Aqueous Solubility of Alkylamino-*s*-triazines as a Function of pH and Molecular Structure

Thomas M. Ward and Jerome B. Weber

Aqueous solubilities of 13 structurally related alkylamino-*s*-triazines were determined over a wide pH range. In general, solubilities of 2-OH, 2-OCH_3, and 2-SCH_3 triazines increased significantly only at pH 3.0 or lower; and of 2-Cl triazines, at pH 2.0 or lower. Results indicated that structural changes at either the 2-position or 4,6-positions significantly affected solubility. Increased solubility was associated with increased basicity of the 2-substituent and decreased size and steric hindrance of the 4,6-*N*-alkyl substituents. Correlations of pK_A values and solubilities at low pH suggest that protonation occurs at the endocyclic nitrogen atoms.

Although *N*-alkyl-*s*-triazine derivatives have found increasing use as herbicides, fungicides, and dyes in recent years, little has been published about their physicochemical properties and behavior, other than a review by Gysin and Knüsli (1960) and certain spectrophotometrically determined ionization constants by Weber (1967). We have initiated a series of investigations by observing the effect of pH and molecular structure on the aqueous solubility of a series of related alkylamino-*s*-triazines. Such a property is significant in both cell entry processes as a function of hydrophilic-lipophilic balance and consideration of whether optimum sorption is attained in ionic or in molecular form.

EXPERIMENTAL

An excess of each triazine was shaken in 100 ml. of distilled, deionized, CO_2-free water, after adjusting to a desired pH by addition of minimum amounts of NaOH or HCl solutions. All pH determinations were made with a Beckman Research Model meter using calibrated glass and calomel electrodes. Samples were shaken in a constant temperature bath at 26° ±0.2° C. for 6 hours, the pH was again adjusted, and shaking continued. Solute concentration determinations were made at 24-hour intervals until four duplicate results were obtained. Aliquots were filtered through a 2.1-cm. disk of Whatman filter paper in a Gooch crucible. Ward and Holly (1966) have shown that *s*-triazines are not adsorbed by cellulose. The concentration of the filtrate was determined by its ultraviolet absorbance, using Beer's law curves for each chemical at each pH. No evidence of supersaturation was observed. Saturated solutions were shaken for 144 hours, but no decrease in concentration by bacterial action was noted. Periodic checks showed the single 6-hour pH adjustment to be sufficient. Each concentration value is the average of four replicas of three different samples. Compounds having a solubility of less than $1 \times 10^{-4} M$ were run five times.

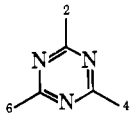
Chemistry Department and Crop Science Department, North Carolina State University, Raleigh, N. C. 27607

RESULTS AND DISCUSSION

Solubility results in Table I are discussed below in three ways: the over-all effect on solubility of the 4- and 6-position substituent, generalizations about the 2-substituent, and the influence of pH on the solubility of individual s-triazines.

Methoxy and methylthio-*s*-triazines, when arranged in order of increasing size and branching of the *N*-alkyl group in the 4 and 6 ring positions, show a general trend of decreasing aqueous solubility at all pH levels. This trend can be attributed to the increased hydrophobic nature of the molecules as a whole as nonpolar substitution occurs. Compounds having two alkyl groups per amine substituent were found to be markedly less soluble than the monosubstituted compounds. The presence of two ethyl groups can cause steric twisting of the amine group out of the plane of the ring and a subsequent decrease in overlap of the lone pair electrons of the amino nitrogen atoms with the π electron system of the ring. The increased conjugation of the monosubstituted triazines causes a greater electron density on the endocylic nitrogen atoms and decreased densities on the alkyl groups. This enhanced molecular polarity can partially account for their greater solubility than the dialkyl substituted amino compounds.

Table I. Molar Aqueous Solubility ($\times 10^{-4}$) of *N*-Alkylamino-*s*-triazines



4-Substituent	6-Substituent	pH	2-OCH_3	2-SCH_3	2-OH	2-Cl
NHC_2H_5	NHC_2H_5		Simatone[a]	Simetryne	Hydroxysimazine	Simazine
		3.0	132	31.7	9.60	0.29
		7.0	119	20.8	0.22	0.25
		10.0	129	21.4	0.25	0.25
NHC_2H_5	NHC_3H_7[b]		Atratone	Ametryne	Hydroxyatrazine	Atrazine
		3.0	90.4	17.8	11.5	1.44
		7.0	76.0	8.57	0.30	1.61
		10.0	77.0	8.46	0.33	1.70
NHC_3H_7	NHC_3H_7		Prometone	Prometryne	Hydroxy-propazine	Propazine
		3.0	44.4	8.53	15.4	0.21
		7.0	30.1	1.67	1.96	0.20
		10.0	29.7	1.73	2.39	0.22
NHC_2H_5	$N(C_2H_5)_2$		Trietatone	Trietatryne	Hydroxy-trietazine	Trietazine
		3.0	10.6	0.74	11.1	1.22
		7.0	1.82	0.09	1.60	1.25
		10.0	1.84	0.09	2.30	1.47
NHC_3H_7	$N(C_2H_5)_2$		Ipatone		Hydroxyipazine	Ipazine
		3.0	13.6		41.2	1.15
		7.0	3.61		30.1	1.13
		10.0	3.71		28.0	1.04
$N(C_2H_5)_2$	$N(C_2H_5)_2$					Chlorazine
		3.0				0.92
		7.0				0.86
		10.0				0.83

