Mechanistic Basis for Rate Enhancements in the Methanolysis of Aliphatic Esters of Quinine

Matthew T. Epperson, Chad E. Hadden, and Thomas G. Waddell*

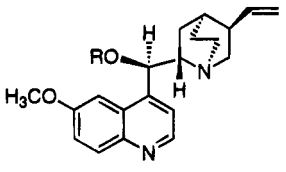
Department of Chemistry, University of Tennessee at Chattanooga, Chattanooga, Tennessee 37403

Received July 17, 1995

Introduction

The famous alkaloid quinine (**1**) has a long history and has played an integral part in the development of organic chemistry and medicine. *Cinchona* extracts were introduced into medical use in Europe in the 17th century when the Countess of Chinchon in 1638 was treated and cured of malaria.[1] Pure quinine was isolated in 1820[2] setting the stage for over 150 years of biological, structural, and synthetic work.[3] Remarkably, quinine has retained a prominent position among organic chemists where, most recently, the properties of this alkaloid as a chiral auxiliary and a ligand for asymmetric catalysis have been investigated.[4]

We have become interested in the chemistry of quinine *esters* for two reasons: (1) quinine-*O*-propanoate (**3**) is active as an antimalarial whereas the corresponding acetate and butanoate esters are inactive;[5] (2) esterification of quinine by an acid chloride proceeds via an intramolecular quinuclidine N to O acyl transfer.[6] The observed biological activity of **3** is most likely due to ester hydrolysis under testing conditions to yield the active quinine.[5] A similar *in vivo* ester hydrolysis has been observed for taxol derivatives.[7] The investigation reported in this paper was undertaken to determine whether **3** shows unusual *inherent* reactivity toward methanolysis (as a model for hydrolysis) and to discover if (and how) the quinuclidine nitrogen participates in the ester cleavage.



1: R = H
2: R = $COCH_3$
3: R = $COCH_2CH_3$
4: R = $COCH_2CH_2CH_3$

Results and Discussion

Table 1 summarizes our kinetic results on the methanolysis in methanol-d_4 of quinine esters **2**–**4** and of simple model esters. The reactions are slow (days–weeks), but the precision of the derived rate constants is high. Moreover, since isoamyl acetate alone in methanol-d_4 is unreactive for *months*, the measured rate constants reflect a clear catalytic effect by the included tertiary nitrogen situated four bonds from the ester C=O. A number of mechanistic conclusions can be gleaned from these results: (1) The relative rates **2** > **3** > **4** reflect, in the expected way, the increasing size of the ester R group.[8] (2) The faster methanolysis of 2-(dimethylamino)ethyl acetate (a model 2-aminoethyl ester), as compared to **2**, is the result of the severely hindered nature of the quinine ester carbonyl. (3) The observed rate enhancements are not due to an inductive effect of the N atom since the Et_3N/isoamyl acetate system also shows a catalytic effect. Although Et_3N/isoamyl acetate is not a precise analog of **2**, this result seems to eliminate a N inductive effect from consideration. (4) *However, the rate enhancement effect of the 2-amino group is demonstrated to be* ***intramolecular***—compare entries 4 and 5.

Table 1. Methanolysis in Methanol-d_4[a]

entry	compd	k_{obsd} ($\times 10^3$ h^{-1})[b]	rel rate
1	**2**	1.47 ± 0.05	6.5
2	**3**	1.02 ± 0.03	4.5
3	**4**	0.227 ± 0.004	1.0
4	2-(dimethylamino)ethyl acetate	36.6 ± 0.1	161
5	Et_3N/isoamyl acetate[c]	0.915 ± 0.04	4.0

[a] 0.04 M solutions in CD_3OD; ambient temperature (21–22 °C). [b] $r > 0.995$. [c] 0.04 M Et_3N.

