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# MECHANISM FOR ANNELATION ([2+4] CYCLOCONDENSATION) OF SCHIFF BASES BY β-DICARBONYL AND β,β'-TRICARBONYL COMPOUNDS IN AMPHIPROTIC MEDIA (REVIEW)

**O. V. Gulyakevich and A. L. Mikhal'chuk**

*The mechanism was established for annelation ([2+4] cyclocondensation) of Schiff bases or azomethines by β-dicarbonyl and β,β'-tricarbonyl compounds in amphiprotic media. The condensation was found to be a self-catalyzed pericyclic process achieved through six-membered transition states. The key reaction intermediates are dipoles of quaternized azomethine ions and enol-anions of the β-dicarbonyl and β,β'-tricarbonyl compounds, which display 1,4-dipolarophilicity.*

**Keywords:** azangular heterocycles, 8-azasteroids, azomethines, 2-acyl-1,3-cyclanediones, β-dicarbonyl compounds, β,β'-tricarbonyl compounds, pyrido[2,1-*a*]isoquinolines, Schiff bases, annelation, keto-enol tautomerism, reaction mechanism, [2+4] cyclocondensation.

The annelation of Schiff bases or azomethines by β-dicarbonyl compounds (β-diCC) and β,β'-tricarbonyl compounds (β,β'-triCC) is given in formal generalized form as **1 + 2 → 3 (**Scheme 1), which was first studied and described for examples of the [2+4] cyclocondensation of 3,4-dihydroisoquinolines with derivatives of acetyl acetone, benzoyl acetone, 2-acetylcycloalkanones, 3-acetyl-4-piperidones, and 2-acetyl-dimedone [1]. The essence of this reaction is the one-stage formation of a partially hydrogenated γ-pyridone ring of molecular cores of azangular heterocycles (AH), namely, condensed heterocyclic compounds with a nitrogen atom at the connection in rings **3**. Compounds with similar fragments, which are commonly found among natural products, display valuable properties and have found use in research and industry and also in hauseholding. These applications account for the interest in the synthesis of these heterocycles and a study of their properties [2].

A mechanism for this reaction represented by the reaction sequence **1 + 2 → 4 → 5 → 6 → 3 (**Scheme 1) initially proposed by von Strandtmann et al. [1] and discussed by other workers [3-6] was found to be unsuitable since it involves the thermodynamically disallowed α ⇌ α'-isomerization ($I_{\alpha\alpha'}$) of the β-diCC and

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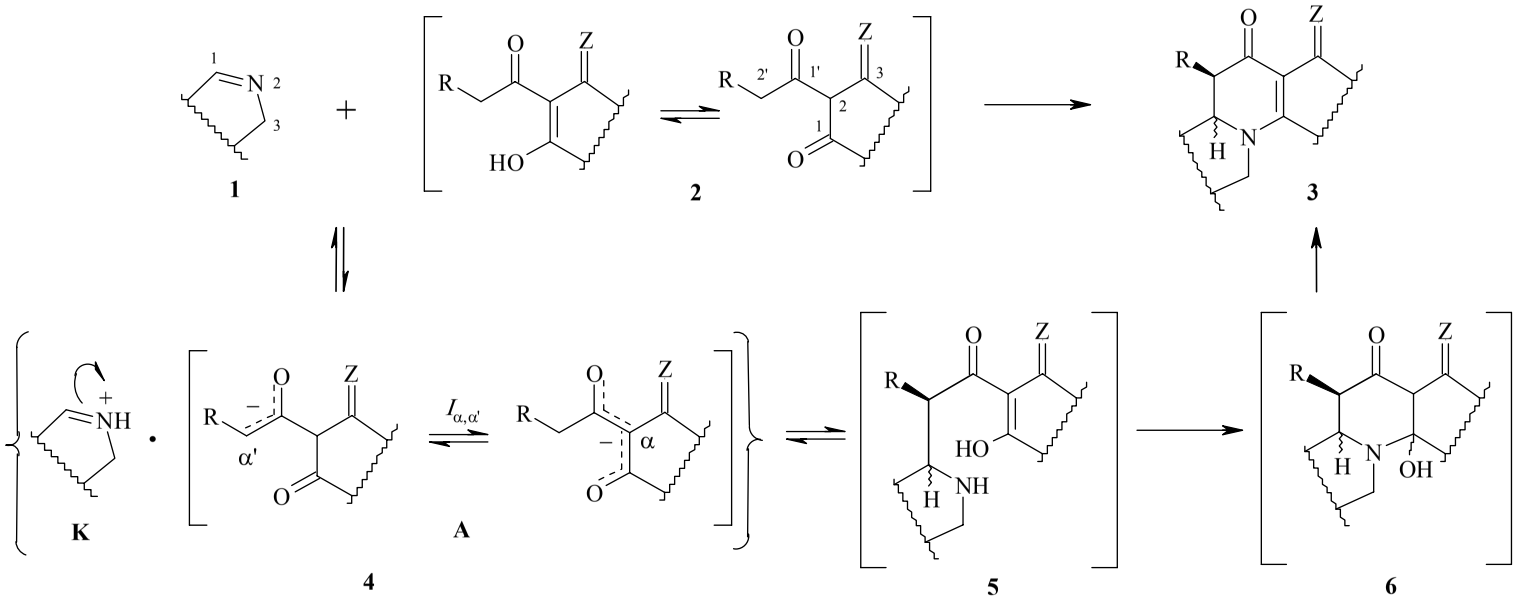
Scheme 1



