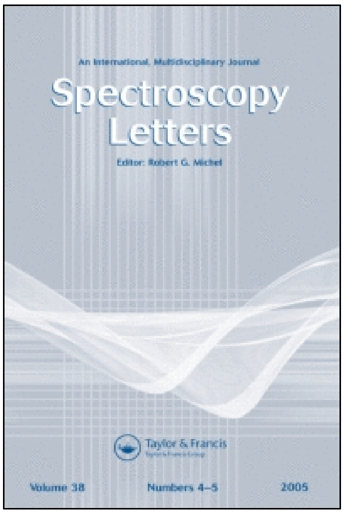

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Infrared Absorption, Nuclear Magnetic Resonance and Electronic Spectra of N-Hydroxyureas and Carbamates

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INFRARED ABSORPTION, NUCLEAR MAGNETIC RESONANCE AND ELECTRONIC SPECTRA OF N-HYDROXYUREAS AND CARBAMATES

Key words: IR, NMR of cyclic N-hydroxyureas and carbamates, Electronic absorption of ferric chelates of cyclic N-hydroxyureas

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During the course of investigating the anticancer activities of new compounds, we have synthesized a series of novel cyclic N-hydroxyurea derivatives and several carbamate intermediates[1-3]. Infrared absorption, nuclear magnetic resonance, and electronic absorption spectra were examined in order to confirm the identities and to study the molecular structure of these compounds.

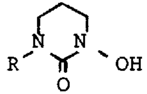
METHOD

Infrared Absorption Spectra

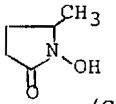
Infrared spectra were recorded on a Beckman IR-4240 Spectrophotometer either in KBr pellet, in pure liquid form, or in CCl_4 solution. The summaries of assignments of the IR spectra for the essential functional groups of cyclic N-hydroxyureas and intermediate carbamates are given in Tables 1 and 2, respectively.

TABLE 1

INFRARED ABSORPTION FREQUENCIES (cm^{-1}) OF CYCLIC N-HYDROXYUREAS AND N-HYDROXYLACTAM



	Absorption in wave number (cm^{-1})									
R	ν_{N-H}	ν_{O-H}	ν_{C-H}	$\nu_{C=O}$	δ_{N-H} (Amide II)	$\nu_{N=O}$	ν_{N-C-N} (assym)	ν_{C-N}	ν_{N-C-N} (sym)	ν_{N-O}
H (KBr pellet)	3270 (m)	3250 (m)	2890	1638 (s)	1530 (s)	---	1445 (s)	1270 (s)	940 (s)	720 (s)
(CL010)	3130 (b)	3040 (b)	2865							
CH_3 (KBr pellet) (CCl_4 solution)[a] (CL020)	---	3160 (s)	2940	1610 (s) 1650 (s)	---	---	1425 (s)	1265 (s)	925 (s)	743 (s)
CH_2CH_3 (KBr pellet)	---	3140 (b,s)	2950 2910 2850	1625 (s)	---	---	1435 (m)	1290 (s)	930 (m)	740 (m)
(CCl_4 solution)	---	3300 (s)	2960	1640 (s)	---	---	1442 (m)	1290 (s)	925 (m)	740 (m)
(CL0210)		3140 (b,s)	2920 2855							
NO (KBr pellet)	---	3480 (s)	2940	1680 (s)	---	1520 (s)	1470 (s)	1270 (s)	938 (s)	720 (s)
(CL012)	---	3120 (s,b)	2870							



(CL300)