The intramolecular catalytic effect of the 2-amino group in these systems might originate by two different mechanisms:[9] (a) nucleophilic catalysis, where the acyl group is transferred to the tertiary N in the initial rate-determining step, and (b) general-base catalysis, where the tertiary N removes the methanol proton (OD) with synchronous nucleophilic addition to the ester carbonyl (Figure 1). These two possible mechanisms of intramolecular catalysis can be distinguished in the classical fashion by detecting a CD_3OH/CD_3OD primary isotope effect, since in (b) an O–H(D) bond is broken in the rate-determining step.[10] Indeed, when a 0.04 M solution of **2** was reacted in CD_3OH, a k_{OH}/k_{OD} primary isotope effect of 2.7 was measured. This result confirms mechanism (b), and we conclude that intramolecular general-base catalysis is operating in the accelerated methanolysis of quinine esters (Figure 1).

The ordinary order of reactivity (**2** > **3** > **4**) observed in this methanolysis study implies that the previously reported antimalarial activity of **3** is *not* due to some inherent susceptibility of **3** toward hydrolytic conversion to quinine.[5] Moreover, we have measured the relative rates of pH = 7 *hydrolysis* (see Experimental Section) and have found that acetate **2** is hydrolyzed to quinine 1.6 times faster than the propanoate **3** at 65 °C. We had suggested[5] that the activity of **3** was most likely due to a specific enzyme in the test organism which selectively

(1) Turner, R. B.; Woodward, R. B. In *The Alkaloids*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press, Inc.: New York, 1953; Vol. III, Chapter 16, p 2.
(2) Pelletier; Caventou, E. *Ann. Chim. Phys.* **1820**, *15*, 291, 337.
(3) Verpoorte, R.; Schripsema, J.; van der Leer, T. In *The Alkaloids*; Academic Press: New York, 1988; Vol. 34, Chapter 6, p 332.
(4) Amberg, W.; Bennani, Y. L.; Chadha, R. K.; Crispino, G. A.; Davis, W. D.; Hartung, J.; Jeong, K. S.; Ogino, Y.; Shibata, T.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 844.
(5) Waddell, T. G.; Woods, L. A.; Harrison, W.; Meyer, G. M. *J. Tenn. Acad. Sci.* **1984**, *54*, 48. See also: Harris, G., Ed. *Dictionary of Organic Compounds*, 4th ed.; Oxford University Press: New York, 1965; p 2838.
(6) Waddell, T. G.; Rambalakos, T.; Christie, K. R. *J. Org. Chem.* **1990**, *55*, 4765.
(7) Nicolaou, K. C.; Riemer, C.; Kerr, M. A.; Rideout, D.; Wrasidio, W. *Nature* **1993**, 364, 464.
(8) Gould, E. S. *Mechanism and Structure in Organic Chemistry*; Holt, Rinehart, Winston: New York, 1959; p 318.
(9) Maskill, H. *The Physical Basis of Organic Chemistry*; Oxford University Press: New York, 1985; pp 349–350.
(10) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1053.

0022-3263/95/1960-8113$09.00/0

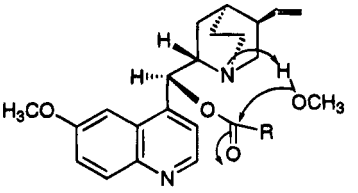


Figure 1. Intramolecular general-base catalysis in the methanolysis of quinine esters.

hydrolyzed **3** to the active quinine. The results reported herein lend further support to this notion.

Experimental Section

General. Esters **2**,[5] **3**,[5] and 2-(dimethylamino)ethyl acetate[11] were prepared by published procedures. Isoamyl acetate, 2-(*N*,*N*-dimethylamino)ethanol, quinine, and all solvents were obtained from Aldrich Chemical Co. and used without further purification. Combustion analysis was performed by Atlantic Microlab, Norcross, GA.

Quinine-*O*-butanoate (4). Pyridine (1.22 mL, 15.1 mmol) was added to a stirred solution of quinine hydrochloride dihydrate (2.0 g, 5.03 mmol) in CH_2Cl_2 (35.0 mL) followed by addition of butanoyl chloride (1.67 mL, 16.0 mmol). The reaction mixture was stirred for 4 h ($CaCl_2$ drying tube). Distilled water (1.4 mL) was added, and the reaction mixture was stirred for an additional 30 min. The resulting solution was then added to aqueous K_2CO_3 (2.0 M, 50 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography on a 2 × 34 cm silica gel column eluting with acetone (1% Et_3N). Combination of intermediate fractions and evaporation afforded a colorless, viscous oil, **4** (1.44 g, 72.7%): TLC (acetone, 1% Et_3N) $R_f = 0.77$; IR (neat) no OH absorption, 3076, 2941, 2874, 1742, 1635, 1593 cm^{-1}; ^1H NMR (CD_3OD) spectrum corresponded closely with the spectrum of quinine and revealed the peaks characteristic of the ester chain δ 0.94 (3H, t), 1.67 (2H, sextet), 2.45 (2H, t). Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 72.79; H, 7.79; N, 6.96.

