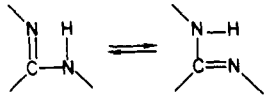
Dynamic NMR Investigation of the Annular Tautomerism in Dihydropyrimidines[1]

A. L. Weis,*† Z. Porat,† and Z. Luz‡

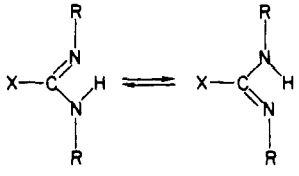
Contribution from the Department of Organic Chemistry and the Department of Isotope Research, The Weizmann Institute of Science, Rehovot, Israel 76100. *Received January 13, 1984*

Abstract: ^1H and ^{13}C NMR spectra of 6-methyl-2,4-diphenyl-1,4-dihydropyrimidine (MDHP) in several organic solvents are reported. In dilute solutions of purified solvents, separate NMR signals from the two tautomeric forms, 1,4-MDHP (A) and 1,6-MDHP (B), are observed. From the relative intensities of the peaks, the equilibrium constant $K = [B]/[A]$ has been determined in $CDCl_3$, dioxane, Me_2SO, and HMPA. In impure solvents and/or a high concentration of MDHP there is fast tautomeric equilibrium between forms A and B, and only a single, average set of peaks is observed. The kinetics of the tautomeric process and its dependence on temperature and MDHP concentration in purified $CDCl_3$ solvent was quantitatively studied by ^1H NMR line-shape analysis. The results indicate that two mechanisms contribute to the reaction, (i) a monomolecular process characterized by the kinetic parameters $k_1(300\ K) = 31 \pm 4\ s^{-1}$ and $\Delta E^{\ddagger} = 4.5 \pm 0.6$ kcal/mol and (ii) a bimolecular reaction with $k_2(300\ K) = (1.0 \pm 0.2) \times 10^3\ M^{-1}\ s^{-1}$ and $\Delta E^{\ddagger} = 3.3 \pm 0.7$ kcal/mol.

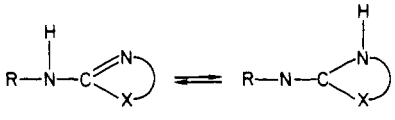
The isodesmic [1,3]-sigmatropic tautomerism[2] in the case of prototropism in amidinic systems may be expressed by the following general scheme:



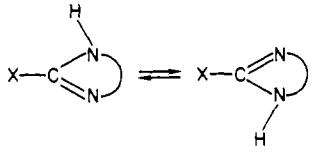
Three classes of tautomeric equilibria can be distinguished according to the molecular structure of the amidinic compounds: (a) Acyclic:



(b) Semicyclic:

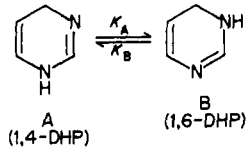


(c) Cyclic or Annular:



The tautomeric equilibrium in the cyclic class of compounds has been studied most extensively for a five-membered ring, i.e., imidazole and its derivatives,[3] using spectroscopic methods. The tautomerism in solutions of these compounds is extremely fast on the NMR time scale, and as yet no separate NMR signals for the two tautomers have been reported, although ^{13}C solid-state NMR measurements indicate that in crystalline imidazole it is slow.[4]

Much less is known about the tautomeric equilibrium in six-membered amidinic rings, i.e., dihydropyrimidine (DHP)[5] and its derivatives:



A (1,4-DHP) B (1,6-DHP) (1)

The tautomerism here was originally also thought to be fast on the NMR time scale; however, Weis and Mamaev[6] have shown that, under certain experimental conditions, solutions of substituted DHP's exhibit separate NMR peaks for the two tautomeric species, A and B. Using IR, X-ray crystallography, and NMR it was possible to characterize the structure of these species and determine the necessary conditions for slowing down the tautomeric conversion.[7-9] In the present paper we present a quantitative analysis of the kinetics of the tautomeric equilibrium in deuterated chloroform, with particular emphasis on the external parameters that influence the rate of the reaction. Analysis of these results provides information on the possible mechanism of the reaction.

