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Effect of the Hydration Rate of Cation-Exchange Resins on Their Catalytic Activity in the Condensation Reaction of Formaldehyde with Aromatic Ketones

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The condensation reaction of aromatic ketones with formaldehyde was carried out in organic media in the presence of cation-exchange resins used as catalysts. The corresponding 1,3-dioxacyclohexane could be obtained in good yield as the reaction selectivity was satisfactory. The investigation of the main parameters of the reaction (structure of the reactants, nature of the catalyst and of the solvent, hydration rate of the medium) showed the prevailing role of the residual water occurring in the organic reaction medium. The Karl Fischer titrimetric method allowed the value of this parameter, which governs the catalytic activity of ion-exchange resins, to be controlled satisfactorily.

INTRODUCTION

The investigation of the synthesis of 1,3-dioxacyclohexanes from alkenes using supported acid catalysis (*1*) led us to consider the choice of new reactants. Ketones having two enolizable positions α to the carbonyl group (*2*) were found to be suitable as they could give rise to the same heterocycles.

Besides the potential interest of these derivatives (*3*), the reaction considered is quite different from the Prins reaction (*4–6*) as water is released. This paper reports the effect of various parameters on the condensation of formaldehyde with acetophenone and propiophenone. These ketones were selected for their structural analogy with substituted styrenes (*1, 6*). The effect of water on the reaction progress was more particularly investigated.

EXPERIMENTAL

Water determination. The Karl Fischer titrimetric method (*7*) was used for the determination of water in the various samples analyzed. This procedure allowed the rate of hydration to be assessed separately within the liquid phase, the resin, and the whole reaction medium (*8, 11*).

The samples were introduced into a closed system protected from atmospheric moisture. The excess of Karl Fischer reagent was titrated with anhydrous methanol. Each milliliter of the Karl Fischer reagent was equivalent to approximately 2 mg of water. The water equivalence factor in milligrams of water per milliliter of reagent was determined using sodium tartrate ($Na_2C_2H_4O_6$, $2H_2O$).

Synthesis of 1,3-dioxacyclohexanes (*2*). The ketone (3×10^{-2} mole) paraformaldehyde (or monomeric formaldehyde, 9×10^{-2} mole), the acid catalyst (1.2×10^{-2} equiv. H^+), and an organic solvent (50 ml) were introduced into a 250-ml reactor fitted with a mechanical stirrer and a reflux condenser. The mixture was stirred at 65°C. The reaction time was 20 hr in every case, with the exception of the experiment listed in Table 4.

The reaction medium was analyzed by means of vapor phase chromatography us-

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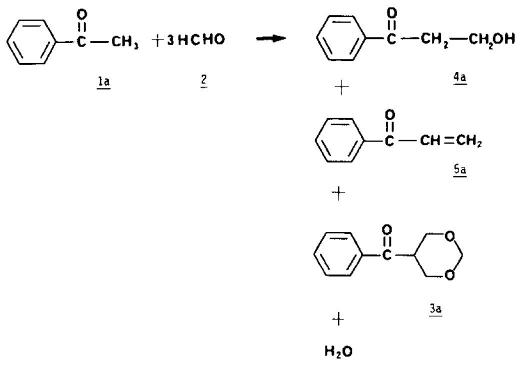
ing an OV 101 nonpolar column and xylene as the external standard.

RESULTS AND DISCUSSION

Effect of Various Parameters on the Condensation Reaction between Formaldehyde and Enolizable Ketones

Paraformaldehyde and aqueous formaldehyde. The condensation reaction between formaldehyde **2** and acetophenone **1a** gives rise to 1,3-dioxacyclohexane **3a** as well as to the hydroxymethyl derivative **4a**, and to the crotonic derivative **5a**; furthermore, a water molecule is released (Scheme 1).

The data listed in Table 1 clearly show that aqueous media preclude the conversion of acetophenone to 5-benzoyl-1,3-dioxacyclohexane whether in homogeneous (experiments 1 and 4) or heterogeneous (experiments 2, 3, 5, and 6) acid catalysis.



SCHEME 1. The products of the condensation reaction of formaldehyde with acetophenone in the presence of ion-exchange resins.

Such a result can be assigned to the fact that the formation of the enol species in the rate-determining step (*12*) is limited in the presence of water (*13*).

