δ 9.85 (1 H, br s), 9.60 (1 H, br s), 8.64 (1 H, d), 8.40 (1 H, br s), 8.28 (1 H, br t), 7.4–7.0 (7 H, m), 4.95–4.80 (4 H, m), 2.90–1.10 (20 H, m); MS, *m/e* 257 (M^+), 239, 216, 211, 176, 158, 148, 120.

Quinoline 5. Crude alcohol **3** (323 mg, contains excess formanilide) was stirred for 18 h in dioxane (15 mL) and 1 N HCl (15 mL). After extraction with ether, the aqueous layer was basified with $NaHCO_3$ and extracted with ether. These ether extracts were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by medium-pressure liquid chromatography (10% EtOAc in hexane) gave the less polar quinoline **5** (37 mg, 17%) as a clear oil, followed by the amino alcohol. Higher reaction temperatures gave increased amounts of the quinoline. Kugelrohr distillation (120 °C, oven temperature, 0.5 mm) gave **5** as a white solid: mp 49–50 °C; MS calcd for $C_{16}H_{15}N$ 221.1204, found 221.1202; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01 (1 H, d, H_8), 7.78 (1 H, s, H_2), 7.65 (1 H, d, H_5), 7.62 (1 H, t) and 7.42 (1 H, t) (H_6 and H_7), 5.11 (1 H, s) and 4.90 (1 H, s) (terminal olefin), 3.66 (1 H, t), 3.26 (1 H, dd), 3.10 (1 H, br s), 2.90 (1 H, d), 2.77 (1 H, m), 2.54 (1 H, d), 2.05 (1 H, m), 2.00 (1 H, d); ^{13}C NMR ($CDCl_3$, 67 MHz) δ 164.6 (s), 154.4 (s), 146.4 (s), 136.0 (d), 128.6 (d), 128.4 (s), 127.7 (s), 126.9 (d), 125.7 (d), (one aromatic doublet peak is assumed to account for two carbons) 107.4 (t), 44.5 (d), 42.2 (t), 41.0 (d), 38.8 (t), 35.4 (t). Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83. Found: C, 87.09; H, 6.94.

General Procedure for Dianion Addition. *o*-Bromoformanilide (4.0 g, 20 mmol) in dry THF (20 mL) was added dropwise to a suspension of oil-free sodium hydride (1.0 g, 50% in oil, 20.8 mmol) in THF (15 mL). After cessation of hydrogen evolution (30 min, 25 °C) the reaction was cooled to −78 °C and *tert*-butyllithium (15.4 mL, 40.04 mmol, 2.6 M in pentane) was added dropwise over 30 min. Following this, HMPA (4 mL, 24.4 mmol) was added. After 30 min at −78 °C, cyclohexanone (2 mL, 19.3 mmol) in dry THF (2 mL) was added over 20 min. After 1 h at −78 °C, the mixture was quenched with saturated NH_4Cl, allowed to warm to room temperature, and extracted with ether. The combined ether extracts were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Trituration of the crude product with 20% EtOAc in hexane followed by filtration gave 2.08 g (49%) **6**[6] as a white solid (mp 136–137 °C), which was used directly in the cyclization: ^1H NMR ($CDCl_3$) indicated a 1/1 mixture of formamide rotamers: δ 9.70 (1 H, br s), 9.50 (1 H, br s), 8.65 (1 H, d), 8.45 (1 H, s), 8.34 (1 H, d), 7.35–7.05 (7 H, m), 2.10–1.70 (20 H, m).

General Procedure for Grignard Addition. 1-Formamidoacetophenone (223 mg, 1.37 mmol) in dry THF (6 mL) was added dropwise to a solution of methylmagnesium bromide (1.1 mL, 2.85 M in THF, 3.14 mmol) at 0 °C. After stirring 16 h at 25 °C, the reaction was partitioned between ether and saturated NH_4Cl. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give 178 mg (72%) crude **13a** as a clear oil: ^1H NMR ($CDCl_3$) ~1/1 mixture of formamide rotamers, δ 9.90 (2 H, br s), 8.63 (1 H, d), 8.40 (1 H, br s), 8.31 (1 H, d), 7.32–7.00 (7 H, m), 1.71 (6 H, s), 1.70 (6 H, s).

