13,500) and 315 mμ (ε 11,300). The chemical, analytical and spectroscopic evidence indicated that the product was 1,3-diphenyl-4-cyclohexylamino-5-(*p*-nitrophenyl)-Δ^2-pyrazoline.

cis **Isomer.**—A solution of 2.1 g. (0.0063 mole) of the *cis* isomer, 0.68 g. (0.0063 mole) of phenylhydrazine and 0.75 g. (0.0126 mole) of acetic acid in a mixture of 18 ml. of chloroform and 12 ml. of absolute ethanol stood at room temperature for 14 hours and then in a refrigerator for 10 hours. The darkened solution was diluted with ether, washed with water, dried, and evaporated. The resulting orange oil was crystallized from petroleum ether (b.p. 65–110°), giving 0.66 g. of orange needles, m.p. 133–139°. Two crystallizations from petroleum ether gave an analytical sample; 0.24 g., small, yellow prisms, m.p. 139–140°. The compound gave a negative Knorr test for a pyrazoline.

Anal. Calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.86; H, 4.20; N, 12.4.

The ultraviolet spectrum in 95% ethanol showed maxima at 242.5 mμ (ε 22,100) and 265 mμ (ε 25,000). Minima were at 227.5 mμ (ε 20.500) and 245 mμ (ε 22,000). The chemical, analytical and spectroscopic data indicated that the product was 1,3-diphenyl-5-(*p*-nitrophenyl)-pyrazole.

Test of Configurational Stability of *cis*-1-Cyclohexyl-2-(*p*-nitrophenyl)-3-benzoylethylenimine (Xb).—A solution of 0.25 g. (0.0007 mole) of the *cis*-ethylenimine ketone and 0.07 g. (0.0007 mole) of cyclohexylamine in 5 ml. of benzene was allowed to stand at 28° for 60 hours. The mixture was diluted with ether, washed with water and dried over magnesium sulfate. Evaporation of the solvents yielded 0.21 g. of white powder, m.p. 119–123° dec. The infrared spectrum of the material indicated that it represented the original *cis* compound in nearly pure form.

Isolation of *cis*-1-Cyclohexyl-2-phenyl-3-benzoylethylenimine from the Reaction of Cyclohexylamine and Iodine with *trans*-Chalcone.—A solution of 3.54 g. (0.014 mole) of iodine in 30 ml. of benzene was added to a stirred solution of 2.90 g. (0.014 mole) of chalcone and 5.52 g. (0.056 mole) of cyclohexylamine in 20 ml. of benzene over a period of 30 minutes. The temperature remained at 28°. After the mixture was stirred for another 110 minutes, filtration gave 6.10 g. (97%) of cyclohexylamine hydroiodide. The filtrate was worked up as were other cyclohexylamine–iodine additions to give 3.98 g. (96%) of crude product.

A 1.5-g. portion of the product was dissolved in 50 ml. of petroleum ether (b.p. 65–110°). After refrigeration, 0.56 g. of a solid, m.p. 89–95°, was filtered out. The filtrate was concentrated to 20 ml. and allowed to stand overnight at room temperature to afford 0.14 g. of a solid, m.p. 90–98°. This material was dissolved in 5 ml. of petroleum ether (b.p. 30–60°) and refrigerated to give 0.05 g. of needles, m.p. 100–104°. A mixed melting point with *trans*-1-cyclohexyl-2-phenyl-3-benzoylethylenimine was 80–87°. A mixed melting point with *cis*-1-cyclohexyl-2-phenyl-3-benzoylethylenimine was 100–106°. The infrared spectrum of the material was determined in a carbon tetrachloride solution (30 mg./ml.) and showed a band for band correspondence with a similarly determined spectrum of *cis*-1-cyclohexyl-2-phenyl-3-benzoylethylenimine,[5a] m.p. 106–107°.

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[Contribution from Organic Research Department, Research Division, Abbott Laboratories]

Specific Solvent Effects in the Alkylation of Enolate Anions. I. The Alkylation of Sodiomalonic Esters with Alkyl Halides

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The pseudo-first-order rate constants for the alkylation of sodio-1-methylbutylmalonic ester with ethyl bromide and of sodio-*n*-butylmalonic ester with *n*-butyl bromide and iodide have been measured in benzene solution at several temperatures and in the presence of varying concentrations of many polar additives. Certain N,N-disubstituted amides and several coordinate covalent N-, P- and S-oxides distinguish themselves from many other polar substances by increasing alkylation rates many-fold at less than 5% concentrations. Evidence is presented to show that this striking rate acceleration is most likely produced by a specific solvation of sodium ion which tends to dissociate the high molecular weight ion-pair aggregate of the sodio-derivative that exists in benzene solution.

The scope of current activity in the study of tautomeric substances and of ambient anions derivable from them witnesses to the importance of this field to both theoretical and practical organic chemistry. Brady and Jakobovits[1] have investigated the effect of varying the cation on the reactivity of many ambient anions. Brändström[2] has been concerned with the effect of the degree of dissociation of the metal derivatives on their reactivities and reaction paths. Kornblum and his co-workers[3a] have undertaken an extensive investigation of the reactions of silver and alkali metal nitrites with alkyl halides, and have formulated a general principle relating the reaction path to the character of the transition state. Zook and Rellahan[4] have examined the alkylation of sodium enolates of alkyl phenyl ketones from a similar point of view; Hauser and co-workers[5] have long been interested in the acylation of enolate anions; and Curtin[6] and Kornblum[3b] and their students have analyzed, from differing points of view, the effect of a number of factors controlling the position of alkylation of alkali metal salts of phenols.

Even the stereochemistry of these substances has been scrutinized. Zimmerman[7] has studied the stereochemical mode of protonation of enolate anions, and Kabachnik and his associates[8] have demonstrated the presence of both *cis*- and *trans*-enolic forms in many α-substituted acetoacetic esters.

Although many kinetic studies of the alkylation of β-ketoesters have been reported,[2a] the only such investigation with malonic esters seems to be that of Pearson.[9] He determined the second-

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(1) O. L. Brady and J. Jakobovits, *J. Chem. Soc.*, 767 (1950).

(2) (a) A. Brändström, *Arkiv Kemi*, **6**, 155 (1953); (b) **11**, 567 (1957); (c) **13**, 51 (1958).

(3) (a) N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, This Journal, **77**, 6269 (1955); (b) N. Kornblum and A. P. Lurie, *ibid.*, **81**, 2705 (1959).

(4) H. D. Zook and W. L. Rellahan, *ibid.*, **79**, 881 (1957).

(5) D. G. Hill, J. Burkus and C. R. Hauser, *ibid.*, **81**, 602, 2787 (1959), and prior references.

(6) D. Y. Curtin, R. J. Crawford and M. Wilhelm, *ibid.*, **80**, 1391 (1958).

(7) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

(8) M. I. Kabachnik, S. T. Yoffe and K. V. Vatsuro, *Tetrahedron*, **1**, 317 (1957).

(9) R. G. Pearson, This Journal, **71**, 2212 (1949).

order rate constants at 25° for the reactions of the sodium derivatives of malonic and ethylmalonic esters with ethyl bromide in absolute ethanol.

The present work was undertaken for the practical purpose of finding optimal solvent conditions for the alkylation of sodiomalonic esters by means of a kinetic study of solvent effects. To this end the pseudo-first-order rates of alkylation of two sodiomalonic ester derivatives were measured in benzene alone and in the presence of varying amounts of a number of additives. To simplify comparisons, additive concentrations were limited to multiples of 0.162 *M*. This odd choice evolved from the fact that an easily prepared five volume per cent. solution of N,N-dimethylformamide (the additive most extensively studied) corresponds to a 0.648 *M* (4 × 0.162) concentration.

