Aldehydes—
Photometric Analysis

Volume 5

Formaldehyde Precursors

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PREFACE

This fifth volume of the series is concerned with the huge variety of formaldehyde precursors in the environment and in biological tissues and fluids. Photometric methods of analysis of these precursors through their derived formaldehyde are discussed. Representative procedures of analysis are given for many of these compounds. In addition some indirect methods of analyses are described for enzymes and other compounds where a secondary reactant is the formaldehyde precursor and analysis is for the test substance in terms of the formaldehyde derived from the reactant.

In this volume we are also concerned with the formation of formaldehyde from the aspects of (i) possible analytical utility of the reaction in the future, (ii) the structure and physiological and environmental prevalence of the precursors, (iii) the reactions involved in the formation of formaldehyde, (iv) the type of environment or living tissue wherein these reactions take place, (v) the physiologically useful or toxic phenomenon resulting directly or indirectly from the formation of formaldehyde in the environment or living tissue, and (vi) the types of structures or bonds formed in the reaction of metabolically-derived formaldehyde with the chemicals and biopolymers in living tissue.

Examples of some of the biological processes in which formaldehyde formation and formaldehyde reactions may play a role are mutagenicity, carcinogenicity, schizophrenia, clastogenicity, teratogenicity, atmospheric lachrymation and aging. There are a fairly large number of carcinogens from which formaldehyde can be derived analytically and/or metabolically. These include 1,2-aminoalkanols, azomethanes, azoxymethanes, cycasin, α-chloromethyl ethers, methylnitrosamines, epoxides, ethylenimine, chlorobutadiene, methylhydrazines, methyltriazenes, methyltetrazenes, N-methyl aromatic amines, N-methyl azo dyes, β-propiolactone, safrole, vinyl chloride, vinylidene chloride, etc.

We do not think that the important roles of physiologically derived formaldehyde in biological processes have as yet been adequately investigated or explained, probably due to the lack of adequate analytical techniques. We do know that formaldehyde can be metabolically derived from many drugs, carcinogens and natural products. We do know that formaldehyde can be used constructively in living tissue and even destructively. There are indications that formaldehyde could form hallucinogenic drugs in the brain; there are

indications that it could affect the vital reactions of DNA. Thus, much needs to be done in improving analytical methods for the analysis of formaldehyde and its precursors in the environment and in living tissue and in investigating the many ramifications of the formation, reaction and biological effects of formaldehyde in the environment and in living tissue.

Raleigh, N.C.

EUGENE SAWICKI
CAROLE R. SAWICKI

To the good guys,
wherever you are.
Though you're losing,
this one's for you.

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I. INTRODUCTION

Among the largest families of widely dissimilar compounds containing the same hidden functional group are the formaldehyde precursors. These compounds can be characterized or determined through the formation of a chromogen or fluorogen from the formaldehyde obtained from the test substance. Examples of this type of functional group analysis are presented in Tables 1 to 4. This type of analysis has been briefly reviewed from two different viewpoints.[521, 522]

The formaldehyde precursors are probably one of the most prevalent groups of organic chemicals in the human environment. Consequently, in attempting to understand and control the environment in terms of these compounds a vast variety of mixtures have to be collected and sometimes separated before analysis. Analysis of the various types of precursors are discussed in the following sections.

Since formaldehyde is reported to be carcinogenic[523] and mutagenic to *Drosophila* with[524] and without[525, 526] hydrogen peroxide, to *Neurospora cassida* with hydrogen peroxide,[527] and to *E. coli*,[528] the formaldehyde precursors can be even more important physiologically especially if formaldehyde can be derived from them metabolically at the target tissue polymer.

There is some evidence of the importance of formaldehyde addition products (essentially potential formaldehyde precursors) in mutagenic reactions. Thus, foods treated with formaldehyde are transformed into effective mutagens for *Drosophila*, e.g. casein treated with formaldehyde and subsequently washed is such a mutagen.[529]

In this respect both free amino acids and amino acids of protein molecules are involved in the reaction of formaldehyde with nucleic acid components.[530] Similarly chromosomal proteins can be joined to DNA by treatment with formaldehyde.[531] The rate of reaction of formaldehyde with nucleotides increases in the presence of amino acids and lysine rich proteins.[530] The reaction is accompanied by a degradation of DNA. The formation of potential formaldehyde precursors under these conditions may be of interest for the study of the cytostatic and mutagenic action of formaldehyde and its precursors.

