$NaHCO_3$(aq)), dried, and evaporated. SG chromatography (20% Me_2CO–CH_2Cl_2) gave the *pyridinone* **40** (0.80 g, 67%) as a yellow powder, mp 188–189 °C: ^{1}H NMR δ 1.39 (t, 3 H, J = 7 Hz), 4.38 (q, 2 H, J = 7 Hz), 4.60 (AB, 2 H, J = 17 Hz), 6.43 (s, 1 H), 7.50 (m, 3 H), 7.74 (d, 1 H, J = 6 Hz), 8.36 (s, 1 H). Anal. Calcd for $C_{16}H_{13}BrN_2O_3$: C, 53.20; H, 3.63; N, 7.76. Found: C, 53.44; H, 3.65; N, 7.74.

Acknowledgment. We thank the Physical–Analytical department for microanalyses.

Notes

Effect of Water on Solid–Liquid Phase-Transfer Reaction of Activated Aryl Halides with Nitrite Salts and Change in Course of Reaction

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Activated aryl halides undergo a variety of nucleophilic substitution reactions in homogeneous[1] and phase-transfer catalyzed conditions.[2] Nitrite ion as a Nu has been used for substitution in alkyl and aryl halides under SLPTC conditions using crown ether as PTC.[3] Dehmlow et al.[4] and Sasson et al.[5-7] have reported that with quaternary ammonium salts as PTC a trace amount of water is essential and the rate of reaction is a function of the amount of water in SLPTC reactions. The kinetics of the overall reaction depends on the relative solubilities[5,8] of the attacking Nu (Y^-) and the displaced ion (X^-) in the solid (eqs 1 and 2).[9]

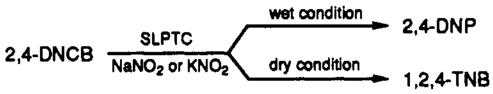
$$-d(RX)/dt = k_2(RX)(QY)_{org} \tag{1}$$

$$(QY)_{org} = (QX)_{org}K_{Y/X}{}^{Sel}(Y^-)_{aq}/(X^-)_{aq} \tag{2}$$

In this paper, we report the formation of 1,2,4-TNB and 2,4-DNP from 2,4-DNCB at different water contents in the system (Scheme I). Therefore, in this reaction, not only rate constants varied with the water content of system but also a change in course of reaction was observed.

Nitrite ion is a poor Nu due to its high solvation in LLPTC, in contrast to when it is used in SLPTC conditions.[3] Conventionally, the nitro group is introduced in the benzene nucleus either by electrophilic substitution[10] or by free-radical substitution of a diazonium group,[11] and not by nucleophilic substitution. Since an activated aryl nitro group is also a good nucleofuge,[12] it can also be hydrolyzed after its substitution in the presence of an aqueous environment. However, use of apolar aprotic solvent in the presence of a trace amount of water minimizes the possibility of its hydrolysis. Therefore, the nitro group is likely to stay once it is introduced in the benzene nucleus. We have prepared 1,2,4-TNB and *o*-dinitrobenzene by carrying out displacement of chlorine in 2,4-DNCB and *o*-chloronitrobenzene, respectively, by NO_2^- in toluene containing BTEAC and solid KNO_2 or $NaNO_2$ under "dry" SLPTC conditions.[13]

Scheme I



If the water content of the system was increased in the previous reaction, i.e., in "wet" SLPTC conditions, 2,4-DNP and *o*-nitrophenol, respectively, were formed after 5 h of heating at 70 °C. In these reactions, $NaHCO_3$ was used as an acid scavenger. Conventionally, these hydrolysis reactions are carried out in 20% Na_2CO_3 solution at 130 °C for 24 h.[14] Thus, under PTC conditions, the rate was enhanced. It has been observed by TLC and UV spectra that there was no simultaneous formation of 1,2,4-TNB and 2,4-DNP at any water content. Therefore, once 2,4-DNP started forming, water generated by neutralization of HCl by $NaHCO_3$ not only leveled the concentration of water in the organic phase but also kept the reaction moving in a forward direction. The formation of nearly 86% product in the reaction mixture using nearly 0.5 mol of water per mole of 2,4-DNCB supported the earlier contention. Of course, total water is not available as a Nu due to its partitioning between the organic and solid phase.