The sodium derivative of 1-methylbutylmalonic ester was chosen first for study in the present work for four reasons: (1) it forms adequately concentrated solutions in benzene, (2) like most malonic esters it undergoes reaction only at the carbon atom so that the measured rate represents the rate of carbon alkylation, (3) as a monosubstituted malonic ester only one further alkylation step is possible, and (4) the alkylation of 1-methylbutylmalonic ester is of commercial importance. During preliminary determinations (all at 30°) using this material with ethyl bromide as the alkylating agent, it became evident that more significant assessment of solvent effects over a wider range of reaction conditions could be expected from the reaction of sodio-*n*-butylmalonic ester with *n*-butyl bromide. Therefore, most of the data reported herein deal with the use of this system. Here again, in many cases, additive concentrations were varied so that their orders of participation in the reaction could be estimated In addition, rough temperature dependence of the rate was determined in the presence of a number of additives in order to gauge their influence, if any, on the activation parameters. The effect of changing the halogen atom of the alkylating agent also was ascertained in several instances by substituting *n*-butyl iodide for the corresponding bromide.

Finally, the nature of the benzene solution of the sodio-*n*-butylmalonic ester was examined cryoscopically and nephelometrically. It was found that this electrolyte exists in a highly associated state in the non-polar medium.

Experimental

Reagents and Solvents.—Reagent grade benzene carefully dried by distillation was used throughout this work. The alkyl bromides were dried, purified by careful distillation, and stored in tightly stoppered containers: ethyl bromide, b.p. 37.5–38°, $n^{25}\mathrm{D}$ 1.4230; *n*-butyl bromide, b.p. 100–101°, $n^{25}\mathrm{D}$ 1.4362. The *n*-butyl iodide was always distilled shortly before use, b.p. 130–131°, $n^{25}\mathrm{D}$ 1.5000.

Malonic Esters.—The diethyl 1-methylbutylmalonate used was a center-cut (b.p. 133–133.5° (20 mm.), $n^{25}\mathrm{D}$ 1.4258) taken from the fractionation of a commercial sample. During the course of the work it became evident from other sources that this sample contained appreciable amounts (5–10%) of the isomeric 1-ethylpropylmalonic ester. However, the same sample was used in all rate measurements, so that comparison of relative rates is still meaningful.

Four different samples of carefully fractionated diethyl *n*-butylmalonate[10] were used. Representative boiling points of the fractions chosen were 116–117° (14 mm.), 128–129° (20 mm.), 135° (22 mm.) and refractive indices (at 25°) varied only between the limits 1.4207 and 1.4211.

Additives.—The following materials were obtained from commercial sources: N,N-dimethylformamide (du Pont), b.p. 152–153°, $n^{25}\mathrm{D}$ 1.4281; N,N-dimethylacetamide (du Pont), b.p. 165–166°, $n^{25}\mathrm{D}$ 1.4359; N-acetylmorpholine (Carbide and Carbon), b.p. 145° (44 mm.), $n^{25}\mathrm{D}$ 1.4826; N-thioacetylmorpholine (Rohm and Haas), m.p. 89–91°; N-methylformanilide (Eastman), b.p. 139° (24 mm.), $n^{25}\mathrm{D}$ 1.5597; N,N-diphenylformamide (Eastman), m.p. 71–73°; N,N-dimethylcyanamide (Eastman), b.p. 162–164°; methyl N,N-dimethyldithiocarbamate (du Pont), m.p. 47–49°; N-methyl-2-pyrrolidone (Antara), b.p. 96° (22 mm.), $n^{25}\mathrm{D}$ 1.4680; N-vinyl-2-pyrrolidone (Antara), b.p. 102–103° (19 mm.), $n^{25}\mathrm{D}$ 1.5112; 1,2,4,4-tetramethyl-2-pyrrolin-5-one (Rohm and Haas), b.p. 85° (24 mm.), $n^{25}\mathrm{D}$ 1.4810; hexamethylphosphoramide (Monsanto), b.p. 121° (19 mm.), $n^{25}\mathrm{D}$ 1.4570; pyridine-N-oxide (Reilly); dimethyl sulfoxide (Stepan), b.p. 87° (23 mm.), $n^{25}\mathrm{D}$ 1.4771; 2,4-dimethylsulfolane (Shell), b.p. 154° (22 mm.), $n^{29}\mathrm{D}$ 1.4698; tetrahydrofuran, b.p. 65.5°, $n^{25}\mathrm{D}$ 1.4037; glycol dimethyl ether (Ansul), b.p. 83–84°, $n^{27}\mathrm{D}$ 1.3745; benzophenone (Eastman), m.p. 48°; and pyridine (Mallinckrodt), b.p. 114–114.5°, $n^{24}\mathrm{D}$ 1.5070.

The following additives were prepared either by the literature method indicated or by the usual reaction of an acid chloride or anhydride with a secondary amine: N-formylpyrrolidine,[11] b.p. 100° (19 mm.), $n^{25}\mathrm{D}$ 1.4780; N-formylpiperidine,[11] b.p. 102° (16 mm.), $n^{25}\mathrm{D}$ 1.4826; N-formylmorpholine,[11] b.p. 118° (16 mm.), $n^{25}\mathrm{D}$ 1.4851; N-methyl-2-pyridone,[12] b.p. 131–131.5° (16 mm.), $n^{25}\mathrm{D}$ 1.5665; N-methyl-2-piperidone,[13] b.p. 101–103° (17 mm.), $n^{26}\mathrm{D}$ 1.4804; N-methyl-ε-caprolactam,[14] b.p. 115–116° (19 mm.), $n^{25}\mathrm{D}$ 1.4812; N,N-dimethyltrifluoroacetamide, b.p. 135–136°, $n^{25}\mathrm{D}$ 1.3601; N,N-dimethylpivalamide, b.p. 105–106° (55 mm.), $n^{25}\mathrm{D}$ 1.4431; N,N-dimethylbenzamide, b.p. 139–139.5° (14 mm.), $n^{25}\mathrm{D}$ 1.5428; N,N-dimethylnitrosamine,[15] b.p. 150–152°, $n^{25}\mathrm{D}$ 1.4337; N-acetylpyrrolidine, b.p. 115–116° (25 mm.), $n^{25}\mathrm{D}$ 1.4723; trimethylphosphine oxide,[16] b.p. 214–215°, m.p. 137–138°; methyl N,N-dimethylcarbamate,[17] b.p. 130–130.5°, $n^{25}\mathrm{D}$ 1.4131; tetramethylurea,[18] b.p. 175–175.5°, $n^{25}\mathrm{D}$ 1.4493; N,N-dimethyl methanesulfonamide,[19] m.p. 50–51°; and tetramethylsulfamide,[20] m.p. 72–73°.

Most of the liquid additives were purified by drying over calcium hydride overnight, decanting, and distilling in oven-dried (100–120°) equipment just before use. However, tetrahydrofuran and glycol dimethyl ether were distilled from lithium aluminum hydride, and pyridine was distilled from potassium hydroxide. When it was not convenient to use an additive immediately after purification, a standard solution of it in dry benzene was immediately prepared in a glass-stoppered volumetric flask and kept in a desiccator over calcium hydride. In this way, absorption of atmospheric moisture by the more hygroscopic compounds was minimized.

Procedure.—The following routine was followed in nearly all determinations of the rate of the alkylation of *n*-butylmalonic ester: to a solution of 10 ml. of diethyl *n*-butylmalonate in 90 ml. of benzene in a 250-ml. three-neck flask equipped with a stirrer, drying tube and nitrogen inlet tube, was added excess (1.5–1.8 g.) sodium hydride. Stirring at room temperature during the night was limited to 4 or 5 hours by means of an automatic timer so that unreacted

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(10) R. Adams and R. M. Kamm, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, 1941, p. 250.

(11) F. F. Blicke and C. Lu, THIS JOURNAL, **74**, 3933 (1952).