	ν_{O-H}	ν_{C-H}	$\nu_{C=O}$	ν_{C-N}	ν_{N-O}
KBr pellet)	3080(b,s)	2950 2910 2800 2760	1650(s)	1275(s)	760(s)
(CCl_4)	3130(s,b) 3090(s,b)	2970 2920 2870 2680	1683(s)	1275(s)	885(m)

a:saturated solution.
(s):strong; (b):broad; (m):medium (w):weak

TABLE 2

INFRARED ABSORPTION FREQUENCIES (cm^{-1}) OF C=O AND N-H OF INTERMEDIATE CARBAMATES

Compound	Condition	ν_{N-H}	$\nu_{C=O}$
$Cl-(CH_2)_2-NHCOOCH_3$	neat CCl_4 solution[a]	3320 (b,s) 3460 (s), 3360 (s)	1690 (s) 1730 (s)
$Cl-(CH_2)_3-NHCOOCH_2CH_3$	neat CCl_4 solution[a]	3310 (b,s) 3465 (s), 3360 (s)	1695 (s) 1730 (s)
$Br-(CH_2)_3-NHCOOCH_2CH_3$	neat CCl_4 solution[a]	3330 (b,s) 3460 (s), 3355 (s)	1705 (s) 1730 (s)
$Br-(CH_2)_2-NHCOOCH_3$	neat CCl_4 solution[a]	3320 (b,s) 3450 (s), 3340 (s)	1705 (s) 1730 (s)
$Br-(CH_2)_2-NHCOOCH_2CH_3$	neat CCl_4 solution[a]	3320 (b,s) 3450 (s), 3340 (s)	1700 (s) 1715 (s)
$Cl-(CH_2)_3-NHCOOCH_3$	neat CCl_4 solution[a]	3340 (b,s) 3460 (s), 3350 (s)	1700 (s) 1715 (s)

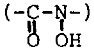
a:the concentration of the solution is approximately 2%.

absorption intensity: b:broad; s:strong.

Nuclear Magnetic Resonance (NMR) Spectra

NMR is one of the most useful tools for studying the molecular structure and properties. Tables 3 and 4 are the summaries of the NMR spectra of the cyclic N-hydroxyureas and the intermediate carbamates, respectively, measured in an Hitachi-Perkin-Elmer R-24 (60 MHz) Spectrometer.

Visible Spectra of Ferric Ion Chelates of Cyclic N-Hydroxyureas

Since the cyclic N-hydroxyureas possess the hydroxamic acid moiety  $(-\underset{\underset{O}{\|}}{C}-\underset{\underset{OH}{|}}{N}-)$ which will form the chelates with the metal ions such as Fe^{+++}, the chelate formation should confirm this essential functional group in the structure.

The chelates were formed by adding 5 ml of modified Trinder's Reagent[4] (without $HgCl_2$) to 1 ml of the cyclic N-hydroxyurea solution. The visible absorption spectra of the chelates were determined in the aqueous media with Perkin-Elmer Coleman 124 double beam spectrophotometer.

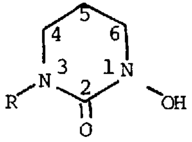
RESULTS AND DISCUSSION

IR Spectra

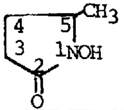
From Tables 1 and 2, one can conclude the following: (1) All the absorptions of the essential functions of these compounds are present and in agreement with the literature values[5,6]; (2) N-H, N-OH, and carbonyl group (C=O) are hydrogen-bonded either in a solid or in a pure liquid state to a greater extent than that in a diluted CCl_4 solution. It has been shown that hydroxyurea forms three hydrogen bonds with neighbor molecules in the crystalline state[7,8]. The difference in the frequency for the carbonyl group of the cyclic N-hydroxyureas between the

