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A Kinetic Study by NMR of the Benzoin Condensation Catalyzed by Thiazolium Salts in Mild Basic Conditions: a Second Order Process in Both Aldehyde and Pre-catalyst.§

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Abstract: A kinetic study of the benzoin condensation catalyzed by thiazolium cations in mild basic conditions monitored by ^{1}H-NMR shows that the reaction is a complex process of second order in both aldehyde and thiazolium cation. These data strongly support our previous mechanistic proposal that the actual catalytic species in that reaction are the bis(thiazolin-2-ylidene)s. Consequences for the biochemical processes mediated by thiamin are also discussed.

INTRODUCTION

Several years ago, we described[1] the formoin reaction, a benzoin condensation with formaldehyde as substrate, that leads to monosaccharides through a complex chain of condensation processes catalyzed by thiazolium salts (**1**) in basic medium. When we started our research we accepted without any restriction the Breslow proposal[2] for the mechanism of such reactions.

One of the anticipated features of the formoin reaction was the absence of ramified sugars as products, because of the inactivity of ketones in the benzoin condensation. Surprisingly, however, we found a large quantity of ramified monosaccharides, with 2-hydroxymethylglyceraldehyde the dominant compound in some cases. Looking for neutral reaction conditions to avoid aldolic condensations, or any other process due to the basicity of the medium, possible origin of the ramified structures, we developed alternative working procedures for the generation of the reputed catalytic species, thiazolin-2-ylidenes (**2**), by thermal decarboxylation of 3-ethyl-4,5-dimethylthiazolium-2-carboxylate[5] and the use of conventional and polymer-supported bis(thiazolin-2-ylidene)s[3,4] (**3**) as catalysts.

It should be remembered here that thiazolin-2-ylidenes (**2**), and bis(thiazolin-2-ylidene)s (**3**) are unavoidably coexistent in protic, basic, conventional conditions[6,7].

The results obtained, especially[8] the fact that bis(thiazolin-2-ylidene)s are always much better catalysts than conventional thiazolium cations plus base, and the poor catalytic behaviour observed when the generation of thiazolin-2-ylidene was carried out by the fast, quantitative and irreversible decarboxylation of thiazolium-2-carboxylate led us to the idea that the actual catalytic species in the benzoin condensation and related processes are the bis(thiazolin-2-ylidene)s,[3] at least in some conditions. To confirm our hypothesis we carried out three complementary studies, two of them directed to discriminate between the activity of the

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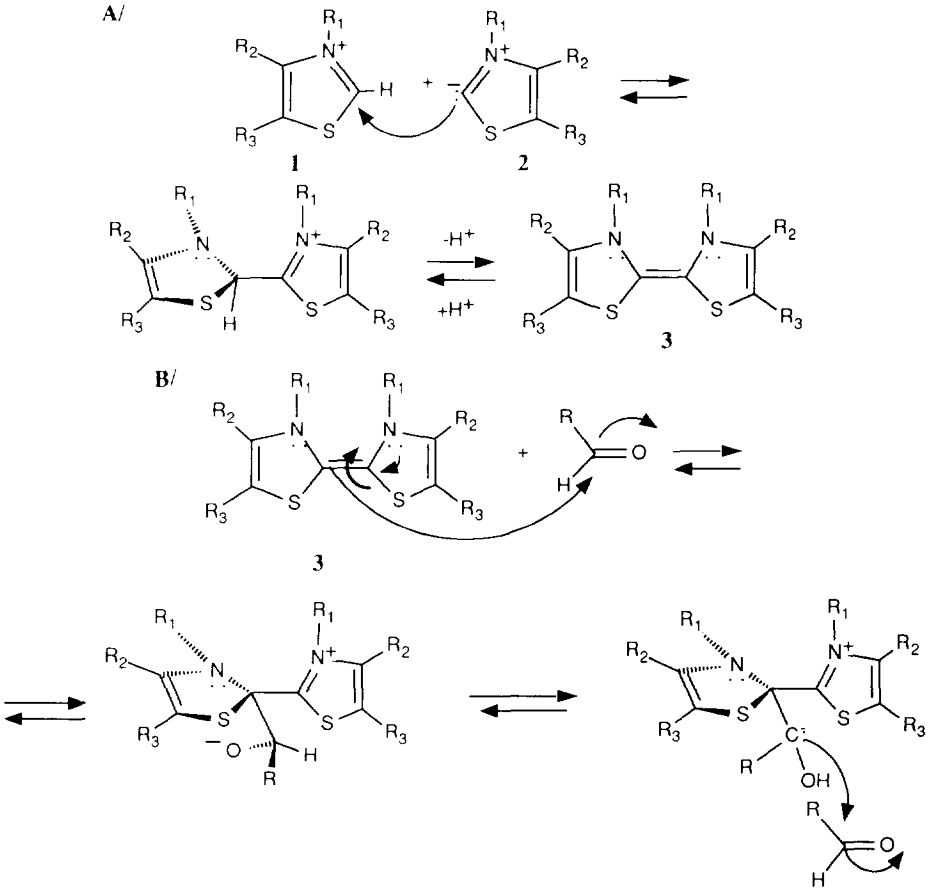
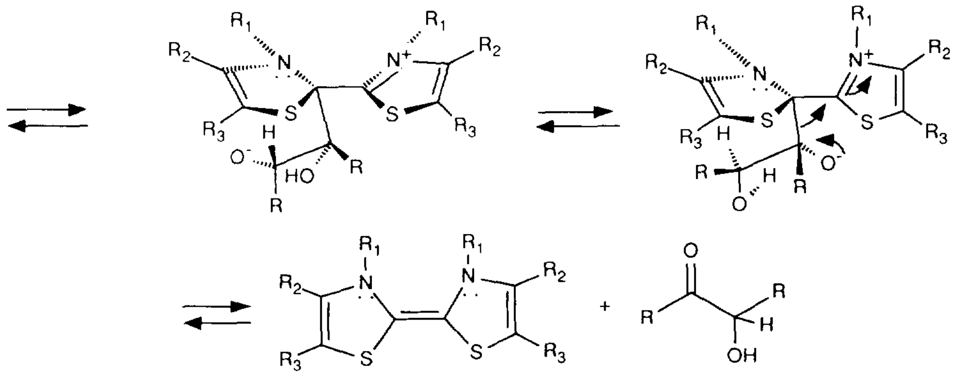
(§) Devoted to the memory of the late Professor Félix Serratosa concomitant thiazolin-2-ylidenes and bis(thiazolin-2-ylidene)s, and the third, a theoretical study of the two alternative mechanistic proposals: the one from Breslow and ours.

