Notes

Intramolecular Catalysis in a Nonhydroxylic Solvent. 2. *n*-Butylaminolysis of Catechol Monoacetate and Methyl (*o*- and *p*-Hydroxyphenyl)acetates[1]

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We have previously reported that the *n*-butylaminolysis of methyl salicylate in dry dioxane is second order in amine and first order in ester and that the *o*-hydroxyl group provides strong intramolecular catalysis. We did not state explicitly that the ratio of rates between methyl salicylate and methyl *p*-hydroxybenzoate is at least one million. These facts served as a basis for description of certain types of enzymatic active sites as "microstereochemically oriented systems" such that exclusion of water from the active site during formation of the enzyme–substrate complexes would maximize orientation effects of the acid and base catalytic groups and of the nucleophilic group, utilize intrinsic acid–base strengths of the catalytic groups, and remove the need for overcoming enthalpy and entropy effects in desolvating all groups concerned in the enzyme-catalyzed reaction itself. We report here our further studies of intramolecularly catalyzed *n*-butylaminolysis reactions in dioxane.

The rate constant found by Chandler for the *n*-butylaminolysis of catechol monoacetate in dry dioxane at 11 °C is 1.1×10^{-2} L mol^{-1} s^{-1}; and a less accurate (due to the rapidity of the reaction) rate constant at 30 °C is 2.5×10^{-2} L mol^{-1} s^{-1}. These results give approximate values for $\Delta H^{\ddagger}$ of 7 kcal/mol and $\Delta S^{\ddagger}$ of −13 eu. For comparative purposes Leach[3] made duplicate runs of the *n*-butylaminolysis of phenylacetate at 10:1 amine/ester and found constants at 11.5 °C of 2.4×10^{-4} L mol^{-1} s^{-1} and at 30 °C, 4.0×10^{-4} L mol^{-1} s^{-1}, which give a $\Delta H^{\ddagger}$ of 4.6 kcal/mol and $\Delta S^{\ddagger}$ of −29 eu as approximate values.

In order to estimate the need for the ether oxygen of dioxane in a proton transfer step, Chandler[2] made duplicate runs with catechol monoacetate in dry benzene and found the reaction to be clearly first order in amine and first order in ester with a rate constant of 2.5×10^{-2} L mol^{-1} s^{-1}.

Hydroquinone monoacetate, free of hydroquinonone and hydroquinone diacetate, proved difficult to obtain so only one set of duplicate runs were made for purposes of comparison with the same concentrations as one of the catechol monoacetate runs. The rate constant for hydroquinone monoacetate at 11 °C in dioxane was 6.7×10^{-5} L mol^{-1} s^{-1}, showing a rate enhancement by the *o*-hydroxyl group of 164 times.

Lossin[4] found no method of purification of *n*-butylamine that would stop its decomposition to give ammonia and unknown products. Leach also observed this behavior of *n*-butylamine though neither Kwok,[1] Kim[1] nor Chandler[2] noticed this problem. There was a slight drift in the third-order rate constants calculated within each run due either to this decomposition or to the incursion of another mechanism or to both. We therefore consider the rate constants for the *n*-butylaminolysis of the methyl (*o*- and *p*-hydroxyphenyl)acetates to be somewhat inaccurate. The rate constant found for methyl (*o*-hydroxyphenyl)acetate at 45.6 °C was 7.7×10^{-5} L^2 mol^{-2} s^{-1} and at 85.6 °C the constant was 3.3×10^{-4} L^2 mol^{-2} s^{-1}. The approximate value for $\Delta H^{\ddagger}$ is therefore 8.0 kcal/mol and for $\Delta S^{\ddagger}$ is −52 eu. There was no detectable *n*-butylaminolysis of methyl (*p*-hydroxyphenyl)acetate after 900 h at 93.7 °C, giving a rate factor greater than one million for catalysis by the *o*-hydroxyl group. It was also observed that Dabco (1,4-diazabicyclo[2.2.2]octane) added a new term, first order in Dabco, first order in *n*-butylamine, and first order in ester, to the rate equation.

Lossin[4] found, within experimental error, no catalysis by the *o*-amino group in methyl *o*-aminobenzoate when compared with the para isomer.

