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THE SIGNIFICANCE OF A CYCLIC π-SEPTET IN SOME REACTIONS OF PYRIDINE AND ITS SALTS

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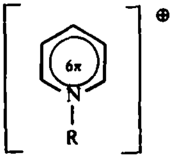
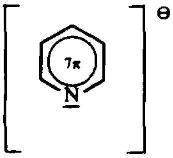
Abstract—A general electron mechanism based on the semiempirical LCAO-MO methods has been proposed for some reactions of pyridine and its salts occuring predominantly at the 4-position of the pyridine ring.

THE transition of a single electron into the lowest anti-bonding π^*-orbital of pyridine (Ia) or its salt (Ib) results in the anion IIa or in the neutral molecule IIb with a cyclic π-electron septet. Experimental evidence of the existence of these "open-shell" systems has been based on ESR spectra by a number of authors.[1–4] These systems have been considered as the reaction intermediates in some cases.[1,3,5,6] Substances of the IIb type ($R = CH_2Ph$ or COPh) may be isolated according to the literature.[7,8] Making use of the semiempirical LCAO-MO method in the investigation of the reactivity, we have now found that, taking the systems IIa and IIb into consideration a satisfactory alternative interpretation can be given for the mechanism of a number of reactions in which the reactivity of the position 4 in the molecules Ia,b is increased in an unexpected manner as compared to simple electrophilic (positions 1 and 3), nucleophilic (position 2) and radical (position 2 in addition to 4 and 3) reactions.

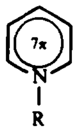
Ia



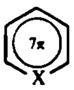
Ib



IIa



IIb



III

RESULTS AND DISCUSSION

The reactivity of the π-electron system of the molecules IIa,b will be strongly affected by the unpaired electron in the π^*-orbital. In this case an adequate index of chemical reactivity corresponds to the probability of finding this electron in the particular positions, i.e. to the frontier density. It follows from Table 1 that, regardless of the method of calculation, the highest value of this index in the quantum chemical model of substances IIa,b is always to be found in the position 4, which is in agreement with determined experimental spin densities.[1–4] The symmetry of the wave function of this electron in position 4 is most favourable for overlapping with the orbital of the attacking reagent as follows from the values of AO coefficients and from the position of both nodal planes a_1 and a_2 of the lowest π^*-orbital (cf. Fig 1). These data permit also a

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qualitative interpretation of the experimentally determined[9] stability of substance IIb substituted by an electronegative alkoxycarbonyl group in the position 4. This substituent is able to decrease the absolute value of the AO coefficient, and consequently also the reactivity of the π-electron septet in the above position. The values of free valences calculated for a HMO model of III with parameters 1,5 > h_X > O also indicate a preferential reactivity of position 4 in IIa,b. The use of the HMO localization theory for distinguishing the one-electron mechanism from a two-electron nucleophilic mechanism does not seem appropriate because the quantum-chemical models of Wheland's σ-complexes, which result from a radical attack of the substrates IIa or IIb and from a nucleophilic attack of the substances Ia or Ib, are identical in structure. Consequently,

$$L_r(7) = L_n(6) - k$$

where $L_r(7)$ is the atomic localization energy of the π-septet IIa or IIb, respectively, $L_n(6)$ is the analogous nucleophilic energy of the π-septet Ia or Ib, respectively, and k is the energy of the π-MO into which the electrons pass from the attacking reagents. In contradiction to the localization theory our interpretation employs a model of the activated complex which more or less approaches a radical pair (the charge-transfer is successive).

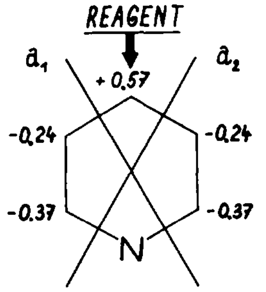


FIG. 1. Coefficients of AO's computed by the SCF method.

Electrolytic reductions. The electroreduction of pyridine in protic media, i.e. with a possibility of the reaction $Ia + H^+ \rightleftharpoons Ib$ leads prevalently to piperidine[11] the formation of which can be elucidated by a further reduction of 1,4-dihydropyridine IV ($R^1 = R^2 = H$) formed by a one electron attack in position 4 according to the following schemes: $Ia + e^- \rightleftharpoons IIa$; $IIa + H^+ = IIb$; $Ib + e = IIb(R = H)$; $IIb + e^+ \rightarrow IV$.