However, in organic media containing the same initial amount of residual water

TABLE 1

Effect of the Catalyst, of the Reactant, and of the Solvent on the Progress of the Reaction:

$$\underset{\mathbf{1a}}{\text{acetophenone}^{a}} + \underset{\mathbf{2a,b}}{\text{formaldehyde}} \xrightarrow[20\ \text{hr},^{a}\ 65^{\circ}\text{C}]{\text{P} - \text{SO}_3^-\text{H}^+} \begin{cases} \text{aldolization product } \mathbf{4a} \\ \text{1,3-dioxacyclohexane } \mathbf{3a} \\ \text{crotonization product } \mathbf{5a} \end{cases}$$

Solvent	Formaldehyde[b]	Cation[c] exchange resin	3a (%)	4a (%)	5a (%)	1a (%)	Experiments[d]
Benzene	HCHO (aqueous)	Conc. H_2SO_4	—	—	2	77	1
Benzene	HCHO (aqueous)	C 350/H^+	—	4	5	91	2
Benzene	HCHO (aqueous)	IR 120/H^+	—	4	5	91	3
1,4-Dioxane		Conc. H_2SO_4	—	—	4	90	4
1,4-Dioxane	HCHO (aqueous)	SP 120/H^+	3	6	5	86	5
1,4-Dioxane	HCHO (aqueous)	IR 120/H^+	3	7	5	85	6
Toluene	$n(CH_2O)$	Conc. H_2SO_4	—	—	—	17	7
1,4-Dioxane	$n(CH_2O)$	Conc. H_2SO_4	4	—	21	29	8
Toluene	$n(CH_2O)$	SP 120/H^+	22	2	4	72	9
1,4-Dioxane	$n(CH_2O)$	SP 120/H^+	59	1	5	35	10
Toluene	$n(CH_2O)$	IR 120/H^+	17	2	2	79	11
1,4-Dioxane	$n(CH_2O)$	IR 120/H^+	60	2	2	36	12

[a] The conversion rate of acetophenone did not increase significantly (experiments 1–19, Tables 1, 2, and 3).

[b] **2a**, aqueous formaldehyde; **2b**, paraformaldehyde.

[c] The hydration rate of the catalysts before the reaction was 180 mg water per gram of resin. The macropore ion-exchange resins used were Baker-C350 and Lewatit SP-120; the gel-like cation-exchange resin was Amberlite-IR 120.

[d] Polymeric products were formed in the experiments carried out in homogeneous acid media (experiments 1, 4, 7, and 8).

(experiments 7–12), the dioxane heterocycle **3a** was obtained in good yield and selectivity only in the presence of polymeric catalysts.

The difference in reactivity observed in organic media between acetophenone and styrene (*6*) in the case of paraformaldehyde is likely to depend on the prior occurrence of the keto-enol equilibrium which is a prerequisite for the condensation reaction. As this equilibrium controls the reaction rate (*12*), it is therefore likely to be promoted in the presence of polymeric catalysts as shown recently by Iditoiu and Gates (*14*) for acetone in the presence of sulfonic membranes.

As the occurrence of keto-enol equilibria can bring about the stabilization of the intermediate reaction species, the reaction pathway leading to the heterocycle is then no longer preferential. This phenomenon may account for the decrease in selectivity with respect to styrene. However, the aldolization reaction (Scheme 1) cannot be considered as a side reaction since the corresponding reaction pathway is analogous to that leading to the diol in the reaction between formaldehyde and styrene (*5, 16*). On the contrary, the crotonization reaction leading to **5a** breaks the reaction pathway to 1,3-dioxacyclohexane, and decreases the reaction selectivity in the same manner as the ethylenic alcohols resulting from the dehydration of the diols in the Prins reaction (*4*).

The proportions of **4a** and **5a**, however, remained limited; furthermore, these derivatives could be easily separated from the 1,3-dioxacyclohexane formed.

Moreover, the difference in reactivity observed between toluene and 1,4-dioxane might also depend on the keto-enol equilibrium, but certainly not to the extent shown by experiments 5 to 8. The behavior of the ion-exchange resins in these two solvents actually depends on their hydration rate which is likely to play a prevailing role (*15*).

The comparison of the results obtained in homogeneous and heterogeneous acid media points out the effect of the structure of the polymeric network on the reaction selectivity. This effect has already been reported for the Prins reaction (*4–6*) and was assigned to the localization of the reactive species within the polymer. As there is nearly no contact between the H^+ ions and the reactive species, polymerization or degradation reactions are thus precluded.

