

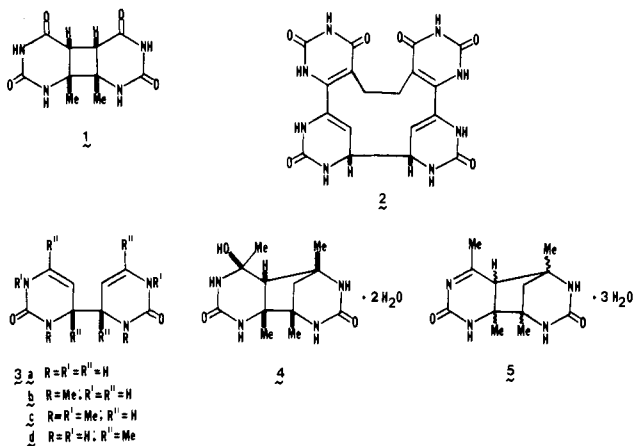
# Structure, Cyclization, and Other Properties of the Electrochemical Reduction Product of 4,6-Dimethylpyrimidone-2

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**Abstract:** At the dropping mercury electrode in neutral aqueous medium, 4,6-dimethylpyrimidone-2 undergoes one-electron reduction to 6,6'-bis(3,6-dihydro-4,6-dimethylpyrimidone-2). This product,  $C_{12}H_{18}N_4O_2$ , also obtained by UV irradiation of the pyrimidone in 2-propanol, crystallizes with two molecules of ethanol in space group  $P2/c$  with  $a = 9.111(2)$ ,  $b = 7.170(3)$ ,  $c = 15.775(5)$  Å,  $\beta = 112.70(2)^\circ$ , and  $Z = 2$ ; an x-ray study (final  $R = 0.044$ ) reveals it to be *meso*. It undergoes photochemical dissociation in water at 254 nm with a quantum yield of 0.03 to quantitatively regenerate the parent monomer, and in dilute acid adds a water molecule with cyclization. The cyclization product,  $C_{12}H_{20}N_4O_3 \cdot 2H_2O$ , crystallizes in space group  $Pca2_1$  with  $a = 9.206(3)$ ,  $b = 11.482(3)$ ,  $c = 14.180(7)$  Å and  $Z = 4$ ; an x-ray study (final  $R = 0.037$ ) shows the previously assigned structure to be incorrect and gives the true structure. The hydrogen-bonding arrangement in this crystal includes base-pairing and a bifurcated hydrogen bond.

Pyrimidone dimerizations have been shown to be responsible for the majority of the photobiological effects of UV irradiation on DNA.<sup>2</sup> Pyrimidone dimerization products include, among others,<sup>3</sup> the cyclobutane-type photodimer **1** from 6-methyluracil,<sup>4</sup> the "tetramer" **2** obtained by UV irradiation of an adduct of thymine and pyrimidone-2,<sup>5</sup> and reduced dimers **3a-c** (stereochemistry unknown) obtained by electrolytic<sup>6</sup>



and **3d** (stereochemistry unknown) by photochemical<sup>7</sup> reactions. Though x-ray studies have established structures **1**<sup>4</sup> and **2**<sup>5</sup> and others,<sup>3c</sup> none has been carried out on a type **3** dimer. We now report the preparation of **3d** by electrolytic means, an x-ray study which shows for the first time the stereochemistry of type **3** dimers, and an x-ray study which shows a cyclization product of **3d** to be **4** rather than **5** as proposed earlier.<sup>7</sup>

## Experimental Section

**Polarography of 4,6-Dimethylpyrimidone-2.**<sup>8</sup> Polarographic curves (Figure 1) were recorded with a Radiometer Polariter PO<sub>4</sub>, using a dropping mercury electrode with the following characteristics: flow rate of mercury,  $m = 2.54$  mg s<sup>-1</sup>; drop time,  $t = 3.3$  s<sup>-1</sup> at open circuit in distilled water at a mercury column height of 60 cm. All potentials are referred to the saturated calomel electrode. Britton-Robinson buffers were employed over the pH range 2–12. Oxygen was removed from the solutions by bubbling nitrogen as described by Meites.<sup>9</sup>

**Dimer **3d** by Electrolysis.** Electrolysis of 4,6-dimethylpyrimidone-2 was carried out with a mercury pool electrode (area = 12 cm<sup>2</sup>) at a

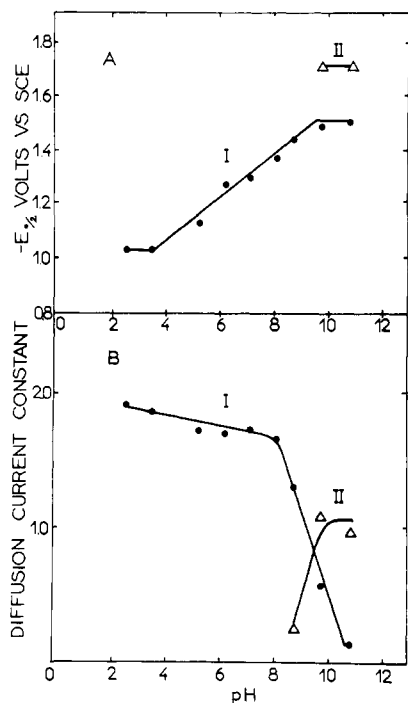
constant potential of  $-1.35$  V at pH 7. A silver coulometer with a Hg-pool electrode was employed to determine the number of electrons involved in the reduction process. The reaction was followed by taking advantage of the difference in absorption spectra (Figure 2) between 4,6-dimethylpyrimidone-2 ( $\lambda_{max}$  305 nm) and its reduction product ( $\lambda_{max}$  250 nm). After reaction, the solution was concentrated under reduced pressure, leaving small crystals which after centrifuging, washing with water, and drying, had mp  $\sim 300$  °C; IR (KBr) 1660, 1710, 3090, 3230 cm<sup>-1</sup>; MS M<sup>+</sup> at  $m/e$  250; UV shown in Figure 3.

