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Tetrasubstituted [14]-1,3,8,10-tetraeneN4 Macrocyclic Complexes: Synthesis, Organic Precursor, and Template Reaction Mechanism

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Template syntheses have been studied for macrocyclic complexes derived from 1,3-diaminopropane (DAP), 1-phenyl-1,2-propanedione (AB), and metal(II) acetate, where metal is iron, cobalt, or nickel. The products were characterized by elemental analyses and conductivity and spectroscopic methods (IR, UV–vis, proton and carbon-13 NMR). Carbon-13 NMR analysis indicates that the template synthesis is regiospecific, producing only one of the two possible isomeric products corresponding to the ligand 2,9-dimethyl-3,10-diphenyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene, *trans*-MePhTIM. X-ray diffraction data for a crystal of [Co(MePhTIM)Cl₂]PF₆ are also consistent with a centrosymmetric trans isomer product. ¹H NMR studies of the 1:1 condensation of AB and DAP in the absence of metals indicate a mixture of products from which the major product was isolated and found to be 2-benzoyl-2-methylhexahydropyrimidine. Reaction of this compound with metal salts yields the isomerically pure *trans*-MePhTIM complexes. The synthetic results and ¹H NMR studies are consistent with a proposed template mechanism in which AB and DAP react first to form 2-benzoyl-2-methylhexahydropyrimidine in equilibrium with its open-chain Schiff-base tautomer. Subsequent condensation of two of the Schiff-base molecules under the influence of a metal ion leads exclusively to the *trans*-MePhTIM complex. Results of other experiments and syntheses using an unsymmetrically substituted alkyl α-diketone indicate that the mechanism is also applicable to related systems.

Introduction

Complexes of the macrocyclic ligand TIM (I)[1] were ori-

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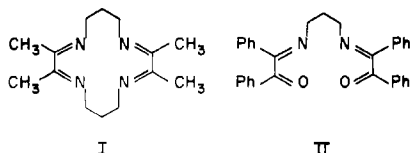
ginally prepared by Baldwin and Rose[2] via a template synthesis in which 1,3-diaminopropane hydrochloride and biacetyl were allowed to react together followed by addition of metal(II) acetate. The nickel(II),[2] cobalt(III),[3–5] and iron(II)[6,7] complexes of TIM all have been prepared by using this procedure. In each case the yield of the template reaction was found to be quite sensitive to a number of factors including order and timing of reagent additions, hydrogen ion concentration, anion of the metal salt, and temperature. From the requirements for these reactions it has been postulated that either an organic intermediate or the macrocyclic ligand itself must be formed prior to the point in the preparation where the metal salt is added.[5] Because of the tendency of 1,3-diaminopropane and biacetyl to polymerize, no organic macrocycle precursors or metal-free ligands have been isolated. However, recently the same template reaction has been applied by using benzil, 1,3-diaminopropane, and cobalt(II) acetate.[8] In this case an

intermediate (II), which is formed prior to addition of the metal salt, was isolated.

The purpose of the studies reported herein is to further elucidate the template mechanism for formation of macrocyclic complexes derived from 1,3-diaminopropane (DAP) and α-diketones. The diketone 1-phenyl-1,2-propanedione (also known as acetylbenzoyl (AB)) was chosen for these studies since it would seem to present several advantages over use of biacetyl or benzil. First, because of the difference in reactivity of the acetyl and benzoyl groups, polymerization should be more easily controlled, and possibly an organic intermediate, if any, could be stabilized enough to be isolated. Second, the choice of an unsymmetrical diketone provides two possible isomeric products, denoted *cis*- and *trans*-MePhTIM.[1] The

cis-MePhTIM   *trans*-MePhTIM
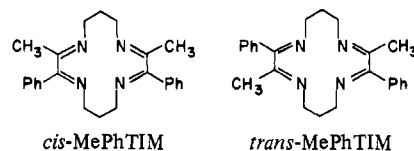
isomeric mixture of products from the template reaction should reflect the template mechanism including any organic ligand precursors. Finally, because AB contains groups common to both biacetyl and benzil, the results can be related to template reactions using these diketones.

It will be shown that, with metals iron(II), cobalt(II), or nickel(II), the template condensation of AB and DAP yields only one of the two possible macrocyclic products, the trans isomer. Proton NMR studies of the organic "preequilibrium" are used to search for the macrocycle precursor. During the course of this work the major product from the 1:1 condensation of acetylbenzoyl and 1,3-diaminopropane was isolated and characterized. This product, 2-benzoyl-2-methylhexahydropyrimidine, was found to react with metal salts in solution to form the isomerically pure trans macrocyclic complexes. The results of these studies allow formulation of a detailed mechanism for the template formation of macrocyclic complexes from acetylbenzoyl and 1,3-diaminopropane.

Experimental Section

Materials. The reagents and solvents used in the following preparations were commercially obtained as reagent grade unless otherwise noted and were used without further purification. The 1,3-diaminopropane (Eastman, practical) showed a trace water impurity by NMR and was used as obtained. Solvents used for electronic

(1) Abbreviations used herein: AB, 1-phenyl-1,2-propanedione; DAP, 1,3-diaminopropane; TIM, 2,3,9,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene; *trans*-MePhTIM, 2,9-dimethyl-3,10-diphenyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene; *cis*-MePhTIM, 2,10-dimethyl-3,9-diphenyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene; MeEtTIM, a mixture of the isomers 2,9-dimethyl-3,10-diethyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene and 2,10-dimethyl-3,9-diethyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene.
(2) D. A. Baldwin and N. J. Rose, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, No. INOR 20.
(3) K. Farmery and D. H. Busch, *J. Chem. Soc., Chem. Commun.*, 1091 (1970).
(4) D. H. Busch, K. Farmery, V. Goedken, V. Katovic, A. C. Melynk, C. R. Sperati, and N. Tokel, *Adv. Chem. Ser.*, No. 100, 44 (1971).
(5) S. C. Jackels, K. Farmery, E. K. Barefield, N. J. Rose, and D. H. Busch, *Inorg. Chem.*, **11**, 2893 (1972).
(6) D. W. Reichgott and N. J. Rose, *J. Am. Chem. Soc.*, **99**, 1813 (1977).
(7) D. A. Baldwin, R. M. Pfeiffer, D. W. Reichgott, and N. J. Rose, *J. Am. Chem. Soc.*, **95**, 5152 (1973).
(8) W. A. Welsh, G. J. Reynolds, and P. M. Henry, *Inorg. Chem.*, **16**, 2558 (1977).

spectra and conductivity measurements were of spectral analytical quality. Deuterated solvents (99% minimum purity) were obtained from Norell Chemical Co.

