hydrocarbon as determined by pressure were transferred to a 10-cm gas ir cell, and the ir spectrum was determined under standard conditions. The ir spectrum of propane showed bands at 2860–3000, 1480, 1470, 1450, 1390, and 1380 cm^{-1}; the ir spectrum of 2-deuteriopropane showed bands at 2860–3000, 2170, 1480, 1470, 1390, 1380, and 1142 cm^{-1}; the ir spectrum of isobutane showed bands at 2850–3000, 1482, 1380, 1330, and 1175 cm^{-1}; and the ir spectrum of 2-deuterioisobutane showed bands at 2860–3000, 2155, 1482, 1380, 1242, and 1232 cm^{-1}. The ratio of absorbance at 2170 to that at 1480 and at 2170 to that at 1380 cm^{-1} for partially deuterated propane and the ratio of absorbance at 2155 to that at 1380 and at 1242 to that at 1482 cm^{-1} for partially deuterated isobutane were determined. Comparisons of the ratios of absorbances to the ratios of absorbances of mixtures with known mole fraction of monodeuterated hydrocarbon were made graphically, and the mole fraction of deuterated hydrocarbon was determined. The results from the two determinations for each sample were within 0.02 mole fraction units and an estimated error of ±0.02 mole fraction units from the mean was assigned as a reasonable limit of accuracy for the method. The error limits assigned in Tables I and II are based on an assumed error of ±0.02 mole fraction units in the final concentrations of the alkyllithium compounds. No fractionation of partially deuterated compound occurred during work-up, since a glpc-purified sample of propane with a known deuterium content was repurified and found to have the same deuterium content.

An alternative analytical method gave results within experimental error of those described above for equilibrated alkyllithium mixtures, and in addition was used to show that added lithium chloride, *tert*-butyl chloride, or *tert*-butyl alcohol did not change the ratio $k_{i\text{-PrLi}}/k_{t\text{-BuLi}}$, whatever effects they may have had on the absolute rates. When the reaction was complete, the solvent and volatile hydrocarbon products of the reaction were removed under vacuum with external heat. The reaction mixture was not allowed to warm above 30°. Benzene containing adamantane as an internal nmr standard was pipetted into each of the flasks. The precipitated aryllithium compound was broken up and dispersed in the liquid. The solution of unreacted alkyllithium compounds and adamantane was filtered from the precipitate using disposable pipets fitted with glass-wool plugs. The nmr resonances of the alkyllithium compounds (*t*-BuLi δ 1.00 (s); *i*-PrLi 1.36 (d)] and the resonance of adamantane (δ 1.75–1.85) were integrated five times. The ratio of the areas of the alkyllithium resonances to the area of the adamantane resonance was used to determine the concentration of the alkyllithium compounds.

Registry No.—*i*-PrLi, 1888-75-1; *t*-BuLi, 594-19-4; indene, 95-13-6; propane, 74-98-6; 2-deuteriopropane, 20717-74-2; isobutane, 78-28-5; 2-deuterioisobutane, 13183-68-1.

Acknowledgments.—This work was supported in part by National Science Foundation grants G-7403, GP-166, and GP-4681, and in part by the Petroleum Research Fund, administered by the American Chemical Society. Grateful acknowledgment is made to the National Science Foundation and to the donors of the Petroleum Research Fund.

The Knoevenagel Reaction. A Kinetic Study of the Reaction of (+)-3-Methylcyclohexanone with Malononitrile

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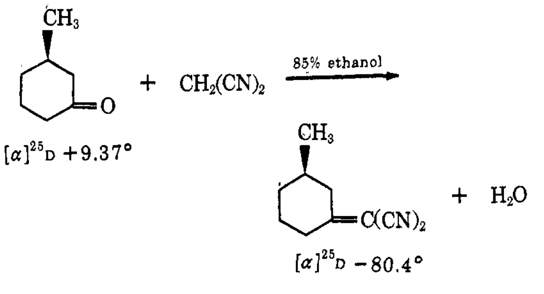
The condensation of malononitrile with (+)-3-methylcyclohexanone produced an 80–85% yield of (−)-3-methylcyclohexylidenemalononitrile. The reaction, followed polarimetrically in alcohol-water, is kinetically second order and efficiently catalyzed by weak bases (ω-amino acids, cyclic amino acids, NH_4OAc), furnishing solutions having an apparent pH of 7.5–8.0. With β-alanine as catalyst, the E_a was 7.6 kcal/mol compared to 11 kcal/mol uncatalyzed. Stronger bases (barbital, NaOAc, KOAc, KF, piperidine) effected more rapid condensation but poorer kinetics because of telemerization of malononitrile at the higher pHs.

Our earlier studies on the Knoevenagel condensation[2,3] have examined catalyst effectiveness in a heterogeneous system. Under these conditions efficiency of the largely insoluble dipolar ions was a function of an undetermined combination of pH and concentration.

A more desirable homogeneous system involved the reaction of (+)-3-methylcyclohexanone with malononitrile (eq 1). This reaction occurred slowly (when not catalyzed) and nearly quantitatively in an alcoholic solution at room temperature. The product can be isolated in 80–85% yield and is probably formed to an extent greater than 95%. The reverse reaction is very slow and can be neglected. With catalysts furnishing an apparent pH no higher than 8, no important side reactions seem to appear. Because the change in rotation during the course of this reaction is large and linear with change in concentration, the progress of the reaction can be followed polarimetrically.



