Reactions Catalyzed by Anion Exchange Resins

KNOEVENAGEL CONDENSATION

MELVIN J. ASTLE AND JOEL A. ZASLOWSKY[1]
Case Institute of Technology, Cleveland, Ohio

ANION exchange resins such as Amberlite IR-4B, Deacidite, and Amberlite IRA-400 are excellent catalysts for promoting Knoevenagel condensations between aldehydes and esters, such as ethyl cyanoacetate, ethyl acetoacetate, and diethyl malonate. Condensations with diethyl malonate cannot be accomplished at room temperature but may be carried out by refluxing in benzene solution. The benzene removes the water as an azeotrope as fast as formed. Condensation with ethyl cyanoacetate can be effected by agitating the aldehyde and ester at room temperature in the presence of the anion exchange resin. Those reactions involving ethyl acetoacetate can be carried out by either of the above-mentioned methods.

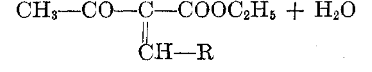
Ion exchange resins may be considered to be insoluble acids or bases, and consequently might be expected to promote reactions which are catalyzed by conventional acids or bases. Cation exchange resins in which the functional group is SO_3H are strong acids while those in which the functional group is COOH are weak acids. Similarly anion exchange resins are strong or weak bases, depending upon whether the functional group is a quaternary ammonium or an amino group.

Cation exchange resins have been used successfully as catalysts in the following reactions: esterification (*20, 26*), ester hydrolysis (*12, 26, 27*), sucrose inversion (*26*), alcohol dehydration (*26*), and acetal formation (*26*). Only a few examples of reactions catalyzed by anion exchange resins are reported in the literature. Jenny (*14*) reported that anion exchange resins catalyzed the mutarotation of glucose and Galat (*11, 18*) converted nicotinonitrile in good yields to nicotinamide by refluxing with a strongly basic anion exchange resin.

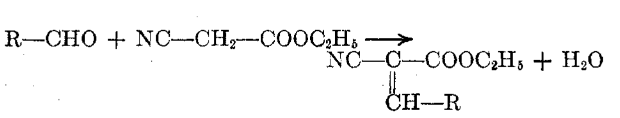
The advantages of solid, substantially insoluble catalysts are that the separation problems are manifestly simpler, the same catalyst can be used repeatedly, and sensitive molecules can, in some cases, be reacted without polymerization or other side reactions—e.g., furfuryl alcohol can be esterified with acetic acid.

The Knoevenagel condensation has been studied quite extensively by Cope and other workers (*7–9*) using amines as catalysts. This reaction was therefore chosen for further investigation using anion exchange resins in place of the more conventional catalysts. This reaction also presented the opportunity to observe the catalytic activity of ion exchange resins in systems which are essentially nonaqueous.

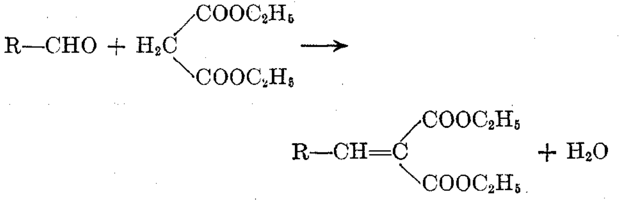
The Knoevenagel reaction involves the condensation of aldehydes or ketones with compounds containing active hydrogen, such as ethyl acetoacetate, ethyl cyanoacetate, and diethyl malonate. These reactions are illustrated in the following equations:



$$R{-}CHO + CH_3{-}CO{-}CH_2{-}COOC_2H_5 \longrightarrow CH_3{-}CO{-}\underset{\underset{CH{-}R}{\|}}{C}{-}COOC_2H_5 + H_2O \qquad (1)$$



$$R{-}CHO + NC{-}CH_2{-}COOC_2H_5 \longrightarrow NC{-}\underset{\underset{CH{-}R}{\|}}{C}{-}COOC_2H_5 + H_2O \qquad (2)$$



$$R{-}CHO + H_2C\begin{matrix}\diagup COOC_2H_5\\ \diagdown COOC_2H_5\end{matrix} \longrightarrow R{-}CH{=}C\begin{matrix}\diagup COOC_2H_5\\ \diagdown COOC_2H_5\end{matrix} + H_2O \qquad (3)$$

