

Spectroscopic Studies of Conjugated Uracil Derivatives⁺

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Ultraviolet spectra of 5- and 6-uracilyl compounds which contain conjugated double bonds were obtained and their characteristic phenomena were examined. 5-Formyluracil and 6-methyl-5-formyluracil showed bathochromic shifts which should be expected from a conjugated carbonyl compound. 6-Formyluracil did not show any shift in absorbing wavelength. 5- and 6-uracilylacrylic acid derivatives, on the other hand, showed absorption at similar wavelengths, indicating the presence of a hexatriene chromophore. The ratio of $\Delta\nu/J$ in nuclear magnetic resonance spectra of those compounds decreased drastically as the acrylic acids or esters were converted into amides.

Introduction

Uracil and its derivatives are important compounds in biological chemistry as well as in synthetic organic chemistry. The uracil skeleton is the key structural requirement in numerous biological systems. Sparsomycin is one of the antibiotics which possesses the 6-methyluracil as a building block of the total structure.¹ In the course of our study on the structure-reactivity relationships of sparsomycin analogues we have come to observe the contrasting spectroscopic characteristics of uracil derivatives which have conjugated double bonds at either 5- or 6-position of uracil. We report the contrasting spectroscopic phenomena among uracil compounds.

Results and Discussion

The absorption maxima and molar extinction coefficient of 5- and 6-uracilyl derivatives are listed in Table 1. One of the striking contrasts is that λ_{max} of 6-formyluracil (orotaldehyde, **2a**) appears at shorter wavelength (261 nm) than that of 5-isomer (**1a**, 275 nm) in distilled water. The UV spectrum of uracil shows two bands at 203 and 260 nm.^{2,3} The fact that the 6-substituent does not contribute to the shifts of the absorption maxima of any of the two bands is even more striking. In fact, the presence of 6-methyl or 6-formyl group causes bathochromic shift of the λ_{max} of uracil by only 1 nm although the absorption intensity increases a little.

The bathochromic shift of the λ_{max} in 5-formyluracil (**1a**) may be due to a formation of a new chromophore consisted of the C₅-C₆ double bond in the uracil ring and the carbonyl double bond. The conjugation may be extended by a resonance structure such as **1'**.

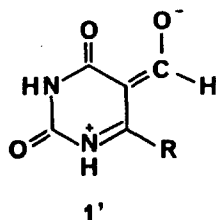
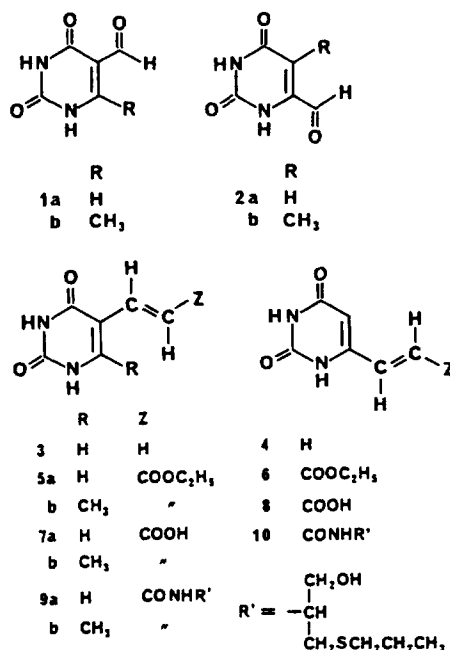


Table 1. Electronic Spectral Data of Uracil Derivatives in Water

Compound	λ_{max} , nm (ϵ)
uracil ^a	260 (9120), 203 (8130)
1a	298 (infl 4420), 275 (8940), 230 (7280)
1b	283 (9870), 233 (7080)
2a	300 (infl 1260), 261 (9280), 202 (10820)
2b ^b	268 (7800)
3 ^c	286 (6820), 238 (11400)
4 ^d	296.5 (9200)
5a	297 (18470), 275 (infl 16000), 220 (infl 17600)
5b	303 (17350), 270 (infl 12880)
6	305 (8770), 228 (infl 12530)
7a	320 (infl 8060), 297 (15500), 266 (13620)
7b	300 (15130), 278 (infl 11700), 217 (infl 13500)
8	300 (12900), 227 (infl 16300), 217 (17910)
9a	298 (18950), 273 (infl 14600)
9b	303 (28200), 271 (infl 17400)
10	303 (13800), 227 (infl 21000), 219 (22500)

^aRef. 2 and 3; at pH 7 and our result. ^bRef. 5; at pH 1. ^cRef. 8; at pH 8. ^dRef. 9; at pH 1.



