and analyzed by gas chromatography as described.[11,15] The nitrophenols and hydroxybenzonitriles were analyzed after methylation with diazomethane.[11,15]

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Registry No. Benzene, 71-43-2; nitrobenzene, 98-95-3; benzonitrile, 100-47-0; disodium peroxydisulfate, 7775-27-1; hydroxycyclohexadienyl, 11084-15-4.

Relative Enthalpies of 1,3-Dimethyl-2,4-pyrimidinedione, 2,4-Dimethoxypyrimidine, and 4-Methoxy-1-methyl-2-pyrimidinone: Estimation of the Relative Stabilities of Two Protomers of Uracil

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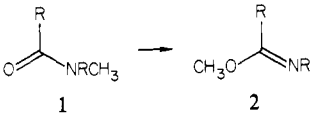
Abstract: The relative gas-phase enthalpies of 1,3-dimethyl-2,4-pyrimidinedione (**5**), 2,4-dimethoxypyrimidine (**6**), and 4-methoxy-1-methyl-2-pyrimidinone (**7**) have been determined by calorimetric measurements of the heats of isomerization in the liquid and estimates of the heats of vaporization. The values of $\Delta H_g°$ are -38 ± 4.7 kcal/mol for **5**–**6** and -27 ± 4.1 kcal/mol for **5**–**7**. These results show the relative energies of the amide–imidate functions in a heteroaromatic system can be quite different. The relative enthaplies for **5**, **6**, and **7** are used to provide estimates of the enthalpy differences between uracil (**11**) and 2,4-dihydroxypyrimidine (**16**) as -22 ± 10 kcal/mol and between **11** and 4-hydroxy-2-pyrimidinone (**13**) as -19 ± 6 kcal/mol. Although the errors are large, this is the first experimentally based estimate for the relative stabilities of these tautomers in the vapor. It is suggested that the relative energies of uracil protomers in solution are affected more by hydrogen bonding than by reaction field effects.

Studies of tautomeric equilibria are of interest in a wide variety of chemical investigations.[1,2] Areas in which the magnitude of the energy difference between amide–imidate isomer pairs is important include studies of solvent effects, protomeric equilibria, sigmatropic rearrangements, molecular orbital calculations, and speculation about nucleic acid base-pair recognition.[1,3–6]

Most determinations of tautomeric energy differences have focused on protomeric cases in which both isomers can be observed directly. Such systems, due to the limits for spectroscopic detection of minor isomers, are those in which the energy differences between the protomers will be no more than a few kilocalories/mole. Highly biased equilibria, which comprise a much larger number of cases and could be most informative about dominant effects, are studied by indirect method.

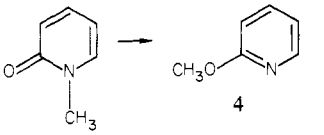
The most widely used indirect approach is the Ebert method in which the relative basicities of alkylomeric isomers is used to provide estimates of the relative basicities of the corresponding protomeric isomers in solution or in the vapor.[6,7] The central assumption of the Ebert method, that the heteroatom–alkyl bond energy is canceled by comparison of the neutral and protonated models, has borne up to analysis,[7] but its application is questionable for cases in which there are multiple sites for protonation.

A different approach involves direct determination of the energy difference between methyltropic isomers, a value of interest in its own right, and extrapolation of that result to the corresponding protomers. On the basis of heats of isomerization and vaporization of representative systems, we have suggested that for unstrained *N*-methyl *O*-methyl amide–imidate pairs, **1**–**2**, in which the



1 2

$\Delta E_g° = 15 \pm 3$ kcal/mol



3 4

$\Delta E_g° = 8 \pm 3$ kcal/mol

functions are not in a heteroaromatic ring, the amide will be the more stable isomer by 15 ± 3 kcal/mol. The corresponding amide–imidic acid protomers have been estimated to favor the amide by 8 ± 3 kcal/mol.[8]