Cope found that piperidine and piperidine acetate were particularly effective catalysts for the condensation of aldehydes with ethyl acetoacetate. It was also shown by Cope that the Knoevenagel reaction was reversible, and better yields were obtained in many cases by using a water separator to remove the water formed during the reaction. This method was analogous to the esterification work of Sussman (*26*) using cationic exchange resins. Although there is some evidence for a noncatalyzed reaction, this does not account for more than a trace of the product formed in these reactions (*7*).

In this investigation, several commercially available aldehydes were condensed with ethyl acetoacetate, ethyl cyanoacetate, and diethyl malonate (Table I).

EXPERIMENTAL

Two general procedures were employed in effecting the Knoevenagel condensation. These procedures will be described below as A and B.

Procedure A. To effect condensations by this method 0.5 mole of ethyl acetoacetate or ethyl cyanoacetate was agitated at room temperature with slightly more than equimolar amounts of freshly distilled aldehyde in the presence of 15 to 30 grams of air-dried resin. The time required to effect maximum yield by this method depends upon the aldehyde and ester employed. Agitation was achieved by means of a shaking device (Burrell), inasmuch as the use of a stirrer caused considerable physical deterioration of the resin. At the end of the reaction period the solution was decanted and the suspended resin was removed by filtration. The resin was then rinsed with benzene, air-dried, and re-used.

The reaction mixture was distilled to remove unreacted aldehyde and heated where applicable to approximately 180° C. to effect the dehydration of the aldol which is formed as a by-product. The residue was fractionally distilled at reduced pressure.

Procedure B. This method involved reflux in the presence of benzene. The same quantities of reactants as in method A were placed in a flask equipped with reflux condenser and water separator together with 100 to 150 ml. of benzene. When reflux

---

[1] Present address, Mathieson Chemical Corp., Niagara Falls, N. Y.

TABLE I. COMPOUNDS PREPARED BY KNOEVENAGEL CONDENSATIONS

Product	Yield, %	Method	Reaction Time, Hr.	B.P. ° C.	Reference
Butylidene ethyl acetoacetate	50	A	10-24	124-128 (23 mm.)	*(8)*
Propylidene ethyl acetoacetate	37	A	24	103-106 (11 mm.)	New cpd.
Isobutylidene ethyl acetoacetate	60	B	10-15	113-117 (17 mm.)	*(16)*
	55	A	10-24		
Hexylidene ethyl acetoacetate	60	B	6	130-132 (10 mm.)	New cpd.
	50	A	42		
2-Ethylbutylidene ethyl acetoacetate	64	B	8	122-123 (11 mm.)	*(8)*
	57	A	72		
Benzylidene ethyl acetoacetate[a]	40	B	4	164-167 (10 mm.)[b]	*(15, 25)*
Heptylidene ethyl acetoacetate	51	A	60	133-136 (8 mm.)	*(16)*
Ethylidene ethyl acetoacetate	51	A[c]	22	106-110 (23 mm.)	*(16, 24)*
2-Ethylhexylidene ethyl acetoacetate	58	B	24	124-128 (14 mm.)	*(8)*
	52	A	204		
Hexylidene diethyl malonate	33	B	5	146-148 (10 mm.)	*(9)*
Heptylidene ethyl cyanoacetate	62	A	30	140-143 (7 mm.)	*(19, 22)*
Hexylidene ethyl cyanoacetate	54	A	22	142-144 (13 mm.)	New cpd.
2-Ethylhexylidene ethyl cyanoacetate	70	A	30	140-141 (9 mm.)	New cpd.
2-Ethylbutylidene ethyl cyanoacetate	83	A	20	118-123 (9 mm.)	New cpd.
Furfurylidene ethyl acetoacetate[d]	42	A	46	155-159 (9 mm.)[e]	*(16)*

[a] Pratt and Werble (*25*) did not obtain a solid product; they recognized the possibility of cis-trans isomerism. A solid product was not obtained in the present work.