[a] Trade names of J. R. Geigy Co.
[b] All C_3H_7 groups are isopropyl.

An opposite trend is observed in the 2-hydroxytriazines, as this class is commonly named, where solubilities increase as *N*-alkyl complexity increases. Infrared spectra (Padgett *et al.*, 1957) and x-ray diffraction studies (Wiebenga, 1952) have indicated that crystalline trihydroxytriazine (cyanuric acid) molecules have a triketo–triamino configuration, while in aqueous solution there is a tautomeric equilibrium between the above keto form (−NHCO−) and an enol form (Cignitti and Paoloni, 1964, Hirt and Schmitt, 1958). The low solubility of the hydroxytriazines in Table I as a whole can be reasonably attributed to strong dipole-dipole attractive forces between the amido groups of adjacent molecules in the solid phase. Further, the increasing trend in solubilities of the hydroxytriazines as alkyl complexity increases is probably due to a decrease in this intermolecular bonding in the solid phase as the bulky alkyl groups block out amido bonding sites.

No adequate explanation, in terms of steric or molecular polarity concepts, can be given for the deviation from the general trends of 2-methoxy- and 2-hydroxy-4-ethylamino-6-diethylamino-*s*-triazines. Ward and Holly (1966) and Gysin and Knüsli (1960) earlier observed the same deviation of these two compounds from general solubility trends.

Solubility data for the 2-chloro compounds show that 4,6-symmetrically substituted *s*-triazines have relatively equal, low solubilities in contrast to the relatively equal but higher solubilities of the unsymmetrically substituted compounds. Differences in molecular symmetry and, therefore, molecular polarity can account for these solubility differences. The solubility similarity of compounds having unlike alkyl substituents (simazine *vs.* propazine) indicates the minor role of the 4,6-substituents in 2-chlorotriazine solubilities. This finding was substantiated in an additional test by the following solubility data for a structurally similar 2-chlorotriazine having an isopropyl group at the 4-position and a normal-propyl group at the 6-position:

pH 3 = $1.73 \times 10^{-4}M$, pH 7 = $1.70 \times 10^{-4}M$, pH 10 = $1.62 \times 10^{-4}M$

A general comparison of the solubility of triazines as a function of different 2-substituents reveals a general change in solubility order of $OCH_3 > SCH_3 > OH$ for compounds with mono-N-C_2H_5 substituents to $OH > OCH_3 > SCH_3$ as the alkyl complexity increases. The low solubility of all chlorotriazines and the dominating influence of symmetry make intraclass comparisons unfeasible.

Weber (1967) has given pK_A values and a decreasing basicity order of four 2-substituted 4,6-bis(isopropylamino)-*s*-triazines as:

OH(5.20) > OCH_3 (4.28) > SCH_3 (4.05) ≫ Cl (1.85)

Table II. Aqueous Solubility ($10^{-4}M$) at Various pH Levels

Chemical	pH 1.0	2.0	3.0	5.0	7.0	10.0
Simazine	5.81	0.78	0.29	0.25	0.25	0.25
Propazine	6.20	0.83	0.21	0.27	0.20	0.22
Prometone		185	44.4	26.5	30.1	29.7
Prometryne		135	8.53	1.73	1.67	1.73
Hydroxypropazine		190	15.4	2.36	1.96	2.39
Ametryne		177	17.8	8.49	8.57	8.46

Table II shows that the solubility of these compounds at pH 2.0 decreases in the same order; hence, the more basic an *N*-alkyl triazine, the more soluble it is in acid solution. A comparison of similar data for the 4-isopropylamino-6-diethylamino-*s*-triazine series of compounds gives a similar correlation. On the other hand, the solubility trend at pH 3.0 of a series of triazines having the same 2-substituent but different alkyl substituents is the exact reverse of their basicity order as found by Weber. He gives a decreasing basicity sequence for three triazines with $-OCH_3$ in the 2-position as:

$$4\text{-}N(C_2H_5)_2\text{-}6\text{-}N(C_2H_5)_2 > 4\text{-}NHC_2H_5\text{-}6\text{-}N(C_2H_5)_2 > 4\text{-}NHC_2H_5\text{-}6\text{-}NHC_2H_5$$

However, Table I shows the third compound to be far more soluble than the second. Data for related 2-methylthio-*s*-triazines also show decreased solubility with increased basicity. Weber's pK_A values and basicity order for hydroxypropazine (5.20) and hydroxyipazine (5.32) agree with the concept that increased basicity results in increased solubility in acid solution (Weber, 1967).