The first study[9] consisted of the generation of thiazolin-2-ylidenes (**2**) in conditions that preclude the formation of bis(thiazolin-2-ylidene)s: the desilylation with fluoride anion of 2-(trimethylsilyl)-thiazolium cations in strictly aprotic medium. In such conditions the benzoin condensation does not take place. However, if an amount of thiazolium cation is added, the yield of benzoin is comparatively excellent.

In the second study[10, 11] we aimed to determine the influence of the factors affecting the formation, stability or evolution of bis(thiazolin-2-ylidene)s (**3**) over its catalytic behaviour in the reaction conditions. We prepared several polymethylene-bridged thiazolium and benzothiazolium salts and we used them in different solvents, directly with base or with previous conversion into their bis(thiazolin-2-ylidene) and showed that catalytic activity depends strongly on the methylene bridge length. We concluded that bis(thiazolin-2-ylidene)s must play a key role in the benzoin condensation.

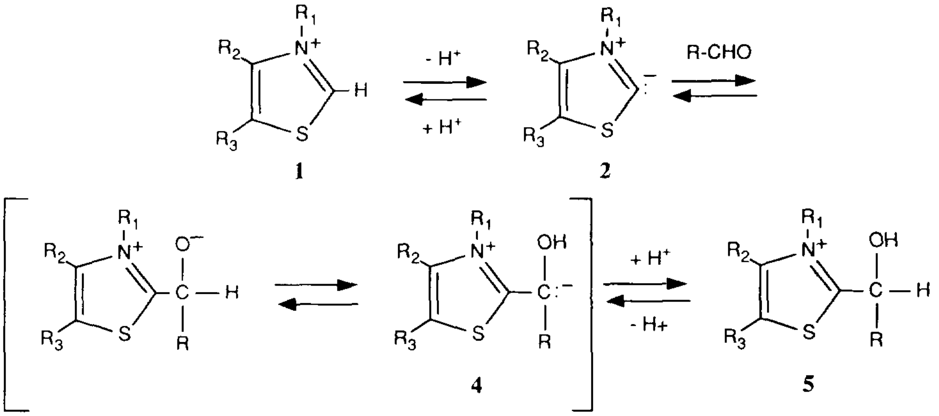
As the result of the experimental work briefly summarized above, we proposed a new mechanism for the benzoin condensation catalyzed by thiazolium cations plus base, in which the only, but important, difference with respect to Breslow's proposal is that the catalytic species are bis(thiazolin-2-ylidene)s **3** (scheme 1).





Scheme 1. Proposed mechanism of the benzoin condensation catalysed by thiazolium cations in basic medium.

Finally, we carried out a theoretical study[11,12] that showed: a/ Breslow's key intermediates (**4**, scheme 1), easily detected[13] in the reaction mixtures as their protonated form (**5**, scheme 2), are stable molecules



Scheme 2. Formation of the Breslow's key intermediate.

formed by the nucleophilic attack of thiazolin-2-ylidenes to aldehydes and, due to their very high stability, are end points of such reactions, and b/ our mechanistic proposal is kinetically and thermodynamically reasonable.

In spite of the precedent of the work of Schowen[14] on the kinetics of the benzoin condensation catalyzed by cyanide ion, up to 1993 no kinetic study of the Breslow proposal -that dates from 1958- had been published. Probably, such a study has been discouraged by the following comment of Tagaki *et al.*[15], published in 1980: "In the cyanide ion-catalyzed benzoin condensation in methanol, Schowen *et al.* employed spectrophotometric method to follow the formation of benzoin at 320 nm. Unfortunately, however, in the thiazolium ion-catalyzed condensation in methanol containing triethylamine, the partial dimerization of thiazolium ion to form N,N'-disubstituted bithiazolinylidene was encountered which disturb the absorbance measurements at 320 nm". In our studies, the statement of the Japanese authors showed itself to be essentially correct, although we believe that the origin of the interference is much more complex than the formation of bis(thiazolin-2-ylidene)s.

With the above information at hand, we thought that Breslow's recent paper[16], reporting a benzoin kinetic study in the above conditions, with the only (and unfavorable) change of methanol to dimethylsulfoxide as solvent, needed confirmation by an alternative kinetic study.

We report here an NMR kinetic study that has led us to the conclusion that the *benzoin condensation catalyzed by thiazolium cation plus base, in mild conditions, is a second order process in both aldehyde and thiazolium cation.*

METHODS

As a preliminary, we needed to verify that ^{1}H-NMR spectroscopy would be an adequate technique for our aims. To test this we prepared a solution in DMSO-d_6 containing all the reagents present in a reaction mixture plus benzoin in concentrations of the same order as for the kinetic experiments. Figure 1 is the spectrum corresponding to such a mixture after some hours at room temperature: reference peaks (benzaldehyde, 10.1 ppm; benzoin, 6.04 ppm; protonated Breslow species **5a** where $R_1 = R_2 = R_3 = CH_3$, 6.4 ppm) show no interferences whatsoever.

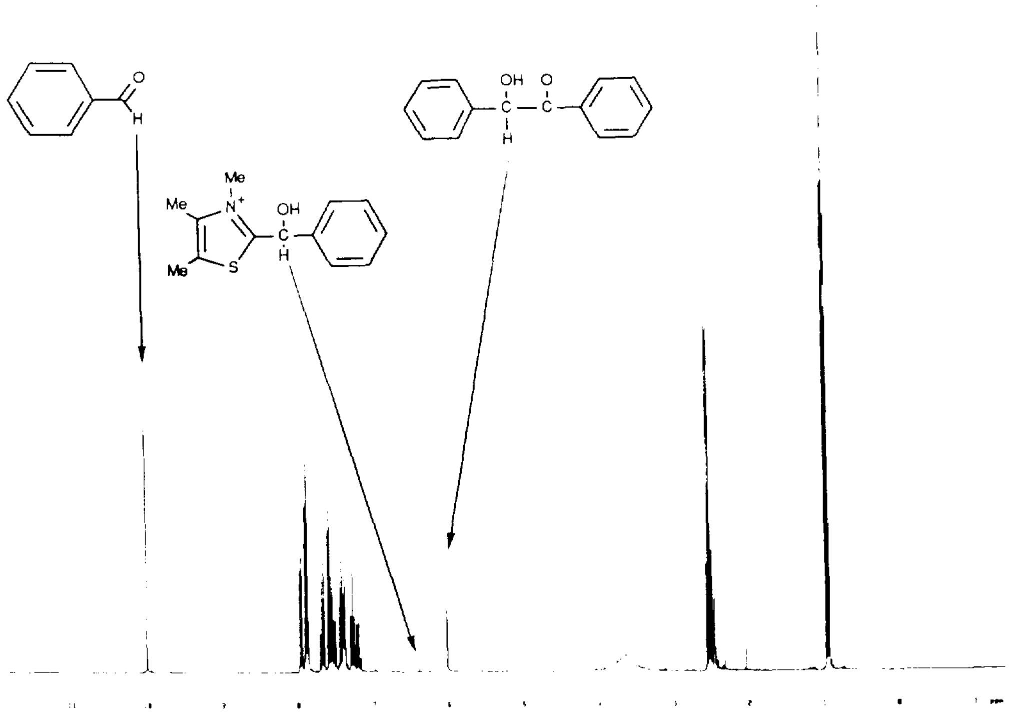
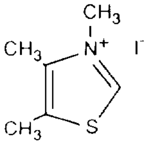


Figure 1. Standard reaction mixture containing benzaldehyde, Breslow's intermediate **5a** and benzoin.

