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REGIOSELECTIVITY OF THE REACTIONS OF PYRIDINIUM AND QUINOLINIUM SALTS WITH VARIOUS NUCLEOPHILES (REVIEW)

I. S. Poddubnyi

The factors determining the regioselectivity of nucleophilic addition to pyridinium and quinolinium cations are examined. Published data of the last 15 years are summarized.

In the present review the regioselectivity in nucleophilic addition to various pyridinium and quinolinium salts and also the related substitution, ring opening, and recyclization reactions, which take place through a stage involving the addition of a nucleophile to a cation, are examined [1-7]. In some papers [1,6,8-16] only isolated aspects of this problem were examined, while in [17-19] brief summaries of the literature on some reactions of pyridinium salts and their analogs with various nucleophilic reagents were given without discussion of the regioselectivity of these transformations. Recently there was a review [20] devoted to functionalization of the pyridine ring. Here the problems of regioselectivity during nucleophilic addition (substitution) were discussed briefly and only for examples of C-nucleophiles. The present review is devoted to an analysis of the factors that determine the regioselectivity of the addition not only of C-nucleophiles but also of heteronucleophiles to pyridinium and quinolinium cations.

Without touching in detail on the lively discussion about the mechanism of the addition of nucleophiles to pyridinium cations [6,8,21-30], we focus attention on the most general and fundamental relationships for this type of reaction and on the factors that give rise to the selectivity in such transformations. Examination of the numerous examples of nucleophilic addition (substitution) involving isoquinolinium and benzoquinolinium salts is intentionally omitted, since such reactions take place at the most electrophilic position 1 of the isoquinolinium cation or at the corresponding free position in benzoquinolinium salts [1,2,6,17-19,31-34]. The following abbreviations will be used: DHP, dihydropyridine; DHQ, dihydroquinoline; Py^+, pyridinium salts; Qu^+, quinolinium salts.

1. GENERAL ASPECTS

Problems associated with the regioselectivity in nucleophilic addition (substitution) reactions, in which pyridinium salts act as activated electrophilic substrates, have for many years been and still remain the subject of various theoretical [1,8,10,11,14-16,20,21,35] and experimental [9,23,25,36-41] investigations. Nevertheless in the scientific literature there has not yet been a consensus of opinion on the reasons and the factors giving rise to regioselectivity or its absence in this type of reaction [1,8-11,14-16,35,40,42].

The contradictions and differences of opinion were due partly to doubts about the fundamental question as to whether the distribution of the isomeric reaction products results from kinetic control of the process or is due to possible isomerization of the less stable isomers into thermodynamically more stable products [16,42]. Thus, it became necessary to draw a clear distinction between the concepts of kinetic regioselectivity, which characterizes irreversible or kinetically controlled reactions, and thermodynamic regioselectivity, which applies to reversible and thermodynamically controlled processes [15,16]. However, the differentiation of these key concepts did not remove and does not remove the fundamental question of the reasons for the selectivity in irreversible and kinetically controlled reactions, i.e., the reasons for kinetic control of the regioselectivity.

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One of the first attempts to explain the factors that determine the selective occurrence of this type of reaction was Kosower's theory [8,43], which postulates that nucleophiles with a low ionization (oxidation) potential, which form a charge-transfer complex (CTC) with the pyridinium cation at the first stage of the reaction, add selectively at the γ position of the heterocycle. At the same time nucleophiles that do not form a CTC with pyridinium cations add mainly at the α positions of the ring. More recently it was demonstrated that practically all nucleophilic reagents that form CTCs with pyridinium cations, such as $S_2O_4^{2-}$ [8,13,43,44], indoles [43], the anions of nitromethane and its substituted derivatives [40,45], PhS^- [40], and the enolate anion of acetophenone [8,43], add exclusively or preferentially at the C-4 atom of the cycloammonium salt [2,8,12,13,29,37,46,47]. These data confirm Kosower's idea that the CTC may be the transition state that gives rise to the specific γ-addition of the nucleophiles [43].

An alternative to Kosower's theory is provided by the views of other authors [9,11,16,48], who suppose that the selectivity or nonselectivity during the addition of nucleophiles to pyridinium and quinolinium cations depends on the relative electron density at the attacked electrophilic carbon center, which is as a rule lower at the α-carbon atoms than at the γ position [6,9,22,28,35,48,50]. Such reactions, which are controlled by charge, must lead preferentially to the products from α-addition or be nonselective, if the charges at the C-2 and C-4 atoms are similar in magnitude [9,28,35,49]. The theory of charge-controlled reactions gives a satisfactory explanation in the case of the addition of most O- and N-nucleophiles and of certain C-nucleophiles, which under the conditions of kinetic control form the α-addition products preferentially [1,3-7,11-13,28,36,39,51,52]. However, this theory is quite unable to explain the high γ-regioselectivity in many irreversible reactions involving C-nucleophiles [12-15,17-20,34] and certain metal hydrides [18,24] or a series of reversible reactions that take place under the conditions of kinetic control [15,37,46].

The third most modern hypothesis that attempts to explain the reasons for regioselectivity or its absence in nucleophilic addition reactions is based on the concept of "hard" and "soft" acids and bases (the HSAB concept), proposed by Pearson [53,54] and developed in detail by Klopman and Hudson [35,49,50,55]. As applied to the reactions involving pyridinium and quinolinium cations the following postulates were advanced: "Hard" nucleophiles (general bases) with low polarizability react more quickly with the α-carbon centers of the cation, which are more "hard" acid centers than the electrophilic center C-4. "Soft" nucleophiles with high polarizability attack selectively at the most "soft" γ position of the pyridinium (quinolinium) cation [35,49,50].

The HSAB concept and the theory of reactions controlled by charge or by interaction of the frontier orbitals emerging from it [35,50,55] make it possible to explain satisfactorily the reasons for the selectivity during nucleophilic addition reactions starting from the classification of hard and soft acids and bases proposed by Pearson [53,54]. Perhaps the clearest example of the application of HSAB theory is the explanation of the regioselectivity in the reactions of organometallic compounds with various electrophiles, including pyridinium cations [56,57]. However, we note that the classification of nucleophiles into "soft," "hard," and "intermediate" [53,54,56] as applied to the reactions is largely based either on individual quantum-chemical calculations [35,49,50] or on the results from the experimentally obtained distribution of 1,2- and 1,4-DHP in reactions of the type under discussion [56-61]. In a number of cases the purely speculative proposals about the "hardness—softness" of certain organometallic nucleophiles have been confirmed by experimental data [57,60].

Thus, there are in the literature no unified substantiated criteria for the definition of the "hardness" or "softness" of nucleophiles or of the corresponding electrophilic centers, although in a number of cases such criteria could be provided by the standardized one-electron oxidation and reduction potentials for nucleophiles and electrophiles respectively [29]. There is no doubt that the one-electron oxidation potential (E_{ox}^0) indicates the ability of a reagent to give up an electron to an oxidizing agent (electrophile) and can serve as a test of its "softness." It should be noted that the ability of a nucleophile to form a CTC during reaction with the pyridinium cation can also be regarded as the ability to undergo one-electron transfer and, consequently, as direct evidence for the "softness" of this nucleophile. Furthermore Klopman emphasized [35] that there are no fundamental contradictions between the HSAB concept and the Kosower CTC theory, since "soft" nucleophiles are the most suitable for the formation of a CTC.

In principle, none of the examined theories defines the stage mechanism of the addition of nucleophiles to pyridinium cations in detail, although it follows from the general context of these concepts that the theory of the charge control of reactions implies addition of the nucleophile by a polar (ionic) mechanism. It follows from the postulates of other theories that the most likely in the case of the addition of "soft" nucleophiles is a mechanism involving a specific transition state of the CTC type or an analogous π complex between the nucleophile and the electrophile [8,35,43,49] and, possibly, taking place through a stage of single-electron transfer (the SET mechanism).

If the results from quantum-chemical calculations by various methods [21,22,28], which predict the highest spin density for the γ position of 1-alkyldihydropyridyl and dihydroquinolyl radicals and the maximum positive charge for the α positions of the corresponding Py^+ and Qu^+ cations, are taken into account it can be concluded that the SET mechanism of the reaction with nucleophiles gives rise to γ-selectivity during the addition to cations [6,10-13,15,21,23,24,26,29,49], whereas the polar [24,27,28,30,62] or alternative mechanism of first-sphere electron transfer [27,28] is characteristic of α-selective addition. The possibility that a different mechanism from those indicated above or a mixed (combined) mechanism is realized in the given transformations is not ruled out. In any case the highly regioselective addition of the nucleophile to the cation presupposes the presence of a specific transition state, which may be either a CTC (a π complex) [1,6,8,12,37,40,43,44], a first-sphere complex [27,28], a different complex [29,30,63-66], or a radical (ion) pair.

To summarize all the foregoing it can be stated that the kinetic γ-regioselectivity of the given type of reaction is determined, on the one hand, by the ability of the nucleophile to undergo single-electron transfer to the pyridinium cation and, on the other, by the ability of the pyridinium or quinolinium cation to accept an electron (reduction) and its delocalization among the electrophilic centers. Here the CTC between the reagents acts as one of the possible transition states that determine the selective γ-addition. If, however, the nucleophilic reagent is incapable of the transfer of a single electron and reacts by a polar (ionic) mechanism [24,27,28,30] or by a first-sphere electron transfer mechanism [27,28], selective α-addition as a rule occurs. Nonselective addition probably takes place in the case where the nucleophile is capable of reacting by the mixed radical—polar mechanism characteristic of certain C-nucleophiles.

2. THERMODYNAMIC REGIOSELECTIVITY

This type of regioselectivity, which applies to thermodynamically controlled processes, is only characteristic of reversible nucleophilic addition reactions or, at least, reactions in which addition of at least at one of the α or γ positions of the pyridinium salt is reversible. Among transformations of the second type it is possible to mention the reaction of pyridinium and quinolinium cations with the hydroxide ion [1,4,5,7,10,67-69], with primary and secondary amines [1,4,5,18,69,70], with hydrazines [1,3,7,19,71,72], and with the anions of certain CH acids [5,15,41,42,73,74]. In such reactions the stage of the addition of the nucleophiles at the α position of the cation can be regarded as irreversible, since the obtained 1,2-DHP or 1,2-DHQ undergo rapid ring opening (or oxidation) under the influence of the base with the formation of more stable products — derivatives of glutaconaldehyde [1,3-5,10,17-19,42,67-74] or oxidation or recyclization products [5,7,15,41,73].

The preferential formation of the thermodynamically most stable product depends only on the factors that determine the stability of the products or isomers [9,16,62]. The factors that give rise to stability in the σ-adducts from the addition (1,2-, 1,6-, or 1,4-DHP and 1,2- or 1,4-DHQ) include both the nature and the position of the substituents in the heterocycle, including those at the nitrogen atom, and the nature of the added nucleophile. In the general case, increase in the accepting characteristics of the substituent at the cyclic nitrogen atom helps to increase the stability of both 1,2- (1,6-) and 1,4-dihydropyridine systems [5,6,12,13,75]. However, it also promotes more ready opening of the 1,2-dihydropyridine ring in the case of the addition of the OH^- ion [1,4,5], hydrazines [1,3-5], primary and secondary amines [1,4,5,10,70], and the anions of certain CH acids [5,42,74]. For instance, the presence of a strongly accepting N-substituent is an essential condition for Zincke—König cleavage [1,4,5,69,70], recyclization under the influence of alkalis, amines, and anilines [5,7,76,77], and cleavage under the influence of alkalis, hydrazines, and methylene-active compounds [1,3-5,69,71-74].

Accepting groups at the β position of azines [5,6,12,13,75] and condensed benzene rings [2,6,31,78] have the very strong ability to stabilize both 1,2- (1,6-) and 1,4-dihydropyridine systems. Here it must be emphasized in particular that in the case of 1-alkyl-substituted pyridines and quinolines the stabilizing effect of a β-substituent with strong accepting characteristics (e.g., $CONH_2$, CO_2R, COR, NO_2, CN, etc.) determines the greater thermodynamic stability of the 1,4-DHP and 1,4-DHQ systems compared with the 1,2-isomers, which as a rule does not depend on the nature of the added nucleophile (H^-, OH^-, RO^-, RNH_2, RR^1NH, RS^-, CN^-, $ROCCH_2^-$, aromatic C-nucleophiles, the anions of CH acids) [9-13,15,24,36,38,39,41,79-82].

For monosubstituted 1-alkyl- and 1-arylpyridinium and 1-alkylquinolinium cations both theoretical calculations [16,39] and experimental data [13,39,83,84] indicate higher thermodynamic stability for the 1,2-adducts with O- and N-nucleophiles. This is explained by the general anomeric effect of the oxygen or nitrogen atom, which stabilizes the 1,2-dihydropyridine system [16]. Analogous enhanced stability of the 1,2-dihydro adducts is also characteristic of 1-alkyl- and 1-aryl-substituted heterocycles carrying a donating or weakly accepting substituent at position 3 [13,36,39]. In the light of data in [16] the more

TABLE 1. Some Examples of Thermodynamically Controlled Regioselectivity in Nucleophilic Addition to Py^+ and Qu^+ Cations

Nucleophilic reagent	N-Substituent and cation	Other substituents	Yield, %	Ratio of 1,2- and 1,4-DHP	Reference
CBr_3^-	1-EtPy$^+$, 1-DCB-Py$^+$ [a)]	—	—	0 : 100	[88]
CCl_3^-	1-DCB-Py$^+$ [a)]	—	—	0 : 100	[88]
Cyclohexanone anion	1-$RC_6H_4Py^+$ [b)]	—	—	< 5 : 95	[86]
O_2NCHR^- [c)]	1-Alkyl -Py+	3-R^1, 3,5-R_2^1	Quant.	0 : 100	[37]
$O_2NCMe_2^-$	1- Alkyl -Py$^+$	3-$CONH_2$	Quant.	0 : 100	[29]
RS^- [d)]	1-MePy$^+$	3,5-R_2^1	Quant.	< 5 : 95	[47, 91]
CN^{-1}	1-CH_2R-Py$^+$ [e)]	3-R^1 [e)]	Quant.	0 : 100	[81]
CN^- [f)]	1-$RC_6H_4CH_2Py^+$	3-$CONH_2$	Quant.	0 : 100	[23]
CN^-	1-$RC_6H_4Py^+$ [b)]	—		0 : 100	[85]
OH^-	1-$RC_6H_4Py^+$ [b)]	—	Quant.	100 : 0	[67]
OH^-	1-MeQu$^+$	3-R, R = H, Br	Quant.	99 : 1	[39]
MeO^-	1-$RC_6H_4Py^+$ [b)]	—	—	100 : 0	[83]
MeO^-	1-MePy$^+$	3-CN	Quant.	20 : 80	[36]
MeO^-	1-MePy$^+$	3,5-Cl_2	Quant.	68 : 32	[36]
$S_2O_4^{2-}$ / H_2O	1-(*p*-$RC_6H_4CH_2$)Py$^+$	3-R^1 [g)]	39...88	0 : 100	[13, 95]
Indole	1-PhOCPy$^+$	—	53	100 : 0	[89]
NH_3 / $KMnO_4$	1-MePy$^+$	—	—	100 : 0	[52]
NH_3	1-(CH_2CO_2Et)Qu$^+$	—	90	100 : 0	[84]

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a) DCB — 2,6-dichlorobenzyl.

b) R = H, 4-Me, 3-Me, 4-Br, 3-Cl, 3-NO_2, 4-NO_2.

c) R = H, Me, R^1 = CN, Cl, NO_2.