Methanolysis Kinetic Measurements. Solutions (0.04 M) of each ester in CD_3OD were sealed in an NMR tube, and spectra were obtained periodically. For each spectrum a total of 16 transients were acquired per FID with a delay of 2 s. Kinetic measurements were made at timed intervals corresponding to 2 half-lives for **2**, 1.2 half-lives for **3**, and 0.3 half-lives for **4** (very slow reaction). The quinine acetate methanolysis experiment in CD_3OH was carried out as described above (3 half-lives); the solvent peak at 4.80 ppm was suppressed using direct, on-resonance, low-power irradiation.

Pseudo-first-order rate constants for the methanolysis of the quinine esters were calculated using the integrated areas of the disappearing ester C-9 proton (6.52 ppm) and the appearing quinine C-9 proton (5.59 ppm). The integrals were referenced to the C-8 proton resonating at 5.83 ppm. For isoamyl acetate, the peaks of the methylene protons α to the oxygen and resonating at 3.57 (alcohol) and 4.08 (ester) ppm were integrated and referenced to the methyl signal at 0.90 ppm. The experiment with 2-(dimethylamino)ethyl acetate utilized the integration of the methylene group β to the nitrogen (4.18 ppm, reactant ester) and α to the oxygen (3.66 ppm, product alcohol).

Given the areas of the dynamic proton signals and the initial ester concentration, c_0, the ester concentration at time t could be easily calculated using a simple proportion. The pseudo-first-order rate constants were determined from the slope of the plot of $\ln(c/c_0)$ versus time according to the integrated first-order rate equation.[12] Linear regression yielded the rate constant as the negative of the slope. The standard deviations of the slopes for each ester were calculated according to the method described by Graham.[13]

Hydrolysis Kinetic Measurements. Hydrolysis reaction solutions of **2** and **3** with initial concentrations of 0.010 M were prepared by placing 0.10 mmol of each quinine ester into a 10.0 mL volumetric flask. After the addition of acetonitrile (2.5 mL) the solutions were diluted to the mark with an aqueous KH_2PO_4 buffer (pH = 7.00).[14] The rate measurements utilized a LDC/Milton Roy Constametric III HPLC with UV monitor (254 nm). The column was a 25.0 cm reversed-phase silica-based Adsorbosphere HS C-18 column with a 7-μm particle diameter and an inner diameter of 4.6 mm. The flow rate was maintained at 1.50 mL/min, and the injection volume was 20 μL. The eluent consisted of 76% 0.02 M KH_2PO_4 and 24% acetonitrile. The mobile phase pH was adjusted to 3.00 with 2.0 N HCl. **2**: $k_{obsd}(65\ °C) = 6.11 \times 10^{-4}\ min^{-1}$. **3**: $k_{obsd}(65\ °C) = 3.86 \times 10^{-4}\ min^{-1}$.

Acknowledgment. We thank Michael G. Cotton for his assistance in the ester syntheses. Financial support by NSF Grant No. DUE-9351199 (300 MHz NMR instrument) and by a UTC Provost Student Research Award is gratefully acknowledged.

JO951281+

(11) Jones, L. W.; Major, R. T. *J. Am. Chem. Soc.* **1930**, *52*, 307.

(12) Connors, K. A. *Chemical Kinetics: The Study of Reaction Rates in Solution*; VCH Publishers, Inc.: New York, 1990; pp 18–24.

(13) Graham, R. C. *Data Analysis for the Chemical Sciences: A Guide to Statistical Techniques*; VCH Publishers, Inc.: New York, 1993; pp 236–238.

(14) Weast, R. C., Astle, M. J., Eds. *CRC Handbook of Chemistry and Physics*, 62nd ed.; CRC Press: Boca Raton, FL, 1981; p D-126.