Anal. Calcd for  $C_{12}H_{18}N_4O_2$ : C, 57.58; H, 7.25; N, 22.38. Found: C, 57.27; H, 7.16; N, 21.87.

Recrystallization from ethanol apparently gave the same ethanol-solvated form, mp 264–265 °C dec [lit. 262 °C dec], reported by Pfoertner.<sup>7</sup>

**X-Ray Study of Dimer **3d**.** Oscillation and Weissenberg photographs of a  $0.3 \times 0.3 \times 0.4$  mm crystal of the ethanol-solvated form indicated space group  $P2/c$ . The cell parameters were found by least-squares fitting of the settings for four angles of eight reflections on a Picker FACS-1 diffractometer (Cu K $\alpha$ ,  $\lambda = 1.54178$  Å, graphite monochromator) to be  $a = 9.111(2)$ ,  $b = 7.170(3)$ ,  $c = 15.775(5)$  Å,  $\beta = 112.70(2)^\circ$ ,  $\rho_{calcd}$  for  $C_{12}H_{18}N_4O_2 \cdot 2C_2H_5OH = 1.19$  g/mL,  $\rho_{obsd} = 1.17$  g/mL (floatation in CCl<sub>4</sub>-hexane) and  $Z = 2$ . Intensity data were collected using a scintillation counter with pulse-height analyzer,  $\theta$ - $2\theta$  scan, 2°/min scan rate, 10-s background counts, attenuators when the count rate exceeded 10<sup>4</sup> counts/s, and 2° scan range with dispersion factor allowing for  $\alpha_1 - \alpha_2$  splitting at large  $2\theta$  values. Of 1399 independent reflections measured, 1263 greater than  $3\sigma(I)$  were considered observed. Three standard reflections were monitored every 50 measurements; no decrease in the intensity of standards was observed. Lorentz and polarization corrections were applied, but no correction was made for absorption.

The structure was solved using the direct method program of Long<sup>10</sup> with  $E$ 's  $> 1.5$ . The correct solution was obtained from the set of phases having the third highest consistency index. In addition to half a molecule of dimer, the asymmetric unit also contained one molecule of ethanol. Two cycles of full matrix isotropic least-squares refinement of nonhydrogen atoms brought the  $R$  value down to 0.126. A difference map revealed all the hydrogen atoms of the dimer and also showed that both ethanol carbon atoms were disordered and had two positions each. The occupancy factors of disordered atoms were refined and finally fixed at 0.63 (C9a and C10a) and 0.37 (C9b and C10b). The structure was further refined using anisotropic temperature factors for nonhydrogens and isotropic temperature factors for hydrogens to  $R$  of 0.056. A difference map revealed the hydrogens of the ethanol. Coincidentally, one of the hydrogens of the ethanol methylene overlapped with one of the hydrogens of the methyl. Ethanol hydrogens were given the same occupancy as the carbons to which they were attached. Further refinement of all parameters brought the

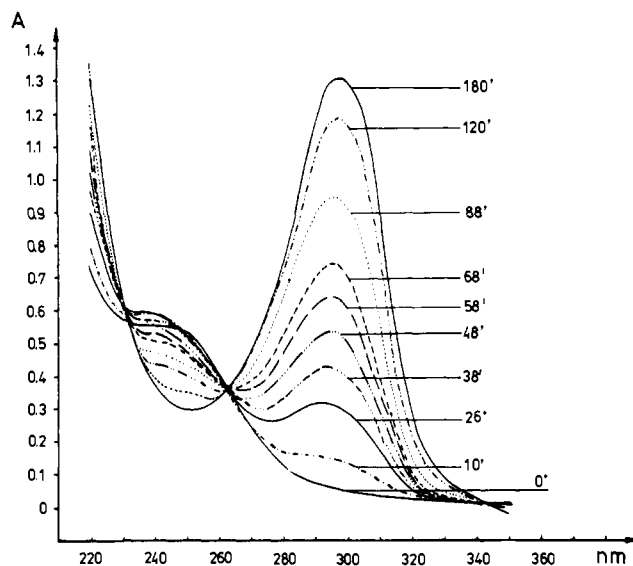


**Figure 1.** pH dependence of  $E_{1/2}$  (A) and diffusion current constant (B) of waves I and II for 4,6-dimethylpyrimidone-2, 0.5 mM in aqueous medium. Capillary characteristics:  $m = 2.54 \text{ mg s}^{-1}$ ,  $t = 3.3 \text{ s}^{-1}$  at open circuit in distilled water.

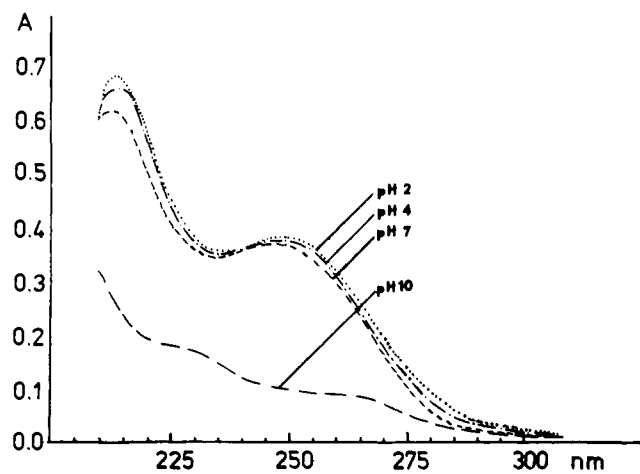
final  $R$  to 0.044. Refinement was terminated at this stage since the shifts in the final cycle were less than one third of the standard deviations for nonhydrogen atoms. The refinement was based on  $|F_o|$ , the quantity minimized being  $\sum w(|F_o| - |F_c|)^2$ . The weighting scheme used was based on counter statistics as defined by Corfield et al.,<sup>11</sup> with  $p = 0.04$ . The scattering factors used were those of Hanson et al.<sup>12</sup> No correction was applied for extinction. The final atomic coordinates and thermal parameters are given in Tables I and II.