Unless otherwise stated the following compounds were collected by suction filtration, washed with ethanol and ether, and then dried in vacuo over Drierite for at least 12 h.

Preparation of [Ni(MePhTIM)]ZnCl₄. Acetylbenzoyl (2.97 g, 0.02 mol) was added to a stirred solution of DAP (1.50 g, 0.02 mol) in methanol (30 mL). Heat was given off, and a pale yellow solution resulted. A solution of NiCl₂·6H₂O (2.38 g, 0.01 mol) and glacial acetic acid (0.57 mL, 0.01 mol) in methanol (25 mL) was added. The color changed immediately to dark brown, and stirring was maintained for 20 min. Then a solution of ZnCl₂ (1.9 g in 10 mL of methanol) was added by gravity filtration, and thereafter stirring was discontinued. The black crystalline product was collected after the solution was allowed to stand at room temperature for 3 h. This crude product was found to be nearly analytically pure and was used without further purification; yield 1.9 g (30%).

Preparation of [Ni(MePhTIM)](PF₆)₂. A solution of NH₄PF₆ (0.6 g) in absolute ethanol (20 mL) was filtered into a stirred, hot solution of [Ni(MePhTIM)]ZnCl₄ (0.5 g) in methanol (60 mL). The solution was cooled to room temperature to give an orange microcrystalline product, dec pt 180 °C. Anal. Calcd for C₂₄H₂₈N₄NiP₂F₁₂: C, 39.97; H, 3.91; N, 7.77. Found: C, 40.01; H, 4.05; N, 7.77.

Preparation of [Co(MePhTIM)Br₂]PF₆. Unless otherwise stated, the following operations were carried out either in an inert-atmosphere drybox (nitrogen) or in suitable glassware under a continuous stream of nitrogen. Acetylbenzoyl (2.97 g, 0.02 mol) was added to a stirred solution of DAP (1.50 g, 0.02 mol) in methanol (50 mL). A solution of CoCl₂·6H₂O (2.38 g, 0.01 mol) and glacial acetic acid (0.57 mL, 0.01 mol) in methanol (25 mL) was added. The color changed immediately to red-brown and then to purple within 30 min. The solution was stirred for 3 h, removed from the nitrogen blanket, and filtered, and then 48% aqueous HBr (10 mL) was added. Air was bubbled through the solution for 30 min, resulting in a green microcrystalline precipitate. This crude product [Co(MePhTIM)Br₂]Br was collected and converted to the PF₆ salt by dissolving in warm 5% HBr/methanol (100 mL), filtering, and adding a solution of KPF₆ (2.76 g) in methanol (20 mL). Upon cooling of the solution, the green crystalline product precipitated: yield 2.1 g (31%); dec pt 202 °C. Anal. Calcd for C₂₄H₂₈N₄CoBr₂PF₆: C, 39.16; H, 3.83; N, 7.61. Found: C, 38.87; H, 3.81; N, 7.47.

Preparation of [Fe(MePhTIM)(CH₃CN)₂](PF₆)₂.[9] Unless otherwise stated, the following operations were carried out in an inert-atmosphere (nitrogen) drybox. A stirred mixture of iron powder (0.28 g, 0.005 mol) and FeCl₃ (0.81 g, 0.005 mol) in methanol (30 mL) was heated to boiling and then removed from heat. Glacial acetic acid (0.80 mL) and SnCl₂·2H₂O (0.03 g) were added, and the mixture was filtered to give a nearly colorless solution. This solution was added with vigorous stirring to a solution prepared by adding AB (2.97 g, 0.02 mol) to DAP (1.50 g, 0.02 mol) in methanol (30 mL). The color changed immediately to deep blue, and the solution was stirred for 1 h. Then CH₃CN (6 mL) and glacial acetic acid (1 mL) were added followed by solid KPF₆ (2.76 g). After being stirred about 10 min, the solution was removed from the inert atmosphere and the burgundy red microcrystalline product was collected. The filtrate volume was reduced to half by rotoevaporation after adding CH₃CN (1–2 mL) to obtain a second crop of red crystals. The second crop was dissolved in 10–15 mL of CH₃CN and filtered. Methanol (10–15 mL) and glacial acetic acid (1 mL) were added to the warmed acetonitrile solution, and the mixture was stirred and warmed for about ¹/₂ h until crystals began to form. Upon cooling of the solution, the product precipitated: yield 2.2 g (28%); dec pt 187 °C. Anal. Calcd for C₂₈H₃₄N₆FeP₂F₁₂: C, 42.02; H, 4.28; N, 10.50. Found: C, 42.12; H, 4.40; N, 10.42.

Preparation of [Co(MeEtTIM)Cl₂]PF₆. Methanol (150 mL) was cooled to 5 °C in a water–ice bath and maintained at or below that temperature during the following procedure. DAP·2HCl (5.88 g, 0.04 mol) was added followed by a solution of acetylpropionyl (4.00 g, 0.04 mol) in methanol (10 mL). To this vigorously stirred mixture was added dropwise a solution of KOH (3.42 g, 0.04 mol) in methanol (20 mL) over a period of 10 min. The resultant milky yellow mixture

was stirred an additional 20 min before addition of Co(OAc)₂·4H₂O (5.00 g, 0.02 mol) in methanol (100 mL). The brown mixture was stirred in a tightly stoppered flask for 12 h during which the color changed to deep purple. Concentrated HCl (1 mL) was added, and, after filtration, a solution of KPF₆ (4.6 g) in methanol (30 mL) was added dropwise with stirring to precipitate the gray-green microcrystalline product, yield 3.4 g (31%). The product may be recrystallized from acetone/water (1:1 by volume) containing concentrated HCl (1 mL/100 mL of solution); dec pt 200 °C. Anal. Calcd for C₁₆H₂₈N₄CoCl₂PF₆: C, 34.86; H, 5.12; N, 10.16. Found: C, 34.74; H, 5.38; N, 10.00.

