Decomposition Pathways of Some 3,6-Substituted *s*-Tetrazines

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The thermal and electron-impact (EI) stabilities of eight 3,6-disubstituted-1,2,4,5-tetrazines were examined. Major EI peaks were also investigated by tandem mass techniques to construct fragmentation pathways. Tetrazine ring structures were not maintained under electron impact ionization nor under conditions of thermal decomposition. Under electron impact, the tetrazines examined shared the same initial fragmentation pathways: elimination of two of the nitrogen atoms as N_2 from the tetrazine ring and cleavage of the remaining N−N bond. This pathway was also applicable to thermal decomposition; however, the main route involved dissociation of the substituent group, in some cases assisted by proton transfer.

Introduction

1,2,4,5-Tetrazine (*s*-tetrazine) is a strongly colored (orange) molecule which is planar.[1] *s*-Tetrazines have been studied for several decades because their spectroscopic and photodissociation properties lend themselves to modeling. Tetrazines are highly reactive for aromatic compounds, forming cycloaddition compounds. Double and triple bonds add across carbon 3 and 6 in *s*-tetrazine, evolving 1 mol of nitrogen and forming 3,6-disubstituted pyridazines (Figure 1).[2] Politzer et al. have calculated the electrostatic potential of several substituted *s*-tetrazines.[3] They found the negative electrostatic potentials associated with the ring nitrogens were weaker than in heterocycles containing fewer nitrogens; they calculated these tetrazines were less basic than pyridine. The positive electrostatic potential is located above the center of *s*-tetrazine. This observation is consistent with the fact that in complexes with acetylene, the latter is above the plane of the ring and bisects the N−N bonds.

The photodissociation of *s*-tetrazines has been examined by many groups.[4,5,6,7] Though all agree the outcome is production of 1 mole of N_2 and 2 moles of nitrile (Figure 2), there is controversy whether the dissociation is stepwise or concerted. By comparison, thermal dissociation has received little attention. Recently 3,6-disubstituted-1,2,4,5-tetrazines were prepared with 3,5-dimethylpyrazole substituent(s);[8] the aim was to produce tetrazines capable of easy substitution for synthetic intermediates. In this work, we examine the dissociation of these substituted tetrazines and related species. Their high nitrogen and low hydrogen content makes them of interest as potential energetic materials or precursors thereof (Figure 3).

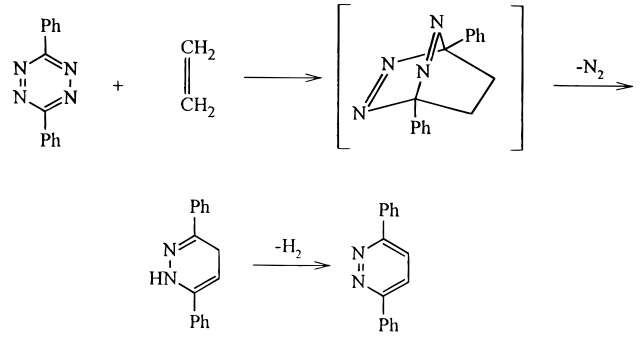

Figure 1. Reactions of 3,6-substituted *s*-tetrazine with dienes.

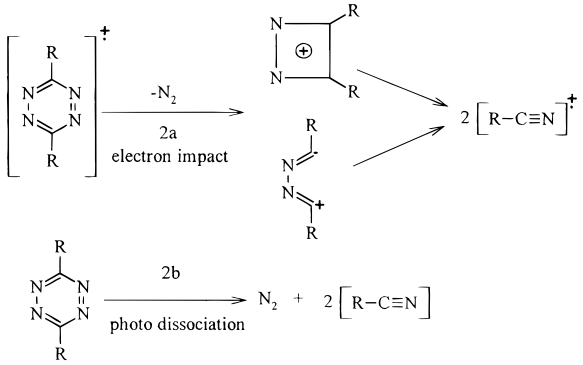

Figure 2. Photodissociation of *s*-tetrazine.

Experimental Section

The *s*-tetrazine samples were provided by Dr. Michael Hiskey of Los Alamos National Laboratory. The compounds included: 3,6-dihydrazino-1,2,4,5-tetrazine [$(N_2H_3)_2$T], 3-hydrazino-6-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine [(N_2H_3)TP], 3-amino-6-(3,5-dimethylpyrazol-1yl)-1,2,4,5-tetrazine [(NH_2)TP], 3,6-bis-(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine [P_2T], 3,6-bis(3,5-dimethylpyrazol-1-yl)-1,2-dihydro-1,2,4,5-tetrazine [P_2TH_2], 3-amino-6-chloro-1,2,4,5-tetrazine [Cl$T(NH_2)$], 3,6-dichloro-1,2,4,5-tetrazine [Cl_2T], and 3,6-diamino-1,2,4,5-tetrazine [$(NH_2)_2$T]. Only Cl$T(NH_2)$ showed a slight impurity by mass spectral analysis. Their syntheses have been described elsewhere.[8−11] Differential scanning calorimetry (DSC) analyses were performed on a TA DSC-2910 instrument. Samples were run under nitrogen flow and calibrated against indium. A typical DSC experiment involved heating samples (0.20−0.80 mg) from 40 to 500 °C in sealed glass capillary tubes (1.5-mm o.d., 0.28 mm-wall thickness, and 8-mm length) held in the DSC head by an aluminum support. In other analyses sample size was held about the same, but glass tube sizes varied. For kinetics and condensed-phase product studies, tubes with an inner diameter of 2.0 mm and total volume 150−200 μL were used. For gas chromatographic (GC) analyses, neat samples and evacuated tubes of inner diameter 0.9−1.1 mm and 40−50 μL total volume were employed. Solution studies used samples as 1% (by

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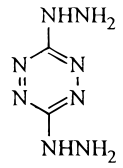
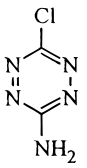
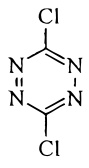


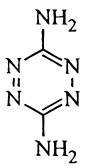
3,6-Dihydrazino-1,2,4,5-tetrazine $(N_2H_3)_2T$



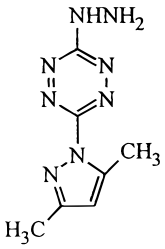
3-Amino-6-chloro-1,2,4,5-tetrazine $ClT(NH_2)$



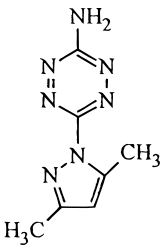
3,6-Dichloro-1,2,4,5-tetrazine Cl_2T



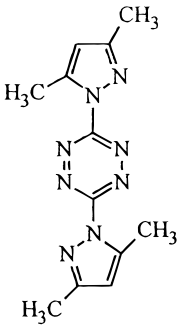
3,6-Diamino-1,2,4,5-tetrazine $(NH_2)_2T$



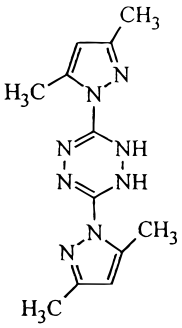
3-Hydrazino-6-(3,5-dimethylpyrazol)-1-yl 1,2,4,5-tetrazine $(N_2H_3)TP$



3-Amino-6-(3,5-dimethylpyrazol)-1-yl 1,2,4,5-tetrazine $(NH_2)TP$



3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine P_2T



3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2-dihydro-1,2,4,5-tetrazine P_2TH_2

Figure 3. Tetrazine compounds studied.

TABLE 1: HPLC Conditions for Tetrazine Compounds

	P_2T	$(N_2H_3)TP$	Cl_2T	$ClT(NH_2)$	$(NH_2)TP$	P_2TH_2
retention time, min	4.66	5.41	5.57	1.50	6.89	10.14
flow rate, mL/min	1.0	1.0	1.0	1.0	1.0	0.8
column temp, °C	38	38	38	38	38	38
phase 1 (% CH_3CN) in H_2O	2 min, 30%	2 min, 15%	2 min, 15%	2 min, 25%	4 min, 10%	2 min, 15%
phase 2	9 min, 100%	5 min, 40%	5 min, 40%	4 min, 100%	9 min, 100%	5 min, 40%
phase 3		10 min, 100%	6 min, 100%			10 min, 100%
injection amount, μL	10	10	10	10	10	10
wavelength, nm	294	294	220	240	274	254

weight) solutions (in benzene, benzene-d_6, acetone, or acetone-d_6); the solution (40−60 μL) was syringed into the sample tube, and the tube was flame sealed. To examine the decomposition of P_2TH_2 in the presence of acid or base, 0.5 μL of 70% nitric acid or pyridine was added to 0.3−0.5-mg samples.

