Thermal and Ultrasonic Dealkylation of *s*-Triazines *via* the Cyclic Transition State

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The possibility of monomolecular dealkylation of *s*-triazines *via* the cyclic transition state (Chugaev reaction) has been demonstrated. The proposed model reaction is similar to the pyrolytic elimination of carboxylic esters, xanthates, and trialkylamine oxide. Evidence for a similar reaction with *s*-triazines having different substituents in position 2 and with ethylamino and isopropylamino groups in positions 4 and 6, respectively, was obtained by heating at 240 to 250° C. Analysis of the evolved olefins provided evidence for the model reaction. The evolution of ethylene and propylene was in accordance with theoretical expectations. Sonication of suspended *s*-triazines in water produced corresponding olefins with ratios similar to the heating experiments.

The metabolism of 2-chloro-4,6-bis(alkylamino)-*s*-triazines in plants and animals has been studied extensively. The phytotoxicity of these compounds decreases when the chlorine is replaced by a hydroxyl group and then dealkylated in positions 4 and 6. Shimabukuro (1968) has established that dealkylation in sorghum and corn does not depend on the substitution of the chlorine by a hydroxyl group. Both the chloro- and hydroxy-*s*-triazines can be dealkylated. This dealkylation involves either of the two alkyl groups of 2-chloro-4-ethylamino-6-isopropylamino-*s*-triazine (atrazine) to form 2-chloro-4-amino-6-ethylamino-*s*-triazine or 2-chloro-4-amino-6-isopropylamino-*s*-triazine. Subsequent metabolism may or may not proceed through a common intermediate (Shimabukuro, 1967, 1968). Montgomery *et al.* (1969) found that 2-hydroxy-4,6-bis(ethylamino)-*s*-triazine (hydroxysimazine) appeared rapidly and then declined with the appearance of other metabolites, indicating that hydroxysimazine was an intermediate in simazine metabolism in corn plants. Shimabukuro (1968) found that ethylamino groups were dealkylated more readily than isopropylamino groups. These researchers agreed that there were two possible pathways for the detoxication of *s*-triazines: (a) substitution of the chlorine by a hydroxyl group; and (b) dealkylation of amino groups. However, they did not agree on the sequence of these chemical changes.

In animals, the major detoxication process occurred by dealkylation rather than the substitution of chlorine with a hydroxyl group (Böhme and Bar, 1967). When rats were fed 2-methylmercapto-4-ethylamino-6-isopropylamino-*s*-triazine (ametryne), the isopropyl group was removed more readily than the ethyl group (Oliver *et al.*, 1969).

The objective of this research was to make a model reaction based on Shimabukuro's results, in which the products of atrazine degradation were 2-chloro-4-amino-6-ethylamino-*s*-triazine and 2-chloro-4-amino-6-isopropylamino-*s*-triazine. The fate of the alkyl groups was of particular interest, since the products of dealkylation have not been clearly identified. There are limitations to any conclusions drawn from model reactions, since *in vitro* results are not necessarily indicative of *in vivo* activity.

The mode of replacement of an alkyl group with a H atom is difficult to explain. This reaction cannot be explained by thermal decomposition of a quaternary ammonium hydroxide or by thermal decomposition of trialkylamine oxides (the Cope reaction). It is proposed that with *s*-triazines there is a reaction similar to the pyrolytic elimination with carboxylic esters or the pyrolytic decomposition of xanthates (the Chugaev reaction). Similar cyclic transition states may be predicted for the *s*-triazines. The previously mentioned reactions are undoubtedly unimolecular and are going through cyclic transition states.

The Chugaev reaction (Figure 1) has been demonstrated to occur with carboxylic esters, xanthates, and organic carbonates (O'Connor and Nace, 1952). Alexander and Mudrak (1950) have shown that the stereochemistry of the reaction provided adequate evidence for the cyclic transition state and "*cis*" eliminations. It is often assumed that the breakage of the C—O bond is synchronous with that of the C—H bond. The time interval between cleavage of the C—O bond and the C—H bond is extremely short. Therefore, it is postulated that the cyclic transition state occurs with "*cis*" elimination because this type of reaction requires the lowest energy of activation.