**4,6-Dimethylpyrimidone from Dimer 3d.** The irradiation source was a Phillips 40 W germicidal lamp (254 nm), the radiation from which was first passed through a 5-mm layer of 35% acetic acid to remove traces of radiation below 230 nm. Solutions were irradiated in 10-mm path length quartz spectrophotometer cuvettes. The radiation intensity at the cuvette surface was determined actinometrically from the rate of photohydration of a  $10^{-4} \text{ M}$  aqueous solution of uridine in the same cuvette, as previously described.<sup>6b</sup> The reaction, essentially quantitative in 3 h, was followed by UV (Figure 2).

**Cyclized Dimer 4 from Dimer 3d.** This conversion occurs slowly in aqueous solutions of 3d, even at 0 °C. To make it faster, 13.5 mg of



**Figure 2.** Photochemical transformation at 254 nm in 0.01 M phosphate buffer pH 7 of dimer 3d, with formation of parent 4,6-dimethylpyrimidone-2. Figures beside each curve are for time of irradiation.



**Figure 3.** Ultraviolet absorption spectrum of dimer 3d,  $1.1 \times 10^{-4} \text{ M}$ , at various pH values.

3d was stirred with 2 mL of 0.001 M HCl at 25 °C for 3 h. Evaporation at 25 °C gave an essentially quantitative yield of 4, mp 251 °C

**Table I.** Coordinates and Thermal Parameters<sup>a</sup> in 3d<sup>b</sup>

Atom <sup>c</sup>	$x/a$	$y/b$	$z/c$	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
N1	0.0720 (2)	0.2453 (2)	-0.4665 (1)	111 (2)	104 (3)	70 (1)	-4 (2)	38 (1)	2 (1)
C2	0.2041 (2)	0.3318 (2)	-0.4629 (1)	120 (3)	111 (4)	59 (1)	-5 (2)	39 (1)	-3 (1)
O2	0.2039 (1)	0.5010 (2)	-0.4817 (1)	137 (2)	115 (3)	99 (1)	-6 (2)	58 (1)	13 (1)
N3	0.3393 (2)	0.2307 (2)	-0.4374 (1)	112 (2)	156 (4)	78 (1)	6 (2)	45 (1)	17 (1)
C4	0.3468 (2)	0.0443 (3)	-0.4086 (1)	129 (3)	150 (4)	54 (1)	14 (3)	27 (1)	5 (1)
C5	0.2157 (2)	-0.0426 (2)	-0.4147 (1)	148 (3)	119 (4)	58 (1)	8 (3)	25 (1)	14 (1)
C6	0.0534 (2)	0.0450 (2)	-0.4520 (1)	126 (3)	101 (4)	53 (1)	-12 (2)	35 (1)	2 (1)
C7	-0.0260 (3)	0.0246 (3)	-0.3833 (1)	184 (4)	212 (5)	56 (1)	-38 (3)	50 (2)	-7 (2)
C8	0.5093 (3)	-0.0396 (3)	-0.3726 (2)	141 (3)	238 (5)	87 (1)	48 (3)	30 (2)	33 (2)
O9	0.3593 (2)	0.5994 (3)	-0.5936 (1)	162 (3)	494 (6)	76 (1)	-83 (3)	32 (1)	30 (2)
C9a [0.63]	0.2452 (9)	0.5112 (11)	-0.6670 (5)	288 (12)	336 (18)	96 (5)	-41 (14)	45 (6)	-26 (8)
C9b [0.37]	0.2500 (14)	0.6034 (15)	-0.6927 (9)	253 (16)	279 (25)	85 (6)	-53 (18)	22 (8)	-5 (11)
C10a [0.63]	0.2901 (10)	0.5217 (11)	-0.7435 (5)	543 (22)	311 (16)	82 (3)	-14 (14)	84 (7)	-5 (6)
C10b [0.37]	0.2052 (18)	0.4235 (15)	-0.7374 (9)	436 (32)	233 (22)	116 (7)	95 (20)	-27 (12)	-31 (11)

<sup>a</sup>  $T_i = \exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)] \times 10^4$ . <sup>b</sup> Standard deviations given in parentheses refer to the last digit. <sup>c</sup> Occupancies for disordered atoms are given in brackets.

**Table II.** Coordinates and Thermal Parameters for Hydrogens in **3d**

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>B</i>
HN1	-0.013 (2)	0.321 (3)	-0.485 (1)	4.2 (4)
HN3	0.427 (2)	0.287 (3)	-0.433 (1)	5.0 (4)
HC5	0.222 (2)	-0.165 (3)	-0.396 (1)	5.1 (4)
H1C7	0.039 (3)	0.076 (3)	-0.323 (1)	6.0 (5)
H2C7	-0.135 (3)	0.092 (3)	-0.408 (1)	6.4 (5)
H3C7	-0.051 (3)	-0.111 (3)	-0.374 (1)	6.2 (5)
H1C8	0.573 (3)	0.012 (3)	-0.316 (1)	5.7 (5)
H2C8	0.508 (3)	-0.165 (4)	-0.366 (2)	8.2 (6)
H3C8	0.562 (4)	-0.020 (4)	-0.413 (2)	8.9 (7)
HO9	0.331 (3)	0.587 (4)	-0.550 (2)	7.9 (6)
H1C9a/ H1C10b <sup>a</sup>	0.234 (5)	0.368 (5)	-0.667 (3)	15.0 (11)
H2C9a [0.63]	0.107 (7)	0.537 (8)	-0.683 (4)	10.8 (14)
H1C9b/ H1C10a <sup>a</sup>	0.312 (5)	0.633 (6)	-0.745 (3)	13.0 (11)
H2C9b [0.37]	0.155 (9)	0.688 (12)	-0.701 (6)	9.4 (19)
H2C10a [0.63]	0.414 (7)	0.486 (8)	-0.715 (4)	11.7 (14)
H3C10a [0.63]	0.178 (9)	0.485 (12)	-0.796 (5)	13.0 (21)
H2C10b [0.37]	0.131 (22)	0.355 (23)	-0.817 (11)	21.1 (52)
H3C10b [0.37]	0.332 (15)	0.378 (17)	-0.753 (8)	12.8 (31)

