Limitations for the Addition of Amides to Formaldehyde and Glyoxal[1]

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Factors which limit the addition of amides to formaldehyde and glyoxal, particularly in base-catalyzed reactions, are considered for several types of amides, *e.g.*, imides, carboxylic acid amides, carbamates, and ureas. Complete substitution of all amido hydrogens available is generally limited by steric effects or by low amide acidity in some cases. The additions of imides to formaldehyde or glyoxal in alkaline media are often thwarted in practice because of hydrolysis of the imide. The addition products, if formed, are also susceptible to hydrolysis. However, some imide–aldehyde addition products may be isolated from mild acidic or base-catalyzed reactions. Complete substitution of all amido hydrogens available becomes more general if cyclization occurs during addition to the aldehyde or if a cyclic amide with nitrogen in the ring, rather than an *N*-alkyl amide, acts as nucleophile.

The reversible addition of amides to aldehydes, especially formaldehyde, to produce *N*-hydroxymethylamides (or *N*-methylolamides) has received much attention as noted in recent reviews.[3,4] Aqueous, basic conditions are usually favored for these additions because acidic catalysis is ineffective or causes the formation of other products in subsequent, rapid reactions.

Addition of unsubstituted amides (eq 1, R = H) to glyoxal to form *N*,*N*′-dihydroxyethylenebisamides

$$2\text{-NHR} + (\text{CHO})_2 \rightleftharpoons \text{-NRCHOHCHOHNR-} \quad (1)$$

is also fairly general;[5] however, the addition of N-substituted amides (eq 1, R ≠ H) is limited.[5,6]

Limiting factors for base-catalyzed addition are considered to be steric effects and low amide acidity.[7] These factors can either prevent additions or result in a slow reaction, thereby allowing the competing Cannizzaro reaction to consume base and reduce the pH of the solution. In this work a number of "substituted" amides will be studied in additions to glyoxal or formaldehyde. Imides are of particular interest because, in general, they possess highly acidic protons compared to other amides.

The addition of imides to formaldehyde has received some attention in the past, whereas addition to glyoxal has not. *N*-Methylol derivatives have been prepared in high yields from formalin and phthalimide (pH 3–4) at the boil,[4] and from maleimide[8] or succinimide[9] and aqueous formaldehyde with a small amount of base present. Further, it was suggested that the imide ring in maleimide was sensitive toward strong bases.

In general, attempts were made to study the additions of phthalimide, maleimide, succinimide, or diacetamide to formaldehyde (formalin) (a) with no base added (pH 3.1–4.0), (b) under mild basic catalysis, *i.e.*, sodium hydroxide added until the pH was about 5, and (c) under basic conditions where sodium hydroxide was added until the pH was between 8 and 10. Reactions were generally performed at room temperature, except with phthalimide, where heat was required to dissolve the materials. Additions under similar conditions were attempted with the imides and glyoxal. In case a only *N*-methylolphthalimide and *N*-methylolsuccinimide were formed. In case b high yields of *N*-methylol derivatives were obtained from solutions containing formaldehyde and phthalimide, maleimide, or succinimide. Hydrolysis of the imide or the *N*-methylolimide appeared to be negligible at pH 5. Formation of *N*-methyloldiacetamide did not occur at pH 3–4 or with base added (pH 5).

In case c hydrolysis of the imide was a problem when attempts were made to maintain the reaction mixture of imides and formaldehyde at a pH of 8 to 10 and only *N*-methylolsuccinimide was isolated.

When aqueous solutions of *N*-methylol derivatives of phthalimide, maleimide, or succinimide were adjusted to a pH of 8–10 with sodium hydroxide, the *N*-methylolimides appeared to hydrolyze in the same manner as the unsubstituted imides. The pH for solutions of *N*-methylolmaleimide or *N*-methylolphthalimide (heated) fell rapidly whereas a pH in the range of 8–10 was easily maintained by a solution of *N*-methylolsuccinimide.