In the polarographic reduction of pyridine no separate wave corresponding solely to the reduction of the pyridine nucleus has been found[12, 13] in addition to the wave of catalytic hydrogen evolution typical for nitrogen containing bases. This may be due to the merging of the two waves owing to instability of the intermediate IIb (R = H) under the given experimental conditions. The π-electron excess obviously lowers the polarity of the N-H bond and makes easier the homolysis $IIb \rightarrow H. + Ia$, $2\ H. \rightarrow H_2$. This reaction is connected with a transfer of one π-electron into the non-bonding orbital of nitrogen. In the electrolytic reductions of quarternary salts Ib(R = alkyl) at the lead electrodes, 1-alkylpiperidines[14] and the corresponding 4,4'-dipiperidyls[14] were isolated as the main products. The formation of the former may be interpreted by electroreduction of 1,4-dihydroderivatives IV (R^1 = alkyl, R^2 = H) which result in a similar manner as the pyridine reduction ($Ib + e^- \rightleftharpoons IIb$, $IIb + e^- + H^+ \rightarrow IV$) and the formation of the later mentioned product by electroreduction of 4,4′-dimers V (R^1 = alkyl, R^2 = H) obtained by the reaction 2 IIb→V. It was Emmert[15] who succeeded in isolating the reduction intermediates V ($R = CH_2Ph$ and Et) using a platinum electrode. Moreover in a potentiostatic reduction of homologous quarternary salts Ib at a mercury electrode, the formation of the blue radical cation VI has been proved[16] by means of ESR spectra.

TABLE 1. FRONTIER ELECTRON DENSITIES OF SUBSTANCES IIA AND IIB

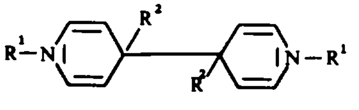
Method of Calculation	Position 1	2	3	4
HMO (h_N=0·5)[a]	0·298	0·134	0·057	0·321
HMO (h_N=1·0)[a]	0·246	0·179	0·039	0·317
HMO (h_N=1·5)[a]	0·196	0·215	0·028	0·317
HMO (h_N=2·0)[a]	0·154	0·243	0·020	0·319
SCF (IIa)[b]	0·280	0·133	0·061	0·331
SCF (IIb)[b]	0·277	0·141	0·057	0·327

[a] Parameters: $\alpha_N = \alpha_C + h_N\beta_{CC}$, $\beta_{CN} = \beta_{CC}$.

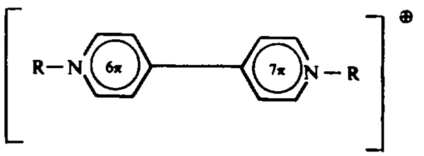
[b] Geometry: bonds 1·4Å, angles 120°; ionization potentials I_C = 11·16 eV, I_N = 14·2 eV, I_N = 13·55 eV; electron affinities A_C = 0·03 eV, A_N = 1·78 eV, A_N = 2·53 eV; gamma-integrals according to Mataga-Nishimoto, h_N = O, β_{CC} = −2·388 eV. All calculations have been carried out by means of standard programs on a E503 computer in the Computer Centre of the Institute of Chemical Technology in Prague.

In a mixed electroreduction of pyridine with acetone at lead cathodes a considerable quantity of the piperidine derivative VII (R = H) has been found[17] in addition to the 2-substituted 3-piperidine derivative. The formation of VII corresponds to an electroreduction of the 1,4-dihydroderivative IV (R^1 = H, $R^2 = (CH_3)_2C(OH)$). The other reaction partner seems to be a transient radical $(CH_3)_2CO + e^- + H^+ \rightarrow (CH_3)_2\dot{C}—OH$ which attacks the π-electron septet in the position 4: IIb (R = H) + $(CH_3)_2\dot{C}—OH \rightarrow$ IV.