2,4-DNP was also formed when a 20% aqueous solution of KNO_2, $NaNO_2$, $NaHCO_3$, Na_2CO_3, or KCl was used under LLPTC conditions. But when 20% $NaClO_4$ was used, 2,4-DNP was not formed. ClO_4^- ion, being a lipophilic anion, carried almost negligible water into the organic phase. Therefore, higher reaction time for such reactions without using PTC can be attributed to the poor miscibility of reactants. It has also been reported[15] that, although water is a weak Nu, it can hydrolyze benzyl and allyl halides in certain solvents, e.g., hexamethylphosphoric triamide and *N*-methyl-2-pyrrolidone. This suggested that water when finely dispersed in a nonpolar aprotic solvent

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Table I. Rate Constants[a] for Formation of 1,2,4-TNB and 2,4-DNP Using $NaNO_2$ and KNO_2 Salts and Solubility Ratio[b]

type of cation	solubility ratio (MNO_2/MCl)	pseudo-first-order rate constants × 10^{-4} s^{-1}	
		1,2,4-TNB (n_f)	2,4-DNP (n_f)
Na^+	4.16	1.5 (0.188)	2.0 (0.317)
K^+	7.28	2.3 (0.210)	3.7 (0.310)

[a] Reaction conditions as given for 1(a), 1(b), 2(a), and 2(b) in Figure 1. [b] Solubility ratio was calculated at 100 °C from ref 16.

should act as a stronger Nu than the solvated NO_2^- ion.

For the study of the effect of water on reaction kinetics and on the course of the reaction, 2,4-DNCB was reacted with solid KNO_2 or $NaNO_2$ at various water contents of the system in the presence of BTEAC in toluene at 70 °C. The water content of the system includes the water content of toluene, nitrite salt, BTEAC, $NaHCO_3$, and the added water. The gain or loss in water content of system was less than 15%, which may be due to evaporation or experimental error. The reaction obeyed pseudo-first-order kinetics (eqs 3 and 4) at any water content, as the concentration of QNO_2 or H_2O in organic phase is constant at any instant.

$$d(ArNO_2)/dt = k_1\,(ArCl) \qquad (3)$$

$$d(ArOH)/dt = k_2\,(ArCl) \qquad (4)$$

Experimental rates of reaction were related to the solubility ratio MNO_2–MCl. The higher this ratio, the higher was the rate constant (Table I). The following conclusions were drawn from Figure 1.

(1) From curves 1(a) and 1(b) are seen the following: (a) In dry conditions ($n_f < 0.14$), the rate constants for 1,2,4-TNB formation with KNO_2 are slightly less than those with $NaNO_2$. However, at $n_f > 0.14$, the rates of formation of 1,2,4-TNB are higher when KNO_2 is used instead of $NaNO_2$. This may well be due to the higher solubility ratio and lower lattice energy of KNO_2 than for $NaNO_2$.[16] (b) The threshold value for 1,2,4-TNB formation is the water content of the reaction mixture above which 1,2,4-TNB is not formed. These threshold values in terms of n_f for 1,2,4-TNB formation with KNO_2 and $NaNO_2$ for 0.24 and 0.22, respectively. This may be due to higher hygroscopicity of KNO_2. (c) The maximum rate of 1,2,4-TNB formation at 70 °C is obtained at $n_f = 0.19$ for $NaNO_2$ and $n_f = 0.21$ for KNO_2, and thereafter the rate decreases.