In contrast to inorganic acids (*12*) (tests 1, 4, 7, 8), no polymeric products could be observed when ion-exchange resins were used as catalysts. This can therefore be considered as an advantage of ion-exchange resins. Experiments (9–12), which were carried out in organic media characterized by their low water content, showed the unexpected identical behavior of the macroporous and gel-like catalysts (*8*) in 1,4-dioxane as well as in toluene, although the catalytic activity was lower in the latter solvent.

Effect of the solvent. The investigation of the solvent effect in the presence of ion-exchange resins was undertaken so as elucidate the difference in reactivity observed in 1,4-dioxane and toluene (experiments 9–12).

Experiments (13–18) (Table 2) corroborated the data obtained in toluene and 1,4-dioxane and showed the importance of the miscibility of the solvent used with the hydration water of the system. The phenomenon observed is enhanced by the water released in the reaction medium. Its effect on the ionization of the active sites (*17, 18*) is likely to account for the lower reactivity of acetophenone as compared to styrene (*6*).

Effect of the structure of the catalyst. The variation in the reticulation rate of the polymeric catalysts used appeared to have no marked effect on their activity (Table 3). A slight decrease in reactivity could be observed as the reticulation rate increased. The access of the reactants to the active sites was then hampered as a result of the change in the size of the unit cells of the catalyst lattice. In that respect, it can be noted that the gel-like ion-exchange resins

TABLE 2

Effect of the Solvent on the Condensation Reaction of Acetophenone with Paraformaldehyde in the Presence of Ion-Exchange Resins

Solvent	Cation exchange resin[a]	**3a** (%)	**4a** (%)	**5a** (%)	**1a** (%)	Experiments
Benzene[b]	SP 120/H$^+$	19	1	3	77	13
Benzene	IR 120/H$^+$	18	1	2	79	14
1-Bromobutane[b]	SP 120/H$^+$	21	1	3	75	15
1-Bromobutane	IR 120/H$^+$	19	1	2	68	16
1,2-Dimethoxyethane	SP 120/H$^+$	60	1	5	34	17
1,2-Dimethoxyethane	IR 120/H$^+$	60	1	6	33	18

[a] The hydration rate of the catalysts before the reaction was 180 mg water per gram of dry resin.
[b] Water-insoluble solvent.

displayed the same behavior as their macroporous homologues.

This particular phenomenon can be assigned to the water released: as the reaction proceeds further, the gel-like ion-exchange is swelling. The diffusion of the reactive species should therefore be easier within such a structure at the end of reaction; the effects related to the porosity of the macromolecular network are then attenuated.

Comparative reactivity of acetophenone and propiophenone. When the data listed in Table 4 are compared to those of Table 1 (tests 6 and 8), the reactivity of propiophenone appears to be markedly higher than that of acetophenone. The occurrence of an extra methyl group in propiophenone increases the reactivity of the double bond of the enol species towards electrophilic reactants.

The faster reaction progress in the presence of a macroporous resin (experiment 25) can corroborate the role assigned to the water formed in the course of the reaction, since its favorable effect on diffusion depends on the amount released.

Furthermore, experiment 25 showed that the number of water molecules released in the course of the reaction (Scheme 1) was directly proportional to the amount of ketone **1b** that had disappeared when Lewatit resin SP 120 was used as a catalyst.

Effect of the Hydration Rate on the Progress of the Condensation Reaction

In contrast to the condensation reaction between styrene and paraformaldehyde in organic media characterized by their low water content (*6*), water is released in the course of the reaction investigated here.

The effect of the water initially occurring in the reaction medium was determined prior to the assessment of the role of the water released by the reaction with propiophenone used as a reactant.

Effect of the initial hydration rate. The data listed in Table 5 clearly show that the reactivity of propiophenone in 1,4-dioxane markedly depends on the initial hydration rate of the ion-exchange resin.

