C, 60.48; H, 5.92; S, 13.45. Found: C, 60.42; H, 6.04; S, 13.69.

**1-Vinyl-2,2-pentamethylene-1,3-propanesultone (12a)**: oil; bp 150 °C (1 mmHg); IR (neat film) 2930 (s), 1650 (w), 1350 (s), 1185 (s), 960 (s), 820 (s), 775 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.17–1.99 (m, 10 H), 3.50 (d, $J$ = 9.4 Hz, 1 H), 4.42 (d, $J$ = 9.4 Hz, 1 H), 5.31–5.65 (m, 2 H), 5.90 (ddd, $J$ = 9.0, 10.0, 16.4 Hz, 1 H); mass spectrum, $m/z$ (relative intensity) 216 (M, 0.1), 152 (M – $SO_2$, 0.5), 135 (2), 122 (19), 107 (7), 94 (100). Anal. Calcd for $C_{10}H_{16}SO_3$: C, 55.53; H, 7.46; S, 14.82. Found: C, 55.51; H, 7.54; S, 14.94.

***trans*-1-(1′-Methylvinyl)-2-phenyl-1,3-propanesultone (12b)**: mp 88–89 °C (hexane–ether); IR (neat film) 2940 (m), 1640 (m), 1330 (s), 1160 (s), 940 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.94 (dd, $J$ = 1.0, 1.5 Hz, 3 H), 3.98–3.41 (m, 3 H), 4.55–4.77 (m, 1 H), 5.15–5.28 (m, 2 H), 7.16–7.50 (m, 5 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.9, 45.4, 68.2, 72.3, 120.3, 127.2, 128.4, 129.2, 133.1, 135.0. Anal. Calcd for $C_{12}H_{14}SO_3$: C, 60.48; H, 5.92; S, 13.45. Found: C, 60.37; H, 5.83; S, 13.62.

**1-Vinyl-2,3-tetramethylene-1,3-propanesultone (12c)**: a mixture of diastereomers (3:2:1); oil; bp 160 °C (2 mmHg); IR (neat film) 2950 (m), 1640 (w), 1350 (s), 1165 (s), 990 (m), 815 (s) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.96–2.89 (m, 9 H), 3.50–4.28 and 4.61–4.86 (m, 2 H), 5.25–6.13 (m, 3 H). Anal. Calcd for $C_9H_{14}SO_3$: C, 53.44; H, 6.98; S, 15.85. Found: C, 54.12; H, 7.15; S, 15.76.

***trans*-1-(*trans*-1′-Propenyl)-2-methyl-1,3-propanesultone (12e)**: bp 180 °C (2 mmHg); IR (neat film) 1665 (m), 1450 (m), 1345 (s), 1175 (s), 950 (m), 835 (m), 675 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.13 (d, $J$ = 6.6 Hz, 3 H), 1.81 (dd, $J$ = 1.5, 6.5 Hz, 3 H), 2.36–3.01 (m, 1 H), 3.37 (dd, $J$ = 8.8, 11.5 Hz, 1 H), 3.91 (dd, $J$ = 8.8, 10.0 Hz, 1 H), 4.50 (dd, $J$ = 7.3, 8.8 Hz, 1 H), 5.35 (ddq, $J$ = 8.8, 15.1, 1.5 Hz, 1 H), 5.95 (dq, $J$ = 15.1, 6.5 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.4, 17.9, 37.5, 66.0, 73.0, 119.4, 136.1. Anal. Calcd for $C_7H_{12}SO_3$: C, 47.71; H, 6.86; S, 18.19. Found: C, 47.94; H, 6.92; S, 18.29.

***cis*-1-(*trans*-1′-Propenyl)-2-methyl-1,3-propanesultone (12f)**: bp 180 °C (2 mmHg); IR (neat film) 1665 (m), 1450 (m), 1340 (s), 1165 (s), 970 (m), 870 (m), 815 (m), 770 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.15 (d, $J$ = 7.1 Hz, 3 H), 1.82 (dd, $J$ = 1.5, 6.3 Hz, 3 H), 3.04 (pseudosept, $J$ = 7.2 Hz, 1 H), 3.88 (dd, $J$ = 7.6, 9.8 Hz, 1 H), 4.00 (dd, $J$ = 7.3, 8.9 Hz, 1 H), 4.50 (dd, $J$ = 7.1, 8.9 Hz, 1 H, 5.41 (ddq, $J$ = 9.8, 15.1, 1.5 Hz, 1 H), 5.92 (dq, $J$ = 15.1, 6.3 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.4, 18.0, 35.3, 63.0, 73.2, 118.0, 136.2.

***trans*-1-(*cis*-1′-Propenyl)-2-methyl-1,3-propanesultone (12f′)**: bp 180 °C (2 mmHg); IR (neat film) 1655 (w), 1460 (m), 1340 (s), 1160 (s), 950 (m), 830 (m), 770 (m), 690 (m) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.14 (d, $J$ = 6.6 Hz, 3 H), 1.81 (dd, $J$ = 2.0, 7.1 Hz, 3 H), 2.48–3.01 (m, 1 H), 3.80 (dd, $J$ = 9.8, 10.5 Hz, 1 H), 3.98 (dd, $J$ = 8.8, 10.0 Hz, 1 H), 4.53 (dd, $J$ = 7.3, 8.8 Hz, 1 H), 5.17–5.53 (m, 1 H, coalescing to dd, $J$ = 9.8, 10.6 Hz, by irradiation at 1.81), 6.11 (dq, $J$ = 10.6, 7.1 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 13.4, 14.6, 38.4, 60.7, 73.3, 119.1, 134.7. Anal. Calcd for $C_7H_{12}SO_3$: C, 47.71; H, 6.86; S, 18.19. Found: C, 47.91; H, 6.79; S, 18.34.

