An Unexpectedly Small α-Effect in Nucleophilic Attack at sp-Hybridized Carbon: Michael-Type Additions of Primary Amines to 3-Butyn-2-one

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The term α-effect was given to the abnormally enhanced reactivity shown by nucleophiles having one or more nonbonding electron pairs at the position α to the nucleophilic center.[1] Numerous studies have been performed to investigate the cause of the α-effect,[2] and some suggested origins of the α-effect are as follows: (a) ground-state destabilization of the nucleophile,[3] (b) stabilization of the transition state,[4] (c) enhanced thermodynamic stability of reaction products,[5] and (d) differential solvent effect.[6,7]

The magnitude of the α-effect ($k^{\alpha-Nu}/k^{normal-Nu}$) has been reported to be influenced by many factors, e.g., solvent,[6,7] β_{nuc} value,[8] basicity of nucleophiles,[9] and hybridization type of the electrophilic center.[10−13] Among them, the hybridization type of electrophilic centers has been suggested to dominate the magnitude of the α-effect; i.e., the magnitude of the α-effect increases significantly with increasing "s" character of the carbon atom at the reaction center.[10−13] A small or no α-effect has been observed for reactions at sp^3-hybridized carbons.[10,11] Buncel showed that HOO^- and NH_2-NH_2 are 5.7−11 and 3.0−5.2 times more reactive than the corresponding normal nucleophiles HO^- and glycylglycine, respectively, in the methyl group transfer reaction with methyl sulfates.[10] Recently, Fountain also observed small α-effects ($k^{\alpha-Nu}/k^{normal-Nu} = 2-11$) for the reaction at an sp^3-hybridized carbon atom with hydroxamate anions and hydroxylamine.[11] By comparison, the α-effect for reactions at sp^2-hybridized carbons was generally reported to be ~10^2, while the largest α-effect was observed in the reaction at an sp-hybridized carbon atom.[12,13] For example, HOO^- is 20000−60000 times more reactive than HO^- toward the sp-hybridized carbon of benzonitriles in 50% aqueous acetone[12] or in H_2O.[13]

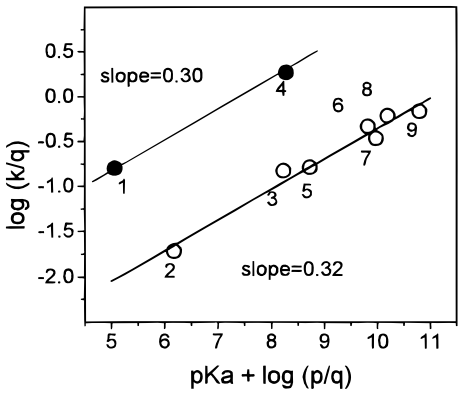

Figure 1. Brønsted-type plots for the addition reactions of primary amines to 3-butyn-2-one in H_2O at 25.0 °C: 1, methoxylamine; 2, (trifluoroethyl)amine; 3, glycine ethyl ester; 4, hydrazine; 5, glycylglycine; 6, benzylamine; 7, ethanolamine; 8, glycine; 9, ethylamine.

Until now, the reaction at the sp-hybridized carbon atom was limited to the reaction at the C≡N group in benzonitriles.[12,13] Reaction at C≡C bonds by α-nucleophiles has never been studied. In this paper, we report the first results for the addition reactions of a series of primary amines including α-effect amines to the activated acetylene, **1**, as shown in the following equation. Our aim was to probe the magnitude of the α-effect with this sp-hybridized electrophile, **1**.

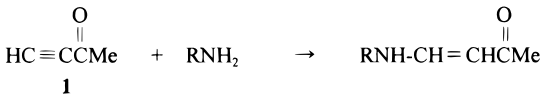

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Figure 1 shows the Brønsted-type plot for the addition reaction of the amines to **1**. As shown, the reactivity of amines increases generally with an increase in their basicity, except for hydrazine and methoxylamine. These two amines are more reactive than the other amines of similar basicity, resulting in positive deviations from the linear Brønsted-type plot. These positive deviations are diagnostic for the α-effect. *However, the magnitude of the* α*-effect in the present system is surprisingly small for the reaction at an sp-hybridized carbon atom, e.g.,* $k^{NH_2NH_2}/k^{glycylglycine} = 11$ *and* $k^{MeONH_2}/k^{CF_3CH_2NH_2} = 8.4$*, α-effects comparable to those of* sp^3 *reaction systems. Clearly, the present result suggests that the* α*-effect is not always large for the reaction at the sp-hybridized carbon atom.*

Bruice and Dixon have demonstrated that the magnitude of the α-effect is strongly dependent on the magnitude of β_{nuc} for a variety of reactions of carboxylic esters with hydrazine and glycylglycine; i.e., the α-effect decreases with decreasing β_{nuc} value.[8a] Similarly, Bernasconi has observed no α-effect for the addition reaction of primary amines including NH_2NH_2 and $MeONH_2$ to Meldrum's acid, systems in which the β_{nuc} value is 0.22.[8b] The β_{nuc} value in the present reaction has been calculated to be 0.32. Therefore, at least in part, the small β_{nuc} value is considered to be responsible for the small α-effect observed in the present system.