(1)

An extensive series of kinetic runs were made using β-alanine as catalyst (Table I). Most runs were made with a 0.400 *M* concentration of reactants and the rate calculations were based on the assumption of second-order kinetics.[4,5] It is clear in runs 11, 15, 49, 50, 52, and 53 that increasing the concentration of catalyst from 6 × 10^{-4} *M* to 2.5 × 10^{-2} *M* increased the rate of

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(1) This investigation was supported by the National Science Foundation Grants for the Undergraduate Research Participation Program of the Science Education Section, Division of Scientific Personnel and Education in (a) 1962, (b) 1963, (c) 1964, (d) 1965, and (e) 1967.

(2) F. S. Prout, *J. Org. Chem.*, **18**, 928 (1953); F. S. Prout, A. A. Abdel-latif, and M. R. Kamal, *J. Chem. Eng. Data*, **8**, 597 (1963).

(3) For an extensive review see G. Jones, *Org. React.*, **15**, 204–599 (1967).

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TABLE I

REACTION OF (+)-3-METHYLCYCLOHEXANONE WITH MALONONITRILE USING β-ALANINE CATALYSIS[a]

Run	[β-Alanine], mol/l.	Temp, °C	k_2,[b] l. mol^{-1} min^{-1}	k_2/[alanine]	Apparent pH[c]
65	None	25	0.0007		6.55
66	None	45	0.0022		
49, 50	6×10^{-3}	25	0.107	18	7.19
52, 53	1.2×10^{-2}	25	0.141	12	7.35
15	2.5×10^{-2}	25	0.152	6.1	7.42
51	6×10^{-3}	15	0.0643	11	
13	6×10^{-3}	35	0.151	25	
47, 48	6×10^{-3}	45	0.179	30	7.05[d]
10	6×10^{-4}	25	0.019[e]	32	
11	6×10^{-4}	25	0.036[e]	47	
16	6×10^{-3}	25	0.0973[f]	16	7.27[h]
17, 54	6×10^{-3}	25	0.0527[g]	9	7.11[h]

[a] The reaction of 2.24 g (0.0200 mol) of ketone with 1.32 g (0.0200 mol) of malononitrile in a volume of 50 ml was observed in a polarimeter and rotatory values were converted to concentrations. [b] k_2 determined graphically plotting time against $1/(a - x)$. [c] Apparent pH determined at 25 ± 5° with catalyst in 5 ml of water and 1.32 g of malononitrile, diluted up to 50 ml with 95% ethanol. [d] pH determined as in *c*, except at 48 ± 5°. [e] Run 10 performed in absolute alcohol, run 11 performed in the usual aqueous alcoholic system. [f] Reaction of 1.0 *M* ketone with 0.20 *M* malononitrile, k_2 determined graphically plotting log $a(b - x)/b(a - x)$ against time. [g] Reaction of 0.20 *M* ketone with 1.0 *M* malononitrile. k_2 determined as in *f*. [h] pH determined as in note *c*, except that in run 16 malononitrile was 0.200 *M* and in runs 17 and 54 malononitrile was 1.00 *M*.

reaction; however, the efficiency of the catalyst (k_2/C) increased as the concentration of catalyst *decreased*. The increase of efficiency must reflect a higher percentage of dissociation into the acidic (RNH_3^+) and basic ($RCOO^-$) ions at lower concentration. Second-order kinetics were apparently confirmed in runs using 1.00 *M* ketone–0.200 *M* malononitrile (run 16) and in runs using 0.200 *M* ketone–1.00 *M* malononitrile (runs 17, 54). However, the rate constant is lower with high malononitrile concentration (runs 17, 54) because the apparent pH of the reaction mixture is lower.

The plot of log k_2 against $1/T$ (runs 51, 49, 50, and 13) is linear between 15 and 35°. However, runs at 45° (47 and 48) give a point far off the line. The activation energy (E_a), calculated between 15 and 35° from the Arrhenius equation, was 7.6 kcal/mol. When no catalyst was used the E_a was 11 kcal/mol.[5]

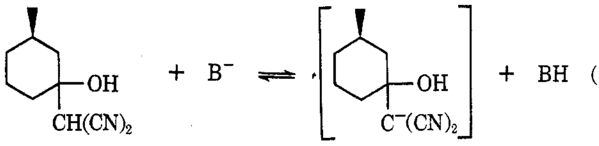
In another series of runs (Table II) the rates were determined with several catalysts. Usually the catalyst concentrations were 6×10^{-3} *M*. The second-order rates increased as the catalyst became more basic. A plot of log k_2/C against apparent pH of the catalysts in alcohol–water (Figure 1) gave a cluster of points, suggesting that the rate is more dependent on the pH than on structural considerations.[6]

Structural features do cause aberrations; for example, the *p*-*N*,*N*-dimethylaminocyclohexanecarboxylic acids give rates which are much faster than the apparent pH would suggest. The rate calculations for the reactions when the apparent pH exceeded 8.5 were somewhat less reliable, but gave reasonable results because reaction plots were nearly linear up to 75% of reaction. (For example, with barbital, the fastest rate, the reaction was about 25% completed when the first reliable rotatory reading at 2 min was observed.)

Data for five constants are assembled in Table III and plotted in Figure 2. The runs catalyzed with β-alanine at 25° (11, 49, and 53) give straight-line plots for the 70-min time. Run 48, which was catalyzed with β-alanine at 45°, slowed markedly after 30 min. This is probably caused by the conversion of malononitrile to dimer and trimer.[7] The potassium fluoride run shows a positive inflection after 18–20 min. This is typical of the more basic catalysts and we do not understand this effect.

Other possible side reactions, such as hydrolysis of malononitrile to cyanoacetamide or dimerization of product,[8] are quite sluggish and do not appear to have a serious effect on the results.