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# Aromatic Nucleophilic Substitution Reactions of 1-(Alkylamino)-2,4-dinitronaphthalenes with Various Primary Amines in Dimethyl Sulfoxide[1]

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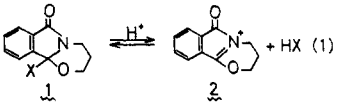
The alkylamino group (e.g., methyl-, ethyl-, butyl, isopropyl, and *tert*-butylamino) of 1-(alkylamino)-2,4-dinitronaphthalenes is found to be quickly and easily replaced by primary alkylamines at room temperature in dimethyl sulfoxide in comparatively high yields. The arylamino group of 1-(arylamino)-2,4-dinitronaphthalenes is also replaced by alkylamines in the same solvent, although detachment for arylamino groups is much slower than that for alkylamino groups in the case of 1-(alkylamino)-2,4-dinitronaphthalenes. The reaction mechanism is discussed.

In the aromatic nucleophilic substitution reaction ($S_NAr$) nucleofuges that have been used thus far include alkoxyl, aryloxy, halogeno, phosphoryl, dialkylsulfonio, trialkylammonio, azido, dimethylamino, alkyl- or arylsulfinyl, alkyl- or arylsulfonyl groups, and others.[2] Since the time that Berliner and Monack measured the rate of reaction of *N,N*-dimethyl-4-bromo-2-nitroaniline with excess piperidine at 25 °C and found it to be very slow,[3] dialkylamino groups have been regarded as poor leaving groups.[4,5] On the other hand, Gravitz and Jencks[6,7] reported the mechanism for the acid-catalyzed hydrolysis of the breakdown and formation of the tetrahedral addition compounds **1** formed from *N,O*-trimethylenephthalimidium ion (**2**) and alcohols or amines and concluded that




for a given basicity secondary amines are expelled from protonated **1** much more rapidly than are alkoxide ions (uncatalyzed) [eq 1, see references for details]. Furthermore, Bernasconi et al.[8] showed that the rate of departure

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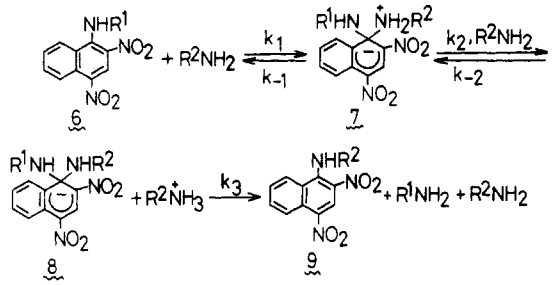
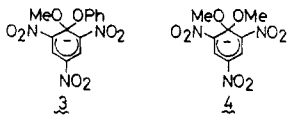
**Scheme I**[a]

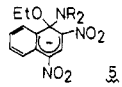


[a] **a**, $R^1$ = Me; **b**, $R^1$ = Et; **c**, $R^1$ = $Bu^n$; **d**, $R^1$ = $Pr^i$; **e**, $R^1$ = $Bu^t$; **f**, $R^1$ = 4-MeOPh; **g**, $R^1$ = 4-MePh; **h**, $R^1$ = Ph; **i**, $R^1$ = 4-$NO_2$Ph.

of phenoxide ion is ca. $10^7$ times faster than that of methoxide ion from complexes **3** and **4** in water and ascribed the faster departure rate of the phenoxide ion to its smaller $pK_a$.



In addition, Bunnett et al.[9] demonstrated a conspicuous difference between the departure rates of ethoxide ion from complexes **5a** and **5b** ($k^{pyr}/k^{pip}$ = ca. $10^4$ in dimethyl sulfoxide [DMSO] at 25 °C), in which the ethoxy group is activated by previously added ammonium ion (pyrrolidinium chloride for **5a** and piperidinium chloride for **5b**). they speculated that such a large difference between $k^{pyr}$ and $k^{pip}$ might arise from the structures of the substitution products rather than from electronic effects of the $NR_2$ groups of **5** ($pK_a$ at 25 °C, 15.9 for EtOH;[10b] 11.27 for pyrrolidine; 11.12 for piperidine[10b]).



**a**, $NR_2$ = pyrrolidino; **b**, $NR_2$ = piperidino

Recently we reported the exchange reaction of 1-(dialkylamino)-2,4-dinitronaphthalenes with primary and secondary amines in DMSO[1,11] in which primary amines are very reactive (except for isopropyl- and *tert*-butylamine) and in which only pyrrolidine, although it is less reactive when compared with primary amines, can more easily relace the 1-(dialkylamino) group among secondary amines.[11,12] We concluded from these studies that the faster departure rate of one of the two amino groups from the anionic $\sigma$ complex, such as **8**, depends upon the stereoelectronic conformation of the transition state at the $k_3$ step, rather than on the $pK_a$ values of the amines ($R^1NH_2$ and $R^2NH_2$) (Scheme I).