For kinetics analyses, after constant temperature thermolysis, the residues in the sample tubes were dissolved in 1.0 or 2.0 mLof acetonitrile, and 10 μL was injected into a high-performance liquid chromatograph (HPLC) using a Hewlett-Packard (HP) 1100 HPLC with autosampler, photodiode array detector, and Hypersil BDS C18 (4.0 mm i.d. x 100 mm) column heated at 38 °C. The HPLC conditions used are listed in Table 1. This method could not be used to determine the kinetics of $(NH_2)_2T$, due to its extreme insolubility. Instead the rate of decomposition was assessed by comparing the amount of gas produced after heating for a given time to the amount of gas produced at full decomposition. To check the validity of this method, the rate constant of $ClT(NH_2)$ at 240 °C was redetermined by monitoring evolved gas; it was found to be within a factor of 1.7 of the rate constant determined by HPLC. The

TABLE 2: First-order Rate Constants (/sec) and Arrhenius Parameters of *s*-Tetrazines

DSC	$(N_2H_3)_2T$	$(N_2H_3)TP$	$(NH_2)TP$	P_2T	P_2TH_2	$CIT(NH_2)$		Cl_2T	$(NH_2)_2T$	
mp, °C			214	226	147	132		151		
E; endo, cal/g			34	32	25	14		30		
exo, °C	164, 299	164	297	297	273	238, 305		341	347	
E; exo, cal/g	307, 196	286	338	240	175	112, 53		196	422	
isothermal										
340									3.59×10^{-3} [a]	
330									1.61×10^{-3} [a]	ASTM
320								3.15×10^{-3} [a]	4.33×10^{-4} [a]	1.65×10^{-1}
310									1.00×10^{-4} [a]	6.41×10^{-2}
300								5.53×10^{-4}	1.81×10^{-5} [a]	2.41×10^{-2}
290									3.80×10^{-6} [a]	
280			9.58×10^{-3}	1.43×10^{-2}				1.52×10^{-4}		
260			4.60×10^{-3}	5.71×10^{-3}	1.61×10^{-2}					
240	estimated	estimated				3.82×10^{-3} [a]	ASTM			
240	3.59	2.13	1.56×10^{-3}	2.63×10^{-3}	5.61×10^{-3}	6.66×10^{-3} [a]	6.09×10^{-1}	3.89×10^{-6}	9.60×10^{-10} [a]	3.05×10^{-5}
220			5.66×10^{-4}	7.55×10^{-4}	2.52×10^{-3}	3.41×10^{-3} [a]	3.25×10^{-1}			
200					1.27×10^{-3}	1.08×10^{-3} [a]	1.65×10^{-1}			
180						4.89×10^{-3} [a]	7.85×10^{-2}			
150		1.40×10^{-2}								
140	2.54×10^{-3}	5.23×10^{-3}				6.28×10^{-5}	1.44×10^{-2}			
130		3.04×10^{-3}								
120	3.33×10^{-4}	1.39×10^{-3}								
100	5.01×10^{-5}									
80	4.11×10^{-6}									
E_a, kcal/mol	3.01	24.5	25.9	26.0	17.3	19.7	15.7	49.7	96.1	64.3
A, s^{-1}	4.38×10^{-13}	6.57×10^{-10}	1.86×10^{-8}	2.59×10^{-5}	1.53×10^{-5}	1.80×10^{-6}	3.18×10^{-6}	7.21×10^{-15}	1.23×10^{-32}	2.52×10^{-22}
R^2	0.999	0.985	0.997	0.994	0.986	0.997		0.998	0.993	
in solvent										
24 °C in benzene		insoluble	insoluble	5.42×10^{-5}	3.17×10^{-4}	5.48×10^{-6}		4.13×10^{-5}	insoluble	
24 °C in benzene-d_6				3.80×10^{-5}	2.96×10^{-4}	3.48×10^{-6}		3.15×10^{-5}	insoluble	
				0.5% (wt)	1% (wt)	1% (wt)		0.5% (wt)		
DKIE				1.4	1.1	1.6		1.2		
24 °C in acetone		2.15×10^{-3} 140 °C	1.67×10^{-4}	2.12×10^{-3}	7.27×10^{-4}	7.15×10^{-4}		3.08×10^{-3}	insoluble	
24 °C in acetone-d_6		1.53×10^{-3} 140 °C	8.28×10^{-5}	2.25×10^{-3}	5.85×10^{-4}	4.81×10^{-4}				
		1% (wt)	1% (wt)	0.5% (wt)	1% (wt)	1% (wt)		0.5% (wt)		
DKIE		1.4	2.0	1.0	1.2	1.5				
					5.49×10^{-4} (2%) acetone			5.72×10^{-5} (1%) benzene		

[a] Kinetics determined by total evolved gas.

TABLE 3: Gaseous Decomposition Products (area percent) of *s*-Tetrazines[a]

gas product	RT(N_2H_3)$_2$		(N_2H_3)TP		(NH_2)TP		P_2T		P_2TH_2		ClT(NH_2)			Cl_2T		(NH_2)$_2$T	
N_2	4.0	91.5	87.9	82.3	88.9	87.3	83.8	83.8	75.2	74.7	41.2	26	31.5	62.4	72	79.8	41.8
CH_4	9.9			0.08			0.34	0.06	0.3	0.06							
CO_2[b]	13.4		1.8	2.7	3.3	2.2	0.96	3.5	3.2	7.9	2.2	10.5	2.1	2.6	18.8	1.4	4.5
NH_3	15.7	1.7	1.6	8.3		3.0	5.4		6.8	0.07						15.2	44.6
H_2O[b]	16.7	3.2	3.6	1.4	4.3	2.0	2.3	3.1	3.2	9.9	0.64			1.8	5.3	1.3	5.8
HCl	17.3										22.6	38.2	33.8				
C_2N_2	18.2										2.6	1.8	2.2	2.9	0.73	0.15	0.11
HCN	18.5		2.4	0.08	2.3	2.2	0.32	0.38	0.16	2.2		0.76	2.2			1.8	1.5
CH_3Cl	19.1										0.46						
ClCN	19.8										6.1			27.4	1.3		
CH_3CH	22.1	0.25	1.2	2.6	1.2	4.3	7.2	9.1	9.3	5.3	0.63	0.18	0.85			0.11	0.73
CH_3CH_2O	23.2															0.09	
CH_3CH_2C	24.6								0.08								
$CHCl_3$	26.1										18.2	9.1	5.6				
toluene	28.2								1.5								
CCl_4	29.0											0.43	0.6	1.1	1.7		
mol N_2/mol compound			0.68		0.43		0.36		0.35			0.34		0.43		0.53	
total mol gas/mol sample			1.2		0.7		0.7		0.6			0.9		1.5		1.2	

[a] Samples decomposed for 24 h at 320 °C—duplicate or triplicate runs. [b] Traces also appear in blanks.

TABLE 4: Mass Fragments of *s*-Tetrazines under EI

mass fragments with relative abundance					
(NH_2)TP	P_2T	P_2TH_2	ClT(NH_2)	Cl_2T	(NH_2)$_2$T
192(9.4)	271(8.4)	273(28.7)	133(19.1)	152(19.2)	112(100)
191(89.8)	270(51.8)	272(100.0	131(59.7)	150(29.3)	84(0.1)
122(7.3)	122(22.7)	230(5.7)	103(1.6)	122 (0.02)	43(63.8)
121(100)	121(100)	149(5.0)	64(7.7)	89(32.7)	42(47.3)
120(24.8)	120(15.8)	123(12.8)	62(23.8)	87(100.0)	28(6.8)
106(25.8)	106(14.1)	122(90.6)	61(6.3)	63(29.5)	27(5.4)
80(16.4)	80(7.4)	97(7.5)	47(6.7)	61(91.3)	
79(6.6)	67(5.1)	96(20.1)	42(100.0)	49(5.1)	
67(11.0)	53(9.6)	95(15.4)	41(8.0)	47(14.3)	
54(7.0)		82(5.7)	29(9.5)	35(8.4)	
53(23.5)		81(10.2)			
42(10.9)		67(7.3)			
39(9.9)		54(9.4)			
		42(9.7)			
		39(6.1)			

activation energy of the thermal decomposition of (NH_2)$_2$T was also assessed by using a DSC method.[12] We find the DSC method sometimes gives activation parameters in good agreement with the reactant loss methods, but this is not always the case. In this case, the activation energy determined for (NH_2)$_2$T was smaller than that determined by gas manometer, but still quite large. Furthermore, checking this method against ClT-(NH_2) showed the DSC method produced an activation energy lower than that from the reactant loss method. For these reasons, the kinetics determined by gas manometry were used.