Table 1. Formation of formaldehyde from precursors

Precursors	Reagent	Reaction[a]	Ref.
2-Acetylamino-2-deoxy-D-glucose diethyl dithioacetal	Periodate	(O)	1, 2
N-Acetylglucosamines	Periodate	(O)	3, 4
N-Acetylhexosamines	Periodate	(O)	5
N-Acetylneuraminic acid	Periodate	(O)	6
Acrylamide	Permanganate–periodate	(O)	7, 8
Acrylic acid	Permanganate–periodate	(O)	7, 8
Acrylonitrile	Permanganate–periodate[b]	(O)	9
Adenosine	Periodate	(O)	4
Adonitol	Periodate	(O)	4
Alar (N-Dimethylaminosuccinamic acid)	Alkali → selenium dioxide	H → (O)	10
Albumin[c]	Periodate	(O)	11
Aldohexoses	Acid	D → (O)	12
Aldoses	Periodate	(O)	5, 13
Aldosterone		(O)	14
Alkanolamines	Periodate	(O)	15
1-Alkenes[d]	Ozone	(O)	16–18
1-Alkenes[e]	Air	Photooxidation	19–23
1-Alkenes	Permanganate–periodate	(O)	7, 9, 24
0-Alkylglycerols	Periodate	(O)	25
Allyl acetate	Permanganate–periodate	(O)	9
Allyl alcohol	Permanganate–periodate	(O)	7, 9, 26, 27
Allylamine	Permanganate–periodate	(O)	7, 9
Allylbenzene	Permanganate–periodate	(O)	7
Allyl bromide	Permanganate–periodate	(O)	7
Allyl chloride	Permanganate–periodate	(O)	7
Allyl ethyl ether	Permanganate–periodate	(O)	9
1-Allylthiourea	Permanganate–periodate	(O)	9

2-Amino-1-alkanols	Periodate	(O)	28–30
2-Amino-2-deoxy-D-glucose diethyl dithioacetal	Periodate	(O)	1, 2
2-Amino-1-ethanol	Periodate	(O)	26, 30, 31
2-Amino-2-hydroxymethyl-1,3-propanediol	Periodate	(O)	32
2-Amino-2-deoxy-D-glucose	Periodate	(O)	3, 11, 30, 33
2-Amino-2-deoxy-D-galactose	Periodate	(O)	3, 11
Aminopyrine	Air + enzyme	(O)	34–36
Aminopyrine	N-Demethylase	(O)	37, 38
Angelic acid	Periodate	(O)	7
Anhydro-D-xylo-benzimidazole	Periodate	(O)	39, 40
Anisyl alcohol	H_2SO_4	(O)	41, 42
Apiole	H_2SO_4	(O)	43
Arabinose	Periodate	(O)	4, 44
Arabitol	Periodate	(O)	4, 44, 45
Aramite[f]	Alkali → Periodate	H → (O)	46, 47
Asarinin	H_2SO_4	H	48
Ascorbic acid	Periodate	(O)	44
Azomethane	Aq. H_2SO_4	Taut → H	49
Azoxymethane	Air + enzyme	(O)	50
Benzphetamine	N-Demethylase	(O)	37
Betaine	Bacterial cells[g]	(O)[h]	51, 52
Bilirubin	ArN_2^+	Displacement	53–56
Bilirubin[i]	MBTH + $FeCl_3$	Diaz. + (O)	57
1,2-Bis(4-hydroxy-3-methoxyphenyl)-1,3-propanediol	Strong acid	DP	58
Bis-chloromethyl ether	Water	H	59, 60
2-Bromo-2-nitropropan-1,3-diol	Acid	H	61
3-Bromopropene	Permanganate + periodate	(O)	9
2,3-Butanedione	Sulfuric acid (hot)	(O)	62
1,2,4-Butanetriol	Periodate	(O)	4
3-Butenenitrile	Permanganate–periodate	(O)	9
1-Buten-3-ol	Permanganate–periodate	(O)	7, 8

Table 1—*continued*

Precursors	Reagent	Reaction[a]	Ref.
3-Buten-1-ol	Permanganate–periodate	(O)	7, 8
Calciferol	RuO_2 + periodate	(O)	63, 64
Camphene	RuO_2 + periodate	(O)	63, 64
Carbohydrates	Periodate	(O)	3–5, 33, 65, 66
Carbon dioxide	Mg + HCl	(H)	67
Carboxymethylcellulose	H_2SO_4	H → (O)	68–71
Carboxymethyloxysuccinate	Acid	H	72
Cellobiose	Periodate	(O)	73
Cellulose	$NaBH_4$ → acid → periodate	(H) → H → (O)	74
Cellulose acetate formal	Aqueous H_2SO_4	H	75
Cellulose formal	Aqueous H_2SO_4	H	76
Chloracetic acid	H_2SO_4	H → DP	77, 78
Chloramphenicol	H_2SO_4	H → DC	79
Chloramphenicol	Acid → periodate	H → (O)	80
2-Chlorethanol	Periodate	H → (O)	81
1-Chloro-2,3-epoxypropane	Aq. H_2SO_4 → periodate	H → (O)	82
Chlorogenic acid	Permanganate–(periodate)	(O)	4, 9
Chloromethyl methyl ether	Water (warm)	H	59, 60
Chlorophenoxyacetic acids[j]	H_2SO_4 [150° (67) or 165°(68)]	H → DP	83, 84
3-(4-Chlorophenyl)-1-methylurea	N-Demethylase	(O)	85
Chlorphenesin	Periodate	(O)	86
Codeine	N-Demethylase	(O)	37, 38
Corticosteroids[k]	Permanganate–periodate	(O)	7, 8
Corticosteroids	Periodate	(O)	4, 26, 87–94
Corticosteroids	Bismuthate	(O)	95, 96
Cortisol	Periodate	(O)	97
Cycasine[l]	Acid	H	98–100
Cyclohexylazomethane	10% H_2SO_4	Taut → H	49
Cytidine	Periodate	(O)	4