<sup>a</sup> H1C9a and H1C10b overlap, making a total occupancy of 1; a similar situation occurs with H1C9b and H1C10a.

dec, then melts at 264–265 °C (lit.<sup>7</sup> 251 °C); <sup>1</sup>H NMR parameters same as literature.<sup>7</sup>

**X-Ray Study of Dimer 4.** A crystal 0.2 × 0.2 × 0.4 mm was used. The cell parameters were: space group, *Pca*2<sub>1</sub>; *a* = 9.206 (3), *b* = 11.482 (3), *c* = 14.180 (7) Å;  $\rho_{\text{obsd}} = 1.37$  g/mL (floatation in CCl<sub>4</sub>-hexane),  $\rho_{\text{calcd}} = 1.35$  g/mL; and *Z* = 4. The data were collected as for **3d**. Of 1209 independent reflections measured, 1126 greater than 3 $\sigma(I)$  were considered observed.

The structure was solved by the direct method program MULTAN<sup>13</sup> using *E*'s > 1.5. The correct set of phases had a combined figure of merit of 2.579. The first *E* map revealed all nonhydrogen atoms except the water oxygens. Subsequent difference maps revealed the water oxygens and all hydrogens. Several cycles of full-matrix least-squares refinement in which nonhydrogens had anisotropic thermal parameters and hydrogens had isotropic thermal parameters brought the final *R* value to 0.037. The final atomic coordinates and thermal parameters are given in Tables III and IV.

**Table III.** Coordinates and Thermal Parameters in **4**

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$
N1	0.4377 (4)	0.3194 (3)	-0.1476 (3)	106 (4)	51 (3)	30 (2)	8 (3)	4 (3)	6 (2)
C2	0.3613 (4)	0.3983 (3)	-0.1002 (4)	80 (5)	48 (3)	34 (2)	0 (3)	3 (3)	8 (2)
O2	0.3518 (4)	0.5009 (3)	-0.1271 (3)	141 (5)	53 (2)	51 (2)	19 (3)	24 (3)	19 (2)
N3	0.2893 (4)	0.3615 (3)	-0.0228 (3)	106 (4)	39 (2)	43 (2)	6 (3)	16 (3)	2 (2)
C4	0.2604 (5)	0.2414 (3)	-0.0061 (4)	89 (5)	50 (3)	44 (2)	-6 (3)	4 (3)	11 (2)
O4	0.1649 (4)	0.1934 (3)	-0.0792 (4)	124 (5)	87 (3)	68 (2)	-19 (3)	-29 (3)	8 (2)
C5	0.4013 (4)	0.1712 (3)	-0.0185 (4)	90 (5)	46 (3)	33 (2)	-7 (3)	-2 (3)	3 (2)
C6	0.4872 (5)	0.2070 (3)	-0.1078 (4)	104 (5)	39 (3)	30 (2)	1 (3)	3 (3)	3 (2)
C7	0.4734 (6)	0.1177 (4)	-0.1857 (4)	143 (7)	63 (4)	42 (3)	-5 (4)	0 (4)	-19 (3)
C8	0.1848 (6)	0.2269 (4)	-0.0853 (5)	140 (7)	69 (4)	64 (3)	-8 (4)	42 (4)	10 (3)
N1'	0.6726 (4)	0.3336 (3)	-0.0293 (3)	109 (5)	55 (3)	36 (2)	-13 (3)	16 (3)	-8 (2)
C2'	0.6192 (4)	0.3645 (4)	0.0554 (3)	79 (5)	56 (4)	37 (2)	-7 (3)	-7 (3)	-2 (2)
O2'	0.6414 (3)	0.4650 (3)	0.0890 (3)	123 (4)	59 (2)	38 (2)	-22 (2)	9 (2)	-10 (2)
N3'	0.5433 (4)	0.2833 (3)	0.1023 (3)	115 (5)	60 (3)	28 (2)	-19 (3)	3 (3)	-1 (2)
C4'	0.5144 (5)	0.1686 (3)	0.0634 (4)	113 (6)	45 (3)	33 (2)	-4 (3)	-8 (3)	5 (2)
C5'	0.6507 (5)	0.1315 (4)	0.0080 (4)	105 (6)	57 (4)	51 (3)	10 (4)	-13 (3)	1 (3)
C6'	0.6488 (5)	0.2177 (3)	-0.0714 (4)	93 (5)	42 (3)	51 (3)	4 (3)	5 (3)	-5 (2)
C7'	0.7662 (6)	0.2009 (4)	-0.1449 (5)	107 (6)	71 (4)	69 (3)	4 (4)	27 (4)	-17 (3)
C8'	0.4801 (6)	0.0860 (4)	0.1437 (4)	164 (8)	69 (4)	42 (3)	-3 (4)	-7 (4)	22 (3)
W1	0.4340 (3)	0.3630 (2)	0.2906 (3)	132 (3)	81 (2)	49 (1)	-20 (2)	7 (2)	1 (1)
W2	0.9137 (3)	0.4165 (3)	0.1836 (2)	147 (4)	150 (3)	56 (2)	-37 (3)	-27 (2)	28 (2)