β,β'-triCC anions **A** in salts **4** with subsequent Michaels C,C-addition of the α'-anions of the β-diCC and β,β'-triCC to the polarized CN fragment of the 3,4-dihydroisoquinolines **K** with formation of the adducts **5** and following cyclodehydration through tertiary ketol-hemiacetal **6** to the desired products **3**.

In subsequent investigations, which expanded the scope of this reaction to other β-diCC, β,β'-triCC, and azomethines and demonstrated the considerable synthetic potential of this reaction for the one-stage preparation of various AH [2, 4-7], additional information was obtained relevant to improving the reaction conditions. New questions arose concerning the steps and intermediates as well as even the reaction sequence **1 + 2 → 4 → 5 → 6 → 3** on the whole.

Thus, the chemistry of azomethines, and β-diCC, β,β'-triCC was characterized at that stage, on one hand, by existence of an efficient method for constructing molecular cores of AH wich are of scientific and practical interest and, on the other, lack of knowledge of the mechanism and driving forces for this reaction. This situation clearly required resolution since it was slowing the development and application of this synthetic method.

In order to elucidate the mechanism and range of application of this reaction as well as its regio- and stereospecificity, we studied the role of the structure and properties of the reagents, solvent effects, and other physicochemical factors on the course of this reaction [2, 7, 8].