Therefore, cyclic imides, in general, act as good nucleophiles in their addition to formaldehyde. However, in systems about pH 7 or higher, hydrolysis of the imide or *N*-methylolimide was often rapid and these conditions for synthesis and isolation of a pure product were generally impractical. The failure of diacetamide to add to formaldehyde is puzzling. Apparently, this linear imide and formaldehyde develop an unfavorable steric interaction, which is not present in additions with cyclic imides, and the addition is prevented.

The addition of imides to glyoxal was limited to base-catalyzed additions of maleimide and succinimide. No additions were successful without base present. The imide–glyoxal addition products which formed from maleimide and succinimide were highly insoluble. Evidently these materials formed and precipitated before much hydrolysis occurred. Yields were low, pH control was difficult, and no specific procedure is expected to yield reproducible results for addition of imides to glyoxal solutions. No addition products from phthalimide or diacetamide and glyoxal under acidic or basic conditions were encountered. These results are in agreement with the prior general success of additions of N-substituted amides to formaldehyde[7]

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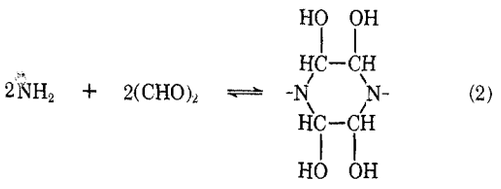
TABLE I

Compd	Mp, °C[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
N,N'-Dihydroxyethylenedisuccinimide	184.5–186	46.88	4.72	10.93	46.99	4.78	11.05
N,N'-Diacetoxyethylenedisuccinimide	~250	49.41	4.74	8.23	49.10	4.56	8.52
N,N'-Dihydroxyethylenedimaleimide	172–173.5	47.63	3.20	11.11	47.58	3.23	11.08
N,N'-Dihydroxyethylenebis(ε-caprolactam)	144–145	59.13	8.51	9.85	58.94	8.65	9.83
N,N'-Dihydroxyethylenebis(methoxyacetamide)	151–153	40.63	6.82	11.85	40.21	7.08	11.88

[a] All compounds displayed signs of decomposition on melting.

compared to the limited successful additions of N-substituted amides to glyoxal.

Similar problems exist which limit additions of amides (other than imides) to glyoxal. For example, cyclizations of *N,N'*-alkylenebisamides with glyoxal to form dihydroxyimidazolidines or dihydroxypiperazines are limited to selected bisamides.[5] Further, the



(2)

cyclization of primary amides with glyoxal to form tetrahydroxypiperazines is limited to formamide and sulfonamides.[5,6,10] The inability of other strongly acidic primary amides and glyoxal to cyclize, as shown in eq 2, has been noted in this and prior[6,10] work. Methoxyacetamide and glyoxal produced only the linear adduct and is another example of an acetamide, substituted with an electron-withdrawing group, which failed to cyclize with glyoxal. It is noted that the linear adduct is not generally isolated in high yield in those reactions which allow formation of the cyclic product.

Limitations for the addition of ureas to formaldehyde and glyoxal follow an interesting pattern. Under the reaction conditions used in this study, urea adds to an excess of formaldehyde to form only the trimethylol derivative. However, if cyclization is allowed to occur and a uron[11] is formed, then urea effectively adds with ease to 4 mol of formaldehyde. Similarly, urea adds to four aldehyde moieties in the formation of the commercially important 1,3-bis(hydroxymethyl)-4,5-dihydroxy-2-imidazolidinone as, again, cyclization occurs (with glyoxal) and urea substitutes at all four positions.