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Scheme I

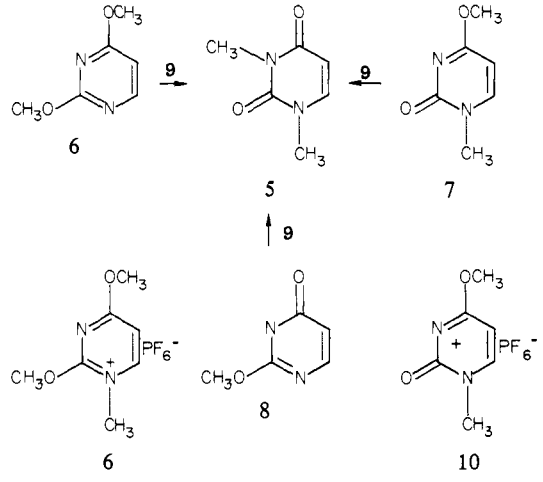

Table I. Enthalpies of Isomerization

reaction	$\Delta H_l°$, kcal/mol	$\Delta H_g°$, kcal/mol	$\Delta E_{cb}°$, kcal/mol
6 → 5	−44 ± 3.1[a]	−38 ± 4.7	−38 ± 6.2
7 → 5	−24.8 ± 1.3[a]	−27 ± 4.1	−27 ± 5.6
8 → 5	<−4		

[a] Standard deviation for six runs.

We undertook the present study, in part, to determine if the enthalpy difference of 8 ± 3 kcal/mol which we have measured for 2-methoxypyridine (**3**) -1-methyl-2-pyridone (**4**) would prove to be general for amide–imidate functions in heteroaromatic systems. The specific cases we have studied, 1,3-dimethyl-2,4-pyrimidinedione (**5**), 2,4-dimethoxypyrimidine (**6**), 4-methoxy-1-methyl-2-pyrimidinone (**7**), and 2-methoxy-3-methyl-4-pyrimidine (**8**), reveal the amide–imidate energy difference is different in different heteroaromatic environments. This work also provides a basis from which an estimate can be made of the enthalpy difference for the corresponding uracil protomers in the vapor. In conjunction with previous work, the values obtained can be used to suggest the energies of the uracil protomers in solution will be strongly affected by hydrogen bonding.

Results

Methyltropic Isomers. The rearrangements of **6**, **7**, and **8** to **5** are achieved by heating at 147–150 °C in the presence of a few mole percent of the hexafluorophosphate salt **9** as shown in Scheme I.[9,10] The conversions of **6** and **7** to **5** were complete in 5 min, but the conversion of **8** to **5** required 4 h for completion.[11] It was also observed that **9** underwent rearrangement to **10** concomitant with the conversions depicted in Scheme I.

The enthalpies of reaction were measured at 147 °C in order to obtain the energy difference between the isomers **5**, **6**, and **7**. The calorimeter has been previously described.[8] Reactions were carried out by breaking a bulb containing 1–15 mol % **9** into neat liquid **6** or **7** and measuring the heat evolved. The evolution of heat was complete in a few minutes, and analysis of the products showed less than 0.1% of **6** and **7** to be present and that **5** and the hexafluorophosphate salts **9** and **10** were the only materials detectable. The enthalpy of conversion of **9** to **10** was determined to be 41 ± 5 kcal/mol, and the observed heats of isomerization shown in the second column of Table I are corrected for this contribution.

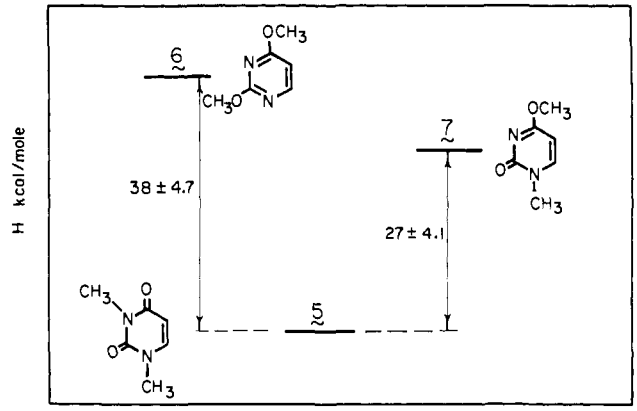

Figure 1. Relative enthalpies of **5**, **6**, and **7**.

Control experiments established **5**, **6**, **7**, and **9** were stable at 160 °C, and that the heats of stirring, bulb breaking, and of solution of **9** in **5** were negligible. Due to the slow rate of reaction of **8**, the enthalpy of conversion of **8** to **5** could not be measured by this technique and can only be estimated as greater than 4 kcal/mol.