**Table IV.** Coordinates and Thermal Parameters for Hydrogens in **4**

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	<i>B</i>
HN1	0.485 (5)	0.343 (4)	-0.194 (3)	3.8 (10)
HN3	0.244 (4)	0.413 (3)	0.003 (3)	3.8 (8)
HO4	0.114 (7)	0.271 (6)	-0.123 (6)	12.5 (18)
HC5	0.372 (4)	0.085 (3)	-0.035 (3)	3.6 (9)
H1C7	0.378 (6)	0.111 (5)	-0.198 (4)	6.8 (13)
H2C7	0.545 (5)	0.150 (4)	-0.244 (4)	5.9 (11)
H3C7	0.526 (5)	0.046 (4)	-0.169 (3)	5.5 (10)
H1C8	0.253 (5)	0.275 (3)	0.136 (3)	4.1 (9)
H2C8	0.085 (5)	0.281 (4)	0.077 (4)	5.7 (11)
H3C8	0.158 (5)	0.129 (5)	0.090 (4)	5.8 (12)
HN1'	0.728 (5)	0.395 (3)	-0.061 (3)	4.6 (9)
HN3'	0.503 (4)	0.301 (3)	0.147 (3)	3.8 (8)
H1C5'	0.740 (4)	0.137 (3)	0.043 (3)	3.2 (8)
H2C5'	0.636 (3)	0.058 (3)	-0.020 (3)	3.5 (7)
H1C7'	0.845 (5)	0.207 (4)	-0.136 (4)	5.5 (11)
H2C7'	0.759 (5)	0.124 (3)	-0.171 (3)	4.2 (8)
H3C7'	0.752 (6)	0.249 (3)	-0.189 (3)	4.7 (8)
H1C8'	0.450 (5)	0.011 (4)	0.118 (3)	4.7 (11)
H2C8'	0.397 (4)	0.104 (3)	0.167 (3)	3.3 (8)
H3C8'	0.584 (5)	0.073 (4)	0.184 (3)	5.5 (10)
H1W1	0.492 (4)	0.391 (3)	0.310 (3)	4.3 (8)
H2W1	0.346 (4)	0.418 (3)	0.285 (3)	5.5 (9)
H1W2	1.020 (5)	0.455 (5)	0.155 (4)	8.3 (14)
H2W2	0.851 (6)	0.437 (5)	0.165 (5)	10.8 (18)

## Results and Discussion

In aqueous medium, over the pH range 2–9, 4,6-dimethylpyrimidone-2, which is predominantly in the keto form in solution,<sup>6c,14</sup> exhibited a single diffusion-controlled polarographic wave (wave I). In acid medium the wave height was constant and the diffusion current constant corresponded to a one-electron reduction process (Figure 1), as reported for pyrimidone-2.<sup>15</sup> Coulometric measurements for wave I gave a value of *n* = 0.93, in agreement with one-electron reduction. In general, the polarographic behavior of 4,6-dimethylpyrimidone-2 was very close to that of pyrimidone-2.<sup>6b,15</sup>

The linear pH dependence of *E*<sub>1/2</sub> for wave I, which followed the relationship *E*<sub>1/2</sub> = 0.78 – 0.075pH, exhibited two breaks corresponding to p*K* values for the compound of 3.5 and 9.8, in reasonable agreement with values of 3.75 and 9.9 deter-

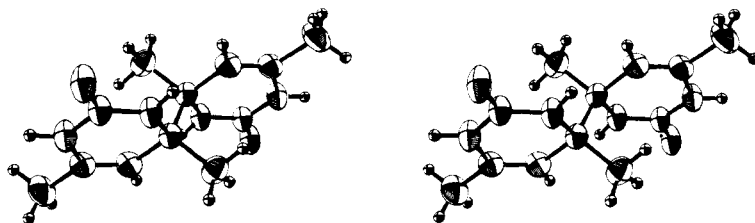


Figure 4. Stereoscopic view of a dimer **3d** molecule. Hydrogens are depicted as spheres, and other atoms as 50% probability ellipsoids.

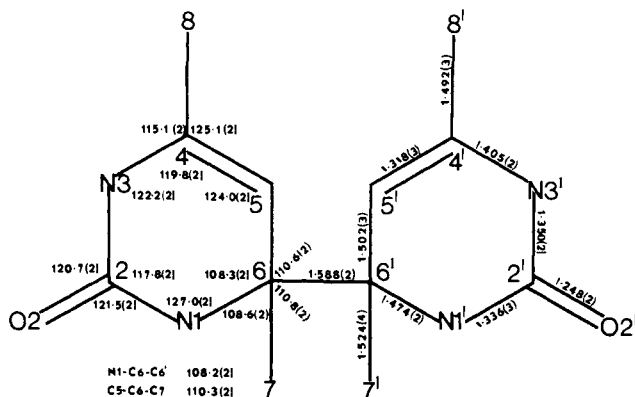


Figure 5. Bond lengths (Å) and angles (deg) in dimer **3d**.

mined potentiometrically<sup>14a</sup> (Figure 1). In alkaline medium (pH  $\sim$ 8) a second wave (wave II) appeared at more negative potentials. The half-wave potential of wave II was independent of pH, and the wave height increased with increasing pH; simultaneously the height of wave I decreased, following the form of a dissociation curve, while the sum of the heights of the two waves was constant up to about pH 10. Above pH 10.5 wave I disappeared, while wave II was only partially visible due to overlapping by the discharge wave of the buffer. The behavior of waves I and II pointed to the existence of an acid-base equilibrium related to the disappearance of the neutral form of the depolarizer (wave I) and reduction at a more negative potential of the anionic form (wave II).<sup>16</sup>