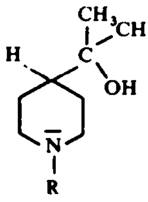
IV



V

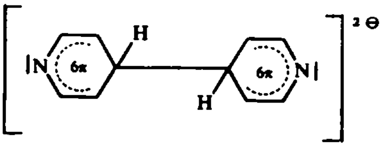


VI



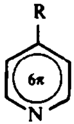
VII

VIII

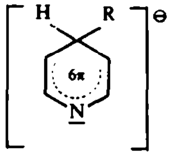


IX

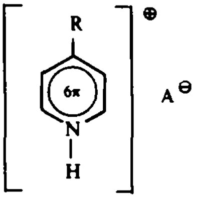
Reactions with metals. Reaction of pyridine with alkali metals in aprotic media leads prevalently to 4,4′-bipyridyl (VIII).[1,18] The mechanism $Ia + M \rightarrow IIa + M^+$, $2\ IIa \rightarrow IX$, $IX \rightarrow VIII + 2\ H^-$ was considered by several authors,[1,3,6] but the prevailing 4,4′-coupling was ascribed to sterical effects.[6] In protic media piperidine is the main product[19] formed from 1,4-dihydropyridine IV ($R^1 = R^2 = H$) according to the scheme: $Ia + Na \rightarrow IIa + Na^+$, $IIa + H^+ \rightarrow IIb + (Na + H^+) \rightarrow IV + Na^+$. The presence of substance IV in the reaction mixture was proved by hydrolysis to glutaraldehyde.[20] In the reduction of quaternary salts Ib ($R = $ alkyl) by the sodium amalgam, a 4,4′-dimerization to substance V ($R^1 = $ alkyl, $R^2 = H$) occurs[21]. The reaction mechanism is as follows: $Ib + Na \rightarrow IIb + Na^+$, $2\ IIb \rightarrow V$. An analogous bis-dihydropyridine derivative V ($R^1 = Ac$, $R^2 = H$) results in the reduction of pyridine by zinc in acetic anhydride[5][$Ia + Ac_2O \rightleftharpoons Ib + AcO^-$ ($R = Ac$), $2\ Ib + Zn \rightarrow IIb + Zn^{2+}$ or $2\ Ia + Zn \rightarrow 2\ IIa + Zn^{2+}$, $IIa + Ac_2O \rightarrow IIb + AcO^-$ and in the last step $2\ IIb \rightarrow V$] and is regarded[6,22] as the key intermediate of the Wibaut-Arens 4-alkylation of pyridine.[22] In accordance with the experimental knowledge about the fission of V ($R^1 = Ac$, $R^2 = H$) to pyridine and 4-acetylpyridine X ($R = Ac$)[22] one may write $V \rightleftharpoons 2\ IIb$ (cf.[23]) where, owing to the presence of a π-septet a homolysis of the N-Ac bond is made possible: $IIb \rightarrow Ia + Ac\cdot$; this is followed by the reaction $IIb + Ac\cdot \rightarrow IV$ ($R^1, R^2 = Ac$) and $IV \rightarrow X$ $(R = Ac) + AcH(?)$. The smaller quantity of 4-substituted products in the Emmert reaction of pyridine by action of ketone and metal[6] could be interpreted by an analogous mechanism as in the mixed electroreduction[17] under consideration of $Ia + Al \rightarrow IIb$ ($R = Al$-) but the prevailing 2-substitution points either to the important role of the sterical factor owing to a polyvalency of the metal[6] or to the simple nucleophilic substitution of the π-septet in Ia by the action of the reagent $(R_2\overline{C}—OM)^-$.[24] It cannot be excluded that the reaction with the metal ($R = Hg$) affects in a decisive manner the potentiostatic reduction of pyridine and acetone at the mercury cathode because exclusively 2-substituted products[25] were isolated (contrary to the same reaction at a lead cathode[17]).