Estimates of contributions from intermolecular forces and zero-point and kinetic energy differences are required to make a reliable estimate of the difference in chemical binding energies of the isomers **5**, **6**, and **7**.[8] The former can be elimated by conversion of the liquid-phase equilibria in Table I to the vapor phase by estimation of the differences in heats of vaporization of the isomers. The procedure, using nonreduced Cox–Antoine vapor pressure data in a Clausius–Clapeyron calculation previously shown to be reliable,[12] provides $\Delta\Delta H_{vap}°$ of 5.5 (±1.6) and −2.4 (±2.8) kcal/mol for **6**–**5** and **7**–**5**, respectively. Addition of these values to the liquid-phase enthalpy measurements gives the gas-phase enthalpy differences shown in the third column of Table I. Correction for possible differences in zero-point and kinetic energies, estimated essentially as heretofore,[8,12,13] adds ±1.5 kcal/mol to the uncertainty in these values and provides the difference in chemical binding energies shown in the last column of the table.

Discussion

The gas-phase enthalpies of the isomer **5**, **6**, and **7** are compared in Figure 1. As expected from the established chemical conversions,[10] **5** is the most stable and **6** the least stable isomer. The magnitude of the energy difference between **5** and **6** is much larger than might be expected. On the basis of an 8-kcal/mol difference between 2-methoxypyridine (**3**) and 1-methyl-2-pyridone (**4**), an estimate of 16 kcal/mol might be made for the two imidate–amide transformations in the conversion of **6** to **5**. The observed value of 38 ± 4.7 kcal/mol, however, is over twice this value. Moreover, the imidate–amide energy difference is not evenly divided between the two functions. The energy of the imidate–amide conversion for N_1 and C_2, which can be obtained from the energy difference of **6** and **7** as ca. 9 kcal/mol, does agree with the value of 8 kcal/mol from the model system **3**–**4**. The energy of the conversion of the imidate–amide for N_3 and C_4 provided by the comparison of **7** and **5**, however, is 27 kcal/mol or approximately 3 times the value for the simple heteroaromatic model **3**–**4** and twice the value for the nonaromatic model **1**–**2**.[1] A rationale for this observation is that the conversion of **7** to **5** involves N_3, a urea nitrogen, and that the urea–isourea energy difference is not adequately modeled by the suggested comparison.

(9) The use of a common alkylated derivative to achieve equilibration of alkyltropic isomers has been used previously.[8] The structure of **9** rests on the observation that it is the common product from separate methylations of **6** or **7**.

(10) The conversion of **6** to **5** and **7**, and of **7** to **5** and analogous reactions catalyzed by alkyl halides or acid are well-known. (a) Hilbert, G. E.; Johnson, T. B. *J. Am. Chem. Soc.* **1930**, *52*, 2001. (b) Pume, J.; Dryston, M. *Adv. Heterocycl. Chem.* **1967**, *3*, 115. (c) Ueda, T.; Nishimo, H. *J. Am. Chem. Soc.* **1968**, *90*, 1678. (d) Wong, J. L.; Fuchs, D. S. *J. Org. Chem.* **1970**, *38*, 3786.

(11) Consideration of the sequential methyl group displacements required for equilibration shows that the reaction of **8** involves generation of three adjacent methyl or methoxyl groups on the pyrmidine ring. This unfavorable steric interaction apparently impedes the conversion.

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(13) White, J. M. Ph.D. Thesis, University of Illinois at Champaign-Urbana, 1982, available from Michigan Microfilms, An Arbor, MI.

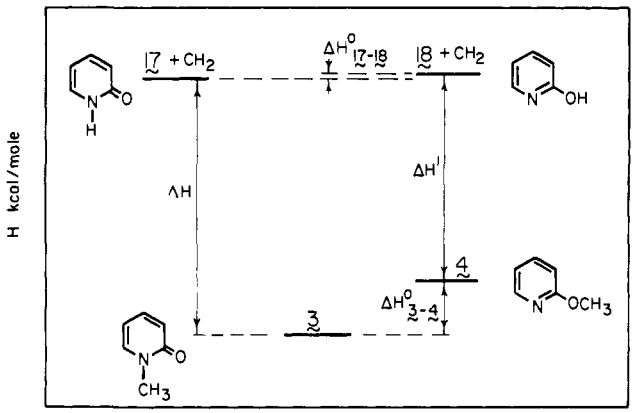


Figure 2. Relative enthalpies of **3**, **4**, **17** + CH_2, and **18** + CH_2.