(12) E. A. Prill and S. M. McElvain, "Organic Syntheses," Coll. Vol. 11, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 419.

(13) P. S. Ugryumov, *J. Gen. Chem.* (*U.S.S.R.*), **14**, **81** (1944); *C. A.*, **39**, 935 (1945).

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(17) A. P. N. Franchimont and E. A. Klobbie, *Rec. trav. chim.*, **8**, 299 (1889).

(18) W. Michler and C. Escherich, *Ber.*, **12**, 1162 (1879).

(19) O. Eisleb, German Patent 735,866 (1943); *C. A.*, **38**, 4101 (1944).

(20) R. Behrend, *Ann.*, **222**, 116 (1884).

hydride would have time to settle. The solution of the sodiomalonic ester was then drawn by vacuum into a dry 100-ml. pipet from which the tip had been removed to allow for insertion of a plug of glass wool into the lower part of the stem. The solution was transferred to a nitrogen-filled 125-ml. conical flask and placed in a constant temperature bath held at the desired reaction temperature.

To a 100-ml. volumetric flask containing 25 ml. of the *n*-butyl halide previously thermostated was added a standard solution of the additive in benzene, the volume being determined by the multiple of 0.162 *M* which was needed for the final concentration. Occasionally, when dimethylformamide was used as the additive, either 5 ml. or 10 ml. (9.477 g.) of the pure liquid was pipetted directly into the reaction flask to make the final concentration 0.648 or 1.296 *M*, respectively.

To this mixture was added 25 ml. of the stock solution of the sodio-derivative followed immediately by enough thermostated benzene to make 100 ml. (The resulting solutions were 2.37 *M* with respect to *n*-butyl bromide and 2.20 *M* in halide when *n*-butyl iodide was used.) The solutions were then well mixed (zero time), and at intervals, 10-ml. aliquots of the reaction mixture were withdrawn, and added to excess (25 ml.) 0.05 *N* hydrochloric acid containing phenolphthalein indicator. In most instances, immediate agitation (swirling) was required in order to dispel the initial alkaline indicator color which persisted in the organic phase in spite of contact with aqueous acid. The excess acid was then backtitrated with 0.05 *N* sodium hydroxide.

Two separate runs were usually carried out simultaneously using sodio-derivative from the same stock solution. Several aliquots of the stock solution were also titrated so that initial concentrations of the sodiomalonate could be calculated. These varied between the limits, 0.110 to 0.130 *M*, with most of them falling between 0.117 and 0.123 *M*.

All alkylations of the sodio-*n*-butylmalonic ester were carried out at one of three corrected temperatures: 15.00 ± 0.05°, 25.00 ± 0.02° and 37.44 ± 0.06°. For each run, the slope and standard deviation of the plot of the logarithm of the concentration of unreacted sodium derivative against time in seconds was calculated by the statistical method of least squares. Multiplying this slope by the factor −2.303 gave the pseudo-first-order rate constant directly.

Heats of activation were calculated, in most instances, from the rates at the two temperatures, 25 and 37.44° using the equation $\Delta H^{\ddagger} = E_a - RT$ where $E_a = 2.303RT_2T_1 (\log k_2 - \log k_1)/T_2\text{-}T_1$. The free energies and entropies of activation at 25° were then found using the relationships $\Delta F^{\ddagger} = -2.303RT \log K^{\ddagger}$ where $K^{\ddagger} = hk_r^{25°}/kT$ and $\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta F^{\ddagger})/T$.[21] In addition, the activation parameters for dimethylformamide and dimethyl sulfoxide were determined more precisely from an Arrhenius plot (Fig. 1) obtained from rate measurements at a third temperature (15°). The slopes of the two plots of log *k vs.* $1/T$ were calculated by the least squares method. Multiplication of the slopes and their standard deviations by the constant $2.303R$ gave directly the energies of activation (*Ea*) and their standard deviations. From these, the corresponding $\Delta H^{\ddagger}$, $\Delta F^{\ddagger}$ and $\Delta S^{\ddagger}$ values could be calculated in the usual way.[21]

Rates of alkylation of the sodio-1-methylbutylmalonic ester were measured essentially in the same way as described above for the *n*-butyl analog, except that all runs were restricted to one temperature: 30.00 ± 0.02°. Also, 30 ml. of ethyl bromide, giving a 3.99 *M* solution, was used as the alkylating agent in each run.

Examination of the Sodio-*n*-butylmalonic Ester Solutions.—Freezing-point measurements of these benzene solutions were made in a small jacketed rotating tube (open to the atmosphere) in which a thermistor was eccentrically placed. Changes in temperature of the solution were indicated by a potentiometric recorder, previously standardized with pure benzene.

Turbidity measurements of benzene solutions of the sodio derivative were carried out in a Coleman model 9 nepho-Colorimeter. Freshly and thoroughly centrifuged solutions were compared with Coleman Nephelos standards.

Results

Alkylation of Diethyl Sodio-1-methylbutylmalonate with Ethyl Bromide.—The pseudo-first-order rate constants at 30° for this reaction are listed in Table I in roughly increasing order of additive efficiency. Also included are the relative rates based on the measurement made in the absence of additive (relative rate = $k_1/1.29 \times 10^{-5}$ sec.$^{-1}$).

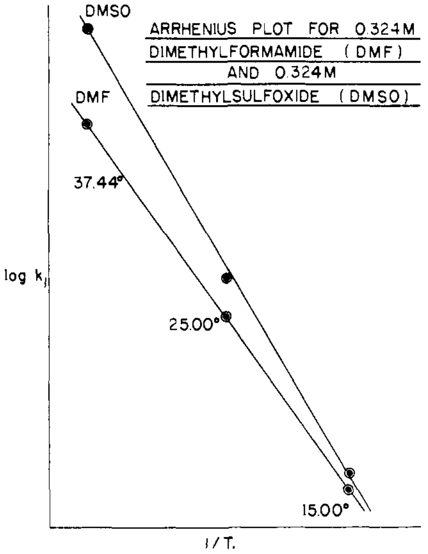

Fig. 1.

In the absence of additive as well as in the presence of most of the ineffective ones, the reaction rate showed a curious discontinuity. For example in benzene alone, the first 40% of the reaction gave a good first-order plot (log *c vs. t*). At this point the rate decreased rather abruptly to approximately half the original, but it still showed good graphic first-order characteristics. This phenomenon was also observed in the presence of all but one of the first seven additives listed in Table I. These discontinuities, however, all occurred between 20 and 30% of reaction. In contrast, when more effective additives were present, the reaction proceeded at a continuous pseudo-first-order rate, at least in the approximate range 10 to 80% of completion. Whatever the reason for this discontinuity may be, it provides an empirical diagnostic tool to use along with comparison of relative rates for differentiating effective additives from many ineffective ones.

The standard error accompanying each constant merely represents its deviation from linearity or degree of precision. Its accuracy must derive from its reproducibility. Invariably, when two identical measurements were conducted simultaneously using the same stock solution of sodiomalonate, the results were mutually indistinguishable. For this reason two different additives were usually employed in concurrent experiments. As expected, when identical conditions were employed at different times, somewhat greater variation in rate resulted. The largest variation was encountered with dimethylacetamide; but even in this case it amounted to only ±6% (8.86 to 9.98) in the three experiments conducted.

Two general observations derivable from the results of Table I deserve emphasis. First, many of the substances usually considered to be good polar solvents are relatively inefficient in accelerat-

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(21) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 95–97.