This pattern continues with *N,N'*-dimethylurea and its cyclic (alkylated) counterpart, 2-imidazolidinone, in that 1 mol of 2-imidazolidinone adds readily to 2 mol of formaldehyde, whereas the alkylated, linear urea adds to only 1 mol of formaldehyde. Similarly, *N,N'*-dimethylurea adds readily to two aldehyde moieties when it cyclizes with glyoxal to form the substituted 2-imidazolidinone.[12]

In the addition of N-substituted monoamides to glyoxal (eq 1, R ≠ H) to form linear *N,N'*-dihydroxyethylenebisamides, only the lactam, 2-pyrrolidone, reacted readily with glyoxal. ε-Caprolactam has been found to be less reactive to formaldehyde than 2-pyrrolidone,[13] and some difficulty was encountered in this present work in obtaining addition of ε-caprolactam to glyoxal. Nevertheless, as noted in this paper and references herein, the ability of cyclic amides (ureas, 2-oxazolidone,[14] lactams, and imides) to undergo a high degree of addition to formaldehyde or glyoxal is significant. By comparison the inability of many similar linear N-alkyl substituted amides (ureas, carbamates, and carboxylic acid amides) and linear imides to undergo a high degree of addition (no addition in some cases), certainly indicates a great dependence upon steric effects in these additions.

Experimental Section[15]

A general procedure for attempted imide–aldehyde additions was to mix the reactants at room temperature in stock, aqueous solutions of about 40% formaldehyde or glyoxal. Molar ratios were 1:1 for imide–formaldehyde additions and 2:1 for imide–glyoxal additions. Distilled water was added to the mixture on occasions where it was needed to dissolve the imide or to provide a fluid mixture. The reactants were either left at the pH of the mixture (about 3.1–4), adjusted to a pH of 5.0–5.2 with 20% sodium hydroxide, or adjusted to a pH of about 9 with more sodium hydroxide. The procedures varied widely at this point depending upon conditions and are best discussed under a particular reaction. However, before providing these details, a comparison should be made of the drop in pH above 7 due to imide hydrolysis and the Cannizzaro reaction. Essentially no drop in pH was noted in a 30-min period for formalin or 40% glyoxal adjusted to pH 8–9 at room temperature. At room temperature, aqueous solutions of maleimide and diacetamide adjusted to pH 9–10 decresed rapidly in pH to about 7 or less in 30 min. A heated solution of phthalimide decreased in pH at an even faster rate. On the other hand, the pH of aqueous succinimide in the 8–9 range was constant for 30 min at room temperature. This rapid hydrolysis of the imides, except succinimide, limited potentially successful additions at pH 8–10 to very fast additions at room temperatures. Otherwise, hydrolysis products would be formed which would compete for the aldehyde.

Phthalimide–Formaldehyde.—*N*-Methylolphthalimide is prepared in high yield by heating the reactants (no adjustment in pH) for several minutes on a steam bath. This is the usual procedure for the synthesis of this material.[3,4]

A similar addition at pH 5 (with added water) produced a solution with some solids on heating to 75°. Upon filtration and cooling, *N*-methylolphthalimide was obtained. The melting point of crude product was 143°. The pH of the filtrate was unchanged.

Similar additions at pH 8–10 were attempted with no *N*-methylolphthalimide obtained. Addition of base to the heated solution was followed by a decrease in pH and unreacted phthalimide was recovered. If the pH was allowed to fall after the original adjustment at room temperature to pH 8–10, *N*-methylolphthalimide (mp 145–146°) was obtained in high yield after the mixture had stood at room temperature for several

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(15) All the melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus. Room temperature was 24–25°. Nmr spectra were obtained with a JEOLCO MH-60-II spectrometer. Chemical shifts are reported in hertz downfield from TMS as internal standard. Elemental analyses on new compounds are reported in Table I. DMSO stands for dimethyl sulfoxide.

months (the pH had decreased to 4.4 during this period): nmr (DMSO-d_6) 4 H singlet 471.5 Hz, 1 H triplet 384 Hz (J = 6 Hz), 2 H doublet 298 Hz (J = 6 Hz).

Succinimide–Formaldehyde.—*N*-Methylolsuccinimide was obtained from solutions at pH 3.6, 5.1, and 8–10. For example, the imide and formalin were mixed and the pH was adjusted to 5.0. The mixture was stirred for 30 min, at which time there was complete solution. After 24 hr the pH was 4.8. Water was removed under vacuum on a rotary evaporator at 40° to produce an almost quantitative yield of crude product which crystallized slowly: mp 53–61° [one recrystallization from ethyl acetate raised the melting point to 62–64.5° (lit.[9] mp 66°)]; nmr (DMSO-d_6) 1 H triplet 371 Hz (J = 7.1 Hz), 2 H doublet 282.5 Hz (J = 7.1 Hz), 4 H singlet 157 Hz.

