

substituted. The properties of this last compound will be reported in a later paper.

Experimental Section

Compound Preparation. All analyses were performed by the microanalytical laboratory of the University of Illinois' School of Chemical Sciences. All reactants were reagent grade or purchased from commercial sources.

The π -arene mono(π -cyclopentadienyl)iron hexafluorophosphate salts were prepared by the method described for the benzene derivative.²⁰ The π -arene bis(π -cyclopentadienyl)iron hexafluorophosphate salts studied in this work were prepared by the following procedure. A Schlenk flask (250 ml) is flushed thoroughly with nitrogen. Then under a continuous stream of nitrogen, 5.58 g (0.030 mol) of ferrocene, 20.0 g (0.15 mol) of anhydrous aluminum chloride, 1.35 g (0.050 mol) of aluminum powder, 50.0 ml of cyclohexane (or decalin), and 0.0015 mol of the arene compound to be exchanged were added to the flask. The reaction mixture is then heated under reflux, with rapid stirring, in a nitrogen atmosphere, for 12–16 hr (overnight). Then the reaction flask was cooled to room temperature and placed in an ice bath, and the reaction mixture (still under N_2) was slowly hydrolyzed with 50 ml of ice-water. The mixture was filtered, and the aqueous layer was separated after washing with several 30-ml portions of cyclohexane. The aqueous layer, which is air stable, was then filtered into a concentrated aqueous solution of ammonium hexafluorophosphate (2 g in a few ml) to isolate the desired compound. The precipitated material was filtered to give a solid which was quite frequently yellow in color. A greenish coloration indicates impurities. Two solids (naphthalene and chrysene) were orange colored. The yields were

generally 35–50% based on the arene. The compounds were recrystallized either from a warm acetone–water solution (do not heat excessively), or by dissolving the solid in acetonitrile and then adding anhydrous ether. They were then dried for at least 24 hr *in vacuo* over P_2O_5 .

Physical Measurements. All proton nmr spectra were obtained with either Varian 60- or 220-MHz spectrometers at ambient probe temperatures. Carbon-13 nmr spectra were obtained on a Varian Model XL-100-15 spectrometer with a 15-in. magnet and at a frequency of 25.5 MHz. A Digit Lab FTS-NMR/3 Model Fourier transform system was used. For many samples D_2SO_4 (for locking purposes) was used as a solvent and acetone was used as an internal standard. Other samples were run in CD_3CN with TMS internal standard. Data collection took from 1 to 1.5 hr for each ^{13}C run. All ^{13}C spectra were run in the proton-decoupled mode with a 1.5-kHz noise bandwidth. Pulse conditions were nominally, width, 15 μ sec; acquisition time, 1.5 sec; and delay, 0.025.

Acknowledgment. We are grateful for partial funding of this research by National Institute of Health Grant HL 13652. The Varian XL-100 spectrometer was purchased in part, by a National Science Foundation departmental instrument grant.

Supplementary Material. Tables I and II and Figures 2 and 3 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 \times 148 mm, 24 \times reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfiche, referring to code number JACS-74-3603.

(20) R. B. King, *Organometal. Syn.*, 1, 138 (1965).

Hydration of Carboxamides. Evaluation of the Free Energy Change for Addition of Water to Acetamide and Formamide Derivatives

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Abstract: The method employed for estimating the free energy of formation of ortho acids from the free energy of formation of ortho esters was extended to estimate the free energy of formation of ortho acid monoamides ($RC(OH)_2NR'_2$) from the free energies of formation of amide dimethyl acetals. The heat of formation of liquid $RC(OCH_3)_2N(CH_3)_2$ was determined calorimetrically by measuring the heat of hydrolysis in aqueous base. This permitted calculation of the required free energies of formation in aqueous solution. The free energies for addition of water (standard state, the pure liquid) to *N,N*-dimethylformamide and *N,N*-dimethylacetamide (standard states, 1 *M* solutions with an infinitely dilute reference state) are respectively +19.3 and +19.6 kcal/mol. These results permit construction of more detailed reaction coordinate diagrams for amide hydrolysis and ester aminolysis than has previously been possible.

Recently it has been shown¹ that the equilibrium constant for reaction 1 is only slightly dependent



on the nature of R and that for a given number of substituents on the carbon bearing the hydroxyl it is essentially constant. This fact was used to evaluate the free energies of formation in aqueous solution of orthoformic and orthoacetic acids from the free energies of formation of the corresponding trimethyl esters. This approach has now been extended to estimate the

free energies of formation of species $RC(OH)(OCH_3)N(CH_3)_2$ and $RC(OH)_2N(CH_3)_2$, which are the intermediates in the aminolysis of the methyl ester and the hydrolysis of the amide. In order to do this it was necessary to determine the heats of formation of the corresponding amide dimethyl acetals, which could be done by measuring the heats of hydrolysis in aqueous base. With the equilibrium constants for formation of the tetrahedral intermediates, the results of earlier kinetic investigations of amide hydrolysis² and ester

(1) J. P. Guthrie, *J. Amer. Chem. Soc.*, **95**, 6999 (1973).

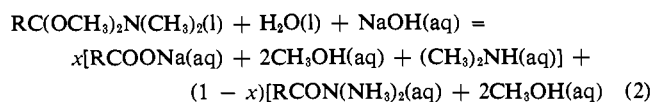
(2) (a) P. D. Bolton, *Aust. J. Chem.*, **19**, 1013 (1966); (b) S. Langlois and A. Broche, *Bull. Soc. Chem. Fr.*, 812 (1964); (c) P. D. Bolton and G. L. Jackson, *Aust. J. Chem.*, **24**, 969 (1970).

aminolysis³ can be examined and a more detailed picture of the energetics of these reactions arrived at.

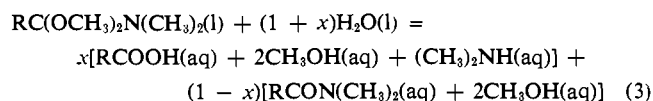
Thermochemical calculations have suffered a strange neglect at the hands of organic chemists, and in particular those engaged in investigations of reaction mechanisms. A vast body of thermochemical information⁴ is now available, and standard methods for estimating thermochemical quantities for homologs of compounds which have been studied are well worked out.^{4b,c,5} Quite often a few straightforward measurements will permit an indirect evaluation of an otherwise inaccessible equilibrium constant.

