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THE MECHANISM OF ISOMERIZATION RECYCLIZATION OF DIACETYL DERIVATIVES OF PYRIDINIUM SALTS

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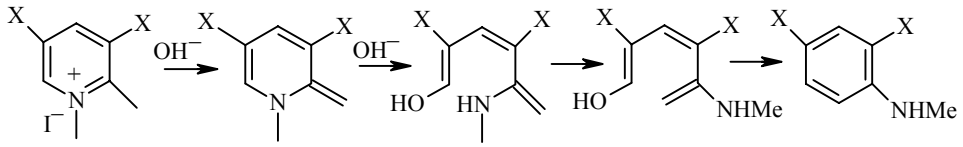
A mechanism has been considered for the recyclization of pyridinium salts using their diacetyl derivatives as an example. The enthalpies of formation of the intermediates were estimated by the molecular mechanics method (MMX88). The nature of the rate-determining step of the reaction is discussed.

Keywords: pyridinium salts, recyclization, MMX88.

The range of compounds capable of isomerization recyclization has been broadened significantly because of derivatives of pyridinium salts containing acyl, amide, ester, and also cyano and bridge polymethylene substituents. Conversions have been carried out which extend the traditional ideas on the synthetic possibilities of recyclization [1,2]. Discussion of the results obtained and the search for new synthetic directions require specification of the mechanism of this reaction and the development of methods for the theoretical prediction of recyclization. The results considered below were obtained for 3,5-diacetyl derivatives of pyridinium salts but they may probably be extended to other compounds capable of recyclization.

In early studies the first step of isomerization recyclization of pyridinium salts was represented as an acid-base equilibrium with the formation of anhydro bases, which made definite advances possible in the quantum chemical description of recyclization [3].



Subsequently this mechanism was abandoned for the following reasons.

1) In several cases (recyclization of indolizines, nicotyrine, opening of Zincke salts, etc.) the formation of anhydro bases is impossible in principle.

2) Compounds which readily form anhydro bases proved to be generally incapable of recyclization until the formation of the anhydro base was not blocked [4].

3) The considerable value of the difference in enthalpies of formation of pseudo bases and anhydro base–water systems (90 kcal/mole* for α-picoline) makes their simultaneous existence impossible in solution (but this does not prevent removal of the initial salt from the reaction sphere as a precipitate of anhydro base).

* Here and subsequently the first value refers to the unsubstituted picolinium salt (X = H), and the second (in parentheses) to its 3,5-diacetyl derivative (X = $COCH_3$).

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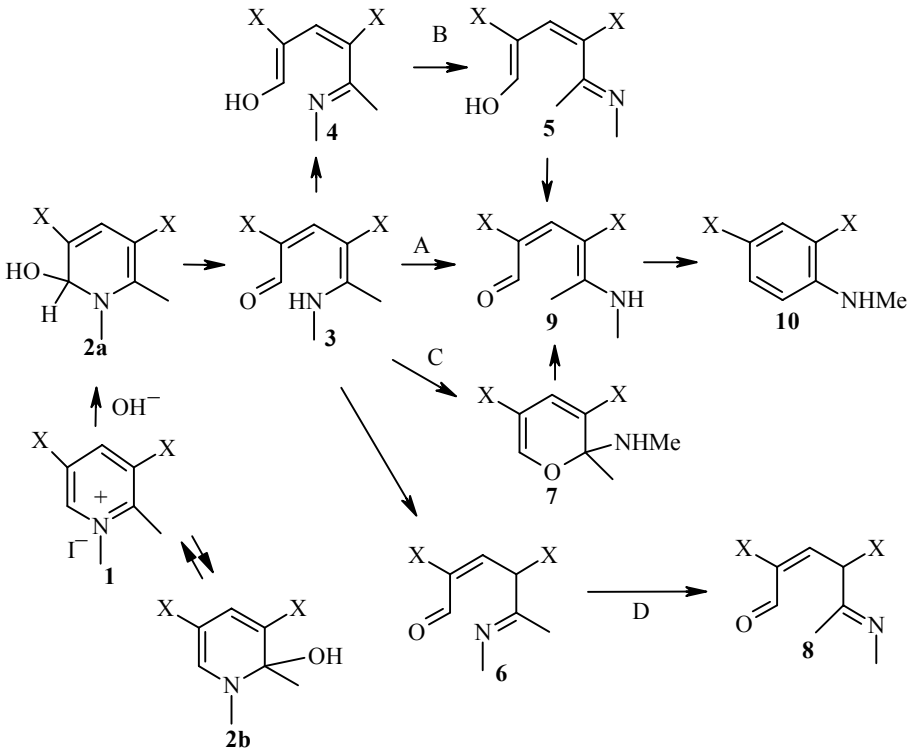
It is therefore more natural to postulate pseudo bases, the neutral analogs of anionic σ-complexes, as intermediates of the recyclization [5] and to regard anhydro bases as side products of the reaction.