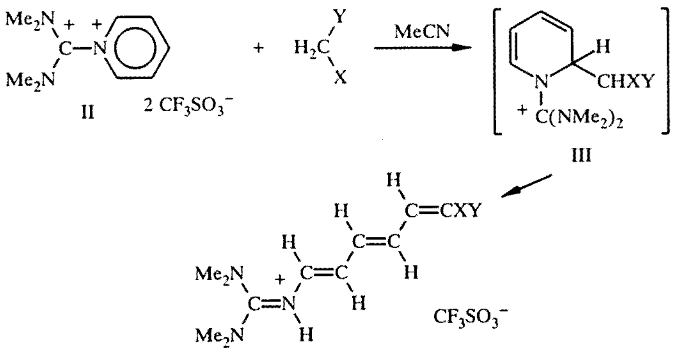
d) R = *t*-Bu, CH_2Ph, Ph, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$, R^1 = CONHEt, $CONEt_2$, $CONAlk_2$.

e) R = Me, Et, CH_2Ph, R^1 = $CONH_2$, H, CN; 3,5-Cl_2, 3-CO_2Et-5-Br.

f) 4-R = MeO, Me, H, F, Cl, CO_2Me, CN, NO_2.

g) R = NMe_2, OMe, Me, H, F, Cl, CO_2Me, CN, R^1 = $CONH_2$, CN.

significant thermodynamic stability of the 1,4-adducts of various C- and S-nucleophiles with 1-alkyl-, 1-aryl-, and 1-acylpyridinium and 1-alkyl-, 1-aryl-, and 1-acylquinolinium cations [13,15,30,48,62,73,81,85-88] is explained by the absence of the anomeric effect only characteristic of the adducts with O- and N-nucleophiles. However, it has already been mentioned above that if the accepting character in the N-substituent is sufficient the 1,2-adducts of certain CH acids are capable of undergoing further irreversible transformations, shifting the position of the equilibrium toward the most stable products [5,42,73,74,89] as, for example, in the syntheses of azahexamethineneutrocyanines I from the 1-(tetramethylformamidinio)pyridinium salt (II) [42,74]:



I up to 96%

Investigations by PMR spectroscopy have shown that with kinetic control the addition of the anions of dimedone and malononitrile leads with excellent regioselectivity to the respective 1,4-DHP derivatives, and the latter are transformed after

60 h at room temperature into the ring opening products through 1,2-DHP [42,74]. The reactions are typical examples of the competition between thermodynamic and kinetic selectivity. However, many transformations in which the products from thermodynamic and kinetic control coincide are found in the literature [3-6,12,13,23,24,30,36,39,52,67,81,83,85,86]. Apart from the cleavage and recyclization reactions it is possible to mention the selective addition of the anions of nitromethane and its derivatives [37,46,90], dithionite and sulfite anions [5,12,13,24], thiolate ions [46,47,91], the anions of cyclohexanone and certain CH acids [73,80,86,92,93], and tribromo- and triiodomethylcarbanions [88]. Examples of reactions with identical thermodynamic and kinetic control are given in Table 1. We note, however, that the isomerization of certain products to other thermodynamically more stable products is possible for some irreversible addition reactions. For example, the isomerization of 1,2-DHP and 1,2-DHQ to the 1,4 isomers was detected during the reduction of the respective cations by the action of sodium borohydride [38,94] or tributylstannane [30]. Consequently, it is possible to speak of the thermodynamic distribution of the products for such reactions, since the conditions of isomerization can coincide with the reaction conditions [30,38]. On the whole the process conditions play a significant role in the reversible reactions, since they determine the ratio of the kinetically and thermodynamically controlled products and, consequently, the regioselectivity of the transformation [48,62,78,88]. While discussing the thermodynamic selectivity, we will only consider the main components and features of the reaction conditions that make it possible to reach thermodynamic equilibrium.

Increase in temperature and increase in the reaction time are among the most effective and most often employed means of realizing thermodynamic control [15,25,36,42,48,82,86]. There is much information on the successful use of such polar aprotic solvents as acetonitrile, dimethyl sulfoxide, tetrahydrofuran, and dimethylformamide for this purpose [13,15,41,81, 87,88,96-102], whereas the use of nonpolar or weakly polar aprotic [9,13,81,86] or polar protic [13,15,41,88,96,98,103-105] solvents as a rule prevents isomerization of the 1,2-DHP and 1,2-DHQ to the more stable isomers. The bimolecular isomerization of 1,2-DHP and 1,2-DHQ to the 1,4 isomers under the influence of the respective cation is also well known [38,94]. Such isomerization can be used on the preparative scale for the conversion of the mixture of isomers into the 1,4-dihydro isomer.

Thus, the thermodynamic regioselectivity and the associated thermodynamic control of the reaction play a key role in this type of reversible reaction or in irreversible processes, where rapid isomerization to a more stable product is possible. By varying the reaction conditions and the type of nucleophilic reagent it is possible to obtain the desired thermodynamic distribution of the isomers simply and with high regioselectivity. Thermodynamic control of the discussed reactions plays a special role in one-pot syntheses of various alkaloid systems, in which the key stage is the addition of the stabilized carbanions to 1-alkylpyridinium salts [15,25,41].

3. KINETIC REGIOSELECTIVITY

Usually this type of selectivity applies to irreversible nucleophilic addition reactions, although it can also be considered quite legitimately for reversible reactions, if special kinetic investigations of the transformations at the initial stages of addition or under the conditions of kinetic control are undertaken. A limited number of such investigations that make it possible to speak unambiguously of kinetic α- or γ-selectivity during nucleophilic addition in reversible processes are known. For example, high kinetic α-selectivity has been demonstrated during the addition of the hydroxide ion to 1-arylpyridinium [67] and 1-alkyl-3-R-quinolinium [39] salts, of the methoxide ion to 1-arylpyridinium [83] and 1-alkyl-3,5-dichloropyridinium [36] salts, of the nitromethane anion to the 1-methyl-3-methoxypyridinium cation [46], of NH_2^- to various 1-alkyl- and 1-aryl-3-R-pyridinium cations [51, 106], of the cyanide ion to mono-, di-, and trisubstituted 1-methylquinolinium salts [48] or to certain 1-alkyl-3,5-R,R′-pyridinium cations [9,96], and of the trichloromethylcarbanion to 1-ethyl- and 1-(2,6-dichlorobenzyl)pyridinium cations [88] and to various substituted 1-alkylquinolinium salts [62]. Also well known is the exclusive 1,6-addition of piperidine to 3-substituted 1-alkylpyridinium cations [13,103] and the α-addition of alkoxide ions or N-nucleophiles to 1-alkyl-3-R-pyridinium [13, 98] and 1-alkyl-3-carbamoylquinolinium salts [82] respectively. Strong kinetic γ-regioselectivity during addition was also detected in the following reactions: The addition of the anions of nitromethane and its substituted derivatives to various 1-alkyl- and 1-arylpyridinium [29,37,46,90,92] and 1-alkylquinolinium [29,90,93] salts; the addition of cyanide ion to 1-arylpyridinium [85] and 1-benzyl-3-carbamoylpyridinium [23] salts and to mono-, di-, and trisubstituted pyridinium cations [81]; the addition of the anions of acetone, cyclohexanone, methyl acetoacetate, and methyl malonate to 1-arylpyridinium salts [73,86]; the addition of the anions of dimedone and malononitrile to the 1-(tetramethylamidinio)pyridinium II and quinolinium cations [42,74]; the addition of tribromo- and triiodomethylcarbanions to 1-alkylpyridinium salts [88]; the addition of EtS^- to 1-alkyl-3-

TABLE 2. Examples of the Kinetic Regioselectivity of Nucleophilic Addition in Certain Reversible Reactions

Nucleophilic reagent	N-substituent and cation	Other substituents	Yield, %	Ratio of 1,2- and 1,4-DHP	Reference
$(NC)_2CH^-$	1-$[(Me_2N)_2C^+]Py^+$	—	up to 96	10 : 90	[42, 74]
$(MeOOC)_2CH^-$	1-$(4\text{-}RC_6H_4)Py$ a)	—	—	< 10 : 90	[73]
$MeCOCH_2^-$	1-$(4\text{-}MeC_6H_4)Py^+$	—	—	20 : 80	[86]
$O_2NCH_2^-$	1-$MePy^+$	3-R b)	Quant.	0 : 100	[13, 46]
O_2NCHR^- c)	1-$AlkPy^+$	3-R^1	Quant.	0 : 100	[37]
CN^-	1-$RC_6H_4Py^+$ d)	—	—	0 : 100	[85]
CN^-	1-RPy^+ e)	3-R^1	—	0 : 100	[81]
CN^-	1-$MeQu^+$	R f)	Quant.	100 : 0	[48]
EtS^-	1-$MePy^+$	3-R g)	Quant.	0 : 100	[13, 46]
CCl_3^-	1-DCB-Py^+ h)	—	90	100 : 0	[88]
CCl_3^- i)	1-Me, Et-Qu+	—	70, 90	100 : 0	[62]
HO^-	1-$RC_6H_4Py^+$ j)	—	Quant.	100 : 0	[67]
HO^-	1-$MeQu^+$	3-R k)	Quant.	100 : 0	[39]
MeO^-	1-$RC_6H_4Py^+$ j)	—	100	100 : 0	[83]
MeO^-	1-$MePy^+$	3,5-Cl_2	100	97 : 3	[36]
H_2N^-	1-$AlkPy^+$ l)	3-R b)	100	100 : 0	[51]

a) R = Me, Br, NO_2.
b) R = H, I, Me, $CONH_2$, COMe, CO_2Me, CF_3
c) R = H, Me, R^1 = CN, 3,5-Cl_2, NO_2, CN, Alk = Me, Et, *p*-Pr, CH_2Ph.
d) R = 4-Me, 3-Me, H, 4-Br, 3-Cl, 3-NO_2, 4-NO_2.
e) R = Me, Et, CH_2Ph, R^1 = $CONH_2$, CN, 3,5-Cl_2.
f) R = H, 2-Me, 4-Me, 2,4-Me_2.
g) R = H, I, Me.
h) DCB — 2,6-dichlorobenzyl.
i) Generated from CCl_3COONa in MeCN by ultrasonic treatment at 20°C.
j) R = H, 4-Me, 3-Me, 4-NO_2, 3-NO_2, 3-Cl, 4-F.
k) R = H, Br, CN, NO_2, $CONH_2$, CO_2Et.
l) Alk = Me, CH_2Ph, $CH_2C_6H_4NO_2$-4, $CH_2C_6H_4OMe$-4.

R-pyridinium salts [46] and of RS^- to 1-methyl-3,5-bis(dialkylaminocarbonyl)pyridinium salts [47,91]; also probably the reactions of certain CH acids and their anions with 1-alkyl- and 1-alkenylpyridinium and quinolinium cations [80,92,93,107]. Table 2 gives some examples of reversible addition reactions with kinetic control of the regioselectivity.

By and large the kinetic regioselectivity shows the "true" distribution of the isomeric products due to the specific nature of both the nucleophilic reagent and the attacked cation. Disregarding the effect of steric and certain specific factors, which will be discussed below, it is possible to state that the kinetic regioselectivity is due exclusively to the specific electronic nature of both the nucleophile and the electrophilic substrate, i.e., are due to the specific type of nucleophilic addition mechanism and to the specific transition state ("hard—hard" and "soft—soft" interactions [35,49,55]). It has already been mentioned above that there is no common view in the literature about the factors that determine the kinetic regioselectivity of addition to pyridinium and quinolinium cations, although most authors adhere to the explanation proposed by the HSAB theory [35,49,50,53,54] and by the concepts of reactions controlled by charge or frontier-orbital interactions emerging from it [35,49,50,55]. Unfortunately, there are only fragmentary data on the quantitative and qualitative determination of the electrophilicity ("hardness—softness") of the α and γ positions of the pyridinium and quinolinium cations from the standpoint of the concept of hard and soft acids and bases. Most often these data concern either the N-unsubstituted pyridinium cation [35] or N-alkyl-substituted 3-carbamoylpyridinium and 3-carbamoylquinolinium salts, i.e., the analogs of $NADH^+$ [22,28]. Such data do not make it possible to form an opinion about the relative change in the electrophilicity ("hardness—softness") of the α and γ positions of the ring during the transition from "donating" N-alkyl to accepting N-alkenyl, aryl, and acyl substituents in monosubstituted pyridinium and quinolinium cations.

The situation is no better with the determination of the "hardness" and "softness" of nucleophiles. After the classical papers by Pearson, Hudson, and Klopman [35,49,53,54] only the papers by Ho [56] have made a substantial contribution to

TABLE 3. Reactions of Pyridinium Salts with Reducing Agents under Conditions with Kinetic Control

Nucleophilic reagent	N-Substituent and cation	Other substituents	Yield, %	Ratio of 1,2- and 1,4-DHP	Reference
$Na_2S_2O_4/H_2O$	Me	3-R[a]	75...100	< 10 : 90	[13]
$Na_2S_2O_4/H_2O$	CH_2Ph	3-R[a]	71...100	< 5 : 95	[13]
$Na_2S_2O_4/H_2O$	CH_2CONH_2	3-R[b]	64...66	0 : 100	[13]
$Na_2S_2O_4/H_2O$	Ph	$3-CONH_2$	65	0 : 100	[13]
$Na_2S_2O_4/H_2O$	$CH_2C_6H_4X$-*p*	$3-CONH_2$	39...88	0 : 100	[95]
CuH[c]	COR[c]	—	20...65	0 : 100	[24, 127]
CuH[c]	COOPh	3-R[d]	40...52	< 2 : 98	[24, 127]
$LiCuH_2$	COOPh	—	50...75	21 : 79	[127]
$NaCuH_2$	COOPh	—	50...75	30 : 70	[127]
$(Ph_3P)_2CuBH_4$	COOPh	—	50...75	30...70	[127]
$NaBH_4/EtOH$	CO_2R[e]	—	51...74	100 : 0	[87]
$NaBH_4/MeOH$	CO_2Me	—	60	100 : 0	[97]
$NaBH_4/EtOH$	R[f]	2,4,6-Ph_3	—	100 : 0	[13]
$NaBH_4/MeOH$	Me	3-Et	86	100 : 0	[13]
$NaBH_4/MeOH$	Ph	$3-CONH_2$	100	29 : 71[g]	[13]
$NaBH_4/MeOH$	CO_2Ph	3-R[h]	35...56	0 : 100[g]	[123]
$NaBH_4/MeOH$	CPh_3	—	96	77 : 23	[112]
$NaBH_4/MeOH$	Me	$3-SO_2NMe_2$	70	100 : 0[g]	[98]

a) R = CN, $CONH_2$, $CONEt_2$.

b) R = COME, $CONH_2$.

c) CuH was obtained *in situ* from $Li(t\text{-}BuO)_3AlH$ and CuBr, R = Et, *n*-Bu, OEt, OPh, OCH_2Ph.

d) R = Me, Et, Cl, CO_2Me.

e) R = Ph, CH_2Ph, CH_2CCl_3.

f) The reactions were conducted in DMFA or acetonitrile/methanol; R = Me, Ph, 2-pyridyl, $(CH_2)_nPh$, $4-ClC_6H_4CH_2$, $n-C_8H_{11}$.

g) The ratio of 1,6- and 1,2-DHP is given.

h) R = Me, Br, Cl, OMe.

the classification of nucleophiles and of organometallic compounds in particular. However, the deciding factor here was the accumulated experimental data and not theoretical developments. It must be pointed out that there have so far been no unified quantitative criteria for determining the "hardness" and "softness" of nucleophiles and electrophiles or for predicting the regioselectivity of specific transformations. Taking this into account, in the subsequent discussion we will use the concept of "hard," "soft," and "intermediate" nucleophile simply to define the corresponding α- and γ-selectivity or nonselectivity of addition to pyridinium and quinolinium cations, although these definitions will as a rule correspond to the traditional classification of hard and soft acids and bases. We will briefly discuss the principal characteristics of kinetically controlled nucleophilic addition reactions in relation to the nature of the nucleophilic center.

3.1. O-Nucleophiles

Nucleophiles of this type include the hydroxide ion and alkoxide ion, which are all without exception "hard" nucleophiles [49,53,54] and exhibit exclusive kinetic α-selectivity during addition both to pyridinium cations [4,5,10,13,36,67-69,83,98] and to quinolinium cations [6,39]. The addition of OH^- to 1-alkyl- and 1-arylpyridinium cations usually involves further transformations of the initially formed 1,2-DHP (ring cleavage [1,4,5,10,67-69], oxidation [10,17,108,109], recyclization [5,7,17,108,109]), whereas the adducts with quinolinium cations are more stable [5,39]. The 1,2-adducts of alkoxide ions with 1-alkyl- and 1-arylpyridinium [13,83,98] and 1-alkylquinolinium [39] cations are fairly stable, although some of them are capable of isomerizing under the conditions of thermodynamic control to the more stable 1,4-dihydro isomers [36,39,79].

3.2. N-Nucleophiles

With rare exceptions practically all N-nucleophiles are "hard" nucleophiles [49,53,54,78] and demonstrate exclusive α-selectivity during addition to 1-alkyl- and 1-arylpyridinium (quinolinium) cations. Such N-nucleophiles include ammonia [4,13,51,52,84,106], primary and secondary aliphatic and aromatic amines [1,4,5,7,13,70,76,77,103,110], hydrazines, hydrazides, semicarbazide and thiosemicarbazide [3,4,7,71,72,76], and other N-nucleophiles [13,82]. As in the case of the reactions with the hydroxide ion, the transformations of 1-alkyl- and 1-arylpyridinium cations under the influence of many N-nucleophiles do not stop at the formation of 1,2-DHP but lead to the products from ring opening (derivatives of glutaconaldehyde) [1,3-5,7,69-72] and recyclization [5,7,71,72,76,77]. The oxidative amination (NH_3 + $KMnO_4$) of various pyridinium and quinolinium cations [6,52], leading to the corresponding imino derivatives, is also well known. Pyridine and aniline are usually regarded as "intermediate" N-nucleophiles [49,53,54,78], although aniline and its analogs add preferentially at the α position of 1-arylpyridinium salts [5,70] (the Zincke—König reaction) and exhibit the character of "hard" nucleophiles. Only in [21] was the possibility of the formation of 1-(4-pyridyl)pyridinium salts by substitution of the chlorine atom in the 4-chloropyridinium salt considered.