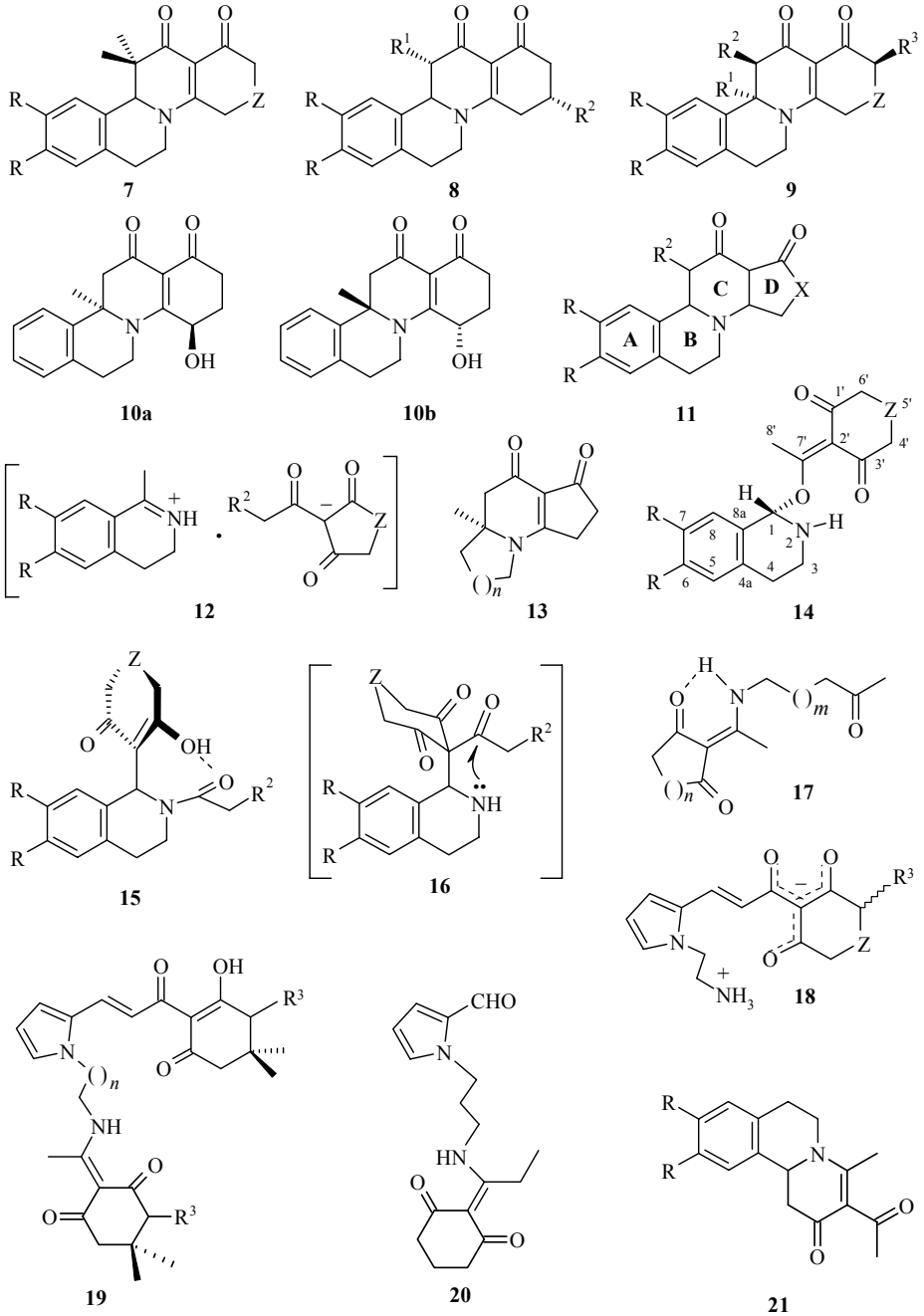
We should note that the discoverers of this reaction reported that it proceeds less readily for β-diCC than for β,β'-triCC and that its rate depends on the acid-base properties of the medium. They sought to relate these findings to differences in the acid-base properties of β-diCC and β,β'-triCC and competition between the acid-base properties of the medium and of the reagents [1]. A similar approach was adopted by subsequent workers who studied this reaction [4-6].

This work [2, 7-15] provided extensive experimental data, whose analysis and correlation in conjunction with finding of the keto-enol tautomerism of β-diCC and β,β'-triCC anions [9] led to noncontradictory conclusions in accord with experiments concerning the mechanism of the [2+4] cyclocondensation of azomethines with β-diCC and β,β'-triCC in amphiprotic and aprotic proton-accepting media.

These studies established

- that the reaction has specific sensitivity to the structure of both the azomethine and the β-dicarbonyl or β,β'-tricarbonyl reagents. In particular, the introduction of alkyl(methyl, ethyl, or isopropyl) substituents into position 1 in the 3,4-dihydroisoquinolines or replacement of the acetyl substituent in the β,β'-triCC by a propanoyl, butanoyl, or isobutanoyl substituent has no significant effect on the reaction rate or the product yields [2, 7];
- the reaction does not proceed with 3-substituted 3,4-dihydroisoquinoline derivatives (3-Me or 3-$CO_2$Me) [2, 7];
- the condensation with 5-substituted (5-Me, 5-Ph), asymmetrical 4-substituted (4-Me, 4-$CO_2$Me, 4-Cl, 4-Br, 4-OAc), and optically-active ((+)-4(*R*)- and ((-)-4(*S*)-OH) 2-acyl-1,3-cyclohexanediones proceeds regio- and stereoselectively to give isoquino[2,1-*a*]quinolines (dibenzo[*a,f*]quinolizines or 8-aza-D-homogonanes) **7-10a,b** (R = H, OMe; $R^1$ = H, Me, Et, *i*-Pr; $R^2$ = Me, Ph; $R^3$ = Me, $CO_2$Me Cl., Br; Z = $CH_2$, $CMe_2$, Scheme 2) [2, 7, 10];
- while heating is necessary for the cyclodehydration **5 → 6 → 3** (Scheme 1) [1, 4-6], the condensation with 2-acyl-1,3-cyclohexanediones containing normal acyl(propanoyl, butanoyl) substituents also occurs without heating [2, 7];
- the reaction rate was found to depend on the reagent concentrations and the reaction stops in the concentration range from $2.5\cdot10^{-2}$ to $7.5\cdot10^{-3}$ mol/liter;
- condensation occurs with β,β'-triCC with five-membered heterocyclic fragments (3-acetyltetronic, 3-acetyltetramic, and 3-acylthiotetronic acids) only in protic media such as acetic acid, trifluoroacetic acid, and AlkOH·HCl [5, 6].

