Synthesis and Characterization of 2-Ureylene-4,6-diamino-*s*-triazines

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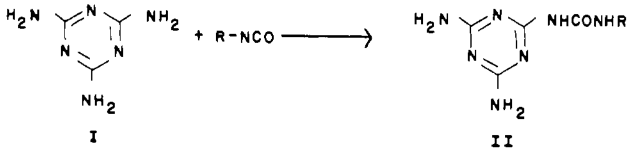
2-Ureylene-4,6-diamino-*s*-triazines were prepared in good yield by reaction of aromatic and aliphatic isocyanates with 2,4,6-triamino-*s*-triazine in dimethyl sulfoxide at 110° C. The products were characterized by detailed interpretation of NMR spectra, elemental analysis, and infrared spectra.

The reaction of equimolar amounts of 2,4,6-triamino-*s*-triazine (melamine) (I) and organic isocyanates to prepare 2-ureylene-4,6-diamino-*s*-triazines (II) was investigated.

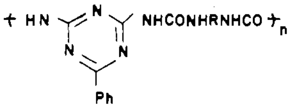


I II

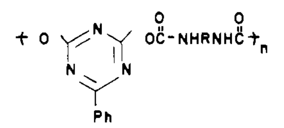
Smolin and Rapoport (*5*) report that I undergoes many reactions wherein the —NH_2 groups function chemically as amido rather than amino groups. Isocyanates are known to react with amides under forcing conditions (*4*). Unlike many reactions of isocyanates with active hydrogen-containing compounds, an effective catalyst for reaction with amides has apparently not been found.

The reaction of isocyanates and isothiocyanates with I to form monoureido-4,6-diamino-*s*-triazines has been reported (*1*). The reaction was effected by reaction of I or its mono salt with cyanates, thiocyanates, isocyanates or isothiocyanates in aqueous solution. The only example given described the reaction of an inorganic cyanate with an aqueous solution of melamine monohydrochloride to yield 2-ureido-4,6-diamino-*s*-triazine (II, R = H).

To circumvent the obvious difficulties of side reactions and low solubility of organic isocyanates in aqueous media, we chose dimethyl sulfoxide (DMSO) as a solvent. The use of this polar aprotic solvent also provided for some solubility of the coreactant, melamine (I), at elevated temperatures and permitted the use of relatively high reaction temperatures at atmospheric pressure. At least 17.5 grams of (I) will dissolve in 100 ml of DMSO at 100° C. Japanese workers reported (*3*) the reaction of diisocyanates with benzoguanamine and 2-phenyl-4,6-dihydroxy-*s*-triazine in DMSO and dimethyl formamide (DMF) to yield intractable polyaddition products formulated as polyureas (III) and polyurethanes (IV), respectively.



III

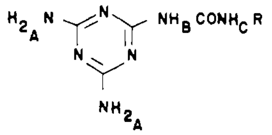


IV

In this investigation a variety of aromatic and aliphatic isocyanates were found to react with I in DMSO at 110° C to give the 2-ureylene-4,6-diamino-*s*-triazines (II) in good yield (Table I). The reaction products were characterized by elemental analysis and infrared and NMR spectra. Although, in general, aliphatic isocyanates are less reactive than their aromatic analogs, under the conditions of the present reaction no distinction in reactivity could be made as judged by product (II) yield. Phenyl isothiocyanate was also reacted with I in DMSO, using equimolar amounts of the reactants under reaction conditions similar to those used for the preparation of IIa through IIf. No identifiable product was isolated.

The reaction of I with organic isocyanates was also examined in several other solvents. When an equimolar mixture of I and *p*-tolyl isocyanate in xylene is refluxed for 5 hours, little if any reaction occurs, as evidenced by the accounting of 79% of the isocyanate as ethyl *N*-*p*-tolyl carbamate. Similarly, an equimolar mixture of I and *n*-butyl isocyanate heated in *o*-dichlorobenzene at 110° C for 6 hours fails to react; I is recovered. *n*-Butyl isocyanate

Table I. Characterization of 2-Ureylene-4,6-diamino-*s*-triazines (II)[a]