The evidence we have assembled seems to indicate that the controlling rate of reaction is mainly a function of pH. The controlling reaction, following Zabicky's mechanism, would probably be eq 2.[9] The efficiency



(2)

of tertiary amine and nonamine catalysts seems to eliminate the imine intermediate for the reaction under these reaction conditions.[10]

Experimental Section

All melting points and boiling points were uncorrected. Fractional distillations were carried out in a 60-cm, heated Vigreux column with no head. Gas chromatographic analyses were performed on a column with silicone gum rubber (SE-30) as liquid phase in an F & M Model 720 or a Wilkins Aerograph 600C. Optical rotations were observed on a Rudolph high-precision polarimeter, Model 80. Constant temperatures were maintained to a precision of ±0.1° with a Haake Model E water circulator. The accuracy of the thermometer was ±0.2° against an NBS-calibrated thermometer. Dissociation constants were determined with a Beckman Model 76 pH meter. Infrared spectra were determined on a Perkin-Elmer Model 22 spectrophotometer.

Pulegone was obtained from Givaudan-Delawanna, Inc., $\alpha^{30}\mathrm{D}$ +23.33 ± 0.02°. *dl*-3-Methylcyclohexanone was obtained from Distillation Products Industries. The amino acids came from Distillation Products Industries (glycine, β-alanine, γ-aminobutyric acid, and *N*,*N*-dimethylglycine hydrochloride) and Nutritional Biochemicals Corp. (ε-aminocaproic acid). The aminophenols were crystallized commercial products previously reported.[2] Malononitrile, obtained from Kay-Fries, Inc., was distilled prior to use, bp 95–99° (2 mm), fp 32°, homogeneous when gas chromatographed at 165°. The ethyl *cis*- and *trans*-*p*-dimethylaminocyclohexanecarboxylates were kindly given to us by Dr. Frank J. Vilani of the Schering Corp., Bloomfield, N. J.

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(6) Similar plots result when log k_2/C is plotted against pI (Table II), pK_1, or pK_2. The pI values are from E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold, New York, N. Y., 1943, pp 84, 99, 128.

(7) A mixture of 0.66 g of malononitrile and 27 mg of β-alanine in a 50-ml ethanol–H_2O solution was allowed to stand overnight at room temperature. Crude malononitrile remaining when the solvent was removed showed development of infrared absorption at 3370, 3270, 2230, 2215, and 1660 cm^{-1}, suggesting the formation of malononitrile dimers and/or trimers. A sample of dimer, prepared inefficiently by boiling a mixture of malononitrile and β-alanine in ethanol–water, had ir absorptions at 3360, 3210, 2270, 2230, 2210, and 1660 cm^{-1}, just as reported by R. A. Carboni, D. D. Coffman, and E. G. Howard, *J. Amer. Chem. Soc.*, **80**, 2838 (1958).

(8) M. R. S. Weir and J. B. Hyne, *Can. J. Chem.*, **41**, 2905 (1963); **42**, 1440 (1964).

(9) J. Zabicky, *J. Chem. Soc.*, 687 (1961).

(10) The Knoevenagel reaction in benzene with piperidine catalysis might well involve an enamine intermediate; *cf.* G. H. Alt and G. A. Gallegos, *J. Org. Chem.*, **36**, 1000 (1971); F. S. Prout, *ibid.*, **38**, 399 (1973).

