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Catalysis with Ion Exchange Resins. Knoevenagel Condensations of Cyanoacetic Acid

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Weakly basic anion exchange resins are excellent catalysts for promoting condensations between aliphatic aldehyde and cyanoacetic acid. Ketones, with the exception of cyclohexanone, do not react satisfactorily. Aromatic aldehydes condense with cyanoacetic acid at room temperature but aliphatic aldehydes require the use of moderate temperatures. Organic salts of weakly basic anion exchange resins are more effective catalysts for the Knoevenagel reactions than the free amine resin. Different organic acid salts of weakly basic anion exchange resins have varying degrees of effectiveness as catalysts for the low temperature reactions but these differences are minimized when higher reaction temperatures are used.

Weakly basic anion exchange resins have been shown to be effective catalysts in promoting the Knoevenagel condensation of aldehydes with ethyl acetoacetate, ethyl cyanoacetate, or diethyl malonate.[3] It was also shown that the resin, either as the free amine or as the acetate of the free amine formed by treatment of the resin with acetic acid, were found to be effective catalysts with the acetates somewhat more effective. This is in agreement with the observations of Cope[4] that piperidine acetate was a more effective catalyst for Knoevenagel condensations than piperidine itself.

There might be some question whether the resins acting as heterogeneous catalysts would behave in exactly the same way as conventional amines or amine salts, particularly when the resins are to be used in condensations where one of the reactants is an acid. It seemed desirable to investigate the condensation of aldehydes with cyanoacetic acid and to determine the relative effectiveness as catalysts of weakly basic anion exchange resins pretreated with a series of organic acids in order to convert the resins to different amine salts.

It has now been shown that weakly basic resins do not lose their activity as catalysts for the Knoevenagel condensation even though one of the reactants is an acid. Resins such as Amberlite IR-4B, Deacidite, or Dowex 3 are very effective in catalyzing the condensation of cyanoacetic acid with aldehydes and with cyclohexanone. Furthermore the salts of these amine resins, such as the benzoate, phenylacetate, isovalerate, fumarate, etc., have proved to be more effective catalysts than the free amine resin for promoting condensations between cyanoacetic acid and both aliphatic and aromatic aldehydes.

Ion exchange resins have certain inherent advantages over conventional acid and base catalysts. The resin may be removed by simple filtration; this eliminates the necessity of neutralizing the reaction mixture as in the case when conventional catalysts are used. This greatly simplifies the separation problems as has been demonstrated in the present work. In addition, the ion exchange resins can be adapted to continuous column operations utilizing fixed bed catalysts. This is of particular importance as an alternate method of procedure especially for large scale reactions. Also from previous work[3] it has been shown that the ion exchange resins may be used repeatedly as catalysts for Knoevenagel condensations without appreciable loss of activity.

The Knoevenagel reactions involves the condensation of a carbonyl compound with compounds containing an activated methylene group, such as is found in ethyl acetoacetate, diethyl malonate, and

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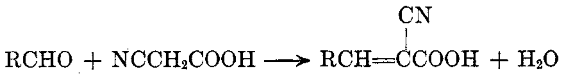
(2) From the M.S. thesis of W. C. Gergel.

(3) Astle and Zaslowsky, *Ind. Eng. Chem.*, **44**, 2867 (1952).

(4) Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937).

cyanoacetic acid. The reaction with cyanoacetic acid is illustrated in the following equation:



$$RCHO + NCCH_2COOH \longrightarrow RCH{=}\overset{CN}{\overset{|}{C}}COOH + H_2O$$

Cope$^{4-10}$ has worked out the most favorable conditions for effecting Knoevenagel condensations utilizing conventional catalysts, and has found that the best method varies with the reactants used.

The Knoevenagel condensation between cyanoacetic acid and aliphatic and aromatic aldehydes has been extensively studied in the past using conventional basic catalysts (amines or amine salts.)[7,11–20] It was the purpose of this investigation to examine the use of anion exchange resins as catalysts for this condensation and particularly to determine whether or not the cyanoacetic acid would inactivate the weakly basic resin catalyst.

In this investigation, commercially available carbonyl compounds were condensed with cyanoacetic acid. Weakly basic anion exchange resins and salts of these anion exchange resins were used as catalysts for the condensations.

EXPERIMENTAL

A. Resin preparation. The anion exchange resins used were all commercially available (20 to 50 mesh) and were used without screening for particle size. The resins used in this investigation include Amberlite IR-4B, Dowex 3, Deacidite, and Polyvinylpyridine.

The conversion of these resins to the hydroxyl form was accomplished by washing the resin in a Buchner funnel with 5 per cent aqueous sodium hydroxide (5 to 6 times the volume of the resin), followed by rinsing with distilled water until the washings were neutral, then washing with acetone and air drying.

