The racemic aldehyde component used in our kinetically controlled enzymatic synthesis was obtained as shown in Scheme II. Glycidaldehyde diethyl acetal (2)[12] was treated with adenine in the presence of cesium carbonate as a base to generate 3-adenyl-2-hydroxypropanal diethyl acetal (3) in 54% yield. The protected aldehyde was hydrolyzed to form the free aldehyde 4 in situ. DHAP[13] was added, and the solution was neutralized to pH 7. The FDP aldolase from rabbit muscle was then added, and the solution was stirred slowly at room temperature. After the reaction was complete, the phosphate moiety was cleaved with acid phosphatase in situ to afford 6-adenyl-6-deoxy-D-fructose (5) in 20% yield.[14] In this representative reaction, 4 equiv of aldehyde were used to obtain the kinetically preferred product 5. The minor product 6-adenyl-6-deoxy-L-sorbose (6) was obtained in <10% of the reaction mixture. In a separate synthesis of 6, enantiomerically pure (S)-3 (97% ee)[15] was prepared from (S)-2[16] and used as a substrate for the enzymatic reaction (Scheme III, 33% yield). Compound (S)-4 was further reduced with sodium borohydride to (S)-3-adenyl-2-hydroxy-propanol (7),[17] an analog of the biologically active compound 9-(3,4-dihydroxybutyl)-guanine.[18]

In summary, this paper illustrates that nucleoside analogs can be prepared effectively based on enzymatic aldol reactions. With the increasing availability of different aldolases, this enzymatic stragegy should provide a new entry to a variety of novel nucleosides.

Supplementary Material Available: Experimental procedures (3, 5, 6, and 7) and ^{1}H NMR spectra (5, 6, and 7) (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(14) Compounds 5 and 6 were purified with Bio-gel P-2 column. Compound 5: $[\alpha]^{23}_D$ = +24.50 (c = 1, H_2O); ^{1}H-NMR (D_2O) δ 3.31–3.38 (2 H, m), 3.84–3.96 (3 H, m), 4.27 (1 H, dd, J = 15, 6 Hz), 4.31 (1 H, dd, J = 15, 4 Hz), 7.94 (1 H, s), 7.99 (1 H, s) ppm; ^{13}C-NMR (D_2O) δ 46.47, 63.17, 75.73, 76.20, 78.90, 102.72, 119.5, 143.89, 149.72, 153.1, 156.148 ppm; HRMS (M+Na$^+$) calcd 320.0971, found 320.0971. Compound 6: $[\alpha]^{23}_D$ = −28 (c = 1, H_2O); ^{1}H-NMR (D_2O) δ 3.45 (1 H, d, J = 12 Hz), 3.50 (1 H, d, J = 12 Hz), 4.05 (1 H, dd, J = 14.5, 9 Hz), 4.13 (1 H, d, J = 6 Hz), 4.28 (1 H, dd, J = 14.5, 3 Hz), 4.38–4.44 (2 H, m), 7.91 (1 H, s), 7.94 (1 H, s) ppm; ^{13}C-NMR (D_2O) δ 45.37, 63.17, 75.37 (2×C), 76.87, 103.02, 118.61, 143.27, 149.35, 152.67, 155.75 ppm; HRMS (M + H$^+$) calcd 298.1151, found 298.1157.

(15) The enantiomeric excess of (S)-3 was determined to be greater than 97% ee after converted to the corresponding acetate by ^{1}H-NMR in the presence of Eu (hfc)$_3$. The relative intensities of the acetoxy group at 3.04 and 2.85 were used for ee determination.

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(17) Compound 7: $[\alpha]^{23}_D$ = −24 (c = 0.8, H_2O); ^{1}H-NMR (D_2O) δ 3.48 (1 H, dd, J = 12, 6 Hz), 3.59 (1 H, dd, J = 12, 4.5 Hz), 3.96–3.98 (1 H, m), 4.00 (1 H, dd, J = 14, 8.5 Hz), 4.14 (1 H, dd J = 14, 3 Hz), 7.83 (1 H, s), 7.87 (1 H, s); ^{13}C-NMR (D_2O) δ 47.0, 49.6, 63.6, 70.4, 118.5, 143.3, 149.1, 152.7, 155.6 ppm; HRMS (M + H$^+$) calcd 210.0991, found 210.0993.

