# Notable Substituent Effects on the Rate Constant of Thermal Denitrogenation of Cyclic Azoalkanes: Strong Evidence for a Stepwise Denitrogenation Mechanism

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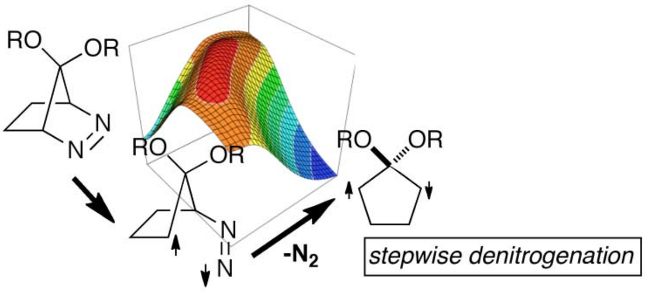
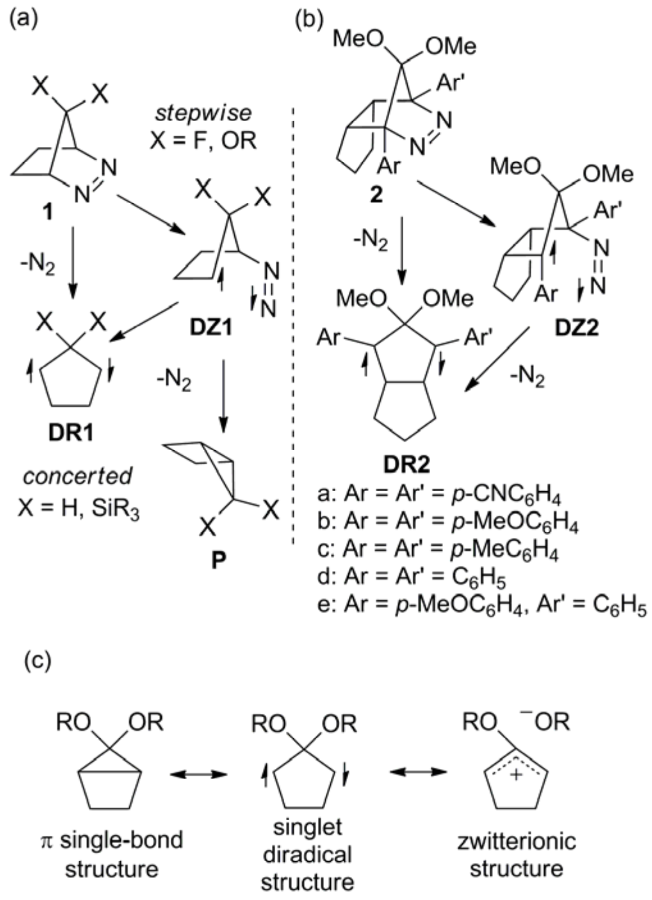


A kinetic analysis of the denitrogenation of 7,7-dimethoxy-1,4-diaryl-2,3-diazabicyclo[2.2.1]hept-2-ene derivatives with a variety of aryl groups was performed in the present study. The observed substituent effect was highly correlated with the radical-stabilizing parameters of benzylic-type radicals. Thus, stepwise denitrogenation is a mechanism for the thermal denitrogenation reaction.

**Abstract.** The thermal denitrogenation rates (*k*) of a series of 7,7-dimethoxy-1,4-diaryl-2,3-diazabicyclo[2.2.1]hept-2-ene derivatives **2** with a variety of aryl groups (*p*-$CNC_6H_4$, $C_6H_5$, *p*-$MeC_6H_4$, *p*-$MeOC_6H_4$) were determined to investigate the denitrogenation mechanism. A linear correlation ($r = 0.988$) between the relative rate-constant ($\log k_{rel}$) of the denitrogenation reaction and Arnold's $\sigma^{\bullet}_{\alpha}$ parameter for benzylic-type radical-stabilization was observed. However, the relative rate-constant was not correlated with the substituent effect on the lifetime of the resulting singlet diradicals **DR2**. These results indicate that the rate-determining step of denitrogenation of 7,7-dimethoxy-2,3-diazabicyclo[2.2.1]hept-2-ene derivatives involves stepwise C–N bond cleavage.