Gas products were identified by GC with mass selective detection (GC/MS): a HP5890 GC, equipped with electronic pressure control and a model 5971 electron impact (EI) quadruple MS, a PoraPLOT Q (Chrompack) capillary column (25 mm × 0.25-mm i.d.), and helium carrier gas. The sample injection system consisted of a six-port gas sampling valve with

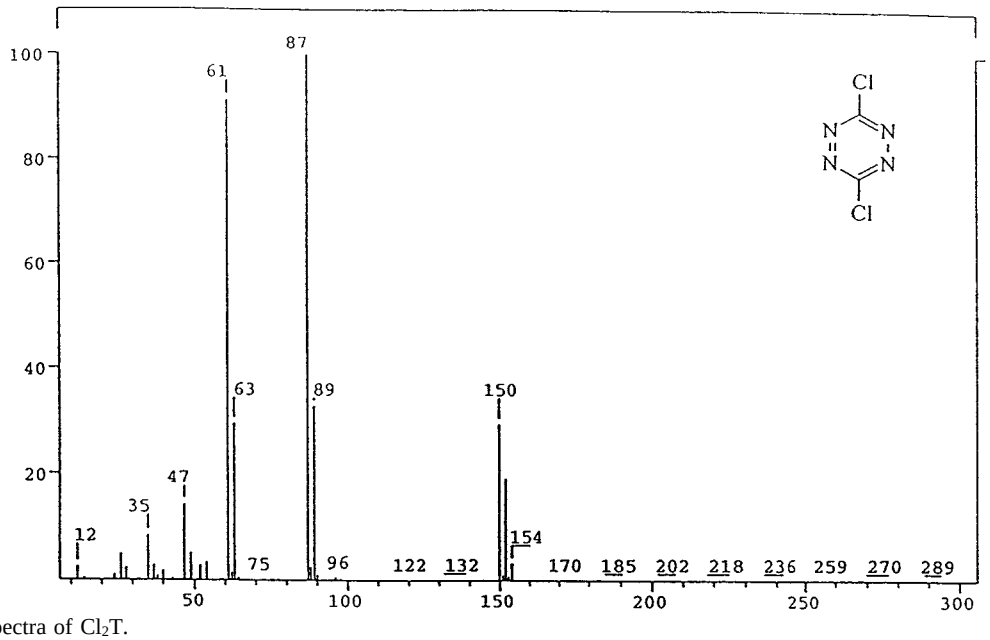


Figure 4. Mass spectra of Cl_2T.

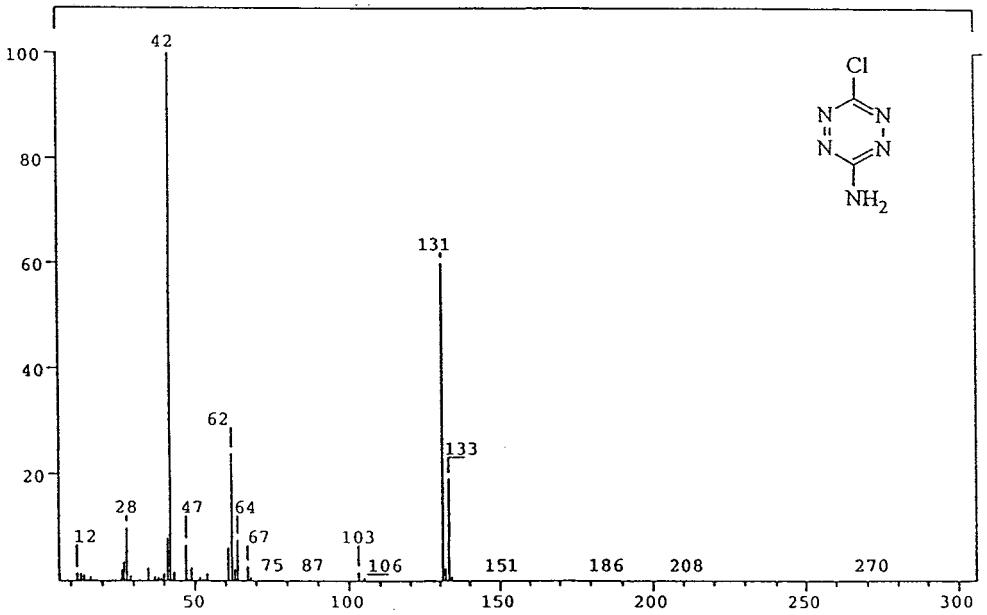


Figure 5. Mass spectra of ClT(NH_2).

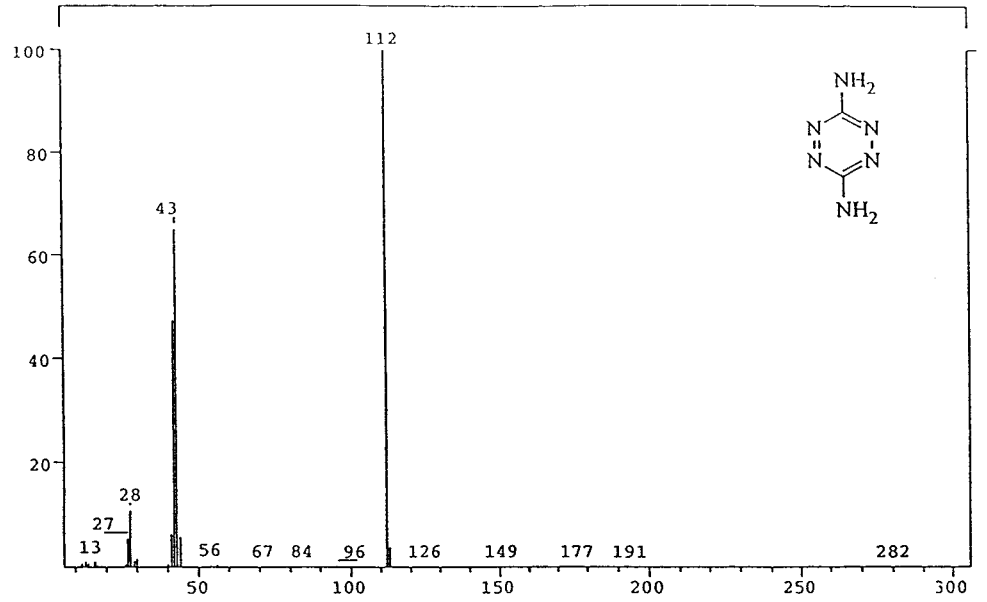


Figure 6. Mass spectra of $(NH_2)_2$T.

a flexible Nalgene 870PFA sample loop into which the sealed samples were placed. The flexible sample loop was purged with helium before sample tubes were broken by bending the loop to introduce the decomposition gases into the GC. Column temperature was ramped from −80 °C at 15 °C/min to 180 °C and held for 5 min for gas identification. Permanent gases (N_2, CO, CO_2) were quantified by using GC with a thermal conductivity detector (GC/TCD). The HP5890 GC was equipped with a Heyesep DB 100/120 (30 ft x $^1/_8$ in.) column. The oven temperature was held at 35 °C for 5 min and then ramped to 190 °C at 10 °C/min. Authentic gases were used for calibration.

To identify the condensed phase decomposition products, tetrazines were thermolyzed neat, in benzene, acetone, or acetone-d_6. After thermolysis, samples (neat samples were dissolved in acetone) were injected into a Varian 3400 GC with J&W DB-5MS column (30m × 0.25 mm i.d.), coupled to a Finnigan-MAT TSQ-700 tandem MS. The injector temperature was 220 °C, the transfer line was 260 °C, and the column temperature was held for 1 min at 50 °C and then ramped to 260 °C at 15 °C/min. The electron energy was 70 eV, with emission current 200 μA, and the ion source operated at 150 °C. In the chemical ionization (CI) mode, methane was used as reagent gas. The thermolyzed samples were examined by electron impact (EI) and CI in positive ionization modes. Product assignments were based on the M + 1 ions in CI and/or fragmentation patterns in EI. MS/MS was used to study the fragmentation pathway of the compounds. In the collision-induced dissociation (CID) study, argon was used as collision gas at a gas pressure of 1×10^{-3} Torr. The collision energy was 15 eV. Samples were injected as 1μL of 0.1% (wt%) acetone solutions.