Results and Discussion

Hydrolysis of an amide acetal in aqueous base will give a mixture of ester and amide products, with the proportions depending on the partitioning of the intermediates. Ester formation is followed by saponification and generates one equivalent each of a weak and a



strong base, so the stoichiometry can be determined by titration of the product solution to pH 2.7; it is necessary to do the titration before significant amounts of base-catalyzed amide hydrolysis occur, but for dilute base (0.1 M) this is not a problem.⁶ Once the stoichiometry is settled, it is convenient to calculate (from the heat of reaction of reaction 2 and the known⁷ heat of neutralization for acetic acid) the heat of reaction for the hypothetical process (reaction 3). Then, using



$\Delta H_f^\circ(\text{aq})$ values from Table II it is straightforward to calculate the standard enthalpy of formation of liquid amide acetal. In Table I are found the experimental results, and the final $\Delta H_f^\circ(\text{l})$ values for dimethylformamide and dimethylacetamide dimethyl acetals. As a test of the experimental technique, the heat of reaction of acetic anhydride was measured, again in aqueous 0.1 N NaOH. The values obtained are in good agreement with those in the literature. An error analysis shows that the value calculated for $\Delta H_f^\circ(\text{l})$ for either amide acetal is insensitive to errors in x ; a 10% error in x leads to a 0.4 kcal error for $\text{R} = \text{CH}_3$ and a 0.03 kcal error for $\text{R} = \text{H}$.

From heats of vaporization and standard entropies, estimated by accepted methods (see Appendix), the

(3) (a) G. M. Blackburn and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 2638 (1968); (b) A. R. Fersht, *ibid.*, **93**, 3504 (1971).

(4) (a) F. D. Rossini, D. D. Nagman, W. H. Evans, S. Levine, and I. Jaffe, *Nat. Bur. Stand. (U.S.) Circ.*, No. 500 (1952); (b) D. R. Stull, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1967; (c) J. D. Cox and G. Pilcher, "Thermochemistry of Organic and Organometallic Compounds," Academic Press, New York, N. Y., 1970.

(5) S. W. Benson, "Thermochemical Kinetics," Wiley, New York, N. Y., 1968.

(6) The pseudo-first-order rate constants for base catalyzed hydrolysis in aqueous solution of dimethylformamide and -acetamide, at 25°, are 1.8×10^{-3} and 1.8×10^{-6} sec⁻¹, respectively; see Table V.

(7) J. W. Larson and L. G. Hepler in "Solute-Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969.

standard free energy of formation of the gaseous amide acetals can be calculated. In order to calculate the free

Table I. Evaluation of Heat of Formation of Amide Dimethyl Acetals^a

Compd	$\Delta H_{\text{rxn}}^\circ$ ² obsd	x	$\Delta H_{\text{rxn}}^\circ$ ³	$\Delta H_f^\circ(\text{l})$
$\text{HC}(\text{OCH}_3)_2\text{N}(\text{CH}_3)_2$	-16.1 ± 0.2^b	0.093	-14.9	-94.4 ^d
$\text{CH}_3\text{C}(\text{OCH}_3)_2\text{N}(\text{CH}_3)_2$	-23.1 ± 0.6^b	0.64	-14.5	-102.4 ^d
$(\text{CH}_3\text{CO})_2\text{O}$	$-40.6 \pm 0.8^{b,c}$			-150.2 ^d -149.22 ^e

^a In aqueous solution, initially 0.1 N NaOH, at $25 \pm 2^\circ$, with total concentration of compound ≤ 0.03 M. ^b Average of three runs; limits represent twice the standard deviation from the mean. ^c Reaction was $(\text{CH}_3\text{CO})_2\text{O}(\text{l}) + 2\text{OH}^-(\text{aq}) = 2\text{CH}_3\text{COONa}(\text{aq})$. ^d Calculated using $\Delta H_{\text{rxn}}^\circ$ and ΔH_f° values in Table II. ^e Literature value, ref 4c.

energies of transfer from gas to aqueous solution, the solubilities and vapor pressures were needed. The solubilities could not be measured, because the acetals react rapidly and exothermically with water; however, a reasonable estimate can be made by taking advantage of the known linear free energy relationship between the logarithm of solubility and π ; since OCH_3 and $\text{N}(\text{CH}_3)_2$ have very similar π values,⁹ the solubility of an amide acetal may be assumed to be the same as that of the corresponding ortho acid trimethyl ester.¹ Thus the free energies of transfer can be obtained. Then, with standard free energies of formation of the amide dimethyl acetals in aqueous solution in hand, application of the known equilibrium constant for reaction 1 with a total of three or four substituents on the central carbon (making suitable allowance for symmetry effects) permits calculation of the free energies of formation of the amide hydrates and hemiacetals. The values so obtained are found in Table II.

Now, by combining the standard free energy of formation values in Table II, the standard free energy changes and equilibrium constants for tetrahedral intermediate formation can be calculated; in Table III are found the values so obtained. In order to calculate values for reaction in acid or alkaline solution, it was necessary to estimate $\text{p}K_a$ values for the possible acid-base reactions of the tetrahedral species. Suitable equations were derived for this purpose. The $\text{p}K_a$ values calculated from these equations as well as the literature values for other compounds which were used in this paper are found in Table IV. The estimation procedure is described in the Appendix.

It is noteworthy that the ΔG° values for hydration of dimethylformamide and dimethylacetamide are very similar; this is at first sight rather surprising but is very consistent with the rates of, for example, acid-catalyzed hydrolysis of these amides which are also very similar. For the corresponding methyl esters, the ΔG° values for hydration¹ differ by 4.8 kcal/mol, and the rate constants for acid-catalyzed hydrolysis show a difference of 2.1 kcal/mol in free energy of activation. This contrast between the behavior of amides and esters is curious but, as yet, inexplicable.

It is of great interest to examine the results of kinetic studies of amide hydrolysis and ester aminolysis in the

(8) C. Hansch, J. E. Quinlan, and G. L. Lawrence, *J. Org. Chem.*, **33**, 347 (1968).

(9) M. S. Tute, *Advan. Drug. Res.*, **6**, 1 (1971).