Azo compounds with the functional group (–N=N–) are widely used in chemistry. In particular, these compounds have attracted considerable attention for their denitrogenation reactivity, which is a synthetically useful radical chain reaction.[1] Moreover, the photochemically or thermally induced isomerization of these compounds results in a change in their color.[2] To fully understand the general characteristics of azo-compounds and to capitalize on their properties in various applications, the thermal and photochemical reactivities of azoalkanes should be thoroughly investigated. Current topics in this area of chemistry are the mechanism of denitrogenation of cyclic azoalkanes, such as 2,3-diazabicyclo[2.2.1]hept-2-ene (DBH) derivatives **1**, and the stereoselective formation of bicyclo[2.1.0]pentane derivatives **P** (Scheme 1).[3] In the last decade, Carpenter and coworkers found that for *thermal* denitrogenation of the parent DBH (**1a**, X = H, Scheme 1), simultaneous cleavage of two C–N bonds (concerted denitrogenation) was the energetically favored process, resulting in the double-inversion product bicyclo[2.1.0]pentane **Pa** (X = H).[4] Adam and coworkers reported that the *photochemical* denitrogenation reaction of



**Scheme 1.** (a) (b) Mechanisms for the denitrogenation of the cyclic azoalkanes and (c) the character of the singlet state of 2,2-dialkoxycyclopentane-1,3-diyls.

DBH derivatives, which also produces the double-inversion compound **Pa**, might reasonably proceed via stepwise C–N bond cleavage.[5] The stepwise C–N bond cleavage was proposed to be a mechanism for the denitrogenation of acyclic azo compounds.[6]

Recently, we used a theoretical analysis to investigate the mechanism of thermal denitrogenation. We found that whether thermal denitrogenation of the DBH derivatives **1** proceeds via the *concerted* mechanism versus the *stepwise* mechanism can be controlled by simply changing the substituents X at the methano-bridge carbon C(7) of the DBH derivatives (Scheme 1).[7] The stepwise mechanism was favored by electron-accepting C–X bonds (X = F, OR), while the concerted mechanism predominates with electron-donating C–X bonds (X = H, $SiR_3$). The notable substituent effect was attributed to the substituent-X-dependent change in the lowest electronic configuration of the singlet state of the resulting diradicals **DR1**.[6a] Concerted denitrogenation is the favored mechanism of the parent DBH (**1a**, X = H), which is consistent with the results of Carpenter and coworkers.[4c] It has been quite difficult to prove experimentally that alkoxy-groups (X = OR) notably favor the stepwise denitrogenation mechanism, because the lifetime of diazenyl diradicals **DZ1** is expected to be quite short. In a theoretical study, the activation energy of the C–N bond cleavage was calculated to be just ca. 3 kcal/mol.[8]

To quantify the substituent effect of alkoxy groups (X = OR) on the thermal denitrogenation mechanism (Scheme 1b), it is useful to probe the aryl-substituent effect on the thermal denitrogenation of azoalkanes **2** with a variety of aryl-substituents, Ar and Ar’ ($p$-$CNC_6H_4$, $C_6H_5$, $p$-$MeC_6H_4$, $p$-$MeOC_6H_4$). When the concerted denitrogenation mechanism predominates, the substituent Ar,Ar’ effect on the denitrogenation rate constant ($k$) should be correlated with the substituent effect on the lifetime, i.e., the thermodynamic stability of the resulting singlet diradicals **DR2**.[9] For the stepwise-denitrogenation mechanism via the diazenyl diradical **DZ2**, the *para*-substituent effect of the aryl-group on the denitrogenation rate-constant should be correlated with the radical-stabilizing parameters of benzylic-type radicals, such as Arnold’s $\sigma^{\bullet}_{\alpha}$[10] and Creary’s $\sigma^{\bullet}_{C}$ parameter.[11]

In our previous study, the *para*-substituent effect on the lifetime of singlet diradicals **DR2** was not correlated with the radical-stabilizing parameters (Table 1), because the singlet state of the 2,2-dialkoxycyclopentane-1,3-diyls possesses a zwitterionic and a π single-bonding nature (Scheme 1c).[6],[12]

The thermolysis of azoalkanes **2a-e** (0.03 M) was carried out in $d_6$-benzene in a sealed tube under vacuum at 420 ± 0.5 K. The absolute and relative rate constants $k$ and $k_{\mathrm{rel}}$ of the thermal denitrogenation of **2a-e** were easily measured by $^1$H NMR spectroscopy of the thermolysate in $d_6$-benzene (Figure 1, Table 1). As shown in Figure 1, the thermolysis followed clean first-order kinetics. The data below 30% conversion were used for the kinetic analyses. Also listed in Table 1 are the Arnold's $\sigma^\bullet_\alpha$, the Creary's $\sigma^\bullet_C$ parameters, and the lifetime of the singlet diradical **DR2**.