Results

For a quick assessment of the thermal stability of the various substituted tetrazines, DSC scans were performed. The tetrazines examined were orange to red in color; upon heating most exhibited a melting endotherm and a single, sharp exotherm and formed a black, insoluble residue. Only the most stable

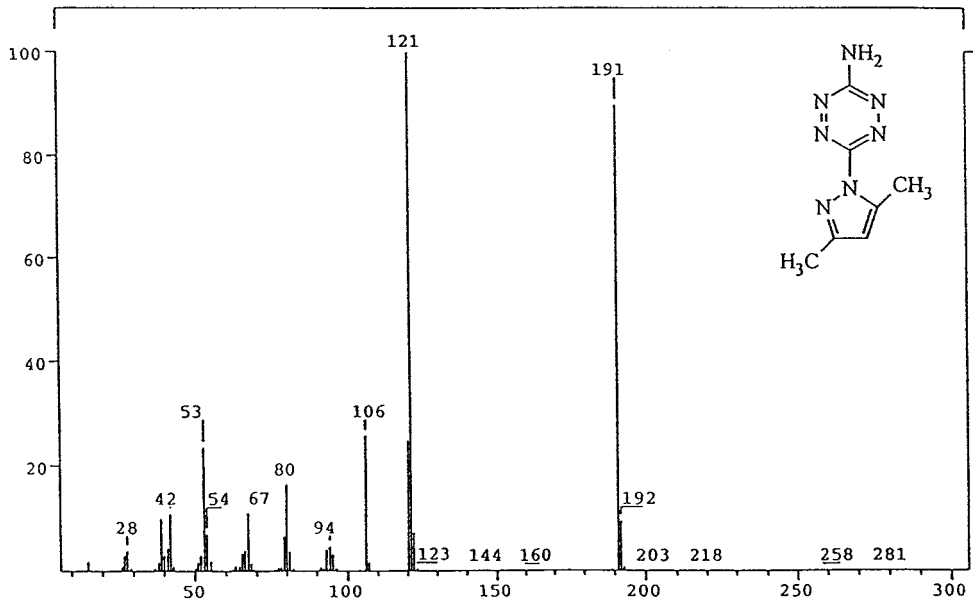


Figure 7. Mass spectra of $(NH_2)TP$.

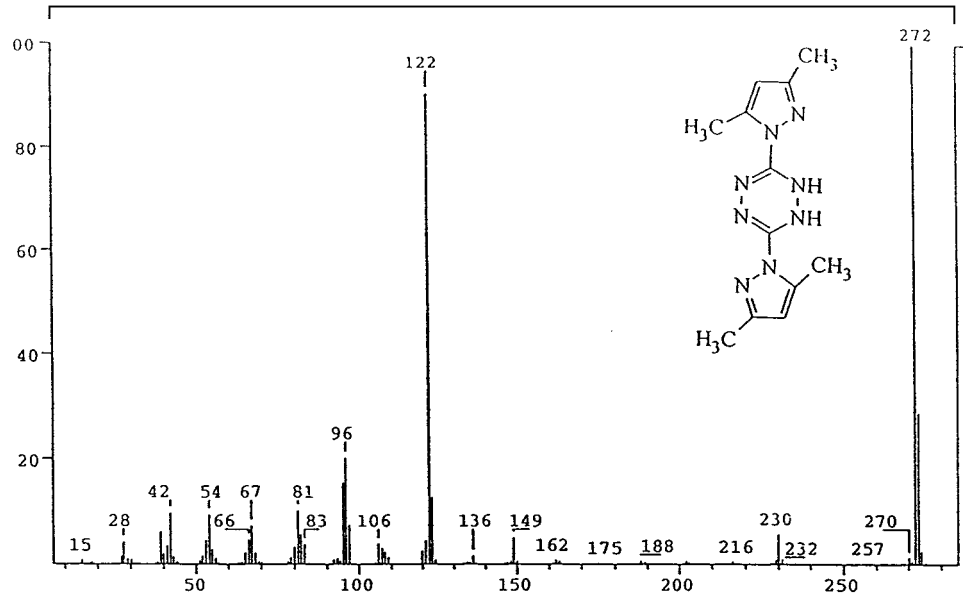


Figure 8. Mass spectra of P_2TH_2.

$(NH_2)_2T$ and the least stable $(N_2H_3)TP$ and $(N_2H_3)_2T$ tetrazines did not show a melt (Table 2). Only two had a second exotherm: $(N_2H_3)_2T$ and $ClT(NH_2)$. The tetrazines showed wide variation in stability. The least stable, $(N_2H_3)TP$ and $(N_2H_3)_2T$, exhibited an exotherm at 164 °C, while the most stable, $(NH_2)_2T$ and Cl_2T, exhibited exotherms at 347 and 341 °C, respectively. These trends were mirrored by the isothermal kinetics of the neat compounds, which, depending on the tetrazine, were collected over the temperature range from 80 to 340 °C. First-order rate constants, activation energies and preexponential factors are shown in Table 2.

If the tetrazine was sufficiently soluble (0.5 wt %), isothermal kinetics were collected at 240 °C in benzene and acetone. Of the four tetrazines soluble in benzene, three decomposed more slowly in benzene and one, more quickly (Cl_2T). The decomposition rate constants of P_2T, P_2TH_2, $ClT(NH_2)$ were from 10 to 1000 times slower in benzene. Three of the six tetrazines [$ClT(NH_2)$, $(NH_2)TP$, P_2TH_2] which dissolved in acetone decomposed at about a tenth of the rate in acetone than they did neat. The decomposition rate of dichlorotetrazine increased 1000 times in acetone and increased by a factor of 10 in benzene. The decomposition rate of P_2T and $(N_2H_3)TP$ were unaffected in acetone, but P_2T slowed by a factor of 100 in benzene. Decomposition neat or in solvent was generally first-order out to 50% reacted. This was rechecked by doubling the concentration of Cl_2T in benzene (0.5 to 1 wt %) and the concentration of P_2TH_2 in acetone (1 to 2 wt %). Their rate constants were unchanged. To probe for a intermolecular deuterium kinetic isotopic effect (DKIE), tetrazines were decomposed in proteo- and deuterobenzene and acetone. The amine substituted tetrazines $ClT(NH_2)$ and $(NH_2)TP$ clearly showed a primary DKIE (Table 2). (A rate ratio of 1.6 or greater is considered a primary DKIE.[13]) To examine the acid and base stability of tetrazines, P_2TH_2 was mixed with nitric acid and with pyridine. When acid was added, the sample instantly turned into a yellow liquid; HPLC analysis showed all the tetrazine had reacted. When pyridine was added, the orange sample turned partially liquid; subsequent HPLC analysis showed partial decomposition.

To determine the gaseous decomposition products, the examined tetrazines were heated neat in evacuated tubes at

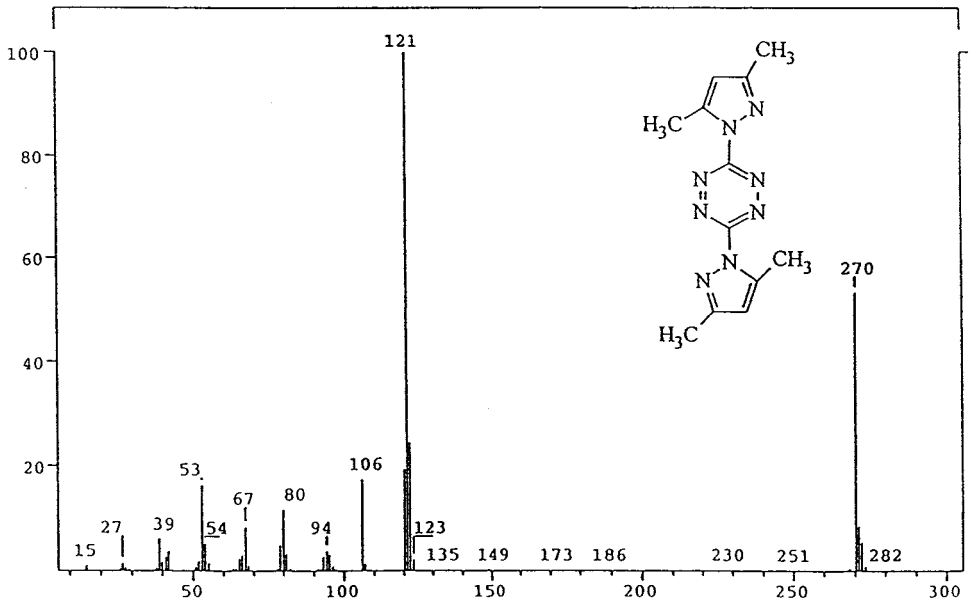


Figure 9. Mass spectra of P_2T.