Table II. Thermochemical Data^a

Compd	$\Delta H_f^\circ(\text{g})^b$	$S^\circ(\text{g})^c$	$\Delta G_f^\circ(\text{g})^b$	$\Delta H_v^{b,d}$	$\Delta H_f^\circ(\text{l})^b$	$\Delta H_s^{b,e}$	$\Delta H_f^\circ(\text{aq})^{b,f}$	$\Delta G_s^{b,g}$	$\Delta G_f^\circ(\text{aq})^b$
H ₂ O	-57.80 ^h	45.11 ^h	-54.68 ^h		-68.32 ^h				-56.69 ^{h,i}
HCOOH	-90.49 ⁱ	59.45 ⁱ	-83.89 ⁱ		-101.60 ^m	-0.16 ⁿ	-101.76 ^m	-4.94 ^k	-88.83 ^k
CH ₃ OH	-48.08 ^h	56.8 ^h	-38.09 ^h		-57.02 ^h	-1.74 ⁱ	-58.76 ⁿ	-3.19 ^k	-41.88 ^k
CH ₃ COOH	-103.26 ^m	67.52 ⁱ	-89.36 ⁿ		-115.75 ^m	-3.4 ^h	-116.09 ⁿ	-4.85 ^k	-94.21 ^k
HCOOCH ₃	-83.60 ⁱ	72.0 ⁱ	-71.03 ⁱ	6.75 ⁱ	-90.35 ⁿ	-0.85 ^o	-91.20 ⁿ	-0.98 ^k	-72.01 ^k
(CH ₃) ₂ NH	-4.50 ⁱ	65.24 ⁱ	+16.25 ⁱ			-13.26 ^{n,q}	-17.76 ^m	-2.41 ^q	+13.84 ⁿ
CH ₃ COOCH ₃	-97.9 ⁱ	76.45 ^k	-77.0 ⁿ		-105.5 ⁱ	-1.89 ^o	-107.4 ⁿ	-1.38 ^k	-78.4 ^k
HCON(CH ₃) ₂	-46.4 ⁿ			10.8 ^r	-57.21 ^s	-3.8 ^t	-61.0 ⁿ		-27.58 ^u
CH ₃ CON(CH ₃) ₂	-55.6 ⁿ			10.9 ^r	-66.52 ^s	-5.20 ^t	-71.72 ⁿ		-29.5 ^u
HC(OCH ₃) ₂ N(CH ₃) ₂	-85.0 ⁿ	101.53 ⁿ	-31.2 ⁿ	9.4 ^v	-94.4 ^o			-2.15 ^u	-33.4 ⁿ
CH ₃ C(OCH ₃) ₂ N(CH ₃) ₂	-92.5 ⁿ	108.24 ⁿ	-31.1 ⁿ	9.9 ^v	-102.4 ^o			-2.66 ^u	-33.8 ⁿ
HC(OH) ₂ N(CH ₃) ₂									-65.0 ^u
CH ₃ C(OH) ₂ N(CH ₃) ₂									-66.6 ^u
HC(OH)(OCH ₃)N(CH ₃) ₂									-49.6 ^u
CH ₃ C(OH)(OCH ₃)N(CH ₃) ₂									-50.6 ^u

^a At 25°; standard states are ideal gas at 1 atm, pure liquid, and 1 M aqueous solution with an infinitely dilute reference state, unless otherwise noted. ^b kcal mol⁻¹. ^c cal deg⁻¹ mol⁻¹. ^d Heat of vaporization. ^e Heat of solution, liquid to infinitely dilute aqueous solution, unless otherwise noted. ^f Standard state is infinitely dilute aqueous solution. ^g Free energy of transfer from gas to aqueous solution. ^h Reference 4a. ⁱ Standard state is the pure liquid. ^j Reference 4b. ^k Reference 1. ^l E. M. Arnett in "Solute-Solvent Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969. ^m Reference 4c. ⁿ Calculated from values in this table. ^o This work. ^p Heat of solution for gas to infinitely dilute aqueous solution. ^q E. M. Arnett, F. M. Jones, III, M. Taagepera, W. G. Henderson, R. Beauchamp, D. Holtz, and R. W. Taft, *J. Amer. Chem. Soc.*, **94**, 4729 (1972). ^r R. Gopal and S. A. Rizvi, *J. Indian Chem. Soc.*, **45**, 13 (1968). ^s T. F. Vasileva, E. N. Zhiltsova, and A. A. Vvedenskii, *Zh. Fiz. Khim.*, **46**, 541 (1972); *Chem. Abstr.*, **76**, 132316m (1972). ^t E. M. Arnett, J. J. Burke, J. V. Carter, and C. F. Doaty, *J. Amer. Chem. Soc.*, **94**, 7837 (1972). ^u Calculated as described in the text. ^v J. Konicek and I. Wadsö, *Acta Chem. Scand.*, **25**, 1541 (1971).

Table III. Equilibrium Constants Evaluated in This Work for Addition to Acids, Esters, and Amides^a

