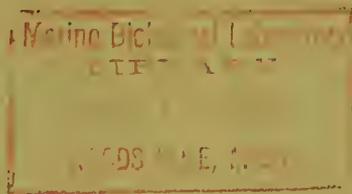


OCCURRENCE AND SIGNIFICANCE OF TRIMETHYLAMINE OXIDE IN MARINE ANIMALS



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THE OCCURRENCE AND SIGNIFICANCE OF TRIMETHYLAMINE
OXIDE IN MARINE ANIMALS

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CONTENTS

	Page
Introduction	1
Chemical nature of trimethylamine oxide	1
Occurrence	1
Occurrence in marine animals	2
Occurrence in fresh-water animals	11
Physiological and biochemical significance of trimethyl- amine oxide	11
Osmoregulation and excretion	11
Elasmobranchs.	11
Teleosts	13
Other marine animals	14
Fresh-water teleosts	14
Nitrogen metabolism	14
Trimethylamine oxide as a product of protein metabolism	14
Trimethylamine oxide from an exogenous source.	15
Trimethylamine oxide as a methyl donor and its relationship to other methylated compounds	16
Other tertiary amine oxides.	16
Formation of trimethylamine oxide in mammals as a result of degradation of choline or choline- containing derivatives	16
Summary.	16
Literature cited	17

TABLES

<u>No.</u>		
1.	Trimethylamine oxide content of marine animals	3
2.	Trimethylamine oxide content of fresh-water animals.	12
3.	Summary of trimethylamine oxide content of marine and fresh-water animals.	13

ABSTRACT

Some pertinent information on the occurrence of trimethylamine oxide in marine animals is reported, and the current ideas on the origin and function of the oxide are examined.

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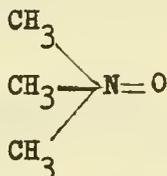
INTRODUCTION

The occurrence of trimethylamine oxide in marine animals is interesting because of its indirect effect on the quality of seafood.

The purposes of this review are (1) to compile pertinent information on the occurrence of trimethylamine oxide in marine animals and (2) to examine current ideas on the origin and function of trimethylamine oxide in these animals.

CHEMICAL NATURE OF TRIMETHYLAMINE OXIDE

Trimethylamine oxide has the following structure:



The oxide is a solid with a melting point of 257° C. It is soluble in water, acting as a weak base with a dissociation constant for the cationic acid of 4.65 (Ronald and Jakobsen 1947). The salts of the oxide have a marked buffering action in the region of pH 4.5 (Castell 1949a, Suyama 1958). In aqueous solution, the oxide is stable between pH 3 and 9 when heated at 107° for 7 hours (Ronald and Jakobsen 1947). The oxide can act as a hydrogen acceptor; it is reduced to trimethylamine in the presence of iron or hemoglobin catalyst and cysteine (Vaisey 1956) and also by an enzyme triamineoxidase (Tarr 1940), which is present in a number of different species of bacteria (Castell 1949b, Tarr 1939). Trimethylamine oxide is not toxic to animals.

OCCURRENCE

Trimethylamine oxide is found with other kinds of nonprotein nitrogen compounds in the fluids and tissues of marine and fresh-water animals. Although this report is concerned primarily with trimethylamine

oxide in marine animals, a short discussion of its occurrence in fresh-water animals is included for comparison.

Occurrence in Marine Animals

Table 1 gives the content of trimethylamine oxide in a number of marine animals. The oxide has been found in a coelenterate, an echinoderm, some molluscs, all crustacea, all elasmobranchs, most teleosts, a reptile, and two mammals. Trimethylamine oxide is not found in marine plants; however, trimethylamine and dimethylamine are found in marine algae (Kapeller-Adler and Vering 1931).

Table 3 gives the mean, range, and standard deviation of trimethylamine oxide in the major groups of marine animals. The mean content of trimethylamine oxide is 134.5 mg.N/100 g. in the elasmobranchs. The mean content of the oxide in the marine teleosts, crustacea, molluscs, and fresh-water teleosts is, respectively, about 0.41, 0.32, 0.26, and <0.1 that of the elasmobranchs.

There is a wide variation in oxide content among the species that compose each group of animals. Values of 38 to 64 mg.N/100 g. have been reported for sprat, Clupea sprattus (Ronald and Jakobsen 1947), whereas values of 3 and 4 mg. N/100 g. have been reported for albacore, Germo alalunga, and bluefin tuna, Thunnus thynnus, respectively (Kawabata 1953). Shewan (1951) has reported that the mean content of oxide in Arctic specimens is higher than that found in North Sea specimens of the same species.