For the actual measurements we have chosen the compound 6-methyl-2,4-diphenyl-1,4-dihydropyrimidine (MDHP) because it is relatively stable and also since, in aprotic solvents, its tautomeric equilibrium constant is in the convenient range,

$$K = [B]/[A] \sim 1$$

Preliminary kinetic NMR measurements were preformed on specially dry and ultrapure Me_2SO-d_6. However, during the experiments impurity signals appeared in the spectrum, particularly from 4-methyl-2,6-diphenylpyrimidine, due to oxidation reactions involving the Me_2SO.[10] Consequently, the kinetic results in this solvent were not reproducible. We had better success with pure $CDCl_3$. This solvent, when properly purified, appeared to

† Department of Organic Chemistry.
‡ Department of Isotope Research.

(1) Dihydropyrimidines, part 5. For part 4, see: Weis, A. L.; Frolow, F.; Zamir, D.; Bernstein, M. *Heterocycles* **1984**, *22*, 657.
(2) Zefirov, N. S.; Tratch, S. S. *Chem. Scr.* **1980**, *15*, 4.
(3) For reviews, see: Katritzky, A. R.; Lagowsky, J. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 311; **1963**, *2*, 1. Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. *Adv. Heterocycl. Chem. Suppl.* **1976**, *1*.
(4) Elguero, J.; Fruchier, A.; Pellegrin, V. *J. Chem. Soc., Chem. Commun.* **1981**, 1207.
(5) For the sake of convenient comparison of tautomers A and B, we have numbered 4-methyl-2,6-diphenyl-1,6-dihydropyrimidine (MDHP-B) as 6-methyl-2,4-diphenyl-3,4-dihydropyrimidine.
(6) Weis, A. L.; Mamaev, V. P. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1975**, 148; *Chem. Abstr.* **1976**, *84*, 121764v.
(7) Weis, A. L. *Tetrahedron Lett.* **1982**, *23*, 449.
(8) Weis, A. L.; Frolow, F. *J. Chem. Soc., Chem. Commun.* **1982**, 89.
(9) Weis, A. L.; Frolow, F. *Heterocycles* **1982**, *19*, 493.
(10) Weis, A. L.; Shyrina, V. M.; Mamaev, V. P. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1975**, 144; *Chem. Abstr.* **1976**, *84*, 105528r. Mamaev, V. P.; Weis, A. L. *Khim. Geterotsikl. Soedin.* **1975**, 1555; *Chem. Abstr.* **1976**, *84*, 90106a.