⁺This paper is dedicated on the occasion of the 60th birthday of Professor Yong-Keun Lee of Yonsei University, Seoul, Korea.

Table 2. Electronic Spectra Data of Uracil Derivatives in Buffer Solutions of pH 8-13

Compound	λ_{max} nm (ϵ)					
	pH 8	pH 9	pH 10	pH 11	pH 12	pH 13
uracil	260 (8100)	262 (8000)	263 (7800)	270 (7230)	284 (6170)	282 (6000)
1a	314i (6400)	315i (6870)	314i (6050)	314i (5640)	317i (4850)	314i (6120)
	297 (9860)	297 (10490)	297 (8930)	297 (8350)	298 (6600)	301 (6730)
	251 (5740)	251 (6040)	251 (5200)	251 (4920)	252 (4130)	266 (4830)
1b	303 (11040)	304 (12090)	304 (12180)	304 (12600)	304 (12500)	308 (11030)
	251 (5690)	251 (6040)	250 (6030)	250 (6030)	250 (6030)	252 (5950)
	202 (8800)	205 (8800)	208 (8900)	212 (8910)	214 (9110)	217 (8050)
2a	264 (5980)	284 (5320)	287 (6170)	287 (6300)	287 (5450)	287 (4540)
5a	319 (15760)	326 (18200)	326 (19300)	327 (20320)	324 (19120)	322 (18480)
	303i (15000)	295i (13750)	295i (14000)	295i (14000)	295i (14120)	282 (13830)
	220i (21750)	220i (17750)	217i (18000)	217i (18000)	218 (16000)	221 (14260)
5b	326 (17780)	329 (19220)	331 (20130)	332 (20500)	329 (30030)	323 (18480)
	295i (12730)	295i (11360)	295i (19550)	295i (10270)	293i (10640)	291i (11270)
	220i (10450)	220i (11360)	220i (11820)	220i (11360)	212 (12740)	215 (7800)
6	317 (4080)	333 (3940)	334 (4070)	327 (4110)	322 (4250)	323 (4160)
	232 (8900)	234 (9580)	233 (9830)	230 (9810)	229 (9510)	229 (9570)
7a	330i (10500)	330i (15000)	330i (19500)	330i (20000)	330i (18500)	330i (22000)
	301 (17870)	314 (20100)	318 (23650)	318 (24030)	318 (23870)	322 (24780)
	270(17200)	278 (17520)	279 (18520)	279 (18510)	279 (18250)	279 (17170)
7b	296 (14070)	297 (13470)	307 (13130)	317 (15130)	320 (16330)	320 (16470)
	278i (12670)	280i (12130)	285i (12000)	290i (11470)	290i (11200)	290i (10870)
	217i (8830)					
8	301 (8760)	305 (7630)	315 (6870)	320 (6970)	323 (6980)	323 (6730)
	224i (13000)	225 (14850)	226 (15740)	227 (16580)	227 (16750)	227 (16930)
	218 (13260)					

i: Inflection.

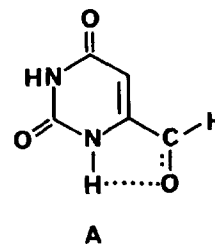
Similar kind of conjugation is not likely in 6-uracilyl compound, **2a**, because the conjugate system thus formed is like a 1,4-dicarbonyl system with a C-C double bond in the middle. In this case the influence by the conjugation should not be significant to cause an appearance of a new band in the longer wavelength region. Therefore, the band from the uracil skeleton is the dominant one in 6-substituted uracil compound.

The rationale is further supported by comparison of the spectra of 6-methyl-5-formyluracil (**1b**) and 5-methyl-6-formyluracil (**2b**). In **1b**, the presence of 6-methyl group causes a bathochromic shift of the λ_{max} by 8 nm. On the other hand, the spectra of 5-methyluracil (thymine, 265 nm)⁴ and its 6-formyl compound (**2b**, 268 nm)⁵ show merely 3 nm difference. The size of red shift by presence of a methyl group on a conjugate system may well reflect the parent skeleton: α, β -unsaturated aldehyde in **1**.⁶

The λ_{max} shifts to longer wavelength region when the spectrum is run in basic solutions (Table 2). This is due to the dissociation of the N-H bond, forming an anionic species of uracil, which has been well documented in the literature.^{2,3,7} The degree of the red shift of unsubstituted uracil and 6-formyluracil (**2a**) are very similar: 24 and 26 nm, respectively, at pH 12. In case of 5-formyluracils (**1a** and **1b**), similar degree of red shifts are observed. But the second bands at 230 and 233 nm shifted to 252 and 250 nm, respectively, although the intensities decreased significantly. The second

band of **2a** appears at 202 nm in water, which indicates no significant effect to the spectrum of uracil itself by the substituent. The band shifts to 217 nm in the basic medium. Here, again, the size of the shift and intensity are notably small compared to those observed in 5-isomer (**1a**).