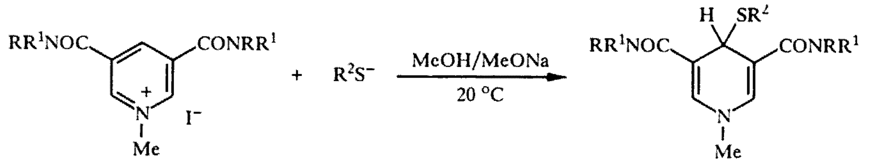
3.3. Hydride-Ion Donors (H-Nucleophiles)

Nucleophilic reagents of this type include various metal hydrides [11-13,19,24,87,111-115], dithionite and sulfite dianions and their analogs [8-12,13,15,19,24,38,44,95,98,101,113,116], tris(trimethylsilyl)silane [30], 1,2- and 1,4-DHP and 1,2- and 1,4-DHQ [38,94], and other specific reducing agents [17,19,117-121], such as triethylamine in the presence of photocatalysts [118] or the tetraphenylborate anion in alcohol in the presence of a photocatalyst [119]. As a rule most metal hydrides exhibit the characteristics of "hard" nucleophiles, and they selectively reduce various pyridinium and quinolinium cations to 1,2-DHP and 1,2-DHQ [11-13,17-19,24]. Such α-selective reducing agents include sodium borohydride [11-13,19,24,38,76,87,97,98,111-115,122-125], $K(i\text{-}PrO)_3BH$ [114,126], tributyl hydride Bu_3SnH [30], $Li(t\text{-}BuO)_3AlH$ [114,115], $(i\text{-}Bu)_2AlH$ [114], $Na(i\text{-}Bu)_3BH$ [114], and $Na(MeOCH_2CH_2O)_2AlH_2$ [115]. Of these reagents the most effective α-selective reducing agent is sodium borohydride, which reduces various pyridinium and quinolinium salts under mild conditions as a rule to 1,2-DHP and 1,2-DHQ (Table 3).

The "soft" nucleophilic reagents that give rise to preferential γ-reduction of the cations include $Na_2S_2O_4/H_2O$ + Na_2CO_3 [8,12,13,15,19,24,38,43,95,98,113,116], aluminum triisopropoxide [98], Comins reagent "CuH" [obtained from $Li(t\text{-}BuO)_3AlH$ and CuBr] [24,127],"$LiCuH_2$" and "$NaCuH_2$" [127], $(Ph_2MeP)_3CuBH_4$ and $(Ph_3P)_3CuBH_4$ [127], HPO_3^{2-}/H_2O [120], 1,2- and 1,4-DHP and 1,2- and 1,4-DHQ [38,94], and Bu_3SnH and $(Me_3Si)_3SiH$ during protonation [30]. Of these "soft" reducing agents the most effective and universal are sodium dithionite in water and Comins reagent "CuH," which reduce various pyridinium [8,12,13,15,19,24,38,43,95,98,116] and quinolinium [24,38,101] salts with high regioselectivity to the corresponding 1,4-DHP and 1,4-DHQ. It should be noted that almost all organocopper reagents exhibit high γ-selectivity during reduction, due probably to the specific nature of the transition state and to the realization of the SET reaction mechanism. Such a mechanism has been considered many times for reactions involving organocopper compounds [25,128]. Some examples of the α- and γ-selective reduction of pyridinium cations by various reagents, which make it possible to judge the effectiveness of one or the other reducing agent, are given in Table 3.

3.4. S-Nucleophiles

The S-nucleophiles include thiolate ions RS^-, the hydrosulfite anion, and the sulfite dianion. Existing published data show that S-nucleophiles mainly exhibit γ-selectivity during addition in most reactions with various 1-alkylpyridinium cations [13,46,47,91], and this coincides with thermodynamic selectivity. Nevertheless, individual cases are known of the addition of RS^- anions at the α and γ positions of 1-alkyl-3-R- and 1-alkyl-3,5-R_2-pyridinium cations [13,46,91]. Typical examples of the highly regioselective γ-addition of RS^- to 1-methyl-3,5-R_2-substituted pyridinium cations (IV) are the following transformations [47,91]:



IV

R = H, Et; R^1 = Et; R^2 = Ph, CH$_2$Ph, 4-MeOC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, *t*-Bu

The selective γ-addition of sulfite dianions (through the S-nucleophilic center) to various N-alkylpyridinium salts with the formation of 4-substituted 1,4-DHP has been postulated as the initial stage in various recyclizations of the Kost—Sagitullin type [5,7,129], whereas the initial γ-addition of the dithionite dianion or the hydrosulfite anion, which takes place through the formation of a CTC [8,13,43,44], gives rise to the selective γ-reduction of various analogs of NADH$^+$ [8,12,13,15,24,43].

Thus, the published data demonstrate the "softness" of all S-nucleophiles, which probably increases in the series of thiolate anions RS$^-$ from alkyl to aryl substituents R [47,91]. The "softness" of S-nucleophiles is also favored by the discovery in some of them (PhS$^-$, $S_2O_4{}^{2-}$, $SO_2{}^{2-}$) of the ability to form a CTC with pyridinium cations [8,13,40,43,44].

3.5. C-Nucleophiles

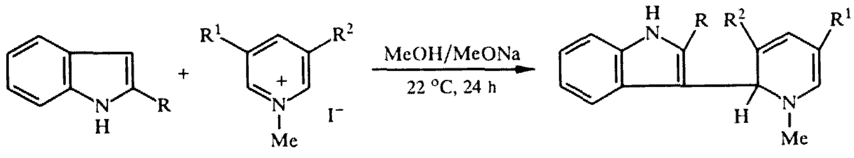
This is the most common type of nucleophile, most widely used for addition reactions to pyridinium and quinolinium cations [1,2,6,10-15,17-20]. The C-nucleophiles that we examined include organometallic compounds [12-15,20], stabilized carbanions, the cyanide ion [1,2,12-15], and aromatic and heteroaromatic nucleophiles (π-excessive systems) [1,2,6,12-15,20]. In contrast to O-, N-, and S-nucleophiles, the various C-nucleophilic reagents are capable of adding both to 1-alkyl-, 1-alkenyl-, and 1-arylpyridinium and to 1-acylpyridinium salts [1,2,12,13,20], and the effectiveness of addition and the stability of the adducts increase with increase in the accepting character of the N-substituent or the β-substituents in the ring. The most convenient and most active for the addition of C-nucleophiles are 1-acyl- and 1-alkoxycarbonylpyridinium and quinolinium salts, produced *in situ* [1,2,12-14,20], whereas monosubstituted 1-alkyl- and 1-arylpyridinium salts are as a rule insufficiently electrophilic for the addition of many C-nucleophiles and do not form stable σ-adducts [12,13,78]. Since C-nucleophiles can be completely different in nature, we will subsequently consider several groups of reagents, similar in structure and properties, classifying them as "soft," "hard," and "intermediate."

3.5.1. Addition of the Cyanide Ion. This nucleophile is usually regarded as an individual reagent, having specific properties, and is assigned in the classification of hard and soft acids and bases to the group of "soft" nucleophiles (bases) [53,54,56]. Several comprehensive reviews [31-33] and a series of experimental papers [9,23,40,48,81,85,96] have been devoted to the addition of CN$^-$ to various pyridinium, quinolinium, and isoquinolinium cations (known as the Reissert, Reissert—Kaufmann reaction). However, the discussion about the "hard" or "soft" nature of this nucleophile has not yet abated. Some authors [9,11,48,78,96] suppose that the kinetic regioselectivity of the addition of CN$^-$ to various cyclic ammonium salts is characterized as α-selectivity and corresponds to a process controlled by charge (by the electron density at the electrophilic centers of the cation). Thus, the reactions of CN$^-$ with various 1-methylquinolinium salts under the conditions of kinetic control [48] undoubtedly indicate that for these cations at least (and, probably, also for 1-acylquinolinium salts [31-33,78]) the cyanide ion behaves as a "hard" nucleophile, exhibiting exclusive α-selectivity during addition. At the same time, in contrast to certain data on the kinetic α-selectivity of the addition of CN$^-$ to 1-methyl-3-bromo-5-ethoxycarbonylpyridinium ions [9,12,13] and 1-methyl-3,5-dicyanopyridinium cations [96] other investigations indicate that the addition of CN$^-$ to 1-alkyl- and 1-arylpyridinium salts is realized predominantly or exclusively with kinetic γ-selectivity [13,23,81,130] and probably takes place through the intermediate formation of a CTC and a single-electron transfer stage [23]. A large number of reactions of CN$^-$ with pyridinium and quinolinium cations are discussed in [12,13,31-33,78].

3.5.2. Reactions with Aromatic C-Nucleophiles (π-Nucleophiles). Some investigators suppose that the reactions of such nucleophiles with the Py$^+$ and Qu$^+$ cations are reversible [15,16,41], although there is no direct evidence for this suggestion. It is probably impossible to state unambiguously that the given transformations are realized either under thermodynamic or under kinetically controlled conditions. As a result we will examine some transformations of this type, on the understanding that kinetic control of the selectivity, which is identical with thermodynamic control, is realized in these reactions.

Among the examples of selective α-addition we mention the following: the exclusive addition of indole and 2-methylindole at position 6 of 1-alkyl-3-cyanopyridinium iodides in acetonitrile in the presence of triethylamine [131]; the preferred addition of indoles (Va, b) at position 6 of 1-methyl-3-R- and 3,5-R_2-pyridinium cations (VIa-d) in methanol/sodium methoxide [41,102]. We note that realization of the last reaction in the DMSO/NaH system gives rise to more selective γ-addition to pyridinium cations (VI), although the selectivity of γ-addition is appreciably lower than the α-selectivity in the first case [41,102].

The exclusive α-selectivity of addition (heteroarylation) of indoles, pyrroles, furans, and other π-excessive systems is typical of the reactions with various quinolinium cations [1,2,6,132-136]



V VI

R = H, Me; R^1 = CH=CHCOOMe, COOMe, COMe; R^2 = H; R^1 = R^2 = COOMe

There are significantly more data on the selective γ-addition (heteroarylation) of π-nucleophiles to various pyridinium cations [1,2,12-14,134-138]. Such transformations include the following reactions: The exclusive γ-addition of indole and its substituted derivatives to 1-acyl- or 1-phenylbenzimidoylpyridinium salts [1,2,13,89,134-136], including the process in the presence of copper [1,2,13]; the γ-addition of N,N-dimethylaniline [1,2,13] and its 3-methyl-substituted derivative [139,140] to 1-benzoylpyridinium salts (with subsequent aromatization), which takes place in the presence of copper [13,139,140] or aluminum chloride [2,138]; the regioselective γ-addition of 1-methylpyrrole to 1-ethoxycarbonylpyridinium chloride [61]; the γ-addition of lithium triethyl(1-methyl-2-indolyl)borate to 1-phenoxycarbonyl-3-R-pyridinium and quinolinium chlorides, including the process taking place in the presence of CuCN [26]; the γ-addition of furan to 1-benzoylpyridinium chloride [137]. All these data demonstrate the exclusive γ-selectivity of the indicated nucleophiles toward monosubstituted 1-acyl- and 1-imidoylpyridinium cations and, in the case of the lithium indolylborates, toward the 1-phenoxycarbonylquinolinium cation [26].

3.5.3. Reactions with Organic Metallic Compounds. The addition reactions of these reagents have been postulated as irreversible processes [16,56]. These transformations do therefore make it possible to obtain the most reliable information on the kinetic selectivity of this type of reaction and to reveal the specific nucleophilic character of various organometallic reagents. In this section we consider not only traditional organometallic compounds with a C—metal bond but also other reagents such as the silyl ethers of the enols of carbonyl compounds $R^2CH{=}C(OR)R^1$, where R = $SiMe_3$ or t-$BuMe_2Si$ [34,141], the titanium enolates of carbonyl compounds $R^1CH{=}C(OM)R$, where M = Ti(i-PrO)$_3$ or TI(i-PrO)$_4{}^-$Li$^+$ [14,142,143], and trialkylalkynylborates $(R^3B{-}C{\equiv}C^*R^1)^-Li^+$, where R = Alk, R^1 = Alk, Ph (here and subsequently the asterisk indicates the nucleophilic addition center) [13,14,144].

The "hard" organometallic nucleophiles, which exhibit high α-selectivity during addition to various 1-acylpyridinium cations and to certain 1-alkyl-3-R-pyridinium salts, include the following reagents: Silver phenylacetylide PhC≡CAg [145], PhMgX 1126, 146-149], Ph_2Cd [147], ArMgBr [14, 146, 148], MeMgX [60,113], MeCO−O$(CH_2)_4$MgCl [150], RCH=CHMgBr(R=H, E-Hex) [14,56,57,60], RC≡CMgBr [14,56,57,60,65,151,152], RC≡CSnMe$_3$ [65], Bu$_3$SnC≡CSnBu$_3$ [153], and various allyl reagents $CH_2{=}CH{-}CH_2M_nX_p$ [154-156]. It should be noted that some of these nucleophiles [34,145,153,156] and also allenyltin reagents $H_2C^*{=}C{=}C(R^1)SnR_3$ [157], the silyl ethers of enols [34], and the methylating complex of trans-dimethylcobalt(III) [27,28] exhibit high α-selectivity during addition to 1-acyl- and 1-methylquinolinium cations, although few transformations of such type are known. Table 4 gives data on the regioselective α-addition of certain organometallic compounds to 1-acyl- and 1-acyl-3-pyridinium and quinolinium and 1-alkyl-3-cyanopyridinium cations.

The "soft" nucleophiles include the following reagents: Lithium trialkylalkynylborates $(R_3B{-}C{\equiv}C^*R^1)^-Li^+$ [14,144], R_2CuLi (R = Alk, Ar) [25,158], Grignard reagents in the presence of 5% of CuI [14,123,148,149,159-164], RCu [34,58,59,141,165], RCu·BF$_3$ [34,56,58,59,166], organolithium reagents in the presence of 5% of CuI [20,61,167-171], mixed copper—zinc reagents RCu(CN)ZnX, where X = Br, I and R = $YC_6H_4CH_2$ or YC_6H_4 (Knochel reagents) [172-175], 4-$RC_6H_4CH_2SnMe_3$ [20,176], $RC_6H_4CH_2MgBr$ [164] and PhTi(*i*-PrO)$_3$ [177], *n*-BuZnCl [56,60], $Me_2C^*{=}CHCH_2SnBu_3$ [156], $MeC^*{\equiv}CCH_2Al_{2/3}Br$ and *n*-$BuC^*{\equiv}CCH_2Al_{2/3}Br$ [155], $(EtOCO)_2(Me)CZnBr$ [155], the silyl ethers of enols $R^2CH{=}C(OR)R^1$, where R = $SiMe_3$ or t-$BuMe_2Si$ [34,141,165], and titanium enolates $R^1CH{=}C(OM)R$, where M = Ti(i-PrO)$_3$ or Ti(i-PrO)$_4{}^-$Li$^+$ [14,20,142,143]. It is possible to conclude on the basis of the data in Table 5 that the most "soft" and γ-selective reagents are the organocopper nucleophiles R_2CuLi, RCu·BF$_3$, RCu (including RCu generated *in situ* from

TABLE 4. Kinetic α-Regioselectivity of Some "Hard" Organometallic Compounds in Reactions with Py^+ Cations

Nucleophilic reagent	N-substituent	Other substituents	Yield, %	Ratio of 1,2- and 1.4-DHP	Reference
MeMgI	COOMe	—	54	92 : 8	[57, 60]
BuMgBr	COOMe	—	80	78 : 22	[57, 60]
$AcO\text{-}(CH_2)_4MgCl$	COOPh	—	85	> 95 : 5	[150]
$RC_6H_4MgBr^{a)}$	$CH_2R^{1\ a)}$	3-CN	25...94	100 : 0	[146]
Ph_2Cd	$COR^{b)}$	—	32...38	100 : 0	[147]
PhMgCl	COOPh	$3\text{-}SnBu_3$	80	99 : 1	[126]
$RCH{=}CHMgBr^{c)}$	COOMe	—	71, 81	99 : 1	[14, 57, 60]
$PhC{\equiv}CAg$	$COC_6H_4R^{d)}$	—	70...90	100 : 0	[145]
$RC{\equiv}CMgBr^{e)}$	COOMe	—	62...99	> 99 : 1	[14, 57, 60]
$RC{\equiv}CMgBr^{f)}$	COOMe	$2\text{-}R^{1\ f)}$	66...79	> 99 : 1	[57, 151, 152]
$Bu_3SnC{\equiv}CSnBu_3$	$CO_2CHClMe$	—	62	100 : 0	[153]
$CH_2{=}CHCH_2MgBr$	COOEt	—	60	94 : 6	[155]
$CH_2{=}CHCH_2ZnBr$	COOEt	—	70	87 : 13	[155]
$(CH_2{=}CHCH_2)_2CuLi$	COOEt	—	80	96 : 4	[155]
$CH_2{=}CHCH_2Al_{2/3}Br$	COOEt	—	80	98 : 2	[155]
$CH_2{=}CHCH_2SnBu_3$	$COOR^{g)}$	—	64...87	> 91 : 9	[154, 156]
$CH_2{=}CHCH_2SnBu_3$	COOMe	$3\text{-}R^{h)}$	74...96	> 90 : 10	[154, 156]
$RC{\equiv}CSnMe_3{}^{i)}$	COOMe	$3\text{-}COR^1$	51...75	$100 : 0^{i)}$	[65]

a) R = H, 4-Me, 2-Me, R^1 = H, Ph.

b) R = Me, OEt.

c) R = H, *n*-(*E*)-Hex.

d) R = H, $3\text{-}NO_2$, $4\text{-}NO_2$.

e) R = Bu, Pent, Hex, Ph, Me_3SiOCH_2, Me_3Si, $(EtO)_2CH$.