Scheme 2



R = H, OMe; $R^1$ = H, Me, Et, i-Pr, $CF_3$; $R^2$ = H, Me, Et, COOMe, $CH_2COOMe$, $CHNHR^4$; $R^3$ = H, Me, COOMe, Br, Cl, OH, OAc; $R^4$ = Ph, 4-$MeC_6H_4$; $R^5$ = Me, Ph, 2,4,6-$Me_3C_6H_2$; X = $CH_2$, N, O, S; Z = $CH_2$, $CHR^5$, $CMe_2$, $CH_2CH_2$; *n* = 1, 2, *m* = 1,2

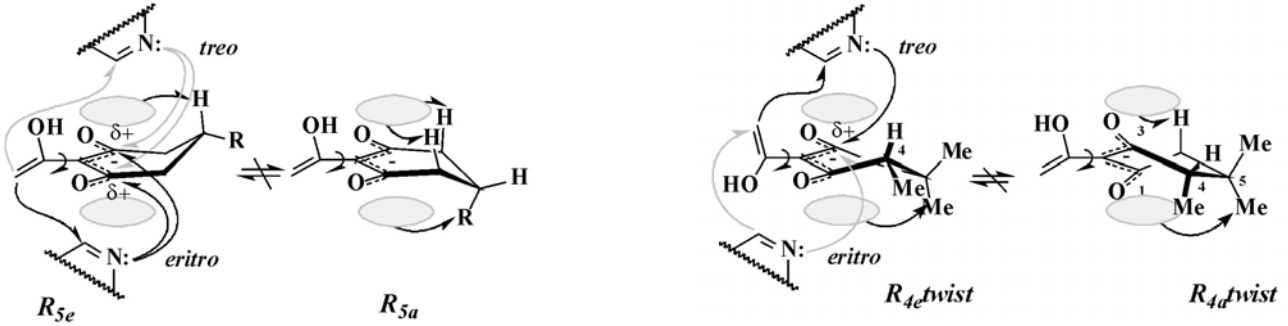
Syntheses were reported in these studies for 12,12-dimethylisoquino[2,1-*a*]quinolines **7** and angularly alkylated derivatives **8-10** [2], *cis*-diastereomeric 3,11*b*-derivatives of isoquino[2,1-*a*]quinolines **8** (represented by the α,α-diastereomer, Scheme 2), diastereomeric 2,11*b*,12-derivatives of isoquino[2,1-*a*]quinolines **9** [2,7], and enantiomeric (-)-(4*R*,11*bR*)- and (+)-(4*S*,11*bS*)-hydroxy derivatives of isoquino[2,1-*a*]quinolines (15-hydroxy-8-aza-D-homogona-12,17*a*-diones) **10a** and **10b** [10], and diheteroatomic derivatives **11** (X = O, N,

S) [5, 6, 8]. These results are also evidence against the mechanism given in Scheme 1, in particular, since the hypothetic Michael addition C,C adducts with ketimine azomethines (1-Alk-3,4-dihydroisoquinolines) etc. such as **5** are unknown and, thus, intermediates and products of the [2+4] cyclocondensation **8-10a,b** ($R^1 \neq H$) cannot be formed by this mechanism in principle. Furthermore, it is difficult to explain the regio- and stereospecificity of the ring annelation [2, 6] and the dependence of the reaction rate on the reagent concentration in the framework of this mechanism.