0002-7863/84/1506-8021$01.50/0

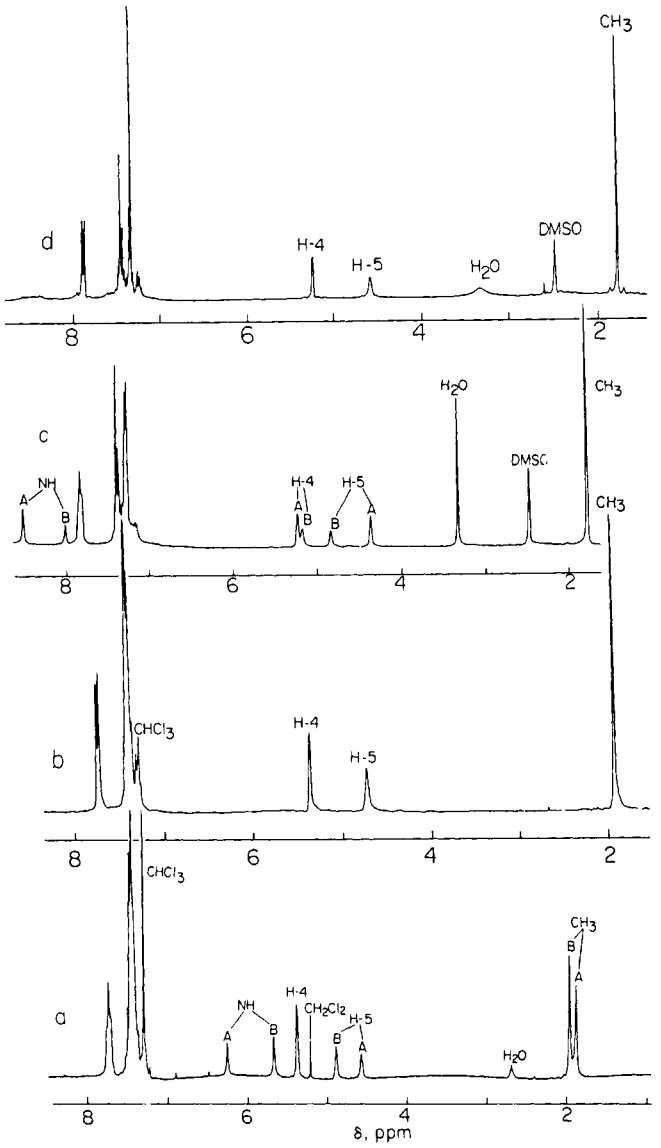


Figure 1. ^1H NMR spectra (at 270 MHz of MDHP in $CDCl_3$ and Me_2SO-d_6). Trace a is for a 0.026 M solution in $CDCl_3$ purified by method d (see text) at −60 °C. Trace b is for a 0.026 M solution using commercial untreated $CDCl_3$. Traces c and d are for a 0.04 M solution at room temperature using respectively purified and untreated commercial Me_2SO-d_6.

be stable, and the kinetic results were quite reproducible. Solutions of MDHP in $CDCl_3$, sealed in NMR tubes, could be kept for several days in the dark at −4 °C without showing signs of deterioration. As discussed below, the results depended very critically on the purity of the solvent and solute used.

Experimental Section

(A) Materials. 6-Methyl-2,4-diphenyl-1,4-dihydropyrimidine (MDHP) was prepared from freshly distilled commercial benzalacetone (Merck) and benzamidine (yield: 87%).[6] For the final dynamic NMR experiment the MDHP was recrystallized twice from respectively benzene and ethanol–ether. The melting point of the purified crystals was 144–145 °C.

Me_2SO-d_6 (99.8% or 99.95% deuterium, Merck) was fractionally distilled from calcium hydride at 0.05 torr under dry N_2. The middle 70% fraction was collected and stored over activated molecular sieves (4 Å). Me_2SO-d_6 prepared in this way showed no water signal in the NMR spectrum.

$CDCl_3$ (99.98% deuterium, Aldrich, Merck) was purified by three different methods: (a) elution through a dry Al_2O_3 column (Woelm-200); (b) distillation over P_2O_5 and subsequent elution through dry Al_2O_3; (c) drying and distillation over P_2O_5 followed by fraction distillation over K_2CO_3, and finally, the middle 60% fraction was redistilled. 1,4-Dioxane-d_8 (99% deuterium, Merck) was distilled over sodium wires and stored over molecular sieves 4 Å. Commercial grade HMPA-d_{18} (99% deuterium, Merck) was stored over molecular sieves 4 Å and used without further treatment.

Preparation of the solutions was done in a drybox under an argon atmosphere.

(B) NMR Measurements. The ^1H and ^{13}C NMR spectra were recorded on a WH 270 Bruker spectrometer operating in the FT mode. The corresponding frequencies were 270 MHz for ^1H and 67.9 MHz for ^{13}C. The sample temperature was controlled by using the BST 100/700 unit, and its absolute temperature was repeatedly calibrated with a Fluka 2190A digital thermometer.

The kinetic measurements employed the H-5 proton signals using standard line-shape analysis methods.[11] The specific rates k are given (in s^{-1}) for the A form only: $k_A = (1/[A])(d[A]/dt)$. Clearly $k_B = k_A K$. The accuracy of k_A's is estimated to lie in the range 10% to 30% depending on the quality of the spectra.