Seasonal variations in oxide content of herring have been observed by Ronald and Jakobsen (1947). They have reported that the oxide content in the tissue in winter is up to 100 percent greater than that found in summer.

The mean content of oxide in cod, Gadus morrhua, haddock, Gadus aeglefinus, and whiting, Gadus merlangus, is greater in large than in small fish.

Uneven distribution of the oxide in different parts of the fish has been observed (Shewan 1951, Suyama and Tokuhiko 1954). The dark lateral line of the flesh of herring and tunny contains only about half as much trimethylamine oxide as is found in the rest of the muscle.

Aside from the differences in diet among the various species, no explanation can be given for the differences in trimethylamine oxide content correlated with geographic area, season, or size of the fish. The finding of a tissue trimethylamine oxide reductase in the dark meat of albacore, Germo alalunga, and frigate-mackerel tissue, Auxis tapeinosoma, (Kawabata 1953) suggests that the variation in content between different parts of the fish is due to the enzymatic breakdown of trimethylamine oxide to trimethylamine. Other investigators have been unable to show that trimethylamine oxide is reduced in swordfish, cod, and halibut muscle (Anderson and Fellers 1949, Shewan and Jones 1957, Tarr 1939).

Table 1.--Trimethylamine oxide content of marine animals

Species	Common name	Concentration	Reference
Coelenterata Scyphozoa <u>Cyanea capillata</u>	Jellyfish	Present	Mohr 1937
Echinodermata Asteroidea <u>Asterias vulgaris</u>	Starfish Atlantic starfish	20 0	Dyer 1952 Shewan 1951
Echinoidea <u>Strongylocentrotus franciscanus</u>	Sea urchin	0	Norris and Benoit 1945a
Holothuroidea <u>Cucumaria frondosa</u> <u>Cucumaria miniata</u> <u>Stichopus californicus</u>	Sea cucumber (Atlantic) Sea cucumber (Pacific) Sea cucumber	76, 86 0 0	Dyer 1952 Norris and Benoit 1945a Norris and Benoit 1945a
Mollusca Amphineura Katharina tunicata <u>Cryptocniton steileri</u>	Black chiton Giant chiton	0 0	Norris and Benoit 1945a Norris and Benoit 1945a
Gastropoda Anisodoris nobilis Thais lamellosa Littorina silchana Polinices heros Haliotis gigontea <u>Turbo cornutus</u>	Sea slug Snail Snail Moonshell Ear-shell Wreath-shell	0 0 0 0 61 20	Norris and Benoit 1945a Norris and Benoit 1945a Norris and Benoit 1945a Dyer 1952 Simidu et al. 1953 Simidu et al. 1953

Table 1.--Trimethylamine oxide content of marine animals (continued)

Species	Common name	Concentration	Reference
Mollusca (cont.)		<u>Mg.N/100 g.</u> <u>wet tissue</u>	
Pelecypoda			
<u>Mya arenaria</u>	Clam	0	Dyer 1952
<u>Spissula solidissima</u>	Bar clam	0	Dyer 1952
<u>Paphia straminea</u>	Clam	0	Norris and Benoit 1945a
<u>Paphia undulata</u>	Clam	38	Simidu and Hibiki 1957
<u>Soxidomus giganteus</u>	Clam	0	Norris and Benoit 1945a
<u>Macoma inquinata</u>	Clam	0	Norris and Benoit 1945a
<u>Mytilus edulis</u>	Mussel (Pacific)	0	Dyer 1952
<u>Mytilus edulis</u>	Mussel (Atlantic)	0	Simidu and Hibiki 1957
<u>Ostrea gigas</u>	Oyster (Pacific)	2	Norris and Benoit 1945a
<u>Ostrea japonica</u>	Oyster (Pacific)	0	Norris and Benoit 1945a
<u>Ostrea virginica</u>	Oyster (Atlantic)	0	Dyer 1952
<u>Ostrea cucullata</u>	Oyster (Indian)	0	Velankar and Govindan 1958
<u>Cardium californiense</u>	Cockle	33	Norris and Benoit 1945a
<u>Cardium corbis</u>	Cockle	15, 18	Norris and Benoit 1945a
<u>Pecten hercivius</u>	Scallop (muscle)	32	Norris and Benoit 1945a
	(organs)	45-73, 63 (9)*	Norris and Benoit 1945a
		3-6, 4 (4)	Norris and Benoit 1945a
	Scallop (muscle)	42-110, 71 (7)	Norris and Benoit 1945a
<u>Pecten hindsii</u>	Scallop (muscle)	45	Norris and Benoit 1945a
<u>Pecten jordanii</u>	Scallop (Atlantic)	79-84, 82 (3)	Norris and Benoit 1945a
<u>Pecten grandis</u>	Scallop (Atlantic)		Dyer 1952
Cephalopoda			
<u>Polyopus hongkongensis</u>	Octopus	24	Norris and Benoit 1945a
<u>Octopus vulgaris</u>	Octopus (basal foot muscle)	11-15, 13 (3)	Asano and Sato 1954
	(terminal foot muscle)	10-11	Asano and Sato 1954
	(abdominal muscle)	10-11	Asano and Sato 1954
	(digestive tract)	2-4	Asano and Sato 1954

