Gas chromatography of N-hydroxymethyl derivatives

A number of hydroxymethyl (methylol) derivatives, such as the methylol amides (*viz.*, N-methylol derivatives of urethan[1–3], urea[1,4] and methacrylamide[5]) are of current interest in the textile field for their utility in the production of crease-resistant and wash-wear cotton fabrics.

Syntheses of alkyl N-methylol carbamates have been accomplished by reaction of formaldehyde with urethans[3], by fusion of urethans with polymers of formaldehyde in the presence of alkali-condensing agents such as barium hydroxide[6], and via hydrolysis of azidomethyl urethans[7]. More recent work has focused on the preparation and use of dimethylol derivatives such as N,N'-(1,2-ethylene glycol)-diethyl dicarbamate[8], ethyl N-β-hydroxy (alkyl) methyl carbamates[9], bis-N-hydroxymethyl carbamates (prepared via reaction of formaldehyde[10] or higher aldehydes[11] with diol dicarbamates) and the dimethylol derivatives of melamine[5,12], urea[12] and succinamide[12].

The role of hydroxymethylation prior to hydroxylation has been a subject of additional interest in the biosynthesis of metabolites of *p*-aminobenzoic acid[13,14] and in the microsomal metabolism of benzene to phenol via the intermediate benzyl alcohol[15]. The role of hydroxymethylation in diverse cytostatic alkylation reactions has also been recently reported[16].

The present note describes the gas chromatographic behavior of several derivatives of the N-hydroxymethyl class and reports the infrared spectral shifts for a variety of related compounds.

Experimental

The methoxyethyl and methoxyethyl N,N-dimethylol carbamates were obtained from Dr. H. B. GOLDSTEIN, Sun Chemical Corporation, Wood River Junction, Rhode Island (U.S.A.). All other samples were procured from commercial sources. Hexamethyldisilazane and dimethylchlorosilane or alternately, a silylation reagent preparation ("Tri-Sil") were obtained from Peninsular ChemResearch, Inc., Gainesville, Fla., and Pierce Chemical Company, Rockford, Ill., respectively, for silylation purposes.

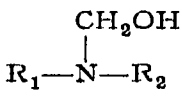
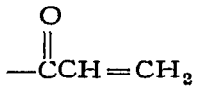
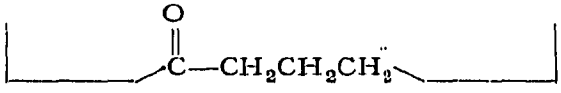
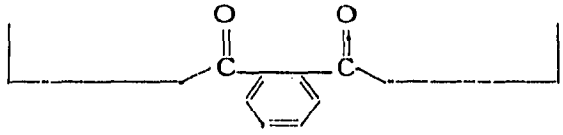
Gas chromatographic analysis was carried out on an F & M Model 1609 flame ionization instrument containing a 6 ft. by 0.25 in. glass column packed with 4% Carbowax 20M terminated with terephthalic acid on 60–80 mesh HMDS-pretreated Chromosorb W. Specific analytical operating conditions are given in the footnotes to Table I. Infrared absorption spectra were determined on a Perkin-Elmer Model 337 grating spectrophotometer.

Results and discussion

The gas chromatographic results for the N-hydroxymethyl derivatives may be seen in Table I. Significant differences in elution values were noted between the carbamates and between their respective trimethylsilyl (TMS) derivatives. The mono N-substituted carbamate emerged much earlier than the N,N-disubstituted compound owing to both the lower molecular weight of the former and the obviously negligible loss of molecular polarity upon replacement of the amine hydrogen with the polar methylol group. The reverse order of elution has been reported for N-alkyl and N,N-dialkyl substituted carbamates[17]. Infrared spectral analysis revealed an absorbance ratio of

TABLE I

GAS CHROMATOGRAPHY OF N-HYDROXYMETHYL DERIVATIVES

Compound 	R_1	R_2	*Elution, t_R° (min)*[a]	
			Compound	*TMS derivat*
Methyl N-hydroxymethyl carbamate	$-COOCH_3$	H	0.8	—[c]
N-hydroxymethyl acrylamide		H	4.2	4.6
N-hydroxymethyl-2-pyrrolidinone			6.9	2.3
Methoxyethyl N,N-dimethylol carbamate[b]	$-COOCH_2CH_2OCH_3$	$-CH_2OH$	7.7	0.25
N,N′-bis(hydroxymethyl) urea		H	—[d]	—[e]
N-hydroxymethyl phthalimide			(4.4)[f]	(1.4)[f]

[a] Column: 4% Carbowax 20M terminated with terephthalic acid on 60–80 mesh HMDS-pretreated Chromosorb W, 6 ft. by 0.25 in. glass coil. Conditions: column 120°; injector 70 V; detector 200°; range 1000; nitrogen carrier 75 ml/min; hydrogen 68 ml/min; air 300 ml/min; flame ionization detector.