[b] Melting point, 60° to 61° C. (*7*).

[c] 100 ml. benzene were employed as a diluent.

[d] Two products were isolated—a solid melting at 61° to 62° C. and a liquid; 10 days were required for crystallization; possibly cis-trans isomers; analysis of liquid gave %OEt: found 21.4, calcd. 21.6; Knoevenagel reported a 2-month crystallization period.

[e] Melting point, 61° to 62° C.

commenced the water was removed from the reaction mixture as fast as it was formed. The mixture was refluxed at least as long as water was being evolved. The reaction mixture was worked up in a manner similar to method A.

This method was the most successful with aldehydes which do not undergo the aldol condensation too readily—e.g., alpha-substituted aldehydes, aromatic aldehydes, and long-chain aliphatic aldehydes, such as hexaldehyde.

Yields are based upon the amount of ester converted to product, i.e., the ratio of product to ester added.

The resins employed were all of the commercial type (20 to 50 mesh) and were used without any screening for particle size or determination of the water content of the air-dried resins. It is recognized that these factors do probably affect the efficiency of the catalysts, but they are being neglected in this study for simplicity. It is not believed that these factors are too important in synthetic work.

Amberlite IR-4B, Amberlite IR-45, Deacidite, and Duolite A-4 are weakly basic resins whose basicity is attributed to amino groups. These are shipped in the basic form (except Duolite A-4), and simply required rinsing with water and air drying before use. Amberlite IRA-400 and Dowex 1 are strong bases and are shipped as the chloride salt. These resins must be regenerated before use. The regeneration was effected by washing with 5% sodium hydroxide (5 to 6 times the volume of resin) in a Buchner funnel. The resins were then rinsed with distilled water until the washings were neutral. The resins were air-dried and employed in a manner similar to the weakly basic resins.

In some cases the weakly basic resins were converted to their acetate salts by washing with glacial acetic acid. The excess acid was filtered off, and the resins were washed with acetone and air dried.

DISCUSSION OF RESULTS

The main purpose of this investigation was to determine whether or not anion exchange resins are effective catalysts for the Knoevenagel condensation and to determine what yields (as previously defined) can be obtained by the methods developed. It was also of great interest to determine the catalytic life of these resins.

Table I lists the various compounds prepared and gives the yields obtained in representative runs by the two general methods used.

Table II lists several specific runs attempted with butyraldehyde and isobutyraldehyde.

The efficiency of the strongly basic Amberlite IRA-400 and Dowex 1 is seen to be less than that of Deacidite, Deacidite acetate, IR-4B, IR-4B acetate, and Duolite A-4. This could probably be attributed to the lower capacity of these resins (the strong bases have a capacity of about 2.5 meq. per gram, while the weak bases have capacities in the neighborhood of 1 meq. per gram).

The efficiency of the weakly basic resins is further enhanced by the undiminished catalysis of the carboxylic acid–neutralized form of these resins. The strongly basic resins are not recommended for long-term use. A yet unpublished work by the authors on the aldol condensations indicates that the strongly basic resins are rapidly deactivated by the addition of acetic acid or by exposure to the atmosphere for several days. The latter observation has been verified in this work.

The above facts are in agreement with the known catalytic activity of the carboxylic acid salts of weak bases (*7–9*).

Procedure B is preferred for condensing high molecular weight and alpha-substituted aldehydes with ethyl acetoacetates. These condensations when conducted at room temperature (method A) require very long reaction times. The amount of by-product and residue formed during the condensations of alpha-substituted aldehydes with ethyl acetoacetate is almost nil. This has been attributed to the sluggishness of the competing aldol condensation of these aldehydes and to the inability for the aldol to dehydrate in an essentially unreversible manner.

Condensations of aldehydes with ethyl cyanoacetate proceed more rapidly and usually in better yield than the corresponding condensations with ethyl acetoacetate. Method A was exclusively used for the reactions of ethyl cyanoacetate. Even unreactive aldehydes gave good yields by this method.