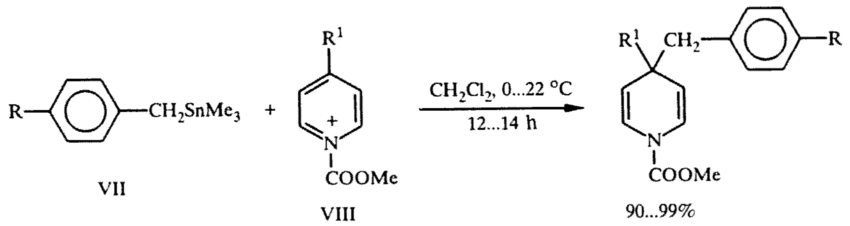
f) R = Me_3Si, *n*-Hex, $n\text{-}C_9H_{19}$, R^1 = Me, Et.

g) R = Me, Et, CH_2CCl_3, $CH_2CH{=}CH_2$.

h) R = Me, Cl, Br, CHO, OAc.

i) R = Bu, Hex, CH_2OBn, $(CH_2)_2$, R^1 = H, Me, OMe; ratio of 1,2- and 1,6-DHP = 93:7.

RMgX or RLi and CuI), RCu(CN)ZnX, and trimethylbenzyl- and tributylprenyltin reagents. Such exclusive γ-selectivity in these nucleophiles is clearly due to the presence of a specific transition state during the reaction with the electrophile and to the realization of the SET mechanism (in the cage) [25,128]. This proposal is favored by the exclusive γ-selectivity during the addition of trimethylbenzyltin reagents (VII) to 4-substituted pyridinium cations (VIII) [176]:



VII

VIII

R = H, Me, OMe; R^1 = CN, COOMe

At the same time data on the selective γ-addition of organometallic compounds to quinolinium salts are only encountered in isolated papers [56,63,178].

Among the organometallic compounds exhibiting "intermediate" nucleophilic character and undergoing fairly nonselective addition to 1-acyl- and 1-alkylpyridinium cations it is possible to include almost all alkyl Grignard reagents (except $MeCO{-}O(CH_2)_4MgCl$ [150], $RC_6H_4CH_2MgBr$ [164], and MeMgX [60,113,179]), i.e., AlkMgX [13,14,56-60,126,155], the methylating complex of trans-dimethylcobalt(III) [27,28], methyl-substituted allyl reagents $MeC^*H{=}CHCH_2M$ (where M = $Al_{2/3}Br$, MgBr, ZnBr [155], or M = SnR_3 [156]), $RC^*H{=}C(Me)CH_2SnR_3{}^1$ (where R = H, Me [66,156]), RCH_2ZnBr (where R = EtOCO, Et_2NCO [155]), and $C^*H_2{=}C{=}CHAl_{2/3}Br$ [155].

TABLE 5. Examples of Kinetic γ-Regioselectivity in the Reaction of Py^+ Cations with Organometallic Compounds

Nucleophilic reagent	N-substituent	Other substituents	Yield, %	Ratio of 1,2- and 1,4-DHP	Reference
$(R_3B^-C{\equiv}C^{\bullet}R^1)$ $^{a)}$	COMe	—	66...78 $^{b)}$	0 : 100 $^{b)}$	[144]
R_2CuLi $^{b)}$	COOMe	—	56...86	< 10 : 90	[25, 158]
RMgX + 5% CuI $^{c)}$	COOEt	—	62...77 $^{b)}$	< 5 : 95	[14, 159]
RMgX + 5% CuI $^{d)}$	COOPh	—	80...92	< 5 : 95	[14, 149]
ArMgX + 5% CuI $^{d)}$	COOPh	3-Br	57...66 $^{b)}$	< 5 : 95	[14, 148]
MeMgCl + 5% CuI	COOPh	3-R $^{f)}$	85...92	< 5 : 95	[163]
$ArCH_2MgBr$ + 5% CuI $^{g)}$	COOEt	—	25...60 $^{b)}$	0 : 100	[164]
ArLi + 5% CuI $^{h)}$	COOEt	—	54...59 $^{b)}$	0 : 100	[167—171]
RCu $^{e)}$	COOMe	3-COOMe	71...78	0 : 100	[34, 165]
$RCu \cdot BF_3$ $^{j)}$	COOEt	$3\text{-}R^1$	81...100	< 1 : 99	[58, 59, 166]
$4\text{-}RC_6H_4Cu(CN)ZnI$ $^{k)}$	COOEt	$3\text{-}R^1$ $^{k)}$	38...60 $^{b)}$	< 10 : 90	[174, 175]
$RC_6H_4CH_2Cu(CN)ZnBr$ $^{i)}$	COOEt	$3\text{-}R^1$ $^{k)}$	25...89 $^{b)}$	0 : 100	[172, 173]
$4\text{-}RC_6H_4CH_2SnMe_3$ $^{m)}$	$COOR^1$ $^{m)}$	$3\text{-}R^2$ $^{m)}$	70...100	0 : 100	[20, 176]
$R^2CH{=}C(OSiMe_2X)R$ $^{n)}$	COOR1 $^{n)}$	$3\text{-}R^3$ $^{n)}$	51...95	< 3 : 59	[141, 165]

---

a) R = *n*-Hex, *c*-Pent, *c*-Hex, R^1 = *n*-Bu, *n*-Hex, Ph.

b) Adduction yield or ratio of aromatization products.

c) R = Me, Et, *n*-Pr, *i*-Pr, *i*Bu, Ph, $4\text{-}MeC_6H_4$.

d) R = Me, Et, *i*-Pr, Bu, *c*-Hex, Ph.

e) Ar = Ph, $4\text{-}MeC_6H_4$, $2\text{-}MeC_6H_4$, $1\text{-}C_{10}H_7$.

f) R = Me, Cl, Br, OMe, $OCONEt_2$, $CH(OCH_2)_2$.

g) Ar = RC_6H_4, where R = H, 4-Me, 2-Me, 4-OMe, 4-Bu-*t*.

h) Ar = 2-R and 2,6-RR^1-pyridyl-3, -5- or -6,5-methyl-2-furyl.

i) R = Me, $4\text{-}MeC_6H_4$.

j) R = *n*-Bu, *i*-Bu, *n*-Hex,CH_2CH_2Ph, Ph, 2-ethoxymethoxy-3-methoxyphenol, R^1 = H, CH=CHCOOEt, CH_2CH_2COOEt.

k) R = 4-CN, 4-COOMe, R^1 = H, Me, F, Br, COOMe, OMe, CN.

l) R = H, 2-Me, 2-Br, 2-CN, 3-Cl, 4-Bu-*t*.

m) R = H, Me, OMe, R^1 = Me, CH_2CCl_3, R^2 = H, Cl, Br, CHO, CN.

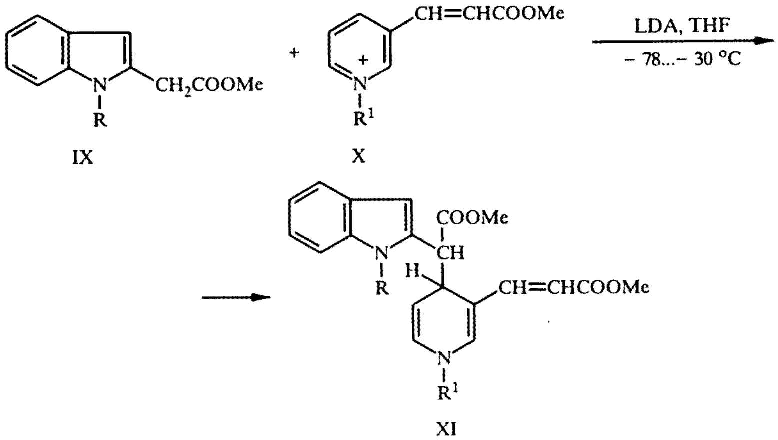
n) X = Me, *t*-Bu, R = OMe, Et, Ph, R,R^2 = $(CH_2)_4$, R^1 = Me, Et, NMe_2, R^2 = H, Me, Ph, R^3 = H, COOMe.

Thus, it can be concluded on the basis of the published data that the "hardness" of nucleophiles in the series of alkyl organometallic compounds RM increases in the following order: RCu, R_2CuLi, RCu(CN)ZnX, $ArCH_2SnMe_3$ < $ArCH_2MgBr$ < RZnX < RMgX < MeMgX < RLi. As a rule organolithium reagents attack the electrophilic center of the carbonyl group in the N-substituent and not the C-2 and C-4 atoms of the cation [56,57,60]. The "hardness" of the organometallic compounds also increases in the transition from the alkyl to the aryl, alkenyl, and alkynyl reagents and from prenyl- to crotyl- and allyltin reagents.

3.5.4. Reactions with Stabilized Carbanions and CH Acids. The reactions of this type of nucleophile with pyridinium and quinolinium cations are usually reversible [15,16]. This is confirmed both by kinetic investigations of the reactions [73,86] and by the subsequent isomerization or transformations of the products from kinetic control to the thermodynamically most stable isomers [15,25,62,73,88] or products [25,42,73,74,89]. Some examples of the kinetic selectivity of such reversible reactions were given above (Tables 1 and 2).

"Hard" nucleophilic agents of this type, which exhibit high α-selectivity during addition to Py^+ and Qu^+ salts, include the following nucleophiles: The trichloromethylcarbanion CCl_3^- [15,25,62,88,105]; the anion of Meldrum's acid [15,25,42,74]; the methylcyanoacetate anion $NC(COOMe)CH^-$ [73,89]; the barbiturate anion [42,74]; trinitrotoluene [only toward 1-benzoyland 1-(4-nitrobenzoyl)quinolinium chlorides!] [180]; thiazolyl-2- and thiazolyl-4-methyloxazolyl-2-carbanions [6,181]; the anions obtained from 2-(dimethylthiomethyl)indoles [19].

The group of "soft" γ-selective reagents includes the following nucleophiles: Tribromo- and triiodomethylcarbanions [88]; the anions of cyclohexanone [86] and acetone [86,92]; the anions of methyl and ethyl acetoacetate, methyl and ethyl malonate [73,79,80,89,92], malononitrile [6,42,74,79,80,107], and dimedone [42,74]; the anion of ethyl cyanoacetate [80,107,182]; the anions of nitromethane and its substituted derivatives [13,29,37,90,92,93]; the anions of acetophenone and its derivatives [1,2,13,92,93]; the anions of 2-phenyl-4-R-oxazol-5-ones [183] and 3-phenyl-4-R-thiazolid-2-one [184]; the lithium enolates of 1-, 2-, and 3-indolylacetic esters [15,41,185]; the anions of certain other CH acids [6,13,80,92,93,107,182]. We note particularly the selective γ-addition of the lithium enolates of indolylacetic acids, produced *in situ* from the respective esters (IX) and lithium diisopropylamide [15,41,185], to pyridinium salts (X). In the opinion of the authors this takes place under the conditions of thermodynamic control. However, the very mild reaction conditions (between −78 and −30°C, THF), analogous with those for the γ-addition of the above-mentioned silyl ethers of enols [34,141,165] and titanium enolates [142,143], favor kinetic control for the process, leading to 4-substituted 1,4-DHP (XI), which is used in the synthesis of alkaloids.



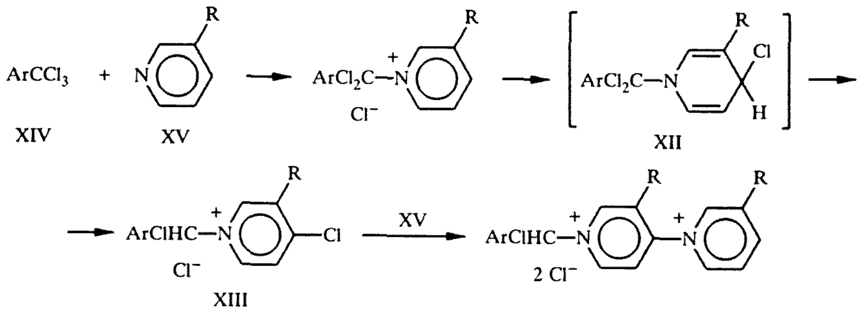
IX R = H, Me; R^1 = Me, CH_2CH_2OAc

It can thus be seen that the majority of stabilized carbanions exhibit high γ-selectivity during addition. This is probably due to the ambident character of the nucleophiles and to their ability to form a CTC with the pyridinium cations [8,40,43,45], i.e., their ability to undergo single-electron transfer in the cage [29,45]. In the case of "hard" nucleophiles (CCl_3^-, the anions of Meldrum's acid and barbituric acid, 2-thiazolyl- and 2-oxazolyl carbanions) addition takes place by a polar mechanism as direct addition of the carbanion to the electrophilic center C-2 [62,181].

3.6. Halide Ions

There are limited data in the literature on the addition of halide ions to pyridinium cations. Such addition of bromide or chloride ions was proposed as the key stage in the syntheses of N-(4-pyridyl)pyridinium salts [21,186-194, e.g., in the well-known synthesis of 1-(4-pyridyl)pyridinium dichloride from pyridine and thionyl chloride [21,186-192]. It was postulated that the 4-chloro-1-chlorosulfinyl-1,4-dihydropyridine formed from N-(chlorosulfinyl)pyridinium chloride at this stage is attacked by the pyridine with substitution of the chlorine atom and the formation of pyridiniodihydropyridine, which gives the 1-(4-pyridyl)pyridinium salt as a result of aromatization [186-194].

The exclusive γ-regioselectivity of the process was left unexplained. Only in [21] on the basis of quantum-chemical calculations was it concluded that such selectivity was due to the SET mechanism of addition of the chloride ion, including transfer of an electron from Cl^- to the pyridinium ion with the formation of a dihydropyridyl radical, in which position 4 has the highest spin density; the process is completed by the addition of the $Cl^{\bullet}$ radical at position 2. It should be noted that the authors [21] considered an alternative mechanism for the formation of 1-(4-pyridyl)pyridinium dichloride through the aromatization of 4-chloro-1-chlorosulfinyl-1,4-dihydropyridine and nucleophilic substitution of the chlorine atom in the obtained 4-chloropyridinium salt by pyridine. Such a mechanism first found experimental confirmation in our work [195]. This was demonstrated by the discovery and/or isolation of the 4-chloro-1,4-dihydropyridines (XII) and 4-chloropyridinium salts (XIII) in the reaction of trichloromethylarenes (XIV) with pyridines (XV). The γ-regioselectivity of the addition of Cl^- in the last case can be explained not only by the SET mechanism of the process but also by steric hindrances to α-attack, created by the bulky α,α-dichlorobenzyl N-substituent.



R = H, CONH₂, COOEt, Br

R = H, Me, OH

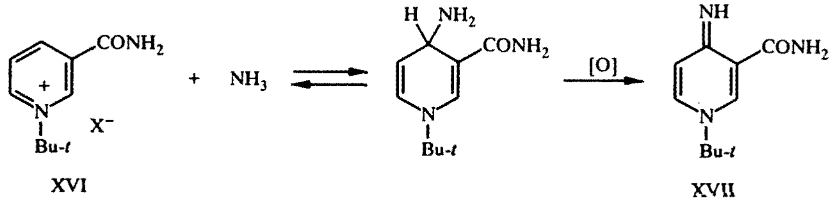
4. STEREOCONTROLLED REGIOSELECTIVITY

This type of selectivity is due both to the presence of certain (most often bulky) substituents in the pyridine ring and by the size of the nucleophilic reagent. Several different alternatives for stereocontrol of the selectivity are possible, depending on the position and steric demands of the substituent determining the direction of nucleophilic attack and on the size of the nucleophile.

4.1. Bulky Substituent at Position 1 of the Ring

The screening of the α positions of the pyridinium cation by a bulky N-substituent determines the preferred or exclusive addition of the nucleophile at position 4 of the ring. Substituents of such a type include, for example, the following groups: CPh_3 [13,112,146,196], t-Bu [6,52,106], $CPh_2{-}N{=}NAr$ [78,197], 2,4,6-$Me_3C_6H_2$ [106], disaccharide residues [13], 1-oxido-2-pyridyl [13], and others (Table 6).