TABLE I

RATES OF ALKYLATION AT 30° OF DIETHYL SODIO-1-METHYLBUTYLMALONATE WITH ETHYL BROMIDE (3.99 *M*)

Additive (A)	Concn. of A, *M*	$k_1 \times 10^5$ sec.$^{-1a}$	Relative rate $= k_1/1.29 \times 10^{-5}$
None	0	$1.29 \pm 0.02^{b,d}$	1.0
		$0.64 \pm .02^{c,d}$	0.5
$(C_2H_5O)_2CO$	0.648	$1.55 \pm .06$	1.2
$CH_3SO_2N(CH_3)_2$	.648	$2.03 \pm .26^{e}$	1.6
		$0.98 \pm .01^{c}$	0.8
CH_3CN	.648	$2.14 \pm .58^{f}$	1.7
		$0.83 \pm .05^{c}$	0.6
$(CH_3)_2NCOOCH_3$	.648	$2.64 \pm .04^{g}$	2.0
		$1.79 \pm .16^{c}$	1.4
$C_6H_5NO_2$	.648	$3.16 \pm .21^{h}$	2.5
		$1.18 \pm .10^{c}$	0.9
$(CH_3)_2NSO_2N(CH_3)_2$	.648	3.60^{h}	2 8
		$1.10 \pm .05^{c}$	0.9
C_6H_5CN	.648	4.13 ± 47^{f}	3.2
		$0\ 94 \pm 07^{c}$	0.7
C_2H_5OH	1.296	$5.08 \pm .32^{d}$	3.9
	2.592	$6.94 \pm .08$	5 4
$(CH_3)_2NCON(CH_3)_2$	0.648	$7.03 \pm .07^{d}$	5.5
$HCON(CH_3)_2$	0.648	$7.44 \pm .18^{i}$	5.8
	1.296	$15.4 \pm .3^{d}$	12
$(CH_3)_2SO$	0.648	$8.15 \pm .16^{d}$	6.3
$CH_3CON(CH_3)_2$	.648	$9.34 \pm .10^{i}$	7.2
$HCON(CH_2)_4{}^{j}$	.324	$5.31 \pm .06$	4.1
	.648	$10.5 \pm .3$	8.1
$CH_3CON(CH_2)_4{}^{k}$	.324	$6.03 \pm .15$	4.7
$(CH_3)_3PO$	324	$6.72 \pm .35$	5.2
$C_5H_5NO^{l}$	.648	$16.4 \pm .3^{d}$	13
$[(CH_3)_2N]_3PO$	.648	$27.1 \pm .6^{d}$	21

[a] Pseudo-first-order rate constant. [b] First 40% of the reaction. [c] Measured rate after occurrence of the discontinuity. [d] Average of two runs. [e] First 33% of the reaction. [f] First 25%. [g] First 30%. [h] First 20%. [i] Average of three runs. [j] N-Formylpyrrolidine. [k] N-Acetylpyrrolidine. [l] Pyridine N-oxide.

ing this alkylation reaction, especially when compared to the group of effective additives comprising the N,N-disubstituted amides and the coördinate covalent P-, S- and N-oxides. Second, from the few examples studied of rate dependence on concentration, it appears that the better additives (dimethylformamide and N-formylpyrrolidine) show a high order (unity in these cases) of participation in the reaction compared to that of the poorer additives exemplified by ethanol (participation order less than one). Similar comparative concentration effects will be considered in more detail in connection with the following alkylation.

Alkylation of Diethyl Sodio-*n*-butylmalonate with *n*-Butyl Bromide.—The pseudo-first-order rate constants, all at 25° and some at 37.44°, measured in the presence of specified concentrations of thirty-two different additives are listed in Table II. Numbers in parentheses denote rates of alkylation relative to that found in the absence of additive at the corresponding temperature (see footnote *b*, Table II). The additives are grouped according to either a general lack of catalytic activity or to a common structural resemblance.

Although the rate of the first third of the reaction in the absence of catalyst was of the same order (0.83 *vs.* 1.29) as the corresponding rate of ethylation of sodio-1-methylbutylmalonic ester, the discontinuity, observed after 35% of reaction, was less marked (0.83 to 0.54 *vs.* 1.29 to 0.64). Furthermore, in only two other instances [$(CH_3)_2NNO$ and tetrahydrofuran] was a recurrence of this discontinuity observed, even though a number of inferior additives were tested in runs carried well beyond the point (40–50% of reaction) at which a discontinuity is most likely to occur.

In one run at 25° (Table II, footnote *d*) using twice the usual initial concentration of sodiomalonate the rate constant for the first phase of the reaction proved to be essentially the same as those of the normal runs. However, the rate constant obtained for the second phase did not check with the normal values. Apparently, the first phase (before the discontinuity) of the reaction is a true pseudo-first-order reaction (rate constant independent of initial concentration), but the second phase appears to be complex.

With the single exception of dimethyl sulfoxide, all eight of the additives of the preliminary work (Table I), which were also used in this alkylation, fell into the same order of activity as before. In this study, dimethyl sulfoxide was relatively more active than the other seven, even though all of the effective catalysts showed greater efficiency than they did previously.

As before (Table I) the scope of distinct catalytic activity appears to be limited to the coördinate covalent compounds and members of the group of N,N-disubstituted amides. A sufficient number of the latter have now been studied to permit tentative generalizations of several structure–activity relationships in the amide series.

Replacement of methyl on nitrogen by electron-withdrawing groups clearly impairs activity [*e.g.*, $HCON(CH_3)_2$ *vs.* $HCON(CH_3)C_6H_5$ or $HCON(C_6H_5)_2$; and N-methylpyrrolidone *vs.* N-vinylpyrrolidone]. Likewise, substitution of increasingly electronegative groups on the carbonyl carbon reduces activity [*e.g.*, $CH_3CON(CH_3)_2 > HCON(CH_3)_2 > C_6H_5CON(CH_3)_2 > CF_3CON(CH_3)_2$; $(CH_3)_3CCON(CH_3)_2$ is an exception to this rule]. Incorporation of both the nitrogen and carbon atoms of the amide group into a five or six-membered ring enhances activity [*e.g.*, $CH_3CON(CH_3)_2 <$ N-methylpiperidone $<$ N-methylpyrrolidone]. But this effect, which is more marked for the five-membered ring, reverses itself in the seven-membered ring [N-methyl-ε-caprolactam $< CH_3CON(CH_3)_2$]. Although it is not strictly comparable structurally, the completely planar N-methyl-2-pyridone is the best of any of the carboxamides studied.

Activation parameters for those reactions which were conducted at two temperatures are listed in the last three columns of Table II. Since they were derived from rate measurements at only two temperatures differing by no more than 13°, little quantitative importance can be attached to any one set of values. However, inspection of them as a group discloses a definite trend toward higher $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values among the better compounds, N-methyl-2-pyridone, pyridine N-oxide and dimethyl sulfoxide.

To estimate the significance of this trend, rates of alkylation were determined at a third temperature (15°) in 0.324 *M* dimethylformamide and in 0.324 *M* dimethyl sulfoxide (Table II, footnotes *l* and *v*). From the Arrhenius plot (Fig. 1) thus obtainable, parameters with precisions of known significance could be calculated (see Experimental). The functions obtained for dimethylformamide and dimethyl sulfoxide, respectively, are $\Delta H^{\neq}$ = 12.64 ± 0.13 and 15.40 ± 0.76 kcal. mole^{-1}; $\Delta F_{25°}^{\neq}$ = 23.2 and 22.8 kcal. mole^{-1}; and $\Delta S_{25°}^{\neq}$ = −35.5 and −24.8 cal. mole^{-1} deg.$^{-1}$. Apparently, the activation parameters in the presence of dimethylformamide differ little from those in the presence of the majority of the other additives, or even from those in benzene alone. However, the $\Delta H^{\neq}$ value for the alkylation in dimethyl sulfoxide is significantly higher than that for dimethylformamide, and, presumably, than those for most of the other additives.[22] Yet the effect of this increase in $\Delta H^{\neq}$ on the rate is clearly counterbalanced by an increase in $\Delta S^{\neq}$, for the $\Delta F^{\neq}$ values in dimethylformamide (23.2 kcal.) and in dimethyl sulfoxide (22.8 kcal.) do not differ significantly.