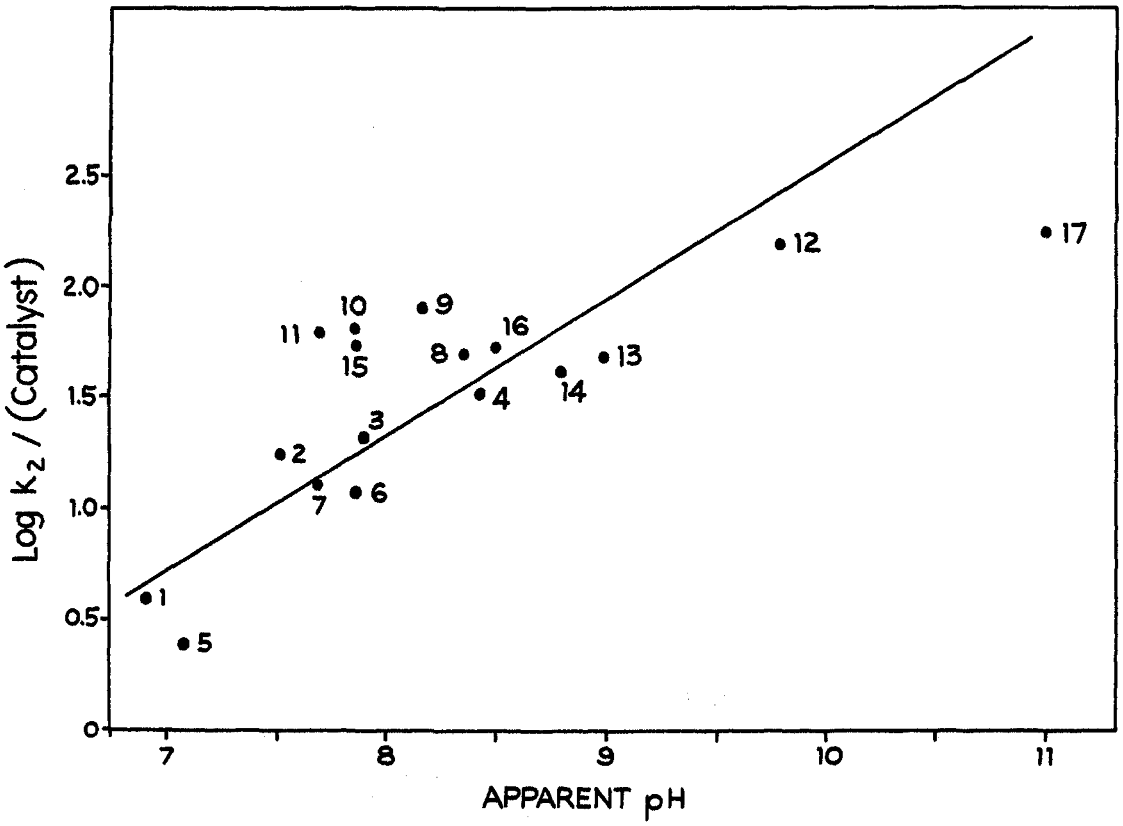

Figure 1.—Plot of log k_2/(catalyst) against apparent pH, data from Table II: 1, Glycine; 2, β-alanine; 3, γ-aminobutyric acid; 4, ε-aminocaproic acid; 5, *N*,*N*-dimethylglycine; 6, *cis*-HHAA; 7, *trans*-HHAA; 8, *cis*-*p*-ACHCA; 9, *trans*-*p*-ACHCA; 10, *cis*-*p*-DMACHCA; 11, *trans*-*p*-DMACHCA; 12, barbital buffer; 13, NaOAc; 14, KOAc; 15, NH_4OAc; 16, KF; 17, piperidine.

TABLE II

CONDENSATION OF (+)-3-METHYLCYCLOHEXANONE WITH MALONONITRILE USING SEVERAL CATALYSTS AT 25°[a]

Catalyst (C), 6×10^{-3} *M*	k_2,[b] M^{-1} min^{-1}	k_2/C	Log k_2/C	pI[c]	pH[d]
Glycine	0.024[e]	4.0	0.602	5.97	6.91
β-Alanine	0.107[e]	18	1.252	6.90	7.52
γ-Aminobutyric acid	0.12	21	1.32	7.33	7.90
ε-Aminocaproic acid	0.20	33	1.52	7.59	8.43
N,*N*-Dimethylglycine	0.015	2.5	0.399	5.87	7.07
cis-HHAA[f]	0.071[e]	12	1.08	7.02	7.86
trans-HHAA[f]	0.077[e]	13	1.11	6.72	7.69
cis-*p*-ACHCA[g,h]	0.150	50	1.70	7.49	8.36
trans-*p*-ACHCA[g,h]	0.250	81	1.91	7.37	8.17
cis-*p*-DMACHCA[h,i]	0.195[e]	65	1.81	7.46	7.86
trans-*p*-DMACHCA[h,i]	0.190[e]	63	1.80	7.28	7.70
Glycylglycine[j]	0.017	7.1	0.85	5.60	6.49
Barbital buffer[k]	0.61	153	2.18	8.00[k]	9.80
Sodium acetate	0.29	48	1.68		8.99
Potassium acetate	0.25	42	1.62		8.80
Ammonium acetate[l]	0.33	55	1.74		7.87
Potassium fluoride	0.32	53	1.73		8.50
Piperidine[h]	0.53	176	2.25		11.10
o-Aminophenol	0.027	4.5	0.65		
m-Aminophenol	0.0067	1.1	0.048		7.70
p-Aminophenol	0.056	9.3	0.97		

[a] Mixture containing 1.32 g (0.0200 mol) of malononitrile, 2.24 g (0.0200 mol) of (+)-3-methylcyclohexanone, and catalyst in 5 ml of water diluted to 50 ml with 95% ethanol.

[b] K_2 determined graphically, $1/(a - x)$ *vs.* time.

[c] pI determined in water, from Cohn and Edsall (ref 6), pp 84, 99, and 128, or Table IV.

[d] Apparent pH of catalyst in a solution of 5 ml of water diluted to 50 ml with 95% ethanol.

[e] Average of two runs.

[f] HHAA is hexahydroanthranilic acid.

[g] *p*-ACHCA is *p*-aminocyclohexanecarboxylic acid.

[h] Catalyst concentration was 3×10^{-3} *M*.

[i] *p*-DMACHCA is *p*-dimethylaminocyclohexanecarboxylic acid.

[j] Catalyst concentration was 2.4×10^{-3} *M*.

[k] Buffer contains 2×10^{-4} mol each of barbital and sodium barbital in 5 ml of water. Thus C is 4×10^{-3} *M*. Reported pH 8.00: R. Nasanen and T. Heikkila, *Suom. Kemistilehti B*, **32**, 163 (1959); *Chem. Abstr.*, **54**, 5215*i* (1960).

[l] Ammonium acetate prepared by the action of 0.0178 mg of acetic acid with 0.0170 mg of ammonium carbonate (30% NH_3).