(2) From curves 1(b) and 1(c), it is seen that the threshold value for 1,2,4-TNB formation becomes less when the PTC concentration is increased. When the BTEAC concentrations are 0.001 and 0.002 M, the threshold values in terms of n_f are 0.24 and 0.13, respectively.

(3) For 2,4-DNP, rates of formation are higher with KNO_2 than with $NaNO_2$.

(4) The rates increase for both 1,2,4-TNB and 2,4-DNP formation when the PTC concentration is increased.

Experimental Section

All the reagents used were commercially available high purity materials. The solid reagents and PTC's were dried in an oven at 105 °C and stored in a vacuum desiccator. Toluene was dried over CaH_2. The residual water (wt % H_2O) in these reagents as determined by Karl Fischer titration was as follows: $NaNO_2$, 0.027; KNO_2, 0.47; BTEAC, 1.3; toluene, 0.01; $NaHCO_3$, 0.036. UV spectra and absorbance were recorded on a Shimadzu 240 UV–vis spectrophotometer. IR spectra were recorded on a Shimadzu IR-440 using KBr pellets.

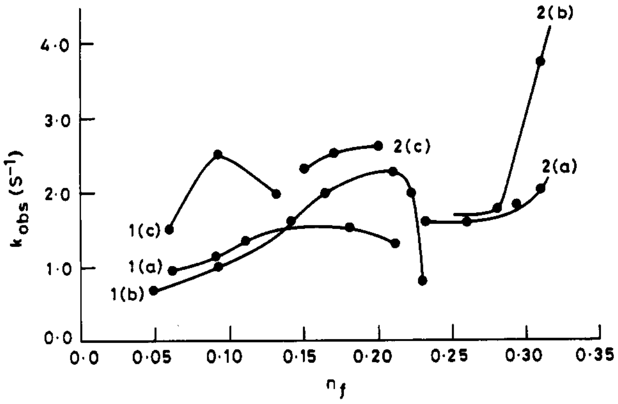

Figure 1. Plot of pseudo-first-order rate constants for 1,2,4-TNB (1(a), 1(b), and 1(c)) and 2,4-DNP (2(a), 2(b), and 2(c)) formation with n_f. Reaction conditions: 2,4-DNCB, 10 mmol; toluene, 100 mL; temperature, 70 °C; for 1,2,4-TNB, residual water is from toluene, BTEAC, and $NaNO_2$ or KNO_2; for 2,4-DNP, residual water is from toluene, BTEAC, $NaNO_2$ or KNO_2, and $NaHCO_3$; 1(a), $NaNO_2$, 20 mmol; BTEAC, 1 mmol; residual water 0.0129 mL; 1(b), KNO_2, 20 mmol; BTEAC, 1 mmol; residual water, 0.0230 mL; 1(c), KNO_2, 20 mmol; BTEAC, 2 mmol; residual water, 0.0232 mL; 2(a), $NaNO_2$, 20 mmol; BTEAC, 1 mmol; residual water, 0.0149 mL; 2(b), KNO_2, 20 mmol; BTEAC, 1 mmol; residual water 0.024 mL; 2(c), KNO_2, 20 mmol; BTEAC, 2 mmol; residual water 0.0244 mL.

Preparation of 1,2,4-TNB. 2,4-DNCB (2.02 g, 0.01 mol), BTEAC (0.227 g, 0.001 mol), and KNO_2 (1.70 g, 0.02 mol) in 25 mL of toluene were stirred magnetically at 70 °C for 6 h. The toluene layer was separated, washed with water (10 mL × 3), and dried over anhydrous Na_2SO_4. When toluene was evaporated under reduced pressure, crude 1,2,4-TNB was obtained. This was recrystallized from methanol (1.51 g, yield 71%, mp 61 °C). The product showed an IR spectrum that was superimposable upon that of an authentic sample prepared from 2,4-dinitroaniline.[17] The C–Cl stretching frequency at 730 cm^{-1} was absent, while the nitro group frequencies were prominent at 1616, 1320, and 865 cm^{-1}. The UV spectrum was also identical with an authentic sample (λ_{max} 360 nm).