The salts of these resins were prepared by permitting the resins to stand in contact with a 7 to 10 fold excess of a solution of the organic acid in an appropriate solvent for several hours, followed by removal of the excess acid by washing. The resins were then air-dried. The acids were adsorbed onto the resins from 5 to 20 per cent solutions.

B. Methods of reaction. Two general procedures were employed in effecting the condensations. These procedures will be designated as A and B. The amount of ion exchange resin used in each case was 15 per cent by weight based on the cyanoacetic acid.

Procedure A. Equimolar amounts of cyanoacetic acid and the desired aldehyde were agitated at room temperature in the presence of the ion exchange resin and a solvent, usually benzene. At the end of the reaction period, the reaction mixture was filtered, and the resin was washed with benzene and acetone, and then was air-dried. The benzene washings were combined with the original filtrate.

The condensation of benzaldehyde with cyanoacetic acid is illustrative of this procedure. Benzaldehyde (53 g., 0.5 mole), cyanoacetic acid (42.5 g., 0.5 mole), Amberlite IR-4B-acetate (6.5 g.), and 100 ml. of benzene were charged into a flask and shaken for 24 hours on a Burrell Wrist-Action shaker. The reaction mixture was filtered and the ion exchange resin was washed with benzene. The washings were added to the original filtrate and the entire mixture was distilled. Distillate was collected until the pot temperature reached 135°. The material in the flask then was transferred to a beaker where a crystalline material formed on cooling. Crude β-cyanocinnamic acid was obtained which when recrystallized from acetone gave a product which melted at 179–180° (conversion of 45%) which corresponds to a melting point of 178–180° found in the literature for the same condensation product.[17] Higher conversions were obtained using procedure B, or by converting the resin to salts other than the acetate.

Procedure B. Equimolar amounts of the reactants and the desired amount of ion exchange resin were refluxed in benzene with removal of the water of reaction as the benzene azeotrope as fast as formed. In most cases, refluxing was continued as long as water was being removed from the reaction mixture.

The condensation of butyraldehyde with cyanoacetic acid is illustrative of this procedure. *n*-Butyraldehyde (18 g., 0.25 mole), cyanoacetic acid (21 g., 0.25 mole), 3.2 g. of Amberlite IR-4B-butyrate, and 200 ml. of benzene were charged into a one-liter flask and refluxed for about 4 hours with continuous removal of water until 4.6 ml. of water was removed.

The reaction mixture then was filtered to remove the resin, and crystals separated as the filtrate was cooled. These crystals were removed by filtration and the filtrate was evaporated under a vacuum to obtain a second crop of crystals. In this manner an 87 per cent conversion to a product melting 98–99° was obtained. This compound was not described in the literature.

DISCUSSION OF RESULTS

Weakly basic anion exchange resins such as Amberlite IR-4B and salts of these resins such as the benzoate, acetate, isovalerate, etc., are excellent catalysts for promoting Knoevenagel condensations between cyanoacetic acid and aliphatic aldehydes, aromatic aldehydes, and some ketones.

Condensations of aromatic aldehydes can be carried out both at room temperature and at the reflux temperature of benzene. The benzene was used as a solvent and to remove the water of reaction as the benzene azeotrope. Reactions of aromatic aldehydes and cyanoacetic acid resulted in

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(5) Cope, *et al., Org. Syntheses*, **31**, 25 (1951).

(6) Cope, *et al., J. Am. Chem. Soc.*, **63**, 3452 (1941).

(7) Cope, D'Addieco, Whyte, and Glickman, *Org. Syntheses*, **31**, 25–28 (1951).

(8) Cope and Hancock, *J. Am. Chem. Soc.*, **60**, 2645 and 2901 (1938).

(9) Cope, Hoffman, Wycoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

(10) Cope and Hoffman, *J. Am. Chem. Soc.*, **63**, 3456 (1941).

(11) Bruylants, *Bull. soc. chim. Belges*, **41**, 333–337 (1932).

(12) Dewael, *Bull. soc. chim. Belges*, **41**, 324–326 (1932).

(13) Heim, *Bull. soc. chim. Belges*, **41**, 320–323 (1932).

(14) Lapworth and McRae, *J. Chem. Soc.*, **121**, 1699–1712 (1922).

(15) Lapworth and McRae, *J. Chem. Soc.*, **121**, 2741–2755 (1922).

(16) McRae and Hopkins, *Can. J. Research*, **7**, 248–257 (1932).

(17) Rodionov and Fedorowa, *Arch. Pharm.*, **271**, 292–296 (1933).