Alkylation of Diethyl Sodio-*n*-butylmalonate with *n*-Butyl Iodide.—The pseudo-first-order rate constants at 25° for several of these reactions, corrected to enable comparison with the corresponding butyl bromide alkylations,[25] are given in Table III. The usual relative rates (k_r) are included in parentheses. To simplify comparisons, the rates of the corresponding bromide alkylations (from Table II) are listed in the last column.

Several points derivable from the data of Table III deserve emphasis. Unlike the bromide alkylation, iodide alkylation in benzene alone and in the presence of 0.324 *M* dimethylnitrosamine proceeds without discontinuity for at least 65% of the reaction. However, the rates of the two iodide alkylations are not much greater than those of the first phases of the two bromide alkylations (1.13 *vs.* 0.83 for benzene alone, and 3.28 *vs.* 1.61 for $(CH_3)_2NNO$). Yet the presence of an amide (N-methylformanilide), which in the bromide alkylation is not conspicuously effective (k_r = 2.6), results in marked acceleration (k_r = 15) of the iodide reaction.[26] Despite this fact, the differences between the two amides are essentially the same for both halides (60.1/17 = 3.53 and 7.24/2.14 = 3.38). Furthermore, the effect of concentration on the rate is substantially independent of the halide when an effective additive like dimethylacetamide is involved (18.9/7.24 = 2.61; 7.24/2.86 = 2.53; 60.1/22.6 = 2.66). In other words, effective additives show the same differences when corresponding rates of bromide and iodide alkylations are compared (17/2.14 = 7.94; 22.6/2.86 = 7.90; 60.1/7.24 = 8.31). The iodide alkylations proceed at approximately 8 times the rates of the comparable bromide alkylations.[27]

Order of Additive Participation in the Alkylations with *n*-Butyl Bromide and Iodide.—In the preliminary work (Table I) it was found that the alkylation rate in the presence of dimethylformamide or formylpyrrolidine was substantially first-order with respect to additive; but that the rate in the presence of the weakly effective ethanol showed less than first-order dependence on ethanol concentration.

In Table IVA are listed the calculated orders of participation in the bromide alkylation of the eleven additives that were run at more than one concentration. Table IVB includes the two additives studied in this manner in the iodide alkylation. These orders were calculated from the appropriate pseudo-first-order rate constants (Tables II and III) by the differential method.[28] Also included are the observed relative rates for the two concentrations most commonly employed.

The participation order, *n*, is defined in the empirical rate law by

$$k_1 = k[\mathrm{A}]^n$$

where k_1 is the pseudo-first-order rate constant and [A] is the additive concentration. This means that when *n* varies from one additive to another, valid comparisons of catalytic efficiencies can be made only at unit concentrations ([A] = 1). For this reason the relative rate extrapolated to unit concentration has been calculated from the observed order for each additive. These values are listed in the last column of Table IV.

The compounds of Table IVA divide themselves into four groups according to magnitude of participation order. The first three, representative of the least effective group, possess only fractional

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[22] The question as to the source of this increase in activation energy in dimethyl sulfoxide presents itself. Does it arise from the interaction of the sulfoxide with *n*-butyl bromide or with the sodiomalonate derivative? Recently, Smith and Winstein[23] have shown that alkyl iodides, nitrates and tosylates are reversibly solvolyzed in pure dimethyl sulfoxide to reactive ionic species of type, $[(CH_3)_2SOR]^+X^-$. Assuming the extension of this behavior to the less reactive *n*-butyl bromide, even in relatively dilute benzene solutions of the sulfoxide, nucleophilic attack of the cation $[(CH_3)_2SO\text{–}n\text{-}C_4H_9]^+$ by sodium enolate should be energetically more favorable than attack of neutral *n*-butyl bromide. Consequently, a decreased rather than the increased $\Delta H^{\neq}$ value, actually observed in the presence of the sulfoxide, would be expected if interaction of this type is important in the present system.

On the other hand, interaction of dimethyl sulfoxide with the sodium enolate to give a solvate more stable than the one formed with dimethylformamide would be reflected in a higher activation energy for the former, since desolvation of the sodium enolate must occur during the alkylation. That such interaction between the sodium enolate and dimethyl sulfoxide does indeed occur is clearly revealed by a rough thermometric titration.[24] When benzene solutions of the sulfoxide and of the sodio-derivative (each so dilute that no temperature change is observable on further dilution) are combined, a readily measurable exothermicity results.

[23] S. G. Smith and S. Winstein, *Tetrahedron*, **3**, 317 (1958).

[24] H. E. Zaugg and R. U. Robinson, unpublished.

[25] Since the concentration of 25 ml. of *n*-butyl halide in 100 ml. of reaction mixture is 2.37 *M* for the bromide (d. 1.299 g./ml.) and 2.20 *M* for the iodide (d. 1.617 g./ml.), the measured rate constants for the iodide alkylations were all multiplied by the factor 1.078 (2.37/2.20) in order to obtain values rightly comparable to the corresponding bromide rate constants.

[26] This means that the iodide alkylation should provide a more sensitive measure of catalytic efficiency than the bromide reaction. Some of the borderline additives of Tables I and II which do not show rate discontinuities (*e.g.*, ethanol and $CH_3OCH_2CH_2OCH_3$) might prove to be relatively more effective in the iodide reaction.

[27] These relationships serve to show that the amides, like dimethyl sulfoxide discussed previously,[22] do not exert their accelerating action through appreciable interaction with the alkyl halides. If they did, these observed regularities, which are independent of the halide, would not be expected. It follows, then, that the effective catalysts must exert their effect by interaction with the sodio-derivative.

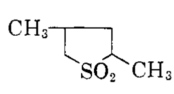
[28] K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, pp. 14–15.

TABLE II

RATES AND ACTIVATION PARAMETERS OF THE ALKYLATION OF DIETHYL SODIO-*n*-BUTYLMALONATE WITH *n*-BUTYL BROMIDE (2.37 *M*)