Macroelectrolysis of wave I at constant potential gave reductive dimer **3d** (stereochemistry unknown), identical (mp, NMR, oscillation and Weissenberg photographs) with the product obtained independently by irradiating the same starting material in 2-propanol.<sup>7</sup> As this reduced dimer (unlike **3a-c**) crystallized well, an x-ray study was undertaken to determine the stereochemistry. The resulting stereodrawing (Figure 4) shows it to be meso with a center of symmetry in the dimer molecule. The rings are virtually planar, with a maximum deviation of 0.06 Å from the least-squares plane. The bond distances and angles, given in Figure 5, are in good agreement with those found in the corresponding part of tetramer **2**.<sup>5</sup> Figure 6 shows a stereoscopic view of the disordered ethanol molecule, which was treated as occupying two positions. In the major position (occupancy 0.63) there is an anti arrangement of methyl and hydroxyl proton about the C-O bond, whereas in the minor position (occupancy 0.37) this arrangement is gauche. Figure 7 depicts the molecular packing, governed partly by a centrosymmetric 12-membered ring containing hydrogen bonds (dashed lines) between ethanol hydroxyl and carbonyl oxygen (O2-O9 distance, 2.744 Å) and N3-H and ethanol oxygen (N3-O9 distance, 2.863 Å). Since further hydrogen bonds, between N1-H and carbonyl oxygen (N1-O2 distance, 2.948 Å), join molecules in the  $y$  direction, the crystals consist of sheets in the  $yz$  plane of hydrogen-bonded molecules. There are no further intermolecular distances  $<$ 3.5 Å between nonhydrogen atoms.

Irradiation at 254 nm of a neutral aqueous solution of dimer **3d** led to the disappearance of the characteristic absorption maximum at 250 nm and the appearance of a new band with  $\lambda_{\text{max}}$  295 nm (Figure 2). All the curves in Figure 2 pass through

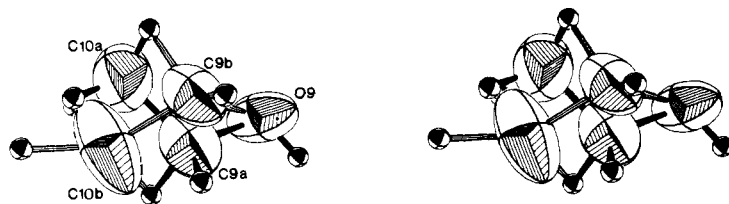


Figure 6. Stereoscopic view of the disordered ethanol molecule which crystallizes with dimer **3d**. Solid bonds connect atoms in the molecule with major occupancy.

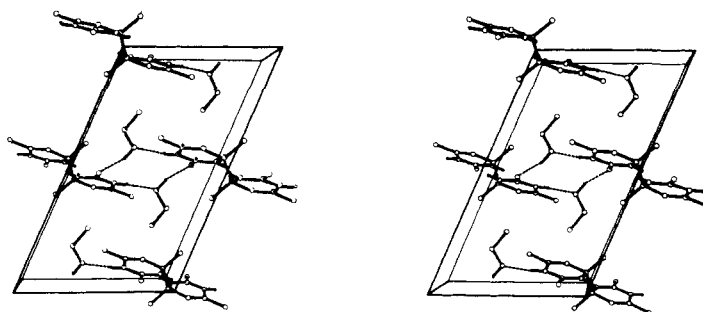


Figure 7. Stereoscopic view of a unit cell of **3d**·2EtOH,  $b$  axis projection,  $a$  axis horizontal.

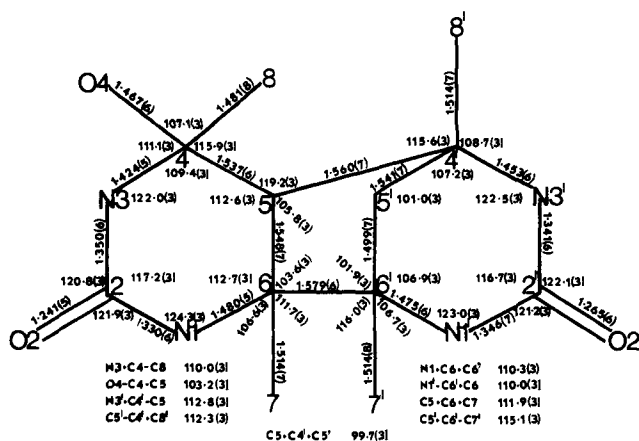


Figure 8. Bond lengths (Å) and angles (deg) in cyclized dimer 4.

Table V. Angles Involving Hydrogen Bonds in 4

Bond	Distance between heteroatoms, Å	Heteroatom-H-heteroatom angle, deg
N1-H...W2 ( $\frac{3}{2} - x, y, -\frac{1}{2} + z$ )	2.973	173.2
N3-H...O2' ( $-\frac{1}{2} + x, 1 - y, z$ )	2.887	170.8
N1'-H...O2 ( $\frac{1}{2} + x, 1 - y, z$ )	2.872	172.5
N3'-H...W1 ( $x, y, z$ )	2.996	166.9
O4-H...W1 ( $\frac{1}{2} - x, y, -\frac{1}{2} + z$ )	2.834	164.1
O2...H-W1 ( $1 - x, -y, -\frac{1}{2} + z$ )	2.773	171.3
O2...H-W1 ( $\frac{1}{2} - x, y, -\frac{1}{2} + z$ )	3.285	143.2
O2'...H-W2 ( $-\frac{1}{2} + x, 1 - y, z$ )	2.837	161.4
O2'...H-W2 ( $x, y, z$ )	2.897	167.2
W1-H...W2 ( $-\frac{1}{2} + x, 1 - y, z$ )	2.958	108.3

an isosbestic point at 262 nm, pointing to the formation of a single UV absorbing photoproduct. The pH dependence of the absorption spectrum and polarographic analysis of this photoproduct showed it to be the parent 4,6-dimethylpyrimidone-2. The ratio of the absorbance of the photochemically regenerated 4,6-dimethylpyrimidone-2 to that of the initial dimer **3d** was 2.08. The  $\epsilon_{\text{max}}$  of 4,6-dimethylpyrimidone-2 at neutral pH is  $7.0 \times 10^3$ , while  $\epsilon_{\text{max}}$  for **3d** is  $3.4 \times 10^3$ , so that their ratio is 2.06, testifying to quantitative photoconversion of **3d** to the parent monomer. The quantum yield of this reaction was about 0.03, considerably lower than that for the analogous photodissociation of **3a** to pyrimidone-2.<sup>6a</sup>