The mechanism of forming aromatic amines **10** from pyridinium salts **1** may be represented in the form of four variants of sequential conversions of intermediates characterized by the means of drawing together the methylene and carbonyl components (by transition of the *E*-form **3** into the *Z*-form **9**; certain intermediates having a large enthalpy of formation and not introduced into this scheme are represented in Table 1).



Variant a assumes the carbonyl and methylene groups come together by rotation directly about the C=C double bond. In variants B and D the order of the corresponding bond is first changed as a result of various tautomeric conversions (other examples of possible tautomers **4a**, **6a-g** are given in Table 1). Variant C considers the possibility of forming the required *Z*-isomer by the intermediate formation and opening of the cyclic system (**7**).

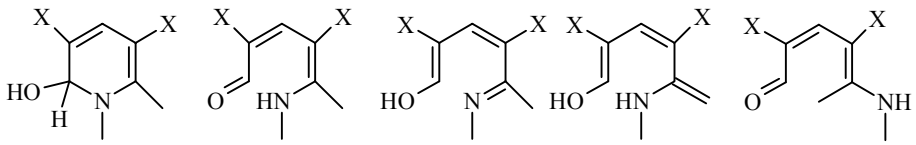
We are specifying that as a result of nucleophilic attack on the initial salt **1** it is possible to form two pseudo bases **2a** (ΔH_{form} = -21 (-116) kcal/mole) and **2b** (ΔH_{form} = -33 (-132) kcal/mole). However it is easy to make sure that the open forms formed from the somewhat more advantageous base **2b** may not lead to the recyclization product. The absence of products of their intermolecular condensation is probably explained by the short life of the intermediates compared with the relaxation time of the hydrate shield of the cation of the pyridinium salt (solvent cage).

Opening of pseudo base **2a** may lead to the formation of a series of tautomeric intermediates (Table 1), however the Boltzman factors of all the forms, apart from enamine forms with an unbroken conjugation chain (**3** and **9**), are vanishingly small.

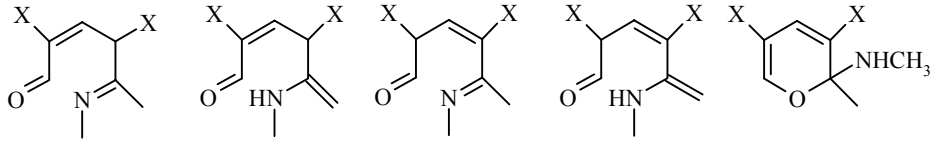
Of the two possible variants of ring opening of the pseudo bases, the electrocyclic (A) and the ionic (B), the ionic variant is probably preferred since:

1) the formation of open forms has never been noted for nucleophiles not capable of ionic opening of the ring (Cl^-, Br^-, I^-, CN^-, etc),

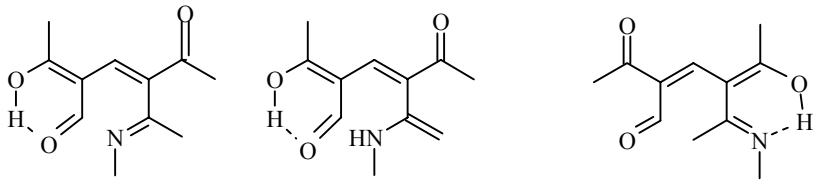
TABLE 1. Enthalpies of Formation of Possible Intermediates of the Recyclization Relative to the Corresponding Pseudo Bases, kcal/mole, X = H (X = $COCH_3$)