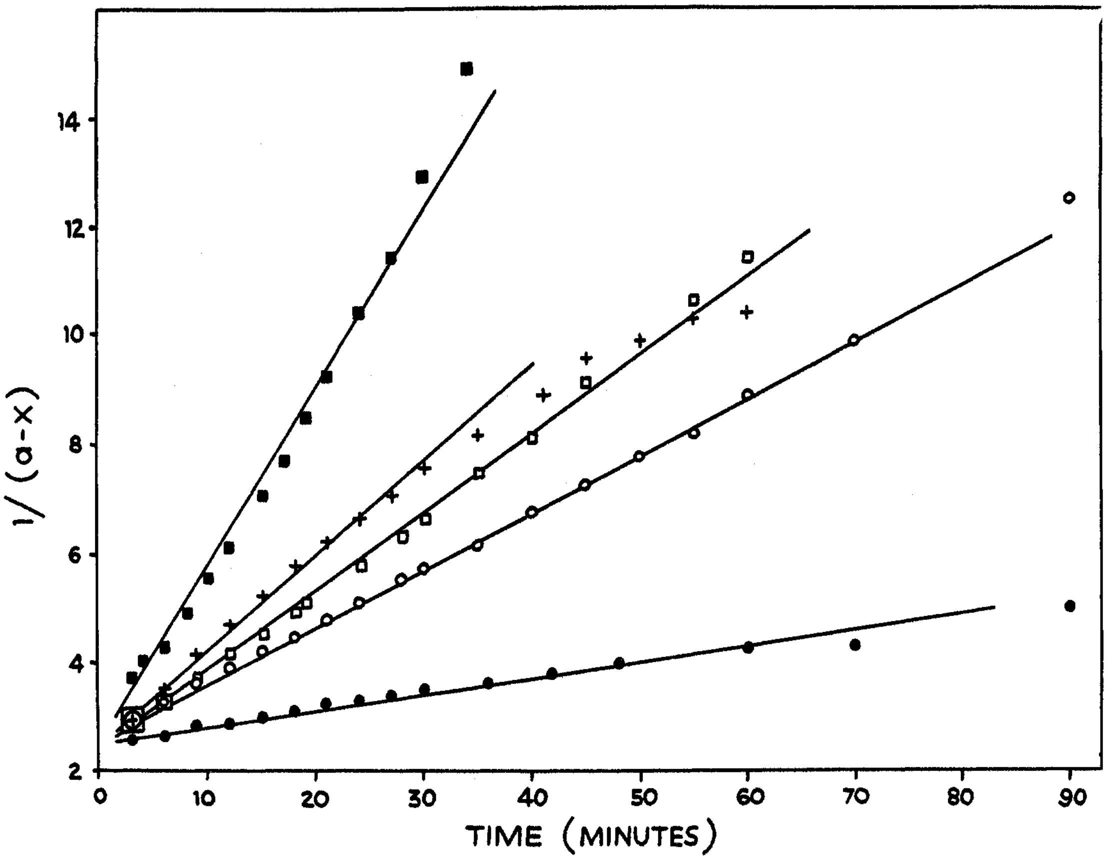

Figure 2.—Reaction of malononitrile with (+)-3-methylcyclohexanone. Plot of data in Table III: ●, run 11, 0.0006 *M* β-alanine; ⊙, run 49, 0.006 *M* β-alanine; ⊡, run 53, 0.012 *M* β-alanine; ■, 0.006 *M* KF all at 25°; +, run 48, 0.006 *M* β-alanine at 45°.

Amino Acids. ***cis*-Hexahydroanthranilic Acid.**—Hexahydrophthalimide[11] (42.7 g, mp 129–134°) was dissolved in a solution of 16 g of sodium in 350 ml of methanol. Dry chlorine generated from the action of 15.8 g of potassium permanganate and 200 ml of concentrated hydrochloric acid[12] was passed into the solution at 40–50°. The mixture was boiled for 15 min. After cooling the salt was removed, and the mixture was diluted with 500 ml of water and continuously extracted with ether.[13]

The crude ester-urethane (51 g) was mixed with 125 ml of concentrated hydrochloric acid and was heated under reflux for 6 hr. The brownish reaction mixture was filtered with Norit and Celite and was concentrated at reduced pressure to furnish a solid residue. This amino acid hydrochloride was dissolved in water and was placed on a 160-g column of Amberlite IR-120 (sulfonic acid resin). After the mineral acid was washed out the amino acid was eluted with 0.9 *M* ammonia. Eluates with pH 7–10 contained the amino acid and were concentrated *in vacuo*. The crude product (mp 213–218°) was crystallized from alcohol-acetone to furnish 16.5 g (41.3%) of product, mp 222–224°. The purified acid was obtained from a mixture of ethanol-methanol diluted with acetone, mp 224.5–226.5°. This acid showed no loss in weight upon heating at 80° *in vacuo*. This acid has been reported to have melting points of 230–231,[14] 235,[15] and 236°.[16]

The benzenesulfonamide as a 1:1 benzene complex was recrystallized from benzene. Drying *in vacuo* at 80° gave the pure product, mp 160–161.5°.

Anal. Calcd for $C_{13}H_{17}O_4NS$: C, 55.10; H, 6.05. Found:[17] C, 55.08; H, 6.56.

***trans*-Hexahydroanthranilic Acid.**—Forty grams of anthranilic acid was reduced by the action of 60 g of sodium in isoamyl alcohol.[18]

The combined aqueous washes containing the sodium salts from this reduction were allowed to stand with 440 g (*ca.* 1.85 equiv) of Amberlite IP-120 to remove much of the sodium ion. The aqueous washes were passed through columns of Amberlite IR-120. The amino acid was eventually collected on the resin after the sodium ion had been adsorbed. The amino acid was eluted with 0.9 *M* ammonia. The amino acid rich eluates (*ca.* 1000 ml) were concentrated to a volume of 25–35 ml and diluted with 150 ml of acetone to give the crude amino acid, 14.4 g (34.6%), mp 248–250°. Recrystallization of the amino acid from 50 ml of water and 75 ml of acetone furnished 6.40 g, mp 264–265°. The purest sample had mp 267–270°. This acid has melting points reported at 274,[18] 273,[15] 269–272,[14] and 269–271°.[16]

The benzenesulfonamide was crystallized four times from acetone-benzene, mp 188–191°. The sample showed no loss upon drying at 80° *in vacuo*.