TABLE 3

CHEMICAL SHIFT OF CYCLIC N-HYDROXYUREAS AND N-HYDROXYLACTAM



Compound			Chemical shift (δ) ppm			TMS external reference		Coupling constant)cps)		
R	NO-H	N-H	NC-H (α)	NCCH (β)	C_4-H	C_5-H	C_6-H	$J_{5,6}$	$J_{4,6}$	$J_{\alpha,\beta}$
H^a (CL010)	9.03 (s)	6.43 (b)	---	---	3.17 (t)	2.02 (qt)	3.49 (t)	6.0	6.0	---
$CH_3{}^b$ (CL020)	9.11 (s)	---	3.00 (s)	---	3.32 (t)	2.15 (qt)	3.68 (t)	6.0	6.0	---
$CH_2CH_3{}^b$ (CL021)	8.41 (b)	--- ---	3.24^c	1.14 (t)	3.24^c	2.08 (qt)	3.66 (t)	6.0	6.0	6.6
NO^b (CL012)	7.60^d (s)	---	---	---	3.70^e (t)	2.12 (qt)	3.70^e (t)	---	---	---



(CL300)

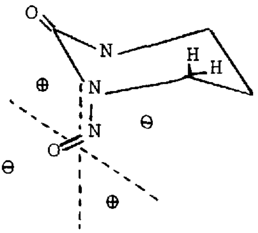
	Chemical shift (δ) ppm	TMS external reference			
Solvent	NO-H	C_3-H	C_4-H	C_5-H	C_5-CH_3
$CDCl_3$	8.85 (b)	2.09 (m)	1.07^f	3.52 (m)	1.07 (d)

a:DMSO-d6 as the solvent. b:$CDCl_3$ as the solvent. c:these two peaks are merged .
d:peaks overlap with $CHCl_3$. e:these two peaks overlap. f:this peak is merged with C_3-H and C_5-H.
peak notations: (s):singlet; (t):triplet; (b):broad; (qt):quintet; (d):doublet; (m):multiplet.

diluted CCl_4 solution and the solid state is about 15 to 40 cm^{-1} (see Table 1). This is also true for the intermediate carbamates (see Table 2); (3) The electron-withdrawing substituent N-NO on 3-N position results in an increased $\nu_{C=O}$ frequency; (4) The higher frequency of $\nu_{C=O}$ of nitroso derivative is also an indication of enhanced partial double character of N - C bond.

NMR Spectra

The chemical shifts (δ in ppm) and the coupling constants (J values) agree with the structure expected (Tables 3 and 4). A few interesting observations are worthwhile mentioning: (1) The chemical shift (δ) for the N-hydroxy proton is relatively high compared to the alcoholic OH, because of the deshielding effect of the ureido $(\text{-N-}\overset{\text{O}}{\overset{\|}{\text{C}}}\text{-N-})$ group. It is also dependent on the concentration due to different degrees of hydrogen bonding. This has also been confirmed by the other investigators[9]; (2) For N-nitroso derivative, the C_4-H is deshielded by the anisotropic effect of the nitroso group, and its peak appears at a lower field than the parent compound[10].



⊕: shielding effect

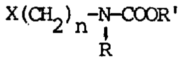
⊖: deshielding effect

Electronic Absorption Spectra of the Metal Chelates of Cyclic N-Hydroxyureas

The color formation and the spectra data indicate that these compounds do behave like hydroxamic acid (see Table 5).