320 °C for 24 h to ensure complete decomposition. Decomposition gases were identified by GC/MS; total amount of gases per mole of sample was quantified by use of a mercury manometer; nitrogen was quantified by gas chromatography with thermal conductivity detector (GC-TCD). Details of gaseous decomposition products are shown in Table 3. The principal decomposition gas of all the tetrazines was nitrogen. All the tetrazines, except Cl_2T, which contained no hydrogen, formed small amounts of acetonitrile (CH_3CN) and hydrogen cyanide (HCN); the tetrazines containing two dimethylpyrazole, P_2T and P_2TH_2, formed moderate amounts (up to 9%) of acetonitrile. The three tetrazines which did not contain dimethylpyrazole [Cl_2T, $ClT(NH_2)$, $(NH_2)_2T$] formed small amounts of CNCN (cyanogen). All but the chlorine-containing tetrazines, Cl_2T and $ClT(NH_2)$, formed moderate amounts of ammonia; $(NH_2)_2T$ with two amine substituents formed substantial NH_3. The fate of chlorine atoms in Cl_2T and $ClT(NH_2)$ was quite different. $ClT(NH_2)$ formed large quantities of HCl and $CHCl_3$, while Cl_2T, which contained no hydrogen, formed neither of these species. Instead, Cl_2T formed large amounts of ClCN and small amounts of CCl_4, while $ClT(NH_2)$ formed only small amounts of these. Minor amounts of methane were found among the decomposition gases of P_2T and P_2TH_2.

Table 4 shows the observed fragments and their relative abundance when the tetrazines were subjected to EI (Figures 4−9). Tandem mass spectrometry was used to examine the collision-induced dissociation (CID) of the major EI peaks. Due to the resolution of the spectrometer, assignments are not definitive but are reasonable based on the mass of parent ions and their MS/MS fragments. Tables 5−8 tabulate the results and Figures 10 and 11 show the postulated MS fragmentation of the tetrazines.

To examine condensed-phase products, tetrazines P_2T, $(NH_2)TP$, P_2TH_2, Cl_2T, and $ClT(NH_2)$ were thermolyzed at 240−320 °C neat and in benzene, acetone, or acetone-d_6 solutions (1 wt %). [$(N_2H_3)TP$, $(N_2H_3)_2T$, and $(NH_2)_2T$ were not examined in this fashion because the former two were too unstable and the latter too insoluble.] The thermolyzed samples were examined by GC/MS using EI+ and CI+ detection. Products assignments were based on the apparent molecular mass and fragmentation patterns (Table 9−12). When the tetrazines were thermolyzed in benzene, biphenyl was usually the largest peak in the GC chromatogram. Generally, no products containing the tetrazine ring were observed. For samples containing 3,5-dimethylpyrazole [P_2T, $(NH_2)TP$, P_2TH_2] the

TABLE 5: CID of Tetrazines XTY (15 eV)[a]

3-Amino-6-chloro-1,2,4,5-tetrazine, $ClT(NH_2)$			
P	131(9.7)	62(100)	
HNC−Cl	62(24.7)		
$NCNH_2$	42(100)		
HCN		27(3.9)	

3,6-Dichloro-1,2,4,5-tetrazine, Cl_2T				
P		150(21.0)	87(100)	61(100)
P−Cl	35		52(2.6)	
P−Cl−N_2	63	87(100)		
NC−Cl	89	61(37.9)		
Cl	35		35(6.6)	35(2.0)

3,6-diamino-1,2,4,5-tetrazine $(NH_2)_2T$		
P	112(15.2)	
NHC−NH_2	43(100)	
NC−NH_2	42(32.0)	

[a] *m*/*z* 80, 108 were observed under 5 eV.

TABLE 6: CID of 3-Amino-6-(3,5-dimethylpyrazolyl)-1,2,4,5-tetrazine (15 eV) $(NH_2)TP$

P		191(5.5)	121(46.8)	120(100)	106(100)
P−H	1		120(34.4)		
P−CH_3	15		106(78.5)		
P−CH_3−H_2	17			103(8.0)	
P−CN	26				80(11.6)
P−HCN	27			93(33.5)	79(24.0)
P−CH_3−CN	41		80(36.5)	79(7.2)	
P−CH_3−HCN	42		79(8.6)	78(6.7)	
P−$NCNH_2$−N_2	70	121(100)			
P−$NCNH_2$−N_2−CH_3	85	106(2.8)			
P−$NCNH_2$−N_2−CH_3−CN	111	80(16.4)			
other ions	67	67(5.6)	67(18.6)		
	66		66(3.7)	66(26.8)	
	54		54(7.4)		54(9.4)
	53	53(20.4)	53(100)		
	42		42(7.6)	42(3.3)	
	41		41(5.2)		
	39			39(3.7)	
	28				28(4.2)
	26				

TABLE 7: CID of 3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2,4,5-tetrazine (15 eV) P_2T

P[a]		270(0.05)	121(39.3)	106(100)	95(100)	80(77.4)	67(100)	53(100)
P−H	1		120(19.8)			79(35.5)		
P−CH_3	15		106(57.6)					
P−CN	26			80(9.4)				
P−HCN	27			79(28.2)				
P−CH_3−CN	41		80(27.2)					
P−(NC)DMP−N_2	149	121(100)						
P−(NC)DMP−N_2−CN	175	95(5.2)						
P−(NC)DMP−N_2−CN−CH_3	190	80(2.0)						
other ions								
	67		67(10.7)			67(16.1)		
	55					55(22.6)		
	54			54(11.1)				
	53	53(3.2)	53(100)			53(100)		
	52							52(13.4)
	51			51(3.4)				
	41				41(35.6)		41(29.0)	
	39					39(19.3)		
	27			27(4.3)		27(16.1)		
	26							26(1.5)

[a] DMP: 3,5-dimethylpyrazol-1-yl.

TABLE 8: CID of 3,6-Bis(3,5-dimethylpyrazol-1-yl)-1,2-dihydro-1,2,4,5-tetrazine (15 eV), P_2TH_2

P[a]		272(9.3)	122(100)	96(46.4)
P−H	1			95(100)
P−CH_3	15		107(7.0)	81(3.9)
P−HCN	27		95(1.7)	
P−CH_3−CN	41		81(16.6)	
P−N_2−DMP(CNH)	150	122(100)		
DMP + H	176	96(17)		
other ions	68			68(4.0)
	67		67(7.4)	
	55			55(2.6)
	54		54(43.4)	54(6.5)
	53		53(14.9)	
	42		42(9.0)	
	41			41(2.3)
	28		28(0.8)	28(1.2)

[a] DMP: 3,5-dimethylpyrazol-1-yl.

major observed products were 1-cyano-3,5-dimethylpyrazole and 3,5-dimethylpyrazole (1A, 1B). P_2TH_2 formed the largest number of products, including P_2T. In some samples P_2T was converted to P_2TH_2 in the inlet of the mass spectrometer, a phenomenon previously reported.[14] The tetrazines without the pyrazole substituents, Cl_2T and $ClT(NH_2)$, showed no condensed-phase products when thermolyzed neat. [$ClT(NH_2)$ had an impurity which remained in the thermolyzed solutions.] In benzene, both formed biphenyl, and Cl_2T formed cyanobenzene and dichlorobenzene. In acetone, $ClT(NH_2)$ formed 3-chloro-6-chloroamino-1,2,4,5-tetrazine (4B).

Discussion

Mass Spectral Fragmentation Studies. Fragmentation of species under EI in a mass spectrometer can sometimes shed light on thermal decomposition pathways. The parent *s*-tetrazine structure has been reported to have an intense molecular ion, and this was observed in many of the tetrazines studied.[15] For $ClT(NH_2)$, $(NH_2)_2T$, $(NH_2)TP$, and P_2TH_2 the molecular ion was 60−100% of the base peak. In contrast, the tetrazine parent skeleton ion is rarely observed. It has been reported for diisopropyltetrazine,[15] and it may have been observed in the MS/MS spectrum of $(NH_2)_2T$ at low collision energy (5 eV). Loss of N_2 followed by cleavage of the other N−N bond to form RCN ions is a mode of dissociation common to both nitrogen- and carbon-substituted tetrazines (see Figure 2), but the $[M - 28]^+$ peak is often weak or absent. [16]

The $[M - 28]^+$ intermediate is usually postulated as an open-chain with resonance stabilization, but a four-membered ring is possible. Both pathways have been proposed in the EI fragmentation of 3,6-dimethyl-*s*-tetrazine. The diazacyclobutadiene ring was proposed to explain the observation of dimethylacetylene cation.[17] The mass spectrum of 3,6-dichlorotetrazine (Cl_2T) contained a molecular ion at *m*/*z* 150 and chlorine isotopic ions at *m*/*z* 152 and 154. The base peak at *m*/*z* 87 is assumed as $[M-N_2-Cl]^+$. A low intensity peak at *m*/*z* 122 (Figure 4) is probably the $[M - 28]^+$ intermediate (Figure 10). 3-Amino-6-chloro-1,2,4,5-tetrazine [$ClT(NH_2)$] exhibited a molecular ion at *m*/*z* 131 with chlorine isotopic ion at *m*/*z* 133 (Figure 5). A base peak $[N_2CH_2]^+$ at *m*/*z* 42 and another major fragment $[HNCCl]^+$ at *m*/*z* 62 (with an isotopic ion at *m*/*z* 64) were formed via cleavage of the N−N in $[Cl-C{=}N-N{=}C-NH_2]^+$; a low intensity fragment was found at *m*/*z* 103. For 3,6-diamino-1,2,4,5-tetrazine [$(NH_2)_2T$)], the molecular ion (*m*/*z* 112) was also the base peak (Figure 6). A tiny peak was observed at *m*/*z* 84 which could be the fragment resulting from N_2 loss. Cleavage of the remaining N−N bond produced the major fragments $[HN{\equiv}C-NH_2]^+$ (*m*/*z* 43) and $[NH{=}C{=}NH]^+$ (*m*/*z* 42). With a decrease in collision energy from 15 to 5 eV, the peak at *m*/*z* 43 remained the most intense daughter ion of *m*/*z* 112, but ions were observed with *m*/*z* 80 and 108. We assign these peaks as N_4C_2 and N_6C_2, respectively, thus, representing all the atoms of the tetrazine ring.