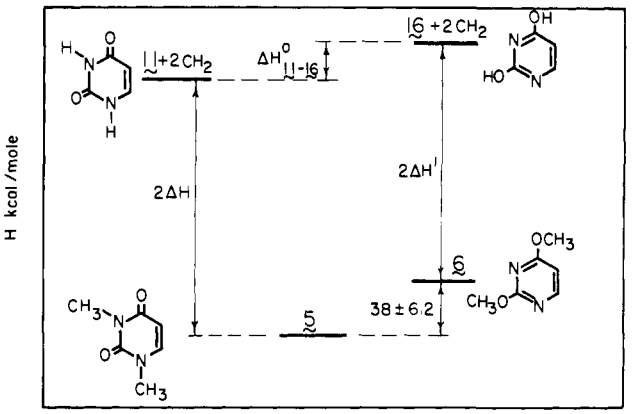
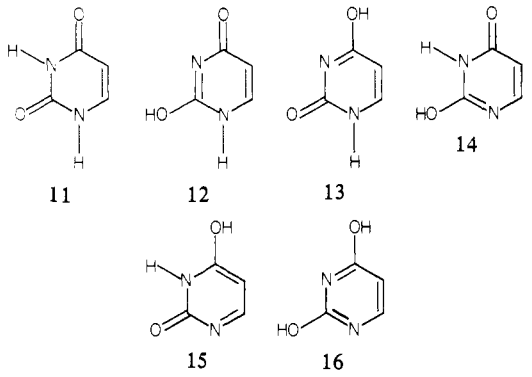


Figure 3. Relative enthalpies of **5**, **6**, **11** + $2CH_2$, and **16** + $2CH_2$.

The major interest in the area of pyrimidinedione tautomerization has been in the structure and function of protomeric derivatives. Solid,[14] solution,[15] and vapor-phase[16] studies indicate uracil (**11**) to be the most stable isomer. Although hydrogen bonding and environmental effects could be a factor in the solid and in solution, the vapor-phase studies should be free of such effects.[16,19] It should be noted that the energy differences between the isomers **11–16** could vary by several kilocalories/mole as a



function of the medium and such changes would not be detectable as long as **11** is favored by a factor of greater than 10^2. The careful work of Shugar and co-workers has shown that minor isomers of **11** cannot be detected in the vapor while Poulter and Frederick have estimated that **13** and **14** are 5 and 7 kcal/mol less stable than **11** in aqueous acidic solution by a pK_a method.[16-18]

In order to obtain an estimate of the equilibrium constants for **11–16** in the vapor, we calculate that −8.3 ± 2.3 kcal/mol is an appropriate enthalpy difference ($\Delta H - \Delta H'$) for the change of NH and OH bonds of the amide–imidic acid pair to the NCH_3 and OCH_3 bonds of the corresponding *N*-methylamide–*O*-methyl imidate pair.[1] This value is obtained by comparison of 2-methoxypyridine–1-methyl-2-pyridinone (**3–4**) with 2-pyridine–2-hydroxypyridine (**17–18**) as shown in Figure 2, and it represents the energy difference between the σ frameworks involved in the transformation. The values for $\Delta H_{3-4}°$ and $\Delta H_{17-18}°$ are known from our previous work[1-8] and allow the calculation:

$$\Delta H + \Delta H_{17-18}° = \Delta H' + \Delta H_{3-4}°$$

$$(\Delta H - \Delta H') = \Delta H_{3-4}° - \Delta H_{17-18}° = 8.6 \pm (2) - 0.3\ (\pm 0.3) = 8.3 \pm 2.3$$

Table II. Comparison of Theoretically and Experimentally Estimated Energy Differences for 11-16 and 11-13

tautomers	exptl est	theory				ab initio[d]
		MNDO/3[a]	CNDO/2[a]	CNDO/2[b]	SCF[b]	
11-16	21 (±9)	13.3	−34.5	10.4	33.4	−15
11-13	19 (±6)					7

[a] Reference 20a. [b] Reference 20b. [c] Reference 20c. [d] Reference 20d. [e] Reference 20e.