Preparation of 2-Benzoyl-2-methylhexahydropyrimidine. Acetylbenzoyl (6.0 g, 0.04 mol) was added all at once to a vigorously stirred solution of 1,3-diaminopropane (3.0 g, 0.04 mol) in 30 mL of CCl₄. Heat was evolved immediately. After being stirred for 10–15 minutes the solution became cloudy, and stirring was discontinued. The orange water layer was drawn off, and the flask was stoppered and placed in a refrigerator for 12 h. Then the white solid was collected, washed with ether, and dried in vacuo at room temperature; yield 3.5 g (47%). Because the product was unstable, decomposing to an orange viscous material and water, recrystallization and elemental analyses were not attempted.

Physical Measurements. Elemental analyses were commercially obtained from Galbraith Microanalytical Laboratories, Knoxville, Tenn. Decomposition points were determined by using a Mel-Temp apparatus with a heating rate of 2 °C/min and are uncorrected. Conductivity measurements were made with an Industrial Instruments, Inc., Model RCM-15B1 conductivity bridge and an immersion-type cell at room temperature (approximately 23 °C). Infrared spectra in the range 4000–650 cm⁻¹ were recorded by using Perkin-Elmer Models 621, 21, or 700 spectrophotometers and were calibrated by using polystyrene film. Electronic spectra in the range 800–200 nm were recorded by using a Cary 14 spectrophotometer and 1-cm quartz cells. Proton nuclear magnetic resonance spectra were recorded with a Perkin-Elmer R32 spectrometer (90 MHz) at 35 °C unless otherwise indicated and with approximately 3% Me₄Si as internal standard. Carbon-13 NMR spectra were recorded with a Varian XL-100 multinuclear spectrometer using 1% Me₄Si as an internal standard.[10] The ¹³C NMR spectrum of 2-benzoyl-2-methylhexahydropyrimidine was obtained with a 0.5 M solution of a freshly prepared sample; the spectra of macrocyclic complexes were obtained by using approximately 0.2 M solutions.

Results

Preparation and Characterization of MePhTIM Complexes. Nickel(II)−, cobalt(III)−, and iron(II)−MePhTIM complexes can be prepared by appropriate modification of the procedures for the analogous TIM complexes.[2-7] The preparations in the Experimental Section have been yield-optimized. In each case the order of addition of reagents is important for obtaining maximum yield. In contrast to the template syntheses with biacetyl, reaction time and the presence of 1 equiv of hydrogen ion are not critical for the organic reaction mixture. However, 1 equiv of acid, usually acetic, if added concurrently with the metal halide salt, prevents rapid decomposition of the macrocyclic product in air, presumably by neutralizing the basic reaction mixture. A cobalt complex of MeEtTIM, prepared from the template condensation of 2,3-pentanedione with DAP, requires the same conditions as the complexes derived from biacetyl.[5]

Carbon, hydrogen, and nitrogen elemental analyses reported for each compound in the Experimental Section are within the range 0–0.3% of calculated values and are thus consistent with each formulation. All of the compounds decompose upon heating to about 200 °C. Conductivities of the MePhTIM and MeEtTIM complexes exhibit the expected behavior in solution. Solutions (1 × 10⁻³ M) of [Fe(MePhTIM)-(CH₃CN)₂](PF₆)₂ and [Ni(MePhTIM)](PF₆)₂ in CH₃CN/1% acetic acid (1%) and CH₃CN, respectively, gave values of 285 and 317 cm²/(Ω mol), in agreement with the expected range[11]

(9) The iron(II) complex of MePhTIM has recently been reported by R. G. Goel, P. M. Henry, and P. C. Polyzou, *Inorg. Chem.*, **18**, 2148 (1979).

(10) The ¹³C NMR spectra were recorded by Dr. David Harris at the University of North Carolina, Chapel Hill, N.C.

Table I. Selected Infrared Bands for Macrocyclic Complexes[a]

compd	band	assignt
[Ni(MePhTIM)](PF₆)₂	1640 w	ν(C=N)$_{asym}$
	1600 m, sp	ν(C=N)$_{sym}$
	1220 s, sp	α-diimine
	1590, 1580 m	ν(C=C)
[Co(MePhTIM)Br₂]PF₆	1640 w	ν(C=N)$_{asym}$
	1600 m, sp	ν(C=N)$_{sym}$
	1210 s, sp	α-diimine
	1585, 1575 m	ν(C=C)
[Fe(MePhTIM)(CH₃CN)₂](PF₆)₂	1600 w	ν(C=N)$_{sym}$
	1210 s, sp	α-diimine
	1590, 1580 w	ν(C=C)
[Co(MeEtTIM)Br₂]PF₆	1645 w	ν(C=N)$_{asym}$
	1595 s	ν(C=N)$_{sym}$
	1210, 1205 s	α-diimine

[a] Nujol mulls; all bands reported in cm^{-1}; s = strong; m = medium; w = weak; sp = sharp.

for di-univalent electrolytes in CH₃CN. Conductivity values of 130 and 95 cm²/(Ω mol) determined for 1 × 10^{-3} M solutions of [Co(MeEtTIM)Cl₂](PF₆) and [Co(MePhTIM)-Br₂](PF₆) in CH₃CN and CH₃NO₂, respectively, are also consistent with uni-univalent electrolytes.[11] Color changes and nonlinear plots of equivalent conductance vs. square root of concentration for the cobalt and iron complexes in solutions less than 10^{-3} M indicate lack of stability in dilute solutions. These problems could arise from decomposition or axial ligand substitution in the cobalt complexes or partial oxidation of the iron complex. The inclusion of a small amount of acetic acid in solutions of the iron complex inhibited the changes.

The infrared spectra (Table I) are comparable to spectra reported for TIM[5,7] and Ph₄TIM[8] complexes. The medium intensity ν(C=N) band at 1600 cm^{-1} and the weaker band at 1640 cm^{-1} in the spectra of Ni(II)– and Co(III)–MePhTIM are very weak or absent in the spectrum of the Fe(II) complex. Similar distinctive intensity differences have been noted previously for analogous TIM complexes by Rose et al.[7] and may be attributed to delocalization of d-electron density onto the ligand in low-spin pseudooctahedral Fe(II) species.[12] A strong, sharp band at 1210–1220 cm^{-1} associated with the α-diimine structure of the ligand is seen in all of the spectra. This band has been reported in spectra of TIM complexes but is absent in the spectrum of [Co(Ph₄TIM)Br₂]PF₆.[8] In the spectrum of [Fe(MePhTIM)(CH₃CN)₂](PF₆)₂ the band at about 980 cm^{-1} analogous to that reported for Fe^{II}TIM complexes is very weak; also no absorption associated with the C≡N vibrations of acetonitrile are observed. In addition to the bands reported in Table I, all of the MePhTIM complexes show bands assigned[13,14] to aromatic and aliphatic C–H stretching near 3100, 2960, and 2860 cm^{-1}. The combination band pattern characteristic of monosubstituted benzene is observed in the 2000–1780-cm^{-1} region as are two intense bands at 700 and 750 cm^{-1} due to aromatic C–H out of plane modes. Medium intensity bands attributed to aromatic ν(C=C), seen at 1590 and 1580 cm^{-1} in the nickel and cobalt complexes, are also very weak in the spectrum of the iron complex.