More recently we have tried to expand this exchange reaction to include the 1-(alkylamino)-2,4-dinitronaphthalene **6** system and have found the exchange reaction to occur easily. These exchange reactions could be very useful in elucidating the factors that might promote

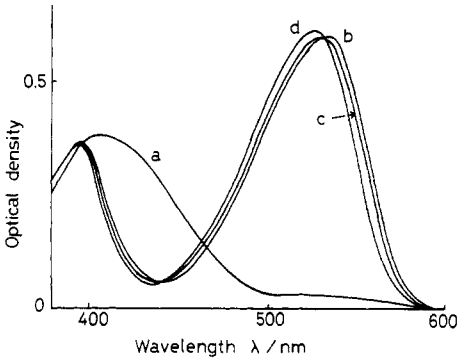



**Figure 1.** Time-dependent absorption spectra for the reaction of 1-(isopropylamino)-2,4-dinitronaphthalene (**6d**, $2.5 \times 10^{-5}$ M) with aqueous methylamine ($2.5 \times 10^{-2}$ M) at 30 °C in DMSO: a, **6d**; b, c, and d, immediately, 6, and 24 h after addition of methylamine, respectively.

detachment of the amino group from 8.

In accordance with the mechanism described in the previous work,[1] the present reactions would be presumed to proceed as shown in Scheme I (see Discussion). In Scheme I, the question of which amino group departs faster in the conversion of 8 to **9** ($k_3$ step) is very important in allowing the reaction to proceed, as are the rates of the $k_1$ and $k_2$ steps. If two primary amines ($R^1NH_2$ and $R^2NH_2$) of similar $pK_a$ are used as a substituent and a nucleophile, the electronic effects of both alkylamino groups on 8 may be neglected, and only their steric factors will be important in determining their relative ease of detachment.

## Results

**Time-Dependent Absorption Spectra of the Reaction of 1-(Isopropylamino)-2,4-dinitronaphthalene (6d) with Methylamine.** The time-dependent absorption spectra of the reaction of **6d** with methylamine was measured in DMSO at 30 °C (Figure 1). Upon addition of excess amine to a DMSO solution of **6d**, the mixture immediately turned red [curve a → b in Figure 1]. Curve b ($\lambda_{max}$ 530 and 395 nm) could be attributed to $\mathbf{6d}^-$, formed by deprotonation of the amino hydrogen of **6d**. Curve b gradually changed into curve d ($\lambda_{max}$ 523 and 392 nm) in 24 h, which could be attributed to deprotonated **9** ($R^2$ = Me), i.e., $\mathbf{9}^-$ (≡ $\mathbf{6a}^-$). These assignments are supported by the reactions of **6a** and **6d** with diethylamine under the same conditions as those shown in Figure 1, giving only $\mathbf{6a}^-$ and $\mathbf{6d}^-$, respectively, where only deprotonation of the amino hydrogen occurred.[1,11] Concerning these assignments the question remained whether curve b or curve d could be attributed to 8 ($R^1HN$ = *i*-PrNH and $R^2NH$ = MeNH). In order to elucidate this point, the time-dependent absorption spectra of the reaction of **6a** with isopropylamine were measured in DMSO under the same conditions as shown in Figure 1 (curve not shown). Just after addition of isopropylamine, a spectrum identical with curve d instantly appeared and did not change over a period of 6 h, the time-dependent process of which was very different from that shown in Figure 1. Consequently, neither curve b nor curve d could be attributed to 8, because if so, the same absorption curve should appear in both reactions.

From these results and a wealth of information obtained thus far on $S_NAr$ systems, Scheme I should be rewritten as Scheme II. In Scheme II the $K_4$ (≡ $k_4/k_{-4}$) equilibrium would be estimated very fast, lying almost entirely to the right, as would the $K_6$ (≡ $k_6/k_{-6}$) equilibrium. The $k_1$ step could be expected to be comparatively fast, since steric

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**Table I. Exchange Reactions of 1-(Alkylamino)-2,4-dinitronaphthalenes 6 with Various Primary Amines[a]**