TABLE 4

CHEMICAL SHIFT OF CARBAMATE DERIVATIVES IN $CDCl_3$



$X(CH_2)_n\text{-}\underset{\underset{R}{\downarrow}}{N}\text{-}COOR'$

X	n	R	R'	Chemical shift (δ) ppm							
							R			R'	
				$X\text{-}CH_2\text{-}$	$\text{-}CH_2\text{-}$	$\text{-}CH_2\text{-}N$	H	$\text{-}CH_2\text{-}$	$\text{-}CH_3\text{-}$	$\text{-}CH_2\text{-}$	$\text{-}CH_3$
Cl	3	H	CH_2CH_3	3.65(t)	2.00(qt)	3.31(t)	5.98 (b)	---	---	4.15 (qt)	1.25 (t)
Br	3	H	CH_2CH_3	3.55(t)	2.13(qt)	3.32(t)	5.72 (b)	---	---	4.15 (qr)	1.30 (t)
Cl	3	H	CH_3	3.51^a	1.98(qt)	3.28^a	6.00 (b)	---	---	---	3.66 (s)
Cl	3	CH_3	CH_2CH_3	3.60(t)	2.03(qt)	3.44(t)	---	---	2.93 (s)	4.17 (qr)	1.30 (t)
Cl	3	CH_3	CH_3	3.54^a	1.99(qt)	3.36^a	---	---	2.89	--- (s)	3.62 (s)
Cl	3	CH_2CH_3	CH_3	3.57(t)	1.97(qt)	3.25^b	---	3.25^b	1.09 (t)	---	3.65 (s)
Cl	2	H	CH_3	3.58^b	---	3.58^b	5.96 (b)	---	---	---	3.68 (s)
Br	2	H	CH_3	3.54^b	---	3.54^b	6.40 (b)	---	---	---	3.72 (s)
Br	2	H	CH_2CH_3	3.58^b	---	3.58^b	6.12 (b)	---	---	4.12 (qr)	1.37 (t)

				Chemical shift (δ) ppm							
							R			R'	
X	n	R	R'	X-CH_2-	-CH_2-	-CH_2-N	H	-CH_2-	-CH_3	-CH_2-	-CH_3
Cl	2	H	CH_2CH_3	3.65[b]	---	3.65[b]	5.88 (b)	---	---	4.21 (qr)	1.34 (t)
I	2	H	CH_3	3.60(t)	---	3.39(t)	6.06 (b)	---	---	---	3.82 (s)
I	2	H	CH_2CH_3	3.57(t)	---	3.36(t)	5.95 (b)	---	---	4.27 (qr)	1.40 (t)
NO_2	2	H	CH_3	4.57(t)	---	3.75[b]	6.08 (b)	---	---	---	3.75[b]

a:partially overlapped.
b:completely overlapped

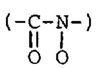
peak notations: (b):broad; (t):triplet; (s):singlet; (qr):quartet; (qt):quintet.

TABLE 5

VISIBLE ABSORPTION MAXIMA AND MOLAR EXTINCTION COEFFICIENT OF FERRIC CHELATES OF CYCLIC N-HYDROXYUREAS IN WATER

Code No	Compound	Transition	λ_{max} (nm)	$(M^{-1}cm^{-1})$ $\times 10^{-3}$
CL010		$n \rightarrow \pi^*$	590	1.36
CL020		$n \rightarrow \pi^*$	605	1.36
CL210		$n \rightarrow \pi^*$	600	0.80
CL012		$n \rightarrow \pi^*$	535	1.05
CL300		$n \rightarrow \pi^*$	540	1.12

There is a bathochromic shift (red shift) for the chelates from CL010 to CL020 and CL210 (see Table 5). The electron-donating character of CH_3 or C_2H_5 group contributes to the higher electron density of the carbonyl group and this auxochromic $N-CH_3$ or

$N-C_2H_5$ lowers the exciting energy for the nearby chromophore[11]  $(-\underset{\underset{O}{\|}}{C}-\underset{\underset{O}{|}}{N}-)_2Fe^+$. This coincides with the observed lower $\nu_{C=O}$ for CL020 (N-hydroxy-N'-methyl-N,N'-trimethyleneurea) or CL210 (N-hydroxy-N'-ethyl-N,N'-trimethyleneurea). On the other hand, hypsochromic shift (blue shift is found for the chelates from CL010 to CL012. This is due to the electron-withdrawing effect of the NO group decreasing the electron density on the carbonyl group. This raises the excitation energy of the nearby hydroxamic acid-Fe chromophore. This is parallel to the finding that $\nu_{C=O}$ of CL012 (N-hydroxy-N'-nitroso-N,N'-trimethyleneurea) higher than that of CL010 (N-hydroxy-N,N'-trimethyleneurea).

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*To whom inquiries should be addressed.

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