One may draw a structure such as **A** in order to explain the absence of the λ_{max} shift in **2**. We examined the possibility of this kind of hydrogen bonding by comparing the chemical shifts of the aldehyde protons. However, the δ values were very close (**1a**: δ 9.73; **2a**: δ 9.65). Therefore, we ruled out the effect of H-bond as a cause of the absence of λ_{max} shift in **2**.



Unlike to formyluracils, the vinyluracil compounds show quite different characteristics in the UV spectra. Both 5-vinyluracil (**3**, 286 nm)⁸ and 6-vinyluracil (**4**, 296 nm)⁹ show significant red shifts. The larger shift in **4** seems to be due to the chromophore consisted of $\text{CH}_2=\text{CH}-\text{C}_6=\text{C}_5-\text{C}_4$

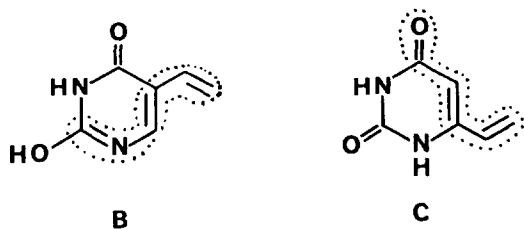
Table 3. ¹H-NMR Data of Uracilylacryc Acid Derivatives in Dimethyl Sulfoxide-d₆

Compound	H _a , δ	H _b , δ	J, Hz	Δv/J	H ₅ , δ	H ₆ , δ
1a	—	—	—	—	—	8.12
1b	—	—	—	—	—	2.45 ^a
2a	—	—	—	—	6.33	—
5a	6.85	7.45	16.00	3.38	—	8.08
5b	6.91	7.39	15.60	3.18	—	2.29 ^a
6	6.84	7.19	16.00	1.75	5.95	—
7a	6.75	7.26	15.82	3.13	—	7.97
7b	6.85	7.35	15.30	2.94	—	2.28 ^a
8	6.77	7.13	16.00	1.88	5.92	—
9a	6.96	7.15	15.60	1.11	—	7.83
9b	7.10	7.43	16.00	1.21	—	2.25 ^a
10	6.75	7.03	16.00	1.19	5.73	—

^a δCH₃ values.

= O. The new chromophore seems to dominate to the chromophore of uracil itself. It is notable that both **3** and **4** have an identical λ_{max} value (307 nm) in solutions of pH 11.^{8,9}

Very similar phenomena are observed with the uracilylacrylates (**5** and **6**). That is, the 6-uracilylacrylate (**6**) shows larger λ_{max} (305 nm) than 5-isomer (**5a**, 297 nm) in distilled water, while they absorb at 327 nm in a medium of pH 11. Introduction of an ethoxycarbonyl group to either vinyluracil (**3** or **4**) causes a bathochromic shift of only ca. 10 nm. One would expect a greater shift in the 5-uracilylacrylate (**5a**) because of the extended conjugation⁸. Apparently the principal conjugate system here is one represented by the dotted line in **B**. It may be considered as a hexatriene system. Similarly, 6-vinyluracil (**4**) may also be considered nothing but a hexatriene system as represented in **C**. The effect of the same substituent (ethoxycarbonyl group), therefore, should be similar, as showed in **5a** and **6**. Although the λ_{max} values of **5a** and **6** are close the absorption coefficient of **6** is notably smaller than that of **5a**. This is not surprising because **6** is a dicarbonyl system with conjugated double bonds in the middle. The π-π* transition probability should be much smaller here compared to a simple enone-type compound.



The λ_{max} values of 5- and 6-uracilylacrylic acids (**7** and **8**) are very similar to their ethyl esters, **5** and **6**, respectively. Furthermore, their amides (**9** and **10**) derivatives also do not show any significant shifts in λ_{max} values.