The use of this approach to provide an estimate to enthalpy difference between **11–16** is illustrated in Figure 3. The enthalpy of isomerization is then calculated as

$$\Delta H_{11-16} = 2\Delta H' - 2\Delta H + 38\ (\pm 4.7) = -16.6\ (\pm 4.6) + 38\ (\pm 4.7) = 22 \pm 10\ \text{kcal/mol}$$

This appears to be the first estimate based primarily upon experimental measures of the energy difference between these tautomers of uracil. The additive errors are large and probably overestimated in view of the likely cancellations. By a similar comparison the energy difference between **11** and **13** can be estimated to be 19 (±6) kcal/mol.

A number of theoretical calculations are compared with the above estimates of the protomeric energy differences in Table II.[20] The range of predictions from the different methods is reminiscent of that previously noted for calculations of the relative energies of **17–18**, and caution about acceptance of this approach still seems appropriate.[1,20a] When reliable calculations are available for the pyridine protomers, application to the pyrimidone protomers could be interesting.

We have recently reported a quantitative model for the effect of molecular environment on equilibria between protomers which expresses the relative free energies in solution ($\Delta G_s°$) and the vapor ($\Delta G_v°$) in terms of reaction field ($\Delta G_{el}°$) and hydrogen-bonding effects ($\Delta G_{Hb}°$).[5] If our above estimate of an energy difference of 19 ± 6 kcal/mol for **11–13** is provisionally accepted and compared with the value of 5 kcal/mol estimated for aqueous

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solution,[18] there is a large solvent effect on this equilibrium. If the molecular volumes of **11** and **13** are approximated as 5.0×10^{-23} cm^3/molecule[21] and the dipole moments of **5** and **7** of 3.98[20] and 4.77 D are used as models for the protomers **11** and **13**,[22] the reaction field term would account for only ca. 1 kcal/mol of the differences in energy between solution and vapor.[13,23] Accordingly, the apparent large effect of the molecular environment on this equilibrium may be attributed to the hydrogen-bonding term.[24]

$$\Delta G_s^\circ - \Delta G_v^\circ = \Delta G_{el}^\circ + \Delta G_{Hb}^\circ$$

$$\Delta G_{el}^\circ = \left(\frac{\mu_A^2}{a_A^3} - \frac{\mu_B^2}{a_B^3}\right)\left(\frac{\epsilon - 1}{2\epsilon + 2}\right)$$

$$\Delta G_{Hb}^\circ = + A\alpha + B\beta$$

μ_A = dipole movement of isomer n

a_n^3 = molecular volume of isomer n

ϵ = dielectric constant of the solvent

α,β = Taft's hydrogen-bonding parameters

A,B = linear regression parameters

Comparison of the amide–imidic acid equilibrium for **17–18** and **11–16** shows that for the pyridine derivatives the protomers are of equal energy while for the pyrimidine derivatives the amide is favored by ca. 20 kcal/mol. The relationship of these results to the protomers of the pyrimidine bases in the nucleic acids is of some interest. Qualitatively it seems clear that there is a large enthalpic driving force favoring **11**, and presumably its derivatives, over the other protomers. That driving force, along with the role hydrogen bonding plays in the relative stabilities of these tautomers, is consistent with a uracil being chosen for its efficiency in maintaining fidelity in the selection and/or replication of nucleic acids.[4]

Experimental Section[25]

All reagents and solvents employed were commercially available and used without further purification unless otherwise specified. 1,4-Dioxane and tetrahydrofuran (Aldrich gold label) were freshly distilled from benzoquinone ketal before use.