We have carried out our NMR kinetic study in essentially the same conditions of solvent (in our case deuterated), concentrations and temperature described[16] by Breslow - DMSO-d_6 solutions 500 mM in benzaldehyde, 90 mM in triethylamine, 10 mM in triethylammonium hydrochloride, and variable amounts of pre-catalyst - but we directly recorded the ^{1}H-NMR spectra of the reacting mixtures, using the integration of the aldehydic proton as a parameter measured to follow its consumption. Three series of experiments were performed: two using the same pre-catalyst as Breslow, 3,4,5-trimethylthiazolium iodide (**6**), in concentrations of 10, 20, 30, 40, 50, 60 and 70 mM, and the third with 1,6-bis(4,5-dimethyl-3--thiazolio)hexane dibromide (**7**) in concentrations of 5, 7, 10, 15, and 25 mM.



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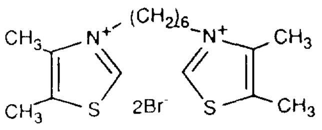

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The reacting mixtures were prepared by weighing the necessary amounts of reagents, dissolving them in DMSO-d_6 and making up to a total volume of 2 mL; the base was added in the last moment. All the reactions were studied at 45°C, recording the spectra from the samples placed in the pre-heated probe of the spectrometer and maintaining this temperature throughout the experiment. The first series of experiments with 3,4,5-trimethylthiazolium iodide as pre-catalyst, permitted us to determine the process order in benzaldehyde, working at long observation times and recording a spectrum each 30 min; this series has also permitted us to calculate an approximate benzaldehyde half-consumption time, though this was more accurately re-calculated in the second series, by registering consecutive spectra until the approximate half-consumption of benzaldehyde was experimentally observed; the time interval between spectra was of 1, 2 or 15 min (spectra accumulation time included), depending on the expected total duration of each experiment. To ensure the same base concentration in all cases, reaction mixtures in this second series were prepared from a solution of triethylamine and triethylammonium hydrochloride in DMSO-d_6, adding then an aliquot of this solution to another solution containing the corresponding amounts of benzaldehyde and pre-catalyst. The third series was also performed using these last conditions.

The spectrometer acquisition parameters were tuned up using, as reference, a blank identical to the sample; then the blank was replaced by the sample itself and the system was allowed to recover the pre-optimized operating status. This equilibration took a few minutes. The moment of addition of base was taken as zero time of the reaction. The reported reaction time for the first spectrum of each experiment is the period between the addition of base and the end of the recording of the spectrum.

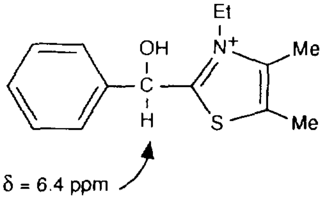
Kinetic treatment.

We have plotted the logarithms and the inverses of the observed integrations of the aldehydic peak of benzaldehyde, expressed in arbitrary area units, against the time, as for first and second order standard treatments. In the cases of linear plots, the regression lines have been calculated and, from the relation between the ordinates at origin and the known initial concentrations of benzaldehyde for each experiment, we converted area units to concentrations, calculated pseudo-rate constants, k, for the consumption of benzaldehyde, and represented these constants against pre-catalyst concentration. The results are discussed below.

RESULTS AND DISCUSSION.

Preliminary question.

In a previous experiment we studied the behaviour of a Breslow intermediate **5b**, 3-ethyl-2-hydroxybenzyl-4,5-dimethylthiazolium fluoborate. This compound had been prepared by alkylation of 2-hydroxybenzyl-4,5-dimethylthiazole with triethyloxonium fluoborate in anhydrous chloroform, and it shows a characteristic peak at 6.4 ppm (DMSO-d_6) corresponding to the benzylic proton.



5b

When **5b** is placed in the reaction conditions, but in absence of benzaldehyde, the formation of benzoin (peak at 6.04 ppm) is observed rapidly and to a significant extension; that implies the decomposition of **5b** to benzaldehyde and 3-ethyl-4,5-dimethylthiazolin-2-ylidene **2b** and the autocondensation of benzaldehyde to benzoin in the basic used conditions, and, also, **2b** would be in equilibrium with the 3-ethyl-4,5-dimethylthiazolium cation **1b**. This experiment shows: a/ the formation of species **5** is easily reversible in the reaction conditions; b/ thiazolin-2-ylidenes **2** and thiazolium cations **1** are co-existent in the reaction mixture; c/ consequently, bis(thiazolin-2-ylidene)s can be formed, and could act as catalyst.

Kinetic study.

In both the Schowen and Breslow studies the consumption of benzaldehyde was deduced by measuring the formation of benzoin. As we have explained before, we believe that in our case this is not valid because of interference in the same u.v. region by, at least, bis(thiazolin-2-ylidene)s. We have repeated the work reported by Breslow[16], and, in contradistinction to that author's conclusions, we believe that it is hard to accept that both a first order and a second order treatment applied to benzaldehyde concentrations determined in this way "fit moderately well".

Reaction order in [benzaldehyde].

The aim of our first series of experiments (3,4,5-trimethylthiazolium iodide as pre-catalyst, long reaction times and spectra registered each 30 min) was the determination of the reaction order in [benzaldehyde]. The results obtained were the same in all cases, but for the sake of brevity we present only a detailed study for a reacting mixture exactly 497.16 mM in benzaldehyde, 89.60 mM in triethylamine, 10.54 mM in triethylammonium hydrochloride and 41.17 mM in 3,4,5-trimethylthiazolium iodide; the first spectrum was registered 45 min after base addition, and the other 24 consecutive spectra at 30 min 49 s intervals.