II

Compd.	R	Yield, %	M.P., ° C	Empirical Formula	Chemical Shifts, PPM (δ) (TMS = O)[b] H_A	H_B	H_C
IIa	*n*-Butyl	84[c]	287–90	$C_8H_{15}N_7O$	6.80(s,b)	9.21(s,b)	9.47(t,b)
IIb	Allyl	74[d]	276–78	$C_7H_{11}N_7O$	6.74(s,b)	9.23(s,b)	9.60(t,b)
IIc	Cyclohexyl	81[d]	306–09	$C_{10}H_{17}N_7O$	6.72(s,b)	9.14(s,b)	9.40(s,b)
IId	1-Naphthyl	55[e]	>400[f]	$C_{14}H_{13}N_7O$	6.73(s,b)	9.43(s,b)	11.85(s,b)
IIe	Phenyl	73[g]	>400[f]	$C_{10}H_{11}N_7O$	6.80(s,b)	9.22(s,b)	11.78(s,b)
IIf	*p*-Tolyl	66[g]	>400[f]	$C_{11}H_{13}N_7O$	6.79(s,b)	9.10(s,b)	11.61(s,b)

[a] Elemental analyses for C, H, and N have been reviewed and are in accord with theory. [b] s,b = singlet, broad; d,b = doublet, broad; t,b = triplet, broad. [c] Recrystallized from DMF, 5 g/35 ml. [d] Recrystallized from DMSO, 5 g/10 ml. [e] Recrystallized from DMSO, 5 g/35 ml. [f] Underwent partial sublimation. [g] Recrystallized from DMSO, 5 g/40 ml.

(84%) was accounted for as the mixed urea with *p*-toluidine. I is essentially insoluble in both xylene and *o*-dichlorobenzene at elevated temperatures.

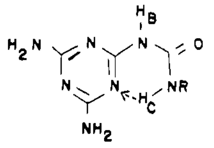
The 2-ureylene-4,6-diamino-*s*-triazines (II) are white solids, insoluble in common organic solvents. They dissolve to varying degrees in DMF and DMSO on heating. The 2-ureylene-4,6-diamino-*s*-triazines (IId, IIe, and IIf) prepared from 1-naphthyl isocyanate and aryl isocyanates, respectively, failed to melt below 400° C; partial sublimation, however, was observed above 300° C.

Recently, a phenylureido-*s*-triazine (IIe) was prepared from melamine and a mixture of urea and aniline (*2*). The reaction was heated at 225° to 235° C for 20 minutes to give a 90% yield of a product claimed to be IIe, melting with decomposition at 305° to 306° C. The above reaction was repeated and gave an 80% yield (based on starting I) of a white solid that partially sublimed above 300° C, but failed to melt below 400° C. The NMR spectrum of this solid product is the same as that for IIe obtained from the direct reaction of phenyl isocyanate with I.

NMR spectra of the 2-ureylene-4,6-diamino-*s*-triazines (II) in deuterated DMSO at 80° C exhibit the expected patterns for protons associated with alkyl and aryl groups. Elevated temperatures were necessary to achieve and maintain solution of II in deuterated DMSO. The chemical shifts for the various N—H protons are summarized in Table I. Protons (H_A) associated with the two amido-like groups remaining on the *s*-triazine ring give, in all cases, a somewhat broad singlet centered at 6.76 ± 0.04 ppm. The six amido protons of I, under identical conditions, give a similar signal centered at 5.84 ppm.

The protons of the ureylene group (H_B and H_C) give signals below 9.0 ppm. The relatively constant broad singlet at 9.25 ± 0.15 ppm is assigned to the NH proton (H_B) of the ureylene group adjacent to the *s*-triazine ring. This assignment follows from the fact that the remaining downfield signal, subsequently assigned to H_C, shifted with variation of the R group. The direction of shift for H_C coincides with the nature of the R group. In general, the difference (ca. 2.3 ppm) in the position of the H_C proton, when R = alkyl (IIa, IIb, and IIc, Table I) *vs.* R = aryl (IId, IIe, and IIf, Table I) is in agreement for NH protons in similar environments. The signal for H_C is a relatively broad singlet, except where R is an aliphatic group bearing at least one proton on the carbon adjacent to the urea nitrogen. In these cases, a multiplet is observed due in part to interaction with the adjacent methylene or methine protons of the alkyl group (Table I).