Tetrazines $(NH_2)TP$, P_2T, and P_2TH_2 share a common fragmentation pathway: elimination of N_2 and cleavage of the remaining N−N bond in the ring formed the 1-cyano-3,5-dimethylpyrazol ion at *m*/*z* 121 (Figure 11). In subsequent fragmentation, the pyrazole structure lost the CN and CH_3 groups. Both $(NH_2)TP$ and P_2TH_2 exhibited intense molecular ions *m*/*z* 191 and 272, respectively (Figures 7 and 8). The mass spectrum of P_2T sometimes exhibited the molecular ion at *m*/*z* 270 and sometimes that peak was replaced by *m*/*z* 272 (Figure 9). The appearance of $[M+2]^+$ rather than M^+ has been observed in other tetrazines. The $[M + 2]^+$ peak was rationalized in terms of the catalytic reduction of tetrazine to dihydrotetrazine by protonic species (eg, H_2O) on the surface of the ionization chamber.[14] The base peak for P_2TH_2 was its molecular ion, with an ion of *m*/*z* 122 as a dominant fragment. 1-Cyano-3,5-

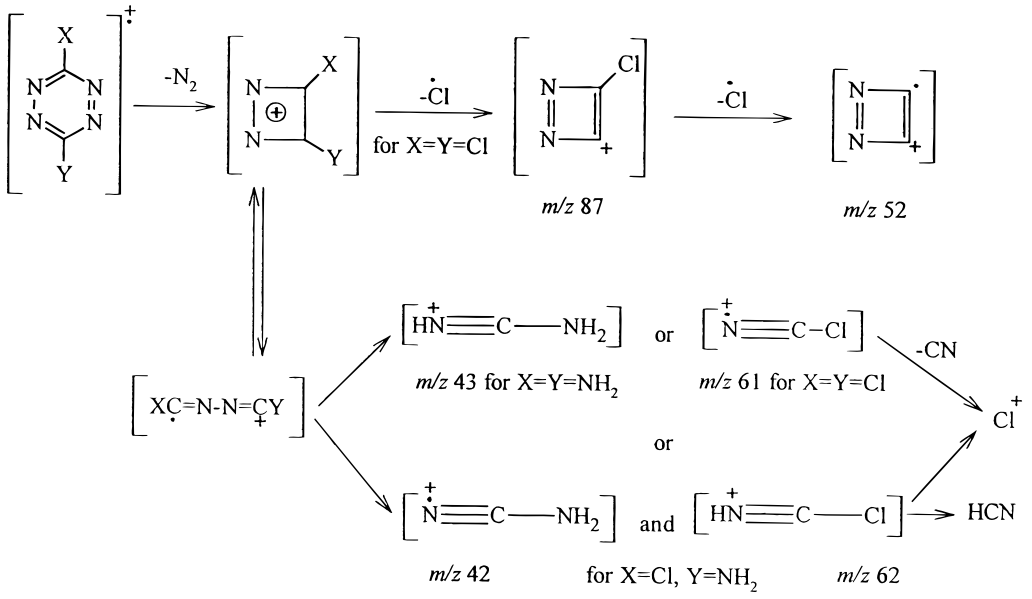


Figure 10. Mass fragmentation pathway of Cl_2T, $(NH_2)_2T$, and $ClT(NH_2)$.

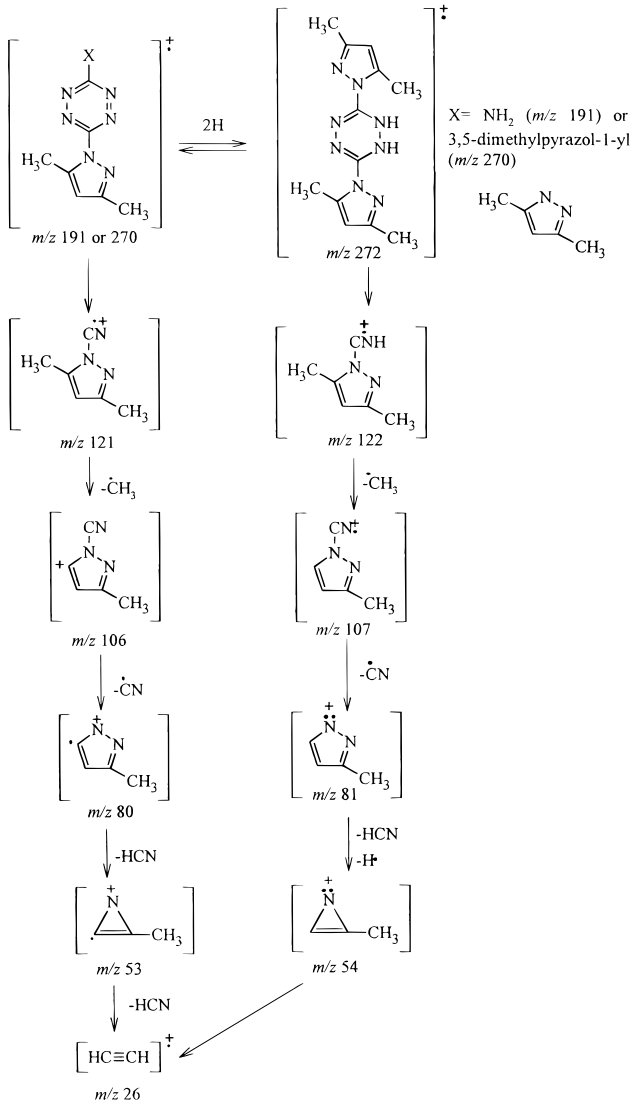


Figure 11. Mass fragmentation pathway of P_2T, $(NH_2)TP$, and P_2TH_2.

dimethylpyrazolium cation (*m/z* 121) was the base peak for P_2T and $PT(NH_2)$.

Thermal Decomposition Studies—Products. The mechanism observed for dissociation by electron impact or photodissociation (Figure 2)[5,6] —loss of N_2 and formation of nitriles—is consistent with the thermal decomposition products (Tables 9−12). However, the substituent determines whether the resulting nitriles are observed. Where the substituent was 3,5-dimethylpyrazole [P_2T, $(N_2H_3)TP$, $(NH_2)TP$, and P_2TH_2], 1-cyano-3,5-dimethylpyrazole was observed. Where the substituent was NH_2 or $NHNH_2$, the corresponding nitriles were not stable. Further decomposition formed ammonia [observed in large quantities in the decomposition of $(NH_2)_2T$], hydrogen cyanide, and cyanogen. For Cl_2T and $ClT(NH_2)$ where the substituent was chlorine, ClCN was produced (Table 3). The formation of dichlorobenzene and 3-chloro-6-chloroamino-1,2,4,5-tetrazine (4B) (Table 12) suggested chlorine radical was produced as a secondary product from ClCN. In fact, the tetrazines which did not contain dimethylpyrazole [Cl_2T, $ClT(NH_2)$, $(NH_2)_2T$] all formed small amounts of cyanogen, presumably as a decomposition product of the intermediate nitrile (Table 3). Product 4B observed in the decomposition of $ClT(NH_2)$ in acetone is one of the few products where the tetrazine ring was observed. Though the tetrazine ring rarely survived under the thermolysis conditions, the 3,5-dimethylpyrazole ring did. The expected nitrile (1A) and the ring alone (1B) were observed as major products of each tetrazine with the pyrazole substituent [P_2T, $(NH_2)TP$, P_2TH_2]. In addition, products resulting from interaction with the solvent were found. Fragments of acetone are thought to be attached to species designated 1C, 1D, and 1L; the latter also appears to contain an intact tetrazine ring. Minor products (1N and 1P) of uncertain assignment may also contain the tetrazine ring. The formation of the pyridazine ring in 1J is thought to arise by addition of ethylene to the tetrazine ring. Such products have been observed with tetrazines such as 3,6-diphenyl-*s*-tetrazine (Figure 1).[2] The source of ethylene for production of 1J or 1F would be the diazacyclobutadiene ring (Figure 2a) intermediate postulated in the fragmentation of 3,6-dimethyl-*s*-tetrazine[17] and 3,6-dichloro-*s*-tetrazine above.

