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REACTIONS OF MOLECULES WITH TWO EQUIVALENT FUNCTIONAL GROUPS. 3. NUCLEOPHILIC SUBSTITUTION REACTIONS OF α,ω-DIBROMOALKANES [$Br(CH_2)_nBr$, $n = 3,4,5$] WITH POTASSIUM CYANIDE

IOANNIS CONSTANTINIDES AND ROGER. S. MACOMBER*

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221-0172, USA

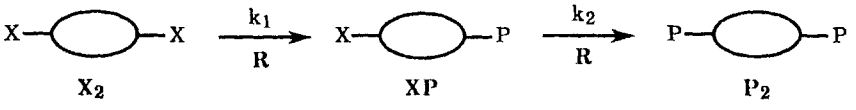
The substitution reactions of $Br(CH_2)_nBr$(1, $n = 3$–5) with KCN in methanol were studied in detail. Second-order rate constants k_1 [formation of the mononitrile (2) from 1] and k_2 (formation of the dinitrile (3) from 2] were determined, as were the rates for the reaction of $H(CH_2)_nBr$ (4, $n = 3$–5) with KCN under the same conditions. The ratios $k_2/k_1(=x)$ of the three homologs of 1 were found to be 1·15, 0·77 and 0·61 for $n = 3$, 4 and 5, respectively; a x value of 0·5 indicates that the functional groups behave independently. The second-order rate constants k_1 (statistically corrected) and k_2 exhibit modest enhancements compared with model compound 4 when any of the following substituents are present: δ- or ε-bromo, γ-, δ-, or ε-cyano. By contrast, a γ-bromo substituent slightly retards the rate. These results indicate that the functional groups do influence each other to a modest degree by field effects which accelerate the reactions. Steric effects do not appear to play a significant role.

INTRODUCTION

Recently our group began a study of competitive-consecutive reactions as depicted generically in Scheme 1, where a substrate molecule X_2 (with two symmetry-equivalent functional groups) reacts with reagent R that converts group X to P.[1–3] Chemists often face the problem of carrying out a reaction at just one of two similar functional groups in a substrate molecule; hence there is always interest in the development of methodologies for controlling the outcome of such reactions.[4]

Normally, when less than two equivalents of R are used, the final reaction mixture contains both products, XP and P_2, in addition to starting material X_2. It can be shown[1] that if the functional groups in X_2, XP and P_2 are truly independent, and the reactions are kinetically controlled (irreversible), the fraction of each compound in the final product mixture can be readily calculated from r, the initial mole ratio of R to X_2 ($0 < r < 2$). A consequence of the independence of the functional groups is that X_2 is exactly twice as reactive as XP (i.e. $k_2/k_1 \equiv x = 0{\cdot}5$).

The independent functional groups model was recently tested using the acetylation of *p*-, *m*- and *o*-bis(hydroxymethyl)benzene.[2] The *para* and *meta* isomers behaved essentially as predicted ($x = 0{\cdot}548$ and 0·521, respectively), presumably because the functional groups are rigidly constrained from direct interaction and long-range electronic effects are minimal. The



Scheme 1

* Author for correspondence.

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largest deviation from the model was exhibited by the *ortho* isomer ($\rho = 0{\cdot}605$), and this was interpreted as a quantitative measure of the intramolecular interactions between functional groups.[2]

Although the mutual influence of two functional groups in a molecule has long been at the heart of physical organic chemistry, the factors that control such interactions are still debated[5] and often unknown.[6] Quantitative descriptions of such interactions should lead to a better understanding of their nature and magnitude.

We report here a continuation of this work, a study of nucleophilic substitution reactions of several α,ω-dibromoalkanes [**1**, $Br(CH_2)_nBr$, $n = 3,4,5$] with KCN (Scheme 2). The selected substrates contain two functional groups (the bromines) attached to a conformationally flexible backbone. Our goal was to determine the magnitude of their interactions with each other and/or with the product functional group (—CN) through detailed kinetic analyses.

$$\underset{\mathbf{1}}{Br(CH_2)_nBr} \xrightarrow[KCN,\ MeOH]{k_1} \underset{\mathbf{2}}{Br(CH_2)_nCN} \xrightarrow[KCN,\ MeOH]{k_2} \underset{\mathbf{3}}{NC(CH_2)_nCN}\ (n = 3\text{–}5)$$

Scheme 2

The effect of variation in the alkyl chain length of the substrate was expected to provide information about possible intramolecular steric and stereoelectronic effects. It was hoped that determination of actual rate constants for these reactions, and comparison with the corresponding rates of monofunctional model substrates, would lead to a consistent explanation of non-statistical product ratios previously observed by other workers in related systems. For example, it has been reported that α,ω-dichloroalkanes react with NaCN to give mainly ω-chloronitriles if n is odd (implying that $k_1 \gg 2k_2$) and α,ω-dicyanoalkanes if n is even ($k_1 \ll 2k_2$).[7] However, other studies found no such effect.[8] To the best of our knowledge, only isolated product ratios have been studied in such systems; the direct measurement of k_1 and k_2 has not been reported.