It has often been suggested that the thermodynamic α-effect is more important than the kinetic α-effect for

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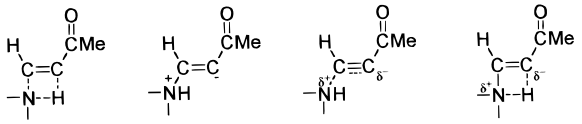
reactions with nitrogen nucleophiles.[8] Morris and Page have shown that the α-effect in hydrazinolysis of benzylpenicillin can be dissected into a 15-fold increase in the rate constant but, importantly, a 350-fold increase in the equilibrium constant for formation of the addition intermediate.[14] Similarly, Jencks found a small α-effect for reactions involving nitrogen nucleophiles when nucleophilic attack is the rate-determining step (RDS) but a large α-effect when nucleophilic attack occurs before the RDS,[8c] indicating that the magnitude of the α-effect is dependent on the RDS. Consequently, it is necessary to investigate the reaction mechanism for the present system.

Addition reactions of amines to activated acetylenes have been reported to produce *E* and *Z* enamines. The *E*/*Z* isomer ratio has been suggested to be influenced by many factors such as solvent, structure of acetylenes and amines, concentration of amines, etc.[15,16] However, in our present study, no detectable *Z* isomer was observed in the ^{1}H NMR spectrum of the reaction mixture. Besides, the plots of k_{obs} vs amine concentration were linear for all the amines studied in the present system, indicating absence of general base catalysis by the amine. Therefore, three different reaction pathways would be suggested, i.e., a one-step concerted mechanism with a transition state (TS) structure similar to TS I or stepwise processes with an intermediate modeled on **2**. The latter mechanism can have two different transition state structures; i.e., TS II represents the transition-state structure in the rate-determining formation of the intermediate **2**, and TS III applies to the rate-determining proton transfer from the intermediate **2** to yield the product.



TS structures I and III are favored by the fact that only the *E* isomer is produced. In these mechanisms, one might expect to see a large primary kinetic isotope effect (KIE), since the N−H bond cleavage is involved in the RDS. However, the rate of reaction of **1** with non-α-effect amines in H_2O was found to be almost identical with the one in D_2O ($k^{H_2O}/k^{D_2O} = 1.00 \pm 0.04$). Therefore, one can suggest that the reaction of **1** with these amines proceeds via TS II but not via either TS I or TS III. On the other hand, the α-effect nucleophiles, NH_2NH_2 and $MeONH_2$, exhibit a primary KIE; i.e., the KIE value (k^{H_2O}/k^{D_2O}) has been calculated to be 2.00 and 2.30 for $MeONH_2$ and NH_2NH_2, respectively. The primary KIE clearly suggests that the N−H bond cleavage occurs at the RDS,[17] and therefore, the reaction of these two α-effect amines with **1** would proceed via either TS I or TS III but not via TS II. However, one cannot differentiate TS I from TS III on the basis of this KIE value alone.

Useful information about reaction mechanisms can be inferred from the magnitude of the β_{nuc} value. The magnitude of β_{nuc} values for various aminolyses has been reported to decrease sharply from 0.8 ± 0.1 to 0.2 ± 0.1 as the RDS changes from a rate-determining breakdown of the addition intermediate to a rate-determining attack of the amine to form the addition intermediate.[18−20] The β_{nuc} value has been calculated to be 0.30 for the reaction of **1** with NH_2NH_2 and $MeONH_2$. Although this value includes the uncertainty inherent in a two point analysis, the magnitude is fairly small as in the corresponding reactions with the non-α-effect amines (Figure 1). If the reaction proceeded via TS III, in which bond formation between the nucleophile and the substrate is fully advanced, one would have expected a significantly large β_{nuc} value. Therefore, the small β_{nuc} value obtained in the present system suggests that the reaction with these α-effect amines proceeds via TS I but not via TS III.

Although the TS structure for the reaction with the α-effect amines appears to be different from the one for the reaction with non-α-effect amines (TS I vs TS II), the attack of amines occurs at the RDS for both systems. As mentioned previously, the α-effect has generally been found to be small for aminolyses in which the attack of amines is rate limiting. Therefore, one might attribute the small α-effect observed in the present reaction system to either the difference in the transition-state structure (TS I vs TS II) or the nature of the RDS (rate-limiting amine attack for both systems).[8c] Alternatively, the small β_{nuc} value may dictate a small α-effect. Clearly, differentiation of these possibilities awaits further study on other acetylenic systems.

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Supporting Information Available: Experimental procedures and kinetic data (Tables 1−10) (6 pages).

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