Under thermolysis some P_2TH_2 is oxidized to P_2T (Table 9). However, the reverse reaction does not occur in the thermolysis of P_2T; its conversion to P_2TH_2 appears to occur only in the catalytic environment of the GC injector port.[14] However, both P_2T and P_2TH_2 form 1G, which is thought to contain a

TABLE 9: GC/MS Analysis of the Decomposition Products of P_2TH_2[a]

	P_2TH_2		1F		1A		1B		1D			1C			1E		1G			1H	
amount	L	M,M	S	S	L		L	M, M	S			L			M		T			T	S
found in	n	b,a	n	b	b		n	b,a	a			a			b		a			n	a
retent. min.	20:30		5:00		5:17		6:08		6:20			6:36			9:00		12:30			18:16	
M.W.	272		124		121		96		138			136			148		178			258	
	EI	CI+	EI	CI+	EI	CI+	EI	CI+	EI	CI+	EI d6	EI	CI+	EI d6	EI	CI+	EI	CI+	EI d6	EI	CI+
	273	274	124	125	121	122	96	97	138	139	140	136	137	136	148		178	179	179	258	259
	272	273	96	97	120	97	95	96	110	138	138	121	122	121	121		163	178	178	243	258
	230	272	95		106		81	95	96	125	97	96	121	106	120		152	152	152	187	
	149	122	81		96		65		95	97	96	95	95	96	95		122	125	97	163	
	123		54		95		54		81	96	95	94		95	94		97	97	96	123	
	122		39		81		39		43	95		80		94	81		96	96	95	95	
	96				67							53		80	80		95		40	67	
	95				54							39		53	53		56				
	81				53									39	39		40				
					39																

	1J		1K		1L			1M		1N		1P		P_2T		biphenyl	
			unassigned														
amount	S	S,S	T	S	T			T		S		S		M		L	
found in	n	b,a	n	a	a			b		b		b		b		b	
retent. min.	19:49		20:10		16:00			10:04		12:39		13:47		16:39		8:29	
M.W.	268		282		234			175		203		218		270		154	
	EI	CI+	EI	CI+	EI	CI+	EI d6	EI	CI+	EI	CI+	EI	CI+	EI	CI+	EI	CI+
	268	269	282	283	234	236	240	175	176	203	203	218	219	270	273	155	155
	251	268	267	282	192	235	239	160	121	202	202	190	191	122	272	154	154
	173		265		191	234	238	133		175		175		121	271	153	
	156		240		178	191	234	121		160		149		120	121	152	
	133		187		165	138	193	120		107		121		106		151	
	96		96		150	122	192	106		97		96		80		115	
	95		95		135	97	179	95		96		95		67		76	
					122		178	94		95				53		53	
					95		166	80									
					67		165	53									
					56		150										
					43		122										

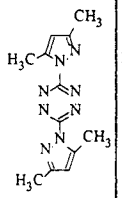
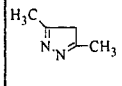
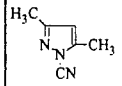
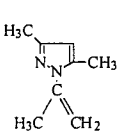
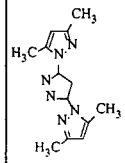
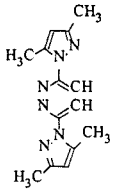
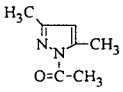
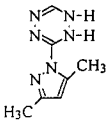
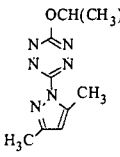
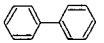
[a] n = neat heated at 240 °C; b = 1% in benzene heated at 320 °C; a = 1% in acetone heated at 240 °C.

dihydrotetrazine ring. Compound 1M is thought to result from trimerization of nitrile fragments; 1A contains a single cyano group; 1E two cyano groups, and 1M, the trimer. Such products have previously been observed in the thermolysis of tetrazine (Figure 12) and of nitroguanidine.[18] They thermolyze to black, insoluble residues such as have been observed in this study.[18] Compound 1H is postulated to form by replacement of N_2 with a methylene group. While ring reduction of tetrazines have been reported, the products are usually 3,5-R_2-1,2,4-triazole rings such as shown in Figure 12.[19]

Thermal Decomposition Studies—Kinetics. While the decomposition products of the eight tetrazines can be explained in terms of a mechanism initiated by loss of N_2 (Figure 2), some of the kinetics data is difficult to justify with this rationale. Table 13 tabulates properties considered. With the exception of dichlorotetrazine, solvent retarded the decomposition of the tetrazines studied. Three of the four tetrazines soluble in benzene decomposed a factor of 10−1000 times slower in benzene than neat. Acetone had a smaller effect; the rate was retarded a maximum of one-tenth. Dichlorotetrazine was the exception; its decomposition rate increased by a factor of 10 in benzene and a factor of 1000 in acetone. These observations are not necessarily out of line with nitrogen loss and formation of two nitriles, but they indicate a concerted free-radical dissociation (i.e., Figure 2b) does not occur in solution. Such a dissociation would be expected to be largely unaffected by the reaction media (for example, the dissociation of *tert*-butyl peroxide[20,21]). However, there is a tendency for solvent to hold radical fragments in proximity long enough to allow the reverse reaction. Although this effect would retard decomposition, it would not be expected to be effective if three radicals were formed (e.g., Figure 2b). These kinetic data and the observed intermediate in the EI fragmentation of dichlorotetrazine suggest stepwise decomposition. Reactions producing products more polar than the reactants are generally favored in polar solvents.[20] In the case of 3,6-dichloro-1,2,4,5-tetrazine, the product ClCN is markedly more polar than the starting material and the decomposition is accelerated 1000-fold in acetone and 10-fold in the less polar benzene.

Facts which are not readily explained by the mechanism shown in Figure 2 are the low yield of evolved nitrogen gas, the dramatic variation in decomposition rate constants, and the observation of a primary intermolecular DKIE in the decomposition of some tetrazines. If decomposition proceeds by the mechanism shown, we would expect at least 1 mole of N_2 would be evolved per mole of tetrazine. In contrast, we observed only 0.34−0.43 mol of nitrogen per mole of tetrazine for tetrazines without amine or hydrazine substituents (i.e., this N_2 is from the tetrazine ring itself), and 0.43−0.68 mol of nitrogen from tetrazines with these substituents (Table 13). Furthermore, for

TABLE 10: GC/MS Analysis of the Decomposition Products of P_2T[a]

	P_2T 		1B 		1A 		1C 			1H 		1J 		1K		1D 			1G 			1L 			biphenyl 		naphthalene 	
amount	L	M	L	S	L	L	L			T	S	T	S	T	M	T			T			T			M		S	
found in	n	b	n	a	n	b	a			n	a	n	a,b	n	a	a			a			a			b		b	
retent. min.	17:05		5:45		6:07		6:45			15:45		23:03		23:29		6:37			12:33			18:31			8:24		6:50	
M.W.	270		96		121		136			258		268		282		138			178			234			154		128	
	EI	CI+	EI	CI+	EI	CI+	EI	CI+	EI d6	EI	CI+	EI	CI+	EI	CI+	EI	CI+	EI d6	EI	CI+	EI d6	EI	CI+	EI d6	EI	CI+	EI	CI+
	270	273	96	97	121	122	136	137	141	258	259	268	269	282	283	138	139	141	178	179	184	234	236	239	156	155	129	129
	122	272	95	96	120		121	136	121	187	258	251	268	267	282	96	138	126	163	178	183	207	235	238	155	154	128	128
	121	122	81	95	106		106	135	106	163		207		265		95	125	121	152	152	182	192	234	194	154		102	97
	120		54		80		96	122	96	123		173		187		81	97	99	122	125	181	179	191	179	153		77	
	106		39		67		95	121	80	120		95		96		54	96	98	97	97	158	165	138	166	152		64	
	80				53		94	95	67	95				95		43	95	97	96	96	97	135	122	165	128			
	53				39		80		53									96	95		96	121	97	148	102			
	39						53		39									82	56		95	96		123	76			
							39											42	40		64	95		121	63			
																					62	56		97				
																								96				
																								95				
																								84				
																								67				
																								54				
																								42				
																								40				

[a] n = neat heated at 280 °C; b = 1% in benzene heated at 320 °C; a = 1% in acetone heated at 280 °C.