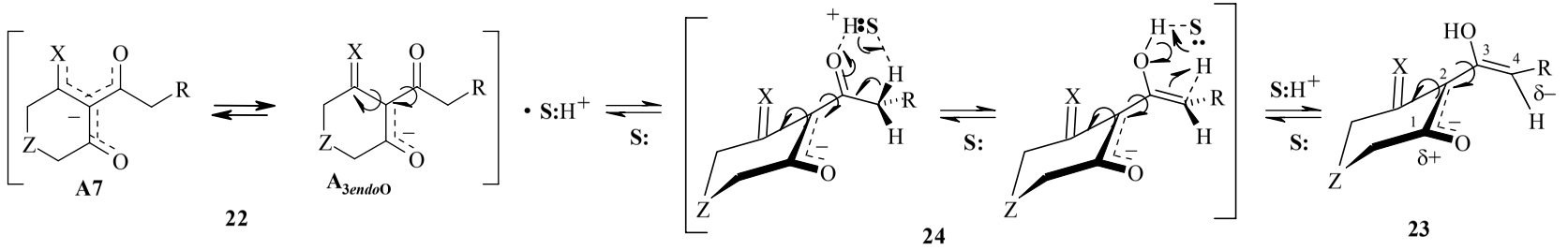
The results of the reaction of 3,4-dihydroisoquinolines and related cyclic azomethines (5-methyl-3,4-dihydro-2H-pyrrole, 6-methyl-2,3,4,5-tetrahydropyridine) with β,β'-triCC containing five-membered cyclic fragments completely eliminates the mechanism discussed [1] and led to development of an alternative mechanism. It is known that and became a stimulus and a basis of development of an alternative mehanism the reactions of 2-acyl-1,3-cyclopentanediones with 3,4-dihydroisoquinolines not substituted at C-1 lead to annelation products **9** ($X = CH_2$), while the reactions with 3-acetyltetronic, 3-acetyltetramic, and 3-acetylthiotetronic acids give annelation products **11** (X = N, O, S) only in protic media, excluding the formation of β,β'-triCC amions **4A** (4-6, 8]. On the other hand, all attempts to achieve condensation of 1-Alk-3,4-dihydroisoquinolines with β,β'-triCC containing five-membered cyclic fragments were unsuccessful. This failure indicates, firstly, the importance of the structure of the cyclic fragment for achieving this reaction and, secondly, the possibility of two different pathways, which lead to similar results. We should note that cyclocondensation also occurs under proton-donor conditions with 2-acyl-1,3-cyclohexanediones as in the work of Akhrem [2] and Pshenichnyi [6] but at lower rates and product yields. This finding is also evidence for the proposed two mechanisms. The reactions of 1-Alk-3,4-dihydroisoquinolines with 2-acetyl-1,3-cyclopentanedione, 3-acetyltetronic acids, 3-acetyltetramic acids, and 3-acetylthiotetronic acids stop upon formation of salts **12** (R = H, OMe; $R^2$ = H, Me; $Z = CH_2$, S) [11, 12]. Similar salts were also obtained in the reactions of 3-methyl-3,4-dihydroisoquinoline with 2-acyl-1,3-cyclohexanediones. In these cases, [2+4] cyclocondensation could not be carried out despite varying the conditions. On the other hand, the condensation of 5-methyl-3,4-dihydro-2H-pyrrole and 6-methyl-2,3,4,5-tetrahydropyridine with 2-aceetyl-1,3-cyclopentanedione gave the expected [2+4] cyclocondensation products, namely, cyclopenta[*e*]indolizine ($n = 1$) and cyclopenta[*c*]quinolizine ($n = 2$) **13** upon ordinary heating of a mixture of the reagents in ethanol at reflux [13]. Such a fundamental difference in the reaction course between six-membered [2, 4] and five-membered 2-acyl-1,3-cyclanediones [11, 12] or with 1- and 3-alkyl-3,4-dihydroisoquinolines [2] and monocyclic azomethines [13] indicates extremely high sensitivity of the reaction toward the reagent structure and an important role for stereochemical and stereoelectronic factors in this reaction or, strictly speaking, taking account of the stereochemical results obtained **8-10a,b** [3, 7, 11], in the formation of the cyclic transition state required for this reaction.