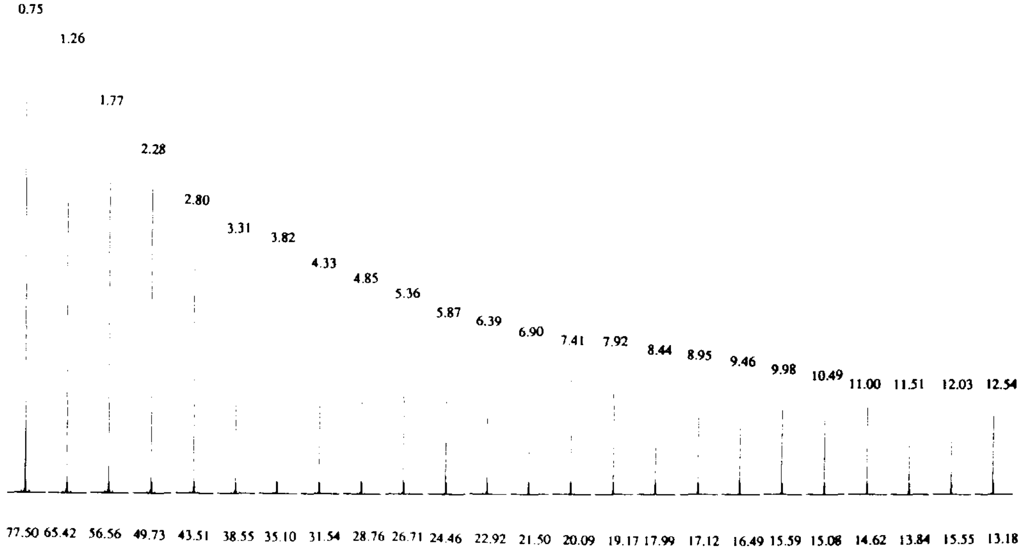


Figure 2. Array representing the variation of the aldehydic proton of benzaldehyde during experiments of the first series using 41.17 mM of 3,4,5-trimethylthiazolium iodide (**6**) as catalyst and 497.16 mM of benzaldehyde. The number at the top of each peak indicates the observation time in hours, and the one below the integration value in arbitrary area units.

In figure 2 are represented benzaldehyde concentrations along with time as observed in the ^{1}H-NMR spectra and expressed in arbitrary area units; in figure 3-A are plotted their inverses and in figure 3-B their logarithms.

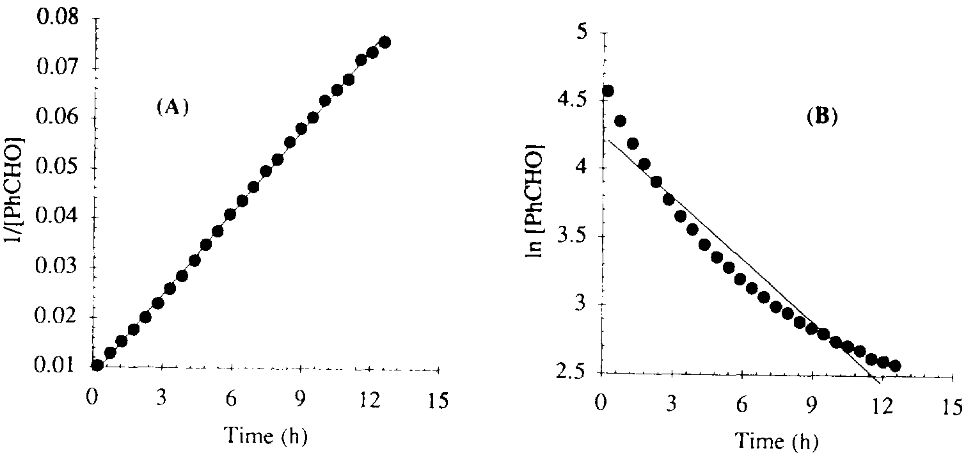


Figure 3. Representation of benzaldehyde concentration, expressed in arbitrary area units, inverses (**A**) and logarithms (**B**) *vs* time. Conditions as given in figure 2.

As can be observed the plot of the inverses is a straight line (regression lineal coefficient **r** = 0.9995) and the logarithmic representation is a clear parabola, that is to say, the process is of second order in benzaldehyde. From the value of the ordinate at origin of the regression line and the exact benzaldehyde concentration, we calculated the approximate rate constant, $k_{1\text{-}40}$= 3.74 x 10^{-4} $M^{-1}s^{-1}$, of consumption of benzaldehyde, and the half-consumption time $t_{1/2\text{-}1\text{-}40}$ = 1.49 h.

In all studied cases, the resulting plots were always straight lines for the representations of inverse values, and parabolas for the logarithmic ones, indicating that *the consumption of benzaldehyde is a second order process in [benzaldehyde] under the conditions used*. In Table 1 are collected the parameters of the seven reactions that constitute this first series of experiments.

Table 1. Concentrations of Reagents and Calculated Parameters for a Second Order Reaction in [Benzaldehyde] with 3,4,5-Trimethylthiazolium Iodide as Pre-catalyst

$[Tz^+]$	[PhCHO]	$[Et_3N]$	$[Et_3NH^+]$	r[a]	$k_1(10^4\ M^{-1}s^{-1})$[b]	$t_{1/2}(h)$[c]
10.00	511.79	102.97	9.82	0.9977 (26)	0.41	12.94
19.60	509.90	92.07	9.45	0.9974 (25)	1.16	4.16
30.39	504.71	89.60	9.45	0.9993 (22)	2.56	2.14
41.17	497.16	89.60	10.54	0.9995 (24)	3.74	1.49
50.00	500.47	88.61	10.18	0.9988 (27)	2.52	2.19
60.00	503.30	90.09	9.82	0.9979 (20)	4.59	1.20
70.39	512.73	94.05	9.80	0.9992 (16)	6.29	0.86

([a]) Lineal regression coefficient of the straight line obtained plotting the inverses of the arbitrary area units of the aldehydic peak of benzaldehyde against time (number of spectra registered). ([b]) Approximate rate constants of consumption of benzaldehyde. ([c]) Half-consumption time of benzaldehyde calculated from k_1.

It is important note.

a/ the disappearance of benzaldehyde is not accompanied by a simultaneous appearance of a corresponding quantity of benzoin; this means that, between the disappearance of benzaldehyde and the appearance of benzoin, there are several steps involving species (carrying one or two benzaldehyde moieties) that, with the exception of **5**, are not observable either because of NMR time scale or because the spectrometer sensitivity. The experiments were performed at a relatively low temperature, and this must slow down the rate of all intermediate steps.

b/ The application of the same kinetic treatment to the benzoin, or better, to the benzaldehyde consumed determined as twice the benzoin formed, does not lead to any standard kinetic model, as it is easy to see in figure 4-A, where the inverses of twice the integration of benzoin are represented *vs* time, and in figure 4-B, which represents the corresponding logarithmic plot. This observation can be explained from our mechanistic proposal: the benzoin condensation is a complex process, involving as first step the formation of the catalyst bis(thiazolin-2-ylidene) from the pre-catalyst, and that this is much slower than the simple acid-base reaction needed for the formation of thiazolin-2-ylidenes; this previous process, together with the competitive fast formation of some **5** (see next paragraph) modifies the rate of formation of benzoin, specially in the early stages, giving rise to a complex macroscopic kinetic behaviour.