The addition of succinimide to formaldehyde at pH 8–10 was followed closely using nmr and observing changes in pH. Formalin was adjusted to pH 9.5 with dilute NaOD and left overnight. The pH fell to 9.0. Succinimide was partially dissolved in a minimum of D_2O with a slight amount of heat and 1 molar equiv of formaldehyde (pH 9.0) was added. The pH immediately fell to about 7. NaOD was added to increase the pH to 8.7 and the undissolved imide went into solution almost immediately. A spectrum was obtained rapidly. There was no evidence of free formaldehyde in the solution and the pH had increased from 8.7 to 9.3. The spectrum was identical with that of *N*-methylolsuccinimide prepared as directed above at pH 5. The sample of *N*-methylolsuccinimide at pH 9.3 was heated in the nmr spectrometer to 62°. No change was observed except for movement of the HOD peak. To this sample at 62° was added 2–3 drops of 40% NaOD. New peaks occurred rapidly and stopped growing as the pH fell below 7 in about 15 min. Only a slight trace of free formaldehyde was noted. The new peaks were believed to have formed from *N*-methylolsuccinamic acid, because the same pattern of peaks was obtained from heating succinamic acid and formaldehyde at pH 9.

Maleimide–Formaldehyde.—*N*-Methylolmaleimide was obtained from solutions at pH 5.1. After stirring for about 5 min there was an exotherm. The solution was stirred for 30 min and cooled to room temperature, and the product was precipitated. After one recrystallization from ethyl acetate, the product melted at 102–103° (lit.[8] mp 104–106°): nmr (DMSO-d_6) 2 H singlet 421 Hz, 1 H triplet 374 Hz (J = 7.1 Hz), 2 H doublet 287.5 Hz (J = 7.1 Hz).

Reaction at pH 3.1 with or without heating appeared to be questionable—no reaction occurred or it was very slow. In reactions at pH 8–10 only the unreacted imide was isolated. The pH fell rapidly and no attempt was made to maintain the pH in this range.

Diacetamide–Formaldehyde.—The desired addition did not appear to occur under the general conditions at pH 4, 5.1, or 8–10. Unreacted diacetamide was the only product recovered. For those mixtures adjusted to pH 8–10, it was noticed that the pH decreased on standing. A second series of experiments was performed at pH 3 (dilute hydrochloric acid added), 4, 8, and 10 and was followed by nmr. No evidence of the formation of *N*-methyloldiacetamide was encountered.

Acetamide–Formaldehyde.—The addition of acetamide to formaldehyde at pH 9 at 30° was followed by nmr, but the chemical shifts of the peaks of the products and reactants were quite close. The addition appeared to be going very slowly compared to imide–formaldehyde additions. This conclusion was confirmed by titration of the solution for free formaldehyde.[7]

Imide–Glyoxal.—Glyoxal solutions often do not provide a reaction system from which reproducible data can be obtained. This appears to be especially true in those cases when a slow addition of an amide is attempted under basic conditions.[5] The general procedures for imide–aldehyde additions were attempted but in no case was an addition product from phthalimide or diacetamide produced. Heating solutions of phthalimide or diacetamide and glyoxal was also ineffective.

Addition of succinimide or maleimide to glyoxal in the presence of base was achieved; however, results were not reproducible for various glyoxal solutions. Procedures for the synthesis of these addition products are given below.

***N,N'*-Dihydroxyethylenedisuccinimide.**—To 10 g of succinimide were added 50 ml of water and 13.6 g of 40% glyoxal. The pH was adjusted to 8–9 with dilute NaOH. Crystallization of the product commenced with 1 hr. After standing for 3 days, the solution was filtered and the solids were collected and washed with water and then with absolute ethanol. The product melted at 182.5–184.5° dec, yield 24%. The crude compound decomposed easily and attempts to recrystallize it from alcohol caused reversal to the starting materials. Recrystallization from dimethyl sulfoxide raised the melting point to 184.5–186°.