13b (1/1 mixture of formamide rotamers): mp 115–116 °C; ^1H NMR ($CDCl_3$) δ 9.00 (2 H, br s), 8.20 (2 H, m), 8.00 (1 H, s), 7.45–7.05 (17 H, m), 3.20 (1 H, br s), 2.80 (1 H, br s), 2.00 (3 H, s), 1.99 (3 H, s).

13c: mp 149–150 °C; ^1H NMR ($CDCl_3$) δ 8.65 (1 H, br s), 8.00 (1 H, d), 7.48 (1 H, d), 7.30–7.10 (7 H, m), 1.95 (3 H, s), 1.70 (3 H, s).

13d: mp 145–146 °C; ^1H NMR ($CDCl_3$) δ 9.90 (1 H, br s), 8.23 (1 H, d), 7.30–7.22 (2 H, m), 7.03 (1 H, t), 2.50 (1 H, s), 2.12 (3 H, s), 1.70 (6 H, s).

13e: oil; ^1H NMR ($CDCl_3$) δ 9.05 (1 H, br s), 8.05 (1 H, d), 7.27 (1 H, t), 7.18–7.00 (2 H, m), 4.95 (1 H, q), 2.18 (3 H, s), 1.60 (3 H, d).

11: oil (1/1 mixture of formamide rotamers); ^1H NMR ($CDCl_3$) δ 10.05 (1 H, br s), 9.87 (1 H, br s), 8.65 (1 H, d), 8.42 (1 H, s), 8.37 (1 H, d), 7.31–7.00 (7 H, m), 1.95 (4 H, m), 1.68 (3 H, s), 1.67 (3 H, s), 0.87 (6 H, m).

Olefin 8: Titanium tetrachloride (40 μL, 0.4 mmol) was added to a solution of alcohol **6** (30.5 mg, 0.14 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C. After 1.5 h at −78 °C the mixture was diluted with ether, washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give crude **8** (27.7 mg, 99%) as an oil: IR ($CHCl_3$, cm^{-1}) 3490, 1690, 1600, 1580, 1510; ^1H NMR ($CDCl_3$, 1/1 mixture of formamide rotamers) δ 8.70 (1 H, d), 8.43 (1 H, d), 8.32 (1 H, d), 7.60 (2 H, br s), 7.30–7.05 (7 H, m), 5.75 (2 H, m), 2.20 (8 H, m), 1.78 (8 H, m); MS, *m/e* 201 (M^+), 183, 172. The crude olefin (27.7 mg) was directly cyclized following the standard procedure (PPA, 130 °C) to give **9** (25.0 mg, 61%), mp 61–62 °C (lit.[10a] mp 64 °C), identical with a sample of **9** obtained by direct PPA cyclization of **6**.

General Cyclization Procedure. 4-Phenylquolinoline. Crude alcohol **13b** (1.28 g, 5.3 mmol) and polyphosphoric acid (80 g) were admixed and stirred under N_2 for 20 h at ~160 °C (bath temperature). The cooled reaction mixture was diluted with water and washed with ether. The aqueous layer was basified with solid $NaHCO_3$ and extracted with ether. This organic phase was washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give virtually pure (TLC, 300-MHz NMR[7]) 4-phenylquinoline as a tan solid. Recrystallization of a small sample ($CHCl_3$/hexane) gave white crystals, mp 61–62 °C (lit.[10b] mp 61 °C).

Acknowledgment. We thank Research Corporation for partial support of this worrk.

Registry No. **2**, 89936-95-8; *endo*-**3**, 89936-96-9; *exo*-**3**, 89936-97-0; **4**, 89936-98-1; **5**, 89936-99-2; **6**, 82757-20-8; **7b**, 41797-85-7; **8**, 89937-00-8; **9**, 62833-92-5; **10**, 5257-06-7; **11**, 89937-01-9; **12**, 2436-92-2; **13a**, 89937-02-0; **13b**, 89937-03-1; **13c**, 89937-04-2; **13d**, 41797-86-8; **13e**, 89937-05-3; **14a**, 491-35-0; **14b**, 605-03-8; **14c**, 1721-92-2; **14d**, 1198-37-4; **14e**, 91-63-4; *o*-BrC_6H_4NHCHO, 10113-38-9; *o*-AcC_6H_4NHAc, 5234-26-4; acetophenone, 98-86-2; cyclohexanone, 108-94-1.