A typical example of this type of stereocontrol is the oxidative amination of the 1-tert-butyl-3-carbamoylpyridinium salt (XVI), leading exclusively to the 4-imino derivative (XVII) [6,52]:



This type of bulky 1-substituent, blocking the α positions of the pyridinium cation, can probably include the 3-methyl- and 3,5-dimethyl-4-pyridyl groups in the respective 1-(4-pyridyl)pyridinium salts (XVIII) (R, R^1 = H, Me) [198]:

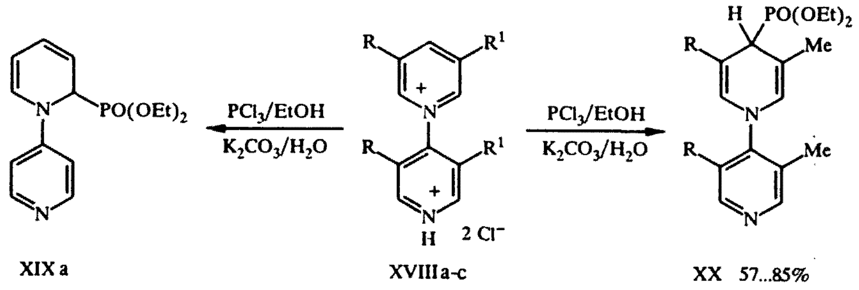


TABLE 6. Reaction of Nucleophiles with Pyridinium Salts Containing a Bulky Substituent at the N Atom

Nucleophilic reagent	N-Substituent	Other substituents	Yield, %	Ratio of 1,2- and 1,4-DHP	Reference
$NaPO(OPr\text{-}i)_2$	CPh_3	—	30	0 : 100	[197]
$NaPO(OPr\text{-}i)_2$	CPh_3	3-Me	53	0 : 100	[197]
$NaPO(OPr\text{-}i)_2$	CPh_3	3,5-Me_2	28	0 : 100	[197]
PhMgBr	CPh_3	—	35	0 : 100	[146]
CN^-	$Ph_2C{-}N{=}NAr$	—	75	0 : 100	[197]
$NH_3/KMnO_4$	*t*-Bu	3-$CONH_2$	—	0 : 100	[6, 52]
$NH_3/[O]$ a)	2,4,6-$Me_3C_6H_2$	3-$CONH_2$	—	0 : 100	[106]
$PCl_3/EtOH$ b)	3-Methyl-4-pyridyl	3-Me	85	0 : 100	[198]
$PCl_3/EtOH$ b)	3,5-Dimethyl-4-pyridyl	3,5-Me_2	57	0 : 100	[198]
$NaBH_4$	CPh_3	—	96	77 : 23	[112]
$NaBH_4$	1-Hydroxy-2-pyridyl	2,4,6-Ph	—	0 : 100	[13]
$NaBH_4$	Disaccharide residue	—	—	0 : 100	[13]
RMgX c)	*t*-$BuMe_2Si$	—	60...70	1 : 99	[14, 34, 59]
RMgBr d)		—	72...82	0 : 100	[34, 200]

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a) Enzymatic oxidation.

b) See the discussion on the next page.

c) R = *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *n*-Pent, *n*-Hex, *n*-Oct, CH_2CH_2Ph, Ph.

d) R = Et, *n*-Pr, *i*-Pr, *n*-Bu.

TABLE 7. Regioselective Nucleophilic Addition Reactions at the ipso Position of α- or γ-Substituted Py^+ and Qu^+ Cations

Nucleophilic reagent	N-Substituent and cation	Other substituents	Yield, %	Ratio of 1,2- and 1,4-DHP	Reference
$PhCH_2SnMe_3$	1-$COOMePy^+$	4-CN, 4-CHO	98, 90	0 : 100	[20, 176]
4-$MeC_6H_4CH_2SnMe_3$	1-$COOMePy^+$	4-CN, 4-CHO	99, 91	0 : 100	[20, 176]
4-$MeOC_6H_4CH_2SnMe_3$	1-$COOMePy^+$	4-CN	99	0 : 100	[20, 176]
$CH_2{=}CR{-}CH_2SnBu_3$ a)	1-$COOMePy^+$	4-CHO, 4-COOMe	64...92	< 5 : 95	[66]
$CH_2{=}CR{-}CH_2SnBu_3$ a)	1-$COOMePy^+$	4-COMe	70, 76	36 : 64, 20 : 80	[66]
$(Me_3Si)_3SiH$ b)	1-$MeQu^+$	4-Me	100	0 : 100	[30]
CN^- (-50 °C)	1-$MeQu^+$	2-Me	quant.	100 : 0	[48]
CCl_3^-/ ultrasound c)	1-$MeQu^+$	2-Me	70	84 : 16	[62]
trans -$(CoMe_2(L))$ d)	1-$MeQu^+$	2-Me	quant.	100 : 0	[27, 28]

---

a) R = COOMe,CN. b) The reaction was conducted with irradiation by monochromatic light (λ = 315 nm). c) The CCl_3^- was generated from sodium trichloroacetate in acetonitrile at 22°C. d) The methylating complex of trans-dimethylcobalt(III).

Although the authors propose 1,2-DHP structures of type (XIX) for all the products from the addition of $PCl_3/EtOH$ to the salts (XVIII), only the structure of the 1,2-DHP (XIXa) was confirmed conclusively [for the reaction with the 1-(4-pyridyl)pyridinium salt (XVIIIa)] [198], whereas the data from the ^1H NMR spectra of the products from addition to the salts (XVIIIb, c) [where R = R^1 = Me (b) and R = H, R^1 = Me (c)] and of the pyridylphosphonic acids obtained during aromatization of the latter (cf. [196]) favor the 1,4-DHP structures (XX). For example, the DHP structure (XXb) agrees well with signals for the protons of pyridine rings (in deuterochloroform), situated at δ, ppm, 3.46 (d, 1H, J_{P-CH} = 22 Hz, 4-H), 5.92 (δ, 2H, 2,6-H) and 8.41 (s, 2H, 2′,6′-H). The PMR spectrum of the adduct (XXc) has a similar form. The chemical shifts of the protons in the dihydropyridine ring of adducts (XX) agree well with published data for various 1,4-DHP com-pounds [12,13,59,102], including the analogs of compounds (XX) [199], and differ strongly from the chemical shifts of the protons of 1,2-dihydropyridine (XIXa) [198]. In addition, the above-mentioned substituents with methyl groups at positions 3 and 3,5 of the pyridine ring can be regarded as structural analogs of the 2,6-dimethyl-4-oxo-1,4-dihydro-1-pyridyl [13,34,200] and 1-hydroxy-2-pyridyl [13] N-substituents, which effectively screen the α positions of the pyridinium cation for attack by nucleophiles less bulky than PCl_3 (RMgX and $NaBH_4$, see Table 6). Thus, we suppose that in this case 3-methyl- and 3,5-di-methyl-4-pyridyl N-substituents in cations (XVIIIb) behave as bulky groups screening the α positions of salt for attack by PCl_3.

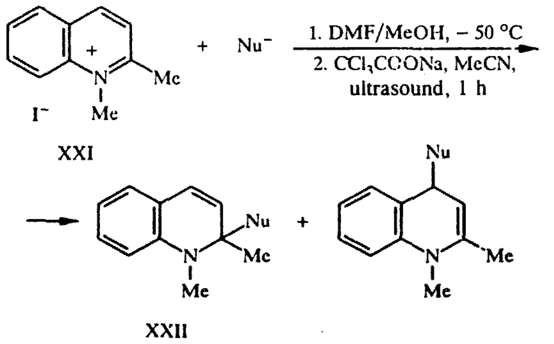
It is also necessary to mention the successful use of pyridinium cations with other N-substituents that effectively screen the α positions of the pyridine ring (t-BuMe$_2$i [13,14,34,59] and 2,6-dimethyl-4-oxo-1,4-dihydro-1-pyridyl [34,200]) in the syntheses of 4-substituted 1,4-DHP compounds and pyridines (see Table 6).

It can be concluded on the basis of the published data that the use of bulky N-substituents that effectively screen the α positions of the pyridinium cation and of sufficiently activating rings is limited to a few examples and has little preparative significance. It is interesting to note that attempts to use 2,6-di-tert-butyl-4-methylphenyl chloroformate as acylating agent to screen the α positions of the obtained pyridinium salt sterically were unsuccessful [199].

4.2. Substituent at Position 2 (or 2 and 6) and/or 4

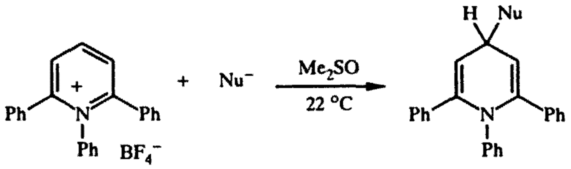
Substituents at the α and/or γ position of the pyridinium salt screen the corresponding position for ipso attack and give rise to attack by the nucleophile at the unsubstituted position of the ring. In the case of the addition of organometallic reagents and other C-nucleophiles this relationship is also fulfilled for pyridinium salts containing good nucleofugic groups such as chlorine and bromine [14,19,20,175,179,201-204] or $SnMe_3$ [143,205] at position 4 of the cation. On the basis of numerous published data [11-14,19,20,30,40,105,113,147,175,179,201-213] it can be concluded that the significant steric hindrances for ipso attack on α- or γ-substituted pyridinium and quinolinium cations give rise to preferential addition of the reagent at the free α or γ position of the ring, irrespective as a rule of the nature of the nucleophile and the size and nature of the existing substituent.

Some exceptions from this rule (Table 7) are due to the specific nature of the nucleophilic reagent [27,28,30,48,62, 176], e.g., $4\text{-}RC_6H_4CH_2SnMe_3$ [20,176] certain allyltin reagents [66] in reactions with 4-substituted pyridinium salts and/or to the specific nature of the transition state [27,28,66], e.g., in reactions taking place through the stage of photoinduced electron transfer [30]. All these exceptions are probably due to the realization of the SET mechanism in the case of γ-addition [30,66,176], or the mechanism of direct transfer of cyanide ion [48] and carbanion [27,28,62], or the alternative mechanism of first-sphere electron transfer [27,28] (in the case of α-addition under the conditions of a kinetically controlled process). Table 7 gives examples of the "anomalous" addition of nucleophiles to the ipso positions of α- or γ-substituted pyridinium and quinolinium salts. Among these examples we note in particular the regioselective α-addition of trichloromethylcarbanion CCl_3^- [62] and cyanide ion [48] to 1,2-dimethylquinolinium iodide (XXI) under the conditions of kinetic control. Conversely, under thermodynamically controlled conditions rapid and quantitative isomerization of the 1,2-DHQ (XXII) to the more stable 1,4-DHQ occurs [48,62].



1. Nu = CN, α-selectivity 100%; 2. Nu = CCl_3, α-selectivity , 84%

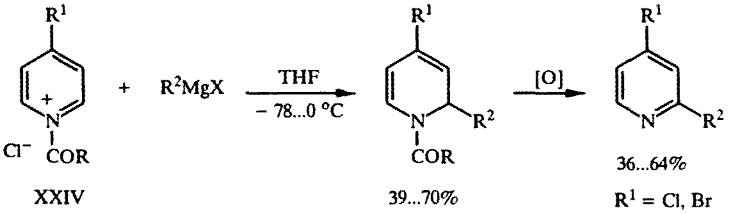
Clear examples of the "normal" stereocontrolled selectivity of this type are the reactions of 1-alkyl-2,6-diphenylpyridinium and 1,2,4- and 1,2,6-triphenylpyridinium cations (XXIII) with various nucleophiles (OH^- [108], MeO^-, CN^-, PhS^-, $CH_2NO_2^-$, and $CR_2NO_2^-$ [40]). All these reactions lead to the products from addition at the unsubstituted α or γ position of the respective salts, for example:



XXIII

Nu = HO, MeO, CN, PhS, $O_2N(R)R^1C$

Among the examples of selective addition to pyridinium cations having good nucleophilic substituents at position 4 [14,175,179,201-205] it is possible to mention the exclusive α-addition of Grignard reagents to 4-chloro-, 4-bromo-, and 4-trimethylstannylpyridinium salts (XXIV) [201,203-205]:

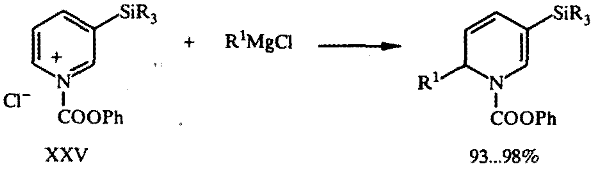


XXIV R = OPh, OEt, Ph, Pr, OCH_2Ph; R^1 = Cl, Br, $SnMe_3$; R^2 = Alk, Ph, Ar

A similar type of stereocontrol of selectivity is realized in the reactions of organozinc reagents with 4-chloro-1-acylpyridinium salts [143,175,202] or in the reactions of Grignard reagents with 4-methoxypyridines and various quaternized esters of chloroformic acid [207-212]. We omit the numerous examples of nucleophilic addition to α- and/or γ-alkyl-, aryl-, cyano-, and dimethylamino-substituted Py^+ and Qu^+ cations since they demonstrate the standard type of stereocontrol with addition at the free electrophilic position [12-14,42,147,175,203,206].

4.3. Bulky Substituent at the β Position of the Heterocycle

Such a substituent is capable of screening positions 2 and 4 in the cation from nucleophilic attack by various Grignard reagents [14,19,126,149,179,208-210] and by certain bulky metal hydrides [114,115,126]. Triisopropyl-, triethyl-, and trimethylsilyl groups [14,114,149,179,208-210,212] and less effectively screening tri-n-butylstannyl and tricyclohexylstannyl substituents [14,114,126] usually behave as such ortho-screening β-substituents (Table 8). The selectivity of addition at C-6 [126,179], including reduction by metal hydrides [114,115,126], increases regularly with increase in the size of the nucleophilic reagent. An example of the steric screening of position 4 in a 3,5-disubstituted pyridinium salt during amination with liquid ammonia is known [106]. Of all the available ortho-screening β-substituents the most widespread is the triisopropylsilyl group, which effectively blocks attack by various Grignard reagents at positions 2 and 4 of the cations (XXV) and gives rise to addition at the electrophilic center C-6 with 100% specificity [179]:



R = *i*-Pr; R^1 = Me, Bu, *c*-Hex, Ph

TABLE 8. Stereocontrolled Nucleophilic Addition to Pyridinium Salts Containing a Bulky β-Substituent

Nucleophilic reagent	N-Substituent in pyridinium cation	β-Substituent and other substituents	Yield, %	Ratio of (1,2- and 1,4-DHP) and 1,6- DHP	Reference
PhMgCl	COOEt	3-SiMe$_3$	> 35	0 : 100	[149]
PhMgCl	COOPh	3-SnBu$_3$	80	1 : 99	[126]
RMgCl a)	COOPh	3-SnBu$_3$	63...77	From 44 : 56 to 23 : 77	[126]
C$_6$H$_{11}$MgCl	COOPh	3-Sn(*c*-Hex)$_3$	62	13 : 87	[126]
K(*i*-PrO)$_3$BH	COOPh	3-SnBu$_3$	—	18 : 82	[126]
RMgCl b)	COOPh	3-SiEt$_3$	79...91	From 29 : 71 to 0 : 100	[179]
RMgCl b)	COOPh	3-Si(*i*-Pr)$_3$	93...98	0 : 100	[179]
RMgCl c)	COOPh	3-Si(*i*-Pr)$_3$, 4-Cl	52, 66	0 : 100	[179]
RMgCl c)	COOPh	3-SiPr$_3$, 4-Cl	79, 85	13 : 87, 7 : 93	[179]
RMgCl d)	COOR^1 d)	3-Si(*i*-Pr)$_3$, 4-OMe	77...95	0 : 100	[208]
RMgCl/(COOH)$_2$ e)	COOR^1 e)	3-Sn(*i*-Pr)$_3$	58...87	0 : 100	[214]
RMgBr f)	COOR^1 f)	3-Si(*i*-Pr)$_3$, 4-OMe	85	0 : 100	[210]

---

a) R = *c*-Hex, *i*-Pr, 5-pentenyl.

b) R = Me, *n*-Bu, *c*-Hex, Ph.

c) R = Me, *n*-Bu.

d) R = Ph, 2-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, Me, *i*-Bu, *c*-Hex, R^1 = (−)-menthyl, (−)-8-phenylmenthyl.