* The figures 45-73, 63 (9) means that the range of values was from 45 to 73, that the average value was 63, and that the number of samples was 9.

Table 1.--Trimethylamine oxide content of marine animals (continued)

Species	Common name	Concentration Mg. N/100 g. wet tissue	Reference
Mollusca (cont.) Cephalopoda <u>Octopus fangsiao</u>	Octopus (basal foot muscle) (terminal foot muscle) (abdominal muscle) (digestive tract)	27 24 28 6	Asano and Sato 1954 Asano and Sato 1954 Asano and Sato 1954 Asano and Sato 1954
<u>Octopus dofleini</u>	Octopus (basal foot muscle) (terminal foot muscle) (abdominal muscle)	22 32 40	Asano and Sato 1954 Asano and Sato 1954 Asano and Sato 1954
<u>Loligo opalescens</u> <u>Loligo pealeii</u> <u>Loligo kensaki</u> <u>Sepioteuthis lessoniana</u> <u>Ommastrephes sloanipacificus</u>	Squid Squid Squid Squid Squid	150-156, 153 110-122, 116 87, 66, 261, 138 195 73	Norris and Benoit 1945a Dyer 1952 Simidu et al. 1953 Simidu et al. 1953 Simidu et al. 1953
Arthropoda (Crustacea) Copepoda (A mixture largely of) <u>Corycaeus affinis</u> <u>Calanus finmarchius</u> <u>Tortanus discaudatus</u> <u>Epidablocera amphirites</u>	Zooplankton	63	Norris and Benoit 1945a

Table 1.--Trimethylamine oxide content of marine animals (continued)

Species	Common name	Concentration Mg. N/100 g. wet tissue	Reference
Arthropoda (Crustacea) (cont.)			
Copepoda (A mixture of nearly completely) <u>Corycaeus affinis</u>	Zooplankton	22	Norris and Benoit 1945a
(Mainly) decapod larvae	Zooplankton	47	Shewan 1951
Cirripedia			
<u>Balanus cariosus</u>	Barnacles	24	Norris and Benoit 1945a
<u>Balanus nubila</u>	Barnacles	59-99, <u>80</u> (4)	Norris and Benoit 1945a
<u>Amphipoda</u> sp.	Sand-flea	3	Norris and Benoit 1945a
Decapoda			
<u>Pandalus danae</u>	Shrimp	39-88, <u>64</u> (3)	Norris and Benoit 1945a
<u>Pagurus alaskensis</u>	Hermit crab	36	Norris and Benoit 1945a
<u>Pagurus ochotensis</u>	Hermit crab	66	Norris and Benoit 1945a
<u>Pagurus setosus</u>	Hermit crab	64	Norris and Benoit 1945a
<u>Pagurus tenuimanus</u>	Hermit crab	38, 42, 40, <u>40</u>	Norris and Benoit 1945a
<u>Oregonia gracilis</u>	Spider crab	18	Norris and Benoit 1945a
<u>Pugettia gracilis</u>	Spider crab	13	Norris and Benoit 1945a
<u>Cancer gracilis</u>	Crab	31	Norris and Benoit 1945a
<u>Cancer productus</u>	Crab	64	Norris and Benoit 1945a
<u>Hemigrapsus nudus</u>	Shore crab	15	Norris and Benoit 1945a
<u>Homarus vulgaris</u>	Lobster (muscle) (hepatopancreas)	100-110, <u>105</u> (4) 17, 21	Norris and Benoit 1945a Kermack, Lees and Wood 1955 Kermack, Lees and Wood 1955
Fishes			
Holocephali			
<u>Hydrolagus colliei</u>	Ratfish (muscle) (blood serum)	169, 188, <u>178</u> 10, 11	Norris and Benoit 1945a Norris and Benoit 1945a
	Lobster (Europe) (tail muscle)	19	Hoppe-Seyler 1934

Table 1.--Trimethylamine oxide content of marine animals (continued)