In the presence of a highly dehydrated catalyst (experiment 22), 1,4-dioxane cannot replace the hydration water of the ion-exchange resin. This observation is less surprising if the shift of the keto-enol equilibrium is considered to be the rate-determining step (*12*). The appearance of the enol species, which is a prerequisite for the condensation reaction, depends on the ionization of the active sites. As a matter of fact, the ionization of the catalytic sites requires a definite amount of water so that the reaction can start. However, a too high hydration of the reaction medium simultaneously enhances the dissociation of the sul-

TABLE 3

Effect of the Reticulation Rate of the Catalyst on the Reaction between Acetophenone and Paraformaldehyde in 1,4-Dioxane

Cation exchange resin[a]	Reticulation percentage	**3a** (%)	**4a** (%)	**5a** (%)	**1a** (%)	Experiments
IR 116	2	64	1	4	31	19
IR 120	8	60	2	2	36	20
IR 124	12	57	1	2	40	21
SPC 108	8	63	1	6	30	22
SP 120	20	59	1	5	35	23

[a] Hydration rate before reaction: 180 mg of water per gram of dry resin.

fonic groups and the solvation of the protons. The reactivity is then decreased as the approach of the reactants is hampered (*17, 18*).

These phenomena may also account for the poor results of the condensation in hydrated organic media. It was therefore interesting to investigate the distribution of the water molecules within each phase of the reaction medium.

Effect of the water released in the course of the condensation reaction. The hydration water occurring in the reaction medium is in equilibrium with the two phases of the system as it is miscible with 1,4-dioxane. The determination of the water content of the whole reaction medium was not considered as it would have required too large amounts of reagent.

The plot of the water content of the resin against the water content of the liquid phase (Fig. 1) was obtained from different water–1,4-dioxane–resin SP120/H$^+$ mixtures. This plot allowed the water content of each phase to be calculated directly from only one determination on the solution. The datum point X corresponds to the amount of water found in 1,4-dioxane, for the reaction between formaldehyde and propiophenone, after 20 hr.

The total amount of water in the reaction medium was 360 mg; the water contained in 4 g of resin was $172 \times 4 = 688$ mg (Fig. 1). Taking into account the amount of water introduced initially together with the resin ($174 \times 4 = 696$ mg), the water released in the course of the reaction corresponded to $360 + 688 - 696 = 352$ mg. This value

TABLE 4

Reactivity of Propiophenone in the Condensation Reaction:

$$\underset{\mathbf{1b}}{\text{Propiophenone}} + n(\text{CH}_2\text{O}) \xrightarrow{\text{1,4 dioxane}} \begin{cases} \text{aldolization product } \mathbf{4b} \\ \text{1,3-dioxacyclohexane } \mathbf{3b} \\ \text{crotonization product } \mathbf{5b} \end{cases}$$

Cation exchange resin[a]	**3b** (%)	**4b** (%)	**5b** (%)	**1b** (%)	Experiments
Reaction time (hr)	10 20 40	10 20 40	10 20 40	10 20 40	
IR 120/H$^+$	27–62–64	3–2–0	2–4–6	68–32–30	24
SP 120/H$^+$ [b]	35–64–65	0–0–0	5–8–8	60–28–27	25

[a] Hydration rate: 175 mg water per gram dry resin.

[b] After 15 hr the yield in 1,3-dioxacyclohexane **3b** was 63%.

TABLE 5

Effect of the Hydration Rate of the Ion-Exchange Resin on the Reaction:

$$\underset{\textbf{1b}}{\text{propiophenone}} + \underset{\textbf{2b}}{\text{paraformaldehyde}} \xrightarrow[\text{1,4-dioxane}]{\text{SP 120/H}^+} \left\{ \begin{array}{l} \text{1,3-dioxacyclohexane } \textbf{3b} \\ \text{crotonization product } \textbf{5b} \end{array} \right.$$

Hydration rate of the resin SP 120/H$^+$ (mg H_2O/g dry resin)	**3b** (%)	**5b** (%)	**1b** (%)	Experiments
41	—	—	100	26
172	63	7	30	27
500	—	—	100	28

shows that 2×10^{-2} mole of water was formed; the yield of the reaction, as calculated with respect to water, is then ca. 70%.

The gas chromatographic determination showed that the reaction yielded 64% of 5-benzoyl-5-methyl-1,3 dioxacyclohexane, and 8% of phenylisopropenylacetone. The latter derivative originated from the aldolization reaction which was followed by the crotonization reaction. A molecule of water was then released as in the heterocyclization reaction. The agreement between the values of the yield obtained from the water determination and from the gas chromatographic determination is therefore satisfactory.