Carrying out the condensations under kinetic control conditions in order to trap intermediates showed that the condensation of $C^1H$-3,4-dihydroisoquinolines with 2-acyl-1,3-cyclohexanediones in aprotic and amphiprotic nonaqueous media (1,4-dioxane, glymes, alcohols) is accompanied by the formation of enol-hemiacetals **14** (R = H, OMe; Z = bond, $CH_2$, $CMe_2$). In individual experiments, isoquinoline derivatives **15** (R = H, OMe; $R^2$ = H, Me; Z = bond, $CH_2$, $CMe_2$) were detected as minor by products. In particular, the following compounds were isolated and characterized: 2-[1-(1,2,3,4-tetrahydro-1-isoquinolinyloxy)ethylidene]-1,3-cyclopentanedione, 2-[1-(6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinyloxy)ethylidene]-1,3-cyclohexanedione, 2-(2-acetyl-1,2,3,4-tetrahydro-1-isoquinolinyl)-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one, and 3-hydroxy-2-(6,7-dimethoxy-2-propionyl-1,2,3,4-tetrahydro-1-isoquindinolinyl)-2-cyclohexen-1-one. The formation of derivatives **14** results from a side process involving an equilibrium Michael O,C-addition reaction. This hypothesis finds support in the conversion of derivatives **14** to the corresponding tetracyclic derivatives such as **8** or **9** upon heating in moist ethanol at reflux. The removal of water liberated during the condensation leads to an increase in the yield of hemiacetals **14**, while the yields of the desired condensation products such as **8** or **9**

Scheme 3




Scheme 4




R = H, Me, Et; $R^1$ = Me, Ph; X = $CH_2$, O, NOEt; Z = –, $CH_2$, $CHR^1$, $CMe_2$, $CH_2CH_2$

are correspondingly reduced. The minor products **15** are the result of a Michael C,C-addition and subsequent C,N-isomerization taking place through adducts **16** (R = H, OMe; $R^2$ = H, Me; Z = bond, $CH_2$, $CMe_2$). By-products **17-20** (*n, m* = 1, 2; $R^3 = CO_2Me$) were isolated upon the condensation of 5-methyldihydropyrrole, 6-methyltetrahydropyridine, and 3,4-dihydropyrrolo[1,2-*a*]pyrazine with 2-acetyl-1,3-cyclanediones due to hydrolytic ring-chain transformation of the azomethines under the reaction conditions. Furthermore, other by-products due to specific properties of the reagents were isolated in individual experiments but the formation of these by-products proved irrelevant in regard to the mechanism and, thus, will not be discussed in this review (see [14]). Therefore, the attempts to detect hypothetical Michael C,C-adducts such as **5** (Scheme 1) have so far proven fruitless, possibly due to their equilibrium formation. As noted above, the transformations studied occur through transition states extremely sensitive to reagent structure and the conditions, which lead to regio- and stereoselective [2], and in some cases, regio- and stereospecific [10] formation of AH molecular cores **8-10** with definite stereochemistry of the substituents.

The cyclic transition states serving as models for the formation of **8** and **9** are graphically represented by structures $\boldsymbol{R_{5e}}$ and $\boldsymbol{R_{4e}}$***twist*** (Scheme 3).