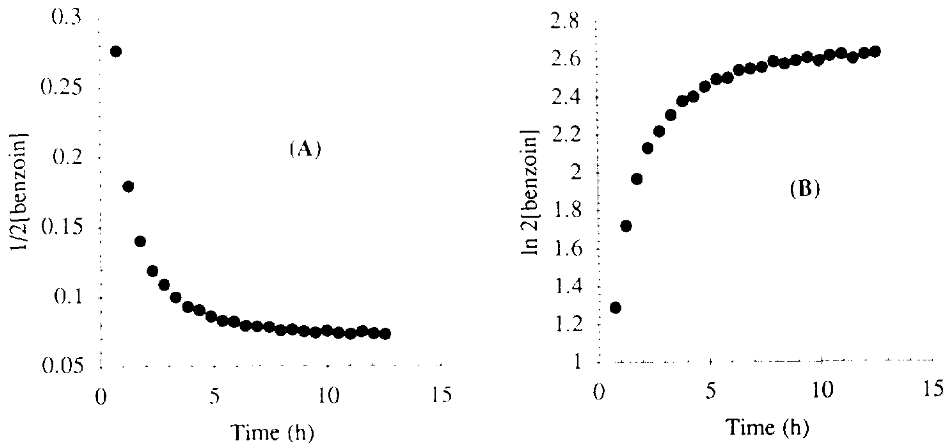


Figure 4. Representation of twice the benzoin concentration, expressed in arbitrary area units, inverses (**A**) and logarithms (**B**) *vs* time. Conditions as given in figure 2.

c/ From the very earliest moments of the reaction until the end of the observations, **5** is present in a relatively small and practically constant amount, which depends on the relative concentration of pre-catalyst and benzaldehyde; the amount of **5** decreases very slowly with time. In accord with the proposed mechanistic model, this observation means that small amount of benzaldehyde is consumed very rapidly during the first moments of the reaction and remains in this state during the benzoin condensation introducing a factor of experimental error in the determination of the real rate constants of the actual benzoin condensation; but, in the context of our study, the global consumption of benzaldehyde during the observed process would only take place because of its transformation into benzoin; for this reason the determination of the reaction order in [benzaldehyde] is not affected by the fast formation of **5**.

Accurate calculation of constants of half-consumption of benzaldehyde with 3,4,5-trimethylthiazolium iodide as pre-catalyst.

In the second series of experiments, which were carried out to improve the previously obtained data, the following changes were introduced.

a/ In the first series, the amounts of triethylamine and triethylammonium hydrochloride varied in 14 and 7 %, respectively, from the highest to the lowest concentration, and its relative proportion in a 19 %. This change in the base concentration is reflected in the rate constant, and we have observed a linear dependence between rate constants and base concentration. To avoid this cause of modification of the observed values, in this second series of experiments we have basified the reaction mixtures adding 396 μL of a previously prepared solution 454.55 mM in triethylamine and 50.41 mM in triethylammonium hydrochloride; the final concentration in all cases was 90.00 mM and 9.98 mM in the two species respectively.

b/ The time lag between spectra was chosen in every case as a function of the expected half-consumption time, varying from 1 to 15 min (including the spectra recording time), and the reactions were followed until experimental observation of the half-consumption of benzaldehyde.

The kinetic treatment was the same as above, the results are collected in Table 2, and figure 5 represents the plots of the seven experiments.

Table 2. Concentrations of Reagents[a] and Calculated Parameters for a Second Order Reaction in [Benzaldehyde] with 3,4,5-Trimethylthiazolium Iodide as Pre-catalyst and Constant Base Concentration.

$[Tz^+]$	[PhCHO]	t(min)[b]	r[c]	$k_2(10^4\ M^{-1}s^{-1})$[d]	$t_{1/2}(h)$[e]
9.60	502.35	15	0.9972 (51)	0.37	14.94
20.00	497.16	15	0.9995 (23)	0.94	5.94
30.39	497.64	2	0.9983 (56)	2.06	2.71
40.00	501.41	2	0.9988 (58)	2.20	2.51
51.17	495.28	2	0.9996 (52)	2.81	1.97
60.00	496.22	2	0.9994 (46)	3.13	1.78
70.78	506.13	1	0.9977 (71)	4.31	1.27

([a]) All reacting mixtures were 90.00 mM in triethylamine and 9.98 mM in triethylammonium hydrochloride. ([b]) Time between spectra. ([c]) Lineal regression coefficient of the straight line obtained plotting the inverses of the arbitrary area units of the aldehydic peak of benzaldehyde against time (number of spectra registered). ([d]) Rate constants of consumption of benzaldehyde. ([e]) Half-consumption time of benzaldehyde calculated from k_2.

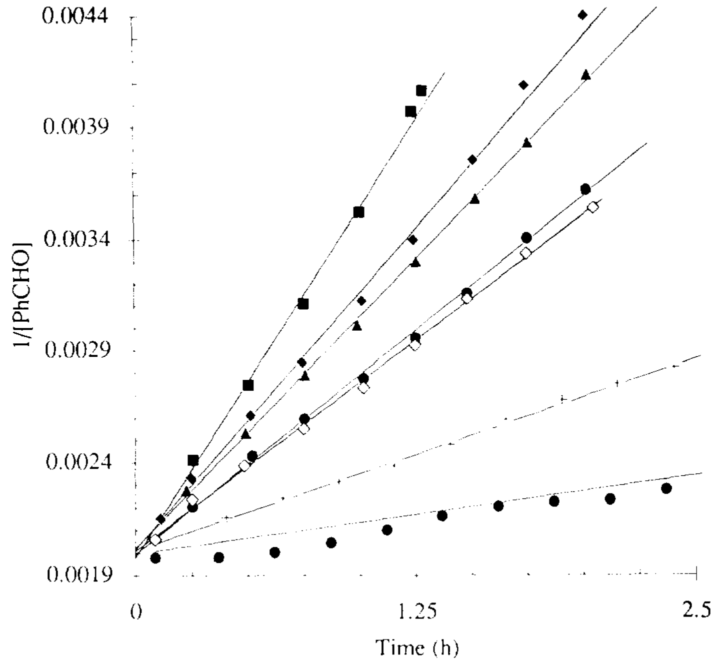


Figure 5. Representation of benzaldehyde concentration inverses, expressed in mM, *vs* time for the seven experiments of the second series (Table 2). Only the first points of each experiment are represented.