(18) Shemyakin and Trakhtenberg, *Compt. Rend. Sci. U.S.S.R.*, **24**, 763–767 (1939).

(19) Shemyakin and Trakhtenberg, *J. Gen. Chem. (U.S.S.R.)*, **13**, 477–480 (1943).

(20) Shemyakin and Trakhtenberg, *J. Gen. Chem. (U.S.S.R.)*, **13**, 552 (1943).

TABLE I

CONDENSATION OF EQUIMOLAR AMOUNTS OF CARBONYL COMPOUNDS WITH CYANOACETIC ACID

Carbonyl Compound	Resin Used	Solvent		React. Method	React. Time, Hrs.	M.p., °C. of Product		Conv.[e] %	Lit. Ref.
		Kind	Ml./mole of React.			Found	Lit.		
n-Butyraldehyde[a]	IR-4BB[f]	Benzene	400	B	1.75	98–99	—	100	—
Isobutyraldehyde	Dowex 3	Benzene	400	B	4	89–90	87–88	80	21
Benzaldehyde	IR-4BB	Benzene	400	B	1.25	179–180	178–180	94	17
Anisaldehyde	IR-4BB	Benzene	100	A	24	227	222	40	17
Cinnamaldehyde	IR-4BB	Benzene	100	A	24	209	212	25	22
Vanillin	IR-4BB	Benzene	300	A	24	214	197–199	65	17
Piperonal	IR-4BB	Isopropyl ether	400	B	11	231	220–222	47	17
o-Chlorobenzaldehyde	IR-4BB	Benzene	100	A	22	208–209	208	55	16
Salicylaldehyde[c]	IR-4BB	Benzene	100	A	22	228	—	20	—
m-Nitrobenzaldehyde	IR-4BB	Isopropyl ether	400	A	22	167–168	—	50	—
p-Hydroxybenzaldehyde[d]	IR-4BB	Isopropyl ether	100	A	22	223–224	—	75	—
Furfural	IR-4BB	Isopropyl ether	200	A	22	221–222	218	57	17
Methyl ethyl ketone[b]	IR-4BA[g]	MEK	2 moles, excess	B	23	77–78	—	6	—
Cyclohexanone	IR-4BA	Benzene	200	B	6	110–111	110–111	65	4

[a] Neutral equivalent of product 140.1 (Theor. 139.2). [b] Neutral equivalent of product 142.1 (Theor. 139.2). [c] Per cent N in product (Found 7.38, Calc'd 7.41). [d] Per cent N in product (Found 7.36, Calc'd 7.41). [e] Based on aldehyde or ketone reacted. [f] IR-4BB is IR-4B benzoate. [g] IR-4BA is IR-4B acetate.

higher conversions to product when the reactions were conducted at the reflux temperature of benzene.

Considerable difficulty was encountered in the preparation of products from aliphatic aldehydes and cyanoacetic acid when condensations were attempted at room temperature. The reaction mixture after removal of the benzene was very deliquescent and consisted of a mixture of products including unreacted cyanoacetic acid. Gummy, resinous materials were formed during attempts to isolate the product.

Condensations of aliphatic aldehydes with cyanoacetic acid were easily accomplished at the reflux temperature of benzene.

The only ketone which was successfully reacted with cyanoacetic acid was cyclohexanone. Previous investigators,[8,15,18] using conventional catalysts, have also found that cyclohexanone was the only ketone which would give satisfactory yields of the unsaturated cyano acids.

The compounds prepared from a series of aldehydes and ketones with cyanoacetic acid are shown in Table I. In most cases, the conversion to products was as good as when conventional catalysts were used. No appreciable conversions to by-products were observed so that the yields were very high. The separation of the catalyst from the reaction mixture was much easier than when conventional acid-base catalysts were used. Several of the compounds prepared have not been previously reported in the literature.

The salts of Amberlite IR-4B, prepared from various organic acids, were found to be better catalysts than the unmodified anion exchange resin. There is not sufficient evidence to show that the extent of salt formation of the resin with the different acids was the same. However, a sufficiently large excess of the organic acid was used in each case to make it seem probable that most of the amino groups would be converted to salts. It made no significant difference in the activity of the catalyst whether the acid was absorbed from a five per cent or a twenty five per cent solution. The difference in the degree of salt formation is probably small and even though these differences may account in part for the activities of the catalysts which were observed it does not seem likely that this is the only factor involved. It might be expected that, in the presence of the large amounts of cyanoacetic acid used as one of the reactants, the resin or any of the salts of the resin would be converted to the cyanoacetate and therefore all catalyst would be equally effective. This is not in accord with the observations. Thus the untreated resin was less active than the resin pretreated with cyanoacetic acid and this catalyst in turn was less active than the resin pretreated with an acid such as benzoic

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(21) Braun, *Monatsh*, **17**, 207 (1896).