| run | substr | $R^1$ | $R^2$ | reactn temp, °C | reactn time, h | yield, % |
|---|---|---|---|---|---|---|
| 1 | **6b** | Et | Me[b] | 30 | 10 min | 70 |
| 2 | **6b** | Et | Me[b] | 30 | 0.5 | 82 |
| 3 | **6b** | Et | Me[b] | 30 | 1 | 85 |
| 4 | **6c** | Bu | Me[b] | 30 | 10 min | 22 |
| 5 | **6c** | Bu | Me[b] | 30 | 1 | 74 |
| 6 | **6d** | $Pr^i$ | Me[b] | 30 | 10 min | 63 |
| 7 | **6d** | $Pr^i$ | Me[b] | 30 | 0.5 | 100 |
| 8 | **6d** | $Pr^i$ | Me[b] | 30 | 1 | 100 |
| 9 | **6a** | Me | Et[c] | 30 | 10 min | 28 |
| 10 | **6a** | Me | Et[c] | 30 | 0.5 | 45 |
| 11 | **6a** | Me | Et[c] | 30 | 1 | 47 |
| 12 | **6c** | Bu | Et[c] | 30 | 10 min | 26 |
| 13 | **6c** | Bu | Et[c] | 30 | 1 | 57 |
| 14 | **6d** | $Pr^i$ | Et[c] | 30 | 10 min | 40 |
| 15 | **6d** | $Pr^i$ | Et[c] | 30 | 0.5 | 76 |
| 16 | **6d** | $Pr^i$ | Et[c] | 30 | 1 | 87 |
| 17 | **6c** | Bu | $Pr^n$ | 30 | 10 min | 30 |
| 18 | **6c** | Bu | $Pr^n$ | 30 | 1 | 63 |
| 19 | **6a** | Me | $Pr^i$ | 30 | 10 min | 4 |
| 20 | **6a** | Me | $Pr^i$ | 30 | 0.5 | 9 |
| 21 | **6a** | Me | $Pr^i$ | 30 | 1 | 14 |
| 22 | **6b** | Et | $Pr^i$ | 30 | 10 min | 4 |
| 23 | **6b** | Et | $Pr^i$ | 30 | 0.5 | 12 |
| 24 | **6b** | Et | $Pr^i$ | 30 | 1 | 18 |
| 25 | **6c** | Bu | $Bu^t$ | 30 | 10 min | 0 |
| 26 | **6c** | Bu | $Bu^t$ | 30 | 1 | 0 |
| 27 | **6g** | *p*-MePh | Me[b] | 30 | 1 | 0 |
| 28 | **6f** | *p*-MeOPh | Me[b] | 50 | 23 | 74 |
| 29 | **6g** | *p*-MePh | Me[b] | 50 | 23 | 53 |
| 30 | **6h** | Ph | Me[b] | 50 | 23 | 41 |
| 31 | **6i** | *p*-$NO_2$Ph | Me[b] | 30 | 1 | 0 |
| 32 | **6i** | *p*-$NO_2$Ph | Me[b] | 50 | 23 | 40 |
| 33 | **6g** | *p*-MePh | Et[c] | 50 | 23 | 40 |
| 34 | **6f** | *p*-MeOPh | Bu | 70 | 23 | 67 |
| 35 | **6g** | *p*-MePh | Bu | 70 | 23 | 64 |
| 36 | **6h** | Ph | Bu | 70 | 23 | 53 |
| 37 | **6i** | *p*-$NO_2$Ph | Bu | 70 | 23 | 53 |
| 38 | **6g** | *p*-MePh | $Pr^i$ | 50 | 23 | 12 |
| 39 | **6i** | *p*-$NO_2$Ph | $Pr^i$ | 50 | 23 | 3 |
| 40 | **6g** | *p*-MePh | $Bu^t$ | 50 | 23 | 0 |
| 41 | **6a** | Me | *p*-MePh | 80 | 21 | 3 |
| 42 | **6b** | Et | *p*-MePh | 50 | 23 | 0 |
| 43 | **6c** | Bu | *p*-MePh | 50 | 23 | 2 |
| 44 | **6d** | $Pr^i$ | *p*-MePh | 50 | 10 | 0 |
| 45 | **6e** | $Bu^t$ | *p*-MePh | 50 | 3 | 65[d] |
| 46 | **6i** | *p*-$NO_2$Ph | *p*-MePh | 50 | 23 | 0 |
| 47 | **6g** | *p*-MePh | *p*-$NO_2$Ph | 50 | 23 | 0 |

[a] $[6]_0$ 0.5 mmol; $[amino]_0/[6]_0$ 3 (molar ratio); solvent (DMSO) 10 mL. In $R_1$ or $R_2$ *p*-MeOPh, *p*-MePh, *p*-$NO_2$Ph, Ph, and $PhCH_2$ mean *p*-methoxy-, *p*-methyl-, and *p*-nitrophenyl, phenyl, and benzyl, respectively. [b] 40% aqueous solution used. [c] 70% aqueous solution used. [d] Slightly inaccurate owing to peak overlapping in the determination with HPLC.

interference between the $R^1NH$ group and the approaching $R^2NH_2$ would be much less severe than in the corresponding reactions of 1-(dialkylamino)-2,4-dinitronaphthalenes with secondary amines.[12] As for the $K_2$ ($\equiv k_2/k_{-2}$) equilibrium, several values have been reported: in the reaction of 1,3,5-trinitrobenzene (TNB) with pyrrolidine and piperidine, where Scheme I applies, $K_2$ is ca. 330 in 30/70 DMSO–$H_2O$ at 20 °C for the former[13] and 500 in DMSO at 25 °C for the latter;[14] in the reaction of TNB with butylamine in DMSO at 25 °C, where Scheme I applies, $K_2$ is 500[15] (this value is assumed; see the reference concerning the details).

From these results the $K_2$ equilibrium can be expected to be comparatively fast. One may assume that the $k_3$ step is also fast if one considers the $k_3$ value in the reaction of 1-ethoxy-2,4-dinitronaphthalene with pyrrolidine in DMSO, where Scheme I applies and in which the 1-ethoxy group exclusively departs from **8** (with an ethoxy group in place of $R^1NH$),[9] because the present reactions involve nucleophilic primary alkylamines.[16]

Furthermore, the $k_5$ step is probably slow, since nucleophilic attack of $R^2NH_2$ against $\mathbf{6}^-$ (anionic species) is considered to be slow.[17] Therefore, both reaction sequences (**6** ⇄ **7** ⇄ **8** ⇄ **9** and **6** ⇄ $\mathbf{6}^-$ ⇄ **8** ⇄ **9**) would take place. The overall rate for the former sequence is probably slow owing to the sluggishness of the $k_1$ step, due to extremely low concentrations of **6**, and that for the latter sequence is also probably slow owing to the sluggishness of the $k_5$ step.