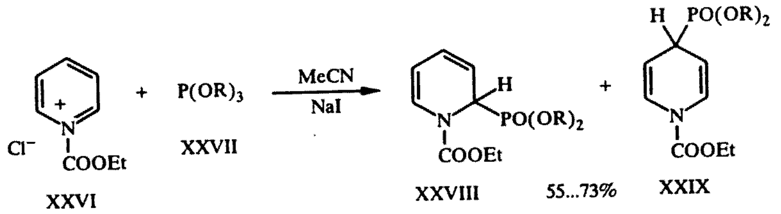
e) R = *n*-Pr, *c*-Hex, CH$_2$Ph, CH$_2$=CH, Ph, 4-MeC$_6$H$_4$, R^1 = (−)-8-(4-phenoxyphenyl)menthyl and (−)-8-phenylmenthyl, diastereoselectivity of reaction between 76 and 92%.

f) R = CH$_2$=CH(CH$_2$)$_3$, R^1 = (−)-8-phenylmenthyl.

No less an effective blocking group of such a type was the triisopropylstannyl group [214]. Chiral pyridinium salts with such a substituent were used successfully in asymmetric syntheses of 1-acyl-2-alkyl-1,2-DHP [19,214]. Other examples of the effective use of pyridinium salts with bulky β-substituents in the asymmetric syntheses of alkaloid systems are known [19,208-210].

4.4. Addition of Bulky Nucleophiles

This type of stereocontrol is well known both for simple 1-substituted Py$^+$ salts [13,34,127,141,180] and for pyridinium salts containing a β-substituent [34,114,115,165]. However, it has not become widely used in preparative syntheses, since the range of suitable bulky nucleophiles is fairly restricted [13] (Table 9). The clearest example of regioselective addition due to the size of the nucleophile is the reaction of 1-ethoxycarbonylpyridinium chloride (XXVI) with trialkyl phosphites (XXVII) [34,199]:



R = Me, Et, *i*-Pr

TABLE 9. Stereocontrolled Reactions of Pyridinium Cations with Bulky Nucleophiles

Nucleophilic reagent	N-Substituent	Yield, %	Ratio of 1,2- and 1,4-DHP	Reference
$P(OMe)_3$ [a)]	COOEt	55	46 : 54	[34, 199]
$P(OEt)_3$	COOEt	70	8 : 92	[34, 199]
$P(OPr\text{-}i)_3$	COOEt	73	0 : 100	[34, 199]
$CH_2{=}CMe{-}OSiMe_3$ [a)]	COOEt	91	37 : 54	[34, 141]
$CH_2{=}CPh{-}OSiMe_3$	COOEt	90	21 : 69	[34, 141]
$MeCH{=}CEt{-}OSiMe_3$	COOEt	67	0 : 100	[34, 141]
$MeCH{=}CPh{-}OSiMe_3$	COOEt	51	0 : 100	[34, 141]
$MeCH{=}C(OMe){-}OSiMe_3$	COOEt	87	0 : 100	[34, 141]
$CH_2{=}C(OMe){-}OTi(OPr\text{-}i)_3$ [a)]	COOPh	81	26 : 74	[14, 142]
$CH_2{=}C(OMe){-}OTi(OPr\text{-}i)_4^-Li^+$	COOPh	90	13 : 87	[14, 142]
$MeCH{=}CEt{-}OTi(OPr\text{-}i)_3$	COOPh	78	7 : 93	[14, 142]
$MeCH{=}CPh{-}OTi(OPr\text{-}i)_3$	COOPh	74	2 : 98	[14, 142]
$CH_2{=}C(OEt){-}OTi(OPr\text{-}i)_3$ [a)]	COOPh	68	70 : 30	[14, 142]
2,4,6-Trinitrotoluene	COPh	36	0 : 100	[20, 180]
$LiC_2RB_{10}H_{10}$ — Lithio-carboranes, R = Me, Ph	Me	—	0 : 100	[13]

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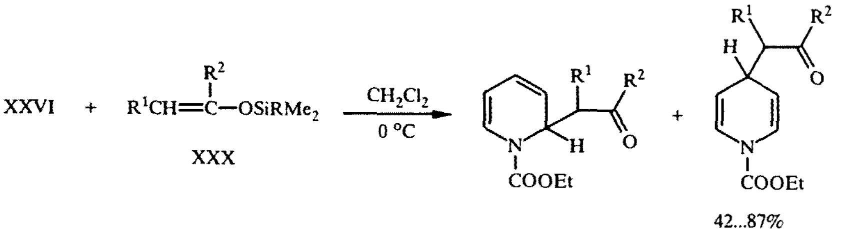
a) The data for the reactions of Py^+ cations with small nucleophiles are given for comparison.

In the transition from trimethyl phosphite to triethyl and triisopropyl phosphites (XXVII) the ratio of the obtained 1,2-DHP (XXVIII) and 1,4-DHP (XXIX) varies from 46:54 to 8:92 and 0:100. We note that in the reactions of the analogous quinolinium salt with the same phosphites 1,2-dihydroquinolyl-2-phosphonates are obtained with almost quantitative yields [34]. This probably indicates more significant steric hindrances to nucleophilic attack at C-4 than at C-2 of the quinolinium cation for these reagents, which exhibit intermediate "hard—soft" character.

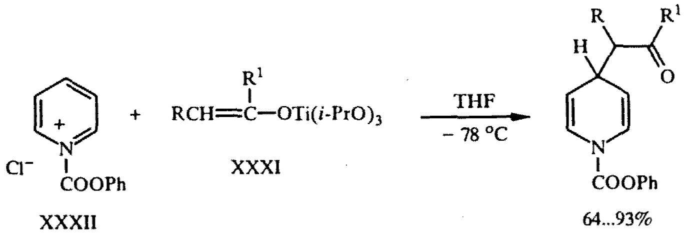
Other examples of the selective γ-addition of bulky nucleophiles are the reactions of the silyl ethers of enols (XXX), which exhibit moderate "softness," with 1-ethoxycarbonylpyridinium chloride (XXVI) [34,141]. Thus, with increase in the volume of the nucleophilic reagent (XXX) the γ-selectivity of addition increases appreciably in comparison with the fairly nonselective addition of the trimethylsilylenols of acetone and acetophenone (XXX) (R^1 = H, R^2 = Me, Ph) [141] (Table 9).



R = Me, t-Bu; R^1 = H, Me, Ph; R^2 = Me, Et, OMe, Ph

The analogous reactions of the silyl ethers of aliphatic enols of type (XXX) with 1-methoxycarbonylquinolinium chloride are α-regioselective [34].

It is also known that the addition of relatively "soft" titanium enolates (XXXI) to 1-phenoxycarbonylpyridinium chloride (XXXII) with increase in the size of the nucleophilic reagent takes place with higher γ-selectivity [20,142] (Table 9):



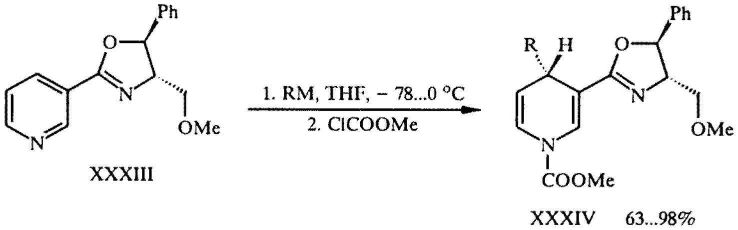
R = Me; R^1 = Et, OEt, Ph; R, R^1 = $(CH_2)_5$; selectivity > 73%

A similar effect from the structure of the nucleophile also shows up in the reduction of Py$^+$ cations by complex metal(19 hydrides [114,115,127]. However, such stereocontrol only gives good results in conjunction with the "soft" nature of the nucleophilic reagent [127] or with the steric effect of the substituents in the ring [114,115,126].

To summarize the examples of stereocontrolled regioselectivity given in this section it can be concluded that this regiocontrol factor plays a deciding role in many nucleophilic addition reactions involving reagents having bulky groups. The rare exceptions from this rule are explained by the specific nature of the reagents and the transition state [27,28,30,48,62,66,176]. Although the range of effective blocking substituents [13,14,19,149,179,208-214] and bulky nucleophiles [13,34,141,142,180,199] is fairly restricted, it makes it possible in many cases to obtain the desired structures with high selectivity and good yields [13,14,18-20,34,179,196-214]. It can be supposed that further search for effective and available blocking substituents, particularly at a cyclic nitrogen atom, will make it possible to increase the selectivity of the reactions and, in particular, of reactions involving stabilized carbanions and other C-nucleophiles.

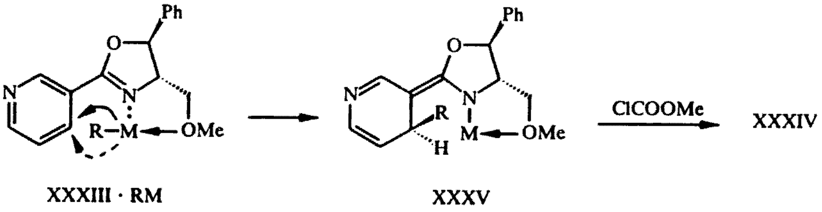
5. SPECIFIC REGIOSELECTIVITY FACTORS

In this section factors that are not due to the electronic and steric effects of the substituents in the pyridinium cation but are due to specific interaction between the substituent in the ring and the nucleophilic reagent are considered. Such characteristic interactions include primarily the formation of organometallic compounds of a chelate or complex with certain atoms or functional groups of a substituent at position 3 of the pyridinium or quinolinium cation [14,63-65]. It must be emphasized that the specific regiocontrol factors operate under kinetically controlled conditions, and this does not as a rule depend on the "soft" or "hard" nature of the nucleophile. One of the first examples of the regioselective addition of nucleophiles to pyridinium (quinolinium) salts, due to the formation of a complex, is the reaction of chiral 2-(3-quinolyl)- and 2-(3-pyridyl)oxazolines (XXXIII) with various organolithium and organomagnesium reagents in the presence of methyl chloroformate [63]:



M = Li, MgCl; R = Me, Et, Bu, Ph

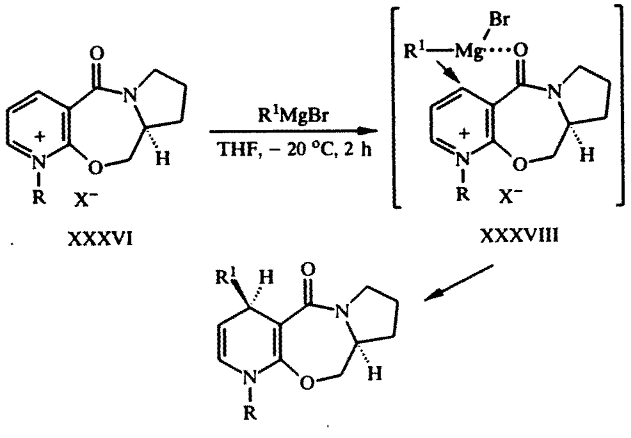
As a result of this reaction the corresponding 1,4-DHP (XXXIV) and 4-methyl-1,4-DHQ are formed with good yields, 100% γ-selectivity, and high diastereomeric purity (de > 95%). The authors explain the high stereoselectivity by initial coordination of the organometallic compound at the nitrogen atom and the methoxy group of the oxazoline substituent [with the formation of the complex (XXXIII)·RM] and subsequent entry of the group R at position 4 of the pyridine ring. Addition of the RM on the other side of the plane (the dotted arrow in the scheme) may lead to different stereochemistry. The lithium or magnesium derivative (XXXV) formed after the addition of RM to the pyridine (XXXIII) is presumably acylated by the methyl chloroformate and transformed into the product (XXXIV) [63].



The examined coordination of the organometallic reagent, which determines the high regio- and stereoselectivity of the addition of RM, recalls the familiar asymmetric addition to the related 2-alkenyl- and 2-(3-pyridyl)oxazolines [14,63]. During such complex formation the nucleophilic particle is directed exclusively at position 4 of the pyridine ring, in spite of the clearly defined "hard" nature of the lithium and magnesium reagents [56-58,60]. It is very likely that contrary to data in

[63] the addition of the alkyl or phenyl residue R at C-4 of the heterocycle takes place only after activation of the ring by quaternization of the azine by the ethyl chloroformate.

Another example of the "anomalous" regioselective γ-addition of relatively "hard" nucleophiles (Grignard reagents) is the reaction of 1-methyl- and 1-benzylpyridinium salts (XXXVI) with alkyl-, alkenyl-, and phenylmagnesium bromides, which leads to the 1,4-DHP (XXXVII) with high regio- and stereoselectivity and with good yields [64]:



XXXVI

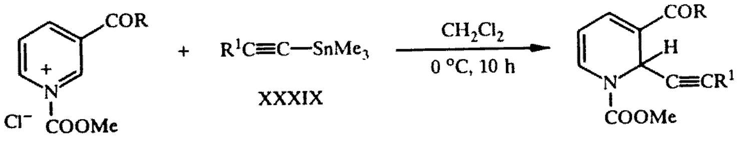
XXXVIII

XXXVII 60...95%

R = Me, CH_2Ph; X = I, Br; R^1 = Me, Bu, CH_2=CH, Me_2CHCH_2, Ph

It is noteworthy that under analogous conditions the very "hard" allylmagnesium bromide (see [56,154,155]) shows appreciably lower γ-selectivity during addition to (XXXVI) (ratio of 1,4- and 1,6-DHP 5.5:1), whereas the most "hard" of the organometallic reagents [alkyllithium (MeLi and BuLi)] [14,56-59] exhibit even lower selectivity in these reactions (ratio of 1,4- and 1,6-DHP between 1:1 and 3:1) [64]. These data probably indicate that complexation of the alkyllithium reagents with the O atom of the amide group is less effective than with the Grignard reagents (the nature of the metal! [56,128]), and as a result the "hard" nature of the alkyllithium nucleophiles shows up to a greater degree.

A specific type of regiocontrol is also demonstrated by the highly selective addition of alkynyltin reagents (XXXIX) at position 2 of the 3-acylpyridinium salts (XL), which leads to the 2,3-disubstituted 1,2-DHP (XLI) (1,2-selectivity > 93%) [65]:



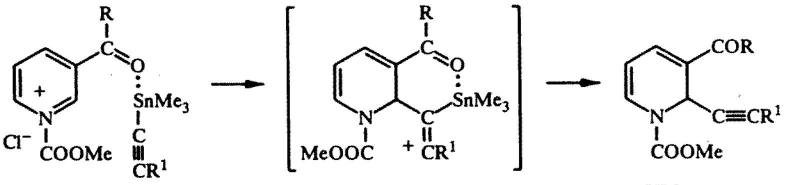
XL

XXXIX

XLI 51...75%

R = H, Me, OMe; R^1 = Bu, Hex, CH_2OBn, $(CH_2)_2OBn$, $(CH_2)_3OBn$

In view of the "hard" nature of alkynyl reagents [56,57,60,151-153] (Table 4) and of the fact that the addition of 1-hexynylmagnesium bromide to the corresponding 3-acetylpyridinium salt (XL) (R = Me) under analogous conditions is completely nonselective (ratio of 1,2- and 1,6-DHP 47:53) [65] the authors explain the preferred addition at position 2 quite logically by coordination of the tin atom with the acyl group of the β-substituent in the salt (XL). This is demonstrated by the following scheme and agrees with the familiar published data for related reactions with other carbonyl compounds [65].

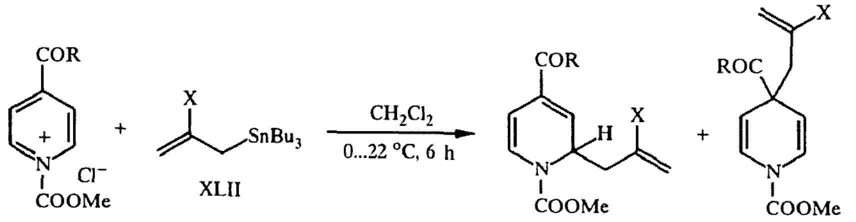


XL

XLI

It is probably also necessary to include the possibility of concerted coordination of the alkynyltin reagent by the carbonyl groups of the substituents at positions 1 and 3 of the pyridinium salt (XL) with the formation of a five-membered bridge —C═O···Sn···O═C—, which may be promoted by the large size of the tin atom.