1,3-Dimethyl-2,4-pyrimidinedione (5),[26] **2,4-dimethoxypyrimidine (6)**,[10a] **4-methoxy-1-methyl-2-pyrimidinone (7)**,[10a] and **2-methoxy-3-methyl-4-pyrimidinone (8)**[10d] were prepared by established methods and characterized by NMR and IR spectroscopy and combustion analysis.[13] For the synthesis of **8** the lithium salt of 2-methoxy-4-pyrimidine was generated in tetrahydrofuran with *n*-butyllithium and methylation carried out with dimethyl sulfate to give 18% of **8**.[13]

2,4-Dimethoxy-1-methylpyrimidinium Hexafluorophosphate (9). From 6. To a slurry of 9.3 g (63 mmol) of trimethyloxonium tetrafluoroborate in dichloromethane was added 6.0 g (43 mmol) of **6**, and the mixture was stirred for 12 h at ambient temperature. The solution was reduced in volume in vacuo to provide an oil which was dissolved in 75 mL of 2:1 ethanol/water. To this solution was added 50 mL of a solution of 18.0 g (110 mmol) of ammonium hexafluorophosphate in water, and the solution was stirred for 3 h at ambient temperature. The white precipitate was isolated and recrystallized twice from dichloromethane/hexane to provide 7.6 g (59%) of **9** as a white powder: mp 147–148 °C; ^{1}H NMR (CD_2Cl_2) δ 8.33 (d, 1, J = 6Hz, H_6), 6.95 (d, 1, J = 6Hz, H_5), 4.40 (s, 3, O_4CH_3), 4.30 (°, 3, O_2CH_3), 3.92 (s, 3, N_1CH_3); IR (Nujol) 990 (PF_6^-). Anal. Calcd for $C_7H_{11}O_2N_2PF_6$: C, 28.01; H, 3.69; N, 9.33; P, 10.32. Found: C, 28.28; H, 3.75; N, 9.30; P, 10.18.

From 7. A salt with the identical spectra and physical properties was prepared in 40% yield from **7** in an otherwise identical procedure.

Thermal Stabilities. Separate samples of **5**, **6**, **7**, and **9** heated at 160 °C for 6 h showed no evidence of decomposition by NMR, TLC, and mp or bp criteria. A sample of **8** showed partial rearrangement of **5** at heating at 160 °C for 3 h.

Calorimetric Determination of the Liquid-Phase Heats of Isomerization. The calorimeter and the general procedure employed have been previously described. The electrical calibration of the calorimeter was checked by finding the heat evolved by the methyltropic rearrangement of 2-methoxypyridine (**4**) to a 1-methyl-2-pyridone (**3**) in the presence of a catalytic amount of 2-methoxy-1-methylpyridinium tetrafluoroborate to be within experimental error of the reported value.[8]

The equilibrations of **6** to **5** and **7** to **5** were initiated at 147 °C with all species in the melt by breakage of the bulb that contained **9**. The evolution of heat for the reaction was complete in less than 1 min.

Analysis of the reaction mixtures after the equilibrations by HPLC and ^{1}H and NMR showed **5** to be the only detectable isomer. Examination of standard mixtures of **5** and **6** and **5** and **7** with HPLC established that 1 in 10^3 parts of the minor isomers would have been detected. Analysis of the products also showed the catalyst **9** had rearranged to 1,3-dimethyl-4-methoxy-2-pyrimidinonium hexafluorophosphate (**10**). Correction for the heat of the conversion of **9** to **10** was accomplished by employing a multiple linear regression where $\Delta H_{1t\rightarrow m}$, the methyltropic rearrangement of the pyrimidones, and $\Delta H_{9\text{-}10}$, the rearrangement of the catalysts, are evaluated. The data for the $\Delta H_{15\text{-}6}^\circ$ are summarized in Table III. The regression analysis yields a $\Delta H_{1k\text{-}6}^\circ$ of -44 ± 3.1 kcal/mol and $\Delta H_{9\text{-}10}^\circ$ of -41 ± 5 kcal/mol. The statistics for this regression are $R^2 = 0.9975$, $P = 1.2 \times 10^{-4}$, and SE = 0.0012 and established the correlation's significance and reliability. The error reported for $\Delta H_{15\text{-}6}^\circ$ of 2.6 kcal/mol was calculated from the relative experimental error, since this error was larger than the standard deviation calculated from the regression. The error reported for $\Delta H_{9\text{-}10}^\circ$ is the calculated standard deviation. The value of $\Delta H_{15\text{-}7}$ is calculated to be 24.8 ± 1.3 kcal/mol as is summarized in Table III. The $\Delta H_{15\text{-}7}^\circ$ was calculated by factoring out from the heat observed on the contribution of $\Delta H_{9\text{-}10}^\circ$, and the error is the standard deviation.