[b] The unsubstituted carbamate (methoxyethyl carbamate) eluted at 7.5 min; its N-TMS derivative eluted at 1.7 min.

[c] Three major peaks eluted at 1.6, 1.0 and 0.6 min.

[d] Not detected; melting point: decomposes with discoloration at 265°.

[e] Silylation in dimethylsulfoxide; no TMS peak.

[f] Column 190°; nitrogen carrier 77 ml/min.

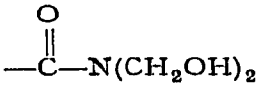
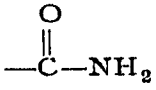
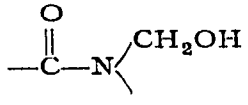
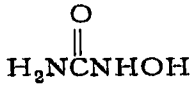
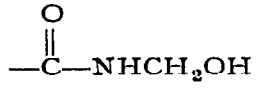
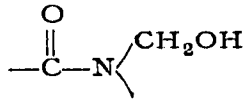
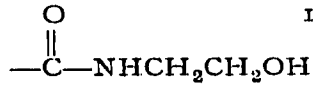
approximately 1:2 for the O–H stretching band relative to the carbonyl band for the N-mono to N-di-substituted carbamate, respectively.

The ureas and salicylamide derivatives were difficult to chromatograph; the acrylamide and pyrrolidinone structures were analyzed quite readily; and the phthalimide compound required a more elevated column temperature. N-Hydroxymethyl acrylamide produced a prolonged elution time upon silylation.

Silylation reactions are quite often notably exothermic, the amount of heat released being related to the rate of the chemical reaction. In this regard, the twelve compounds listed in Table II were qualitatively observed to have the following heats of reaction: 1,5,9 > 12 > 2,7 > 6,8 > 3,4,11 > 10. Several general remarks may be made regarding the relationship of structure to reaction rate. The rate of silylation for compound 2 is probably under steric control of the second methylol grouping attached to the nitrogen atom, while the methylol group of compound 7 could also be expected to have steric restrictions via its attachment to the five-membered ring. In the ureas (compounds 4,6 and 8) the presence of an additional nitrogen atom alpha to the

TABLE II

INFRARED SPECTRA ASSIGNMENTS FOR N-HYDROXYMETHYL DERIVATIVES AND RELATED COMPOUNDS[a]

No.	*Compound*	*Principal structural interest*	*Wave number (cm^{-1})*		
			C=O carbonyl stretch	*O–H stretch*	*N–H bend*
1	N-hydroxymethyl methyl carbamate		1720	3330	1610
2	N,N-bis(hydroxymethyl) methoxyethyl carbamate		1710	3350	—
3	Methoxyethyl carbamate		1720	—	1615[b]
4	N,N′-bis(hydroxymethyl) urea		1650	3325	1610
5	N-hydroxymethyl acrylamide		1670	3305	1630
6	N,N′-bis(hydroxyethyl) urea		1625	3325	1590
7	N-hydroxymethyl-2-pyrrolidinone		1670	3260	—
8	Hydroxyurea		1650	3300	1595
9	Ethanolamine	$H_2NCH_2CH_2OH$	—	3350	1605
10	N-hydroxymethyl salicylamide		1650	3310	1605
11	N-hydroxymethyl phthalimide		1710	3410	—
12	N-β-hydroxyethyl ethyl carbamate		1700	3325	—[c]

[a] All compounds as Nujol mulls on KBr plates.
[b] N–H stretching bands at 3420 (s), 3185 (m) with a medium doublet at 3310 and 3275 cm^{-1}.
[c] N–H bending band obscured by carbonyl stretching band.

carbonyl group could conceivably result in the N-methylol (or N-hydroxy) nitrogen atom having a relatively greater electron density owing to the lessened demand by the carbonyl oxygen, thereby enabling the alcoholic proton to be retained more strongly. However, with compounds 4 and 6, their relatively low solubility in the reaction medium is also an important factor. Silylation of compound 3 occurs via removal of an amine hydrogen. Steric factors are also significant considerations in the silylation of compounds 11 and 10, the more notable effect being observed in the latter compound. Since the TMS derivative of N-hydroxymethyl salicylamide (compound 10) was not detected by gas chromatography, it is possible that this compound did not undergo silylation under the conditions employed.

Infrared spectral assignments are given for carbonyl stretching, oxygen–hydrogen stretching and nitrogen–hydrogen bending vibrations for a number of diverse N-hydroxymethyl derivatives and related structures in Table II. A general displacement was observed for carbonyl stretching towards lower wave numbers (lower vibrational energy) when nitrogen or C=C (in contrast to oxygen) were attached to the left of the carbonyl carbon in the —C(O)N= moiety possibly due to withdrawal of electron density from the C=O bond.

The gas chromatographic behavior of a large selection of hydroxyethyl compounds and the relative influence of silylation is presently under investigation.

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Bionetics Research Laboratories, Inc.,
Falls Church, Va. (U.S.A.)

WALTER L. ZIELINSKI, JR.
LAWRENCE FISHBEIN

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