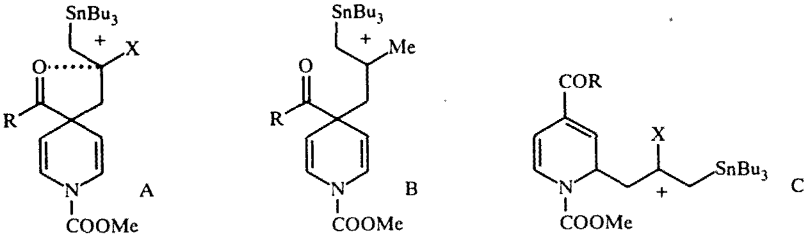
A surprising change in regioselectivity was recently observed in the nucleophilic addition of 2-substituted allyltributyltin reagents (XLII) to the 4-acylpyridinium salts (XLIII) [66]. Thus, in the transition from 2-methylallyltributyltin (XLII) (X = Me) to the 2-cyano- and 2-methoxycarbonylallyl reagents (XLII) (X = CN, COOMe) the direction of addition changes sharply from α-addition [> 95% of the 1,2-DHP (XLIV)] to γ-addition [ratio of 1,2- and 1,4-DHP (XLIV):(XLV) between 36:64 and 5:95, Table 7] [66]:



XLIII XLIV XLV

X = Me, CN, COOMe; R = H, Me, OMe   X = Me (69...80%)   X = CN, COOMe

The explanation for the obtained results proposed by the authors treats structures A, B, and C as possible intermediates, of which the structures of type A can be stabilized as a result of coordination (donor interaction) of the carbonyl group in the γ-substituent with the carbanionic center in the geometrically favorable five-membered transition state [66]:



X = COOMe, CN   R = H, Me, OMe   X = Me, COOMe

It is also considered that since the carbanionic center in the intermediate B is stabilized by the donating methyl group the donating stabilizing effect of the carbonyl group does not appear, and the 1,2-adducts are formed exclusively through the intermediate C as a result of steric hindrances on the side of the γ-substituent [66]. We propose an alternative approach to explanation of the marked change of selectivity in these reactions. Thus, it follows from the data of the same authors [66] that the nucleophilicity of 2-methoxycarbonylallyltributyltin (XLII) (X = CO_2Me) is insufficient for addition to the C-unsubstituted 1-methoxycarbonylpyridinium salt. However, the more electrophilic 1-methoxycarbonyl-3-acetylpyridinium cation adds the same reagent nonselectively, forming a mixture of 1,2-, 1,6-, and 1,4-DHP in ratios of 26:47:27 [66]. These data indicate that 2-methoxycarbonylallyltributyltin and, probably, its 2-cyano analog (XLII) (X = CN) in reactions with Py^+ cations exhibit both the characteristics of relatively weak nucleophiles compared with other allyltin reagents [154,156] and the character of "intermediate" nucleophiles. It is this combination of the weakly nucleophilic and "intermediate" character of the investigated nucleophiles that determines the preferred direction of attack at the γ position of the 4-acylpyridinium salts (XLIII), i.e., at the center with enhanced electrophilicity. Here it is quite likely that the carbonyl group of the γ-substituent coordinates the allyl reagent by donor interaction with the carbanionic center of the nucleophile similar to that proposed above [65,66]. This also holds in the case of the realization of the SET mechanism of addition, characteristic of the γ-addition reactions to Py^+ salts [13,21].

Extremely significant also is the fact that with the exception of the above-mentioned nucleophiles only very "soft" benzyltin reagents add regioselectively under analogous conditions at the γ position of 4-substituted 1-acylpyridinium salts (VIII) [20,176], thereby demonstrating the identity of the mechanism of addition with the contrasting strength ("weak—strong") and character ("hard—soft") of the nucleophilicity.

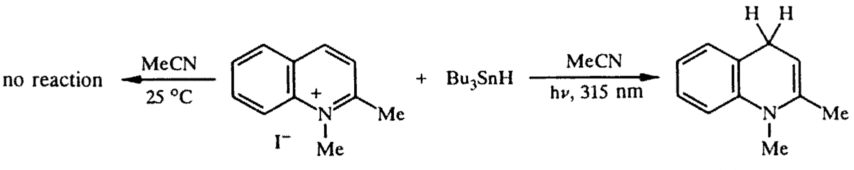
To summarize all these data we supposed that the γ-selectivity of addition of 2-cyano- and 2-methoxycarbonylallyltributyltin (XXXIX) to the 4-acylpyridinium salts (XL) is due to a combination of three different factors, i.e., the enhanced electrophilicity of the C-4 atom in the cation, the specific nature of the nucleophilic agent, and the possible coordination of the nucleophile with the carbonyl group of the γ-substituent. The concerted action of these factors promotes the radical mechanism of addition, leading to the 4,4-disubstituted 1,4-DHP compounds (XLV).

As far as the selectivity of the α-addition of 2-methylallyltributyltin (XLII) (X = Me) to the salts (XLIII) is concerned, the sufficiently nucleophilic and "intermediate" ("hard—soft") nature of the reagent with respect to the C-unsubstituted 1-methoxycarbonylpyridinium chloride is well known (ratio of 1,2- and 1,4-DHP between 36:64 and 30:70) [156]. The α-selectivity of this allyl reagent in the reactions with 4-acylpyridinium salts is therefore due exclusively to the steric effect, i.e., the screening of the C-4 center of the acyl group (by the γ-substituent), as occurs in numerous examples of the α-addition of organometallic [13,14,20,175,179,201-213] and other nucleophilic reagents [10,13,30,40,42] to the 4- or 2-substituted Py^+ and Qu^+ cations.

Thus, all the presented examples of regioselectivity controlled by particular characteristic factors indicate that addition to pyridinium salts in such cases is realized through a specific transition state, which can be regarded as an analog of a CTC and which brings about the highly regioselective and, in individual cases, also stereoselective addition of the nucleophiles.

6. EFFECT OF REACTION CONDITIONS ON REGIOSELECTIVITY

One of the important factors that give rise to regioselectivity during nucleophilic addition to Py^+ and Qu^+ cations is the reaction conditions, i.e., the temperature and duration of the reaction [9,30,36,38,42,48,74], the solvent [86,88,96,102,104], the method of generation of the nucleophilic particle [15,41,62,102,105,185], the method of activation of the substrate or the reagent [13,30,118,119], and the presence and the nature of the catalyst [14,20,26,118,119,159]. We note that until now the effect of the reaction conditions on the regioselectivity of nucleophilic addition to pyridinium salts has not been examined as an independent factor of regiocontrol, since it was tacitly assumed that the action of the reaction conditions shows up simply in a change from kinetic to thermodynamic control. In fact, most of the published data do indicate such an effect from the reaction conditions, but only for reversible processes [15,25,30,36,39,41,42,48,62,74,78,82,98-101]. At the same time there are data that indicate other manifestations of this factor. Thus, for example, certain reaction conditions ensure that nucleophilic addition takes place by a radical mechanism, and this is due to features of the methods of activation of the substrate or nucleophile [11,13,30,49,62] or to the use of specific catalysts [14,20,139,140,159]. A clear example of the effect is the surprising change in the selectivity of the reduction of 1-methylquinolinium cations by tributyltin hydride with thermal initiation or photoinitiation [30]:



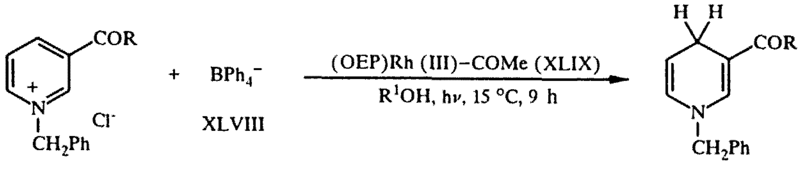
XXI

XLVI

Whereas the reduction of 1-methyl- and 1,4-dimethylquinolinium cations by tributyltin hydride at 25°C under the conditions of kinetic control leads exclusively to 1,2-DHQ, the reduction of the 1,2-dimethylquinolinium ion (XXI) by the same reagent does not occur under the same conditions but is easily realized during irradiation with monochromatic light, leading only to the 1,4-DHQ (XLVI) [30]. Analogous γ-selectivity was detected during the photoreduction of the same 1-methylquinolinium salts by tris(trimethylsilyl)silane $(Me_3Si)_3SiH$. The authors suppose that thermal reduction with tributyltin hydride takes place by a polar mechanism, demonstrating the considerable steric effect of the methyl group at the C-2 atom of the cation (XXI), whereas the photochemical reactions involving Bu_3SnH and $(Me_3Si)SiH$ take place by a mechanism of photoinduced electron transfer, in which the steric effect of the methyl group at C-4 is leveled out [30]. There is no doubt that in this example the change in the reaction conditions (photoinitiation) leads to a change in the mechanism of addition of the nucleophile ("hydride ion") and as a result to a radical change in the selectivity of the process.

The next parameter that applies to the reaction conditions and determines the direction and effectiveness of nucleophilic attack on the Py^+ cation is the presence of specific catalysts [2,13,14,20,34]. Such catalysts include certain Lewis acids (in heteroarylation reactions) [2,138], copper [13,14,139,140], copper(I) iodide [14,20,61,123,148,149,159-164,167-171], CuCN [26], and other more complex catalysts [118,119], such as the photocatalysts of "hydride" transfer (ruthenium complexes with pyridine ligands) [118]. Whereas the role of some catalysts (Lewis acids) probably amounts simply to activation of the Py^+ cations [2,138], the effect of other catalysts such as copper [13,14,139,140] or ruthenium complexes [118] in all probability involves their ability to act as electron donors (in the case of copper) or "hydride-ion" carriers (in the case of the ruthenium complexes). Thus, the key role of catalysts of the second type may involve not only a change in the energy profile of the reaction but also occurrence of the process by the SET or other mechanism and, consequently, the control of regioselectivity. Thus, it was shown in particular that the increase in the accepting characteristics of the ligands in the above-mentioned complexes of ruthenium(II) leads to higher γ-selectivity during the photocatalyzed reduction of the 1-benzyl-3-carbamoylpyridinium cation by triethylamine [118]. Here the authors suppose that the complicated complexes of ruthenium(II) used as catalysts make it possible to avoid one-electron reduction of the cation and secure high γ-regioselectivity during transfer of the hydride equivalent through the initial substitution of the pyridine ligand of the complex by the "hydride ion" [118].

The analogous γ-selective photoreduction of NAD models (XLVII) by tetraphenylborate (XLVIII) in alcohol was discovered when the organometallic acetylrhodium(III) complex of octaethylporphyrin (XLIX) was used as photocatalyst [119]:



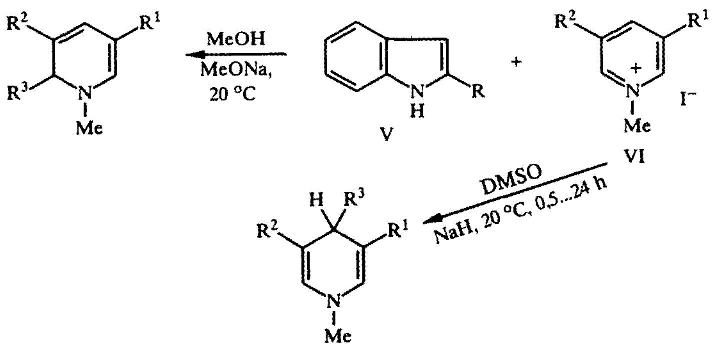
R = NH_2, Me

It was shown that the reaction does not go in the dark, in the absence of alcohol or $B(C_6H_5)_4^-$, or in the absence of the rhodium catalyst (XLIX) [119]. It is assumed that the rhodium complex (XLVI) catalyzes the generation of the "hydride ion" [with two-electron photooxidation of the $B(C_6H_5)_4^-$ anion in the alcohol] and its regioselective transfer to the C-4 atom of the cation (XLVII) [119].

In the investigated examples the role of the ruthenium or rhodium catalysts involves the realization of a specific mechanism of transfer of the "hydride ion" from the reducing agent to the oxidizing agent. This method differs both from the normal mechanism of photoinduced electron transfer [30,119] and from the polar mechanism characteristic of reduction by many metal hydrides and securing α-selectivity during the addition of the "hydride ion" [13,24,30,114,124].

A rather different type of effect from the catalyst on the regioselectivity of nucleophilic addition is the effect of catalytic amounts of copper iodide CuI (5%) in the reactions of Grignard reagents [14,20,123,148,149,159-164] and organolithium compounds [14,20,61,167-171] with 1-acylpyridinium salts. The catalytic action of copper iodide CuI in these reactions undoubtedly involves the generation of reactive and very "soft" nucleophilic organocopper reagents (RCu) from the respective organometallic compounds. Together with the analogous copper reagents R_2CuLi and $RCu \cdot BF_3$ [14,34,56,58,59,158,166] these reagents have the remarkable capacity for selective γ-addition to various 1-acylpyridinium cations [14,34,58,59,165]. After nucleophilic attack by this reagent (RCu) and addition of the residue R at C-4 of the cation the regenerated CuI again forms a "soft" nucleophilic reagent, and the cycle of reactions is repeated. Thus, in this case the catalyst (CuI) acts as a source of the highly regioselective nucleophile RCu, the addition of which to the electrophile clearly takes place by a different mechanism from the addition of the initial Grignard reagents or lithium reagents [25,56,128].

Recently, interesting data were obtained on the effect of the solvent on the selectivity during the addition of indoles (V) to 1-methyl-3-R-pyridinium salts (VI). Thus, it was shown that the use of methanol and sodium methoxide as solvent and base respectively gives rise to regioselective addition of the 3-indolyl anion at position 6 of the Py^+ cations (VI), whereas the DMSO/NaH system promotes preferred γ-addition of the indoles to the salts (VI) [102]:

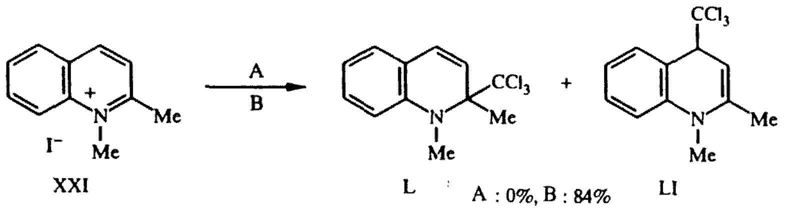


R = H, Me; R^1 = COOMe, COMe, CH=CH–COOMe; R^2 = H, COOMe; R^3 = 3-Indolyl

Attempts to use other solvents (THF, HMPTA, water, ethylene glycol) led to an appreciable reduction in the selectivity or yields of the products (to 7%) [102]. In view of published data [131] on the regioselective addition of the same indoles (V) at position 6 of 1-methyl-3-cyanopyridinium iodide in CH_3CN/Et_3N with boiling and taking account of the analogous results in [41,104] it can be supposed that the discussed change in regioselectivity cannot be explained by a transition from the conditions of kinetic control to thermodynamic control. In this case we are probably concerned with a change in the mechanism of addition of the 3-indolyl anion from polar to radical.

The effect of the solvent on the regioselectivity of nucleophilic attack was noticed during the reactions of N-acylpyridinium cations with organometallic reagents [126] and was associated with the known effect of solvents on the mechanism of the reactions of organometallic compounds with electrophiles [128].

Quite recently interesting data were published on the effect of the activation or generation of the nucleophilic particle on the selectivity of addition [62]. Thus, the generation of the trichloromethylcarbanion from sodium trichloroacetate by ultrasonic treatment gives rise to preferential or exclusive addition of the nucleophile at the α position of 1-methyl- and 1-ethylquinolinium cations of type (XXI), whereas boiling in acetonitrile leads to significantly less selective addition. Extremely significant in this respect is the addition of the trichloromethylcarbanion to 1,2-dimethylquinolinium iodide (XXI) [62].



A : MeCN, CCl_3COONa, boiling for 1 h; B : MeCN, CCl_3COONa, ultrasonic treatment for 2 h

It is very likely that the process during ultrasonic treatment takes place under kinetically controlled conditions, whereas during boiling in acetonitrile the kinetically controlled products L isomerize to the thermodynamically more stable 1,4-DHQ (LI) [62], as was observed in the analogous transformations of 1-alkyl-substituted dihydropyridines [88].

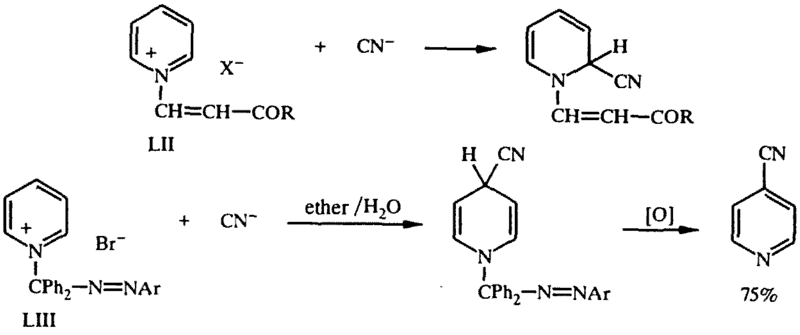
Thus, the data examined in this section show convincingly that the reaction conditions have a significant effect on the regioselectivity of the transformations. The role of this factor is not restricted to the trivial transition from kinetic to thermodynamic control of the process but affects the intimate mechanism of the nucleophilic addition reactions.