Reaction	R = H		R = CH ₃	
	K^b	$\Delta G^\circ c$	K^b	$\Delta G^\circ c$
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH} + \text{HN}(\text{CH}_3)_2 \rightleftharpoons \text{R}-\overset{\text{OH}}{\text{C}}-\text{N}(\text{CH}_3)_2$	4.7×10^{-8}	10.0 ^d	7.8×10^{-11}	13.8 ^d
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OCH}_3 + \text{HN}(\text{CH}_3)_2 \rightleftharpoons \text{R}-\overset{\text{OH}}{\text{C}}(\text{OCH}_3)-\text{N}(\text{CH}_3)_2$	1.1×10^{-10}	13.6 ^e	3.5×10^{-13}	17.0 ^e
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2 + \text{H}_2\text{O} \rightleftharpoons \text{R}-\overset{\text{OH}}{\text{C}}(\text{OH})-\text{N}(\text{CH}_3)_2$	5.0×10^{-7}	8.6 ^d	9.3×10^{-11}	13.7 ^d
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2 + \text{H}_2\text{O} \rightleftharpoons \text{R}-\overset{\text{OH}}{\text{C}}(\text{OCH}_3)-\text{N}(\text{CH}_3)_2$	7.8×10^{-11}	13.8 ^e	2.8×10^{-14}	18.5 ^e
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2 + \text{H}_2\text{O} \rightleftharpoons \text{R}-\overset{\text{OH}}{\text{C}}(\text{OH})-\text{N}(\text{CH}_3)_2$	7.3×10^{-15}	19.3 ^d	4.4×10^{-15}	19.6 ^d
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2 + \text{CH}_3\text{OH} \rightleftharpoons \text{R}-\overset{\text{OH}}{\text{C}}(\text{OCH}_3)-\text{N}(\text{CH}_3)_2$	1.7×10^{-17}	22.9 ^e	2.0×10^{-17}	22.8 ^e
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2 + \text{CH}_3\text{OH} \rightleftharpoons \text{R}-\overset{\text{OH}}{\text{C}}(\text{OH})-\text{N}(\text{CH}_3)_2$	2.7×10^{-15}	19.9 ^d	5.8×10^{-16}	20.8 ^d
$\text{R}-\overset{\text{OH}}{\text{C}}=\text{N}(\text{CH}_3)_2 + \text{H}_2\text{O} \rightleftharpoons \text{R}-\overset{\text{OH}}{\text{C}}(\text{OH})-\text{NH}(\text{CH}_3)_2^+$	4.1×10^{-19}	25.1 ^e	1.8×10^{-19}	25.6 ^e
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2 + \text{HO}^- \rightleftharpoons \text{R}-\overset{\text{O}^-}{\text{C}}(\text{OH})-\text{N}(\text{CH}_3)_2$	1.2×10^{-9}	12.2	8.8×10^{-19}	11.0
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{N}(\text{CH}_3)_2 + \text{HO}^- \rightleftharpoons \text{R}-\overset{\text{O}^-}{\text{C}}(\text{OH})-\text{N}(\text{CH}_3)_2$	1.1×10^{-13}	17.7	1.7×10^{-14}	18.8

^a In aqueous solution at 25°; standard state for water is the pure liquid at unit activity; standard state for solutes is 1 M aqueous solution with an infinitely dilute reference state. ^b Dimensions are M⁻¹ except when water is a reactant, when K is dimensionless. ^c kcal/mol. ^d Reaction leading to the neutral form of the adduct. ^e Reaction leading to the zwitterionic form of the adduct.

light of the equilibria in Table III. The rate constants used in this discussion are found in Table V. As described in the footnotes to this table, it has been necessary to use linear free energy relations to estimate values for reactions of dimethylamine from reactions of

other amines of similar p*K*_a. Blackburn and Jencks^{3a} in an investigation of the aminolysis of methyl formate found that the partitioning of the tetrahedral intermediate was pH dependent in the mildly alkaline pH region. A simplified form of their mechanism, omitting

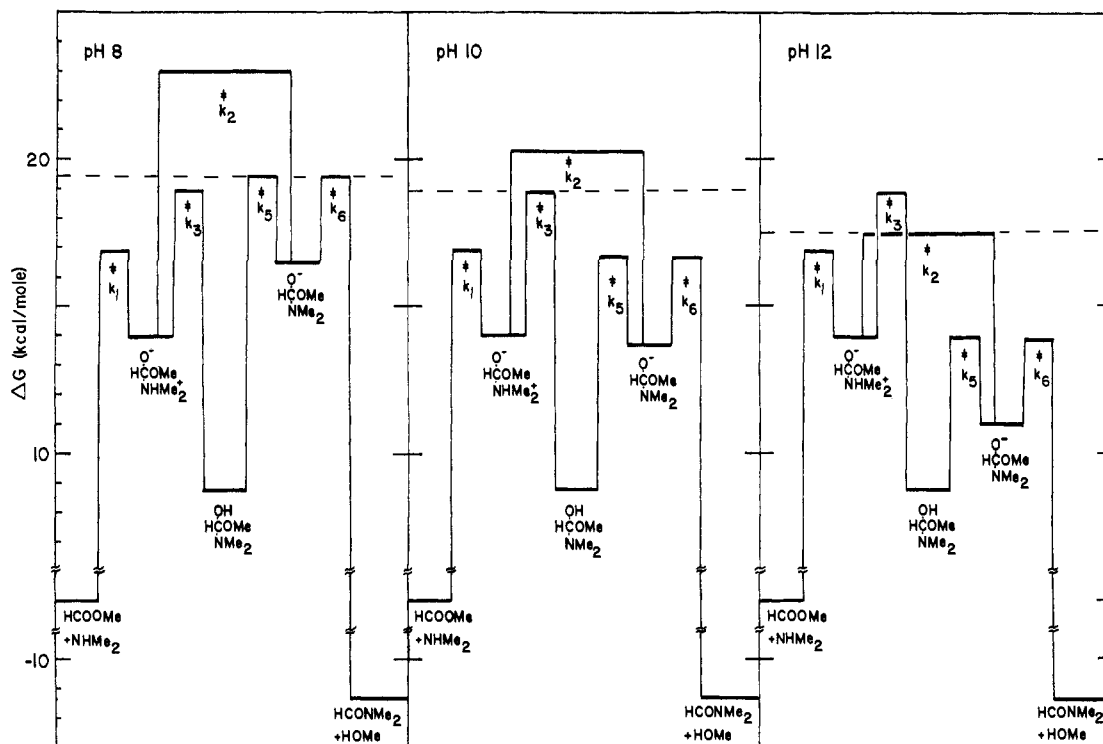
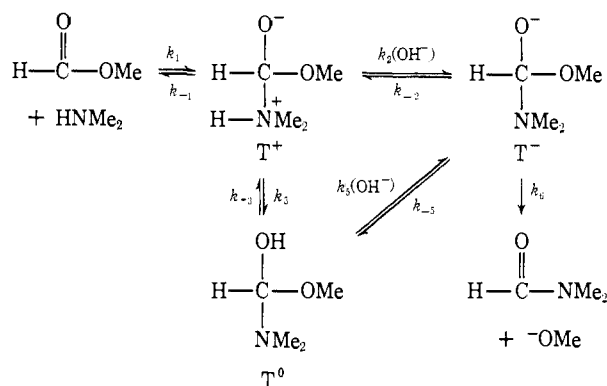


Figure 2. Reaction coordinate diagrams for the reaction of dimethylamine with methyl formate at pH 8, 10, and 12. The free energy levels were determined as described in the text. The effects of general base catalysis by dimethylamine have been omitted in order to simplify the diagrams. In all cases the immediate products of the k_6 step are dimethylformamide and methoxide ion; since conversion of methoxide to methanol is a very rapid process, not affecting the mechanistic discussion, this step is omitted, and the diagrams are constructed as if the immediate products were amide and methanol.