Table I. Chemical Shifts (ppm) of the NH Protons and Equilibrium Constant for the MDHP Tautomerism in Several Organic Solvents

solvent	temp,[a] °C	concn, M	NH(A)	NH(B)	K = [B]/[A]
$CDCl_3$	−60	0.013	6.18	5.56	1.27 ± 0.07
$CDCl_3$	−60	0.073	6.30	5.74	1.27 ± 0.07
$CDCl_3$	−60	0.121	6.54	6.08	1.27 ± 0.07
dioxane-d_8	15	0.01	7.19	6.75	0.82 ± 0.06
Me_2SO-d_6	25	0.01	8.56	8.05	0.67 ± 0.04
HMPA-d_{18}[b]	25	0.01	9.35	8.90	0.50 ± 0.04

[a] Temperature for which the data are reported. [b] Hexamethylphosphoramide, syn., hexamethylphosphoric triamide.

Description of NMR Spectra

In Figure 1 are shown ^1H NMR spectra of MDHP in $CDCl_3$ and Me_2SO-d_6. Spectrum 1a is for $CDCl_3$ solution at −60 °C and corresponds to the slow exchange limit. The signals of the two tautomeric forms A and B are completely separated. The peak assignments given in the figure are from ref 7 and were determined by comparison with the IR of the same compound, as well as N-methylated derivatives of the two tautomers. Spectrum 1b was taken at room temperature, in the commerical $CDCl_3$. The rate of tautomerism is fast, and the observed peaks of H-4 and H-5 occur at the weighted average positions of the corresponding tautomers. The NH peak in this spectrum is not observed, however, apparently due to exchange with an impurity, whose signal is strongly shifted from that of the NH. It should also be noted that in this solvent the position of the NH signal was concentration dependent, and when water was present, so was the H_2O peak. All these peaks shifted to low field with increasing MDHP concentration, probably due to the formation of hydrogen-bonded complexes.

The ^1H NMR spectra of MDHP in Me_2SO-d_6 in respectively the slow and fast exchange limits are shown in traces 1c and 1d. Both spectra were taken at room temperature; however, while spectrum 1c corresponds to a purified solvent, spectrum 1d was taken in an "impure" (commercial grade) solvent. Note that there are several differences between the spectra in the two solvents, in particular, the large low-field shift of the NH signals in Me_2SO relative to $CDCl_3$, the splitting of the H-4 signals observed in Me_2SO but not in $CDCl_3$, and that the signals of the two methyl protons are degenerate in Me_2SO but not in $CDCl_3$.

The equilibrium distribution [B]/[A] is solvent dependent, decreasing from 1.27 in $CDCl_3$ to 0.67 in Me_2SO. Summarized in Table I are the chemical shift data for the NH protons and the equilibrium constant in $CDCl_3$ and Me_2SO and in two other solvents. It appears that there is a significant low-field shift of the NH resonances of both tautomers with increasing polarity apparently due to formation of H-bonding complexes with the solvent. In $CDCl_3$ there is also a low-field shift of the NH signal with increasing MDHP concentration, indicating the formation of dimers or higher clusters. This concentration effect on the NH was not found in the other solvents studied. The equilibrium distribution [B]/[A] also decreases monotonically with increasing

(11) Gunther, H. "NMR Spectroscopy—An Introduction"; Wiley: Chichester, England, 1980; Chapter VIII.

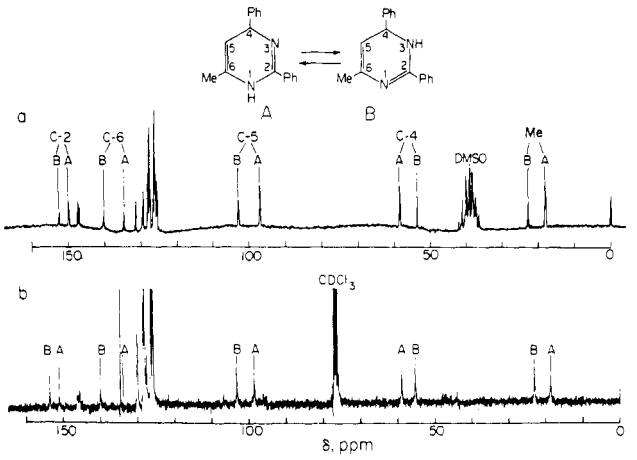


Figure 2. ^{13}C NMR spectra (270 MHz) of 0.06 M MDHP solutions in $CDCl_3$ (a) and Me_2SO-d_6 (b). Purified solvents were used and the recording was done at −60 °C for $CDCl_3$ and at room temperature for Me_2SO-d_6.

polarity, suggesting that form A is more polar than form B.