X



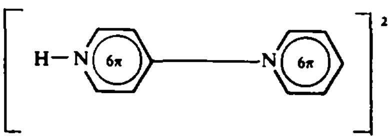
XI



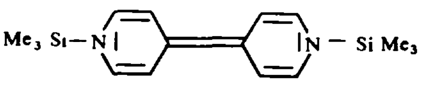
XII

Reactions with organometallic reagents. In contrast to the usual nucleophilic 2-substitution by organolithium reagents, the reactions of pyridine with organometals of the benzyl or allyl type R^1MgR^2 ($R^1 = $ benzyl, $R^2 = Cl$ or benzyl), or RLi ($R = $ benzyl or allyl) take place exclusively or prevalently in the position 4.[26–28] It is characteristic for anions derived from these organometallic reagents that in reactions they represent donors of weakly bonded π-electrons from non-bonding MO. As a result of this, the joining of the alkyl to pyridine may be preceded by a transition of a single π-electron from the reagent to the pyridine nucleus, yielding thus the π-septet of IIa which only in a further step is alkylated by a radical mechanism, e.g. $Ia + R^1MgR^2 \rightarrow IIa + R^1\cdot + MgR^2$, and $IIa + R^1\cdot \rightarrow XI \rightarrow X + H$ ($R^1 = R$), or $Ia + RLi \rightarrow IIa + R\cdot + Li^+$, and $IIa + R\cdot \rightarrow XI$, $XI \rightarrow X + H^-$. The 4-butylation of pyridine by action of butyl chloride and magnesium at increased temperature ($R^1 = Bu$ and $R^2 = Cl$)[29] and probably also the reaction of the cation Ib (R = benzyl) with cyclopentadienyl lithium[30] probably occur in an analogous manner. Phenyl- and ethyl magnesium bromide, which at low temperatures exhibit a poor reactivity towards pyridine, yield only a mixture of bipyridyls at raised temperature.[31] This fact indicates the possibility of a radical mechanism (dimerization of the radical anion IIa).

Thermic transformations. The outstanding 4-alkylation in the Ladenburg thermic transformation of quaternary pyridinium salts (R = alkyl) has been elucidated[10, 32] and is based on more recent experimental information by the following mechanism: $\text{Ib} + \text{A}^-$ (A = Cl, Br,I) $\rightarrow \text{IIb} + \text{R}\cdot$ (R = A), $\text{IIb} + \text{R}\cdot \rightarrow \text{XII}$ (R = alkyl). On longer standing with ketones, l-acylpyridinium salts give rise to 1,4-dihydropyridines IV (R^1 = acyl, R^2 = 2-ketonyl) which have been isolated. In the case of acetophone the following scheme is to be considered: $\text{Ib} + \text{Cl} + \text{PhCOCH}_3 \rightarrow \text{PhCOCH}_2\cdot + \text{HCl} + \text{IIb}$ (R = PhCO), $\text{IIb} + \text{PhCOCH}_2\cdot \rightarrow \text{IV}$ (R^1 = PhCO, R^2 = $PhCOCH_2$). This mechanism could be taken into account in the analogous reaction of salts Ib (R = PhCO) with dimethylaniline.[34]



XIII



XIV

Reactions with inorganic halogenides. By homolysis of the intermediate IIb (R = Cl) one may also explain the prevailing 4-substitution in the reaction of pyridine with thionyl chloride[35, 46] and of pyridine-N-oxide hydrochloride (Ib, R = OH) with sulphuryl chloride.[37] In the first case substance XIII is formed: $\text{Ia} + \text{SOCl}_2 \rightarrow \text{Ib}$ (R = SOCl) + Cl^-, 2 Ib + 2 $\text{Cl}^- \rightarrow$ 2 IIb (R = Cl) + 2 Cl· + 2 S + O_2, IIb + Cl· $\rightarrow$ IV($R^1 = R^2 = Cl$), IV $\rightarrow$ XII (R = A = Cl), XII + Ia $\rightarrow$ XIII. In the second case the reaction evidently stops at the stage of 4-chloropyridine hydrochloride (XII, R = A = Cl); since no free pyridine is present in the reaction mixture: Ib(R = OH) + Cl^- $\rightarrow$ IIb(R = Cl) + OH·, IIb + OH· $\rightarrow$ IV(R^1 = Cl, R^2 = OH), IV $\rightarrow$ XII (A = Cl, R = OH), 2 XII (R = OH) + $SO_2Cl_2 \rightarrow$ 2 XII (R = A = Cl) + H_2SO_4. It cannot be excluded that the role of OH is taken over by the more complex fragment of the —OSO_2Cl type.

Silylation: Also the prevailing formation of substances IV ($R^1 = SiMe_3$, $R^2 = H$) and XIV in the reaction of pyridine with trimethylsilane[38]: Ia + $Me_3Si\cdot \rightarrow$ IIb (R = $SiMe_3$), IIb + H· $\rightarrow$ IV ($R^1 = SiMe_3$, $R^2 = H$), 2 IIb $\rightarrow$ V ($R^1 = SiMe_3$, $R^2 = H$) $\rightarrow$ XIV + 2H.