Recently, Jencks¹⁴ has proposed a more detailed interpretation of the kinetics of the aminolysis of methyl formate and has concluded that proton transfer steps, and not steps involving forming or breaking of bonds between heavy atoms, are rate determining. The results in this paper are in complete accord with this analysis and permit approximate evaluation of all the microscopic rate constants. The pathway proposed is that of Scheme I,¹⁴ the analysis is most readily fol-

Scheme I



lowed by examining both Scheme I and Figure 2. In this figure the known free energy levels are those for the neutral, zwitterionic, and anionic forms of the intermediate and the over-all transition state at each pH. It must, however, be borne in mind that the free energy levels for the intermediates are uncertain by about 2 kcal. Consequently, it is more straightforward to discuss the free energies of activation of the individual

steps than the rate constants, since 2 kcal/mol in ΔG^\ddagger corresponds to a 29-fold change in rate constant. At pH 10, the rate-determining step is the water mediated proton switch, k_3 ; the free energy of activation for this step can be found from the free energy levels for the over-all rate constant and the zwitterion. At pH 12 the rate-determining step is the hydroxide-catalyzed conversion of zwitterion to anion and at pH 8 it is, at least in part, the hydroxide-catalyzed conversion of neutral to anionic intermediate.

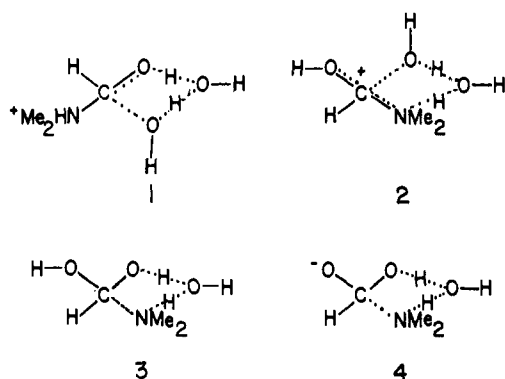
Although the k_5 step cannot be faster than diffusion controlled, the free energy levels of intermediate and transition state do not permit this step to be much slower. Thus the k_5 step must be at least partially rate limiting at pH 8. Nonetheless, there is an ambiguity as to whether $k_5(\text{OH}^-)$ or k_6 is slower; this is not easily resolved, but the rates cannot be very different. Somewhat arbitrarily it has been assumed that at pH 8 (or below) $k_5(\text{OH}^-)$ and k_6 are equal. Thus values of the free energies of activation corresponding to the steps in Scheme I can be calculated. For the k_1 , and k_2 , and k_5 steps, the free energies of activation are calculated for the second-order rate constants. The values so obtained are: $\Delta G_3^\ddagger = 4.7 \pm 2$, $\Delta G_2^\ddagger = 0.5 \pm 2$, and $\Delta G_5^\ddagger = 2.2 \pm 2$; these values are within their uncertainties of the values observed for similar reactions.¹⁵ The activation barrier for the k_6 step, expulsion of methoxide from the anionic intermediate, must be

(14) W. P. Jencks, *Chem. Rev.*, 72, 705 (1972).

(15) (a) The rate constant for the water mediated proton switch converting cysteine to its zwitterion (S-N proton migration) is $4 \times 10^8 \text{ sec}^{-1}$ ^{16b} or $\Delta G^\ddagger = 5.7 \text{ kcal/mol}$. Diffusion-controlled proton transfer reactions have rate constants in the range 10^9 – $10^{11} \text{ M}^{-1} \text{ sec}^{-1}$ ^{16c} or ΔG^\ddagger between 5 and 3 kcal/mol; (b) G. Maass and F. Peters, *Angew. Chem., Int. Ed. Engl.*, 11, 428 (1972); (c) M. Eigen, *ibid.*, 3, 1 (1964).

2.7 \pm 2 kcal/mol; this follows from the free energy levels of the anionic intermediate and the over-all transition state at pH 8. The rate constant, k_{-1} , for expulsion of amine from the zwitterionic intermediate should be no slower than k_6 , since the leaving group is better;¹⁶ a value of 2.7 kcal/mol has been assumed for ΔG_{-1}^\ddagger in Figure 2. Figure 2 is oversimplified in that the effects of general base catalysis have been omitted. A necessary consequence of the above analysis is that for pH > 12 there must be another change in the rate-determining step, with k_1 rate limiting at high $[\text{OH}^-]$; this will be difficult to test experimentally because of competing hydroxide-catalyzed hydrolysis.

Applying a similar analysis to the kinetics of amide hydrolysis leads to strikingly different conclusions; Figure 3 shows the free energy levels used. The acid-catalyzed hydrolysis of dimethylformamide most probably occurs *via* the protonated form of the tetrahedral intermediate since this is the most stable form at low pH. The addition of water to form this intermediate could occur in several ways. (1) Stepwise addition of water to the O-protonated amide, with transient formation of the O-protonated tetrahedral intermediate; this path can be ruled out because estimation of the pK_a of this O-protonated species (Table IV) shows that it is too high energy a species to be on the reaction path. (2) Addition of water to the O-protonated amide with concerted general base catalysis by a second water molecule, leading to the neutral tetrahedral species as a transient intermediate; this mechanism can be ruled out because the change in pK_a of the proton removed in this general base catalyzed reaction is too small. Jencks has shown that concerted general base catalysis is only to be expected when the proton transfer changes from highly unfavorable to highly favorable as the reaction proceeds;¹⁴ in this case the transfer is highly unfavorable initially but only slightly favorable after complete C-O bond formation. (3) Cyclic addition of water to the N-protonated amide, giving rise to the N-protonated tetrahedral species directly by way of transition state 1. From the pK_a for N



protonation,^{3b} one can calculate that the rate constant for the hydration step would have to be $3 \times 10^2 \text{ sec}^{-1}$ which seems not impossible in terms of the rate constant for hydration of formaldehyde, by an analogous mechanism,^{17a} which is 12 sec^{-1} .^{17b} (4) Cyclic addition of

(16) It is assumed that an amine, pK_a 10.6, is a better leaving group than an alkoxide, pK_a 15.5.