Additive (A)	Concn. of A, *M*	$k_1 \times 10^5$ sec.$^{-1}$ at 25°	$k \times 10^5$ sec.$^{-1}$ at 37.44°	$\Delta H^{\ddagger}$, kcal. mole^{-1}	$\Delta F_{25°}^{\ddagger}$, kcal. mole^{-1}	$\Delta S_{25°}^{\ddagger}$, cal. mole^{-1} deg.$^{-1}$
None	0	0.83 ± 0.04[a](1.0)[b]	2.11 ± 0.10[c](1.0)[b]	12.9	24.4	−38.4
		0.54 ± .01[d](0.7)	[e]			
A. Miscellaneous inferior additives						
$(C_2H_5O)_2CO$	0.648	0.76 ± 0.11(0.9)	1.96 ± 0.09(1.0)	13.4	24.4	−36.9
$(CH_3)_2CO$	.324	1.13 ± .02(1.4)				
$(C_6H_5)_2CO$	.324	1.00 ± .02(1.2)				
$(C_6H_5)_2CO$	.648	1.09 ± .03(1.3)				
Tetrahydrofuran	.324	2.9 ± .3[f](3.5)				
		0.80 ± .10[g](1.0)				
Tetrahydrofuran	.648	3.5 ± .4[f](4.2)				
		0.93 ± .02[g](1.1)				
$CH_3OCH_2CH_2OCH_3$	.324	2.35 ± .03[h](2.8)				
$CH_3OCH_2CH_2OCH_3$	.648	5.29 ± .07(6.4)				
Pyridine	.324	1.11 ± .05(1.3)				
Pyridine	.648	1.40 ± .05(1.7)				
$(CH_3)_2NCN$	.648	1.42 ± .12(1.7)	3.44 ± 0.07(1.6)	12.5	24.0	−38.8
$(CH_3)_2NCSSCH_3$	.324		2.45 ± .05(1.2)			
$(CH_3)_2NNO$	.324	1.61 ± .05[h,i](1.9)				
		1.26 ± .07[g](1.5)				
2,4-Dimethylsulfolane[j]	.648	3.30 ± .10(4.0)	8.05 ± .15(3.8)	12.6	23.6	−36.8
C_2H_5OH	.324	1.95 ± .04[h](2.3)	4.98 ± .11[h](2.4)	13.3	23.9	−35.6
C_2H_5OH	.648	3.63 ± .48[k](4.4)	9.06 ± .34[k](4.3)	13.3	23.5	−34.1
B. Formamide derivatives						
$HCON(CH_3)_2$[l]	0.324	5.80 ± 0.10[m,n](7.0)	13.98 ± 0.15[a](6.6)	12.4	24.2	−39.6
$HCON(CH_3)_2$	0.648	15.5 ± .4[h](19)	43.4 ± 1.0[h](21)	14.6	22.7	−27.0
$HCON(CH_3)_2$	1.296	42.6 ± 1.4[k](51)				
$HCON(CH_3)C_6H_5$	.324	2.14 ± 0.04[o](2.6)	4.83 ± 0.10(2.3)	11.5	23.8	−41.5
$HCON(C_6H_5)_2$	.324	2.46 ± .08(3.0)	6.43 ± .09(3.1)	13.6	23.7	−34.0
$HCON(CH_2)_4$[p]	.324	8.09 ± .11[h](9.7)	19.6 ± .2[h](9.3)	12.5	23.0	−35.4
$HCON(CH_2)_5$[q]	.324	5.02 ± .09[k](6.0)	12.8 ± .15[h](6.1)	13.3	23.3	−33.6
$HCON(CH_2)_4O$[r]	.324	3.81 ± .03[h](4.6)	9.95 ± .07[h](4.7)	13.6	23.5	−33.1
C. N,N-Dimethylacetamide and variants						
$CH_3CON(CH_3)_2$	0.162	2.86 ± 0.04[h](3.4)				
$CH_3CON(CH_3)_2$	.324	7.24 ± .07[h](8.7)				
$CH_3CON(CH_3)_2$	.648	18.9 ± .6(23)				
$CH_3CON(CH_2)_4O$[s]	.324	3.83 ± .05(4.6)				
$CH_3CSN(CH_2)_4O$[t]	.324	3.76 ± .30(4.6)				
$CF_3CON(CH_3)_2$	.324	1.39 ± .02(1.7)				
$(CH_3)_3CCON(CH_3)_2$	.324	3.41 ± .05(4.1)				
$(CH_3)_3CCON(CH_3)_2$	.648	9.13 ± .09(11)				
D. Cyclic amides						
1,2,4,4-Tetramethyl-2-pyrroline-5-one[u]	0.648	2.45 ± 0.10(3.0)	6.03 ± 0.15(2.9)	12.7	23.7	−37.1
N-Vinyl-2-pyrrolidone	.648	5.14 ± .11 (6.2)	12.6 ± .3(6.0)	12.7	23.3	−35.7
N-Methyl-2-pyrrolidone	.648	25.3 ± .7[h](30)	61.9 ± 2.0[h](29)	12.7	22.4	−32.5
N-Methyl-2-pyrrolidone	.324	9.18 ± .12[k](11)				
N-Methyl-2-piperidone	.324	8.21 ± .15[k](9.9)				
N-Methyl-ε-caprolactam	.324	6.25 ± .06[k](7.5)				
N-Methyl-2-pyridone	.324	12.9 ± .3(16)	34.4 ± 1.5(16)	14.0	22.8	−29.5
N-Methyl-2-pyridone	.648	49.5 ± 1.4(60)	138 ± 3(65)	14.5	22.0	−24.9
E. Miscellaneous additives						
$C_6H_5CON(CH_3)_2$	0.324	5.14 ± 0.04(6.2)				
$C_6H_5CON(CH_3)_2$	.648	14.7 ± .19(18)				
$(CH_3)_2SO$[v]	.324	12.17 ± .16[k](15)	38.9 ± 1.3(18)	16.6	22.8	−20.8
Pyridine N-oxide	.324	15.15 ± .2(18)	43.3 ± 0.9(21)	14.9	22.7	−26.0
$[(CH_3)_2N]_3PO$	.324	44.9 ± 1.4(54)	111 ± 3(53)	12.7	22.0	−31.2

[a] Average of five runs. [b] Relative rates (in parentheses) = $k_1/0.83 \times 10^{-5}$ for reactions at 25° and $k_1/2.11 \times 10^{-5}$ for reactions at 37.44°. [c] Average of four runs. [d] Measured rate between 35% (point of discontinuity) and 60% of reaction. In one run starting with 0.229 M sodio-derivative (twice the usual starting concentration) k_1 (25°) proved to be $0.78 \pm 0.01 \times 10^{-5}$ sec.$^{-1}$ for the first 45% of reaction. This constancy of k_1(0.78 *vs.* 0.83) even with doubled initial concentration, indicates that the first phase of the reaction is truly pseudo-first-order, and probably kinetically homogeneous. Reproducibility of the second phase, however, was poor (k_1 after 45% of reaction = $0.69 \pm 0.01 \times 10^{-5}$ sec.$^{-1}$ for 0.229 M sodio-derivative as compared to 0.54×10^{-5} sec.$^{-1}$ for the lower concentration). [e] Rate at 37.44° was not measured past point of discontinuity. [f] First 13% of reaction. [g] Measured rate after occurrence of the discontinuity. [h] Average of two runs. [i] First 20% of reaction. [j] See formula i below. [k] Average of three runs. [l] Rate constants for two runs using 0.324 M DMF at 15° were 2.74 ± 0.07 and $2.48 \pm 0.04 \times 10^{-5}$ sec.$^{-1}$ (average = 2.61). [m] Average of six runs. [n] After a lapse of 18 months a check run by a different operator gave $k_1 = 5.40 \pm 0.07 \times 10^{-5}$ sec.$^{-1}$. [o] After a lapse of 19 months a check run by a different operator gave $k_1 = 2.24 \pm 0.19 \times 10^{-5}$ sec.$^{-1}$. [p] N-Formylpyrrolidine. [q] N-Formylpiperidine. [r] N-Formylmorpholine. [s] N-Acetylmorpholine. [t] N-Thioacetylmorpholine. [u] See formula ii below. [v] Rate constants for three runs using 0.324 M $(CH_3)_2SO$ at 15° were 5.52 ± 0.12, 4.88 ± 0.09 and $5.17 \pm 0.09 \times 10^{-5}$ sec.$^{-1}$ (average = 5.19).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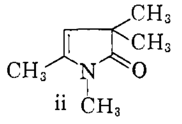
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TABLE III

RATES OF ALKYLATION AT 25° OF DIETHYL SODIO-*n*-BUTYLMALONATE WITH *n*-BUTYL IODIDE (2.37 M)

Additive (A)[a]	Concn. of A, M	$k_1 \times 10^5$ sec.$^{-1}$ for n-C_4H_9I [b]	$k_1 \times 10^5$ sec.$^{-1}$ for n-C_4H_9Br
None	0	1.13 ± 0.03^c(1.0)	0.83(1.0)
$(CH_3)_2NNO$	0.324	$3.28 \pm .05^d$(2.9)	1.61(1.9)
$(CH_3)_2NNO$	.648	$7.50 \pm .11$(6.6)	
$HCON(CH_3)C_6H_5$	.324	$17.0 \pm .16^d$(15)	2.14(2.6)
$CH_3CON(CH_3)_2$	.162	$22.6 \pm .44$(20)	2.86(3.4)
$CH_3CON(CH_3)_2$	.324	$60.1 \pm .5^d$(53)	7.24(8.7)
$CH_3CON(CH_3)_2$	.648		18.9 (23)