Discussion

Lossin[4] found that both methyl salicylate and methyl (*o*-hydroxyphenyl)acetate show intramolecular hydrogen bonding between the hydroxyl groups and the carbonyl oxygens. The mode of catalysis by the *o*-hydroxyl group is probably the same in both cases. It is our viewpoint that the *o*-hydroxyl group ultimately leads to protonation at the carbonyl oxygen. Even though $\Delta S^{\ddagger}$ cannot be determined with accuracy, the relative values for these two compounds, compared with those for catechol monoacetate and phenylacetate, imply a very considerable difference in mechanism and this conclusion is supported by the differences in kinetic order. We do not visualize large, negative $\Delta S^{\ddagger}$ values arising from either the ionic or neutral tetrahedral intermediate as obtained by simple nucleophilic attack nor, since there is hydrogen bonding in both methyl salicylate and methyl (*o*-hyroxyphenyl)acetate, do we visualize simple acid catalysis by the hydroxyl group as leading to a large, negative $\Delta S^{\ddagger}$. We conclude that structures such as those shown here by I, II, and III lie along the respective reaction paths. We realize the possibility of reaction within an aggregate, as with aspirin,[3] but have been unable to detect aggregates except in the case of aspirin. We assume a bimolecular reaction for phenylacetate though Leach's[3] kinetic study did not prove it to be (and even though the $\Delta S^{\ddagger}$ value seems to favor a reaction second order in amine, the second amine acting as a general base).

Certainly a structure such as III allows for catalysis by Dabco, allows a very large, negative $\Delta S^{\ddagger}$, and allows for a modest change for $\Delta S^{\ddagger}$ in a negative direction with methyl (*o*-hydroxyphenyl)acetate as compared to $\Delta S^{\ddagger}$ for methyl salicylate.

Experimental Section

Chemicals. Dioxane was purified as previously described.[1] Carbon tetrachloride was dried over P_2O_5 and distilled. Benzene

(1) Part 1 is Snell, R. L.; Kwok, W.-K.; Kim, Y. *J. Am. Chem. Soc.* **1967**, *89*, 6728.
(2) Taken in part from the M.S. Thesis of Carl D. Chandler, East Tennessee State University, Johnson City, TN, 1967.
(3) Taken in part from the M.S. Thesis of James T. Leach, East Tennessee State University, Johnson City, TN, 1970.
(4) Taken in part from unpublished work done by Richard Lossin in these laboratories.

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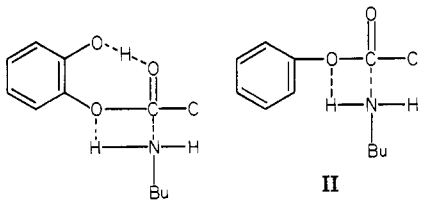
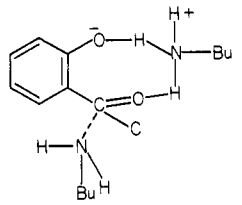


I

II



III

was dried over sodium and distilled. Catechol monoacetate was made by the method of Hansen.[5] Hydroquinone monoacetate was made by treating a basic solution of hydroquinone with acetic anhydride[6] and recrystallization from Skellysolve B. Other chemicals were made and/or purified by standard procedures.

Methods. The experimental procedures previously described[1] were used here. The hydrogen-bonding studies were made with a Perkin-Elmer 521 infrared spectrophotometer.

Third-order rate constants were calculated from the equation

$$k_3t = \frac{1}{(b-a)}\left[\frac{x}{a(a-x)} + \frac{2.303}{(b-a)}\log\frac{b(a-x)}{a(b-x)}\right]$$

which was erroneously printed in ref 1.

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Registry No. Catechol monoacetate, 2848-25-1; methyl *o*-hydroxyphenylacetate, 22446-37-3; methyl *p*-hydroxyphenylacetate, 14199-15-6; *n*-butylamine, 109-73-9.

(5) Hansen, B. *Acta Chem. Scand.* **1963**, *17*, 1375.
(6) Chattaway, F. D. *J. Chem. Soc.* **1931**, 2495.