(17) (a) W. J. Albery, *Progr. React. Kinet.*, **4**, 369 (1967); (b) calculated from the rate constant for dehydration^{17a} and the equilibrium constant; ^{17c} (c) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968); (d) A. R. Fersht and W. P. Jencks, *ibid.*, **92**, 5432 (1970).

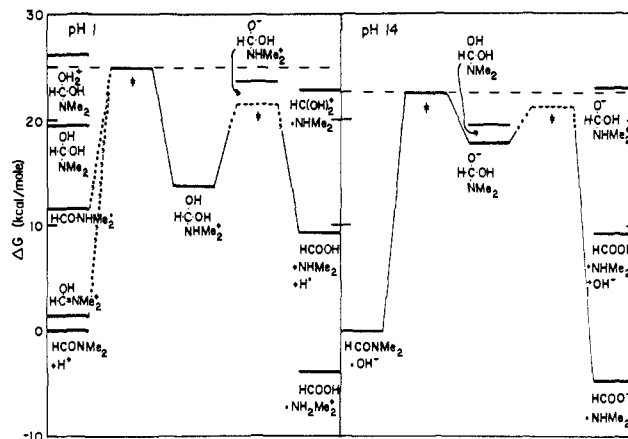


Figure 3. Reaction coordinate diagrams for the acid and alkaline hydrolysis of dimethylformamide. These diagrams are constructed assuming that $k_h > k_e$ with somewhat arbitrary values of $k_{h1} = 374k_e$ for acid solution and $k_h = 10k_e$ for alkaline solution. Free energy levels for various possible intermediates are included; see text for discussion.

water to the O-protonated form of the amide by way of transition state 2. It is hard to judge between mechanisms 3 and 4. A possible argument in favor of mechanism 3 is that the rate constant for the reaction of water with acetylpyridinium ion is 7 sec^{-1} ,^{17c} which is in fair agreement with the rate constant for mechanism 3.¹⁸ It seems reasonable that the addition of water is rate limiting for the hydrolysis of acetylpyridinium ion, though this has not been established.

Similarly there are several possible mechanisms for the expulsion of amine. (1) Expulsion by way of the zwitterion, with zwitterion formation as the rate determining step; this mechanism can be ruled out, because the necessary proton transfer is too slow.¹⁹ (2) Simple expulsion of the amine from the N-protonated tetrahedral species to give protonated acid and amine; this mechanism seems improbable, on the assumption that $k_h > k_e$, since the rate constant for the reverse of this step, attack of amine on protonated acid, would have to be at or greater than the diffusion-controlled limit.²⁰ (3) Expulsion of the amine from the N-protonated tetrahedral species, with concerted general base catalysis by a water molecule to give rise to acid, amine, and hydronium ion; this mechanism seems plausible, since the proton transfer involved in the general base catalysis changes from strongly disfavored to strongly favored as the reaction proceeds.

Turning to the hydroxide-catalyzed hydrolysis of dimethylformamide, it seems clear that the only possible

(18) After submission of this paper I learned of experiments which provide strong evidence that the N-protonated amide is not an intermediate in ordinary amide hydrolysis. I thank Professor Kresge for sending me a copy of this manuscript prior to its publication: A. J. Kresge, P. H. Fitzgerald, and Y. Chang, submitted for publication.

(19) The rate of hydroxyl proton removal from the cationic intermediate by a water molecule can be calculated from the pK_a of the cation (*ca.* 8; see Table IV), assuming that the rate of the recombination reaction of zwitterion with hydronium ion ($pK_a = -1.74$) is diffusion controlled; a value of *ca.* 10^2 sec^{-1} is obtained. Formation of the zwitterion is slower than the over-all reaction and much too slow to satisfy the condition $k_h > k_e$.

(20) The pK_a for $\text{HC}(\text{OH})_2^+$ is assumed to be the same as that for $\text{CH}_3\text{C}(\text{OH})_2^+$. If $k_h = 10k_e$, the rate constant for $\text{NH}(\text{CH}_3)_2$ reacting with $\text{HC}(\text{OH})_2^+$ would have to be *ca.* $10^{10} \text{ M}^{-1} \text{ sec}^{-1}$; if $k_h = 374k_e$ (the limit imposed for benzamide¹⁸), this rate constant would have to be $3 \times 10^{11} \text{ M}^{-1} \text{ sec}^{-1}$. This seems much too large in view of the rate constants for reaction of amines with cations: C. D. Ritchie and P. O. I. Virtanen, *J. Amer. Chem. Soc.*, **95**, 1882 (1973).

intermediates are the neutral or anionic tetrahedral species; the zwitterion is of too high energy to be involved, since it is higher in energy than the over-all transition state. The only reasonable mechanism for formation of the intermediate seems to be simple attack of hydroxide ion; if $k_h > k_e$ this is also the rate-limiting step. The rate constant for expulsion of hydroxide from this anionic species is 10^{10} sec^{-1} in agreement with the rate deduced for expulsion of methoxide from the analogous intermediate in ester aminolysis. Proton transfer to give the neutral form of the tetrahedral intermediate is probably fast enough for this species to be formed, but it seems improbable that it is on the reaction path. If the neutral species could expel amine, it would have to be with some form of cyclic catalysis by water²¹ as is shown in transition state 3; however, there is no reason why this would not be possible for the neutral intermediate in the aminolysis reaction, yet the kinetics there required that expulsion of the amine proceed *via* the zwitterion. Expulsion of the amine from the anionic form of the tetrahedral species could occur by a process involving cyclic catalysis by water, so that the products are formate ion and dimethylamine, *via* transition state 4. This path is not accessible to the intermediate in ester aminolysis, so that the higher energy path from the zwitterion must be used.

The thermochemical approach to the evaluation of otherwise inaccessible equilibrium constants is shown by the above analysis to be a powerful tool for completing the kinetic analysis of acyl transfer reactions. As is shown above, simple thermochemical determinations suffice to give extremely valuable information; it seems probable that this approach will be of wide utility and further studies are in progress.