**Reactions of 1-(Alkylamino)-2,4-dinitronaphthalenes with Various Primary Amines.** The results are listed in Table I. These results are summarized as follows: (a) throughout runs 1–26, methylamine is the most reactive nucleophile, and in general primary amines

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(14) Crampton, M. R.; Greenhalgh, C. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1175.
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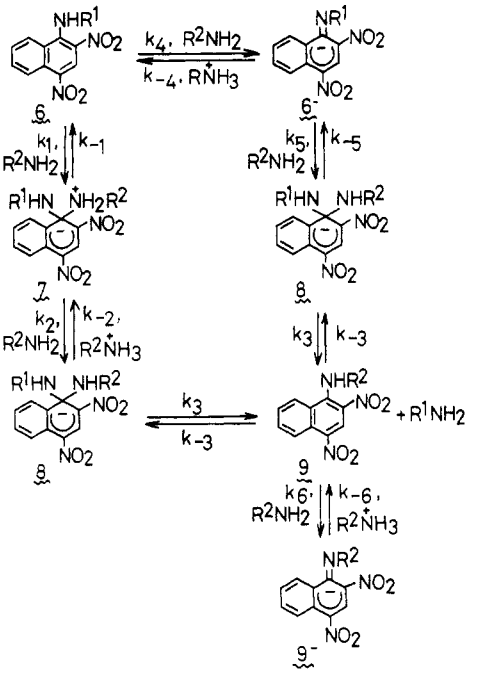
**Scheme II**



involving alkyl groups are more reactive than primary amines involving secondary or tertiary alkyl groups, although their $pK_a$ values are almost the same;[18] (b) interestingly, even if the combination of an amino group ($R^1NH$) and a nucleophilic amine ($R^2NH_2$) is reversed, the exchange reaction occurs (runs 1 and 9, 2 and 10, 3 and 11, 6 and 19, 7 and 20, 8 and 21, 14 and 22, 15 and 23, and 16 and 24), although their $pK_a$ values are not very different,[18] and the yield is always higher in the combination of a larger $R^1$ and a smaller $R^2$ group, especially in the combination of $R^1$ = Pr$^i$ and $R^2$ = Me (runs 6–8), than in the reverse combination; (c) when $R^2$ of $R^2NH_2$ is a secondary or a tertiary alkyl group, the yield is very low (runs 19–26); (d) since the reaction of **6f–i** (with $R^1$ = unsubstituted or substituted anilino group) showed low reactivity, higher temperatures and longer reaction times were used, and among the primary amines methylamine was the most reactive (runs 28–32) and *tert*-butylamine the least reactive (run 40), and the yield is relatively low for **6i** (with an anilino group having a para-electron-withdrawing substituent); (e) the reactions with anilines as leaving groups are slower than those with aliphatic amines as leaving groups (runs 1–8 and 28–32, 10–16 and 33, and 19–24 and 38–39); (f) nucleophilic para-substituted aniline is generally much less reactive (runs 41–44 and 46–47), although the yield for run 45 is relatively high (see Discussion).

The lower reactivities for **6f–i** compared to **6a–e** [(d) above] could be attributed to the high stability of $6^-$, formed by deprotonation with excess nucleophilic amine, owing to the presence of two phenyl groups (unsubstituted or para-substituted phenyl and 2,4,6-trinitrophenyl) and to the less favorable protonation by $R^2NH_3^+$ to the amino nitrogen of 8 (runs 28–30 and 32–37). In runs 38–40 the very low yields would arise from slower nucleophilic addition of the bulkier primary amines in the $k_1$ and $k_5$ steps, as well as to the two factors described above.

(18) The $pK_a$ values (25 °C) for the amines used in the present reactions are as follows:[10b] 10.62 for $MeNH_2$, 10.64 for $EtNH_2$, 10.60 for *n*-$BuNH_2$, 10.63 for *i*-$PrNH_2$, 10.45 for *t*-$BuNH_2$, 5.29 for 4-$MeOPhNH_2$, 5.08 for 4-$MePhNH_2$, 4.60 for $PhNH_2$, 0.99 for 4-$NO_2PhNH_2$.

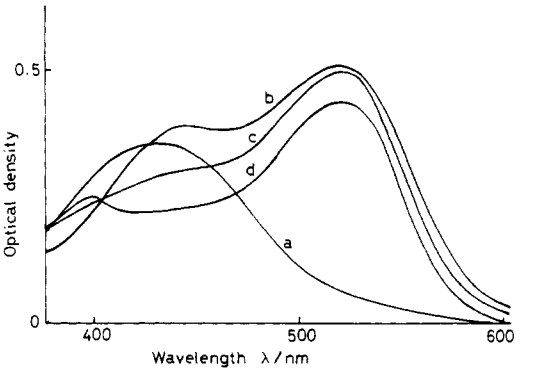



**Figure 2.** Time-dependent absorption spectra for the reaction of 1-(4-methylanilino)-2,4-dinitronaphthalene (**6g**, $2.5 \times 10^{-5}$ M) with aqueous methylamine ($2.5 \times 10^{-2}$ M) at 10 °C in DMSO: a, **6g**; b, c, and d, immediately, 10, and 15 days after addition of methylamine, respectively.

No substitution with *t*-$BuNH_2$ was observed (runs 25, 26, and 40), a result that would stem mainly from the stereoelectronic conformation of the two amino groups ($R^1HN$ and $R^2HN$) of 8 (see Discussion).