Tetracyclo[5.4.0.0^{3,10}.0^{4,8}]undecane (2,9-Ethanonoradamantane) and 12-Oxapentacyclo[6.4.0.0^{2,6}.0^{3,11}.0^{4,9}]dodecane Systems

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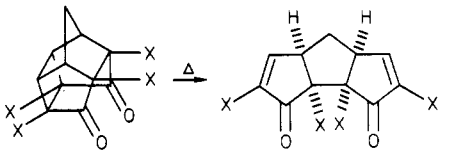
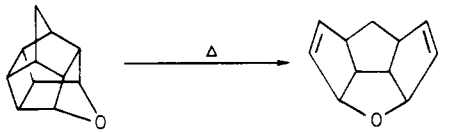
Recently, we reported an efficient and versatile synthetic approach to all-*cis* triquinane bis enones of type **2** and oxatetraquinane of type **4** via the thermal [2 + 2] cycloreversion of pentacyclic undecanedione **1** and the hexacyclic caged ether **3**, respectively.[1] Herein, we describe facile transskeletal cyclization reactions of **2** and **4**, which paves the way for gainful entry into the interesting polycyclic system **5** and **6** mentioned in the title.[2-4] The

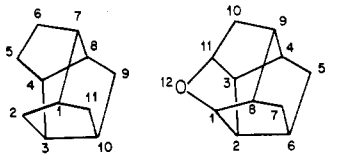


1a, X = H
b, X = Cl

2a, X = H
b, X = Cl



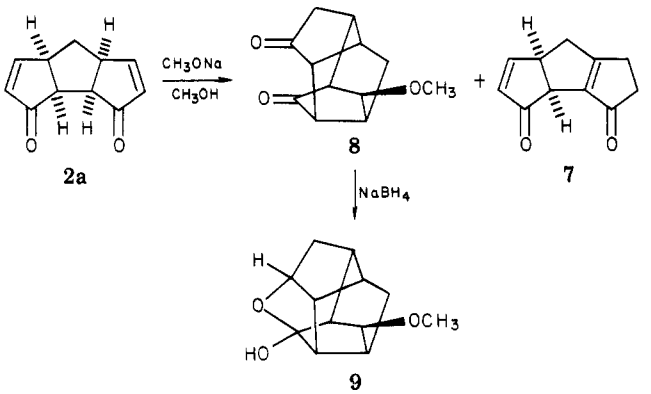
3 **4**



5 **6**

structural similaries between **5** and **6** is quite apparent, and the latter is derived simply through the insertion of an oxygen bridge between the two spatially proximate carbon atoms C_2 and C_5 of **5**. There is considerable interest in these and related ring systems, and they are in fact scarcely accessible.[2-4]

Exposure of **2a** to excess sodium methoxide in methanol furnished a 4:3 mixture of two crystalline products. The minor product was readily recognized as the isomerized bis enone **7** with relocated double bond.[1b] The major



2a **8** **7**

9

product, mp 148-149 °C, was analyzed for $C_{12}H_{14}O_3$ and indicated incorporation of methanol into the product. Its ^{1}H NMR spectrum (δ 3.29, 3 H, s) confirmed this surmise and showed the absence of any olefinic proton resonances. The only other clearly discernible resonance in the ^{1}H NMR spectrum was the presence of a singlet at δ 3.52 due to the proton attached to the carbon bearing the methoxy group. This was corroborated by the ^{13}C NMR spectrum, which exhibited resonances at δ 83. (d) due to the methoxy-bearing carbon and at δ 55.5 (q) due to the methoxy carbon. The absence of any olefinic carbon resonances established the tetracyclic nature of the product. The IR spectrum (1750 cm^{-1}, br) and ^{13}C NMR resonances at δ 214.5 (s) and 211.4 (s) showed the remaining two oxygen

(1) (a) Mehta, G.; Reddy, A. V.; Srikrishna, A. *Tetrahedron Lett.* **1979**, 4863. (b) Mehta, G.; Srikrishna, A.; Reddy, A. V.; Nair, M. S. *Tetrahedron* **1981**, *37*, 4543.

(2) Only one preparatively useful, multistep approach to the tetracyclo[5.4.0.0^{3,10}.0^{4,8}]undecane (2,9-ethanonoradamantane) system has been reported in literature from *exo*-2-noradamantanol.[3] The pentacyclic ether **6** to our knowledge remains unknown. However, synthesis of several oxadiamantanes related to **6** have been reported recently.[4]

(3) Godleski, S. A.; Schleyer, P. v. R.; Osawa, E.; Inamoto, Y.; Fujikura, Y. *J. Org. Chem.* **1976**, *41*, 2596.

(4) Ammann, W.; Jaggi, F.; Ganter, C. *Helv. Chim. Acta* **1980**, *63*, 2019. Doecke, C. W.; Garratt, P. J. *Tetrahedron Lett.* **1981**, *22*, 1051.

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