[a] Dimethylformamide cannot be used in the iodide alkylation reaction because the sodium iodide formed in the process precipitates in the form of a complex with three molecules of the amide. Consequently, the additive concentration diminishes progressively during the reaction, and the first-order plot takes the form of a smooth asymptotic curve. The additives listed in the Table do not behave in this way. [b] Corrected for purposes of comparison as already explained.[25] To obtain experimental justification for this correction, the kinetic order with respect to n-butyl iodide was determined by measuring the rate (in the absence of additive) at five different concentrations of the iodide. The iodide concentrations used and the corresponding observed first-order rates ($\times 10^5$ sec.$^{-1}$) given in parentheses were: 4.40 M (2.05), 2.20 M (1.05^c), 1.76 M (0.85), 1.32 M (0.68^d) and 0.88 M (0.50^d). The least squares treatment of a plot of concentration *vs.* rate constant gives a straight line of slope 0.97 ± 0.01. Hence, over this fivefold concentration range the reaction is first-order with respect to n-butyl iodide, and the extrapolation[25] to 2.37 M of data observed at 2.20 M is justifiable. Thus the initial rate of alkylation in benzene, as in alcoholic[9] solution, appears to be first-order with respect to both the alkyl halide and the sodio-derivative (*cf.* Table II, footnote *d*). [c] Average of six runs. [d] Average of two runs.

orders; the borderline compounds, ethanol and dimethoxyethane, have orders approximating unity; the next five, representing a structural cross-section of the amide group, show an approximate three-halves order; and, finally, N-methyl-2-pyridone is the sole example of a second-order concentration dependency. As the expected consequence of this variation of order, comparisons of inter-group differences are more striking at unit than at lower concentrations. The poor additives are even poorer and good ones are much better in comparison (*e.g.*, the ratio of N-methyl-2-pyridone activity to dimethylformamide activity is 4 to 1 at unit concentration, but only a little better than 2 to 1 at the 0.324 M level). Similar ratios for dimethylformamide *vs.* ethanol are 6 to 1 at 1.0 M and 3 to 1 at 0.324 M concentration.

TABLE IV

KINETIC ORDER OF ADDITIVE PARTICIPATION

Additive	Relative rate[a] 0.324 M	Relative rate[a] 0.648 M	Order (n)	Rel. rate 1 M (calcd.)
A. n-Butyl bromide				
$(CH_3)_2CO$	1.2	1.3	0.12	1.4
Pyridine	1.3	1.7	0.33	1.9
Tetrahydrofuran	1.0	1.1	0.22	1.2
C_2H_5OH	2.3	4.4	0.90	6.4
C_2H_5OH (37°)	2.4	4.3	0.86	6.3
$CH_3OCH_2CH_2OCH_3$	2.8	6.4	1.17	10.6
$(CH_3)_3CCON(CH_3)_2$	4.1	11	1.43	20
$C_6H_5CON(CH_3)_2$	6.2	18	1.51	34
$HCON(CH_3)_2$	7.0	19	1.44[b]	36
$HCON(CH_3)_2$ (37°)	6.6	21	1.63	42
$CH_3CON(CH_3)_2$	8.7	23	1.36[c]	41
N-Methyl-2-pyrrolidone	11	30	1.46	57
N-Methyl-2-pyridone	16	60	1.94	141
N-Methyl-2-pyridone (37°)	16	65	2.00	153
B. n-Butyl iodide				
$(CH_3)_2NNO$	2.9	6.6	1.19	11.6
$CH_3CON(CH_3)_2$	53	..	1.41[d]	294

[a] At 25° unless otherwise specified. [b] The rate constant for 1.296 M concentration (Table IIB) was also used in calculating this order. [c] The rate constant for 0.162 M concentration (Table IIC) was also used in calculating this order. This shows that, for dimethylformamide and dimethylacetamide, the participation order is relatively constant (1.36, 1.44) over the 8-fold concentration range 0.162 to 1.296 M. [d] The rate constant for 0.162 M concentration (Table III) was used in calculating this order.

The relative constancy of participation orders exhibited by the five amides of the third group deserves mention. The range (1.36 to 1.51 at 25°) is very likely within the limits of experimental error, so that individual differences within this group are probably of little significance. These orders are still close enough to each other so that relative rates corrected to unit concentration fall in the same numerical order as do the relative rates (at 25°) at either 0.324 or 0.648 M concentration. Hence, it is safe to conclude that, from the observed rates, mutual comparisons of catalytic efficiencies of amides can be made at any of the concentrations used in this study, provided their structures do not differ from one another any more than do those in this group of five amides.

The conspicuous difference in ability of unit concentrations of dimethylnitrosamine and dimethylacetamide to accelerate the butyl iodide reaction (Table IVB) is compatible with the findings summarized in Table III.

The Nature of the Benzene Solution of Sodio-*n*-butylmalonic Ester.—This solution, varying from water-white to pale straw-colored, is visually homo-

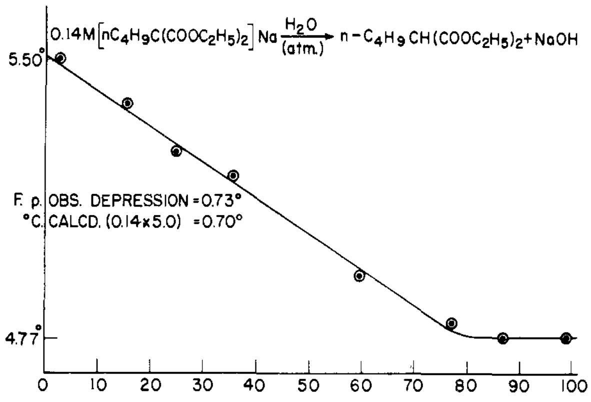

Fig. 2.

geneous. However, the occurrence of aggregation in solutions of electrolytes in low dielectric media, is not uncommon. This possibility was investigated.

Figure 2 illustrates the decrease of freezing point with time, of a stirred 0.14 *M* solution of sodio-*n*-butylmalonic ester in benzene, contained in an open vessel. At the beginning, the freezing point is exactly the same as that of pure benzene; but as the concentration of *n*-butylmalonic ester increases through progressive hydrolysis (by atmospheric moisture) of the sodio-derivative, the freezing point approaches its theoretical minimum.[29] Taking the sensitivity (0.01°) of the temperature measuring device into account, it can be shown by appropriate calculations that the sodio-derivative exists in benzene as an ion-pair aggregate of molecular weight at least 10,000 (association number > 40).[30]

Addition of dimethylformamide, in concentrations comparable to those used in the measurements, to a fresh solution of the sodio-derivative resulted in freezing point depressions proportional only to the concentration of additive.

Another property of this colloidal solution deserves mention. It shows expected slight turbidity in a nephelometer; but doubling the concentration of solute produces little increase in the nephelometric reading. This behavior is characteristic of colloidal solutions in which the suspended particles possess refractive indices very near to that of the solvent. It appears then, that, unless the refractive index of the sodio-derivative itself is coincidentally close to that of benzene, the solution is composed of a *solvated* ion-pair aggregate.