MATERIALS AND METHODS

Chemicals. The 2-halogen, -hydroxy, -methoxy, and -thiomethyl-4,6-(dialkyldiamino)-*s*-triazines were supplied by Geigy Chemical Company, Ardsley, N.Y. These chemicals were purified on a 40 × 1.5 cm alumina oxide column (Bio-rad aluminum oxide; AG-7200 mesh) using chloroform as the eluant. The resulting purified chemicals were dried *in vacuo*. Solutions of $Hg(ClO_4)_2$ and LiCl were made according to Young *et al.* (1952). Analytical grade organic solvents were obtained from Mallinckrodt Chemical Works, St. Louis, Mo. Silica gel (Brinkmann 15 × 20 cm silica gel, F-254) was employed for thin-layer chromatography (tlc). Ethylene, ethane, propylene, and propane were obtained from Matheson Co., Joliet, Ill. Standards were prepared by adding 100 μl of gas per l. of air.

Trapping of Gases. Reactions were performed by heating 1.0 mmole of substance in a 100 ml flask (A—Figure 2) in an oil bath maintained at 240 to 250° C for 2 hr. During this time, valve (a) was closed, creating a slight vacuum throughout the system due to the difference in liquid levels in buret D. After heating, valve (a) was slightly opened to flush all gases out of the system. Air and the evolved gases were passed through scrubbers B and C, which contained 25 ml of $Hg(ClO_4)_2$ solution, cooled by ice.

Olefins were trapped by the scrubbers and the remaining gases were collected in buret D. Two ml of the $Hg(ClO_4)_2$-olefin complex solution was added to 125 ml flasks with rubber stoppers and 1.5 ml of 4.0*N* LiCl was added to liberate the olefins. The olefins were analyzed by gas chromatography. To determine the efficiency of the scrubbers, samples were

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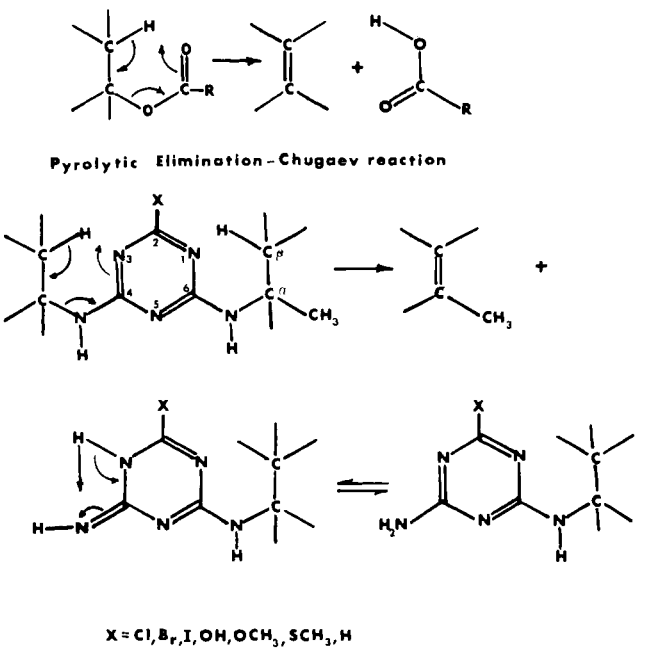

Figure 1. Transition state of Chugaev reaction and proposed reaction with triazine

taken directly from buret D. These tests established that no saturated hydrocarbons were present in the exhausted gases.

All data are expressed as volumes, calculated by comparison with standards.

Gas Chromatography (gc). The gases evolved were analyzed with an Aerograph Model 1200, using a flame ionization detector. The column was 80 cm × 1.5 mm i.d. stainless steel packed with Porapak R (Waters Associates, Inc.). Operating parameters were: column, injection, and detection at 22° C, and nitrogen, hydrogen, and oxygen flow rates of 30, 24, and 250 ml per min, respectively.