The results [(e) above] would arise from the extraordinary stability of a deprotonated substrate and from the less favorable protonation to the amino nitrogen ($R^1NH$) of 8 for the reactions involving anilines as leaving groups.

In the case of nucleophilic aniline and substituted anilines (runs 41–44 and 46–47), much lower reactivities were observed except for the reaction of **6e** with *p*-methylaniline (run 45) [(f) above]. The low reactivity could be attributed mainly to the low nucleophilicity of anilines as reflected in their smaller $pK_a$ values[18] (see below).

**Time-Dependent Absorption Spectra of Reactions of 1-(Methylamino)-2,4-dinitronaphthalene (6a) with 4-Methylaniline and of 1-(4-Methylanilino)-2,4-dinitronaphthalene (6g) with Methylamine.** To elucidate the points discussed above, we measured the time-dependent absorption spectra of the reactions of **6a** with 4-methylaniline and of **6g** with methylamine in DMSO (Figure 2). In the former case, the absorption of **6a** [$\lambda_{max}$ 411 nm ($\epsilon$ 18 200)] did not vary over 15 days after excess 4-methylaniline was added, i.e., 4-methylaniline evidently could not abstract the amino proton of **6a** and also could not add to C-1 of **6a**, as seen from its low basicity[18] (curve not shown). On the other hand, in the latter case (Figure 2), curve a, which is attributed to **6g** [$\lambda_{max}$ 448 ($\epsilon$ 15 400) and 518 nm ($\epsilon$ 20 100)], gradually changed into curve d via curve c, just after addition of excess methylamine. This was thought to be due to deprotonation by methylamine, which is a stronger base than 4-methylaniline.[18] Curve d was confirmed to be attributable to deprotonated **6a**, i.e., **6a**$^-$ [$\lambda_{max}$ 398 and 518 nm) on reaction of **6a** with dimethylamine under the same conditions as those in Figure 2, where $\lambda_{max}$ was 392 ($\epsilon$ 14 200) and 523 nm ($\epsilon$ 23 600). A small deviation in the two wavelengths at the maximum absorptions in Figure 2 may result from the reaction in progress. These results might be interpreted as supporting the discussion described in the preceding paragraph and Scheme II.

The results in Table I (runs 6–8 and 28–29) show that the reaction is very fast, compared with those in Figures 1 and 2. As pointed out previously,[1] the present reactions undergo a concentration effect such that the use of a large amount of DMSO reduces the yields.

## Discussion

**Effects of $pK_a$ of Amines.** As described above, it is an interesting finding that even when the combination of

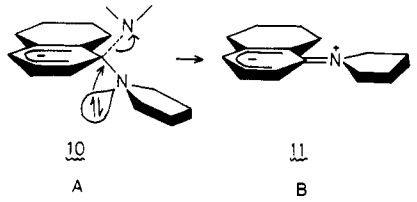



**Figure 3.** Conversion of the transition state **10** to the product **11** in the reactions of 1-(dialkylamino)-2,4-dinitronaphthalene with pyrrolidine in DMSO (2- and 4-nitro groups omitted for clarity).

$R^1$ and $R^2$ is reversed both reactions occur (Table I), although the $pK_a$ values of the alkylamines used are almost the same (runs 1–3 and 9–11, 6–8 and 19–21, and 14–16 and 22–24). The yields, however, are always higher in the case of secondary or tertiary $R^1$ and primary $R^2$ groups, which suggests the importance of the steric factors rather than the $pK_a$ values of the amines.[7] These results were further confirmed by the reactions of **6g–i** with alkylamines (runs 28–37). These reactions were found to proceed only at higher reaction temperatures and longer reaction times, indicating the detachment of the anilino group ($R^1NH$) from **8**. This detachment is unexpected on the basis of the conclusion of Gravitz and Jencks,[7a] i.e., that for the release of amino groups from protonated **1** an amine of higher $pK_a$ departs faster. In the amino departure from **8** ($R^1NH$ = 4-MePhNH or 4-MeOPhNH and $R^2NH$ = MeNH) formed in the reaction of **6f** or **6g** with methylamine (runs 28 and 29), where protonation with $MeN^+H_3$ ($R^2N^+H_3$) would be expected to selectively occur on the MeNH ($R^2NH$) group rather than on 4-MePhNH or 4-MeOPhNH ($R^1NH$), the methylamino group should leave faster than the 4-methyl- or 4-methoxyanilino group according to their conclusion[7a] (note that the $pK_a$ for $MeNH_2$ is higher than that of 4-$MePhNH_2$ or 4-$MeOPhNH_2$[17]).

Based on these results, we would like to propose that the question of which amino group leaves faster from **8** would depend considerably on the stereoelectronic structure of the two amino groups ($R^1NH$ and $R^2NH$) in the transition state at the $k_3$ stage (see next paragraph and Figure 4).[1,11]

**Structure of Transition State at the $k_3$ Step.** As described in the introduction,[1,11] we proposed the following transition state at the $k_3$ step from the specific behavior of pyrrolidine in the reactions of 1-(dialylamino)-2,4-dinitronaphthalenes with secondary amines in DMSO (Figure 3).