The proton magnetic resonance spectra of the MePhTIM complexes are consistent with the spectra of analogous TIM and Ph₄TIM complexes. Peak positions and assignments are given in Table II. The triplet splitting of the methyl resonance ($J \approx 1$ Hz) which is attributed to homoallylic coupling of the methyl protons with the α-methylene protons of the six-
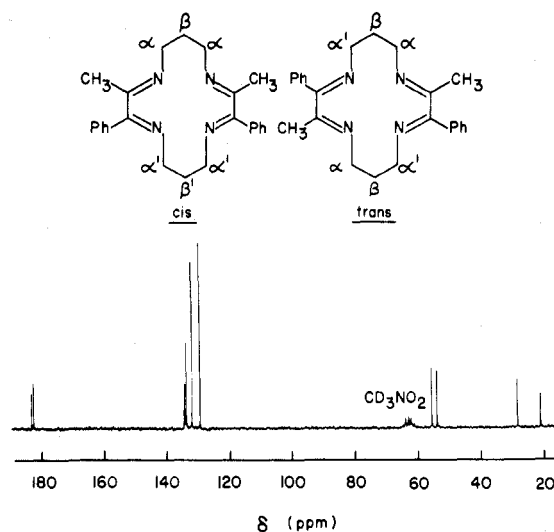

Figure 1. Proton-decoupled ^{13}C NMR spectrum of [Co(MePhTIM)Br₂]PF₆ in CD₃NO₂ (internal Me₄Si).

membered chelate ring[5] is solvent dependent and is observed in CD₃NO₂ but not resolved in CD₃CN. The β-methylene protons of the six-membered chelate rings vary in appearance depending on the metal and often overlap the methyl resonance. The α-methylene resonances appear asymmetric due to overlap of the triplets of the two sets of nonequivalent α-methylene protons. First-order coupling is observed for the α-methylene groups and indicates that rapid flexing of the six-membered chelate rings is taking place. In the spectrum of [Fe(MePhTIM)(CH₃CN)₂](PF₆)₂, no separate resonance due to coordinated CH₃CN is observed and enlargement of the center peak of the solvent pattern indicates that coordinated acetonitrile and bulk solvent are exchanging rapidly on the NMR time scale. The spectrum of [Co(MeEtTIM)Br₂]PF₆ is entirely consistent with all of the other spectra and will not be discussed in detail.

The ^{1}H NMR spectra do not provide an answer to the question of the isomeric purity of the complexes. Fortunately, ^{13}C NMR spectra for complexes such as these are usually quite sensitive to isomeric differences. Considering the structures of the cis and trans isomers of MePhTIM, different numbers of resonances are expected in the proton-decoupled ^{13}C NMR spectra of their complexes. As shown by the labeled structure in Figure 1, the cis isomer would be expected to give rise to 11 peaks since there are the following numbers of nonequivalent carbons: 2 imine, 2 β-methylene, 2 α-methylene, 4 phenyl, and 1 methyl. In the spectrum of the trans isomer only 10 peaks should be observed since the two β-methylene positions are equivalent. The spectrum of [Co(MePhTIM)-Br₂]PF₆ is shown in Figure 1, and the data from this spectrum are gathered with that for the similar spectra of the iron and nickel complexes in Table III. Only 10 resonances are observed in each spectrum. A consideration of the chemical shifts of the resonances along with their patterns in off-resonance decoupled spectra leads to assignment of all the peaks as given in Table III. The methyl, methylene, and imine carbon chemical shifts are similar to those found respectively for methyl-substituted imines[15,16] and α- and β-methylene carbons in other macrocyclic complexes.[17,18] As expected for mono-

(11) W. J. Geary, *Coord. Chem. Rev.*, **7**, 81 (1977). No comparable data in CH₃CN/1% acetic acid are available.
(12) P. Krumholz, *Struct. Bonding (Berlin)*, **9**, 139 (1971).
(13) D. Dolphin and A. Wick, "Tabulation of Infrared Spectral Data", Wiley, New York, 1977.
(14) R. M. Silverstein, G. C. Bassler, and T. C. Morrill, " Spectrophotometric Identification of Organic Compounds", Wiley, New York, 1974.
(15) J. Eilmes and E. Sledziewska, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **26**, 441 (1978).
(16) J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972.
(17) Y. Hung, L. Y. Martin, S. C. Jackels, A. M. Tait, and D. H. Busch, *J. Am. Chem. Soc.*, **99**, 4029 (1977).
(18) N. W. Alcock, N. Herron, and P. Moore, *J. Chem. Soc., Dalton Trans.*, 1282 (1978).

Table II. ^{1}H NMR Data for Macrocyclic Complexes[a]

compd (solvent)	=CCH₃	α-CH₂	β-CH₂	phenyl	other
[Co(MePhTIM)Br₂]PF₆ (CD₃NO₂)	2.47 s	4.10 t	2.55 cm	7.35, 7.70 cm	
[Fe(MePhTIM)(CH₃CN)₂](PF₆)₂ (CD₃CN)	2.44 t	4.08 t	2.16 t	7.50, 7.68 cm	1.96[b]
[Ni(MePhTIM)](PF₆)₂ (CD₃NO₂)	2.20 t	3.56 t	2.12 c	7.50, 7.70 cm	
[Co(MeEtTIM)Br₂]PF₆ (CD₃NO₂)	2.86 s	4.10 t	2.65 cm		3.26 q, 1.25 t[c]

[a] All shifts, in ppm from Me₄Si, refer to center of a resonance pattern; s = singlet; t = triplet; q = quartet; cm = complex multiplet.
[b] CH₃CN.   [c] Resonances for ethyl substituent of this macrocycle.