The trend in values of chemical shift of the proton at C₅ in uracil derivatives may be consistent with the fact that 6-formyl group in **2** exerts a function as an isolated carbonyl rather than a part of conjugation. As shown in the Table 3 the difference in the chemical shift values for C₅-H bet-

ween **2** and **6** is 0.38 ppm. On the other hand, it is 0.04 ppm between **1a** and **5a**. The extended conjugation through resonance in **1a** makes the diamagnetic anisotropic effect of the carbonyl diminish. Therefore, introduction of an additional C-C double bond (like **5a**) does not affect the chemical shift. Contrastingly, the carbonyl which behaves as an isolated function and thus exerts a diamagnetic anisotropic effect in **2** now becomes a part of a conjugated hexatriene system in **6** and the deshielding effect will disappear.

The *trans*-olefinic protons in acrylic acid, its esters and amides show very similar values for H_a and H_b, respectively. However, the ratios of Δv/J show an interesting trend. That is, the ratio is smaller in 6-uracilylacrylic acid and ester than in the corresponding 5-isomer. But the ratio becomes very small in amide derivatives (**9** and **10**) regardless of the linkage positions and the true chemical shift values have been calculated using the second order analysis method for an AB pattern.

Experimental

Melting points were determined on a Fisher Mel-Temp apparatus and were uncorrected. Ultraviolet-visible spectra were recorded on a Hitachi U-3200 double-beam spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 1430 spectrophotometer. Nuclear magnetic resonance (NMR) were recorded on a JEOL 90 MHz FT-NMR spectrometer in dimethyl sulfoxide (DMSO) solution with tetramethylsilane (TMS) as internal standard. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona, U.S.A.

Starting Materials. Compounds **1a**,¹⁰ **1b**,¹¹ **2**,⁵ **5a**,¹² **5b**,¹¹ **7a**,^{8,12} **7b**,¹¹ and **9b**¹³ were prepared by following the procedures in literatures.

Ethyl (E)-3-(1,2,3,4-Tetrahydro-2,4-dioxo-6-pyrimidinyl)propenoate (6). A solution of 6-formyluracil (**2**, 1.00 g, 7.14 mmol) and carbethoxymethylenetriphenylphosphorane (2.49 g, 7.10 mmol) in dimethyl sulfoxide (13 ml) was stirred in dark under nitrogen for 4 days. The solvent was removed by distillation under vacuum and the brown residue was boiled with benzene (50 ml). The hot mixture was filtered and the residue (insoluble in benzene) was recrystallized from ethanol: 1.07 g (72%), mp 255°C (lit.⁹ 255-257°C).

(E)-3-(1,2,3,4-Tetrahydro-2,4-dioxo-6-pyrimidinyl)propenoic Acid (8). A mixture of **6** (1.00 g, 4.76 mmol), methanol (50 ml), *p*-dioxane (38 ml), and 3N-NaOH (10 ml) was stirred in an oil-bath at 50°C for 2 days. After evaporation to dryness under vacuum the residue was dissolved in water (13 ml) and acidified with conc. HCl to pH 2. The white precipitate was collected by filtration and dried under vacuum: 0.73 g (84%), mp 264-268°C: IR (KBr) 3280(NH, COOH), 1705 and 1650(C=O), 1628(C=C), 990(HC=CH) cm⁻¹; NMR (DMSO-d₆) δ 5.92(s, 1H, C₅-H), 6.77(d, 1H, J=16.0 Hz, HC=CH), 7.13(d, 1H, J=16.0 Hz, HC=CH), 10.91(bs, 1H, NH), 11.08(bs, 1H, NH).

Anal. Calcd for C₇H₆N₂O₄: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.01; H, 3.13; N, 15.54.

(E)-N-(DL-1-Hydroxy-3-propylthio-2-propyl)-3-(1,2,3,4-tetrahydro-2,4-dioxo-5-pyrimidinyl)-2-propenamide (9a). To a mixture of **7a** (0.51 g, 2.82 mmol) and 1-hydroxybenzotriazole (Aldrich Chemical Co., 0.48 g, 3.53 mmol) was