In the transition state **10** (Figure 3), the pyrrolidine ring can assume a conformation such that the lone-pair electrons on the pyrrolidino nitrogen are anti-periplanar to the $C_1$–N (leaving dialkylamino nitrogen) bond with respect to the $C_1$–N (pyrrolidino nitrogen) bond. The pyrrolidine plane, therefore, would be coplanar with the naphthalene plane with a certain angle. Accordingly, both the anti-periplanar conformation, in which the back-side attack of the lone-pair electrons could enable the dialkylamino group ($R_2N^2$) to leave more easily, and the coplanarity in **11** (1-pyrrolidino-2,4-dinitronaphthalene), which would make the conversion to **11** very easy, would result in specific behavior of pyrrolidine. It was already proved by absorption and $^1H$ NMR spectra that such a resonance structure (**11**) (Figure 3B) is much more favorable for 1-piperidino-2,4-dinitronaphthalene than other 1-dialkylamino homologues.[1,11]

In the present reaction, therefore, the following transition state at the $k_3$ step in Scheme II would be very reasonable, where the amino group,e.g., $R^1NH$, that can more easily assume the anti-periplanar conformation would expel the other amino group ($R^2NH$) from **8** (Figure 4).

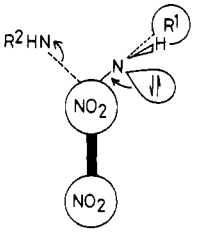



**Figure 4.** Transition state **8** at the $k_3$ step (viewed from the ring with 2- and 4-nitro groups).

Such a conformation could reasonably account for the results in Table I: (a) the highest reactivity of methylamine results from its strongest ability to assume the anti-periplanar conformation; (b) the low reactivities of $i$-$PrNH_2$ and $t$-$BuNH_2$ are attributable to their relative inability to assume this conformation, although the rate for addition ($k_1$ and $k_5$) is also slow (runs 19–26 and 38–40); (c) the results for runs 28–37 correspond to the comparatively strong ability of nucleophilic alkylamines, which indicates that the anti-periplanar conformation is much more important than the $pK_a$ values of the nucleophilic amines for the reaction to proceed.

Although the results for runs 41–47 (except for 45) would arise mainly from the very low nucleophilicity of aromatic amines,[18] the result for run 45 is very interesting on considering the low nucleophilicity of 4-methylaniline, where the yield is somewhat inaccurate (see the footnote in Table I).[18] As indicated by runs 25, 26, and 40, *tert*-butylamine is extremely low in nucleophilicity, which indicates that the reactions involving *tert*-butylamine as a ncucleophile terminate in formation of **8** because of the inability of *tert*-butylamine to assume the anti-periplanar conformation. In this case, the 4-methylanilino group could instead assume the anti-periplanar conformation in **8**.

The conspicuous difference in rates for detachment of the ethoxy group from **5a** and **5b**[9] would result from the stronger ability of the pyrrolidino group to assume the anti-periplanar conformation.

In the case of $MeNH_2$, the yields were generally higher, even at shorter reaction times, except for run 4 (runs 1–8), because all the steps (nucleophilic addition [$k_1$ and $k_5$ steps], proton abstraction [$k_2$ and $k_4$ steps], and stereoelectronic conformation [$k_3$ step]) would be more favorable for $MeNH_2$. The result in run 4 would probably stem from the steric interference of the BuNH group toward the approaching $MeNH_2$ ($k_1$ and $k_5$ steps).

In conclusion, it is found that in the conversion of **8** with two amino groups at C-1 to products, the ability of one amino group to assume the anti-periplanar conformation in preference to the other plays an important role in allowing the reaction to proceed.

## Experimental Section

**Materials.** Dimethyl sulfoxide, dried over calcium hydride, was distilled before use. Aqueous methyl- (40%) and ethylamine (70%) were used as such. Other alkylamines of Anala R grade, dried over potassium hydroxide, were distilled before use. The anilines of Anala R were used as such. $^1H$ NMR spectra were recorded at 60 MHz on a Varian A60 spectrometer and UV–vis spectra on a Hitachi 124 spectrophotometer.

1-(Alkylamino)-2,4-dinitronaphthalenes were prepared as follows. A solution containing weighed amounts of an amine and 1-chloro-2,4-dinitronaphthalene (CDN) ([amine]/[CDN] = 10 molar ratio, with ca. 5 g of CDN used) in 50 mL of DMSO was stirred for 5 h at 50 °C, poured into ice water, and neutralized with dilute $H_2SO_4$ to produce the precipitate. It was filtered and the residue was recrystallized from methanol for **6a–e** and from isopropyl alcohol for **6f–i**; yields 70–92% for **6a–e**. NMR spectral

data, mp, $\lambda_{max}$, and $\epsilon$ for **6** except for **6e** were reported previously.[1]

1-(*tert*-**Butylamino)-2,4-dinitronaphthalene (6e)**: mp 115–115.5 °C; $\lambda_{max}$ 408 nm ($\epsilon$ 11600 [MeOH]); $^1$H NMR (DMSO-$d_6$) $\delta$ 1.33 [s, 9 H, C(CH$_3$)$_3$], 7.97 (br s, 1 H, NH, overlapped with H$^{6,7}$), 8.03 (qui, 2 H, H$^{6,7}$, partially overlapped with NH), 8.70 (m, 2 H, H$^{5,8}$, overlapped with each other), 9.03 (s, 1 H, H$^3$), in which the suffix on hydrogen represents the positional number of a naphthalene moiety.