Reaction order in [thiazolium cation] of the benzoin condensation with 3,4,5-trimethylthiazolium iodide as pre-catalyst.

Representation of the new benzaldehyde half-consumption constants k_2 *versus* concentrations (figure 6-A) and second power of concentrations of pre-catalyst (figure 6-B) shows clearly *that the process is neither a first nor a second order reaction in [thiazolium cation].*

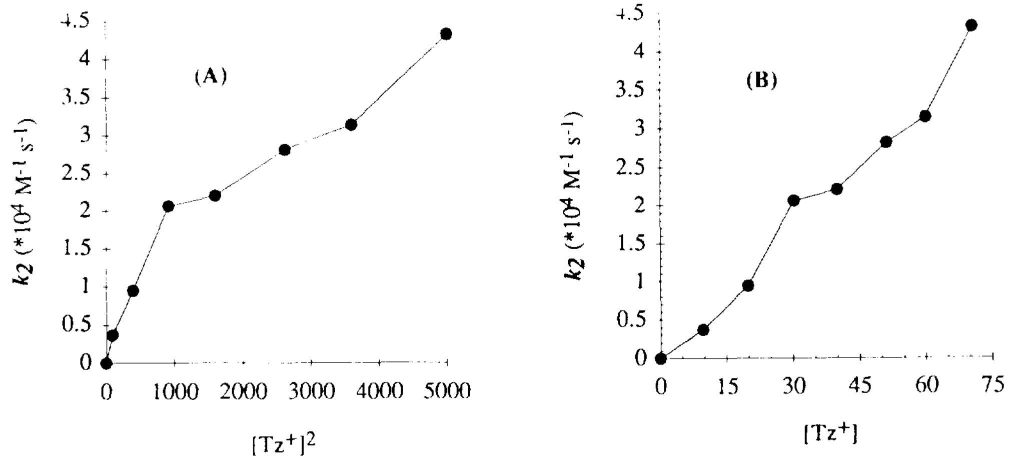


Figure 6. Representation of benzaldehyde half-consumption second order constants k_2, against concentrations (**A**) and second power (**B**) of concentrations of 3,4,5-trimethylthiazolium iodide (**6**) for the seven experiments of second series, Table 2.

From the presented kinetic data, it can be concluded that the benzoin condensation catalyzed by thiazolium cations plus base is a complex process, passing through two successive stages, formation of bis(thiazolin-2-ylidene) and the actual benzoin condensation, and with the concurrent formation of **5**-like species, with a macroscopic result which is impossible to fit in a standard simple model. In fact, the formation of bis(thiazolin-2-ylidene) and **5** are competitive, because both of the reactions take place from thiazolin-2-ylidene; furthermore, formation of **5** is very fast, trapping in this way a non-negligible part of pre-catalyst and slowing down significantly the formation of bis(thiazolin-2-ylidene) and, consequently, the benzoin condensation, especially at low concentrations of thiazolium cation. Maintaining the benzaldehyde concentration constant and increasing the pre-catalyst concentration, an equilibrium situation between benzaldehyde, thiazolin-2-ylidene and **5** should be attained, and from this moment the amount of bis(thiazolin-2-ylidene) should increase rapidly with the concentration of thiazolium cation, and this is indeed the observed situation: a very low rate at low concentrations of pre-catalyst, high rate for high concentrations and an intermediate situation for middle values of concentrations with a non-linear variation.

Kinetic study using 1,6-bis(4,5-dimethyl-3-thiazolio)hexane dibromide as pre-catalyst.

The reasons for doing a third series of experiments using a polymethylene-bridged thiazolium salt as pre-catalyst can be summarized as follows.

We have shown[11] that when polymethylene-bridged thiazolium cations are used as pre-catalyst the catalytic activity depends strongly on the methylene bridge length, because of formation and stability of intramolecular bis(thiazolin-2-ylidene)s and the reaction intermediates are affected by the bridge length.

If bis(thiazolin-2-ylidene)s are the actual catalytic species, then:

a/ any factor favoring their formation or enhancing their stability, or of intermediates leading to them, would give rise to higher reaction rates;

b/ if their formation is favored over other competitive processes, like formation of **5**, the observed rates clearly would be higher;

c/ the reactions carried out with polymethylene-bridged thiazolium cations as pre-catalyst would be of first order in their concentration.

On the contrary, if bis(thiazolin-2-ylidene)s are not the actual catalytic species, then:

a/ at equal thiazolium cation concentrations, the observed rates would be essentially identical to those in the previous experiments;

b/ all circumstances favoring their formation would lead to lower rates of reaction.

The polymethylene-bridged thiazolium salt chosen as pre-catalyst for the present experiments was 1,6-bis(4,5-dimethyl-3-thiazolio)hexane dibromide (**7**) because it has an optimal catalytic activity when used directly (plus base) as well as when previously converted into its bis(thiazolin-2-ylidene)[11].

In this third series of experiments the conditions were the same ones as in the two already described, but using half the molar amounts of pre-catalyst, that is to say, the same thiazolium cation concentrations as in the previous experiments (approximately 5, 7, 10, 15, and 25 mM).

Here again, the results obtained were the same in all cases but for the sake of brevity we discuss only the experiment corresponding to a reacting mixture exactly 496.22 mM in benzaldehyde, 87.62 mM in triethylamine, 9.45 mM in triethylammonium hydrochloride and 4.99 mM in 1,6-bis(4,5-dimethyl-3--thiazolio)hexane dibromide, registering the first spectra 38 min 14 s after the base addition, and the others each 30 min up to 16 consecutive spectra. In figure 7 we represent the concentrations of benzaldehyde against time as observed in the ^{1}H-NMR spectra and expressed in arbitrary area units, in figure 8-A are plotted their inverses and in figure 8-B their logarithms.

Again, the representation of the inverses is a straight line (regression lineal coefficient **r** = 0.9988) and the logarithmic representation is a clear parabola, confirming that the process is of second order in benzaldehyde. Results of the five experiments are collected in Table 3.