Covalent Hydration and Ring Opening of Some 2,4-Disubstituted-Pyrimido[4,5-*d*]pyrimidines[1]

Thomas J. Delia[2]

Medical Chemistry Group, John Curtin School of Medical Research, Australian National University, G.P.O. Box 334, Canberra, A.C.T., 2601, Australia

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The phenomenon of covalent hydration[3] in heterocyclic rings has recently been reviewed.[4] First observed in the pteridine system,[5] covalent hydration has subsequently been reported in a variety of heterocyclic ring systems, including the quinazolines,[6] the isomeric 1,3,*x*-triazanaphthalenes,[7] the pyrazinopyridines,[8] and the pyrimido[5,4-*e*]-*as*-triazines.[9]

Our interest was focused on the pyrimido[4,5-*d*]pyrimidines possessing amino and/or hydroxy substituents in only one of the rings. Taylor has indicated[10] that derivatives of 4-(methylthio)pyrimido[4,5-*d*]pyrimidine undergo

(1) This paper may be considered part 3 in a series entitled Fused Pyrimidines. For parts 1 and 2 see: Delia, T. J.; Sami, S. M. *J. Heterocycl. Chem.* **1981**, *18*, 929. Delia, T. J.; Kirt, D. D.; Sami, S. M. *Ibid.* **1983**, *20*, 145.

(2) This work was conducted while the author was on leave at A.N.U. Correspondence should be addressed to Macolm H. Filson Laboratories, Department of Chemistry, Central Michigan University, Mt. Pleasant, MI 48859.

(3) The hydrogen ion or, less commonly, hydroxyl ion catalyzed reversible addition of water across the C=N bond of a π-deficient heterocycle is a reasonable working definition of covalent hydration.

(4) For a recent review, see: Albert, A. *Adv. Heterocycl. Chem.* **1976**, *20*, 117.

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(6) Albert, A.; Armarego, W. L. F.; Spinner, E. *J. Chem. soc.* **1961**, 5267.

(7) Armarego, W. L. F. *J. Chem. Soc.* **1962**, 4094.

(8) (a) Perrin, D. D.; Inoue, Y. *Proc. Chem. Soc.* **1960**, 342. (b) Inoue, Y.; Perrin, D. D. *J. Chem. Soc.* **1962**, 2600.

(9) (a) Clark, J.; Yates, F. S. *J. Chem. Soc. C.* **1971**, 2475. (b) Brown, D. J.; Sugimoto, T. *Ibid.* **1971**, 2616.

(10) Albert, A.; Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1965**, *4*, 32.

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covalent hydration, followed by acid hydrolysis of the hydrated ring. No details of this work appear to have been published. The results of a detailed investigation of the covalent hydration of **1a,b** are reported here.

Results and Discussion

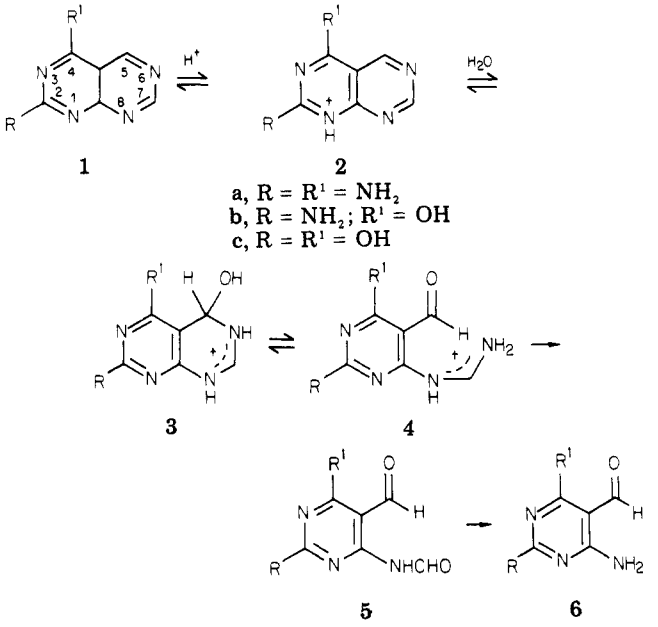
The syntheses of **1a–c** were accomplished according to literature methods.[11,12]

The possibility that covalent hydration was occurring in these molecules was first shown by the UV spectra of **1a**. The long wavelength band in neutral and basic media for **1a** was shifted to shorter wavelength by 40 nm in acidic medium. This behavior is similar to that observed for quinazoline.[13] Protonation should alter this band by only 5 nm.