It was noted that an aqueous solution of **3d** stored for several days at 0 °C underwent spontaneous transformation in the dark, reflected by the gradual disappearance of the absorption band at 250 nm, and a decrease in the extent of photodissociation to the parent monomer. The product on evaporation

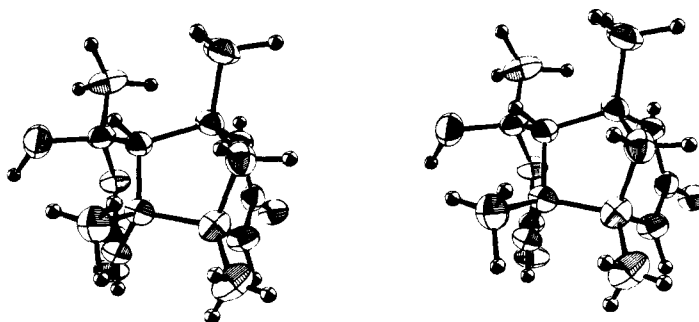


Figure 9. Stereoscopic view of a cyclized dimer 4 molecule.

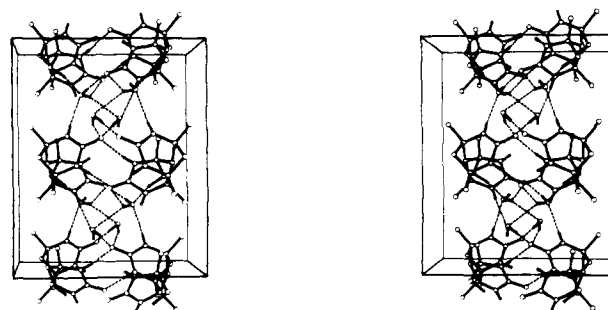


Figure 10. Stereoscopic view of a unit cell of 4·2H<sub>2</sub>O, *a* axis projection, *b* axis horizontal, *c* axis vertical.

is evidently the same substance produced in 40% yield by Pfoertner<sup>7</sup> when he treated **3d** with 0.18 M H<sub>2</sub>SO<sub>4</sub> at room temperature overnight. It is produced essentially quantitatively in a few hours when **3d** is allowed to stand in 0.001 M HCl. Although Pfoertner assigned structure **5** to this substance, the x-ray study described next reveals it to have structure **4**.

The bond lengths and angles in cyclized dimer **4** are given in Figure 8, and the molecular geometry can be seen in the stereo diagram in Figure 9. The six-membered ring comprised of atoms N1-C2-N3-C4-C5-C6 adopts a pseudodiplanar form<sup>17</sup> with torsion angles clockwise starting with the N1-C2 bond of  $-20.0, -17.4, 49.6, -45.0, 15.1,$  and  $19.0^\circ$ , while the other six-membered ring (N1'-C2'-N3'-C4'-C5'-C6') adopts a 1,2-diplanar form<sup>17</sup> having torsion angles counterclockwise starting with the N1'-C2' bond of  $1.1, -2.2, 37.0, -66.9, 65.4,$  and  $35.9^\circ$ . The torsion angles in the five-membered ring clockwise from C5-C6 are  $2.4, -31.8, 50.8, -49.9,$  and  $21.9^\circ$ , indicating an envelope conformation.<sup>17</sup>

The packing diagram (Figure 10) reveals a complex hydrogen-bonding scheme which joins all molecules in each cell and all cells in the *a* and *c* directions. Some parameters for the ten independent hydrogen bonds are given in Table V. The second and third bonds in the table join dimer molecules through "base-pair" type interactions, making chains in the *a* direction; the other eight bonds involve the two water molecules (W1 and W2). W1 is an acceptor for two hydrogen bonds and a donor for three; there is a bifurcated hydrogen bond. Although the distances and angles in Table V for the atoms involved in this bond (seventh and tenth in the table) appear abnormal, Figure 11 shows that the geometry is such that the hydrogen is about equidistant from the two acceptor atoms (O2 and W2).<sup>18</sup> W2 is the acceptor for two hydrogen bonds and donor for two. The only intermolecular distance  $< 3.5$  Å not involving hydrogen bonds is 3.39 Å, between C8' and C7 ( $1 - x, -y, \frac{1}{2} + z$ ).

Presumably the reduced dimers **3a-c**, formed similarly to **3d**, also possess the meso configuration. If this is so, dimers **1, 2,** and **3a-d** all are *meso*. We have not been able to detect the

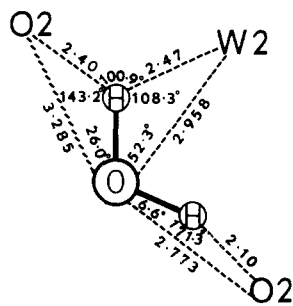


Figure 11. Schematic drawing of water molecule 1 which crystallizes with dimer 4, showing geometry about bifurcated hydrogen bond. Distances are in angstroms.

*dl* stereoisomers of **3d** in the photo- and electrochemical preparations of **3d**. Thus, at least in the case of **3d**, the meso form is found not simply because it crystallizes better than the corresponding *dl* form, but rather because it is formed in considerably higher yield.

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**Supplementary Material Available:** Tables of bond distances and angles involving hydrogen and those in the disordered ethanol molecule

which crystallizes with **3d** (3 pages). Ordering information is given on any current masthead page.