Experimental Section

Dimethylformamide dimethyl acetal (Aldrich) was used without further purification; nmr analysis showed <2% impurities; dimethylacetamide dimethyl acetal was prepared from dimethylacetamide by known procedures²³ and distilled using aspirator vacuum; nmr analysis showed <3% impurities. Methyl formate and methyl acetate were redistilled before use.

Heats of solution and reaction were measured using a simple dewar type calorimeter, calibrated by standard procedures.²⁴ Weighed samples (ca. 1 g) at room temperature ($25 \pm 2^\circ$) were injected into ca. 400 g of 0.1 N NaOH in the calorimeter.

Appendix

As a starting point for estimating the pK_a of tetrahedral intermediates protonated on nitrogen, available data on the pK_a 's of amines of the type $RCH_2NH(CH_3)_2$ ^{25, 26} were plotted *vs.* σ^* ²⁷ for R; these points

(21) Taking as a rough estimate for the pK_a of $HN(CH_3)_2$ the value quoted²² for ammonia, *i.e.*, 35, it can be seen that formation of $HCOOH + N(CH_3)_2^-$ costs ca. 42 kcal relative to the actual products; this is prohibitive, so that some form of general acid catalysis is essential to avoid formation of the amide ion.

(22) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959.

(23) (a) C. Feugas and D. Olschwang, *Bull. Soc. Chem. Fr.*, 4985 (1968); (b) H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Justus Liebig's Ann. Chem.*, 641, 1 (1961).

(24) F. Daniels, J. W. Williams, P. Bender, R. A. Alberty, and C. D. Cornwell, "Experimental Physical Chemistry," 6th ed., McGraw-Hill, New York, N. Y., 1962.

(25) (a) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, London, 1965; (b) W. P. Jencks and J. Regenstein, "Handbook of Biochemistry," 1st ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1968.

(26) (a) Although eq 4 seems to the present author the most reasonable basis for estimation of pK_a 's of N-protonated tetrahedral inter-

were fitted by the equation

$$pK_a = 9.86 - 1.75\sigma^* \quad (4)$$

This equation could be extended to tetrahedral species by allowing for the difference in σ^* between H and OR, leading to equations for

$$RC(OH)_2NH(CH_3)_2^+ \quad pK_a = 6.10 - 1.75\sigma^* \quad (5)$$

$$RC(OH)(OCH_3)NH(CH_3)_2^+ \quad pK_a = 5.67 - 1.75\sigma^* \quad (6)$$

For carbonyl hydrates, $RR'C(OH)_2$, the following equation has been reported.³⁰

$$pK_a = 14.19 - 1.32(\sigma_{R^*} + \sigma_{R'^*})$$

Then by substituting values of σ^* for $N(CH_3)_2$ or $NH(CH_3)_2$ ²⁷ one obtains the equations for

$$RC(OH)_2N(CH_3)_2 \quad pK_a = 13.4 - 1.32\sigma^* \quad (7)$$

$$RC(OH)_2NH(CH_3)_2^+ \quad pK_a = 8.4 - 1.32\sigma^* \quad (8)$$

For alcohols, RCH_2OH , the following equation has been reported.³¹

$$pK_a = 15.74 - 1.32\sigma_{R^*}$$

Then by allowing for the difference²⁷ in σ^* between H and OCH_3 , and between H and $N(CH_3)_2$ or $NH(CH_3)_2^+$, one obtains the equations for

$$RC(OH)(OCH_3)N(CH_3)_2 \quad pK_a = 13.8 - 1.32\sigma^* \quad (9)$$

$$RC(OH)(OCH_3)NH(CH_3)_2^+ \quad pK_a = 8.9 - 1.32\sigma^* \quad (10)$$

Finally, an estimate of the pK_a to be anticipated for a tetrahedral intermediate protonated on oxygen can be obtained following the suggestion of Bunton and De Wolfe³² that ρ^* should be similar for ammonium ions and oxonium ions. Making this assumption, and using a value of -1.98 for the pK_a of methanol,³³ we obtain for $RC(OH)(OH)_2N(CH_3)_2^+$

$$pK_a = -3.2 - 1.8\sigma^* \quad (11)$$

These equations were used to calculate the pK_a 's for tetrahedral intermediates found in Table IV.

The thermochemical quantities used in this work,

mediates, it should be noted that the question of the correct ρ^* value for amine pK_a 's is a matter of some uncertainty and dispute. Fox and Jencks have recently suggested that a ρ^* of 1.33 is most appropriate: J. P. Fox and W. P. Jencks, *J. Amer. Chem. Soc.*, 96, 1436 (1974) (I thank Professor Jencks for sending me a copy of this manuscript prior to its publication). This value of ρ^* would lead to a difference of somewhat over 1 pK_a unit in the pK_a of the N-protonated tetrahedral intermediates and would correspondingly lower the free energy level of the zwitterion relative to the neutral form. The different ρ^* values are a consequence of the different sets of amines used in the correlations.

(27) Values of σ^* were taken from standard compilations.²⁸ No special interactions seems to be involved for hydroxyl α to an ammonium ion, since eq 4 correctly predicts the pK_a shift observed for converting a methylamine to an hydroxymethylamine.²⁹ Values used in deriving eq 5 to 10 were: X, σ_{X^*} ; H, 0.49;^{28a} OH, 1.34;^{28d} OCH_3 , 1.81;^{28d} $N(CH_3)_2$, 0.62;^{28c} $NH(CH_3)_2^+$, 4.36.^{28b}

(28) (a) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956; (b) M. Charton, *J. Org. Chem.*, 29, 1222 (1964); (c) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 2, 334 (1964); (d) G. B. Barlin and D. D. Perrin, *Quart. Rev., Chem. Soc.*, 20, 75 (1966).

(29) (a) J. Hine, J. C. Craig, Jr., J. F. Underwood II, and F. A. Via, *J. Amer. Chem. Soc.*, 92, 5194 (1970); (b) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, 241, 5864 (1966).

(30) J. Hine and G. F. Koser, *J. Org. Chem.*, 36, 1348 (1971).

(31) S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, 36, 1205 (1971).

(32) C. A. Bunton and R. H. De Wolfe, *J. Org. Chem.*, 30, 1371 (1965).