Table III. Carbon-13 NMR Data for MePhTIM Complexes[a]

assignt[b]	[Fe(MePhTIM)(CH₃CN)₂]²⁺	[Co(MePhTIM)Br₂]⁺	[Ni(MePhTIM)]²⁺
CH₃ (q)	20.12	21.10	20.32
β-CH₂ (t)	27.90	28.20	27.85
α-CH₂ (t)	54.03	53.55	51.67
α-CH₂ (t)	55.74	55.27	53.07
Ph (d)	128.80	128.34	128.26
Ph (d)	130.31	131.03	130.91
Ph (d)	131.60	132.82	133.33
Ph (s)	134.36	133.28	131.73
C=N (s)	179.38	181.34	180.53
C=N (s)	181.39	182.07	181.79
solvent	CD₃CN	CD₃NO₂	CD₃NO₂

[a] All shifts in ppm from internal Me₄Si; PF₆⁻ salts used.   [b] Assignment followed by off-resonance pattern in parentheses: s = singlet; d = doublet; t = triplet; q = quartet.

Table IV. Proton-Decoupled Carbon-13 NMR Data for [Co(MeEtTIM)Br₂]PF₆ in CD₃NO₂[a]

assignt	cis isomer[b]	trans isomer[b]
CH₃ (ethyl)	9.92 (73)	9.92 (73)
CH₃	19.58 (27)	19.68 (74)
CH₂ (ethyl)	25.99 (141)	25.99 (141)
β-CH₂	28.22 (125)	28.22 (125)
β-CH₂	27.87 (29)	
α-CH₂	52.57 (151)	52.57 (151)
α-CH₂	53.31 (102)	53.37 (126)
C=N	181.07 (11)	181.34 (34)
C=N	185.42 (14)	185.67 (49)

[a] All shifts in ppm from internal Me₄Si.   [b] Values in parentheses are relative intensities for each peak.

Table V. Visible–Ultraviolet Absorption Spectral Data for Macrocyclic Complexes in CH₃CN[a]

complex ion[b]	observed bands[c]
[Co(MePhTIM)Cl₂]⁺	17.8 (53), 22.6 (140), 24.5 (1580), 25.8 sh (1460), 37.6 (24 000)
[Co(MePhTIM)Br₂]⁺	17.2 (74), 24.8 (3200), 32.8 (27 600), 41.7 (15 700)
[Co(MeEtTIM)Br₂]⁺	16.8 (68), 25.0 (2800), 32.8 (19 400), 41.7 sh (9800)
[Ni(MePhTIM)]²⁺	23.1 sh (1430), 24.5 (1620), 36.6 (7000)
[Fe(MePhTIM)(CH₃CN)₂]²⁺	17.5 (12 800), 18.8 sh (6800), 20.0 sh (2800), 36.6 sh (7300)

[a] Band maxima are in cm⁻¹ × 10³; molar extinction coefficients are in parentheses; sh = shoulder.   [b] PF₆⁻ salts used. Acetic acid (1%) was added to the solution of the iron complex.   [c] All spectra show intense absorption above 42.5 × 10³ cm⁻¹.

substituted benzene, four resonances with chemical shifts characteristic of phenyl carbons[16] are observed, three of which split to doublets and the fourth remains unsplit in the off-resonance spectrum. Unambiguous assignments for all the resonances show that in each of the three compounds the pure trans isomer is obtained since there are only 10 peaks including one nonbroadened β-carbon peak. The possibility cannot be immediately ruled out that the compounds are pure cis isomers with the β-carbon resonances accidently degenerate. However, in the case of MeEtTIM, where a mixture of isomers is clearly observed (vide infra), the two β-methylene resonances of the cis isomer are separated by 0.5 ppm. A mixture of isomers is unlikely since a large number of accidental degeneracies would be required.

X-ray diffraction data from a crystal of [Co(MePhTIM)-Cl₂]PF₆ (prepared by metathesis from the dibromo complex) have yielded the following information.[19] The lattice constants of the monoclinic crystal are a = 11.394 Å, b = 6.831 Å, c = 17.413 Å, and β = 95.7°. The experimental density, determined by flotation, is 1.54 g/cm³. A formula weight of 647 and the lattice constants above give a calculated density of 1.59 g/cm³ for 2 formula units per unit cell. Analysis of the systematic absences in the diffraction patterns places the crystal in space group P2₁/c. Thus, for two formula units per cell, each of the complexes and anions must occupy a site with inversion symmetry. Since trans-[Co(MePhTIM)Cl₂]PF₆ does contain an inversion center whereas the cis isomer does not, it is concluded that, as indicated by the ¹³C NMR analysis, the trans complexes have indeed been isolated. It should finally be noted that no evidence for the presence of cis isomer products has been obtained even though efforts were made to isolate them from the reaction mixtures.

To test whether the reaction is regiospecific with diketones more analogous to biacetyl, we prepared a complex by using 2,3-pentanedione, DAP, and cobalt(II) acetate. The proton-decoupled ¹³C NMR spectra of the cis and trans isomers of MeEtTIM[1] are expected to give nine and eight peaks, respectively. The spectrum of [Co(MeEtTIM)Br₂]PF₆ has 13 peaks and is consistent with a mixture containing both isomers

with an approximately 3:1 ratio of trans:cis. The peak positions and assignments are given in Table IV. Since 17 peaks are expected for a mixture with no coincident resonances, four coincident assignments are necessary. A consideration of relative intensities, chemical shifts, analogies with the cobalt–MePhTIM complex, and internal consistency allows assignment of the coincident resonances to both carbons of the ethyl groups, one of the β-methylene carbons, and one of the α-methylene carbons. Clear evidence for the presence of the two isomers is seen in the imine carbon region where four peaks are observed, two of which are three times more intense than the other two. A consideration of the β-methylene resonances indicates that the more intense spectrum corresponds to the trans isomer. A mixture of isomers is expected to show three peaks, but the spectrum has two peaks, one of which is four times more intense than the other. For consistency with the other assignments, the more intense peak at 28.22 ppm must be assigned to the β-methylene carbons of both cis and trans isomers and the less intense peak at 27.78 to the second resonance of the cis isomer. These assignments imply that the trans isomer gives rise to the more intense of the two overlapping spectra.

Electronic spectral maxima and molar absorptivities for the MePhTIM and MeEtTIM complexes are given in Table V. As is usually found for spectra of complexes containing unsaturated ligands, and α-diimines in particular, the d–d transitions are typically masked by bands of high molar absorptivity in the visible region which are most likely charge

(19) H. W. Baird, unpublished results.