Anal. Calcd for $C_{13}H_{17}O_4NS$: C, 55.10; H, 6.05. Found:[17] C, 55.18; H, 6.40.

***cis*- and *trans*-4-aminocyclohexanecarboxylic acids** were prepared by reduction of *p*-aminobenzoic acid over platinum.[19] The cis acid had mp 301–303°. The trans acid melts with gasing and resolidification when immersed in a block at 380–390°. However, there is no apparent transition when the acid was heated normally. Eventually charring occurred at 480–500°. The cis acid is reported to melt at 302,[19] 304–305,[20] 303–304,[21] 286,[22] and 324–325°.[23] The trans acid has been reported to melt above 340,[19] 486–488,[20] above 495,[22] and above 400°.[23]

***cis*-4-Dimethylaminocyclohexanecarboxylic Acid.**—Ethyl *cis*-4-dimethylaminocyclohexanecarboxylate[24] (5.26 g) was heated under reflux with 25 ml of concentrated hydrochloric acid for 6 hr. The mixture, after concentration to 13 ml, was placed on a column of Amberlite IR-120 (sulfonic acid resin). Elution with

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[12] C. Graebe and S. Rostovzeff, *Ber.*, **35**, 2747 (1902).

[13] J. Cason and H. Rapoport, "Laboratory Text in Organic Chemistry," 2nd ed, Prentice-Hall, Englewood Cliffs, N. J., 1962, pp 261–265.

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[15] S. Hunig and H. Kahanek, *Chem. Ber.*, **86**, 518 (1953).

[16] E. J. Moriconi and P. H. Mazzocchi, *J. Org. Chem.*, **31**, 1372 (1966).

[17] Analysis by Micro-Tech Laboratories, Skokie, Ill.

[18] A. Einhorn and A. Meyerberg, *Ber.*, **27**, 2470 (1894).

[19] Acids prepared by Brian Lawrence according to the procedure of W. Schneider and R. Dillman, *Chem. Ber.*, **96**, 2377 (1963).

[20] G. Wendt, *Ber.*, **75**, 427 (1942).

[21] A. Einhorn and A. Meyerberg, *Ber.*, **27**, 2833 (1894).

[22] M. Freifelder and G. R. Stone, *J. Org. Chem.*, **27**, 3568 (1962).

[23] F. J. Vilani and C. A. Ellis, *J. Org. Chem.*, **29**, 2585 (1964).

[24] F. J. Vilani, U. S. Patent 2,764,519 (1957); *Chem. Abstr.*, **51**, 4443*b* (1957).

Table III

Data for Calculation of Rate Constants or Plotting Graphs in the Reaction of 3-Methylcyclohexanone and Malononitrile

$1/(a - x)$, mol^{-1} l.[a]

Time, min	β-Alanine				KF
	0.0006 *M* Run 11	0.006 *M* Run 49	0.012 *M* Run 53	0.006 *M* Run 48[b]	0.006 *M*
(0)	(2.50)	(2.50)	(2.50)	(2.50)	(2.50)
3	2.58	2.89	2.87	2.95	3.74
4		3.03	3.00	3.15	4.03
6	2.65	3.26	3.26	3.53	4.30
8		3.50	3.54	3.92	4.93
9	2.82	3.60	3.69	4.12	
10		3.70	3.88	4.32	5.56
12	2.94	3.92	4.11	4.66	6.10
14		4.04	4.38	4.99	
15	3.01	4.22	4.52	5.22	7.08
17		4.42	4.81	5.55	7.73
18	3.11	4.44	4.94	5.75	
19		4.61	5.08	5.90	8.50
21	3.23	4.77		6.20	9.24
24	3.31	5.10	5.82	6.60	10.24
27	3.38			7.05	11.62
28		5.53	6.34		
30	3.49	5.72	6.65	7.55	12.92
34					14.89
35		6.13	7.45	8.15	
36	3.63				
40		6.73	8.13		17.3
41				8.90	
42	3.79				
45		7.25	9.13	9.55	20.5
48	3.97				
50		7.78	9.79	9.85	23.9
54	4.13				
55		8.19	10.60	10.3	
60	4.24	8.93	11.42	10.4	29.8
70	4.51	9.90			37.9
90	5.03	12.5			54.2

[a] Calculation based on rotation of synthetic mixtures; thus at 25° $1/(a - x) = 26.5/(\alpha_D + 9.75)$. [b] Reaction at 45°, $1/(a - x) = 26.1/(\alpha_D + 9.66)$ is the equation.

0.6 *M* ammonia liberated the amino acid. Fractions containing the amino acid were concentrated to give 4.26 g of crude product, mp 161–200°. Crystallization from equal portions of alcohol and ether gave 0.63 g of acid which was largely the trans form, mp 160–215°. Dilution of the mother liquor with large amounts of ether furnished the cis acid. After many crystallizations (finally from alcohol–acetone–ether), 1.25 g of pure amino acid was obtained, mp 179–181°. The purest sample had mp 181.5–184° after drying *in vacuo* at 80°.

Anal. Calcd for $C_9H_{17}O_2N$: C, 63.12; H, 10.01. Found:[17] C, 62.82; H, 9.97.

***trans*-4-Dimethylaminocyclohexanecarboxylic Acid.**—A solution of 5.15 g of ethyl *trans*-4-dimethylaminocyclohexanecarboxylate[24] and 2.8 g of potassium hydroxide in 35 ml of 95% ethanol was heated under reflux for 1.5 hr. The mixture was diluted with water and placed on a 70-g column of IR-120. Elution with 3 *N* ammonia furnished fractions containing the amino acid. The richest 100-ml fraction was concentrated to furnish 2.63 g, mp 205–214°. Two crystallizations from alcohol–ether gave 2.66 g of amino acid apparently as the alcoholate. After drying at 80° *in vacuo*, 2.02 g of amino acid remained, mp 223–224°.