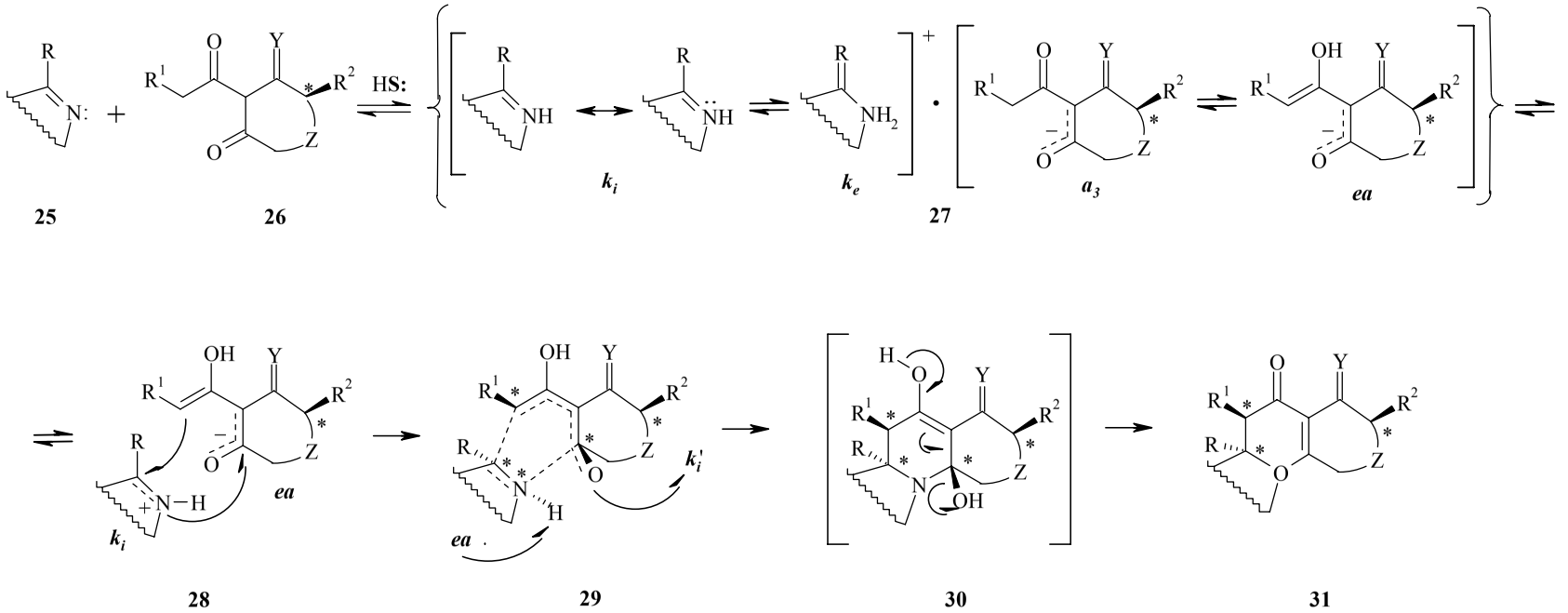
The use of triacetylmethane in the condensation led to a 2-3-fold drop in the yields of desired cyclocondensation products **21** (R = H, OMe) and a 3-4-fold increase in the reaction time (rate decrease) in comparison with the values found for condensations with 2-acyl-1,3-cyclanediones [15]. This result, which initially seems unexpected since conformationally-free triacetylmethane should assume the conformation required for the reaction more readily, confirms the importance of the structure of the β-diCC and β,β'-triCC and, in essence, the hypothesis of cyclic transition states for this reaction. The decrease in the yields of desired condensation products **21** is a consequence of the lability of triacetylmethane [15], while the decrease in rate indicates stereodynamic and stereoelectronic hindrance to achieving the cyclic transition state required for the condensation reaction.

The dependence of the cyclocondensation rate on the reagent concentration and virtually complete cessation of the reaction at reagent concentrations below 0.025 mol/liter are critically important features of this reaction. Since the reaction of azomethines with β-diCC and β,β'-triCC is initially a function of the acid-base properties and leads to the formation of salts **4** (Scheme 1) or **12** (Scheme 2), the success of the condensation depends on the properties and transformations of the conjugated acids (azinium cations **K**, Scheme 1 or **12**, Scheme 2) or bases (β,β'-tricarbonyl anions **A**, Scheme 1 or **12**, Scheme 2) formed in these reactions. The experimental findings and theoretical proposals indicate that benzaliminium (isoquinolinium) cations do not affect the dependence of the reaction rate on the concentration or acid-base properties of the medium, while β,β'-tricarbonyl anions, which display specific prototropic properties, may affect the reaction rate.

Since the reaction in amphiprotic and polar aprotic media, in essence, is self-catalytic and proceeds through the intermediate formation of salts and β-dicarbonyl and β,β'-tricarbonyl substrates displaying acid properties with Schiff bases displaying base properties, the dependence of its rate on concentration is counter-intuitive. Indeed, the azomethinium cations (**K**, Scheme 1, **12**, Scheme 2) and β,β'-triketonate anions (**A**, Scheme 1, **12**, Scheme 2) formed in the reaction of the azomethine and β,β'-triCC are subject to Coulombic attraction and their coupling is independent of the solution concentration. Thus, the reason for the dependence of the rate constant on the concentration of the interacting substrates is hidden in the interaction of the ions in ion pairs or between ion pairs. Therefore, the experimental data indicate that the mystery of the mechanism of this reaction is embodied in the properties of the anions of the β-diCC and β,β'-triCC and the interactions in the ion pairs and between these pairs.