TABLE 11: GC/MS Analysis of the Decomposition Products of $(NH_2)TP$[a]

	$(NH_2)TP$		1B		1A		1D			1L		biphenyl	
amount	L	S,L	L	L	M	M	L			M		L	
found in	n	b,a	n	a	n	b,a	a			a		b	
retent. min.	18:00		6:05		6:30		6:21			16:34		8:25	
M.W.	191		96		121		138			234		154	
	EI	CI+	EI	CI+	EI	CI+	EI	CI+	EI d6	EI	CI+	EI	CI+
	191	192	96	97	121	122	138	139	140	234	236	154	155
	121	191	95	96	120	121	96	138	97	193	235	153	154
	120	150	81	95	106		95	125	96	191	234	152	
	106	122	54		95		81	97	95	178	191	128	
	80	121	39		80		43	96	82	149	138	76	
	67				67			95	40	138	122		
	53				53					122	97		
	42				39					95			
	39									70			
										43			

[a] n = neat heated at 280 °C; b = 1% in benzene heated at 320 °C; a = 1% in acetone heated at 280 °C.

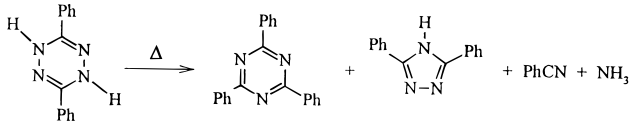


Figure 12. Examples of ring rearrangement during thermolysis of tetrazines.

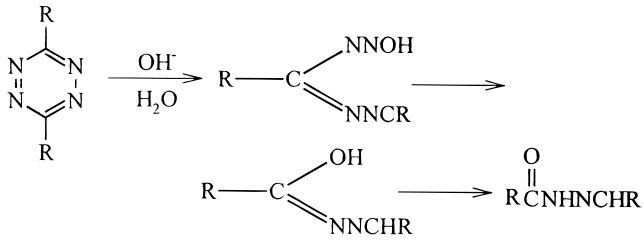


Figure 13. Decomposition of tetrazine in base.

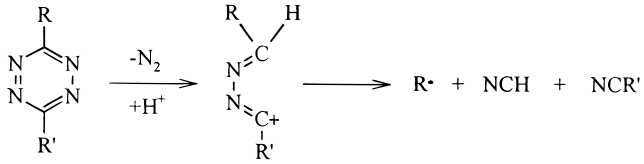
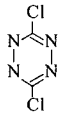
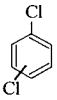
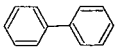


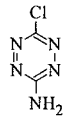
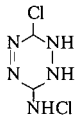
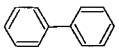
Figure 14. Decomposition of tetrazine in acid.

a decomposition pathway dependent only on the expulsion of nitrogen, we would expect the rates of decomposition among the tetrazines would be reasonably similar. Although substituent effects may be large, we would not expect rates differing by over 10 orders of magnitude (i.e., at 240 °C). Table 13 groups the tetrazines by similar thermal stability. Group 1, the tetrazines with hydrazine substituents, were substantially less stable than the rest. Group 2, with intermediate stability, includes tetrazines with dimethylpyrazole but no hydrazine substituent and ClT-(NH_2). Group 3, Cl_2T and $(NH_2)_2T$, with two chlorines and two amine substituents, respectively, were the most thermally stable. The observation of a primary DKIE in the decomposition of some of the tetrazines, specifically those with amine substituents and possibly those with hydrazine substituents, indicates the addition of a proton to these substituents is part of or precedes the rate-determining step. The mechanism illustrated in Figure 2b does not fit such a model. The data suggest that decomposition may start with a reaction at the substituent.

Decomposition of tetrazines is enhanced by both acids and bases. Base attack cleaves the C−NN bond (Figure 13)[22] and acid attack results in N_2 loss. (Figure 14). Formation of biphenyl results in all the thermolyses carried out in benzene. Typically, biphenyl is formed when the reacting species, in this case the tetrazine ring or its substituents, abstract hydrogen from benzene.[23] The extra instability of the tetrazines with amine or hydrazine substituents and their retarded decomposition in the presence of deuterated solvent (i.e. DKIE) suggest dissociation of these substituents is facilitated by addition of hydrogen. When 3,5-dimethylpyrazole was the substituent on the tetrazine ring, a primary DKIE was not observed, but C−N homolysis between the tetrazine carbon and pyrazole nitrogen still appeared to be the initial decomposition step. Although 1-cyano-3,5-dimethylpyrazole was a major product, there were numerous other products (1C, 1D, 1F) including 3,5-dimethylpyrazole (1B), which suggested the pyrazole radical was present during the decomposition. From the wide range in decomposition rates and the fact that only about a third of a mole of nitrogen was formed per mole of tetrazine (Table 13), we surmise that the mechanism shown in Figure 2b is not the dominant one in condensed-phase thermolysis. We believe a pathway based on substituent loss is. While this mechanism readily explains the low thermal stability of the tetrazines in group 1 (Table 13), it is more difficult to explain the high thermal stability of the group 3 tetrazines. Dichlorotetrazine is likely stabilized by the electron-withdrawing character of the chlorine coupled with the donating character of the ring nitrogens. Hydrogen bonding in diami-

TABLE 12: GC/MS Analysis of the Decomposition Products of Cl_2T and $ClT(NH_2)$[a]

	Cl_2T		cyanobenzene		dichlorobenzene		biphenyl	
								
amount			L		L			
found in	b		b		b		b	
retent. min.	4:10		4:30		4:40		8:39	
M.W.	150		103		146		154	
	EI	CI+	EI	CI+	EI	CI+	EI	CI+
	152	153	103	104	148	149	155	155
	150	151	76		146	147	154	154
	89	87	50		130	95	153	
	87	62	37		128		152	
	63				113		76	
	61				111			
	47				75			
	37							
	35							

	$ClT(NH_2)$		4A		4B			BP	
			impurity						
amount									
found in	n	b,a	n	b,a	a			b	
retent. min.	9:25		7:53		12:20			8:26	
M.W.	131		161		169			154	
	EI	CI+	EI	CI+	EI	CI+	EI d6	EI	CI+
	133	134	163	164	171	172	175	154	155
	131	132	161	162	169	170	173	153	154
	64	62	128	128	108	108	112	152	
	62		126	126	80		84	76	
	47		119	98	79		82		
	42		117		53		56		
			100		52		54		
			98				42		
			84						
			83						
			82						
			47						
			44						

[a] n = neat heated at 260 °C; b = 1% in benzene heated at 320 °C; a = 1% in acetone heated at 280 °C.

TABLE 13: Summary of Experimental Observations

	group 1 $NHNH_2-T-X$		group 2				group 3	
	$(N_2H_3)_2T$	$(N_2H_3)TP$	$(NH_2)TP$	P_2T	P_2TH_2	$ClT(NH_2)$	Cl_2T	$(NH_2)_2T$
mol of N_2/mol of T	*b*	0.68	0.43	0.36	0.35	0.34	0.43	0.53
DSC exo °C	164(299)	164	297	297	273	238(305)	341	347
rate 240 °C × 10^{-3}	3600[a]	2100[a]	1.6	2.6	5.6	6.7	3.9×10^{-3}	9.6×10^{-7}
rate in benzene	*b*	insol	insol	0.05	0.3	0.005	0.04	insol
DKIE	*b*			1.4	1.1	1.6	1.2	*b*
rate in acetone	*b*	2(140 °C)	0.17	2.1	0.73	0.72	3.1	*b*
DKIE	*b*	1.4	2.0	1.0	1.2	1.5	*b*	*b*
solvent effect	*b*	slows	slows	slows	slows	slows	speeds	*b*

[a] Projected rate constants. [b] Experimental data were not obtained.

notetrazine results in a strong packing lattice, low solubility, high melting point, and high thermal stability. However, as one reviewer pointed out, we have not ruled out the possibility of chain reactions, to which these compounds could be susceptible.

Conclusions

Thermal decomposition of 3,6-substituted-1,2,4,5-tetrazines results in complete loss of the *s*-tetrazine ring structure. As in photodissociation, the principal products are nitrogen gas and substituted nitriles. Photodissociation of 3,6-substituted-1,2,4,5-tetrazines proceeds via loss of N_2 from the tetrazine ring and cleavage of the second N−N bond of the ring to form two nitriles (Figure 2b). While thermal decomposition may follow this pathway, it is not concerted, and it is not the main pathway. The rate-determining step is loss of one of the substituents. For this reason, easily lost substituents such as hydrazine greatly lower the thermal stability of the molecule. For certain substituents, protonation enhances the rate of substituent loss.

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