When **1a** was dissolved in 0.5 N DCl/D_2O the ^1H NMR spectrum recorded initially indicated that two species were present. Two sharp singlets at δ 9.28 and 9.57 were attributed to the H_5 and H_7, respectively, of the monocation **2a**, while two additional weaker singlets at δ 6.55 and 8.91 were consistent with the H_5 and H_7, respectively, of the hydrated monocation **3a**.[14] To determine the extent of protonation of **1a**, it was estimated[15] that **1a** has a pK_a of 3.1 while that of the neutral hydrate would be 5.9. Thus for this molecule in 0.5 N DCl/D_2O (pH $\simeq$0.5) none of the neutral species **1a** would exist. The two species present at this pH, then, must be **2a** and **3a**, in equilibrium (Scheme I).

Within an hour a third set of signals appeared. The two new signals, at δ 8.24 and 9.79, were initially ascribed to **5a**, which results from an acid-catalyzed ring opening via **4a** (Scheme I). Evaporation of this solution gave a residue which, when redissolved in 0.5 N DCl/D_2O, gave a ^1H NMR spectrum in which the peak at δ 8.24 was absent. This suggested that the signal at δ 8.24 was due to *H*COOH and that the structure must be **6a**. This sample was monitored for 2 weeks until no further change was seen. At the conclusion of this experiment the ratio of **6a** to **2a** was 6:1. During the entire course of the reaction the signals due to **3a** were always quite small. This is an indication that the rates of hydration of **2a** and its subsequent ring-opening are comparable. Further evidence that **6a** is, indeed, the final product was derived from a comparison

Scheme I



of the UV and ^1H NMR spectra of the final solution with those of an authentic sample of **6a**.[16] The identification of **6a** as the final product confirms the position of hydration at the C_5–N_6 double bond.

No evidence of covalent hydration was detected in the ^1H NMR spectrum of **1a** in aqueous dimethyl sulfoxide, a neutral medium.

The UV spectrum of **1b** provided a less clear-cut example of covalent hydration. When **1b** was dissolved in dilute DCl/D_2O (pH 1–2) and allowed to stand for several hours, two major signals were observed in the ^1H NMR spectrum. These signals, at δ 8.55 and 9.79, could not be attributed to the H_5 and H_7 protons of **1b**, **2b**, or **3b** on the basis of analogy to the series **1a–3a**. Two very much smaller signals were seen at δ 9.06 and 9.23, which, undoubtedly, belong to the H_5 and H_7 protons of either anhydrous species **1b** or **2b**. As the temperature was raised to 82 °C, the proportion of these two sets of signals changed until approximately a 1:1 mixture resulted. Upon cooling, the ratio returned to near the original mixture. The interconverion of these two species suggests that the signals at δ 8.55 and 9.79 may be due to **4b**. Similar behavior has been observed[17] where an equilibrium between a hydrated pteridine and its corresponding *o*-(aminomethylene)amino aldehyde exists. Because the (aminomethylene)amino derivative would be quite a bit more basic that either **1b** or the neutral species of **3b**, the equilibrium would necessarily favor the formation of **4b**. Heating merely serves to alter the equilibrium in favor of the ring-closed system.

The covalent hydration of **1b** is very sensitive to pH. Predictions of pK_a values are –0.3 for **1b** and 2.6 for the neutral species of **3b**.[15] Because the predicted pK_a value was quite near the pH range of the dilute acid solutions used in this study, i.e., 0–4, it was beneficial to determine experimentally the pK_a. This was found to be 2.42 ± 0.03.[18] Thus in a weak acid solution in the pH range of 1–4 an equilibrium very likely exists involving **1b–4b**. This equilibrium is certainly complex, and the pK_a determined experimentally is a reflection of this situation.[10] Even so,

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(12) Granados, R.; Marquez, F.; Melgarejo, M. *An. R. Soc. Esp. Fis. Quim., Ser. B* **1962**, *58*, 479.

(13) Albert, A.; Armarego, W. L. F.; Spinner, E. *J. Chem. Soc.* **1961**, 2689.

(14) For purposes of discussion at this time it is assumed that water has added across the 5,6-double bond. This will be borne out later in the discussion.