Discussion

From results of the present work, conclusions regarding the mode of action of accelerating substances in this alkylation reaction may be summarized as follows: (1) In benzene solution, the sodio-*n*-butylmalonic ester exists as a solvated ion-pair aggregate of molecular weight at least 10,000. (2) Despite the aggregate nature of this substance, its initial rate of alkylation with an alkyl halide in benzene is first-order with respect to each reactant (*cf.* Table II, footnote *d*, and Table III, footnote *b*). (3) The presence of certain polar substances (*e.g.*, disubstituted amides and coördinate covalent compounds) in fairly small amounts (<10%) results in marked acceleration of the reaction of this sodio-derivative with *n*-butyl bromide and *n*-butyl iodide; the acceleration for the iodide reaction is about 8 times that for the bromide alkylation. In contrast, many other polar additives produce negligible effects on these rates. (4) Among effective additives, the comparable rate increases vary with the nature of the additive, and this variation is quantitatively the same for both the bromide and iodide alkylations. (5) The acceleration is not produced by a reduction in activation energy of the rate-controlling step. On the contrary, in one instance (dimethyl sulfoxide) of marked acceleration the activation energy is perceptibly increased. (6) As a consequence of (4)[27] and (5)[22] it is evident that the acceleration arises from interaction of the effective additive with ion-pair aggregate and not with the alkyl halide. Participation orders of different effective additives vary between the values one and two but indications are that the order of interaction for a given additive remains essentially constant with increasing concentration up to at least 1.296 *M*.

These findings are consistent with the following picture of additive action: in benzene alone or in the presence of an ineffective additive, the rate-determining step is different from that in the presence of an effective additive. The rate of the uncatalyzed reaction must be controlled in some manner by the aggregate nature of the sodio-derivative. Whether the dominant factor is the rate of reaction at a particulate surface, or the rate of diffusion of the halide through a micellar structure, or the rate at which lower order "soluble" species are formed by cleavage from the aggregate, can only be conjectured. But, whatever the controlling step may be, the kinetic character of its initial phase is remarkably homogeneous.

In the presence of an effective additive, the reaction rate is no longer governed by the particulate nature of one reactant, but rather by the concentration of a solvated ion-pair species, in equilibrium with the ion-pair aggregate and uncombined additive (solvent). The reaction kinetics then become truly homogeneous as the normal halide displacement step becomes rate-determining. In contrast to the uncatalyzed reaction, *n*-butyl iodide, under comparable circumstances, now reacts eight times faster than *n*-butyl bromide irrespective of the nature or concentration of the effective additive (Table III). The slow step no longer depends on the potentially variable character of a molecular aggregate. Consequently, the catalyzed reaction, unlike the uncatalyzed bromide

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[29] Since the solution of the sodio-derivative was prepared in the same way as described (see Experimental) for the preparation of the stock solutions used in the rate determinations, this freezing point behavior clearly shows that practically no free *n*-butylmalonic ester was present at the beginning of any of the rate determinations.

[30] Apparently, this sodio-derivative falls into the electrolyte classification denoted by Kraus[31] as type 2, in which one ion is large and the other is small. Unlike the other two types in his classification, type 2 shows a particular tendency to agglomerate in benzene and form ion-pair aggregates of high association number [*e.g.*, $(i\text{-}C_5H_{11})_4NSCN_4$ in benzene solution reaches an association number of 26 at 0.14 *N* concentration].

[31] (a) C. A. Kraus, *J. Chem. Ed.*, **35**, 330 (1958); (b) *J. Phys. Chem.*, **60**, 129 (1956).

reaction, exhibits smooth pseudo-first-order behavior throughout virtually its entire course.

Differences in catalytic efficiency among the effective additives can be pictured as arising from differences in the equilibrium between the aggregated and the solvated ion pair species. The larger accelerations brought about by the best catalysts result from higher steady-state concentrations of the solvated species, which in turn derive from larger values of the equilibrium constants.[32]

Because the participation orders of the effective additives vary somewhat, and often exhibit nonintegral values (Table IV), mathematical interpretation of the mechanism of solvent action is not possible without employing many unwarranted assumptions. Nevertheless, further qualitative considerations indicate that some form of specific solvation must be operative.

In the first place, the best catalysts, among the fairly wide spectrum of polar compounds tested, are restricted to the two groups: disubstituted amides and coordinate covalent N-, P- and S-oxides; and in the second, not one of these substances displays a participation order less than one in any of the concentration experiments conducted. This means that whatever the mode of solvation may be, the effective additives interact with the aggregate in an average stoichiometric ratio of at least one molecule of additive per ion-pair.

A better understanding of the possible nature of these specific solvent effects can be reached by considering some of the known properties of electrolyte solutions in benzene. As already noted,[30] Kraus[31b] has shown that "the ion dipoles of all salts having one large and one small ion are all [*sic*] highly associated" in benzene solution. These are so-called type 2 electrolytes. In contrast, type 3 electrolytes, having two large ions, show little tendency to associate in benzene beyond the quadrupole stage (association number $\lesseqgtr 2$).

Now, according to Streitwieser[33] "anions and cations require different solvating characteristics: hydrogen-bonding solvents make good anion solvators; solvents containing atoms having unshared electron pairs such as oxygen and nitrogen make relatively good cation solvators." The effective catalysts of the present work all fall into the latter category. Therefore, it is reasonable to assume that they solvate the sodium ion preferentially thereby increasing its effective size The solvated sodio-derivative now contains two large ions. In short, specific solvation of the sodio-derivative by these additives transforms a type 2 to a type 3 electrolyte, which, whatever the reason may be, no longer can exist in its original highly associated form.[34]

This still does not explain why many other additives, also containing unshared electron pairs, exert little, if any, effect on the alkylation rate. The problem of structure–activity relationships among these additives is the subject of the following paper.

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(32) This explains why dimethyl sulfoxide can accelerate the reaction despite an augmented activation energy. The extent of equilibrium shift, resulting from the unusually stable solvate with this substance,[22] more than compensates for any retardation of the rate-controlling step produced by an increase in its activation energy.

(33) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 605 (1956).

(34) The possibility of the existence in these experiments of kinetically significant concentrations of free ions has been ignored for several reasons. According to Ingold[35] 'two univalent counter-ions attract each other in benzene, with an energy equal to the mean kinetic energy of either along a line, at a separation of 500 Å.; they haul each other in from such distances." Again, Grunwald[36] has shown from a consideration of the potential energy function of a uni-univalent electrolyte, that even in a dilute solution in a medium of dielectric constant as high as 20, ion-pairs possess considerable stability relative to the separately solvated ions: Brändström[20] has shown kinetically that even in alcoholic solutions of 1 *M* concentration the alkylation of the sodium derivative of acetoacetic ester by methyl iodide is nearly a pure ion-pair reaction. Finally, Zook and Rellahan[4] and Hauser and co-workers[5] have found evidence to indicate the virtual absence of free ions in ethereal solutions of sodio-ketones.

(35) C. K. Ingold, *Proc. Chem. Soc.*, 281 (1957).

(36) E. Grunwald, *Anal. Chem.*, **26**, 1696 (1954).

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Specific Solvent Effects in the Alkylation of Enolate Anions. II. Relationships between Structure and Physical Properties of Additives and Their Catalytic Efficiencies

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The ultraviolet behavior of N-methyl-2-pyridone in the presence of sodio-*n*-butylmalonic ester has been studied. Relative basicities of a number of additives have been estimated by titration with perchloric acid in acetic anhydride. Wave lengths of the infrared carbonyl-stretching bands of a group of amide additives have been determined. Molar refractions of a structural cross-section of the amides have been measured. These physical properties, taken together with currently available knowledge of the stereoelectronic nature of many of these additives, have been correlated with catalytic activity in the alkylation reaction. It appears that the presence of a region of high π-electron density is of critical importance in determining the accelerating action of an additive on the alkylation reaction.

In the accompanying paper,[1] evidence was presented which indicates strongly that acceleration of the rate of alkylation in benzene of sodiomalonic esters, by addition of small quantities of certain additives, is brought about, basically,[2] by specific solva-

(1) H. E. Zaugg, B. W. Horrom and S. Borgwardt, This Journal, **82**, 2895 (1960).

(2) The double meaning is intended.