In general, the tautomeric transformation between A and B is slower in the more polar solvents. Thus, separate signals for the two tautomers can readily be observed even in unpurified HMPA, whereas in $CDCl_3$ it can only be observed in a purified solvent and in very dilute solutions. It appears that the proton transfer process is hindered by the formation of the H-bonded complexes with the polar solvents.

Finally, ^{13}C NMR spectra in $CDCl_3$ (at −60 °C) and Me_2SO (room temperature), both corresponding to the slow exchange limit, are shown in Figure 2. The interpretation of these spectra is similar to that discussed above for the ^1H NMR. In a previous ^{13}C study of substituted dihydropyrimidines, no separate signals for the two tautomers were reported.[12]

Kinetic Measurements and Discussion

(A) Effect of Solvent Purity. Even minute amounts of impurities in the $CDCl_3$ solvent strongly catalyze the tautomeric equilibration between A and B, as shown by the so-called "coalescence temperature" (t_c) of corresponding peaks from the A and B species. Thus t_c of the H-5 protons in a 0.01 M solution of MDHP in commercial $CDCl_3$ lies near -60 °C and even lower for higher concentrations of MDHP, while t_c for a 0.01 M solution in very pure (see below) $CDCl_3$ is near +60 °C. We have determined t_c for H-5 in solutions in which the solvent and solute underwent various degrees of purification as follows (for details see Experimental Section): (a) MDHP recrystallized from benzene and $CDCl_3$ dried on Al_2O_3; (b) MDHP recrystallized from benzene and $CDCl_3$ distilled from P_2O_5, followed by elution through dry Al_2O_3; (c) MDHP recrystallized from benzene and $CDCl_3$ triply distilled from respectively P_2O_5, K_2CO_3, and neat; and (d) MDHP recrystallized twice (from benzene and ethanol–ether, respectively) and $CDCl_3$ distilled three times as in c.

In Figure 3 are plotted the coalscence temperatures as a function of MDHP concentration in solutions prepared as described above. It may be seen that purification of both the solvent and the MDHP has a marked effect on t_c. Further crystallization of the MDHP and distillation of the $CDCl_3$ beyond that described in method d did not result in a further increase of t_c. Measurements done by using solutions prepared by this method were highly reproducible, and we therefore used such solutions for the final kinetic studies.

In this connection it is interesting to note that the addition of trace amounts of ammonium salts, HCl, or of a small amount of commercial $CDCl_3$ to the purified solutions of Me_2SO or $CDCl_3$ resulted in complete coalescence of the spectra due to tautomers A and B. On the other hand, the addition of water (up to 0.03 wt %) to $CDCl_3$ had almost no affect on the tautomeric rate. In part, this is no doubt due to the low solubility of water in this solvent.

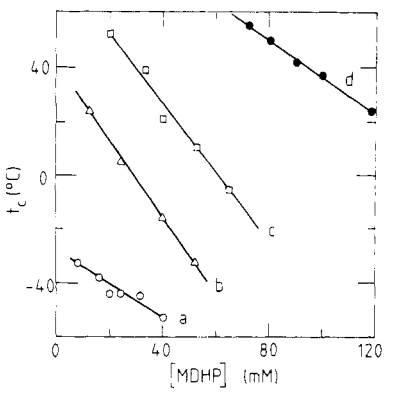


Figure 3. The coalescence temperature, t_c, for the proton peaks H-5 of MDHP in $CDCl_3$ solution as a function of solute concentration. The various series of experiments correspond to solutions which underwent different purification treatment as explained in the text.

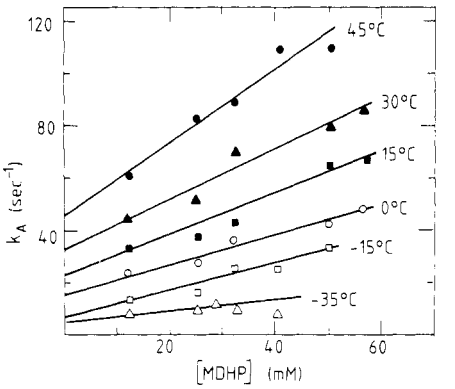


Figure 4. Plots of k_A derived from the experimental spectra as a function of MDHP concentration for different temperatures as indicated in the figure.