Table VI. Tetragonal Crystal Field Splitting Parameters for Some Substituted TIM Complexes[a]

complex	Dq^{xy}	Dt	ref
[Co(MePhTIM)Cl$_2$]$^+$	2860	800	b
[Co(TIM)Cl$_2$]$^+$	2780	754	5
[Co(MePhTIM)Br$_2$]$^•$	2927	876	b
[Co(MeEtTIM)Br$_2$]$^+$	2843	895	b
[Co(TIM)Br$_2$]$^+$	2860	903	5

[a] Calculated by using the same method as in ref 5; units are cm^{-1}. [b] This work.

transfer in nature. However, some d–d transitions are observed for the cobalt complexes. The tetragonal crystal field splitting model for low-spin d^6 complexes has been previously applied to the cobalt(III)–TIM complexes.[5] Since the spectra of MePhTIM and MeEtTIM complexes are quite similar in band position and molar absorptivity to those of the TIM analogues, the tetragonal model has been applied to derive the splitting parameters shown in Table VI. In comparison with TIM, MeEtTIM is seen to impose a nearly identical ligand field, while MePhTIM has a slightly higher ligand field than TIM.

^{1}H NMR Investigation of the Reaction of AB with DAP. A consideration of the regiospecific nature of the metal–MePhTIM syntheses in conjunction with the reaction conditions (order and timing of reagent additions necessary for optimum yields) leads to the hypothesis that a specific ligand precursor is formed in the reaction mixture prior to addition of the metal salt. For investigation and possibly for determination of the identity of this precursor, ^{1}H NMR studies of the 1:1 condensation of AB with DAP were undertaken. Structures III–VIII show six possible products from the 1:1
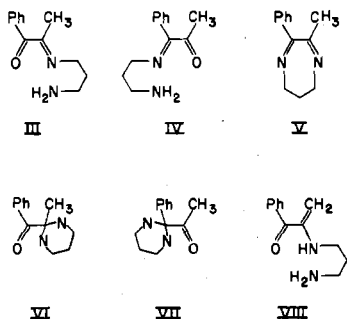

condensation of AB and DAP. In addition, multiple condensation products could also be produced, i.e., 2:1 DAP:AB or 2:1 AB:DAP or higher polymers. Because of the complexity of this reaction, three simpler systems were studied as models. First, for observation of the effect of imine formation on phenyl resonances, the reaction of benzaldehyde with n-propylamine was studied. Second, the reaction between n-propylamine and AB was studied to determine whether imine formation occurs at both carbonyls or preferentially at one carbonyl. Finally, the reaction between benzaldehyde and DAP was studied to observe resonance patterns in a system reported to form a hexahydropyrimidine ring.[20-22] The procedure for monitoring reactions by ^{1}H NMR was to first add 0.6–0.7 mL of solvent to the NMR tube and then add sequentially a stoichiometric amount (1 × 10^{-3} mole) of each reagent. The reactions were monitored at 35 °C with Me$_4$Si as internal standard until no further changes were observed.

Observation of the reaction of benzaldehyde with n-propylamine in CDCl$_3$ to form benzyl-n-propylimine shows that imine formation at a phenyl-substituted carbon atom causes the phenyl proton resonances to shift upfield and closer

together (benzaldehyde (ortho, 7.88 ppm; para and meta, 7.50 ppm) compared to benzyl-n-propylimine (ortho, 7.70 ppm; para and meta, 7.40 ppm)). When AB reacts with n-propylamine in CDCl$_3$, no shift in the phenyl resonances occurs, but the methyl resonance shifts from 2.50 (unreacted diketone) to 2.10 ppm. Thus the acetyl group of AB reacts with primary amines in preference to the benzoyl group. Even in the presence of a large excess of n-propylamine reaction at the phenyl carbonyl is very slow.

The reaction of benzaldehyde and DAP has three possible products: the open-chain Schiff base IX, the substituted hexahydropyrimidine X, and the diimine XI. In an NMR
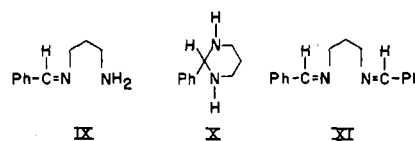
study of the analogous condensation of benzaldehyde with ethylenediamine, Chapuis et al.[23] showed that an equilibrium exists between the imidazolidine and the open-chain Schiff-base products. We found that all three products listed above are observed for 1:1 benzaldehyde and DAP. Changes in the spectra as the molar ratio of benzaldehyde to DAP is increased to 2:1 in comparison with the results of Chapuis et al. allow assignment of all resonances in the 1:1 mixture. The singlet resonance of the imine protons of IX and XI occurs at 8.25 ppm while that for the methine proton of X occurs at 4.50 ppm. Two overlapping triplets at 3.63 and 3.70 ppm are assigned to the α-methylene protons of IX and XI. A sharp complicated pattern between 3.2 and 2.7 ppm is due to the α-methylene protons of the hexahydropyrimidine ring of X. These and the β-methylene protons (complicated pattern between 1.7 and 1.3 ppm) are diasteriotopic, giving rise to second-order coupling even though rapid flexing of the ring is most likely occurring. The N–H proton resonance of X is observed at 1.95 ppm and shifts to 1.70 ppm after passing of the reaction mixture through Drierite. Comparison of the integrated areas of the resonances at 4.50 and 8.25 ppm indicates that the product equilibrium ratio is about 2:1 for X:(IX + XI).

The analysis of the above model systems facilitated the interpretation of the spectra from the 1:1 condensation of DAP with AB. When AB is added to equimolar DAP in CDCl$_3$, water and heat are evolved immediately. Since the methyl resonance shifts from 2.50 to 2.10 ppm and the phenyl resonances remain unchanged, initial condensation occurs at the acetyl carbon. The remainder of the spectrum is consistent with formation of the open-chain Schiff base III. However, further changes in the spectra over a 30-min period indicate that the initial product is further converted to the hexahydropyrimidine VI. The spectrum of the equilibrium mixture has a complicated pattern between 2.6 and 3.1 ppm which is qualitatively the same as the α-methylene pattern in X. Furthermore a β-methylene pattern is observed between 1.7 and 1.3 ppm overlapping a sharp singlet at 1.40 ppm assigned to the methyl of VI. A second sharp singlet at 2.1 ppm is assigned to the methyl of III. A pair of doublets at 8.5 ppm are the ortho phenyl protons of VI, and the remaining phenyl resonances centered at 7.5 ppm are changed in shape compared to AB and correspond to the meta and para phenyl protons of III and VI. The ortho phenyl proton resonances of III are observed at 8.0 ppm. Comparison of the integrated areas of the methyl resonances of III and VI shows that the latter is favored by approximately 3:1 at equilibrium in CDCl$_3$. No evidence of polymers or diazepine (V) formation is observed

(20) J. E. Douglas and R. Dial, *Synthesis*, 654 (1975).
(21) E. Bergmann, D. Herman, and E. Zimkin, *J. Org. Chem.*, **13**, 353 (1948).
(22) R. F. Evans, *Aust. J. Chem.*, **20**, 1645 (1967).

