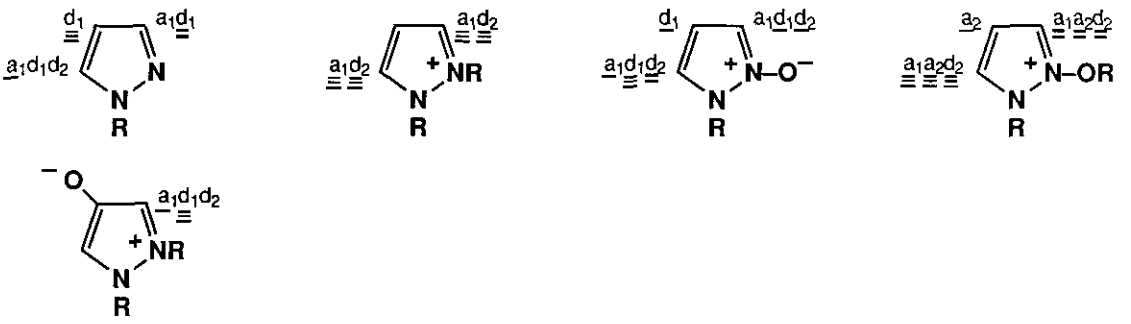
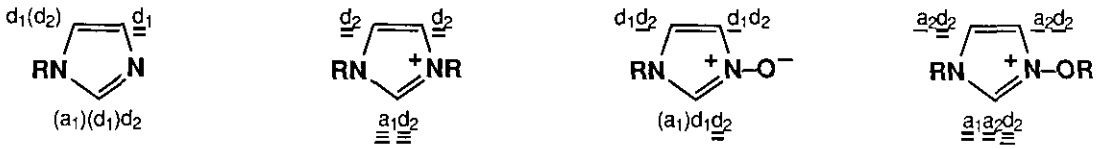
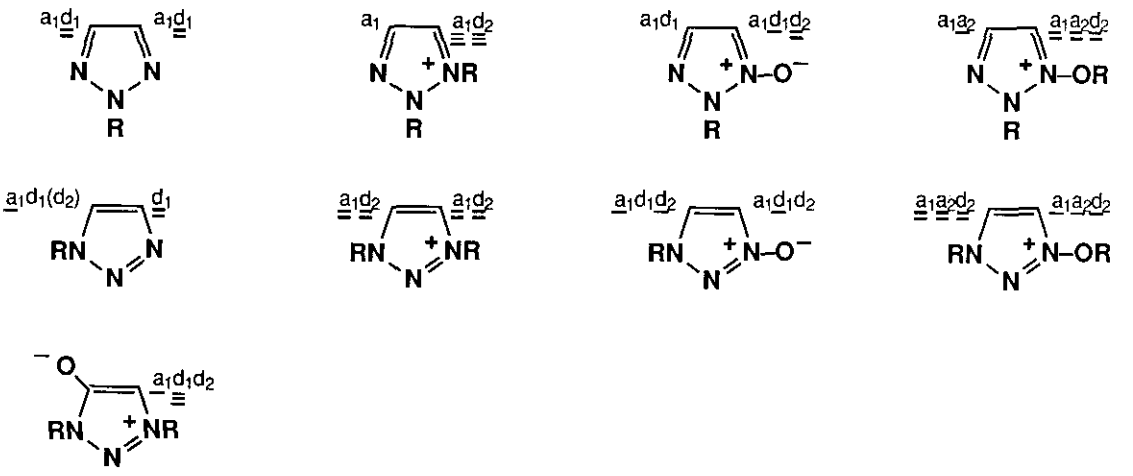
N-Substituted pyrazoles:



N-Substituted imidazoles:

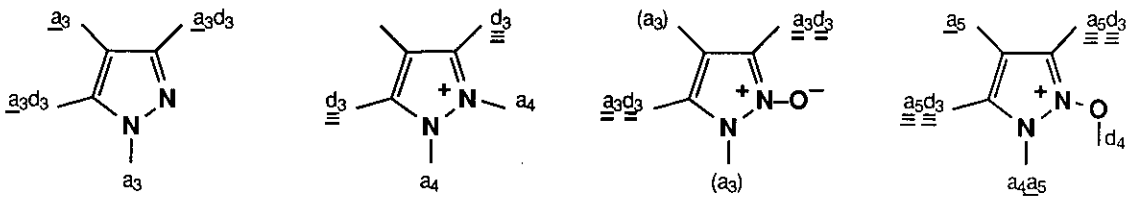


N-Substituted 1,2,3-triazoles:

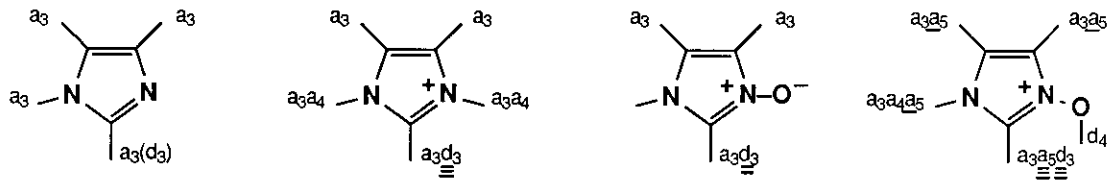


Scheme 30

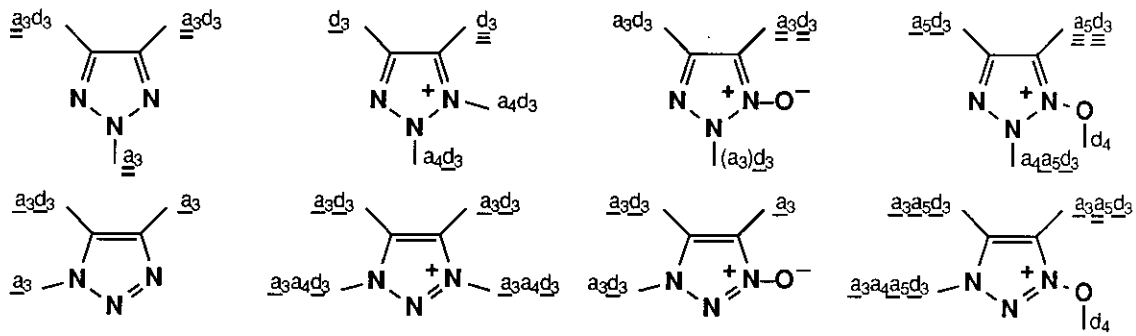
Exocyclic α-positions in N-substituted pyrazoles:



Exocyclic α-positions in N-substituted imidazoles:



Exocyclic α-positions in N-substituted 1,2,3-triazoles:



Scheme 31

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