Residue Analysis. In propazine experiments, the residue was dissolved in 50 ml of chloroform and eluted on an alumina column with an additional 200 ml of chloroform to give fraction (A); 250 ml ether was passed through the column to give fraction (B), followed by 250 ml methanol to give fraction

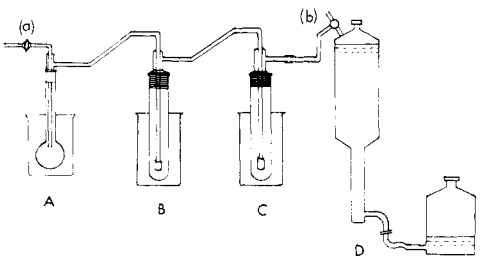

Figure 2. Apparatus for trapping olefins. A is flask for substance, B and C are scrubbers, and D is gas buret

(C). Each fraction was evaporated to concentrate the eluants, which were separated by tlc.

Ultrasonic Dealkylation. Propazine, iodopropazine, atrazine, and iodoatrazine were suspended or solubilized in modified 500 or 1000 ml volumetric flasks. Rubber caps, lined with aluminum foil, were used to maintain a closed system. Flasks were placed in an ultrasonic field (Aerograph Ultrasonic Bath Model D-50) and samples were withdrawn at various time intervals and directly injected into a gas chromatograph. Flasks without compounds and with unlined rubber stoppers were used as controls.

RESULTS AND DISCUSSION

Dealkylation by Heating. It is feasible to conclude that the quantity of olefins evolved depends on two factors: structure of the alkylamino groups in positions 4 and 6, and the substituents in position 2 which are indirectly associated with the reaction.

If we accept the Chugaev mechanism for this reaction, it is expected that, due to its inductive effect, the bond between N—C (α) may be broken more easily if we replace the H on the α-C with the less electrophilic —CH_3 group. The possibility of orientation of one of the two —CH_3 groups of an isopropyl substituent to the *N* in position 3 of the triazine ring should also facilitate the reaction (Figure 3). To test this we may compare simazine (one-α methyl group) with propazine (two-α methyl groups) and atrazine (one of each). The effect of different substituents in positions 4 and 6 on the evolution of gases from the three triazines is presented in Table I. These

Table I. The Evolution of Olefins from Triazines with Different Substituents by Heating at 240 to 250° C for 2 Hr

		Substituents at Position 2							
Triazine	Olefin	Cl	Br	I	OCH_3	SCH_3	OH	OH[a]	H
Propazine	Propylene								
	(ml/mmole)	5.88		21.83	0.03	0.04	0.002	1.15	0.002
	(%)	27.10		100.00	0.13	0.15	0.012	5.30	0.009
Simazine	Ethylene								
	(ml/mmole)	0.27	0.79	1.10			0.004	0.22	0.001
	(%)	1.10	3.46	4.99			0.018	0.97	0.004
Atrazine	Propylene								
	(ml/mmole)	1.91		9.58					
	(%)	8.80		44.10					
	Ethylene								
	(ml/mmole)	0.07		1.36					
	(%)	0.29		6.00					
Simazine + propazine	Propylene								
	(ml/mmole)	8.63							
	(%)	39.77							
	Ethylene								
	(ml/mmole)	0.60							
	(%)	2.66							

[a] Heated at 300 to 340° C.

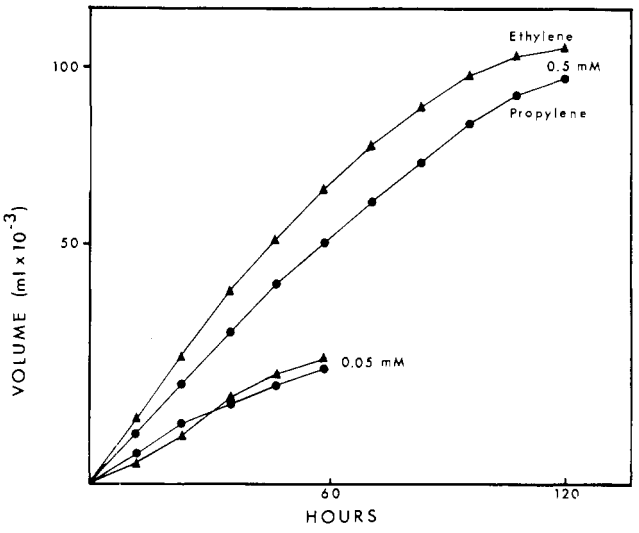

Figure 3. Ultrasonic dealkylation of atrazine with time and at two concentrations