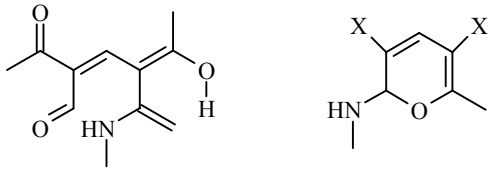
2a: 0 (0) **3**: –14 (–14) **4**: 49 (52) **4a**: 43 (30) **9**: –4 (–17)



6: 76 (142) **6a**: 67 (72) **6b**: 68 (127) **6c**: 15 (17) **7**: 41 (44)

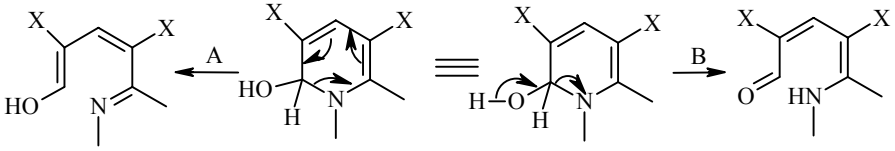


6d: (49) **6e**: (40) **6f**: (64)



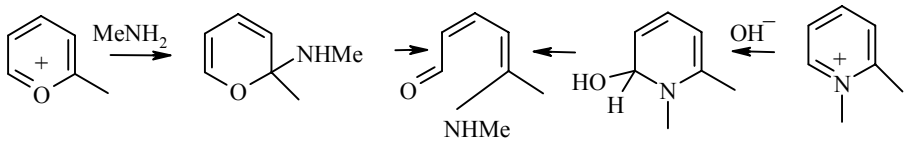
6g: (41) **7a**: 14 (12)

2) the enthalpy of formation of imine forms **4** formed by electrocyclic opening is greater than the enthalpy of formation of the corresponding pseudo bases by 49-52 kcal/mole (Table 1).



This additional contribution to the value of the overall potential barrier to cyclization must have made it practically insuperable, however recyclization of diacetyl derivatives of pyridinium salts proceeds under mild conditions [6]. In addition the formation of enamine forms **3** on ionic opening is exothermic (ΔH = -14 kcal/mole).

It is easy to see that the sets of possible open forms formed from pyrylium salts by the action of methylamine and from picolinium salts in alkaline medium partially coincide (under particular conditions they also lead to the same products).

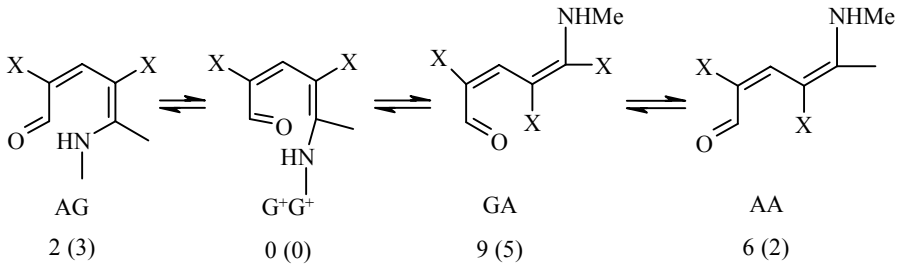


In other words the use of pyrylium salts makes the uncommon possibility of "abandoning" the pyridinium system to the upper part of the potential surface, not by the thermal route but as a result of the internal energy of the reactants. It is known that recyclization of pyrylium salts under the action of methylamine leads to α-picolinium salts, and with secondary amines, for which the formation of the initial salts is impossible, to the corresponding anilines [7]. The fact that the reaction may be directed under mild conditions to the starting materials and to the recyclization products, shows that the open forms are in the upper portion of the potential surface, in the region close to the transition state.