Species	Common name	Concentration	Reference
Fishes (continued)			
<u>Marsipobranchii</u>			
<u>Myxine glutinosa</u>	Hagfish	<u>Mg. N/100 g.</u> <u>wet tissue</u> 63	Dyer 1952
<u>Elasmobranchii</u>			
<u>Lamna nasus</u>	Porbeagle	200	Dyer 1952
<u>Squalus acanthias</u>	Spiny dogfish (muscle) (Atlantic) (blood plasma)	190	Dyer 1952
	Spiny dogfish (muscle)	104	Cohan, Krupp and Chidsay 1958
	(blood serum)	189, 123, <u>156</u>	Norris and Benoit 1945a
	(kidney)	90	Norris and Benoit 1945a
	(liver)	59	Norris and Benoit 1945a
	(pancreas)	25, 11, <u>18</u>	Norris and Benoit 1945a
	(spleen)	10	Norris and Benoit 1945a
	(stomach)	87	Norris and Benoit 1945a
		12	Norris and Benoit 1945a
		86	Norris and Benoit 1945a
		37-160, <u>73</u> (5)	Dyer 1952
		51	Dyer 1952
	Little skate		Beatty and Gibbons 1937
	Prickly skate (Atlantic)		Beatty and Gibbons 1937
	Smooth skate		Love et al. 1959
	Skate	206	Suyama and Tokuhiro 1954
	Skate	254	Beatty and Gibbons 1937
	Barndoor skate	234	Suyama and Tokuhiro 1954
	--	275	Velankar and Govindan 1958
	--	72	Velankar and Govindan 1958
	--	83	Velankar and Govindan 1958
	--	107	Velankar and Govindan 1958
	--	49	Velankar and Govindan 1958
	--	104	Velankar and Govindan 1958
	--	29	Velankar and Govindan 1958
	--	87	Velankar and Govindan 1958
	--	46	Velankar and Govindan 1958
<u>Raja erinacea</u>			
<u>Raja seabrata</u>			
<u>Raja senta</u>			
<u>Raja batis</u>			
<u>Raja hollandi</u>			
<u>Raja laevis</u>			
<u>Mustelus manazo</u>			
<u>Scoliodon sp.</u>			
<u>Chiloscyllium griseum</u>			
<u>Sphyrna mullius</u>			
<u>Trygon microps</u>			
<u>Trygon urnak</u>			
<u>Myliobatis maculata</u>			
<u>Rhynchobatus djeddensis</u>			
<u>Tygron imbricata</u>			

Table 1.--Trimethylamine oxide content of marine animals (continued)

Species	Common name	Concentration <u>Mg. N/100 g.</u> <u>wet tissue</u>	Reference
Fishes (continued)			
Teleostei			
<u>Tarpon atlanticus</u>	Tarpon	43	Dyer 1952
<u>Clupea harengus</u>	Herring (Atlantic)	67-81, <u>74</u> (7)	Dyer 1952
<u>Clupea sprattus</u>	Herring (whole) (entrails) (milts) (roe)	38-64, <u>50</u> (20)	Ronald and Jakobsen 1947
		0	Ronald and Jakobsen 1947
		31-96, <u>75</u>	Ronald and Jakobsen 1947
		4-26, <u>18</u>	Ronald and Jakobsen 1947
<u>Clupea pallasii</u>	Herring (Pacific)	69	Dyer 1952
<u>Oncorhynchus tshawytscha</u>	King salmon	9, 10	Norris and Benoit 1945a
		25	Dyer 1952
<u>Oncorhynchus kisutch</u>	Silver salmon	9-12, <u>10</u> (3)	Norris and Benoit 1945a
<u>Salmo salar</u>	Atlantic salmon	24	Dyer 1952
<u>Menidia notata</u>	Atlantic silverside	28	Dyer 1952
<u>Scomber scombrus</u>	Atlantic mackerel	31-38, <u>34</u> (3)	Dyer 1952
		41-54, <u>48</u> (10)	Beatty and Gibbons 1937
<u>Thunnus thynnus</u>	Bluefin tuna	4	Dyer 1952
<u>Germo alalunga (G)</u>	Albacore (dark meat) (white meat)	3.2	Kawabata 1953
		2.7	Kawabata 1953
<u>Auxis tapeinosoma</u>	Frigate-mackerel (dark meat) (white meat)	15.9	Kawabata 1953
		1.6	Kawabata 1953
<u>Gadus aeglefinus</u>	Cod (Europe) (Arctic)	19-51, <u>44</u> (135)	Love et al. 1959
		60-140, <u>81</u> (136)	Love et al. 1959
<u>Gadus callarias</u>	Cod (Europe) (Arctic)	41-73, <u>62</u> (33)	Love et al. 1959
		19-200, <u>103</u> (260)	Love et al. 1959
<u>Gadus merlangus</u>	Cod (Europe)	44-57, <u>51</u> (70)	Love et al. 1959
<u>Gadus vivens</u>	Cod (Europe) (Arctic)	40	Love et al. 1959
		56-98, <u>77</u> (13)	Love et al. 1959