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Kinetic Evidence for the Solvent Intervention in the Solvolysis of 2-Aryl-2-propyl *p*-Nitrobenzoates. Electronic and Steric Effects

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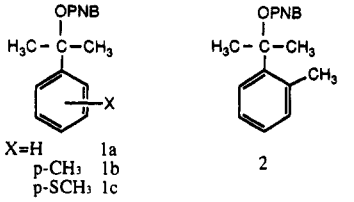
Received June 8, 1992

Summary: Kinetic observation indicates significant nucleophilic solvent intervention at the cationic transition state in the solvolysis of 2-phenyl-2-propyl *p*-nitrobenzoate (1a).

The solvolysis of 2-aryl-2-propyl (*tert*-cumyl) derivatives has long been considered to proceed via a limiting S_N1 mechanism, and from which σ^+ constants are defined.[1] Recently, the absence of nucleophilic assistance by solvent or by azide ion to the reaction of some *tert*-cumyl derivatives was reaffirmed.[2] On the other hand, in our recent solvolytic studies for establishing new Y_{BnX} scales[3-5] and for correlating reactivities with the Grunwald–Winstein equation (1),[6] we observed the depression of log *k*s measured in ethanol-trifluoroethanol solvent systems for several *tert*-cumyl substrates, such as 2-phenyl-2-propyl *p*-nitrobenzoate (1a).[5] Certain kinds of solvent assistance were considered to be involved.[4,5] Now we would like to report kinetic evidence for significant accelerations by nucleophilic solvents in the solvolysis of 2-aryl-2-propyl *p*-nitrobenzoates (1) based on the influence of electronic and steric effects of solvolytic reactivities.

$$\log (k/k_0) = mY \qquad (1)$$



2-Phenyl-, 2-(4′-methylphenyl)-, 2-[4′-(methylthio)-phenyl]-, and 2-(2′-methylphenyl)-2-propyl *p*-nitrobenzoate (1a–1c and 2, respectively) were solvolyzed in a variety of solvents, and their reactivities were monitored conductimetrically. The pertinent rate constants are listed in Table I. Since it is generally accepted that different Y_X scales should be used in the correlation analysis for substrates containing the specific leaving group X,[7] and we have

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Table I. Pertinent Solvolytic Rate Constants for *p*-Nitrobenzoates 1–2

	k, s^{-1} [b]				k_{rel}	
solvent[a]	1a[c]	1b	1c	2[d]	2/1a	1b/1a
100E	1.73×10^{-8}	7.23×10^{-7} [d]	1.05×10^{-5}			41.8
90E	1.53×10^{-7}	5.09×10^{-6}		1.18×10^{-7}	0.77	33.3
80E	6.38×10^{-7}	1.68×10^{-5}	1.45×10^{-4}	4.02×10^{-7}	0.63	26.3
70E	1.72×10^{-6}			8.66×10^{-7}	0.50	
100M	1.92×10^{-7}	5.18×10^{-6}	7.11×10^{-5}	1.68×10^{-7}	0.88	27.0
90M	7.14×10^{-7}	2.11×10^{-5}	2.42×10^{-4}	4.27×10^{-7}	0.60	29.6
80M	2.63×10^{-6}	5.46×10^{-5}	5.99×10^{-4}	1.01×10^{-6}	0.38	20.8
80A	7.20×10^{-8} [e]	1.54×10^{-6} [f]	2.52×10^{-5}	6.58×10^{-8}	0.91	21.4
70A	3.01×10^{-7}	6.58×10^{-6}	8.74×10^{-5}	2.02×10^{-7}	0.67	21.9
60A	1.22×10^{-6}	3.10×10^{-5}	3.18×10^{-4}	5.49×10^{-7}	0.45	25.4
100T	1.27×10^{-5}	1.01×10^{-3}	1.01×10^{-2}	2.17×10^{-5} [b]	1.71	79.5
97T*w*	1.55×10^{-5} [b]	1.07×10^{-3}	8.88×10^{-3}	2.24×10^{-5} [b]	1.45	69.0
70T*w*	1.83×10^{-5} [b]	1.18×10^{-3}	8.34×10^{-3}	2.31×10^{-5} [b]	1.26	64.5
50T		1.36×10^{-3}	9.39×10^{-3}			
80T–20E	2.54×10^{-6}	2.03×10^{-4}	2.42×10^{-3}	4.10×10^{-6}	1.61	79.9
40T–60E	1.79×10^{-7}	1.16×10^{-5}	1.52×10^{-4}	2.86×10^{-7}	1.60	64.8

[a] For abbreviation of solvents: A, acetone; E, ethanol; M, methanol; T, 2,2,2-trifluoroethanol. The numbers denote the volume percent of the specific solvent in the solvent mixture, except those with the italic *w* indicate weight percent. The percentage of water is not recorded. [b] At 25 °C and measured in this work unless otherwise mentioned. [c] Reference 5. [d] Calculated from data obtained at other temperatures. [e] Brown, H. C.; Rao, C. G.; Ravindranathan, M. *J. Am. Chem. Soc* **1978**, *100*, 7946. [f] Brown, H. C.; Ravindranathan, M.; Peters, E. N. *J. Org. Chem.* **1977**, *42*, 1073.