Preparation of 2,4-DNP. 2,4-DNCB (2.02 g, 0.01 mol) and BTEAC (0.227 g, 0.001 mol) in 25 mL of toluene and KNO_2 (1.7 g, 0.02 mol) or $NaNO_2$ (1.38 g, 0.02 mol) and $NaHCO_3$ (3.3 g, 0.04 mol) in 5 mL of H_2O were stirred together magnetically at 70 °C for 5 h. The toluene layer was separated, washed with water (10 mL × 3), and dried over anhydrous Na_2SO_4. When the toluene was evaporated under reduced pressure, 2,4-DNP was obtained. This was recrystallized from alcohol (1.63 g, yield 89%, mp 105 °C). The product was identified by mp, TLC, and IR spectra by comparing it with the standard sample.

Kinetics. The reactants as shown in Figure 1 were stirred (300 rpm) together for 4 h at 70 ± 0.05 °C in a thermostated water bath. The reaction was followed by measuring the absorbance for 1,2,4-TNB (360 nm) and 2,4-DNP (310 nm) at the interval of 30 min. When 2,4-DNP started forming, $NaHCO_3$ (3.3 g, 0.04 mol) was added. Water was added with the help of a microsyringe (10 μL) in solid KNO_2 and $NaNO_2$ and kept overnight for equilibration. Total water content of the reaction mixture (solid and solvent) was also determined after the reaction.

Abbreviations. BTEAC, benzyltriethylammonium chloride; 2,4-DNCB, 2,4-dinitrochlorobenzene; 2,4-DNP, 2,4-dinitrophenol; LLPTC, liquid–liquid phase-transfer catalysis; n_f, total number of moles of water per mole of nitrite salt; PTC, phase-transfer catalysis; Q, quaternary ammonium salt; SLPTC, solid–liquid phase-transfer catalysis; 1,2,4-TNB, 1,2,4-trinitrobenzene.

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Registry No. 2,4-DNCB, 97-00-7; 2,4-DNP, 51-28-5; 1,2,4-TNB, 610-31-1; BTEAC, 56-37-1; $NaNO_2$, 7632-00-0; KNO_2, 7758-09-0; H_2O, 7732-18-5.

Formation and Characterization of Lumitetracycline-Type Photoproducts from Members of the Tetracycline Family[1]

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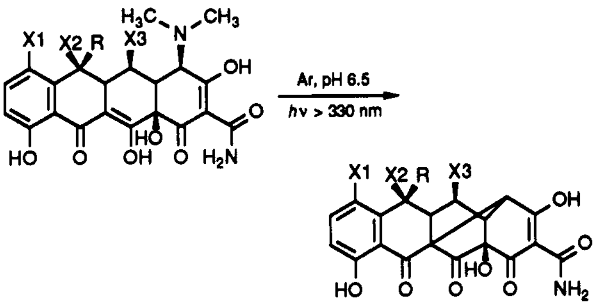
Most of the tetracycline family of antibiotics are known to be phototoxic, but the origin of this effect is not yet understood.[2] For example, it is unclear whether the agent responsible for the dermatoses is the parent tetracycline (Tc) or a photoproduct derived therefrom. It is therefore noteworthy that a Tc photoproduct, lumitetracycline (LTc), has recently been isolated in greater than 70% yield. LTc has been found to form in both organic and aqueous media and to be quenched when the photolysis is conducted in the presence of oxygen.[2] We now report that the Tc to LTc reaction is general for the tetracycline family and has been observed for doxycycline (DOX), oxytetracycline (OTc), chlorotetracycline (CTc), demeclocycline (DEM), and minocycline (MIN) (cf. eq 1).