Table 1.--Trimethylamine oxide content of marine animals (continued)

Species	Common name	Concentration Mg. N/100 g. wet tissue	Reference
Fishes (continued)			
Teleostei			
<u>Gadus morhua</u>	Atlantic cod	67-115, <u>95</u> (25) 110-146, <u>125</u> (50) 44-86, <u>61</u> (7)	Dyer 1952 Beatty 1939 Ronald and Jakobsen 1947
<u>Melanogrammus aeglefinus</u>	Haddock	43-83, <u>70</u> (9) 63-80, <u>71</u> (8) 30-53, <u>43</u> (5)	Dyer 1952 Beatty 1939 Ronald and Jakobsen 1947
<u>Urophycis chuss</u>	Squirrel hake	100-140, <u>120</u> (5) 147-176, <u>166</u> (5)	Dyer 1952 Beatty 1939
<u>Brosme brosme</u>	Cusk	65	Dyer 1952
<u>Macrourus berglax</u>	Smooth spined rat-tail	85	Dyer 1952
<u>Hippoglossus hippoglossus</u>	Atlantic halibut	65-75, <u>70</u> (5)	Dyer 1952
<u>Hippoglossus stenolepis</u>	Pacific halibut	65	Dyer 1952
<u>Hippoglossus platessoides</u>	American plaice	93	Dyer 1952
<u>Limanda ferruginea</u>	Rusty dab	21-88, <u>62</u> (10) 78	Dyer 1952 Beatty 1939
<u>Limanda limanda</u>	--	30-37, <u>34</u> (3)	Love et al. 1959
<u>Pseudopleuronectes americanus</u>	Winter flounder	64-82, <u>70</u> (30)	Dyer 1952
<u>Glyptocephalus glyptocephalus</u>	Lemon sole	36	Ronald and Jakobsen 1947
<u>Glyptocephalus cynoglossus</u>	Witch	43-105, <u>58</u> (6)	Beatty 1939
<u>Lophius piscatorius</u>	Goosefish	42-75, <u>59</u> (2)	Dyer 1952
<u>Panopus argenteus</u>	--	55	Velankar and Govindan 1958
<u>Mugil sp.</u>	--	24	Velankar and Govindan 1958
<u>Chirocentrus dorab</u>	--	36	Velankar and Govindan 1958
<u>Cypsilurus sp.</u>	--	25	Velankar and Govindan 1958
<u>Sardinella albella</u>	--	54	Velankar and Govindan 1958
<u>Athlennes hians</u>	--	43	Velankar and Govindan 1958

Table 1.--Trimethylamine oxide content of marine animals (continued)

Species	Common name	Concentration <u>Mg. N/100 g.</u> <u>wet tissue</u>	Reference
Fishes (continued)			
Teleostei			
<u>Scoberomorus commersonii</u>	--	28	Velankar and Govindan 1958
<u>Plataphrys pentherina</u>	--	36	Velankar and Govindan 1958
<u>Cynoglossus bengalensis</u>	--	36	Velankar and Govindan 1958
<u>Saurida tumbil</u>	--	55	Velankar and Govindan 1958
<u>Sillago sihama</u>	--	21	Velankar and Govindan 1958
<u>Synagris japonicus</u>	--	40	Velankar and Govindan 1958
<u>Lethrinus cinereus</u>	--	55	Velankar and Govindan 1958
<u>Caranx leptolepis</u>	--	54	Velankar and Govindan 1958
<u>Gerres sp.</u>	--	40	Velankar and Govindan 1958
<u>Mulloides flavolineatus</u>	--	51	Velankar and Govindan 1958
<u>Arius sona</u>	--	36	Velankar and Govindan 1958
<u>Scatophagus argus</u>	--	33	Velankar and Govindan 1958
Reptilia			
<u>Chelone imbricata</u>	Sea turtle	5	Velankar and Govindan 1958
Mammalia			
--	Whale	Present	Shewan 1951
--	Porpoise	Present	Shewan 1951
<u>Phocaena phocaena</u>	Porpoise	0	Dyer 1952
<u>Balaenoptera musculus</u>	Blue whale	0	Dyer 1952