percentages were calculated on the basis of 1 mole of olefin to 1 mole of substance, since atrazine and its derivatives have different substituents in positions 4 and 6. Propazine and simazine may be considered with half the percentage values given in Table I, assuming that the reaction of dealkylation can occur on both sides. The ratio between ethylene and propylene after heating atrazine was approximately 1 to 30. Likewise, a ratio of 1 to 25 was obtained when comparing the ethylene evolved by heating simazine and the propylene evolved upon heating propazine. The ratios obtained with iodoatrazine (1 to 7) and iodosimazine, and iodopropazine (1 to 20) exhibited the same trend.

An interesting comparison is that there was also three times as much propylene evolved from propazine as from atrazine, and 2.3 times as much propylene from iodopropazine as iodoatrazine. This supports the hypothesis that the bond between nitrogen and carbon may be broken more easily if the hydrogen on the α-C is replaced with a $-CH_3$ group.

The influence of substituents in position 2 on the evolution of olefins can be observed with halogen derivatives of several triazines. Unfortunately, these results are incomplete because of a lack of bromoatrazine and bromopropazine.

As expected, there was a decrease in resonance effects with I > Br > Cl, with a corresponding lower electronic density occurring on the *N* atom in positions 1 and 3 (Table I). This indicates a corresponding decrease in proton acceptor power at positions 1 and 3 of the ring *N*. This resulted in a decrease in evolved olefins which is in accordance with theoretical expectations, indicating a mechanism of dealkylation through the cyclic transition state. To establish that experimental conditions were not affecting results, simazine and propazine were heated alone and together. The evolution of gases was compared with atrazine, and the ratios were similar (1 to 14, Table I).

Since some compounds did not yield olefins after 2 hr at 240 to 250° C, they were reheated at 340° C to determine if the reaction mechanism occurs at a higher temperature. Several compounds yielded more olefins at the higher temperature. Hydroxypropazine yielded 481 times as much propylene and hydroxysimazine yielded 67 times as much ethylene at the higher temperatures (Table I). Heating triazines with other substituents in position 2 (—H, —OH, $-OCH_3$, $-SCH_3$) resulted in the evolution of a small amount of olefins.

The evolution of olefins is good evidence for the dealkylation of triazines *via* the cyclic transition state. Further proof of this mechanism may be obtained by examining the residue of dealkylated products. Considering the high temperatures used, other reactions may exist in addition to dealkylation. Nevertheless it is difficult to postulate other reactions prior to dealkylation.

Residue analyses were made after heating propazine, since a relatively large quantity of propylene was evolved and no evidence of carbonization of the residue was observed. Complete separation of the residual compounds was not obtained with column chromatography. Propazine was found in fractions A and B, and dealkylated propazine and a mixture of other compounds were found in fractions B and C. Fraction C was separated by preparative tlc using chloroform-acetone (90 to 10), three times in one direction (5, 10, and 15 cm; one two, and three times, respectively).

The column and tlc with four solvent systems confirmed the presence of 2-chloro-4-amino-6-(isopropylamino)-*s*-triazine in the residue (Table II).

These studies confirm the dealkylation of triazines *via* the cyclic transition state according to the Chugaev mechanism. In addition, a new variety of Chugaev reaction has been demonstrated.