Table III. Calorimetrically Determined ΔH_1° between 5 and 6 and 5 and 7 at 147 °C

initial mmol			heat evolved, kcal	ΔH_1°,[a] kcal/mol
6	7	9		
2.99		0.505	0.157 ± 0.014	45
2.60		0.541	0.142 ± 0.014	46
3.89		0.697	0.177 ± 0.0086	38
4.75		0.104	0.218 ± 0.013	46
3.65		0.0943	0.171 ± 0.011	46
3.82		0.111	0.176 ± 0.007	45
				44 ± 3.1
	2.45	0.910	0.066 ± 0.0086	25.4
	2.39	0.887	0.0636 ± 0.0038	25.1
	2.40	0.853	0.0630 ± 0.0057	24.8
	3.02	0.108	0.0786 ± 0.0057	24.1
	3.37	0.539	0.1111 ± 0.006	26.3
	2.79	0.540	0.0852 ± 0.006	24.8
				24.8 ± 1.3

[a] Corrected for the contribution of $\Delta H_{19\text{-}10}^\circ$ of 41 ± 5 kcal/mol.

Calculation of Heats of Vaporization, $\Delta H_{vap}^\circ(T)$. The $\Delta H_{vap}^\circ(T)$ for **5**, **6** and **7** were calculated by employing the Clausius–Claperyon equation and using nonreduced Cox–Antoine vapor pressure data as described by Lee.[13,27] The ΔH_{vap}° values obtained are for **5**, 17 ± 0.8, **6**, 11.5 ± 0.8, and **7** 19.4 ± 2 kcal/mol.

(21) The molecular volume of 4-methoxy-2-pyridine is used as a model. Covington, J. B. PhD. Thesis, University of Illinois, Urbana, 1978.

(22) Kulakowski, L.; Geller, M.; Lesyng, B.; Wiezchoswki, K. L. *Biochim. Biophys. Acta* **1974**, *361*, 119.

(23) A similar conculsion about the effect of the reaction field term for closely related system has been reported by Bensaude, Dubois, and co-workers.[15g]

(24) A similar approach to estimate the effect of the reaction field term on the equilibrium **11–16** suggests it could contribute 2 kcal/mol, and again the hydrogen-bonding term would be important.

(25) All chemical shifts in ^{1}H NMR spectra are reported in δ relative to internal tetramethylsilane. Elemental analyses were carried out by J. Nemeth and associates. Thin-layer chromatography was performed using Brinkman Chromagram Sil G. sheets with fluorescent indicator. All column chromatography was performed using Birkman silica gel as the support.

(26) Brown, D. J. "The Pyrimidines"; Interscience: New York, 1962; Tables XXV–XXVII.

(27) Lee, J. T. Ph.D. Thesis, University of Illinois, Urbana, 1968.

The boiling points of **5** and **6** were determined on a Buchi capillary melting point apparatus and corrected to normal pressure. The boiling point of **7** was measured at several reduced pressures and corrected to 760 nm. The dipole moment of **7** was derived by the method of Guttenheim to be 4.77 D.[28]

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Registry No. 5, 874-14-6; **6**, 3551-55-1; **7**, 7152-66-1; **8**, 27460-04-4; **9**, 83542-65-8; **11**, 66-22-8; **13**, 51953-19-6; **16**, 51953-14-1.

(28) Shoemaker, D. P.; Garland, C. W. "Experiments in Physical Chemistry"; McGraw-Hill: New York, 1962; pp 51–58.