In addition, Fig. 1 shows the gradual water saturation of the resin as the water content of the reaction medium is increasing. The decrease in the reactivity of the functional groups can therefore be assigned to the increase in the water content of the reaction medium, which markedly slows down the progress of the condensation reaction.

This phenomenon was much more pronounced in toluene than in 1,4-dioxane since the hydrophilic character of the latter solvent decreased the number of water molecules in the environment of the active sites. Such a limitation cannot operate in the solvents that are not water miscible (Tables 1 and 2): as the hydration of the functional groups is increasing more rapidly, the reaction is slowed down earlier.

CONCLUSIONS

The use of ion-exchange resins, which allow the introduction of water in the medium to be controlled, together with the application of the Karl Fischer titrimetric method are convenient for following the progress of the condensation reaction.

The water content of the organic reaction medium exerts a decisive effect on the orientation of the reaction. The data reported above, as well as those provided previously by the investigation of the Prins reaction (*15*) and the Wittig reaction (*19*), point to the major importance of this parameter which should be taken into account in synthesis. The Karl Fischer titrimetric method affords a satisfactory control of this param-

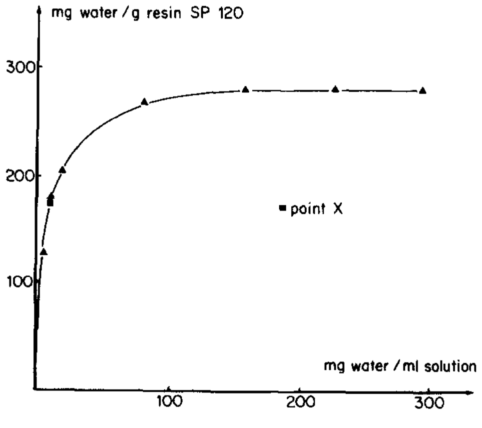


FIG. 1. Plot of the water content of the ion-exchange resin against the water content of the solution.

eter and is therefore particularly convenient for the control of the catalytic activity of cation-exchange resins in organic media.

REFERENCES

1. Delmas, M., Kalck, Ph., Gorrichon, J. P., and Gaset, A., *J. Mol. Catal.* **4,** 443 (1978).
2. Gorrichon, J. P., Delmas, M., and Gaset, A., *Synthesis* 219 (1979).
3. Boher, R. N., Smits, S. E., Turner, W. W., and Pohland, A., *J. Med. Chem.* **20,** 885 (1977).
4. Adams, D. R., and Bathnagar, D. P., *Synthesis* 661 (1977).
5. Delmas, M., Thèse Doctorat ès Sciences, I.N.P. Toulouse, No. 45 (1980).
6. Delmas, M., and Gaset, A., *Synthesis* 871 (1980).
7. Eberins, E., "Wasserbestimmung mit Karl Fischer Lösung." Verlag Chemie, GmbH, Weinheim (Bergstr.), 1954.
8. Pietrzyk, D. J., *C.R.C. Crit. Rev. Anal. Chem.* **6,** 131 (1976).
9. Dickel, G., and Hartman, H., *Z. Phys. Chem.* **23,** 1 (1960).
10. Blasius, E., and Schmitt, R., *Z. Anal. Chem.* **4,** 241 (1968).
11. Richard, J. C., Janier-Dubry, J. L., and Devin, C., *Analusis* **8,** 69 (1980).
12. Wesslen, B., and Ryrfors, L. O., *Acta Chem. Scand.* **22,** 2071 (1968).
13. Reichart, C., "Solvent Effect in Organic Chemistry." Verlag Chemie, Weinheim, New York, 1979.
14. Iditoiu, C., and Gates, B. C., *Rev. Roum. Chim.* **24,** 443 (1979).
15. Delmas, M., and Gaset, A., Inorg. Chim. Acta Letters, Abstracts of Vth International Symposium Solute Solvent, Florence, Italy, June 2–6 (1980).
16. Bocard, C., Hellin, M., Davidson, M., and Coussemant, F., *Bull. Soc. Chim. Fr.* 490 and 877 (1971).
17. Ancilotti, F., Massi-Mauri, M., and Pescarolo, E., *J. Catal.* **46,** 49 (1977).
18. Thornton, R., and Gates, B. C., *J. Catal.* **34,** 275 (1974).
19. Delmas, M., Le Bigot, Y., and Gaset, A., *Tetrahedron Lett.* 4831 (1980).