Anal. Calcd for $C_9H_{17}O_2N$: C, 63.12; H, 10.01; N, 8.18. Found:[17] C, 63.10; H, 9.96; N, 8.15.

***N,N*-Dimethylglycine.**—*N,N*-Dimethylglycine hydrochloride (9.85 g, mp 188–190°) was placed on a column of Amberlite IR-120. Elution with 0.5 *M* ammonia furnished fractions (pH 5–11) which provided 7.0 g of amino acid. Recrystallization from isopropyl alcohol[25] gave the purified *N,N*-dimethylglycine (Table IV), mp 177.5–179°. The reported melting point is 177–182°.[26]

Condensation. (+)-3-Methylcyclohexanone[27] was prepared by retrograde aldol reaction of pulegone in dilute hydrochloric acid. Fractionation furnished a 65.2% yield of ketone: bp 119–120° (119 mm); n^{26}_D 1.4438; $[\alpha]^{26}_D$ +11.90 ± 0.05° (homogeneous); $[\alpha]^{26}_D$ +8.96 ± 0.1° (2.299 g of ketone dissolved up to 50 ml in 95% ethanol, α^{26}_D +0.823 ± 0.01° in a 2-dm tube). Gas chromatography at 100° indicated a purity of about 98%.

Eisenbraun and McElvain[27] have reported bp 166–168° (735 mm), $[\alpha]^{26}_D$ +12.01°.

3-Methylcyclohexylidenemalononitrile. A. *dl* Form.—A mixture of 28.0 g of *dl*-3-methylcyclohexanone, 16.5 g of malononitrile, 50 ml of 95% ethanol, 5 ml of acetic acid, and 0.20 g of β-alanine was heated under reflux for 1.5 hr. Distillation gave two fractions: (1) 3.36 g, bp 120–146° (34–14 mm), n^{26}_D 1.4988; (2) 32.6 g (81.5%), bp 146–154° (14 mm), n^{26}_D 1.5028, mp *ca.* 15°, ir (neat) 2200 (conjugated nitrile), 1590 cm^{-1} (double bond), nmr ($CDCl_3$) δ 1.06 (d, 3 H, *J* = 6 Hz, $=CHCH_3$).

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.49. Found:[28] C, 74.90; H, 7.57; N, 17.51.

Preparation using benzene as solvent while removing water azeotropically gave a 78.8% yield.

B. (−) Form.—A mixture of 22.4 g, $[\alpha]^{27}_D$ +11.76°, of (+)-3-methylcyclohexanone, 13.2 g of malononitrile, and 0.89 g of β-alanine was swirled with 50 ml of 95% ethanol. The mixture then stood at room temperature for 20 hr. The green solution was decanted from the undissolved β-alanine and fractionated: (1) 3.19 g, bp 97–121° (4 mm), $[\alpha]^{25}_D$ −51.2 ± 0.1° (95% ethanol); (2) 9.18 g, bp 121–122° (4 mm), mp 42.2°, $[\alpha]^{27}_D$ −76.7 ± 0.2° (95% ethanol); (3) 17.96 g, bp 122–122° (4 mm), mp 45.8°, $[\alpha]^{27}_D$ −77.8 ± 0.2° (95% ethanol), one component by gas chromatography. Fractions 2 and 3 represent an 84.6% yield.

The infrared absorption of fraction 3 (supercooled liquid) was identical with that of the *dl* form. However, fractions 1 and 2 and the last drop of fraction 3 showed some absorption at 1690 cm^{-1}, suggestive of amide.

The recrystallization of fraction 3 from 25 ml of 95% ethanol furnished 12.12 g of pure nitrile: mp 45.8–46.6° (softens at 42°); $[\alpha]^{25}_D$ −77.9 ± 0.2° (1.661 g of nitrile dissolved up to 25 ml in 95% ethanol, α^{25}_D −10.35 ± 0.02° in a 2-dm tube).

In an earlier run in benzene the product had been obtained in an 82.8% yield as a liquid: bp 148–151° (13 mm); n^{25}_D 1.5030; d^{25} 0.989; $[\alpha]^{27}_D$ −81.02 ± 0.08° (homogeneous, 0.5-dm tube), $[\alpha]^{30}_D$ −78.2 ± 0.2° (95% ethanol). Gas chromatography at 170° revealed only one component in this product.

Kinetic Studies. Synthetic Mixtures.—Eleven mixtures of (+)-3-methylcyclohexanone, malononitrile, and (−)-3-methylcyclohexylidenemalononitrile were made up in *ca.* 80% ethanol. These mixtures (total volume 50.0 ml) represented the potential product and reactant mixtures resulting when 0.020 mol of ketone and 0.020 mol of malononitrile were mixed along with 5 ml of water and diluted to 50.0 ml with 95% ethanol. The results of a 1962 study, cited in Table V, show a linear relationship between optical activity and concentration of reactants. The equation $A = (\alpha_D + 9.75)/26.5$ can be developed from these data for the calculation of the reacting substrates (ketone or nitrile) in moles per liter in kinetic runs. (With purer product later developed, the maximum values were $[\alpha]^{25}_D$ +9.37° and $[\alpha]^{25}_D$ −80.4°. In the equation for *A*, change 9.75 to 10.31 and 26.5 to 27.5.)