(15) Calculations for these values were based on the procedures outlined in Perrin et al. [Perrin, D. D.; Dempsey, B.; Serjeant, E. P. "pK_a Prediction for Organic Acids and Bases"; Chapman and Hall: London, 1981] and are described here. (a) For **1a** and the neutral species of **3a**: The known pK_a value of 2,4-diaminopyrimidine is 7.40. Since this molecule differs from **1b** by the attachment of a fused pyrimidine ring it was necessary to ascertain the net effect of a fused, unsubstituted ring. This is conveniently done by a comparison of pyridine (pK_a 5.3) with 1,3,8-triazanaphthalene (pK_a 1.0). Hence annelation of a fused, unsubstituted pyrimidine ring lowers the pK_a of a molecule by 4.3 units. Therefore, the pK_a for **1a** must be 3.1 (7.40 – 4.3). Furthermore, a comparison of the pK_a of 1,3,8-triazanaphthalene (1.0) with the pK_a of the covalently hydrated form of 1,3,8-triazanaphthalene (3.85) shows that covalent hydration increases the basicity by 2.85 units. Hence, the predicted pK_a of the neutral species of **3a** is 5.9. (b) For **1b** and the neutral species of **3b**: The known pK_a of isocytosine is 3.96. By applying the same comparisons as described above (since isocytosine bears the same relationship to **1b** as 2,4-diaminopyrimidine does to **2a**), the predicted pK_a of **1b** is –0.3 and that of the neutral species of **3b** is 2.6. The validity of these predictions is supported by comparisons with pK_as of the corresponding pteridines. 2,4-Diaminopteridine (pK_a 5.30) and 2-amino-4-oxo(3*H*)-pteridine (pK_a 2.27) differ by approximately 3 p*K* units while the difference between **1a** and **1b** is 3.4.

(16) Delia, T. J.; Otteman, R. Heterocycles **1983**, *20*, 1805.

(17) Perrin, D. D. *J. Chem. Soc.* **1962**, 645.

(18) Determined spectrometrically as described in: Albert, A.; Serjeant, E. P. "The Determination of Ionization Constants"; 2nd ed.; Chapman and Hall: London, 1971; p 44 ff.

a pK_a of 2.42 compared to the predicted value of 2.6 for the neutral species of **3b** and of −0.3 for **1b** is a clear indication that the molecule exists predominantly as **3b** in this equilibrium.

As the pH of a solution of **1b** in dilute DCl/D_2O was lowered by the addition of concentrated DCl (to pH 0.8), the signals for **2b** increased sharply at the expense of those for **4b**. Increased acid concentration can promote the ring closure especially if dehydration of **3b** occurs.[10] The assignment of the signals at δ 9.06 and 9.23 to **2b** is based on the fact that, at pH 0.8, nearly all of the molecule would be protonated.

A new set of signals appeared at δ 9.80 and 10.1. It is suggested that these signals belong to **5b**, which must be formed as an intermediate when the molecule is converted from **3b** to **6b**. This, however, is only a transient intermediate. Upon standing at room temperature for several weeks a tan solid separated from the solution. This substance was identified as **6b** on the basis of UV (λ_{max} 290 nm at pH 2, 7, 13) and ^1H NMR (δ 9.67 for CHO) spectra. Subsequently, a solution of **1b** in 0.1 N HCl was heated for 3 h. Upon cooling, a solid separated which had spectral properties (UV and ^1H NMR) identical with the material isolated above. Furthermore, the product from 0.1 N HCl was identical with an authentic sample of **6b**[16] as determined by UV, ^1H NMR, and IR spectra.

Undoubtedly the pK_a of 2.42 creates a more complex set of equilibria and reactions which take place over a much longer period than in the case of **1a**. Furthermore, it was not possible to simplify this situation by going directly to a more concentrated acid solution. When this was attempted **2b** precipitated as the chloride salt.

An examination of **1b** in dimethyl sulfoxide, to which both D_2O and DCl/D_2O were added, gave a similar pattern of covalent hydration. No evidence for the formation of **4b** was seen, and the reaction was not monitored long enough to see the eventual formation of **6b**.