## References and Notes

- (1) (a) University of Warsaw; (b) University of Arizona.
- (2) J. K. Setlow, *Curr. Top. Radiat. Res.*, **2**, 196 (1966).
- (3) (a) S. Y. Wang and A. J. Varghese, *Biochem. Biophys. Res. Commun.*, **29**, 543 (1967); (b) A. J. Varghese, *Biochemistry*, **9**, 4781 (1970); (c) N. Camerman, D. Weinblum, and S. C. Nyberg, *J. Am. Chem. Soc.*, **91**, 982 (1969); (d) I. L. Karle in "Photochemistry and Photobiology of Nucleic Acids", S. Y. Wang, Ed., Academic Press, New York, N.Y., 1976, Chapter 11, and references cited therein.
- (4) J. W. Gibson and I. L. Karle, *J. Cryst. Mol. Struct.*, **1**, 115 (1971).
- (5) J. L. Flippen, R. D. Gilardi, I. L. Karle, D. F. Rhoades, and S. Y. Wang, *J. Am. Chem. Soc.*, **93**, 2556 (1971).
- (6) (a) B. Czochralska and D. Shugar, *Experientia, Suppl.*, **18**, 251 (1971); (b) *Biochim. Biophys. Acta*, **281**, 1 (1972); (c) B. Czochralska, M. Wrona, and D. Shugar, *Bioelectrochem. Bioenerg.*, **1**, 40 (1974).
- (7) K.-H. Pfoertner, *Helv. Chim. Acta*, **58**, 865 (1975).
- (8) Prepared as described by M. Evans, *J. Prakt. Chem.*, **46**, 352 (1892); **48**, 489 (1893); the hydrochloride used in the current work had mp 272–274 °C.
- (9) L. Meites, "Polarographic Techniques", Interscience, New York, N.Y., 1965.
- (10) R. E. Long, Ph.D. Thesis, University of California at Los Angeles, 1965.
- (11) P. W. R. Corfield, R. J. Deodens, and J. A. Ibers, *Inorg. Chem.*, **6**, 197 (1967).
- (12) H. P. Hanson, F. Herman, J. D. Lea, and S. Skillman, *Acta Crystallogr., Sect. B*, **17**, 1040 (1964).
- (13) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
- (14) (a) G. Zwillichowsky, *Tetrahedron*, **23**, 353 (1967); (b) D. D. Brown, "The Pyrimidines", Suppl. I, Wiley, New York, N.Y., 1970.
- (15) D. Smith and P. J. Elving, *J. Am. Chem. Soc.*, **84**, 2741 (1962).
- (16) P. Zuman, "The Elucidation of Organic Electrode Processes", Academic Press, New York, N.Y., 1969.
- (17) R. Bucourt, *Top. Stereochem.*, **8**, 159 (1974).
- (18) Similar bifurcated hydrogen bonds have been observed in magnesium sulfate dihydrate (W. H. Bauer, *Acta Crystallogr.*, **17**, 865 (1964)) and lincormycin dihydrochloride (R. E. Davis and R. Parthasarathy, *Acta Crystallogr.*, **21**, A 109 (1966)). The latter author has observed (private communication) that in almost all cases of bifurcated hydrogen bonds the hydrogen lies approximately in the plane through the donor and two acceptor atoms; in this structure the deviation of the hydrogen from this plane is 0.16 Å.

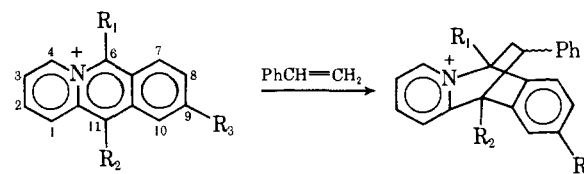
## Steric Effects in Some Cycloaddition Reactions<sup>1,2</sup>

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Contribution from the Paul M. Gross Chemical Laboratories, Duke University, Durham, North Carolina 27706. Received September 21, 1976

**Abstract:** The log of the relative rate constants ( $k/k_0$ ) for the cycloaddition of six 3-substituted-2-methylisoquinolinium iodides gives a significant correlation with the Hammett substituent constant  $\sigma_m$ , but the rate of cycloaddition of a seventh analogue, 3-*tert*-butyl-2-methylisoquinolinium iodide, is much too high for inclusion in a significant correlation. It is suggested that this acceleration of rate has its origin in the relief of steric strain during cycloaddition. The 13.6-fold increase in the rate of cycloaddition observed when a methyl group is substituted at meso position 11 of the acridizinium (benzo[*b*]quinolinium) ion must also have its origin in the relief of strain. Further increase of the strain through introduction of a flanking methyl at position 10 (in 7,10,11-trimethylacridizinium ion) results in an over tenfold increase in the reaction rate. From literature data it can be demonstrated that a large part of the acceleration in the rate of cycloaddition observed when methyl groups are introduced into the meso positions of anthracene has its origin in the relief of peri strain. That the rate of cycloaddition of the acridizinium ion, as well as the enthalpy of activation, is lowered by introduction of a methyl group at meso position 6 indicates a larger negative entropy of activation for the 6-methyl derivatives.

In earlier work<sup>3</sup> it was shown that the rate of cycloaddition of the acridizinium ion (**1**) with styrene was influenced by the nature of the substituent at position 9 of the acridizinium (benzo[*b*]quinolinium) ring. A significant correlation of the log of the relative rate of cycloaddition with Hammett  $\sigma_p$  constants was obtained with the reaction constant  $\rho$  positive (1.69). The suggestion<sup>3</sup> that the substituent at position 9 may act by altering the electron deficiency at position 6 has gained support from the demonstration<sup>4</sup> that there is a significant correlation between the log of the relative rate of cycloaddition



- 1,  $R_1 = R_2 = H$
- 2,  $R_1 = Me; R_2 = H$
- 3,  $R_1 = H; R_2 = Me$