added dried DMF (5 ml). The mixture was stirred for a few min and DL-2-amino-3-*n*-propylthio-1-propanol¹³ (0.70 g, 4.70 mmol) was added. The resulting solution was cooled in an ice bath and dicyclohexylcarbodiimide (Aldrich Chemical Co., 0.60 g, 2.90 mmol) was added in one portion. The mixture was stirred at room temperature for 3 days and filtered to remove dicyclohexylurea (0.56 g, 86%). The filtrate was evaporated to dryness under vacuum and the resulting residue was chromatographed on a column of silica gel (2.5 cm×30 cm) prepared with CH₂Cl₂-MeOH (98:2) and eluted as follow: (1) CH₂Cl₂-MeOH (98:2), 1.00 L; (2) 1.00 L; (3) CH₂Cl₂-MeOH (97:3), 0.50 L; (4); 0.50 L; (5) 0.50 L; (6) CH₂Cl₂-MeOH (95:5), 0.50 L; (7) 0.50 L; (8) CH₂Cl₂-MeOH (93:7), 0.50 L; (9) 0.50 L; (10) CH₂Cl₂-MeOH (9:1), 1.00 L; (11) CH₂Cl₂-MeOH (4:1), 1.00 L. Fraction 1 gave a trace of white solid which could not be characterized. Fractions 2-8 gave trace of yellow gummy material which could not be characterized. Fractions 9 and 10 gave **9a** (0.50 g, 55%), mp 234-236°C: IR (KBr) 3400-3100(broad s, OH, NH), 1720, 1682, and 1605 (C=C), 1540(amide-II), 1440(CH₃), 1250(C-O), 982(*trans* HC=CH) cm⁻¹; NMR (DMSO-d₆) δ 0.91(t, 3H, J=7.5 Hz, SCH₂CH₂CH₃), 1.50(sextet, 2H, J=7.5 Hz, SCH₂CH₂CH₃), 2.50 (m, overlapped by DMSO peaks, SCH₂CH₂CH₃), 3.40(m, 4H, CH₂OH and CHCH₂S), 3.90(m, 1H, CHCH₂), 4.73(bs, 1H, OH), 6.96(d, 1H, J=15.6 Hz, HC=CH), 7.15(d, 1H, J=15.6 Hz, HC=CH), 7.38(s, 1H, C₅-H), 7.95(s, 1H, NH), 11.35(bs, 2H, N₁-and N₃-H).

Anal. Calcd for C₁₃H₁₉N₃C₄S: C, 49.83; H, 6.11; N, 13.41; S, 10.23. Found: C, 49.88; H, 6.25; N, 13.40; S, 10.00.

(E)-N-(DL-1-Hydroxy-3-propylthio-2-propyl)-3-(1,2,3,4-tetrahydro-2,4-dioxo-6-pyrimidinyl)-2-propenamide (10). To a solution of **8** (0.50 g, 2.74 mmol) and 1-hydroxybenzotriazole (0.46 g, 3.44 mmol) in DMF (5 ml) was added DL-2-amino-3-*n*-propylthio-1-propanol¹³ (0.68 g, 4.58 mmol). The resulting solution was cooled in an ice bath and was added dicyclohexylcarbodiimide (0.58 g, 2.82 mmol) at once. The mixture was stirred under nitrogen in dark for 4 days. The precipitate (dicyclohexylurea) was removed by filtration and the filtrate was concentrated by distillation to dryness under vacuum. The residue was recrystallized from ethanol twice to give **10** as a pale yellow needles (0.26 g, 30%), mp. 185-186°C: IR (KBr) 3600-3020(NH, OH), 2959, 2923, 2850(CH₂,

CH₃), 1725 and 1665(C=O), 1623(C=C), 1570(amide-II), 1440, 1420, 1360(CH₂), 1282, 1240, 1180, 1010, 1005(C-O, C-N), 973(*trans* HC=CH) cm⁻¹; NMR (DMSO-d₆) δ 0.91(t, 3H, J=7.0 Hz, SCH₂CH₂CH₃), 1.50(sextet, 2H, J=7.0 Hz, SCH₂CH₂CH₃), 2.58(m, 4H, CHCH₂S and SCH₂CH₂CH₃), 3.40(m, 2H, CH₂OH), 3.89(m, 1H, CHCH₂), 5.73(s, 1H, C₅-H), 6.75(d, 1H, J=16.0 Hz, HC=CH), 7.03(d, 1H, J=16.0 Hz, HC=CH), 8.12 (d, 1H, J=8 Hz, NH), 10.70(bs, 2H, N₁-and N₃-H).

Anal. Calcd for C₁₃H₁₉N₃O₄S: C, 49.83; H, 6.11; N, 13.41; S, 10.23. Found: C, 49.78; H, 6.33; N, 13.25; S, 10.41.

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