Dealkylation by Sonication. Dealkylation of *s*-triazines *via* the cyclic transition state requires less activation energy than any other known mechanism. Therefore, it may be possible to produce olefins from solutions of *s*-triazines *via* the cyclic transition state using another energy source. The

Table II. R_f Values from Thin-Layer Chromatography of Residual Compounds after Heating Propazine at 240 to 250° C for 2 Hr

Column Fraction	Solvent[a] System	R_f values: Standard: Monodealkylated Propazine	R_f values: Standard: Propazine	R_f values: Residual Compounds
Chloroform (A)	A	0.16	0.44	0.44, 0.05
Ether (B)	A	0.16	0.44	0.16, 0.44, 0.05, 0.60
Methanol (C)	A	0.16	0.44	0.16, 0.05
	B	0.83		0.83
	C	0.69		0.68
	D	0.79		0.79
	A[b]	0.25		0.25, 0.05

[a] Solvent Systems: (A) Chloroform-acetone (90 to 10); (B) *n*-propanol-ammonium hydroxide-water (73:20:7); (C) *n*-butanol-acetic acid-water (90:29:10); and (D) *n*-propanol-water (70 to 30). [b] Solvent system (A) used three times in same direction, first 5 cm, second 10 cm, third 10 cm.

evolution of gases from triazines, suspended in water and placed in an ultrasonic field, was approximately linear with time (Figure 3). However, the production of gases in this manner may be due to contamination of the water or triazine, although this seems unlikely, since water containing no triazines was also sonicated and assayed without the detection of gases.

An increase in pH from 3.48 to 10.00 caused a decrease in evolved olefins during sonication of atrazine (Table III). The percent of evolved olefins from atrazine was higher at 0.05 mM than at 0.5 mM over a 120 hr period of sonication (Figure 3). The relationship of evolved gases from atrazine, iodoatrazine, propazine, and iodopropazine was similar to the heating experiments (Table IV). The ultrasonication studies resulted in two different observations; the relationship between pH and olefin evolution, and the production of ethane, a saturated hydrocarbon, which was not obtained in the heating experiments.

The effect on olefin production indicates that this reaction, in water, is not a monomolecular reaction as it was in the heating experiments, but probably occurs through a cyclic transition state. It is postulated that protonation occurs with alkylamino groups or tertiary nitrogen atoms of the triazine ring. In the first case, if there is protonation of the alkylamino groups, the reaction should occur more rapidly, but if it occurs on the tertiary nitrogen atom of the triazine ring, the reaction may stop. To clarify this problem, three experiments were conducted with propazine in HCl water solutions with pH's of 0.5, 2.0, and 6.5. Propylene evolution, after 10 hr of sonication from the solutions of different pH was 1.33, 4.21, and 2.32 $\times 10^{-3}$ ml/0.05 μmole, respectively. It is probable that with H^+ at the lowest pH (0.5), there is protonation of the alkylamino groups and the tertiary nitrogen of the triazine ring. At pH 2.0, there is protonation only on the alkylamino groups, resulting in a more rapid reaction. At pH 6.5 there is no protonation, which is responsible for the slowness of the reaction.

In tests with ultrasonication in water, ethane was evolved. It is possible that ethane may be evolved from the triazines at the same time as dealkylation, or it may be produced later from ethylene. However, the residues after sonication were not analyzed and thus direct proof for dealkylation is lacking.

Table III. The Effect of pH on the Evolution of Gases from Atrazine Sonicated for 8 Hr at Room Temperature

pH	Gas Evolved (μl/0.5 mmole/50 ml)		
	Ethylene	Ethane	Propylene
(1) 3.48	1.61	0.97	1.27
(2) 4.38	1.50	0.99	1.20
(3) 5.55	1.14	0.78	0.98
(4) 7.00	0.94	0.63	0.84
(5) 8.00	0.93	0.70	0.79
(6) 10.00	0.83	0.63	0.65

Table IV. The Effect of Substituents on Dealkylation of Triazines in an Ultrasonic Field for 5 Hr

Triazine	Gas Evolved (μl/0.05 mmole)					
	Ethylene		Ethane		Propylene	
	(μl)	(%)	(μl)	(%)	(μl)	(%)
Atrazine	6.70	0.59	3.39	0.30	5.21	0.48
I-Atrazine	10.67	0.95	4.06	0.37	10.73	0.99
I-Propazine	3.34	0.29	8.10	0.73	20.80	1.91

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