For other mixtures and temperatures, the synthetic mixtures calculated for the start and for the end at 100% conversion were prepared. From the rotatory values observed the appropriate equations were developed (60% perchloric acid (0.5 ml) was added to prevent the uncatalyzed reaction).

Kinetic Runs.—For rate studies aliquot portions of malononitrile (1.32 g, 0.200 mol) and (+)-3-methylcyclohexanone (2.24 g, 0.0200 mol) in 95% ethanol were mixed in a 50-ml volumetric flask. After short equilibration in the constant-temperature bath, the catalyst in 5 ml of water was added, the mixture was diluted to precise volume with 95% ethanol, and the mixture was transferred to a 2-dm, thermostated polarimeter tube. Timing was begun when the catalyst was added to the

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[25] F. H. Westheimer, *J. Org. Chem.*, **2**, 431 (1938).

[26] L. Kahovec and K. W. F. Kohlrausch, *Monatsh. Chem.*, **68**, 371 (1936).

[27] E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.*, **77**, 3383 (1955).

[28] Analysis by Weiler and Strauss, Oxford, England.

TABLE IV
APPARENT DISSOCIATION CONSTANTS FOR SOME AMINO ACIDS IN WATER[a]

Registry no.	Amino acid	pK_1	pK_2	pI
1118-68-9	*N*,*N*-Dimethylglycine	1.74[b]	10.00	5.87
5691-20-3 (36805-33-3)[e]	*cis*-Hexahydroanthranilic acid	3.31	10.73	7.02
5691-19-0 (38605-35-5)[e]	*trans*-Hexahydroanthranilic acid	3.25[c]	10.18[c]	6.72
3685-23-2	*cis*-*p*-Aminocyclohexanecarboxylic acid	4.24[d]	10.73[d]	7.49
3685-25-4	*trans*-*p*-Aminocyclohexanecarboxylic acid	4.13	10.59	7.37
38605-38-8	*cis*-*p*-*N*,*N*-Dimethylaminocyclohexanecarboxylic acid	4.34	10.58	7.46
38605-39-9	*trans*-*p*-*N*,*N*-Dimethylaminocyclohexanecarboxylic acid	4.18	10.37	7.28

[a] pK_1 and pK_2 determined at room temperature (22–30°) by titration with standard acid and base to determine the pH at the half-equivalence point with a Beckman Model 76 pH meter. Precision was ±0.02 units. [b] pK_1 reported to be 1.85 (ref 25). [c] pK_1 of 3.4 and pK_2 of 10.1 reported by J. P. Greenstein and J. Wyman, Jr., *J. Amer. Chem. Soc.*, **60**, 2341 (1938). [d] pK_1 of 4.3 and pK_2 of 10.4 reported by Greenstein and Wyman. [e] Benzenesulfonamide.

TABLE V
SYNTHETIC MIXTURES OF (+)-3-METHYLCYCLOHEXANONE (A), MALONONITRILE (B), AND (−)-3-METHYLCYCLOHEXYLIDENEMALONONITRILE (C)

Moles of reactants[a]		Observed rotation[b] $\alpha^{28}\text{D}$, deg
A and B	C	
0.020	0.000	+0.85[c]
0.018	0.002	−0.24
0.016	0.004	−1.28
0.014	0.006	−2.36
0.012	0.008	−3.35
0.010	0.010	−4.46
0.008	0.012	−5.60
0.006	0.014	−6.63
0.004	0.016	−7.66
0.002	0.018	−8.76
0.000	0.020	−9.75[d]

[a] Moles of A, B, and C mixed with 5 ml of water, diluted up to 50 ml with 95% ethanol. [b] Readings ±0.01°, average of two. [c] The specific rotation of (+)-3-methylcyclohexanone in the presence of malononitrile, $[\alpha]^{28}\text{D}$ +9.4 ± 0.1°. [d] The specific rotation is $[\alpha]^{28}\text{D}$ −76.0 ± 0.5°.

mixture. Rotatory values were determined as quickly as possible and as often as seemed indicated by the rate of reaction.

Rotatory values were converted to concentration, A, from the equation developed above. The reciprocal of the concentration, $1/A$, was calculated and a plot of $1/A$ against time was used to calculate the second-order rate constant. Straight lines were usually observed up to at least 75% conversion. Results of five runs are collected in Table III and plotted in Figure 2.

Study of the rate of uncatalyzed reaction indicated a reaction rate $k_2 = 0.0007$ mol^{-1} min^{-1} at 25° and $K_2 = 0.0022$ mol^{-1} min^{-1} at 45°. The rate of reversal could be neglected in these reactions (1.6% reaction after 4 hr uncatalyzed at 45° and 6.7% reaction after 2 hr at 30° with 2.4×10^{-2} mol/l. of ε-aminocaproic acid.)

The effects of several parameters were tested when β-alanine was used as a catalyst. These results are recorded in Table I.

The influence of various amino acids, aminophenols, lithium fluoride, and buffer at pH 8 are assembled in Table II.

Apparent pH values in Table II are pH's observed in solutions containing the solvent system but omitting the reactants (Tables I and II). In Table I the malononitrile was added too.

Registry No.—Hexahydrophthalimide, 1444-94-6; anthranilic acid, 118-92-3; ethyl *cis*-4-dimethylaminocyclohexanecarboxylate, 38615-90-6; ethyl *trans*-4-dimethylaminocyclohexanecarboxylate, 38615-91-7; (+)-3-methylcyclohexanone, 13368-65-5; malononitrile, 109-77-3; (±)-3-methylcyclohexylidenemalononitrile, 38614-92-8; (−)-3-methylcyclohexylidenemalononitrile, 38615-93-9.