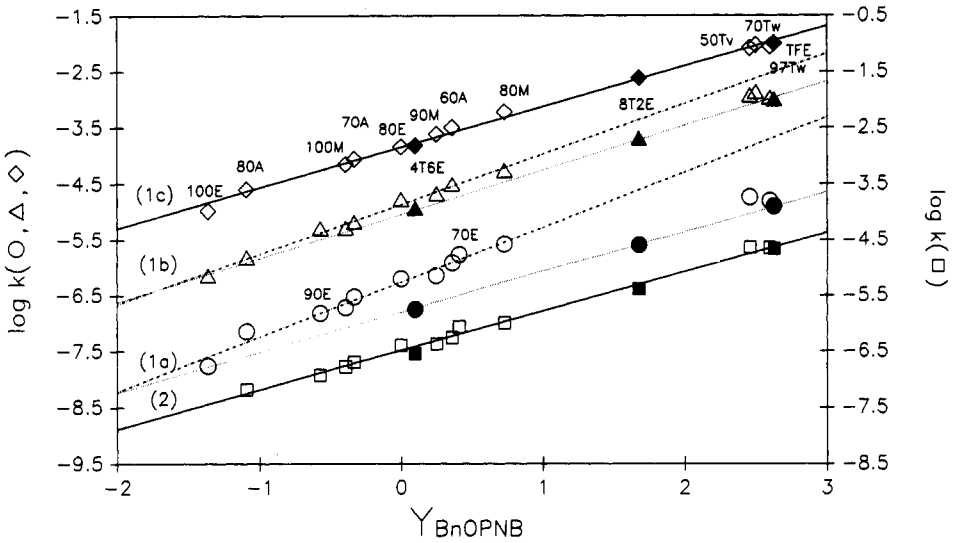

Figure 1. Correlations of logarithms of rate constants for **1a** (○), **1b** (△), **1c** (◇), and **2** (□) against Y_{BnOPNB}. Solid symbols stand for the *k*s measured in TFE and in TFE–EtOH. Lines—refer to those m_{AEM} and m_{TE} that are close, whereas the line –·– refers to log k_{AEM} and the line ··· refers to log k_{TE} in the cases of **1a** and **1b**.

demonstrated the necessity of employing Y_{BnX} for benzylic systems, the correlation analyses were carried out by using log k – Y_{BnOPNB}[5,8] plots. The results are shown in Figure 1.

The rate data in Table I indicate that the *p*-methyl substrate (**1b**) is about 30–50 times more reactive than the ortho analogue **2**, larger than the factor of 7.2[9] for the corresponding chloride. Introducing a *p*-CH_3 group causes a 21–42-fold increment of reactivity (k_{1b}/k_{1a} in Table I) in nucleophilic solvents, which is similar to the value of 26 for the chloride in 90% acetone.[9] In the less nucleophilic aqueous trifluoroethanol (TFE–H_2O) and ethanolic trifluoroethanol (TFE–EtOH), however, this ratio increases to 65–80. More remarkably, the *o*-methyl substrate **2** is *less* reactive than the unsubstituted **1a** in nucleophilic solvents ($k_2/k_{1a} < 1$), contrary to what has been found for *tert*-cumyl chloride,[9] but *more* reactive than **1a** in TFE–H_2O and TFE–EtOH ($k_2/k_{1a} > 1$). Moreover, a significant deviation from linear correlations was realized for **1a** (Figure 1, $R = 0.957$) but not for **2** ($R = 0.996$). If the log k – Y_{BnOPNB} plots were made only with nucleophilic solvents (k_{AEM}), essentially no deviation would be found in either case. Obvious splitting of the line defined by log *k*s measured in the isodielectric TFE–EtOH (k_{TE})[10] from that defined by log k_{AEM}s, i.e., $\Delta m > 0.1$, would be observed

Table II. Pertinent Data for Correlation Analyses

	m Value		
substrate	*m*(all)[a]	*m*(AEM)[b]	*m*(TE)
1a	0.657 ($R = 0.957$, $n = 15$)	0.983 ($R = 0.987$, $n = 10$)	0.719 ($R = 0.999$, $n = 4$)
1b	0.784 ($R = 0.996$, $n = 15$)	0.896 ($R = 0.995$, $n = 9$)	0.789 ($R = 0.999$, $n = 4$)
1c	0.722 ($R = 0.998$, $n = 14$)	0.808 ($R = 0.997$, $n = 8$)	0.752 ($R = 0.999$, $n = 4$)
2	0.704 ($R = 0.996$, $n = 14$)	0.691 ($R = 0.986$, $n = 9$)	0.742 ($R = 0.999$, $n = 3$)

[a] All solvents. [b] Aqueous acetone, ethanol, and methanol.