(B) Concentration and Temperature Dependence of k_A. In order to determine the specific rate and mechanism of the tautomeric reaction 1, we have studied the temperature dependence of the ^1H NMR spectra of MDHP in $CDCl_3$ solution containing different concentrations of solute in the range 10–60 mM and between −60 and +60 °C. To determfine the effect of concentration on the rate, plots of k_A vs. the MDHP concentration were made, and these are shown in Figure 4. At each temperature, k_A can be written as

$$k_A(T) = k_1(T) + k_2(T)[\text{MDHP}] \qquad (2)$$

where k_1 corresponds to a monomolecular reaction with respect to form A of MDHP while k_2 corresponds to a bimolecular term. It should be noted that at concentrations greater than 60 mM MDHP, deviations from linearity in the k_A plots were obtained and the results were not always reproducible. This may be due to solubility and aggregation effects at the higher concentrations of MDHP. The analysis was therefore limited to solutions containing up to 60 mM MDHP. k_1 and k_2 values of eq 2 were obtained for six temperatures in the range −35–+45 °C, and Arrhenius plots of these rate constants are given in Figure 5. The kinetic parameters derived from these curves are the following. For k_1

k_1(300 K) = 31 ± 4 s^{-1}; $\Delta E^\ddagger$ = 4.5 ± 0.6 kcal/mol; $\Delta H^\ddagger$ = 3.9 ± 0.6 kcal/mol; $\Delta S^\ddagger$ = −43 ± 3 cal/deg mol

For k_2:

k_2(300 K) = (1.0 ± 0.2) × 10^3 M^{-1} s^{-1}; $\Delta E^\ddagger$ = 3.3 ± 0.7 kcal/mol; $\Delta H^\ddagger$ = 2.7 ± 0.7 kcal/mol; $\Delta S^\ddagger$ = −41 ± 3 cal/deg mol

(12) Van der Stoel, R. E.; van der Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 116.

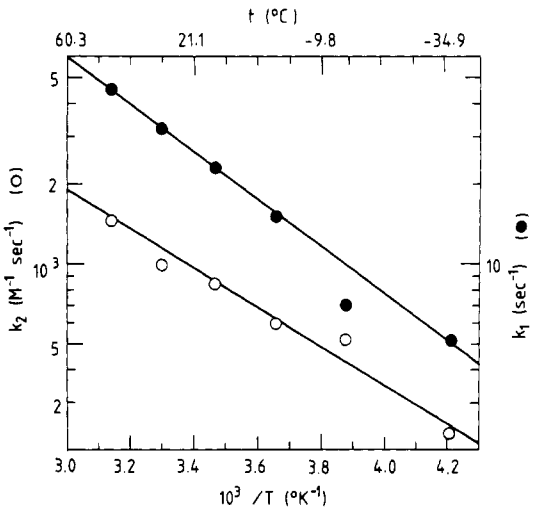


Figure 5. Arrhenius plots for the monomolecular k_1 and bimolecular k_2 rate constants derived from the analysis of the results in Figure 4.

The kinetic behavior suggests that there are two mechanisms involved in the transformation between the tautomers; one is first order with respect to the MDHP concentration while the other is second order. The first-order reaction involves the solvent in the protolytic reaction

$$\text{MDHP} + \text{Sol} \xrightarrow{k_1} \text{Sol H}^+ + \text{MDHP}^- \qquad (3)$$

where in the reverse reaction the protonation may occur at the second nitrogen. Actually this reaction may also proceed with remnant impurities still left in the solution that may serve as conjugate bases to the MDHP molecules. Therefore, the observed k_1 must be considered as an upper limit for the reaction with $CDCl_3$.