(23) C. Chapuis, A. Gauvreau, A. Klaebe, A. Lathes, and J. J. Perie, *Bull. Soc. Chim. Fr.*, 977 (1973).
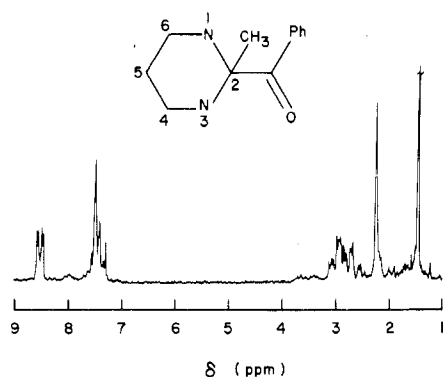
Figure 2. Proton NMR spectrum of 2-benzoyl-2-methylhexahydro-pyrimidine in CDCl₃ (internal Me₄Si).

until about 14 h after the reagents are mixed. Spectra of the reactions in CCl₄ and CD₃OD are nearly identical with those in CDCl₃ indicating that the same reaction takes place in each of these solvents.

Isolation and Characterization of 2-Benzoyl-2-methylhexa-hydropyrimidine (VI). The addition of equimolar AB to DAP in CCl₄ results not only in the evolution of water and changes in ¹H NMR spectra as described above but also in a white precipitate. The infrared spectrum of the precipitate (hexa-chlorobutadiene and Nujol mulls) features a broad band at 3265 cm⁻¹ characteristic of ν(N—H) and bands at 3080, 2950, and 2860 cm⁻¹ characteristic of aromatic and aliphatic ν-(C—H).¹³ A very strong band at 1655 cm⁻¹, assigned to ν(C=O) (vide infra), is slightly lower in frequency compared to the 1710- and 1675-cm⁻¹ bands of the acetyl and benzoyl groups of AB. Two bands at 1590 and 1580 cm⁻¹ are most likely ν(C=C) of phenyl.

The ¹H NMR spectrum of the white solid in CDCl₃ is shown in Figure 2. The assignments and integrated peak areas are consistent with the structure of the hexahydropyrimidine VI. The sharp singlet methyl peak at 1.43 ppm overlaps a complex set of multiplets between 1.3 and 2.0 ppm assigned to the protons of C5 in the hexahydropyrimidine ring. The C5 methylene pattern and the complex pattern between 2.4 and 3.1 ppm (C4 and C6 methylene protons) are both qual-itatively the same as the analogous patterns observed for X. The sharp singlet at 2.21 ppm disappears upon shaking of the sample with D₂O and is thus assigned to the N–H protons. The meta and para phenyl protons are observed as a multiplet at 7.5 ppm, and the ortho protons appear as a multiplet at 8.5 ppm. The large downfield shift of the ortho phenyl resonances is attributed to anisotropic shielding by the adjacent carbonyl group²³,²⁴ which may be further enhanced by deshielding from the nitrogen lone pairs.²⁵⁻²⁷ Similar relative chemical shifts have been reported for phenyl-substituted pyrimidines.²⁸

Further confirmation of the structural assignment is ob-tained from analysis of the ¹³C NMR spectrum. The pro-ton-decoupled resonance positions, off-resonance patterns, and assignments are given in Table VII. All are consistent with the structure in Figure 2. Notably, only one resonance is observed for C4 and C6 and is consistent with the cyclic structure in which these two carbon atoms are equivalent. The resonance at 206 ppm which remains unsplit in the off-reso-

(24) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, 1969, p 75.
(25) A. A. Bothner-By and J. A. Pople, *Annu. Rev. Phys. Chem.*, **16**, 55 (1965).
(26) F. G. Riddell, *J. Chem. Soc. B*, 560 (1967).
(27) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964).
(28) V. M. S. Gil and J. N. Murrell, *Trans. Faraday Soc.*, **60**, 254 (1964).
(29) A. R. Forrester, M. Gill, and R. H. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 3, 616 (1979).

Table VII. Carbon-13 NMR Data for 2-Benzoyl-2-methylhexahydropyrimidine[a]

δ	assignt	off-resonance pattern
26.14	C5	triplet
29.36	–CH₃	quartet
42.53	C4, C6	triplet
76.81	C2	singlet
127.99	phenyl	doublet
130.27	phenyl	doublet
130.78	phenyl (ipso)	singlet
132.71	phenyl	doublet
206.36	C=O	singlet

[a] Chemical shifts given are for proton-decoupled spectrum in CDCl₃ vs. internal Me₄Si. Refer to Figure 2 for numbering of carbon atoms.

nance spectrum is in the range characteristic of carbonyl carbon.¹⁶ The absence of any resonance in the 150–180-ppm range characteristic of imine carbon rules out the Schiff base III. However, in the proton NMR spectrum (Figure 2) the small peaks at 3–4 ppm probably indicate a small amount of open-chain imine in equilibrium with the cyclic form in CDCl₃. The ¹H NMR spectrum in CD₃OD indicates a larger fraction of III present in this solvent.

Preparation of MePhTIM Complexes from VI. When a solution of NiCl₂·6H₂O in methanol is added to a methanolic solution of VI containing 2 mol/mol of nickel, a rapid color change to dark brown occurs. Addition of ethanolic NH₄PF₆ and acetic acid followed by volume reduction yields an orange microcrystalline product identical in properties with authentic *trans*-[Ni(MePhTIM)](PF₆)₂. Likewise, [Fe(MePhTIM)-(CH₃CN)₂](PF₆)₂ can be isolated from a mixture prepared by adding a ferrous solution (prepared as given in the Ex-perimental Section) to a methanolic solution of VI under nitrogen. In contrast, addition of a solution of CoCl₂·6H₂O and 1 equiv of CH₃COOH to a methanolic solution of VI under nitrogen leads to a purple solution from which a green crystalline solid can be isolated by addition of HBr, air, and aqueous NH₄PF₆. The ¹H NMR spectrum of the green ma-terial in CD₃NO₂ is consistent with a mixture of isomeric forms of the carbinolamine XII. Upon recrystallization from hot

XII
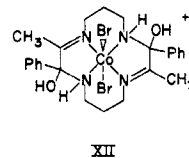
5% aqueous HBr/acetonitrile or in CD₃NO₂ solution (48 h), XII is converted to *trans*-[Co(MePhTIM)Br₂]⁺ and water. XII could also be isolated from the template reaction mixture by air oxidation before the 3-h reaction period had passed.