We note that the preferred formation of pyridinium salts from pyrylium salts and not anilines, the products of recyclization, is probably explained by the significantly lower energy of formation of the pseudo base **7a** (Table 1), leading, in difference to pseudo base **7**, to the pyridine (kinetic control of the reaction).

Within the framework of the mechanism being discussed four stages may claim to have a rate-determining role. These are the formation of the pseudo base (steps **1-2a**), opening of the pseudo base (**2a-3**), *E-Z* isomerization of forms **3** and **9**, and the aldol-crotonic condensation (**9-10**).

It is known that the presence of a methyl group in the γ-position of a pyridine ring leads to a significant reduction in the yield of recyclization product, which was used previously for the development of alternative ideas on the mechanism of recyclization in the presence of sodium hydrosulfite [8]. However this effect may be explained completely within the framework of the proposed mechanism, if the *E-Z* isomerization is taken as the step limiting the rate of recyclization. There is the following conformational equilibrium for the opening of the *E*-form **3**.



Probably the close spatial disposition of the amino and carbonyl groups in the AG and G^+G^+ conformers of the *E*-form is favorable for the running of the reverse reaction of forming pseudo base **2a** and the initial salt **1**, but its isomerization into the *Z*-form requires more significant energy consumption. The mutual separation of these functional groups in the GA and AA conformers makes sterically possible the course of only the direct reaction to give the *Z*-form and then the final product **10**. The introduction of a methyl group into the pyridine ring hinders the formation of the GA conformer, increasing its internal energy due to steric interactions by 2-3 kcal/mole (the closely similar behavior of polymethyl derivatives of butadiene is known [9,10]). In accordance with Hammond's postulate on the closeness of structure of a transition state to the structure of the closest intermediate, the energy of the transition state must also be changed, which leads to a reduction in the reaction rate of approximately 50-fold.

We note that it is possible to explain in a similar manner the inhibiting effect of a γ-methyl substituent, preventing fission of substituted pyridinium salts in alkaline medium (Zincke–Kenig reaction [11]).

It seemed that the transition from the *E*-form to the *Z*-form should naturally be effected by rotation about the single bond of the appropriate tautomeric intermediates (variants a and d of the mechanism). However the

formation of these very intermediates requires the significant energy consumption of 63 (66) kcal/mole (Table 1). The formation of cyclic form **7** (variant C) also requires the large energy consumption of 28 (26) kcal/mole. We note that in both cases we speak not of the barrier of the corresponding stages of routes A, C, and D, but only of the significantly lower value of the difference of enthalpies of formation of intermediates **4** and **6**. In this situation analysis of the possibility of direct rotation about the double bond (mechanism variant B) acquires a definite interest. The high barrier (65 kcal/mole) makes rotation about an ethylenic bond impossible. However cases are known of reducing this barrier by partial reduction of the order of the double bond by interaction with the π-system of substituents or conjugation with the unshared pair of a heteroatom. A particularly significant reduction of the barrier to rotation is observed in the simultaneous presence of donor and acceptor substituents ("push–pull" substitution, 10-25 kcal/mole [12]). Estimation by molecular mechanics of the contributions of substituents shows that the introduction of an acetyl group reduces the value of the barrier from 65 to 44, of an amino group (enamine form of aminoethylene) to 33, and in their combined presence to 18 kcal/mole. The absolute value of the size of the considered barrier is not so important, since it is only one of the contributions to the energy of activation. However a change of the value of this barrier on comparing salts close to one another in structure may serve as an index of reactivity, since the remaining contributions to the energy of activation, connected with transition from the initial salt to the *E*-form **3**, will be approximately the same, because they are put together from the enthalpies of fission and formation of one type of bond. For example, the reduction of this barrier on going from α-picolinium iodide to 3,5-diacetyl-α-picolinium iodide (from 23 to 8 kcal/mole) corresponds to acceleration of the corresponding rate-determining elementary stage by approximately one million times. This is qualitatively in agreement with the inability of α-methylpicolinium iodomethylate to recyclize in difference to the facile recyclizing of its diacetyl derivative.

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