(22) Fiquet, *Ann. chimie.*, [6] **29**, 433 (1893).

acid. All of these resins would probably be converted to the cyanoacetate in time but indications are that the exchange reaction is slow.

The condensations of benzaldehyde and of butyraldehyde with cyanoacetic acid were investigated more extensively. Various anion exchange resin salts were used as the catalysts.

The condensations of benzaldehyde with cyanoacetic acid at room temperature was greatly affected by the nature of the catalyst used. Conversions varied from 30 per cent in 24 hours when the unmodified resin was used as the catalyst, to 80 per cent in 24 hours when the resin was first converted to the benzoate salt by treatment with benzoic acid. When the condensations were carried out at the reflux temperature of benzene, only slight differences in conversions were obtained with these resin salts. In most of the runs an Eastman Kodak grade of benzaldehyde was used with no attempt being made to remove any benzoic acid which might be present. No significant differences in yield were observed when freshly distilled benzaldehyde was used. The condensation of *n*-butyraldehyde with cyanoacetic acid in refluxing benzene was not appreciably effected by modifying the weakly basic resin by conversion to different salts.

Table II shows the variation in conversion to product in the benzaldehyde-cyanoacetic acid condensation when various salts of Amberlite IR-4B were used as the catalysts.

TABLE II

EFFECT OF VARIOUS SALTS OF AMBERLITE IR-4B IN THE CONVERSION OF BENZALDEHYDE AND CYANOACETIC ACID TO α-CYANOCINNAMIC ACID

(Room Temperature for 24 hours)

Salt of Amberlite IR-4B	Per Cent Conversion to Product
Benzoate	82
Phenylacetate	81
Phenoxyacetate	73
Benzolylbenzoate	73
Isovalerate	66
Fumarate	61
Benzilate	58
Cyanoacetate	56
Salicylate	53
Adipate	52
Acetate	48
Maleate	43
Furoate	42
Crotonate	38
Unmodified Amberlite IR-4B	28

It is evident that the effectiveness of the resin as a catalyst can be improved by converting it to a salt formed by the pretreatment of the resin with an organic acid. It is also evident that the effectiveness of the resin can be changed very markedly by proper choice of the acid. The effectiveness of different acids could not be correlated with properties of the acids such as the ionization constant, molecular weight, molar volume, length of the hydrocarbon chain, or the molecular configuration. It is interesting to note that, in general, acids having a benzene ring in the molecule are more effective than are purely aliphatic acids. Minor differences in the degree of salt formations may exist and may be partially responsible for differences in activity of the treated resins. However, some work reported by Hammett seems to offer a better explanation.

Riesz and Hammett[23] investigated the hydrolysis of esters in the presence of a sulfonated polystyrene type of ion exchange resin and found that the replacement of 70 per cent of the hydrogen ions of the resin by cetyltrimethylammonium ions had a specifically favorable effect on the activity of the remaining hydrogen ions for the hydrolysis of ethyl *n*-hexanoate. Similarly replacement of hydrogen ions of the resin by methyltribenzylammonium ions had a specifically favorable effect on the hydrolysis of methyl phenylacetate.

It might be predicted from this work that the Knoevenagel condensation of aliphatic aldehydes with cyanoacetic acid would be more effectively catalyzed by resins treated with aliphatic acids. Unfortunately this could not be tested satisfactorily because the aliphatic aldehydes did not react with cyanoacetic acid at room temperature and at higher temperatures all resins were equally effective with either aromatic or aliphatic aldehydes. The order of effectiveness for condensation of benzaldehyde are about what would be predicted if we assume that the same principles apply.

Bernhard and Hammett[24] investigated the hydrolysis of seven methyl esters of the type RCO_2-CH_3 and found that the rates of hydrolysis depended a great deal upon the structure of the ester. They observed that the decrease in rate of hydrolysis in the presence of the resin catalyst paralleled the entropy of the gaseous compound RH and showed no relation to any other obvious property of the ester. The rate of hydrolysis was therefore directly related to the entropy of formation of the activated complex involving the resin. It is very likely that the same thing is involved in the catalysis of the Knoevenagel condensation in the presence of the modified resins investigated. Unfortunately there is not sufficient data to calculate the entropies for the systems involved in this investigation.

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[23] Riesz and Hammett, *J. Am. Chem. Soc.*, **76**, 992 (1954).

[24] Bernhard and Hammett, *J. Am. Chem. Soc.*, **75**, 1798 (1953).