A study of the properties of the anions of β-diCC and β,β'-triCC in the case of salts **4** (Scheme 1) or **12** (Scheme 2) [11, 12] showed that, in proton-accepting and polar ionizing media (**S:**), these anions exist as a keto-enol tautomeric equilibrium of the anions of β-diCC and β,β'-triCC **22** ⇌ **23**, proceeding through transition state **24** (Scheme 4) [9].

Scheme 5




R = H, Me, Et, *i*-Pr, $CF_3$; $R^1$ = H, Me, Et, COOMe, $CH_2COOMe$; $R^2$ = Me, COOMe, OH, OAc, Br, Cl; $R^3$ = H, Me, Ph; Z = $CHR^3$, $CMe_2$; Y = $H_2$, O, NOEt; Z = –, $CH_2$, $CHR^4$, $CMe_2$, $CH_2CH_2$

Enol-anions **23** formed as a result of the keto-enol tautomerism of anions of β-diCC and β,β'-triCC **22** are 1,4-dipolarophiles and, as a result, undergo a dipole-dipolarophile intereaction with the polarized azomethine cations. The driving force of them is the Coulombic interactions of the oppositely-charged ions, while polarization of the C=N bond (see **K 4**, Scheme 1 or **12**, Scheme 2) and the four-membered enol-anion fragment of β-diCC and β,β'-triCC **23** (Scheme 4) accounts for the regiochemical results of the reaction.

The stereochemical results and the theoretical possibility for success of the reactions are a function of the conformations of β-diCC and β,β'-triCC ***R*$_{5e}$-*R*$_{5a}$** and ***R*$_{4e}$*twist*-*R*$_{4a}$*twist*** and the steric access for nucleophilic attack of the carbonyl groups of the cyclanedione fragments by the azomethine nitrogen atom (Scheme 3).

Combining the experimental data and modern theoretical concepts, we can formulate a mechanism for the condensation of the Schiff bases or azomethines with β-diCC and β,β'-triCC in amphiprotic media in a generalized form given by Scheme 5.

Salts **27** are formed in the first step of the reactions of azomethines **25** with β-diCC and β,β'-triCC **26** in amphiprotic media **HS**. In light of previous data [9, 12, 13] and taking account of the acid-base properties of azomethines **25**, β-diCC, and β,β'-triCC **26**, salts **27** are described by the equilibrium **25** + **26** ⇌ **27**. In turn, the anions of β-diCC and β,β'-triCC [9] in salts **27**, which exist as a keto-enol tautomeric equilibrium ***a*$_3$** ⇌ ***ea***, generate 1,4-dipolarophilic enol-anions ***ea***, while protonation (quaternization) of the azomethines enhances their polarization and activates them for reactions with the 1,4-dipolarophilic enol-anions. Coulombic interactions of the counter-ions and the directing action of the polarization effects draw ions ***k*$_i$** and ***ea*** into a tight ion pair **28** and lead to orbital nucleophilic-electrophilic interaction. The orbital C–C and C–N interactions forming the π-electron complex of cyclic transition state **29** are accompanied by neutralization of the ions with the participation of the neighboring ion pairs ***k*$_i$′** and ***ea*′**, which accounts for the dependence of the reaction rate on concentration. Upon neutralization of the ions, which precedes by orbital interactions, the molecules separate. Neutralization of the ions within the ion pair in transition state **29** is doubtful since simultaneity of the orbital interactions and neutralization of the ions would require a sterically-strained bicyclic transition state. Furthermore, in this case, a dependence of the reaction rate on concentration would not be observed.

Additional evidence for the mechanism given in Scheme 5 is found in the results of running the reactions in a deuterated medium consisting of $CD_3OD$-$D_2O$ at 20°C, which show that derivatives **31** have the deuterium label at the carbonyl group of the reformed partially hydrogenated γ-pyridone ring in **31**, i.e., [12,12-(*n*)$^2$H]-isoquino[2,1-*a*]quinoline-1,13-diones ([11,11-(*n*)$^2$H]-8-aza-D-homogona-12,17*a*-diones) **31** ($R^1$ = D) are formed.

The use of enantiomeric β-diCC and β,β'-triCC **26** leads to the formation of enantiomeric condensation products **31** [10], which indicates a high degree of chiral induction, supporting cyclic transition state **29** and the proposed electrocyclic mechanism.

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