***N,N'*-Dihydroxyethylenedimaleimide.**—To 50 ml of water were added 5 g of maleimide and 3.7 g of 40% glyoxal which had previously been made alkaline (pH 8) with sodium bicarbonate. The desired product crystallized soon after mixing, but additional bicarbonate had to be added to maintain a pH of about 8. After 24 hr at room temperature the mixture, at a pH of 6, was filtered. The precipitate was washed with distilled water and dried over a desiccant, mp 172–173.5° dec, yield 26%.

***N,N'*-(1,2-Diacetoxyethylene)disuccinimide.**—To 3 g of *N,N'*-dihydroxyethylenedisuccinimide were added 50 ml of acetic anhydride and one drop of concentrated sulfuric acid. After standing at room temperature for 1 hr with no apparent change, the mixture was heated slowly to 95° at which point the solids dissolved. The solution was allowed to cool and was left at room temperature overnight. Solids were filtered off and dried, mp 250–260° dec.

Effect of Basic Media on *N*-Methylolimides.—Methylolated imides exhibited a tendency to hydrolyze which paralleled the parent imides. *N*-Methylolsuccinimide was stable at pH 7–9 for at least 2 hr, whereas methylolated maleimide and phthalimide (heated to effect solution) hydrolyzed relatively rapidly; *i.e.*, generally the pH decreased from an 8–10 range to below pH 7 in less than the time required to obtain an nmr spectrum (about 5 min).

***N,N'*-Dihydroxyethylenebis(ε-caprolactam).**—To 22.6 g of ε-caprolactam was added 14.5 g of 40% glyoxal. The pH was adjusted to 10 with 20% sodium hydroxide. The solution was left standing for 48 hr, after which time the pH had decreased to 6.7. The initial level of alkalinity was restored and 20 ml of methanol were added. The solution was chilled for a week, and a small batch of crystals, insoluble in DMSO, was obtained, mp 144–145° dec.

***N,N'*-Dihydroxyethylenebis(methoxyacetamide).**—To 17.8 g of methoxyacetamide was added 14.5 g of 40% glyoxal solution. The pH was adjusted to 9 with 10% sodium hydroxide. Product was obtained by filtration after 2 days. Chilling and working up the filtrate resulted in a 50% yield. After recrystallization from ethanol the solids melted at 151–153° with some decomposition. Much of the work reported by Currie, *et al.*,[6] with acidic carboxylic acid amides was performed in this work and the same results were encountered: nmr (DMSO-d_6) 6 H singlet 198 Hz, 4 H singlet 225 Hz, 2 H multiplet 306 Hz, 2 H singlet (broad) 332 Hz, 2 H doublet 446 Hz (J = 8.0 Hz).

Extent of Addition of Ureas to Formaldehyde.—Procedures for titration of free formaldehyde in the presence of the methylolated product in base-catalyzed additions were described previously.[7] A 50% excess over that quantity require for complete methylolation was used. The following values represent formaldehyde reacted for each amido hydrogen theoretically replaceable: urea, 0.74; *N,N'*-dimethylurea, 0.60; 2-imidazolidinone, 1.0; and 4,5-dihydroxy-2-imidazolidinone, 1.0.

Registry No.—*N,N'*-Dihydroxyethylenedisuccinimide, 32854-87-8; *N,N'*-diacetoxyethylenedisuccinimide, 32854-88-9; *N,N'*-dihydroxyethylenedimaleimide, 32969-93-0; *N,N'*-dihydroxyethylenebis(ε-caprolactam), 32969-94-1; *N,N'*-dihydroxyethylenebis(methoxyacetamide), 32969-95-2; phthalimide, 85-41-6; succinimide, 123-56-8; maleimide, 541-59-3; formaldehyde, 50-00-0; glyoxal, 107-22-2.