(33) P. Bonvicini, A. Levi, V. Lucchini, G. Modena, and G. Scorrano, *J. Amer. Chem. Soc.*, 95, 5960 (1973).

Table VI. Equilibrium Constants for Acyl Transfer Reactions^a

Reaction	R = H		R = CH ₃	
	K ^b	ΔG ^c	K ^b	ΔG ^c
RCOOH + HN(CH ₃) ₂ ⇌ RCON(CH ₃) ₂ + H ₂ O	6.4 × 10 ^{8d}	-9.29 ^e	1.8 × 10 ^{4d}	-5.8 ^f
RCOOCH ₃ + HN(CH ₃) ₂ ⇌ RCON(CH ₃) ₂ + HOCH ₃	5.8 × 10 ⁹	-11.29 ^g	9.6 × 10 ⁴	-6.8 ^g
RCOOH + H ₃ N ⁺ (CH ₃) ₂ ⇌ RCON(CH ₃) ₂ + H ₃ O ⁺	1.3 × 10 ⁻⁴	+5.3 ^h	3.6 × 10 ⁻⁷	+8.8 ^h
RCOO ⁻ + HN(CH ₃) ₂ ⇌ RCON(CH ₃) ₂ + HO ⁻	3.5 × 10 ⁻⁴	+4.72 ^h	8.8 × 10 ⁻⁶	+6.9 ^h

^a In aqueous solution at 25°; standard state for water is the pure liquid at unit activity; standard state for solutes is 1 M aqueous solution with an infinitely dilute reference state. ^b Dimensionless unless otherwise noted. ^c kcal mol⁻¹. ^d M⁻¹. ^e Reference 19. ^f See text. ^g Calculated from ΔG_f^o(aq) values in Table II. ^h Calculated from ΔG^o for the neutral molecules and pK_a values from Table IV as well as K_w = 10⁻¹⁴ M².

including those evaluated here, are contained in Table II. Heats of formation, vaporization, and solution of dimethylformamide and dimethylacetamide have been published, so the ΔH_f^o(aq) values needed for the thermochemical calculations were easily obtained. The equilibrium constant for the reaction of dimethylamine with formic acid to form dimethylformamide is known,³⁴ so ΔG_f^o(aq) for dimethylformamide is calculable from other values in the table. The equilibrium constant for formation of dimethylacetamide from dimethylamine and acetic acid was assumed to be the same as for the analogous reaction of propionic acid;³⁵ amide forming reactions are normally insensitive to substituent effects in the acid, but there does appear to be a steric effect on going from dimethylformamide to dimethylamides of higher fatty acids, since the mea-

(34) A. R. Fersht and Y. Requenna, *J. Amer. Chem. Soc.*, **93**, 3499 (1971).

sured value for dimethylpropionamide³⁵ is smaller than that predicted by a linear free energy relationship for primary or secondary amides.³⁴

Heats of vaporization of the dimethylamide dimethyl acetals were calculated from the Wadsö equation;³⁶ standard entropies of the gaseous compounds were estimated from the entropies of the corresponding hydrocarbons using correction factors proposed by Stull, *et al.*^{4b}

In Table VI are listed equilibrium constants for the acyl transfer reactions considered in this work; they were calculated from the thermochemical data in Table II and the pK_a values in Table IV.

Acknowledgment. I thank the National Research Council of Canada for financial support of this work.

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(36) I. Wadsö, *Acta Chem. Scand.*, **20**, 544 (1960).

Pentacyclodecane Chemistry. X. The Synthesis and Acetolysis of *syn*- and *anti*-6-Methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]dec-6-yl *p*-Toluenesulfonate. Further Evidence Concerning Bridging in Secondary 1,3-Bishomocubyl Systems^{1,2}

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Contribution from Chemicals Research, Dow Interdiscipline Group, The Dow Chemical Company, Midland, Michigan 48640. Received July 26, 1973

Abstract: Irradiation of 3-methyl-*endo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-*syn*-3-ol (**14**) in acetone gave 6-methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-*syn*-6-ol (**15**). Peracid oxidation of 6-methylenepentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane (**19**) gave the corresponding isomeric epoxides **20** and **21** which were reduced with lithium aluminum hydride to give a 56:44 mixture of 6-methylpentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-*anti*-6-ol (**22**) and **15**. Acetolysis of the tertiary *syn* and *anti* tosylates **16** and **23** of the alcohols **15** and **22**, respectively, and the acid-catalyzed addition of acetic acid to the olefin **19** at 45° gave the corresponding *syn* and *anti* acetates **17** and **24** in 63:37, 75:25, and 69:31 ratios, respectively. These product distributions indicate that no inherent steric or strain effect, which could account for the high degree of stereospecificity observed in the solvolysis of the corresponding secondary tosylates, is present in the 1,3-bishomocubyl system. The acetolysis rates of **16** and **23** at 34.5° are nearly equal. The addition of methylmagnesium iodide and methyllithium to pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (**18**) gave the alcohols **15** and **22** in 82:18 and 78:22 ratios, respectively. Acid-catalyzed equilibration of **15** and **22** at ~25° gave a 48 ± 4:52 ± 4 ratio, respectively.

Stereochemical,^{1,3} isotopic labeling,^{1,3c} and kinetic^{3a,b} studies are consistent with the postulate that the

(1) Part IX: W. L. Dilling, R. A. Plepys, and R. D. Kroening, *J. Amer. Chem. Soc.*, **94**, 8133 (1972).

(2) A preliminary account of part of this work was reported in part VII: W. L. Dilling and J. A. Alford, *Tetrahedron Lett.*, 761 (1971).

(3) (a) W. L. Dilling and C. E. Reineke, *Tetrahedron Lett.*, 2547

solvolyses of the *syn*-**1** (and **2**) and *anti*-**8** 1,3-bishomocubyl tosylates involve the σ -bridged ions **4** (and **5**) and

(1967); (b) W. L. Dilling, C. E. Reineke, and R. A. Plepys, *J. Org. Chem.*, **34**, 2605 (1969); **37**, 3753 (1972); (c) W. L. Dilling, R. A. Plepys, and R. D. Kroening, *J. Amer. Chem. Soc.*, **91**, 3404 (1969); **92**, 3522 (1970); (d) S. F. Brown, Senior Thesis, Princeton University, 1967.