Bull. Environm. Contam. Toxicol. 25, 118-121 (1980)

Formate Esters of 1,2-Ethanediol: Major Decomposition Products of *p*-Dioxane During Storage

D. Jewett and J. G. Lawless
Ames Research Center, NASA, Moffett Field, CA 94035

In the course of using the hydroxamate assay for high-energy biochemical intermediates (STADTMAN and LIPMANN 1950), we noted that samples from six of eight bottles of p-dioxane from different sources gave a positive response for highly reactive acyl groups. Neither dioxane nor its reported contaminants (HESS and FRAHM 1938) could be expected to show such activity, which is limited to thiol- and formate esters, acylphosphates, amides, halides, anhydrides and lactones. Of the few such compounds to which there has been wide environmental exposure, acetamide and beta-propiolactone are probable carcinogens (CHRISTENSEN 1976), and formamide is an experimental teratogen. Thus, it seemed that the positive hydroxamate response might indicate an unsuspected hazard. For this reason, we decided to identify the contaminants responsible. We found that all acyl groups transferred were formyl groups and identified the mono- and diformates of 1,2-ethanediol as major sources of this activity. Further experiments indicated that the formate esters were formed by way of peroxide intermediates. Concentrations of the formate ester group as high as 1.8 M were found in partially consumed bottles of dioxane, but not in other common ethers stored under similar conditions. In view of this, exposure to the glycol formates is probably much wider than expected, and studies on the metabolism and toxicity of purified p-dioxane (YOUNG 1977) may not reflect the total hazard from long-term storage and handling of this solvent.

EXPERIMENTAL

A 100 mL sample of p-dioxane, 1.8 M in reactive formate (see Table 1), was treated as follows: The low-boiling fraction, 96.5 mL, was removed in a rotary evaporator under vacuum. The remaining material was distilled in a short-path apparatus, under vacuum, from a reservoir at 20° to a cold finger at 0°, to give 1.5 mL of distillate. A portion of this distillate was fractionated by preparative GLC (20% Carbowax 20M TPA on Chromsorb W). Portions of the fractions corresponding to the major peaks were treated with 5 µL of a 10% solution of hydroxylamine, free base (HURD 1939) in methanol. Two of these fractions gave a color reaction characteristic of a hydroxamic acid when treated with acidified ferric chloride as in STADTMAN and LIPMANN (1950). When compared with known hydroxamate standards by TLC (Cellulose MN; developed with butanol saturated with water; detected by acidified ferric chloride), this material had an R_f uniquely characteristic of the formate group. These two

0007-4861/80/0025-0118 $01.00

hydroxamate-active fractions, when examined by GC in three different systems (Carbowax 20M TPA on Chromsorb W; EGA on Aeropak 30; Chromsorb 101), each gave a single peak corresponding to 1,2-ethanediol. The original untreated fractions gave single peaks corresponding to the mono- and diformates of 1,2-ethanediol, synthesized by the method of BIJEN (1973) (Fig. 1). These tentative identifications were further confirmed by GC-MS (monoformate m/e 31, 60, 44, 29, 32, 28, 27, etc.; diformate m/e 44, 31, 29, 60, 28, 32, 27, etc.).

Samples of reagent-grade dioxane were assayed for relative amounts of mono- and diformate esters of 1,2-ethanediol by GC on Chromsorb 101 at 180°, for total formate ester by colorimetric assay of the ferric hydroxamate complex at 435 mμ (SLY and STADTMAN 1963), and for peroxides with ferrous thiocyanate (ABRAHAM et al. 1957). Results of these tests are summarized in Table 1. To test the hypothesis that the esters were formed by a photochemical route, samples of purified dioxane (VOGEL 1962) were photolyzed for 1 h in septum-stoppered containers of various types in a Rayonet photochemical reactor fitted with 254 mμ lamps, then assayed for formate ester and peroxides as above.