Structural Characterization of Channel Inclusion Compounds Formed by Furaltadone Hydrochloride: Comparison to the Crystal and Molecular Structures of Furaltadone Base and Moxnidazole Hydrochloride[1]

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Abstract: This paper reports new inclusion complexes of furaltadone [5-(morpholinomethyl)-3-[(5-nitrofurfurylidene)-amino]-2-oxazolidinone] hydrochloride with acetic acid, propionic acid, and water as substrate molecules. The inclusion compounds crystallize in the monoclinic space group $P2_1/c$ ($Z = 4$) and represent channel-type clathrates in which the guest molecules are accommodated in continuous canals running through the crystal parallel to the c axis. The canals have an approximately cylindrical shape and are lined with oxygen and chlorine nucleophiles; nevertheless, the enclathrated species are translationally disordered in their location in the channel. The crystal structures of the inclusion compounds are compared with those observed for the furaltadone base and moxnidazole hydrochloride. The latter is a closely related species to furaltadone hydrochloride, with an *N*-methylnitroimidazole ring instead of the nitrofuran moiety. However, the observed configuration of moxnidazole and, consequently, the relative orientation of its polar groups are different in order to avoid intramolecular steric hindrance. As an apparent result, no clathrate-type channels are formed when a hydrate of moxnidazole hydrochloride crystallizes from water. The solvent-free structure of furaltadone is dominated by characteristic dipole–dipole interactions between molecules located across crystallographic centers of symmetry. Remarkably similar interactions of dipolar "dimerization" are present in the compounds containing furaltadone (but not moxnidazole) hydrochloride; we thus suggest that they are significant to the formation of the observed channel inclusion structures. Relative stability of the inclusion compounds is discussed, and molecular geometries of all the involved species are described in detail. Molecules of acetic acid appear in the channel complexes as isolated monomeric species.

One of the most interesting aspects of host–guest chemistry relates to the formation of crystalline clathrate inclusion compounds in which guest species are enclosed by channels or cages that occur in a given host lattice.[2] Selected series of such inclusion systems have been particularly useful in recent studies of photochemical reactions in the solid state[3] and of selective molecular complexation[4] that is central to biological phenomena. In the course of our investigations into the structural properties of inclusion compounds, we observed that furaltadone hydrochloride, $C_{13}H_{16}N_4O_6 \cdot HCl$, an antibacterial agent derived from nitrofuran, tends to form clathrate-type complexes when crystallized from various solvents. On the other hand, the closely related species of furaltadone and of moxnidazole hydrochloride (in which the nitrofuran moiety is replaced by an *N*-methylnitroimidazole ring) exhibit different habits of crystallization. Since no relevant structural data have previously been reported, and in order to understand the stereochemical features of these phenomena, we decided to investigate a series of crystals in greater detail.

The present account is thus concerned with the crystal structures of three channel inclusion complexes of furaltadone hydrochloride with acetic acid (I), propionic acid (II), and 2 mol of water (III), as well as with those of furaltadone (IV), furaltadone monohydrate (V), and moxnidazole hydrochloride monohydrate (VI). We examine the molecular structures of moxnidazole and furaltadone (in the various environments) moieties and compare their configurational details. There is an emphasis on the characteristic intermolecular interactions found between the furaltadone species that seem to play an important role in the formation of the inclusion structures.

Experimental Section

The hydrochloric salts of furaltadone and moxnidazole were prepared by TEVA Pharmaceutical Industries, Ltd. Single crystals of the inclusion

(1) A short account of this work has been presented at the Sixth European Crystallographic Meeting, Barcelona, Spain, July 28, 1980. The nontrivial names of furaltadone and moxnidazole are 5-(morpholinomethyl)-3-[(5-nitrofurfurylidene)amino]-2-oxazolidinone and 5-(morpholinomethyl)-3-[1-*N*-methyl-5-nitroimidazolyl-2-methylene)amino]-2-oxazolidinone, respectively.

(2) For a recent review, see, e.g.: MacNicol, D. D.; McKendrick, J. J.; Wilson, D. R. *Chem. Soc. Rev.* **1978**, *7*, 65–87.

(3) (a) In tri-*o*-thymotide clathrates: Arad-Yellin, R.; Brunie, S.; Green, B. S.; Knossow, M.; Tsoucaris, G. *J. Am. Chem. Soc.* **1979**, *101*, 7529–7537. (b) In inclusion complexes of the choleic acids: Popovitz-Biro, R.; Chang, H. C.; Tang, C. P.; Shochet, N. R.; Lahav, M.; Leiserowitz, L. Work presented at the 47th Meeting of the Israel Chemical Society, Rehovot, 28–29 Sept 1980. See also *J. Am. Chem. Soc.* **1978**, *100*, 2542–2544.

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