**Determination of Products.** The typical procedure for determination of the reaction products is described for the reaction of **6d** with methylamine. The 10-mL DMSO solution containing 5 mmol (0.137 g) of **6d** and 3 equiv of methylamine (40% solution) was stirred for the prescribed time at the prescribed temperature, and then the mixture was poured into 200 mL of water, acidified with the equiv of HCl based on the methylamine added, extracted with 200 mL of benzene three times, and dried over anhydrous MgSO$_4$. After the mixture was filtered, the benzene layer was subjected to HPLC (Shimazu LC-6A, silica gel, hexane–2-propanol (20:1 v/v).

**Registry No.** **6a**, 39139-78-1; **6b**, 27210-67-9; **6c**, 124855-05-6; **6d**, 118209-15-7; **6f**, 116062-03-4; **6g**, 124855-07-8; **6h**, 92859-08-0; **6i**, 68105-52-2; **9** (R = Pr), 124855-08-9; MeNH$_2$, 74-89-5; EtNH$_2$, 75-04-7; PrNH$_2$, 107-10-8; *i*-PrNH$_2$, 75-31-0; t-BuNH$_2$, 75-64-9; BuNH$_2$, 109-73-9; *p*-MeC$_6$H$_4$NH$_2$, 106-49-0; *p*-NO$_2$C$_6$H$_4$NH$_2$, 100-01-6; DMSO, 67-68-5.

# Convenient Syntheses of Cytidine 5′-Triphosphate, Guanosine 5′-Triphosphate, and Uridine 5′-Triphosphate and Their Use in the Preparation of UDP-glucose, UDP-glucuronic Acid, and GDP-mannose

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This paper compares enzymatic and chemical methods for the synthesis of cytidine 5′-triphosphate, guanosine 5′-triphosphate, and uridine 5′-triphosphate from the corresponding nucleoside monophosphates on scales of ~10 g. These nucleoside triphosphates are important as intermediates in Leloir pathway biosyntheses of complex carbohydrates; the nucleoside monophosphates are readily available commercially. The best route to CTP is based on phosphorylation of CMP using adenylate kinase (EC 2.7.4.3); the route to GTP involves phosphorylation of GMP using guanylate kinase (EC 2.7.4.8); chemical deamination of CTP (prepared enzymatically from CMP) is the best synthesis of UTP. For the 10–200-mmol-scale reactions described in this paper, it is more convenient to prepare phosphoenolpyruvate (PEP), used in the enzymatic preparations, from D-(−)-3-phosphoglyceric acid (3-PGA) in the reaction mixture rather than to synthesize PEP in a separate chemical step. The in situ conversion of 3-PGA to PEP requires the coupled action of phosphoglycerate mutase (EC 2.7.5.3) and enolase (EC 4.2.1.11). The enzyme-catalyzed syntheses of uridine 5′-diphosphoglucose (UDP-Glc), uridine 5′-diphosphoglucuronic acid (UDP-GlcUA), and guanosine 5′-diphosphomannose (GDP-Man) illustrate the use of the nucleoside triphosphates.

## Introduction

As part of a broad program[3] to develop synthetic techniques based on glycosyl transferases for the preparation of glycoproteins, glycolipids, and proteoglycans,[4] we wished to develop convenient routes to cytidine 5′-triphosphate (CTP), guanosine 5′-triphosphate (GTP), and uridine 5′-triphosphate (UTP). Enzyme-catalyzed reactions of these three compounds with monosaccharides are central reactions in the biosynthesis of the nucleoside phosphate sugars required by glycosyl transferases in mammalian biochemistry (CMP-NeuAc, GDP-Fuc, GDP-Man, UDP-Gal, UDP-GalNAc, UDP-Glc, UDP-GlcNAc, UDP-GlcUA, and UDP-Xyl).[3]

An important issue in planning synthetic tactics concerns the method of synthesizing the NTPs and nucleoside phosphate sugars for use in enzyme-catalyzed reactions: should they be synthesized independently and used as stoichiometric reagents (in which case chemical, enzymatic or fermentation syntheses would all, in principle, be acceptable) or should they be generated and used in situ (in which case only enzymatic syntheses would be acceptable)? We have decided initially to develop synthetic methods that generate the NTPs and nucleoside phosphate sugars as stoichiometric reagents, rather than relying on their generation in situ, for five reasons. First, this type of approach is the most practical. Developing complex systems of coupled enzymes is difficult. If the syntheses of the NTPs and nucleoside phosphate sugars can be developed and optimized separately, the final systems are simpler. Second, this approach has greater generality. If convenient routes to all of the NTPs and nucleoside phosphate sugars can be developed, these compounds are then available for the full range of oligo- and polysaccharide syntheses. Third, this approach is the most flexible. By conducting syntheses of these compounds separately, it is possible to use whatever synthetic method works best for each, without concern for the compatibility of these methods. Fourth, separating syntheses of the nucleoside phosphate sugars from the steps involving use of these compounds in forming glycosidic bonds permits the latter reactions to be conducted in a way that optimizes the use of the glycosyl transferases (normally the most difficult enzymes to obtain and use).[3] Finally, this approach is more likely to be successful for the synthesis of unnatural compounds, where analogues of the natural reactants may have to be synthesized chemically.

CTP, GTP, and UTP are all available from commercial sources, but their cost precludes their use in multigram-scale reactions. We do not discuss in detail the synthesis of adenosine 5′-triphosphate (ATP) here because it is relatively inexpensive compared with other NTPs,[5] and

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(2) NATO Postdoctoral Fellow 1988–89 (administered by the Deutscher Akademischer Austauschdienst).
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