DISCUSSION

The rapid formation of peroxides in dioxane and other ethers is well known, and the formation of formate esters from peroxides by a free-radical mechanism has been observed in many cases (SOSNOVSKY and RAWLINSON 1971, SCHAAP 1971). However, the rapid formation of formate esters under ordinary conditions of storage seems to be unique to dioxane. No formate esters were detected in partially used bottles of diethyl ether (3 samples), tetrahydrofuran (3 samples), diethylene glycol monomethyl ether (1 sample), ethylene glycol monomethyl ether (3 samples) or diisopropyl ether (1 sample). However, formate ester did appear in a sample of tetrahydrofuran after photolysis in a quartz tube under an air atmosphere. In dioxane, the inhibition of formate ester formation by the exclusion of air (Table 1) is consistent with a peroxide intermediate. It is of practical significance to note that bottles of dioxane stored unopened for many years developed neither peroxide nor formate ester, whereas both types of contamination developed rapidly after bottles were opened. The simple expedient of purging containers of dioxane with nitrogen each time they are opened and storing them in the cold away from light could prevent both the economic loss and possible health hazard from this contamination. Suppliers might, by explicit information on the labels concerning the special problems with dioxane, help to encourage such a practice. While the acute toxicity of the glycol formates (VONOETINGEN 1959) is not inordinately high compared to other compounds to which people are commonly exposed, a possible mechanism for chronic toxicity by way of acylation of nucleophilic groups is indicated by the reactivity of these compounds in the hydroxamate assay.

Acknowledgment: We thank Frank Church for obtaining the mass spectra.

TABLE 1. Formate Esters and Peroxides in Samples of p-Dioxane After Different Histories of Exposure to Air and Light

p-Dioxane sample, source and treatment	Total molarity formate ester	Peroxide by spot test	Relative amounts of glycol esters by GLC	
			Monoformate	Diformate
Reagent samples				
Unopened, room temp., more than 5 yr	trace	±	0	0
Unopened, room temp., more than 5 yr, dark	trace	±	Not measured	
Partly used, 4°C, many yr, dim light	trace	±	Not measured	
Open 3 mo	0.31	+	40	25
Open, history unknown	0.53	++	95	65
Open, history unknown	0.39	++	85	45
Open, history unknown	1.79	++	245	135
Open, history unknown	1.14	+	Not measured	
Photolysis, 1 h				
Control, purified p-dioxane	0	-		
Quartz tube, air	0.1	++		
Quartz tube, N_2	0	-		
Quartz tube, vacuum	0	-		
Quartz tube, air, foil covered	0	-		
Quartz tube, air, benzophenone	0.8	+++		
Flint glass, air	trace	-		
Same + benzophenone	0.2	+++		
Brown glass, air	0.05	-		
Same + benzophenone	trace	+		

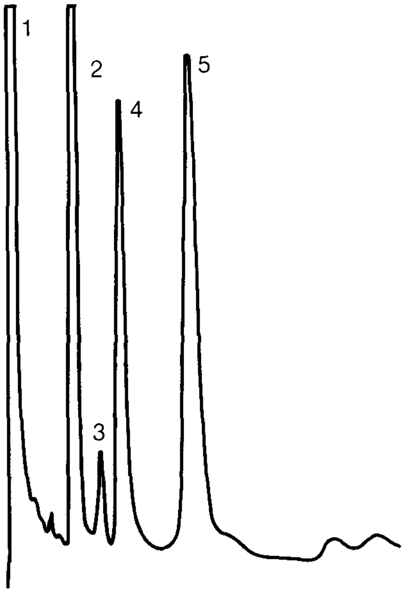

Figure 1. GC separation of distillate from p-dioxane. Chromsorb 101, 2 mm x 2 m, N_2 carrier at 35 mL/min, 150°C isothermal. Peak 1 p-dioxane; 2, 3 unidentified; 4 1,2-ethanediol monoformate; 5 1,2-ethanediol diformate.

REFERENCES

ABRAHAM, M. H., A. G. DAVIES, D. R. LLEWELLYN, and E. J. THAIN: Anal. Chim. Acta 17, 499 (1957).
BIJEN, J. M. J.: J. Mol. Struct. 17, 69 (1973).
CHRISTENSEN, H.: Suspected Carcinogens, 2 ed. Cincinnati; NIOSH 1976.
HESS, K., and H. FRAHM: Chem. Ber. 71B, 2627 (1938).
HURD, D.: Inorg. Synth. 1, 87 (1939).
SCHAAP, A. P.: Tetrahedron Lett. 1757 (1971).
SLY, W. S., and E. R. STADTMAN: J. Biol. Chem. 238, 2639 (1963).
SOSNOVSKY, G., and D. J. RAWLINSON: Organic peroxides. Vol. II. New York: D. Swern, ed., Interscience 1971.
STADTMAN, E. R., and F. LIPMANN: J. Biol. Chem. 185, 549 (1950).
VOGEL, A. I.: A textbook of practical organic chemistry. 3 ed. New York: Wiley 1962.
VONOETINGEN, W. F.: AMA Arch. Ind. Health 20, 517 (1959).
YOUNG, J. D., W. H. BRAUN, L. W. RAMPY, M. B. CHENOWETH, and G. E. BLAU: J. Toxicol. Environ. Health 3, 507 (1977).