(1)

		X1	X2	X3	R
tetracycline	(Tc)	H	OH	H	CH_3
oxytetracycline	(OTc)	H	OH	OH	CH_3
doxycycline	(DOX)	H	H	OH	CH_3
chlorotetracycline	(CTc)	Cl	OH	H	CH_3
demeclocycline	(DEM)	Cl	OH	H	H
minocycline	(MIN)	NMe_2	H	H	H

Results and Discussion

Formation and Isolation of Photoproducts. Solutions of CTc, DEM, OTc, DOX, and MIN in pH 6–6.5 phosphate buffer were irradiated under anaerobic conditions with long-wavelength UV light ($\lambda > 330$ nm) to yield photoproducts that were isolated as light yellow powders in yields of 35–49%. HPLC analysis of the photolysate gave evidence for little unreacted starting material, with the exception of MIN where the conversion to LMIN was low (8%) and most of the starting material was found to be present after the photolysis. Both the photolysis and isolation conditions were those developed for the Tc to LTc conversion and thus were not optimized for these other members of the tetracycline family.

Table I. Absorption Maxima for Tetracyclines and Lumitetracyclines[a]

	λ_1	ϵ_1	λ_2	ϵ_2	λ_3	ϵ_3
Tc	363	13800	268	18600		
OTc	357	12600	267	20900		
DOX	351	13200	267	17400		
CTc	355	10000	270	10000		
DEM[b]	370	12309	267	18356		
MIN[b]	357	13361	265	18040		
LTc	340	4440	265	20800	212	17400
LOTc	337	4840	266	23000	209[c]	20000
LDOX	343	4930	269	25800	209[c]	20100
LCTc	355	4780	265	21100	224	20000
LDEM	353	5010	264	23400	220	21900
LMIN[d]	378	5300	269	38000		

[a] All data for 0.01 N HCl in methanol unless otherwise noted; tetracycline values from ref 3. [b] Determined in these laboratories by Changhe Xiao. [c] Base-line drift in the 200–210 region may have affected this value. [d] Determined in MeOH.

Spectroscopy. UV absorption spectra of the lumi compounds were taken in 0.01 N HCl in methanol, and the results are presented in Table I, together with UV data for several of the tetracyclines drawn from the literature.[3] The UV data for the photoproducts are generally consistent throughout the series, with a longer wavelength band at 330–350 nm having an extinction coefficient of ca. 5000, and a second maximum at 265–270 nm with an extinction coefficient of ca. 20 000. All the lumi products show a marked reduction in the extinction coefficient associated with λ_1, the transition centered in rings BCD (the aryl ring is ring D). LOTc and LDOX also show a blue shift in λ_1 relative to their parent substrates, as is seen for LTc relative to Tc. Both effects are anticipated as a consequence of the change in the BCD chromophore upon forming the C11a to C4 bridge.

In every case the mass spectrum of the lumi product contains a molecular ion 45 amu less than the mass of the parent compound, consistent with the net loss of dimethylamine in each of the transformations. The ^1H NMR spectral data for the lumi products in acetone-d_6 are presented in Table II and in each case one observes (1) the number of aliphatic and aromatic protons anticipated for a parent compound minus dimethylamine, (2) the presence of the hydroxyl, phenol, amide, and 3-enol protons, but the absence of a resonance corresponding to the 12-enol hydrogen (expected at δ 13–15), and (3) downfield shifts associated with the bridgehead H4 and H4a resonances. The assignments of the aliphatic region resonances were based on matching their coupling patterns to the coupling patterns for the parent tetracyclines (there is an excellent correlation among the coupling constants for the various lumi derivatives). The aromatic region resonances were assigned by comparison of the chemical shifts to those observed for Tc.[2]

Proton-decoupled ^{13}C NMR and APT (attached proton test) spectra were obtained for each of the photoproducts in acetone-d_6, with the exception of LMIN for which insufficient material was available. The ^{13}C chemical shifts are summarized in Table III. Calculated chemical shifts derived from the LTc spectral data, with adjustments for

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