While the UV spectrum of 2,4-dioxo-(1*H*,3*H*)-pyrimido[4,5-*d*]pyrimidine (**1c**) bore some resemblance to that of **1b**, ^1H NMR studies in dilute DCl/D_2O did not indicate any evidence of covalent hydration comparable to either **1a** or **1b**. The pK_a for **1c** was estimated to be at or below zero. This estimate is undoubtedly low because protonation could only be expected to occur in the unsubstituted ring, leaving **2c** an unlikely species. Consequently, acid-catalyzed covalent hydration would require far stronger acid solutions and be less well stabilized by resonance than is the case for either **1a** or **1b**. Indeed, indications are that such strongly acid solutions would very likely promote dehydration[10] due to the decreased activity of water. Even so, the poor solubility of **1c** in aqueous acid solutions prevented any further examination of this species. In dimethyl sulfoxide, **1c** is more soluble but when DCl/D_2O was added no evidence of covalent hydration was observed. As the acid concentration was increased, **1c** precipitated from the aqueous dimethyl sulfoxide solution.

Experimental Section

All ^1H NMR spectra were recorded on a JEOL FX 90Q fourier transform spectrometer in either deuterium oxide (with sodium (trimethylsilyl)propanesulfonate, TPS, or dioxane as internal standard) or dimethyl sulfoxide (with tetramethylsilane as internal standard). Mass spectra were measured on a Varian MAT-CH7. UV spectra were recorded on a Unicam SP 1800 ultraviolet spectrophotometer in aqueous solution. IR spectra were determined on a Unicam SP 1050 infrared spectrophotometer.

Syntheses of Pyrimido[4,5-*d*]pyrimidines 1a–c. 1a was prepared according to literature methods[11] in 79% yield: ^1H NMR (Me_2SO-d_6 + Me_4Si), δ 6.99 (2 H, br s, 4-NH_2), 7.91 (2 H, br s, 2-NH_2), 8.88 (1 H, sharp s, H_5), 9.24 (1 H, sharp s, H_7).

1b was prepared according to literature methods[12] in 88% yield: ^1H NMR (Me_2SO-d_6 + Me_4Si) δ 7.64 (2 H, br s, 2-NH_2), 8.94 (1 H, sharp s, H_5), 8.97 (1 H, sharp s, H_7); N_3-H readily exchanges with H_2O in solvent.

1c was prepared according to literature methods[12] in 71% yield: ^1H NMR (Me_2SO-d_6 + Me_4Si) δ 8.96 (2 H, unresolved d, H_5 and H_7); N_1-H and N_3-H readily exchange with H_2O in solvent.

Acknowledgment. I am grateful to the Australian National University and the Staff of the Medical Chemistry Group, John Curtin School and Medical Research, for the opportunity to conduct this work in their laboratories. Dr. D. D. Perrin was most instrumental in the calculation of pK_as based on prediction rules he has formulated. Special appreciation is given to Dr. D. J. Brown for his efforts in providing this opportunity and to the Australian–American Educational Foundation for financial support through a Fulbright Senior Scholar Award. Finally, a very warm thank you is given to Dr. W. L. F. Armarego for his advice and encouragement throughout this study without which this work would not have reached this stage.

Registry No. **1a**, 16357-81-6; **1b**, 89890-99-3; **1c**, 89891-00-9; **2a**, 89891-01-0; **2b**, 89891-02-1; **3a**, 89891-03-2; **3b**, 89891-04-3; **4b**, 89891-05-4; **5a**, 89891-06-5; **5b**, 89891-07-6; **6a**, 88075-69-8; **6b**, 88075-70-1.

Formation of Alkyl Carbanions by Alkoxide Fragmentation in HMPT

John. S. Lomas and Jacques-Emile Dubois*

Institut de Topologie et de Dynamique des Systèmes de l'Université Paris 7 (associé au CNRS), 1 rue Guy de la Brosse, 75005 Paris, France

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Saturated hydrocarbons are the weakest carbon acids known.[1] The weakest studied to date is isobutane whose pK_a is about 13 units higher than that of methane (58 ± 5).[2] No other system giving a tertiary alkyl carbanion has yet been investigated directly. Indirect comparisons of such acids by organolithium exchange[3] are unreliable because of solvation and/or association phenomena that mask the contribution of carbanion stability to the equilibria.

We now report that the fragmentation of tertiary alkoxides, $R^1R^2R^3CO^-Li^+$, in HMPT can be used to study the relative rates of formation of *tert*-butyl and bridgehead tertiary alkyl carbanions by intramolecular competition. By means of molecular mechanics (MM) calculations[4] the steric contribution to these relative rates can be evaluated, revealing discrepancies that are associated with the relative carbanion stabilities.

Tertiary alcohols have been decomposed via the alkoxide ion by Zook,[5] at elevated temperatures, and by Cram,[6] when resonance stabilizing aromatic or cyano groups were

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