7. EFFECT OF THE STRUCTURE OF THE Py^+ AND Qu^+ CATIONS ON THEIR REACTIVITY AND ON THE SELECTIVITY OF NUCLEOPHILIC ADDITION

The structure of pyridinium and benzopyridinium salts and the associated electrophilicity of the α- and γ-positions of the heteroaromatic cation not only determine the reactivity of the cation but also give rise to the regioselectivity of the reactions with nucleophiles as a result of the specific distribution of electron density in the heterocycle. The reactivity of pyridinium and benzopyridinium salts of the same type in these reactions increases in the following order: Pyridine < quinolinium < isoquinolinium. This is due both to the accepting effect of the condensed ring and to the distribution of the charge in the heterocyclic cation [1,2,5,6,34,78]. Thus, the electrophilicity of the C-1 atom in the isoquinolinium salts is higher than the electrophilicity of the C-2 and C-4 centers in the analogous quinolinium and pyridinium salts. This determines the higher reactivity of the N-substituted isoquinolinium cations in many reactions with nucleophiles and the exclusive α-selectivity of these reactions [1,2,6,31,34,62,78,156]. Since the electrophilicity of the α and γ positions of the heteroaromatic cation and the associated reactivity and regioselectivity in nucleophilic addition reactions depend on the donor—acceptor characteristics of both the N-substituent and the substituents at the C atoms of the ring, we will consider their effects separately.

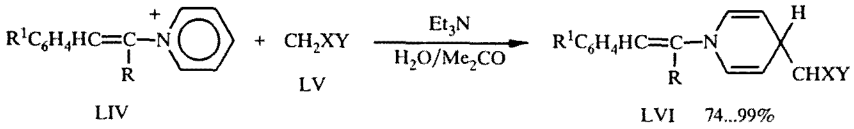
7.1. Effect of the N-Substituent on the Reactivity and Regioselectivity

It is considered generally accepted that increase in the accepting characteristics of the N-substituent leads to an increase in the electrophilicity of an azinium cation and its reactivity [1,2,4-6,42,78]. In fact, even a small increase in the accepting character of the 1-substituent in the monosubstituted salts makes it possible to realize nucleophilic addition reactions, which cannot be conducted with less electrophilic cations [1,5,34,78]. Thus, for example, it is known that the reaction of 1-alkylpyridinium salts with the cyanide ion or with ethylene-active compounds does not lead to stable σ-adducts or does not take place at all [31-33,78,92], whereas the reaction of the cyanide ion with the more electrophilic 1-(2-acylvinyl)- and 1-(arylazodiphenylmethyl)pyridinium cations (LII, LIII) leads to stable 2-cyano-1,2-DHP [215] and 4-cyano-1,4-DHP [197] respectively:



Ar = Ph, 4-ClC$_6$H$_4$

The analogous reaction of α-pyridiniostilbenes and β-pyridiniostyrenes (LIV) with methylene-active compounds (LV) in the presence of triethylamine leads to the 4-R-1,4-DHP (LXVI) with excellent yields [92,93]:



R = H, Ar; R^1 = H, 4-NO$_2$, 3-NO$_2$, 4-Cl; X = H, COMe, COOEt, NO$_2$; Y = COR^2, Ph

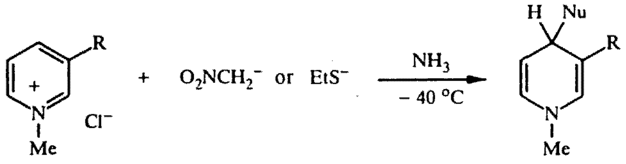
The N-substituents that we examined can be arranged in the following order of increasing accepting characteristics: Me < Et < *n*-Pr < *n*-Bu < CH$_2$Ph < *t*-Bu, CR$_3$ < CPh$_3$ < CPh$_2$−N=NR < Ph, Ar < CH=CHCOR, CH=CHAr, CR=CHAr < 3-pyridyl < 2-pyridyl < 2,4-(NO$_2$)$_2$C$_6$H$_3$, 4-pyridyl < CN < CR=NR^1 < CONR$_2$ < COR, COOR < $Me_2N-C^+-NMe_2$. Analysis of the published data shows that the most reactive N-acyl- and N-alkoxycarbonylpyridinium and quinolinium monosubstituted cations are most often used in reactions with C-nucleophiles [1,2,6,11-14,17-20,34,75] and reducing reagents (metal hydrides) [13,17-19,24,114]. On the other hand, this is due to the extreme ease and effectiveness of the method for their preparation; the respective cations are usually generated *in situ* by the action of the acyl chloride on pyridine or quinoline [1,2,14,17-20,31-34]. On the other hand, these salts are some of the most reactive N-substituted salts that are sufficiently activated for the addition of many organometallic reagents [14,17-20,147-176,201-214], stabilized carbanions, and neutral C-nucleophiles [1,2,6,89,137,138] and also for reductions with metal hydrides [24,96,114,127]. If the aim is to realize the transformations of the pyridine ring by the action of O- and N-nucleophiles in a reaction of the Zincke—König type [1,3-5,10,70] or recyclization [5,7], Zincke salts less electrophilic but neutral with respect to these nucleophiles [1,5,7,19,34,70-72,76,77] and 1-cyano-, 1-(dimethylcarbamoyl)-, 1-styryl-, and 1-α-arylstyrylpyridinium salts [1,5,10,68,108,129] are used. It should be noted that increase in the accepting character of the N-substituent leads to an increase in the stability of the obtained 1,2- or 1,4-dihydropyridine systems [5,6,12,13,75], although in the case of the reactions with alkalis, N-nucleophiles, or the anions of certain CH acids it nevertheless gives rise to the more ready cleavage of the 1,2-dihydropyridine ring [4,5,42,74]. Nevertheless stable 1,2-adducts with the epoxide ion are known for certain 1-arylpyridinium salts [13,83]. In the general case for all types of 1-monosubstituted pyridinium salts the 1,4-adducts with C-nucleophiles and the "hydride ion" are more stable than the 1,2-isomers [13,15,16,20,78]. This relationship also holds at least for 1-alkylquinolinium salts [30,38,48].

Thus, it can be stated that the electronic effect of the 1-substituent, irrespective of its nature, does not have a significant effect on the thermodynamically controlled selectivity of reactions with C-nucleophiles and the "hydride ion," which is characterized as γ-selectivity [9,12,13,15,16,20]. At the same time some data on the kinetically controlled selectivity of the reactions of C- and S-nucleophiles with various 1-monosubstituted pyridinium salts [51,52,73,86,106] indicate a decrease in γ-selectivity for some transformations with increase in the accepting characteristics of the N-substituent, particularly in the transition from alkyl to aryl substituents [73,86,106].

7.2. Effect of β-Substituents on the Regioselectivity and Reactivity

In view of the fact that the presence of any substituent at the α or γ position of the ring promotes preferential attack at the unoccupied electrophilic center [14,18,40,108] we will only consider reactions with the Py^+ and Qu^+ cations that contain various β substituents with the exception of bulky groups.

The presence of weakly donating or weakly withdrawing substituents at the β position of pyridinium and quinolinium salts probably only has a small effect on the electron density distribution in the cation compared with the analogous monosubstituted salt, since both the thermodynamic and the kinetic regioselectivity of the addition reactions are almost identical to the selectivity for the transformations of the analogs with a free β position [13,39,51]. Thus, for example, the results in [37,46] show that the kinetic γ-selectivity during the addition of the anions of nitromethane and ethanethiolate to 3-R-substituted 1-methylpyridinium salts (LVII) corresponds fully to the γ-selectivity in the addition of the same anions to the 1-methylpyridinium cation (LVII) (R = H):



LVII

R = H, I, Me; Nu = CH_2NO_2, EtS

A similar pattern was observed during the selective α-addition of the hydroxide ion to 1-methyl-3-R-quinolinium iodides (R = H, Br) [39], during the highly regioselective γ-addition of the organocopper reagents R^1Cu and $R^1Cu{\cdot}BF_3$ [34,58,59,165,166], CuH [127], Grignard reagents in the presence of CuI [14,123,148,149,159-164], titanium enolates [14,142,143], trimethylbenzyltin reagents [18,20,176], and mixed copper—zinc benzyl and aryl reagents (Knochel reagents) [172-175], to 1-acyl-3-R-substituted pyridinium salts (R = H, Br, Cl, Me, Ph), and during the selective γ-addition of nitromethane and nitroethane anions to 1-alkyl-3,5-dichloropyridinium cations [37].

Exclusive α-selectivity was observed during nucleophilic addition to the various 3-R-substituted pyridinium and quinolinium cations both with kinetic and with thermodynamic control in the reactions with "hard" nucleophiles: Ammonia [51,52,81], amines [1,4,5,13,78,103], hydrazines [3-5,7,71,72], hydroxide ion [4,5], methyl, alkenyl, and alkynyl Grignard reagents [57,60,65,151-152], alkynyl- and allyltin reagents [65,153,154,156], and various metal hydrides [24,114,127]. Here, in the case of the addition of "hard" nucleophiles to 3-R-substituted pyridinium cations two types of regioselectivity are possible, i.e., 1,6- or 1,2-addition. The data presented in Table 10 show convincingly that under the conditions of kinetic control donating (OAc, OMe), weakly donating, and certain weakly accepting β-substituents give rise to preferential addition of "hard" nucleophiles at the C-2 atom of the 1-alkyl- and 1-acylpyridinium cations (the so-called "ortho-directing" effect of the β-substituent). Such "ortho-directing" substituents include the following groups: [154,156], OMe [46,114,123], SMe [114], Me, Et, CH_2R [51,65,113,114,122,123,146,156], I, Br, Cl [51], 114,123,126,154,156], $SnMe_3$, $SnBu_3$, $SiMe_3$ [114]. These substituents exhibit the above-mentioned effect in the reactions of the respective pyridinium cations with complex metal hydrides [114,122,123,126], with ammonia [51,52], and with C-nucleophiles [65,113,146,154,156]. In contrast accepting β-substituents like the $CONH_2$, CONHR [27,28,38,51,52,97,103,106,121], COR [15,41,51,97,102-104,147], COOR [14,51,102], $CH{=}CH{-}COR$ [15,25,41,102,104], CF_3 [51], Ph and Ar [52,212], SO_2Me_2 [98], and CN [98,103,131,146] groups undoubtedly exhibit a "para-directing" effect in the reactions of 1-alkyl-, 1-aryl-, and 1-acylpyridinium salts with "hard" nucleophiles (alkoxide ions [13,98], ammonia [51,52,106], amines [103,121], sodium borohydride [24,38,98], and various C-nucleophiles [14,15,25,27,28,41,102,131,146,147,212]) under the conditions of kinetic control. Under the conditions of thermodynamic control, however, preferential or exclusive γ-selectivity is as a rule observed during the addition both of "hard" [36,38,41,79,80,98-100,104] and of "soft" nucleophiles [23,26,37,80,81,86,90,130]. There is no doubt that such contrasting effects from the donating (or weakly accepting) and accepting β-substituents are due primarily to their electronic effect on the electron density distribution in the cation and the electrophilicity of the reaction centers C-2, C-4, and C-6, although the role of the steric factor, which may give rise to preferred addition at C-6, increases with increase in the steric demands of the β-substituent and the size of the attacking nucleophile. On the other hand, the electronic effect of donating and weakly accepting β-substituents leads to greater thermodynamic stability in the 1,2-adducts of 1-alkyl- and 1-arylpyridinium salts with O- and N-nucleophiles. This agrees both with the theoretical calculations [16] and with the experimental data [36,39,52,83,84] for the stability of the 1,2-adducts of the same nucleophiles with monosubstituted 1-alkyl- and 1-arylpyridinium cations.

TABLE 10. Effect of β-Substituents on the Kinetic Regioselectivity of Nucleophilic Addition to Pyridinium Cations

Nucleophilic reagent	N-Substituent	Other substituents	Yield, %	Ratio of 1,2- and 1,6-DHP	Reference
ArMgBr [a]	CH_2R [b]	3-CN	25...94	0 : 100	[146]
PhMgBr	Me	3-CN, 5-Me	70	0 : 100	[146]
PhMgBr	COPh	3-COPh	62	13 : 49 [c]	[146]
NH_2^-	CH_2R [d]	3-R^1 [d]	Quant.	0 : 100	[51]
NH_2^-	CH_2R [e]	3-$CONH_2$	Quant.	0 : 100	[52, 106]
$NH_3/KMnO_4$	CH_2R [b]	3-R^1 [f]	—	0 : 100	[6, 52]
Piperidine	CH_2R [b]	3-R^1 [g]	70...85	0 : 100	[103]
RO_3^- [h]	CH_2R^1 [h]	3-R^2 [h]	19...74	0 : 100	[98]
2-Methylindole	Me	3-CN	95	0 : 100	[131]
$NaBH_4/EtOH$	CH_2Ph	3-Et	95 [i]	100 : 0	[122]
$NaBH_4/EtOH$	COOMe	3-Et	90	100 : 0	[205]
$NaBH_4/MeOH$	Me	3-SO_2NMe_2	70	100 : 0	[98]
$NaBH_4/MeOH$	COOPh	3-R [j]	35...56	100 : 0	[123]
$NaBH_4/MeOH$	COOR [k]	3-R1 [k]	60...95	> 90 : 10	[114]
$O_2NCH_2^-$	Me	3-OMe	—	100 : 0	[46]
$CH_2{=}CHCH_2SnBu_3$	COOMe	3-R [l]	74...96	100 : 0	[154]

a) Ar = Ph, 4-MeC_6H_4, 2-MeC_6H_4.

b) R = H, Ph.

c) The ratio of 1,4- and 1,6-DHP is given.

d) R = H, Ph, 4-$NO_2C_6H_4$; R^1 = $CONH_2$, COOMe, COMe, CF_3.

e) R = H, Me, Et.

f) R^1 = $CONH_2$, Ph.

g) R = CN, COMe, $CONH_2$.

h) R = Me, Et, *n*-Pr, *i*-Pr, *t*-Bu, R^1 = H, 2,6-$Cl_2C_6H_3$, 4-FC_6H_4, R^2 = COPh, CN, CONHMe, SO_2NMe_2.

i) The yield of 1-benzyl-3-ethyl-1,2,5,6-tetrahydropyridine is given.

j) R = Me, Br, Cl, OMe.

k) R = Et, CH_2Ph, R^1 = Me, Et, Cl, Br, MeO, MeS.

l) R = Cl, Br, OAc.

Some exceptions from the investigated relationships are known [7,51,66,126,146,206]; they are probably due to the specific electronic or steric effect of the β-substituents of the cations in the reactions with certain nucleophiles or to the size or nature of the attacking C- and H-nucleophile [65,115,126,206].

It is necessary to mention the unexpected "ortho-directing" effect of the methoxy group at the β position of the 1-methylpyridinium salt for the reaction with the nitromethane anion in liquid ammonia [46]. Whereas the nature of almost all other substituents does not have a substantial effect on the change in the γ-selectivity of the analogous reactions with this "soft" nucleophile, the methoxy group gives rise to its exclusive 1,2-addition under the conditions of kinetic control [46].

Analysis of the published data indicates that the electronic effect of the substituents at position 1 or 3 of the cation has a substantial effect not only on the reactivity of the pyridinium and quinolinium salts but also on the kinetic and thermodynamic regioselectivity of nucleophilic addition. In the general case the nature of the N-substituent has a more substantial effect on the α- or γ-selectivity of the transformations under the conditions of kinetic control, irrespective of the "hard" or "soft" nature of the added nucleophile. At the same time the nature of the β-substituent has a more significant effect on the predominance of α-selectivity during the addition of "hard" nucleophiles under kinetically controlled conditions and on the predominance of α- or γ-selectivity during the addition of "hard" nucleophiles under the conditions of thermodynamic control. The effect of the structure of the cation hardly shows up at all in the reactions of 1-acylpyridinium salts with clearly defined "soft" nucleophiles, such as organocopper reagents [34,59,165,166], including those generated *in situ* from Grignard reagents or RLi and CuI [14,123,148,149,159-164,167-171], mixed copper—zinc organic reagents [172-175], benzyltin reagents [20,176], copper hydride [24,127], titanium enolates [14,142], silyl ethers of enols [34,165], $Na_2S_2O_4/H_2O$ [12,13,38,95,98], the anions of nitroalkanes [29,37,46,90], and other reagents [13,46,80,177,185] (Tables 1-3, 5). On the basis of the data given in the present review it is possible to state that the regioselective addition of nucleophiles to pyridinium and quinolinium cations is characterized by a specific type of regiocontrol, which depends on the reaction conditions, and by the nature of the nucleophile and electrophile. The investigated types of regioselectivity (regiocontrol) determine the preferential or exclusive addition of the nucleophiles at one of the electrophilic centers of the cation. Here there are several relationships which make it possible to say which type of regiocontrol predominates in relation to the process conditions and the nature of the reagents. Thus, for example, under the conditions of thermodynamic control of the reaction the steric factor of regioselectivity plays a deciding role in determining the composition of the addition products. Under kinetically controlled conditions the steric factor may be of secondary significance, since in this case the selectivity of addition is determined to a greater degree by the electronic nature of the reagents and is due to a specific transition state and addition mechanism.

Thus, by varying the reaction conditions and the type (or nature) of the cation (1-alkyl, 1-alkenyl, 1-aryl, 1-acyl, or α-, β-, and γ-substituted) it is possible to realize one or the other type of regioselectivity effectively during addition and to obtain the desired structures of 1,2-, 1,4-, or 1,6-DHP and 1,2- or 1,4-DHQ or the respective α- or γ-substituted pyridines and quinolines.

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