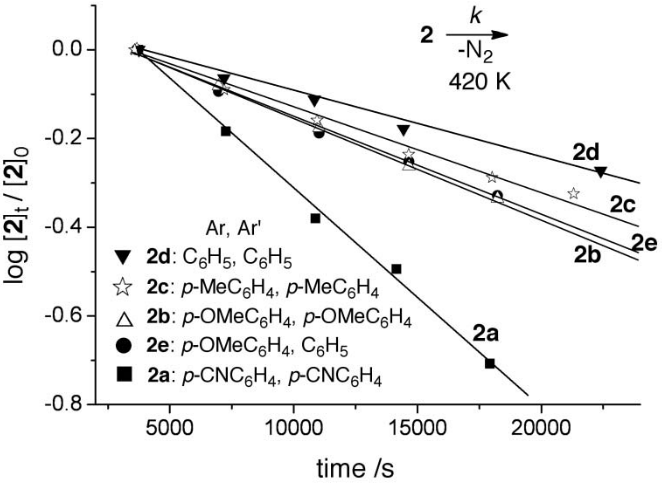


**Fig. 1.** Decay traces of [**2**] for the thermal denitrogenation of **2** at 420 K.

The relative rate constants ($k_{\mathrm{rel}}$) in Table 1 clearly show that the *para*-substituent on the phenyl ring has a significant effect on the thermolysis rates ($k$) of **2**. The magnitude of the substituent effect on the denitrogenation rate ($k$) was as follows: **2a** (Ar = Ar' = $p$-$CNC_6H_4$, $k_{rel}$ = 3.48, entry 1) > **2b** (Ar = Ar' = $p$-$MeOC_6H_4$, $k_{rel}$ = 1.62, entry 2) ~ **2e** (Ar = $p$-$MeOC_6H_4$, Ar' = $C_6H_5$, $k_{rel}$ = 1.59, entry 5) > **2c** (Ar = Ar' = $p$-$MeC_6H_4$, $k_{rel}$ = 1.35, entry 3) > **2d** (Ar = Ar' = $C_6H_5$, $k_{rel}$ = 1.00, entry 4). Thus, the denitrogenation reaction was significantly accelerated by the *para*-cyanophenyl substituent (**2a**: Ar = Ar' = $p$-$CNC_6H_4$), although the lifetime of **DR2a** (625 ns) was significantly shorter than that of the *para*-methoxyphenyl-substituted diradical **DR2b** (1050 ns), as shown in entries 1 and 2.[7a]

**Table 1. Rate constants for the thermal denitrogenation of 2, Arnold's parameter ($\sigma^\bullet_\alpha$), Creary's parameter ($\sigma^\bullet_C$), and the lifetime of the singlet diradicals DR2**

| Entry | **2** | Ar | Ar' | $k$ x $10^5$ /$s^{-1}$ [A] | $k_{rel}$[B] | $\sigma^\bullet_\alpha$[C] for Ar | $\sigma^\bullet_C$[D] for Ar | $\tau_{293}$[E] of **DR2** /ns |
|---|---|---|---|---|---|---|---|---|
| 1 | **2a** | $p$-$CNC_6H_4$ | $p$-$CNC_6H_4$ | 5.06 | 3.48 | 0.040 | 0.47 | 625 |
| 2 | **2b** | $p$-$MeOC_6H_4$ | $p$-$MeOC_6H_4$ | 2.36 | 1.62 | 0.018 | 0.27 | 1050 |
| 3 | **2c** | $p$-$MeC_6H_4$ | $p$-$MeC_6H_4$ | 1.96 | 1.35 | 0.015 | 0.16 | 460 |
| 4 | **2d** | $C_6H_5$ | $C_6H_5$ | 1.46 | 1.00 | 0.000 | 0.00 | 320 |
| 5 | **2e** | $p$-$MeOC_6H_4$ | $C_6H_5$ | 2.31 | 1.59 | 0.015 | 0.27 | 600 |

[A] Thermolysis temperature = 420 K, error ~5% [B] $k_{rel} = k / k_{C6H5}$, error ~5%. [C] Arnold's parameter of the aryl group (Ar). [D] Creary's parameter of the aryl group (Ar). [E] Lifetime of the singlet diradical **DR2** at 293 K.

It should be noted that the relative rate constant ($k_{rel}$ = 1.62) of the symmetrically substituted azoalkane **2b** (entry 2) was nearly identical ($k_{rel}$ = 1.59) to that of the asymmetrically substituted **2e** (entry 5), although the lifetime of **DR2b** (1050 ns, entry 2) was marginally different from that of **DR2e** (600 ns, entry 6).[6a] To clarify the substituent effect on the denitrogenation rate constant of **2**, the values of log $k_{\mathrm{rel}}$ were plotted against Arnold's parameter $\sigma^{\bullet}_{\alpha}$ (Fig. 2a) and Creary's parameter $\sigma^{\bullet}_{\mathrm{C}}$ (Fig. 2b).