The condensation of diethyl malonate with aldehydes proceeds only by method B, as does the condensation of benzaldehyde with ethyl acetoacetate.

TABLE II. CONDENSATION OF ISOBUTYRALDEHYDE AND BUTYRALDEHYDE WITH ETHYL ACETOACETATE (METHOD A)[a]

Catalyst	G. Catalyst/ Mole Aldehyde	Reaction Time, Hours	Yield
	ISOBUTYRALDEHYDE		
Deacidite acetate	40	10	48
Deacidite acetate	40	24	51
Deacidite acetate	30	15	51
Deacidite	40	24	55
IR-4B	45	48	54
	BUTYRALDEHYDE		
Deacidite acetate	25	17	49
IRA-400	45	18	31
IRA-400	45	68	49
Deacidite	45	24	49
Dowex 1	40	22	31
IR-4B	40	30	48
Duolite A-4	45	24	50
IR-4B acetate	40	24	50

[a] In each case 0.55 mole of the aldehyde and 0.5 mole of ester were employed.

TABLE III. TYPICAL REACTIONS[a] USING THE SAME CATALYST WITH NO TREATMENT BETWEEN RUNS

(25 grams of Deacidite)

Aldehyde[a]	No. of Previous Runs	Reaction Time[b], Hr.	Yield, %
WITH ETHYL ACETOACETATE			
Isobutyraldehyde	3	15	53
Isobutyraldehyde	6	24	50
2-Ethyl butyraldehyde	7	24	16
2-Ethyl butyraldehyde	7	72	41
Hexaldehyde	11	42	45
Butyraldehyde	18	66	54
Butyraldehyde	21	24	49
WITH ETHYL CYANOACETATE			
2-Ethyl butyraldehyde	30	19	83
Hexaldehyde	31	9	44
Hexaldehyde	32	23	54

[a] In each case 0.55 mole of the aldehyde and 0.5 mole of the ester were used.

[b] All runs were made at room temperature.

Table III records but one of a series of inactivation studies carried out with the weakly basic resins. This data would indicate that the weakly basic resins do not undergo inactivation even after many runs.

A few general observations can be made concerning these reactions: Most of the anion exchange resins were equally effective in promoting the Knoevenagel condensation. IR-45 gave much poorer conversion after several runs than the other resins investigated. The strongly basic resins apparently required more time to effect maximum conversions and are easily inactivated. This inactivation can be brought about by the presence of acids such as might be found in the aldehydes or carbon dioxide.

The most generally satisfactory resins investigated were Deacidite and Amberlite IR-4B. (Other weakly basic resins, such as Duolite-A-4, are also satisfactory but have not been investigated so thoroughly.) Deacidite and Amberlite IR-4B were converted to their acetate salts and these treated resins were found to be as effective as the free base.

Although anion exchange resins are not considered to be heat stable there was no loss of activity of Deacidite or Amberlite IR-4B after several runs at the reflux temperature of benzene.

The data here submitted suggest that IR-4B and Deacidite might be used in continuous operations using columns packed with resin.

Such procedures were not attempted in the investigation of the Knoevenagel condensation, but the aldol condensation of butyraldehyde has been accomplished using the above techniques.

Compounds which have not been previously reported in the literature are given in the following table, together with some physical and chemical properties:

Compound	Boiling Pt., ° C.	Refractive Index	Analysis					
			Carbon, %		Hydrogen, %		Nitrogen, %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
Propylidene ethyl acetoacetate	103–106 (11 mm.)	n_D^{25}, 1.4500	63.46	63.4	8.23	8.01	..	..
Hexylidene ethyl acetoacetate	130–132 (10 mm.)	n_D^{25}, 1.4571	67.92	67.83	9.42	9.17	..	..
2-Ethylbutylidene ethyl cyanoacetate	122–123 (8.5 mm.)	n_D^{23}, 1.4541	...	...	..	..	7.18	6.89
2-Ethylhexylidene ethyl cyanoacetate	140–141 (9 mm.)	n_D^{26}, 1.4522	...	...	..	..	6.25	5.95
Hexylidene ethyl cyanoacetate	142–144 (13 mm.)	n_D^{26}, 1.4535	...	...	..	..	7.18	7.01