Table 3. Concentrations of Reagents and Calculated Parameters for a Second Order Reaction in [Benzaldehyde] with 1,6-Bis(4,5-dimethyl-3-thiazolio)hexane Dibromide as Pre-catalyst

[bTz$^+$]	[PhCHO]	t (min)[a]	r[b]	$k_3(10^4\ M^{-1}s^{-1})$[c]	$t_{1/2}$(h)[d]
4.99	496.22	30	0.9995 (16)	1.35	4.14
6.91	503.30	15	0.9992 (28)	1.80	3.06
9.89	496.22	5	0.9976 (22)	2.71	2.06
15.10	503.30	2	0.9991 (32)	4.72	1.16
24.89	496.69	2	0.9997 (35)	7.03	0.79

([a]) Time between spectra. ([b]) Lineal regression coefficient of the straight line obtained plotting the inverses of the arbitrary area units of the aldehydic peak of benzaldehyde against time (number of spectra registered). ([c]) Rate constants of consumption of benzaldehyde. ([d]) Half-consumption time of benzaldehyde calculated from k_3.

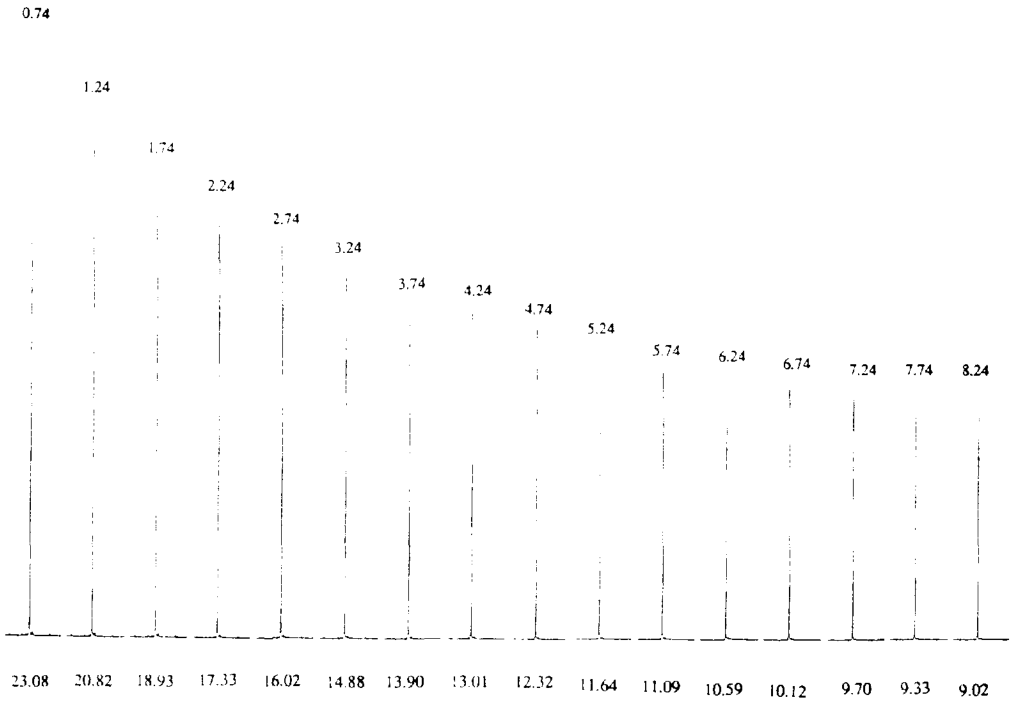


Figure 7. Array representing the variation of the aldehydic proton of benzaldehyde during experiments of the third series using 4.99 mM of 1,6-bis(4,5-dimethyl-3-thiazolio)hexane dibromide (7) as pre-catalyst and 496.22 mM of benzaldehyde. The number at the top of each peak indicates the observation time in hours, and the one below the integration value in arbitrary area units.

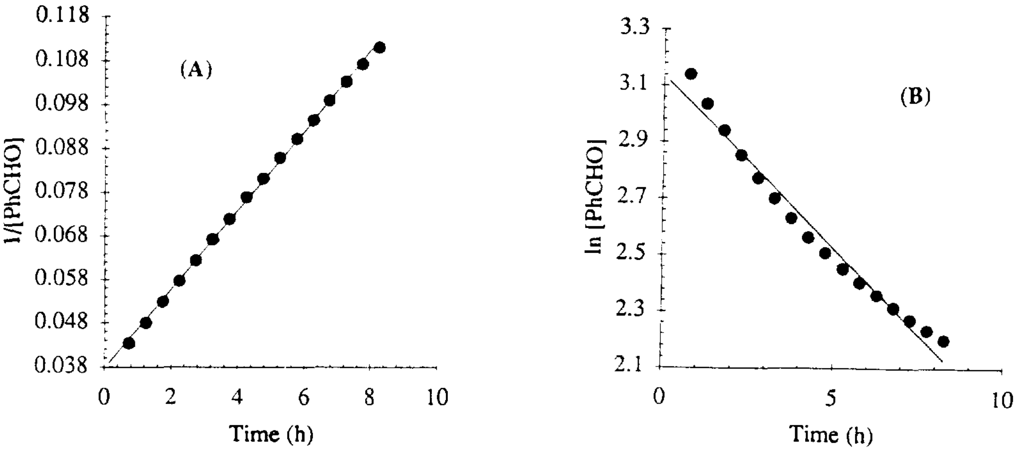


Figure 8. Representation of benzaldehyde concentration, expressed in arbitrary area units, inverses (**A**) and logarithms (**B**) *vs* time. Conditions as given in figure 7.

Important features observed in these reactions with bridged-bisthiazolium salt are:

a/ species **5**-like are also present, as shown by the ^{1}H-NMR spectra, but in a much lower concentration than with conventional pre-catalyst;

b/ the rate constants are independent of base concentration in the narrow range of variation used, consistent with the unimolecular character of the formation of bis(thiazolin-2-ylidene);

c/ the rates of consumption of benzaldehyde are considerably higher; this fact is by itself a confirmation of the importance of the formation of bis(thiazolin-2-ylidene)s in the benzoin condensation;

d/ furthermore, for the same concentration of thiazolium cations, the lower the concentration, the higher the ratio between rate costants; the values are $k_{3\text{-}5}/k_{2\text{-}10}$= 3.64, $k_{3\text{-}10}/k_{2\text{-}20}$= 2.88, and $k_{3\text{-}25}/k_{2\text{-}50}$ = 2.46 (see Tables 2 and 3); such a fact would indicate an approximation of the behaviour of the two catalytic systems at high concentrations, because of an approximate constant concentration of **5a** along the second series of experiments, increasing the relative amount of bis(thiazolin-2-ylidene), and consequently the observed rates, with the concentrations in the case of the conventional pre-catalyst; in the third group of experiments the formation of **5c** (R_1= hexamethylene, R_2=R_3=CH_3) is either negligible or it takes place in approximately the same proportions in all cases, due to the intramolecular character of the formation of bis(thiazolin-2-ylidene), not affecting significantly the amount of catalyst formed or affecting it in the same proportion.

In figure 9 are represented the plots of the five experiments of this third series.