In general, the downfield position of the ureido protons H_B and H_C of II is not totally unexpected, particularly if one considers the field position (8.40 ppm, broad singlet) of the two identical NH protons of diphenylurea. However, the rather extreme downfield shift exhibited by the H_C protons associated with the various derivatives (II) requires further explanation. Effects, in addition to those exerted by the adjacent carbonyl and alkyl or aryl groups, must be influencing the field position of the H_C proton. Intramolecular hydrogen bonding, depicted by structure V, and involving proton H_C and a nitrogen atom of the *s*-triazine ring, is cited as a possible major contributing factor.



V

Some evidence that H_C may be bonded was obtained in several cases, from the observation that its field position undergoes little or no change on varying probe temperature and concentration, respectively. The chemical shifts for the H_A and H_B protons did, however, undergo definite shifts when the conditions referred to were changed.

The infrared spectra of the 2-ureylene-4,6-diamino-*s*-triazines (II) were viewed in KBr disks. The region 3100 to 3500 cm^{-1} (NH stretch region) in general exhibited intense broadened bands when compared to the spectrum of I. The region 1500 to 1700 cm^{-1} is complex for II and exhibits a multitude of strong absorptions attributed to the *s*-triazine ring, NH deformation of the remaining amino-*s*-triazine groups, NH bending, and C—N stretch associated with the urea group and the carbonyl of the latter. Sharp bands of medium intensity in the region 1200 to 1500 cm^{-1} were present for all of the 2-ureylene-4,6-diamino-*s*-triazines (II) and may be due to CH, CH_2, etc., of the hydrocarbon moiety of the ureylene group. The *s*-triazine ring also provides for absorption in this region. All of the derivatives of II showed a single relatively sharp band of medium intensity at 805 ± 10 cm.$^{-1}$

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer 457 grating spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The NMR spectra were determined with a Japan Electron Optics Lab 4H-100 using TMS as an internal standard and deuterated DMSO (5% w./v.) as solvent. All NMR spectra were determined at 80° C, except where noted.

The isocyanates were obtained from Eastman Organic Chemicals. The *p*-tolyl, phenyl, and butyl isocyanates were freshly distilled prior to use. Solvents were dried over appropriate reagents and distilled. Melamine (I), obtained from the American Cyanamid Co. (Aero recrystallized grade), was dried in vacuo at 50° C in the presence of phosphorus pentoxide.

Preparation of 2-Ureylene-4,6-diamino-s-triazines (II). A solution of the isocyanate (0.1 mole) in 10 ml of DMSO was added dropwise in 0.5 hour to a stirred slurry of I (0.1 mole) in 50 ml of DMSO at 110° C ± 2°. In practically all cases, the reaction temperature increased several degrees. After addition of isocyanate, the reaction mixtures were maintained at 110° C ± 2° for 6 hours.

In all cases, except that involving phenyl isocyanate, a precipitate was present at the conclusion of the heating period. A precipitate usually began to form during the addition of isocyanate. The cooled reaction mixtures were filtered with suction and the white filter cakes washed consecutively with DMSO and ether. The dried filter cakes accounted for the major portion of crude II, except in the case of the allyl derivative (IIb), when a second crop or crude product (IIb) was obtained by concentrating the DMSO filtrate in vacuo (3 mm, <90° C).

The colorless, essentially clear reaction mixture from phenyl isocyanate and melamine was concentrated to dryness to provide the desired crude monoureylene (IIe).

All of the monoureylenes (II) were recrystallized from boiling DMSO, except the butyl derivative (IIa), which was purified by recrystallization from DMF (Table I). Analytically pure compounds (II) were obtained after drying the recrystallized reaction products in vacuo (<1 mm at 140° C). The melting points, yields, and elemental analyses for II are given in Table I.

ACKNOWLEDGMENT

The authors are grateful to Daniel Swern of Temple University for helpful suggestions concerning the manuscript.