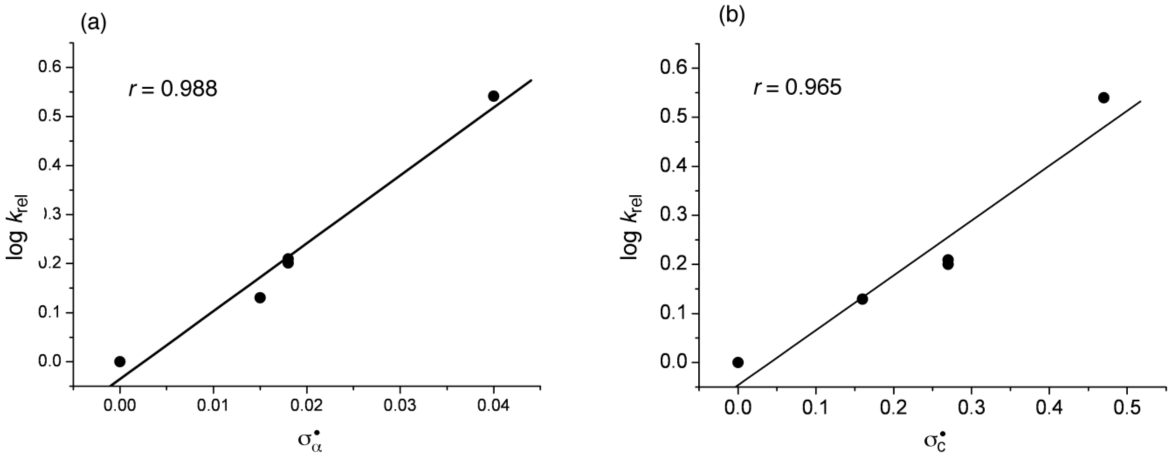


**Fig. 2.** Logarithmic plot of the relative denitrogenation rate ($k_{\mathrm{rel}}$) for azoalkane **2** *versus* (a) Arnold's parameter $\sigma^{\bullet}_{\alpha}$ and (b) Creary's $\sigma^{\bullet}_{\mathrm{C}}$ parameter, see Table 1.

As clearly shown in Fig. 2, both radical-stabilizing parameters were highly correlated with the logarithm of the relative denitrogenation rate ($r = 0.988$ and $r = 0.965$, for the parameters of Arnold and Creary, respectively). On the other hand, $k_{\mathrm{rel}}$ was weakly correlated with the lifetime $\tau_{293}$ of **DR2** (Table 1). These results strongly suggest that the denitrogenation of **2** occurs by stepwise C–N bond cleavage via **DZ2** (Scheme 1).

In summary, the results of the present study, which investigated the thermal denitrogenation of compound **2**, showed that the substituent effect on the denitrogenation rate ($k_{\mathrm{rel}}$) was not correlated with the lifetime of the resulting singlet diradical **DR2**, but was highly correlated with the radical-stabilizing parameters $\sigma^{\bullet}_{\alpha}$ and $\sigma^{\bullet}_{\mathrm{C}}$. These strong correlations provide the first strong experimental evidence that thermal denitrogenation of

7,7-dialkoxy-2,3-diazabicyclo[2.2.1]hept-2-ene derivatives proceeds via stepwise C–N bond cleavage. This remarkable finding should stimulate future theoretical and experimental investigations of azo-chemistry, which is both mechanistically and synthetically fascinating.

## Experimental Section

**Thermolysis of 2.** A sample of ca. 70 mg (0.21 mmol) of **2**[9] was dissolved in 7 mL of $d_6$-benzene.[13] The solution was divided into seven-samples; thus, each sample contained 1 mL of the solution. Each sample in a NMR-tube was degassed by three freeze-and-thaw cycles, and was sealed under vacuum, i.e., at ~0.01 mmHg. The thermolysis was performed at 420 ± 0.5 K in silicone oil. The disappearance of **2** was determined at regular time intervals. The relative amounts of **2** that remained were directly determined by quantitative $^1$H NMR spectroscopy (600 MHz). Triphenylmethane ($Ph_3CH$) was used as an internal standard. The first-order plots were linear (Fig. 1). The absolute thermolysis rate constants ($k$) were determined from the slope of the plots (Table 1).

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