Discussion

The template synthesis of macrocyclic complexes from acetylbenzoyl and 1,3-diaminopropane yields isomerically pure *trans*-MePhTIM complexes with Ni(II), Co(III), or Fe(II). Studies of the "organic" reaction mixture containing only AB and DAP show that the Schiff base III is first formed and then slowly converts to the hexahydropyrimidine VI. Either of these compounds condensed head-to-tail around a metal ion would give the observed macrocyclic product. Isolated VI does indeed react with metal salts in methanol to give the trans macrocyclic product. The efficacy also of III as a ligand precursor is implied by the fact that macrocyclic complexes can be isolated before the 30-min period known to be necessary for VI to form in appreciable concentration. Therefore, in the template synthesis, III most likely reacts directly in the presence of metals to give the observed products. That the condensation reaction actually takes place in the metal coordination sphere
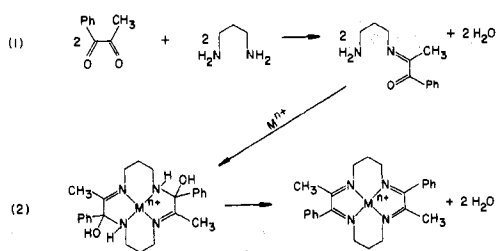
Figure 3. Proposed reaction scheme for the formation of *trans*-MePhTIM complexes.

is evidenced by the isolation of the coordinated carbinolamine XII. This material spontaneously dehydrates even in acidic solution or in solid state to give the MePhTIM complex. These results are summarized in the mechanistic scheme shown in Figure 3. Equation 1 represents the "organic" reaction prior to addition of metal. The competing equilibrium between the Schiff base and hexahydropyrimidine is not shown. In eq 2 is shown the metal-directed condensation to give the carbinolamine and final products. It is not surprising that VI undergoes metal-induced ring opening and subsequent condensation to give the macrocyclic product. Metal-catalyzed ring opening reactions of thiazolidines[30,31] and oxazolidines[32] to give the coordinated Schiff bases are well-known.

There are two other macrocycle precursors, XIII and XIV,
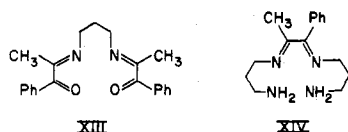
which should be considered on the basis of the established template reaction chemistry of diamines and α-diketones.[8,33] Both of these can be ruled out, first, because there is no evidence for their existence and, second, because they would not be expected to yield specifically the trans product. In fact, the formation of an intermediate analogous to II would result in XIII and specifically the cis isomer product. The intermediate XIV can be ruled out since the nickel complex of this ligand, prepared by the method of Taylor et al.[33] using acetylbenzoyl in place of biacetyl, failed to react with acetylbenzoyl to give the macrocyclic product. Also, a mixture of isomers would be expected from XIV. Finally, there is no evidence for free macrocyclic ligand in solution prior to addition of the metal solution.

The question naturally arises as to whether the mechanism in Figure 3 also applies to the TIM and MeEtTIM complexes. Here, the two carbonyl groups of the ketone are equally or nearly equally reactive so the initial condensation could occur at either. In addition the second carbonyl group would be

much more competitive for reaction with the remaining free amino group than in the acetylbenzoyl case. In fact biacetyl is known to react with ethylenediamine to give polycyclic compounds.[34] Another consequence is that polymerization is much easier, as evidenced by the deep red solutions. Red polymers are known to result from the reaction of alkyl diketones and diamines.[35] The polymerization is inhibited somewhat by lowering the temperature to 0–5 °C and by including 1 equiv of acid in the reaction mixture. ¹H NMR spectra of a 1:1 mixture of 2,3-pentanedione and DAP in CCl₄ yield very complicated patterns due to overlap of the quartet and triplet ethyl group patterns with those of the products. Biacetyl and DAP under the same conditions yield spectra having first-order coupling patterns indicative of open-chain imine polymers or diazepine formation. The orange color of the solution also indicates that polymerization occurs rapidly. In contrast, in spectra of 1:1 biacetyl and DAP in CD₃OD at 5 °C, hexahydropyrimidine-like patterns are observed and increase in intensity until the reaction reaches equilibrium after about 25 min. Resonances characteristic of open-chain imine forms are also present; however, in contrast to reaction in CCl₄ at 35 °C, the cyclic forms predominate. Thus, from these results it can be concluded that hexahydropyrimidines are likely to be among the major products under the reaction conditions of the template synthesis. Thus a mechanism similar to that in Figure 3 is suggested. Such a mechanism is also consistent with the observed products since, in the case of MeEtTIM, the initial condensation could take place at either the proprionyl or the acetyl group to form either 2-acetyl-2-ethylhexahydropyrimidine or 2-proprionyl-2-methylhexahydropyrimidine. Then random condensation between these as in eq 2 of Figure 3 would give an isomeric mixture of products. Finally, there is no evidence for hexahydropyrimidine formation in ¹H NMR spectra of benzil–DAP mixtures. Thus it would appear that II or the 1:1 Schiff base condensate analogous to III is most viable as an intermediate in this case.

(30) M. C. Thompson and D. H. Busch, *J. Am. Chem. Soc.*, **86**, 213 (1964).
(31) L. F. Lindoy and D. H. Busch, *Inorg. Chem.*, **13**, 2495 (1974).
(32) D. C. Liles, M. McPartlin, P. A. Tasker, H. C. Lip, and L. F. Lindoy, *J. Chem. Soc., Chem. Commun.*, 549 (1976), and references therein.
(33) L. T. Taylor, N. J. Rose, and D. H. Busch, *Inorg. Chem.*, **7**, 785 (1968).

(34) H. Stetter, *Chem. Ber.*, **86**, 69 (1953).
(35) V. V. Korshak and S. V. Vinogradova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 925 (1955); *Chem. Abstr.*, **50**, 9325g (1956).