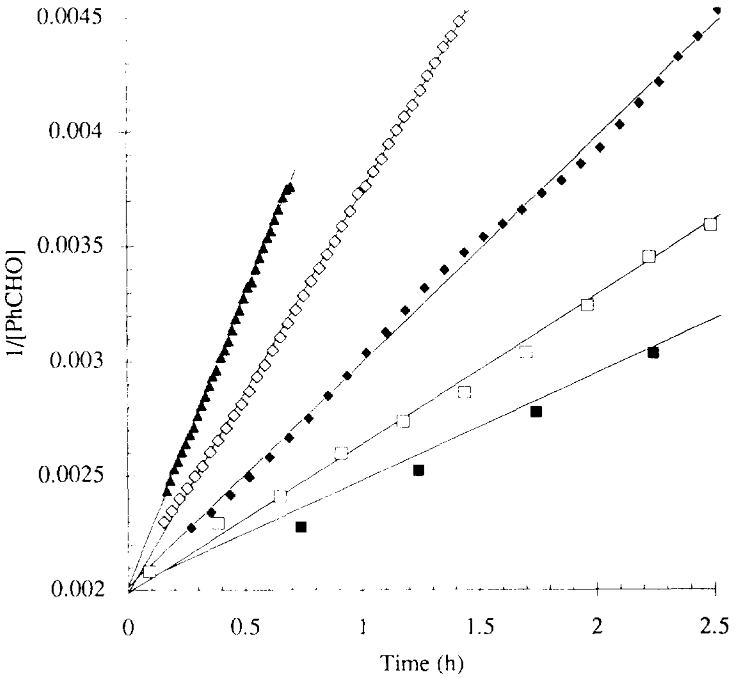


Figure 9. Representation of benzaldehyde concentration inverses, expressed in mM, *vs* time for the five experiments of the third series (Table 3).

Reaction order of the benzoin condensation with 1,6-bis(4,5-dimethyl-3-thiazolio)hexane dibromide as pre-catalyst.

Continuing with the standard kinetic treatment, in figure 10-A the obtained k_3 values are plotted in front of the concentrations of pre-catalyst, and in figure 10-B against of the second power of concentrations of pre-catalyst; the result is a straight line in the first case, with a regression lineal coefficient $r = 0.9944$, and in the second a clear parabola, showing that *the benzoin condensation is a first order process in bridged-bisthiazolium cation, in agreement with our mechanistic model.*

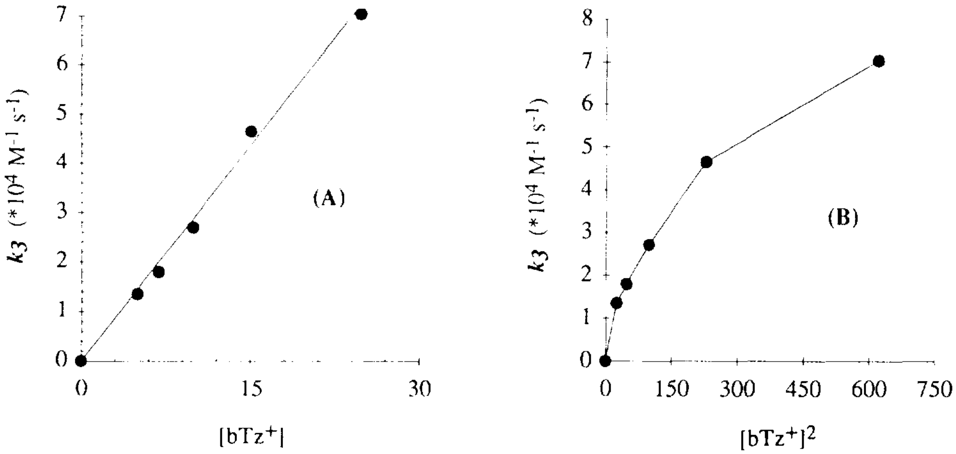


Figure 10. Representation of benzaldehyde half-consumption second order constants k_3, against concentration (**A**) and second power (**B**) of concentrations of 1,6-bis(4,5-dimethyl-3-thiazolio)hexane dibromide (**7**) for the five experiments of third series, Table 3.

Consequences of the new mechanistic proposal.

The kinetic data reported are in complete agreement with the proposal that bis(thiazolin-2-ylidene)s are the actual catalytic species in the benzoin condensation. The value of our study comes from its extrapolation to the mechanistic behaviour of thiamin as co-factor of several important enzymatic processes; it may be significant that fact, some thiamin-dependent enzymes contain more than one thiamin diphosphate unit[17], thus allowing the formation of the bis(thiazolin-2-ylidene) derived from the thiamin. We suggest that our mechanism operates in the transketolase processes involved in the biosynthesis of monosaccharides and that the Breslow mechanism operates in the decarboxilative-oxidative processes, in a way studied recently by Diederich[18]. In other words, Breslow intermediates **5** would be formed, directly or by decarboxylation of α-ketoacids and would be rapidly oxidized by a flavin or other oxidative coenzyme.

CONCLUSION

From the reported data it is possible to affirm that the benzoin condensation catalyzed by thiazolium cations plus base is a complex process, second order in both aldehyde and thiazolium cation. These kinetic data support strongly our previous mechanistic proposal, that is to say, that the real catalytic species in this reaction are the bis(thiazolin-2-ylidene)s. This result can be extrapolated to the *in vivo* transketolasic activity of the thiamine, and, probably, the Breslow mechanism would be also operative, up to the formation of its key intermediate, **5**, in oxidative processes mediated by the same vitamin.

EXPERIMENTAL

Measurement of the variation of benzaldehyde in a reacting mixture by means ^{1}H-NMR spectroscopy. A typical experiment. A solution approximately 500 mM in benzaldehyde, 90 mM in triethylamine, 10 mM in triethylammonium hydrochloride, and 40 mM in 3,4,5-trimethylthiazolium iodide, was prepared by dissolving in DMSO-d_6, until a final volume of 2 mL, 105.4 mg (497.16 mM), 18.1 mg (89.60 mM), 28.9 mg (10.54 mM) and 20.9 mg (41.17 mM), respectively of each reagent. From this solution, a 1 mL aliquot was taken, introduced in a standard 5 mm diameter NMR tube, and the tube placed as fast as possible in the pre-heated (45°C) probe of the spectrometer ; previously, the apparatus was heated and tuned using an identical sample. After introducing the sample under study, the spectrometer was permitted to recover the previously adjusted parameters, altered by the change of samples, and a spectrum was automatically registered each 30 min for 13 h. All the spectra were integrated in a normalized way to allow comparisons of integrations of the benzaldehyde peak throughout the experiment.

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