The second-order reaction can be considered as a proton exchange between two MDHP molecules as a result of a bimolecular collision. Alternatively, the reaction may involve proton transfer between MDHP molecules and disproportionation products of the self-ionization reaction

$$2\text{MDHP} \rightleftharpoons \text{MDHP}^+ + \text{MDHP}^- \qquad (4)$$

$$\text{MDHP}^{\pm} + \langle\text{MDHP}\rangle \rightleftharpoons \text{MDHP} + \langle\text{MDHP}^{\pm}\rangle \qquad (5)$$

where the + and − superscript refer to protonated or deprotonated species.

In concentrated solutions (above 20 mM MDHP) the bimolecular proton-transfer reaction dominates, while in dilute solutions, the exchange process is dominated by the monomolecular protolysis reaction.

There are no other published quantitative kinetic data on similar amidinic systems. However, preliminary results in our laboratory suggest that both structural and substitution effects are important in determining the tautomeric rate. In particular, it appears that the presence of phenyls instead of methyls in positions 2 and 6 of dihydropyrimidine considerably reduces the tautomeric rate, while reduction of the C=C double bond increases it. Similar substitution effects were also observed in dihydro-1,3,5-triazine derivatives.

Registry No. MDHP, 58870-09-0.

A New Water-Soluble Macrocyclic Host of the Cyclophane Type: Host–Guest Complexation with Aromatic Guests in Aqueous Solution and Acceleration of the Transport of Arenes through an Aqueous Phase

François Diederich* and Klaus Dick

Contribution from the Max-Planck-Institut für medizinische Forschung, Abteilung Organische Chemie, D-6900 Heidelberg, Federal Republic of Germany. *Received March 5, 1984*

Abstract: A concept is presented for the design of water-soluble macrocyclic hosts of the cyclophane type which possess a cavity of very pronounced hydrophobic character as binding site for apolar guests in aqueous solution. In host **8** four spiro piperidinium rings attached to the 1,7,21,27-tetraoxa[7.1.7.1]paracyclophane framework locate the water-solubility-providing quaternary ammonium nitrogens remote from the cavity. The geometry of **8** is discussed in terms of CPK molecular models. The aggregation behavior of **8** in aqueous solution was studied by ^{1}H NMR spectroscopy. Aqueous solutions of host–guest complexes of **8** with neutral arenes were prepared by solid-liquid and liquid-liquid extraction. Evidence for the formation of host–guest complexes with exclusive 1:1 stoichiometry was obtained, and host–guest association constants were determined by the two methods of extraction. Hydrophobic and van der Waals interactions are shown to be the major driving forces for the strong complexation of **8** with neutral arenes. The association constants of the complexes of **8** with fluorescing aromatic guests bearing polar or anionic residues were determined either directly from fluorescence titration curves or by a Benesi–Hildebrand treatment of the fluorescence data. Host–guest association constants were also estimated from competitive inhibition experiments. Compound **8** not only binds neutral arenes but also is a good host for aromatic guests bearing anionic (sulfonate) residues. Complexes of the latter type make use of attractive forces of both apolar and electrostatic nature. The transport of neutral arenes through an aqueous phase along a concentration gradient mediated by **8** as molecular carrier was studied in a U-type cell.

There exists a close relationship between the field of synthetic host–guest chemistry[1] and molecular recognition in biological systems. Artificial host–guest systems have been designed to mimic the binding of substrates by enzymes, antibodies, and receptors and the transport of ions across biological membranes mediated by ionophores as natural carriers.[2]

(1) (a) Cram, D. J.; Cram, J. M. *Science (Washington, DC)* **1974**, *183*, 803. (b) Cram, D. J. In "Applications of Biochemical Systems in Organic Chemistry"; Jones, J. B., Sih, C. J., Perlman, D., Eds. "Techniques in Chemistry"; Weissberger, A., Ed.; Wiley: New York, 1976; Vol. 10, Part II, pp 815–873. (c) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8.

(2) (a) "Host Guest Complex Chemistry I"; Vögtle, F., Ed.; "Topics in Current Chemistry"; Springer: Berlin, 1981; Vol. 98. (b) "Host Guest Complex Chemistry II"; Vögtle, F., Ed.; "Topics in Current Chemistry"; Springer: Berlin, 1982; Vol. 101.

0002-7863/84/1506-8024$01.50/0