REFERENCES

[1] R. L. Ward, *J. Am. Chem. Soc.* **83**, 3623 (1961)

[2] C. L. Talcott and R. J. Myers, *Mol. Phys.* 12, 549 (1967)

[3] J. Chaudhuri, S. Kume, J. Jagur and M. Szwarz, *J. Am. Chem. Soc.* **90**, 6421 (1968)

[4] J. Komenda and A. Novák, *Third Symposium on the Heterocyclic Compounds*, Brno, Czechoslovakia. September 23–25 (1969)

[5] O. Dimroth and R. Heene, *Ber. Dtsch. Chem. Ges.* **54**, 2934 (1921)

[6] R. A. Barnes, *Pyridine and Its Derivatives* (Edited E. Klingsberg) Part I, Chapter I. Interscience, New York (1960)

[7] E. Weitz and A. Nelken, *Liebigs Ann.* **425**, 192 (1921)
[8] E. Weitz, A. Roth and A. Nelken, *Ibid.* **425**, 161 (1921)
[9] E. M. Kosower and E. J. Poziomek, *J. Am. Chem. Soc.* **85**, 2036 (1963)
[10] J. Kuthan, N. V. Koshmina, J. Paleček and V. Skála, *Coll. Czech. Chem. Comm.* in press
[11] M. Ferles, *Ibid.* **24**, 2221 (1959)
[12] L. D. Klyukina and S. G. Mairanovkii, *Izvestiya Akad. Nauk SSSR* **1176**, 1183 (1963)
[13] J. Kůta and J. Drábek, *Coll. Czech. Chem. Comm.* **20**, 902 (1955)
[14] E. Ochiai and N. Kawagoye, *J. Pharm. Soc. Japan* **63**, 313 (1943); *Chem. Abstr.* **45**, 5153 (1951)
[15] B. Emmert, *Ber. Dtsch. Chem. Ges.* **42**, 1997 (1909)
[16] J. Volke and M. Naarová, unpublished results
[17] M. Ferles, M. Vanka and A. Silhánková, *Coll. Czech. Chem. Comm.* **34**, 2108 (1969)
[18] C. R. Smith, *J. Am. Chem. Soc.* **46**, 414 (1924)
[19] A. Ladenburg, *Ber. Dtsch. Chem. Ges.* **17**, 157 (1884)
[20] B. D. Shaw, *J. Chem. Soc.* **127**, 215 (1925)
[21] B. Emmert, *Ber. Dtsch. Chem. Ges.* **52**, 1351 (1919)
[22] J. P. Wibaut and J. F. Arens, *Rec. Trav. Chim.* **60**, 119 (1941)
[23] R. L. Frank, F. Pelletier and F. W. Starks, *J. Am. Chem. Soc.* **70**, 1767 (1948)
[24] G. B. Bachman, M. Hamer, E. Dunning and R. M. Schisla, *J. Org. Chem.* **22**, 1296 (1957)
[25] T. Nonaka and K. Sugino, *J. Electrochem. Soc.* **116**, 615 (1969)
[26] R. A. Benkeser and D. S. Holton, *J. Am. Chem. Soc.* **73**, 5861 (1951)
[27] H. Gilman and H. A. McNinch, *J. Org. Chem.* **27**, 1889 (1962)
[28] R. A. Abramovitch and J. A. Poulton, *J. Chem. Soc.* (B) 901 (1969)
[29] D. Bryce-Smith, J. P. Norris and B. J. Wakefield, *Chem. & Ind.* 495 (1964)
[30] D. N. Kussanov and N. K. Baranetskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* 1703 (1961)
[31] N. Goetz-Luthy, *J. Am. Chem. Soc.* **71**, 2254 (1949)
[32] P. A. Claret and G. H. Williams, *J. Chem. Soc.* (C) 146 (1969)
[33] W. E. von Doering and W. E. McEwen, *J. Am. Chem. Soc.* **73**, 2104 (1951)
[34] W. E. McEwen, R. H. Terss and I. W. Elliott, *Ibid.* **74**, 3605 (1952)
[35] E. Koenigs and H. Greiner, *Ber. Dtsch. Chem. Ges.* **64**, 1049 (1931)
[36] D. Jerchel, H. Fischer and K. Thomas, *Chem. Ber.* **89**, 2921 (1956)
[37] B. Bobrański, L. Kochańska and A. Kowalewska, *Ber. Dtsch. Chem. Ges.* **71**, 2385 (1938)