Occurrence in Fresh-Water Animals

Fresh-water animals, in comparison to marine animals, contain little trimethylamine oxide (tables 2 and 3). The mean content of trimethylamine oxide in marine teleosts was 54.9, whereas in fresh-water teleosts it was only 7.5 mg. trimethylamine oxide nitrogen per 100 g. Trimethylamine oxide is not found in fresh-water plants or in fresh-water zooplankton (Kapeller-Adler and Vering 1931). Dimethyl- and trimethylamine are also absent from fresh-water algae, but methylamine is present. Tertiary amines have been reported in a number of land plants (Challinor 1914, Cromwell 1950, Gessner 1950, Guggenheim 1951, Henry and Grindly 1949, Smith and Young 1953, and Steiner and Stein 1954).

PHYSIOLOGICAL AND BIOCHEMICAL SIGNIFICANCE OF TRIMETHYLAMINE OXIDE

It is not unreasonable to expect that trimethylamine oxide, which is widely distributed in marine organisms, is associated with some function or functions in these animals. It has, however, been difficult to show these expected relationships. Consideration is given in the following sections to the probably functions of trimethylamine oxide in different animals and to the theories on the origin of the oxide.

Osmoregulation and Excretion

Since there are differences in osmoregulation and excretion among the groups of marine and fresh-water animals, the possible relationship of trimethylamine oxide to these functions will be discussed for each group of animals.

Elasmobranchs.--The osmotic pressure of the tissue fluids of the marine elasmobranch is greater than that of sea water or of the urine of these animals (Baldwin 1948, Smith 1931 and 1936). A urea content of 2.0 to 2.5 percent plus trimethylamine oxide may constitute 42 to 55 percent of the total osmotic pressure of elasmobranch plasma (Cohen, Krupp, and Chidsey 1958). Trimethylamine oxide contributes 7 to 12 percent of this total (Hoppe-Seyler 1930). Although this contribution is small, it appears to be important, since renal conservation of the oxide has been shown in elasmobranchs. The filtered oxide is almost completely reabsorbed in the kidney. Hoppe-Seyler (1930) observed that the concentration of the oxide in the urine was 10 percent, or less, of that in the plasma. The mean concentration of oxide in the plasma for 39 specimens of dogfish was 99 ± 14 mg. N/100 ml. Over a 24-hour period, this concentration only varied 6 to 9 mg. N/100 ml. per specimen. This shows that the concentration is controlled over a narrow range (Cohen, Krupp, and Chidsey 1958).

Table 3.--Summary of trimethylamine oxide content of marine and fresh-water animals

Kind	No. of species	Concentration		
		Range ^{1/}	Mean	Std. dev. ^{1/ 2/}
		Mg. N/100 g.	Mg. N/100 g.	Mg. N/100 g.
Molluscs	35	0-195	35.2	51.3
Crustacea	18	3-105	43.0	27.6
Elasmobranchs	19	29-275	134.5	65.0
Marine teleosts	72	0-143	54.9	26.1
Fresh-water teleosts	21	0-17	7.5	5.4

^{1/} Where two or more values are reported for a species the mean of these was used to represent the range and to calculate the standard deviation.

^{2/} The standard deviation was calculated using the relationship

$$\sqrt{\frac{\sum x^2 - \frac{(\sum x)^2}{N}}{N-1}}$$

where (x) is the content of oxide in milligrams per 100 g. and (N) is the number of species considered.

Teleosts.--The mean freezing-point depression for the fluids of the marine teleost is about -0.7° C., and that for sea water is about -2.0° C. or more. Since the depression of the freezing point varies proportionately with osmotic pressure, the marine teleost must eliminate metabolic products from its tissues against an osmotic-pressure gradient (Baldwin 1951).

The content of trimethylamine oxide in blood plasma of the teleost is low compared to that in the blood plasma of the elasmobranch. The following values have been reported: Lophius piscatorius 12-17 mg. N/100 ml. (Brull and Nizet 1954), Sebastes sp. negligible, Scorpaenichthys marmoratus negligible, and Pleuronectidae sp. negligible (Norris and Benoit 1945a). The small amount of oxide in the teleost blood and the lower osmotic pressure of this blood compared with sea water make it appear unlikely that trimethylamine oxide functions as an osmoregulator. There are, however, several observations that suggest this function. Smith (1958), in the course of Arctic studies, found that the freezing point depression for fluid in the tissue of Arctic teleosts that live near the

surface fluctuates between approximately -1.5° in winter and -0.8° C. in summer. The content of tissue oxide in herring in winter is about double that found in summer (Ronald and Jakobsen 1947). The tissue of Arctic fish has a greater content of oxide than does that of fish of the same species caught in the North Sea (Shewan 1951). These data suggest the possibility that trimethylamine oxide could function to increase osmotic pressure to allow the teleost to live in cold water without the danger of becoming frozen.