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for **1a** and **1b**. The m values are listed in Table II for comparison.

Depression of the data points corresponding to log k's measured in low nucleophilic solvents from the linear relationship (eq 1) defined by those measured in relatively high nucleophilic solvents, such as the cases of *tert*-butyl bromide[11] and 1,1,1-trifluoro-2-methyl-2-propyl triflates,[12] has been attributed to the assistance by the latter solvents. Although different interpretation had been given to the *tert*-butyl system,[13] a more recent rebuttal[14] confirmed the validity of the original proposal.[11] Therefore, the deviation showed in Figure 1 could be explained similarly. In the solvolysis of **1a** a significant acceleration by nucleophilic solvents is revealed in association with the large difference between m_{TE} and m_{AEM} (0.25).[15] This acceleration effect is so large that the steric prohibition of solvent intervention by an *o*-CH_3 group makes **2** to be less reactive than **1a** in nucleophilic solvents. Furthermore, the observed excellent linear correlation for log ks in all solvents (R = 0.996) and the small difference between various m values (0.05 or less) also suggest the absence of significant nucleophilic solvent acceleration.

The steric ortho effect might be of different origin.[16] In the solvolysis of **2** the steric hindrance to the π resonance in the cationic transition state is likely to be relatively unimportant, for an *o*-methyl group in the corresponding chlorides has been found to give a 3.6-fold increment of the solvolytic reactivity.[9] It is likely due to the steric hindrance to the solvation of cationic transition states. The solvation, and probably the solvent acceleration, will be less significant for the substrate having a better leaving group.

The influence of an electron-releasing substituent can be shown by comparing the different degree of deviation in log k – Y plots. Excellent linear relationships have been observed for both the *p*-CH_3 derivative **1b** and the *p*-SCH_3 derivative **1c** (R > 0.996). However, the small splitting between m_{TE} and m_{AEM} observed for **1b** (0.11)[15] and a negligible one for **1c** (0.05) suggest a small acceleration is still present in the former but is essentially absent in the latter. Obviously the more stable the cationic transition state involved, the less acceleration due to nucleophilic solvent would be necessary.

Although the application of the multiple regression analysis (eq 2)[17] of log k_{1a} against Y_{BnOPNB}[5] and N_{OTS}[7] values gave an improved correlation (m = 0.857, l = 0.298 and R = 0.976), no significant azide effect[18] could be detected in this study. It is in line with the recent conclusion

$$\log (k/k_o) = mY + lN \qquad (2)$$

by Richard and co-workers[2] and thus suggests that the nature of the solvent acceleration should be different from the classical S_N2 type interaction. From the recent recognition of the importance of the solvation effect on delocalized cationic transition states for benzylic substrates,[3-5,19,20] the acceleration is likely the result of an enhanced solvation by nucleophilic solvents. In the acidic and electrophilic TFE,[21] a cation will be poorly solvated,[22] and therefore the depression of ks is resulted. For the more reactive substrates, the solvolytic transition states will be of less cationic character. In addition, steric hindrance to the adjacent reaction site will diminish the importance of solvation (vide supra). In either case smaller extent of rate enhancement by nucleophilic solvents would be expected and indeed was observed.

Consequently, from the present kinetic study the intervention of nucleophilic solvents to enhance the solvolytic reactivity for *tert*-cumyl *p*-nitrobenzoates can be proved. The electronic effect of substituents on the aryl ring[1] cannot be the sole origin responsible for the change of solvolytic reactivities. More work to find out if this is a generalization to other substrates is in progress.

Acknowledgment. We are grateful to the National Science Council for financial support and to Drs. T. W. Bentley and J. P. Richard for helpful comments.

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Synthesis of the Polyol Chain of (–)-Roxaticin

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Received May 26, 1992

Summary: Tetraacetonide **19**, which incorporates the 10 stereogenic centers of (–)-roxaticin, was chosen as a test case to develop a convergent synthesis of alternating polyol chains. This synthesis uses a stepwise alkylation of dibromide **16** followed by a stereoselective reductive decyanation in a three-fold convergent strategy.

Complex polyol chains are important structural components of the polyene macrolide antibiotics such as the antifungal agent amphotericin B.[2] Several of these

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