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RECEIVED for review March 13, 1970. Accepted June 29, 1970

Salting Out of Aqueous Procaine Hydrochloride by Sodium Chloride at 25°C

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Aqueous procaine [2-(diethylamino)ethyl *p*-aminobenzoate hydrochloride] and its aqueous mixtures with sodium chloride have been investigated by isopiestic vapor pressure measurements and solubility measurements. Osmotic coefficients and activity coefficients were derived for aqueous procaine to concentrations of 6.5_6m (its solubility at 25°), and for its mixtures with sodium chloride up to $2m$ total concentration. Solubility measurements permitted calculation of activity coefficients in aqueous mixtures saturated with procaine. A solution saturated with both procaine and sodium chloride had a procaine solubility of only 0.03_6m.

Many organic compounds—proteins, for example—are precipitated from their saturated aqueous solutions by the addition of an inorganic salt (*3*). This salting out phenomenon is accompanied by an increase in the activity coefficient of the organic compound. Conversely, there is a decrease in the activity coefficient if the organic compound is made more soluble by salt addition. Solubility and isopiestic data for such ternary systems can both be related to activity coefficients, and recent measurements of both types have been made on aqueous mixtures of sodium chloride and urea (*1*), of potassium chloride and glycine (*2*) and also of sodium chloride and barium chloride (*8*).

Procaine (the anesthetic novocain) is a water-soluble quaternary ammonium chloride, found from preliminary experiments to be strongly salted out by sodium chloride. This system was chosen for study as part of a program designed to investigate the effect of one electrolyte on the solubility of another.

The isopiestic vapor pressure method is ideally suited to the measurement of activity coefficients of involatile solutes in aqueous solutions. Because of the way the free energy of an *N*-component system is altered by changes in system composition, at constant temperature and pressure $N - 1$ cross expressions of the form

$$(\partial \ln \gamma_i/\partial m_j)_{m_{i,k,\ldots}} = (\partial \ln \gamma_j/\partial m_i)_{m_{j,k,\ldots}} \tag{1}$$

can be defined (*4*). If the activity coefficient, γ_i, of one of the components (water in this case) can be measured as a function of composition, there are left $N - 1$ unknown activity coefficients which can be determined from the $N - 1$ cross expressions. The method is exact and depends only on the premise that the free energy is an exact differential. Although this method can in principle be applied to systems containing any number of components, the treatment of the data is difficult and it has so far been applied to solutions containing only one or two solutes.

EXPERIMENTAL

Materials. The reference salt, sodium chloride, was precipitated with hydrogen chloride and dried at 120°. The osmotic coefficients and activity coefficients of this salt were taken from the compilation by Robinson and Stokes (*9*). Reagent grade procaine was recrystallized once from water; a further recrystallization yielded material that gave the same isopiestic results as the first. Both batches, after drying at 110°, had melting points of 156° and contained 99.5 ± 0.5% of the theoretical chloride content.

Isopiestic Apparatus. The apparatus and procedure were described previously (*6*). Equilibrations were made in silver dishes 2.5 cm in diameter. Some of these dishes contained weighed mixtures of dry NaCl (A) and procaine (B) and the other dishes contained NaCl alone or procaine alone.

To start a run, the lids were removed and enough water (about 1 ml) was added to each dish to make solutions of about the desired concentration. The dishes were placed in recesses in a thick copper block which rested in a 10-cm internal diameter dry seal desiccator. The desiccator was slowly evacuated with a water aspirator and then slowly rocked back and forth in a water bath kept at 25.00°, which with the good thermal conductivity of the apparatus ensured good temperature constancy among the dishes. After equilibration for from 2 days for concentrated solutions to 7 days for the most dilute solutions, the lids were again placed on the dishes (this usually took less than 30 seconds) and the concentrations were determined by weight. Once equilibrium had been reached, there was no change in apparent concentrations of the procaine with periods in the desiccator extended up to 10 days, which indicated that the procaine was not decomposing during the equilibrations.

RESULTS AND DISCUSSION

Isopiestic Activity Coefficients. The isopiestic compositions of nine sets of comparisons are given in Table I. The first value for each set under column *m* is the molality of the sodium chloride reference solution; the subsequent values are total molalities in mixed solutions, with the last value referring to binary aqueous procaine. The column headed y_B gives the fraction of the procaine in the mixed solutions—that is, $m_B/(m_A + m_B)$—and the osmotic