Since the tissue fluids of the teleost are at a lower osmotic pressure than is its sea-water environment, the animal is in constant threat of being dehydrated. Teleost urine has been shown to be hypotonic to plasma. The teleost conserves water that would go into the production of urine by excreting up to 90 percent of its excretory nitrogen through the gills in the form principally of ammonia (Baldwin 1948). About one-half of the urinary nitrogen excreted by Lophius piscatorius was trimethylamine oxide (Grollman 1929). Using the same animal, Brull and Nizet (1954), however, reported that the main nitrogenous constituent in the urine was creatinine. Evidence is also lacking on the permeability of gill tissue to trimethylamine oxide. It has been presumed that the oxide is not excreted via the gills.

Other marine animals.--The physiological function of trimethylamine oxide in marine invertebrates is not known. Marine invertebrates are generally in osmotic equilibrium with their environment (Florkin 1949). These animals apparently maintain this equilibrium by transfer of inorganic salts and water across membranes; therefore, the oxide probably does not have an important osmotic function in these animals.

Fresh-water teleosts.--The depression of the freezing point of fresh water is seldom greater than -0.02° , whereas that for the tissues of the fresh-water teleost is approximately -0.6° (Baldwin 1951). These data show that the tissues of the fresh-water teleost are at a greater osmotic pressure than is their environment. Considering the low concentration of trimethylamine oxide in fresh-water fish (tables 2 and 3), it does not appear that the small degree of osmotic pressure contributed by the oxide could be considered an important function in these animals.

Nitrogen Metabolism

Although the origin of trimethylamine oxide is unknown, a number of suggestions have been made that relate the occurrence of trimethylamine oxide in an animal to metabolism of nitrogen-containing compounds.

Trimethylamine oxide as a product of protein metabolism.--Hoppe-Seyler (1930) has suggested that trimethylamine oxide is the nontoxic end product of protein metabolism. Thus far no metabolic pathway for synthesis of trimethylamine oxide has been worked out for the fish or for any other living organism. Baldwin (1951) suggested that trimethylamine oxide may be endogenous in origin, since some marine teleosts can excrete up to 30

percent of their total excretory nitrogen in the form of trimethylamine oxide. There are data to show that not all teleosts excrete large amounts of trimethylamine oxide. Wood (1958) showed that trimethylamine oxide made up only a small fraction of the excreta of sculpin, Leptocottus armatus, starry flounder, Platichthys stellatus, and blue sea-perch, Taeniotoxa lateralis.

Ogilvie and Warren (1957) reported that trimethylamine oxide may originate in the killifish, Fundulus heteroclitus, by an endogenous process. They offered this as an explanation for the apparent accumulation of the oxide in the tissues of fasting animals and of animals on an oxide-free diet. This interpretation is probably incorrect, since the oxide content was reported in units of mg. N/100 g. flesh and no consideration was given the possibility that the animals may have lost weight and thus have shown an apparent increase in tissue oxide.

It has been presumed that if trimethylamine oxide is synthesized by marine teleosts, the last step will involve the conversion of trimethylamine to trimethylamine oxide. Kapeller-Adler and Vering (1931) reported that an enzyme system to catalyze this reaction is lacking in teleosts and amphibia. Such an enzyme system has been demonstrated in man and in other mammals (Lintzel 1935, Norris and Benoit 1945b, Tarr 1941).

Trimethylamine oxide from an exogenous source.--Benoit and Norris (1945) showed that young salmon raised in a marine environment on an oxide-free diet do not accumulate trimethylamine oxide in muscle tissue. When the salmon were fed a diet containing oxide, some retention resulted. Hashimoto and Okaichi (1958a, b) reported that dietary trimethylamine oxide is accumulated in the muscles of the goldfish, Carassius auratus, and the eel, Anguilla japonica; however, when these fish were fed an oxide-free diet, the oxide was not found in the muscle. Okaichi, Manabe, and Hashimoto (1959) reported that the globefish, Fugu niphobles, and filefish, Monacanthus cerrhifer, accumulate ingested trimethylamine oxide in their tissues, whereas the jack mackerel, Trachurus japonicus, does not.