When one considers that pK_A values vary from 5.20 to 1.85 as the 2-substituents change while only from 4.76 to 4.15 as the 4,6-alkylamino substituents change, it seems likely that if basicity alone governs solubility the 2-position is dominant. The present solubility results, on the other hand, indicate that changes in both 2-position and 4,6-positions are equally significant, and at all pH levels. It is apparent that factors other than relative basicity are responsible for differences in the solubility of related *s*-triazines.

Each *s*-triazine investigated has about the same molar solubility at pH 7.0 and 10.0, and a greater solubility at pH 3.0 (Table I), a result not unexpected because of the Lewis base nature of triazines. However, the magnitude of the difference at pH 3.0 varies widely as a function of both the 4- and 6-substituents and the 2-substituent. In an effort to elucidate this behavior the solubility of selected triazines was determined at additional pH levels (Table II). At pH 2.0 there is a sharp increase in solubility of all compounds. The solubility order of 4,6-bis(isopropylamino)-*s*-triazines is $OH > OCH_3 > SCH_3 \gg Cl$. The relatively greater solubility increase of the hydroxy compound with decreasing pH points out both a shift to the enol form and a relatively greater ease of protonation to form soluble species. The fact that a chlorine atom in the 2-position results in low solubility, even at pH 1.0, may be attributed to a lowering of the electron density on the nitrogen atoms at the 1 and 3 ring positions by the electronegative chlorine atom. Although protonation of the triazines can occur at either ring or amino nitrogen atoms, increasing solubility at low pH levels, the similar, small solubility values of the 2-chloro-4,6-bis(ethylamino) and 2-chloro-4,6-bis(isopropylamino) compounds compared to the value of the 2-chloro-4,6-bis-(diethylamino) compound (Table I) indicates that neither the amino nitrogen nor hydrogen atoms are involved in the solubility mechanism. These deductions agree with the spectrophotometric determinations of Hirt and Schmitt, who found that the *s*-triazines, ammeline and ammelide, are protonated at ring nitrogen positions at pH 1. Fisher-Hirshfelder-Taylor structural models of the various species show that the 1- and 3-endocyclic nitrogen atoms are less sterically hindered than other potential protonation sites, including the 5-nitrogen atom.

It is suggested, therefore, that the aqueous solubility process of *N*-alkylamino-*s*-triazines at low pH levels involves protonation of the 1- and/or 3-ring nitrogen atoms with subsequent cation formation and a greater solubility than at higher pH levels. Results indicate that at all pH levels solubility is a function of both the 2-substituent and the complexity of the alkylamino groups at the 4- and 6-positions.

The low solubility of compounds which find use as commercial herbicides (simazine and atrazine) is a determining factor in the method of application. They are most effective when applied to the soil, where they may be taken up by the roots of germinating seeds or plants. Further, the limited solubility of the compounds enhances their adsorption by soil components, particularly the organic fraction (Harris and Warren, 1964).

ACKNOWLEDGMENT

We thank the J. R. Geigy Co. for supplying the *s*-triazines used in this work.

LITERATURE CITED

Cignitti, M., Paoloni, L., *Spectrochim. Acta* **20,** 211 (1964).
Gysin, H., Knüsli, E., *Advan. Pest Control Res.* **3,** 289–358 (1960).
Harris, C. I., Warren, G. F., *Weeds* **12,** 120 (1964).
Hirt, R. C., Schmitt, R. G., *Spectrochim. Acta* **12,** 127 (1958).
Padgett, W. M., Talbert, J. M., Hamner, W. F., *J. Chem. Phys.* **26,** 959 (1957).
Ward, T. M., Holly, K., *J. Colloid Interface Sci.* **22,** 221 (1966).
Weber, J. B., *Spectrochim. Acta* **23,** 458 (1967).
Wiebenga, E. H., *J. Am. Chem. Soc.* **74,** 6156 (1952).

Received for review February 26, 1968. Accepted July 31, 1968. Study supported by Public Health Service research grant ES-00177-01 from the Division of Environmental Health.