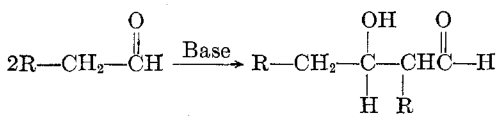
(Reactions Catalyzed by Anion Exchange Resins)

ALDOL CONDENSATION

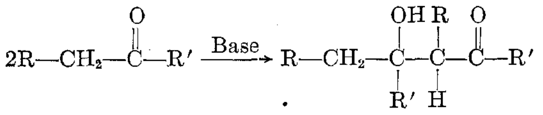
ALDOL condensations of aldehydes can be carried out in much the same manner as the Knoevenagel condensations. The weakly basic resins such as Amberlite IR-4B or Deacidite are more effective than the strongly basic resins because they are effective condensation catalysts even in the presence of organic acids.

The aldol condensation of acetone can be readily effected with strongly basic anion exchange resins such as Amberlite IRA-400 or Dowex-1.

The aldol condensation of aldehydes and ketones can be represented by the following equations:

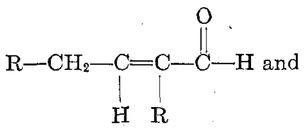


$$2\mathrm{R{-}CH_2{-}}\overset{\overset{O}{\|}}{\mathrm{C}}\mathrm{H} \xrightarrow{\text{Base}} \mathrm{R{-}CH_2{-}}\underset{\mathrm{H}}{\overset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}}\underset{\mathrm{R}}{\mathrm{CH}}\overset{\overset{O}{\|}}{\mathrm{C}}\mathrm{{-}H} \qquad (4)$$

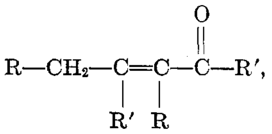


$$2\mathrm{R{-}CH_2{-}}\overset{\overset{O}{\|}}{\mathrm{C}}\mathrm{{-}R'} \xrightarrow{\text{Base}} \mathrm{R{-}CH_2{-}}\underset{\mathrm{R'}}{\overset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}}\underset{\mathrm{H}}{\overset{\mathrm{R}}{\mathrm{C}}}\mathrm{{-}}\overset{\overset{O}{\|}}{\mathrm{C}}\mathrm{{-}R'} \qquad (5)$$

The initially formed aldol in the above cases can easily be dehydrated to give



$\mathrm{R{-}CH_2{-}}\underset{\mathrm{H}}{\mathrm{C}}\mathrm{{=}}\underset{\mathrm{R}}{\mathrm{C}}\mathrm{{-}}\overset{\overset{O}{\|}}{\mathrm{C}}\mathrm{{-}H}$ and



$\mathrm{R{-}CH_2{-}}\underset{\mathrm{R'}}{\mathrm{C}}\mathrm{{=}}\underset{\mathrm{R}}{\mathrm{C}}\mathrm{{-}}\overset{\overset{O}{\|}}{\mathrm{C}}\mathrm{{-}R'}$, respectively.

The aldol condensation of aldehydes was first reported by Wurtz (*29*), who used dry hydrochloric acid, zinc chloride, sodium carbonate, and potassium carbonate as catalysts. Other catalysts reported in the literature included the alkali hydroxides, sulfites, cyanides, and acetates.

Of more recent date are the investigations reporting the uses of amine salts and amino acids as catalysts for the aldol condensation (*10, 13, 17*).

The aldol condensation is a reversible reaction, but can in many cases proceed to form a dehydrated condensation product. At low temperatures (below 25° C.), the aldol is the main reaction product; at higher temperatures the aldol dehydrates to the unsaturated condensation product. The aldol also dehydrates spontaneously when distilled at atmospheric pressure or when heated with an acid.

EXPERIMENTAL

The following anion exchange resins were employed in this study: the strongly basic Amberlite IRA-400, Permutit S, and Dowex 1; the weakly basic Deacidite, Amberlite IR-4B, and Amberlite IR-45.