If we accept this idea that trimethylamine oxide in the food is accumulated in the tissue of fishes, then we should look for the synthetic or metabolic source of the oxide at some point in the food chain. Considering the food chain in reverse, we find that the larger teleosts utilize smaller fishes and other larger marine animals as food; these animals utilize the zooplankton, the zooplankton utilize the phytoplankton, and the phytoplankton synthesize their food by photosynthesis. The first point in the food chain where trimethylamine oxide is found is in the zooplankton. The oxide found in zooplankton could get there by two routes. The simpler would be the conversion of the trimethylamine found in the food--marine plants (Channing and Young 1953, Kapeller-Adler and Vering 1931)--to the oxide by the zooplankton. The more complex route would involve the synthesis of the oxide in the zooplankton from smaller fragments. It appears that a study of zooplankton in which the trimethylamine oxidase system and transmethylation systems are investigated might give valuable information on this

aspect of the problem.

Trimethylamine oxide as a methyl donor and its relationship to other methylated compounds.--Barrenscheen and Pantlitschko (1950) have shown that trimethylamine oxide acts as a methyl donor for the synthesis of choline in the muscle brei of guinea pig. This system, which is called cholinepherase, has not been reported in marine animals.

Since trimethylamine and trimethylamine oxide do not prevent lipotropic changes in the livers of experimental animals as does choline (Moyer and du Vigneaud 1942), the transmethylation functions that have been given to choline have not been ascribed to trimethylamine oxide (Arnstein 1955).

Bach (1945) suggests that some marine animals possess a large methylating capacity, as is shown by the occurrence of tetramine, $[(\text{CH}_3)_4 \text{N}]^+$, in the Actinia (sea anemone). A number of other methylated compounds have been found in marine animals. Some of these are choline, glycine betaine, gamma-butyrobetaine, homarine, trigonelline, stachydrine (Shewan 1951), dimethylthetin (Patton 1958), methionine, and dimethylbetaine (Welsh and Prock 1958).

Other tertiary amine oxides.--Tertiary amine oxides, the family of compounds to which trimethylamine oxide belongs, are known to occur as components of plants and animals (Fish, Sweeley, and Horning 1956). It is not known, however, what the function of these oxides might be in the plants and animals. The frequency with which they occur in living organisms suggests that they are something more than terminal oxidation products of amines (Fish, Johnson, and Horning 1956). It has been found possible to carry out a ferric-ion induced rearrangement of tertiary-amine oxides under mild conditions to yield as products a secondary amine plus formaldehyde or formic acid. This rearrangement has been shown for N,N-dimethyl-tryptamine oxide (Fish, Johnson, and Horning 1956) and trimethylamine oxide (Vaisey 1956).

Formation of trimethylamine oxide in mammals as a result of degradation of choline or choline-containing derivatives.--Choline fed to rats is excreted in the urine as trimethylamine oxide (De la Hueraga and Popper 1952, Norris and Benoit 1945b). This is caused by bacterial breakdown of choline to trimethylamine in the intestinal tract (Dyer and Wood 1947); and following absorption, the trimethylamine is converted to the oxide by trimethylamine oxidase. Very small amounts of trimethylamine oxide and trimethylamine are present in mammal tissues; however, no function has been reported for these compounds.

SUMMARY

Trimethylamine oxide has been reported in a coelenterate, an echinoderm, some molluscs, all crustaceans, all elasmobranchs, most

teleosts, a reptile, and mammals from a marine environment and in a crustacean, most teleosts, and an amphibian from a fresh-water environment. In general, animals from a marine environment contain much greater amounts of the oxide than do animals from a fresh-water environment. The oxide is unevenly distributed among marine animals. In marine teleosts, the factors of geographic environment, species, season, size, and location in the animal affect the content of oxide.

Trimethylamine oxide has not been reported in plants; however, other tertiary amine oxides and tertiary amines have been reported.

Trimethylamine oxide appears to contribute to the osmotic pressure of the elasmobranch. It is not known if the oxide functions as an osmotic pressure agent in the teleost.

Certain marine animals possess a strong methylating capacity. It has been reported that trimethylamine oxide will methylate choline in a system isolated from a mammal; however, no such system has been isolated from a marine animal.

It has been suggested that trimethylamine oxide is endogenous in origin and that it might be a product of protein metabolism. There is, however, no direct evidence to prove this point. Mechanisms for the synthesis of trimethylamine oxides have not been demonstrated in animals or plants.

In higher marine animals, the occurrence of trimethylamine oxide can be caused by an exogenous source, since it has been shown that the oxide can accumulate in the muscles of fish from trimethylamine oxide in the food. The zooplankton are the first animals in the food chain that contain the oxide. Zooplankton could obtain the oxide by converting exogenous trimethylamine to the oxide or by synthesizing the oxide from smaller fragments. The primary origin, however, of trimethylamine oxide in marine animals is still to be explained.

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