RESULTS

Substrate molecules such as those in Scheme 2, containing only primary halides, give kinetically well behaved second-order reactions with mildly basic nucleophiles such as KCN in methanol. In this study, calibrated gas chromatography (GC), NMR and titrimetry[9] were used complementarily for the kinetic analyses (see below).

Initially, the rate of reactions of KCN with 1-bromoalkanes (**4**) having 3–5 carbon atoms were studied at 60 °C (Scheme 3).

$$\underset{\mathbf{4}}{H(CH_2)_nBr} + KCN \xrightarrow[60\ ^\circ C]{MeOH} \underset{\mathbf{5}}{H(CH_2)_nCN} + KBr \qquad n = 3,4,5$$

Scheme 3

In order to avoid possible concentration-based medium effects on the rate constants, the initial concentrations of substrates and KCN were kept within the same range. Control experiments showed that under these conditions, attack by methanol on the bromoalkanes was very slow. This was also confirmed by analysis of the final reaction mixture from each substrate, showing only minor amounts (*ca* 5%) of solvolysis products.

As shown in Table 1, all three homologs of **4** (initial concentration *ca* 0·250 M) reacted with KCN (initial concentration *ca* 0·300 M) in methanol at 60 °C with nearly the same rate constant (*ca* $1{\cdot}1 \times 10^{-4}$ l mol^{-1} s^{-1}, see runs 1–16). All kinetic runs exhibited cleanly linear second-order kinetics (first order in both **4** and KCN) to at least 55% reaction (with correlation coefficients of $\geqslant 0{\cdot}990$). The close agreement between the rate constants of different runs for each substrate, even when different analytical techniques were used, indicates that all three analytical techniques (NMR, GC and titrimetry) give independently accurate results. Analysis of the reaction mixtures versus time by NMR gave the relative concentrations of **4** and **5**; calibrated GC analysis was used to determine the concentrations of **4**; titrimetry was used to determine the concentration of unreacted KCN (see Experimental).[9] In the case of **4**, any one of these techniques alone is sufficient to accurately determine the second-order rate constant of the reaction.

$$\underset{\mathbf{2}}{Br(CH_2)_nCN} \xrightarrow[60\ ^\circ C]{KCN} \underset{\mathbf{3}}{NC(CH_2)_nCN}\ (n = 3\text{–}5)$$

Scheme 4

Exactly the same procedures were used for the reactions in Scheme 4, where the three authentic homologs of intermediate bromonitrile **2** were allowed to react with KCN under the same conditions (runs 17–31, Table 1). Specifically, the rate constants for these three substrates exhibited approximately the same values ($1{\cdot}94 \times 10^{-4}$–$2{\cdot}11 \times 10^{-4}$ l mol^{-1} s^{-1}) with **2** ($n = 3$) giving the slowest reaction and **2** ($n = 4$) the fastest (runs 17–31). Note that these rate constants represent directly determined experimental values for k_2 in Scheme 2. As can be seen from Tables 1 and 3, these rate constants are *ca* 70–80% higher than those of the corresponding 1-bromoalkanes. Again, linear second-order kinetics were observed in all cases to at least 55% reaction (with correlation coefficients of $\geqslant 0{\cdot}994$), and all analytical techniques gave comparable results.

For the reaction of dibromide **1** ($n = 3$–5) with KCN, a combination of analytical techniques was used to

Table 1. Rate constants for the reaction of **2** ($n = 3$–5) and **4** ($n = 3$–5) with KCN in methanol at 60 °C[a]

Compound	Run No.	Analytical technique	$k(10^{-4}$ l mol^{-1} s$^{-1})$[b]	
4($n = 3$)	1	NMR	1·30	$\bar{k} = 1·16 \pm 0·11$
	2	Titrimetry	1·02	
	3	Titrimetry	1·15	
	4	Titrimetry	1·15	
4($n = 4$)	5	Titrimetry	1·12	$\bar{k} = 1·11 \pm 0·08$
	6	Titrimetry	1·22	
	7	Titrimetry	1·08	
	8	Titrimetry	1·03	
4($n = 5$)	9	Titrimetry	1·00	$\bar{k} = 1·07 \pm 0·15$
	10	Titrimetry (and GC)	1·15(1·17)	
	11	Titrimetry	1·13	
	12	Titrimetry	1·35	
	13	Titrimetry	0·88	
	14	GC	0·93	
	15	GC	1·05	
	16	GC	1·07	
2($n = 3$)	17[c]	NMR	2·13	$\bar{k} = 1·98 \pm 0·22$
	18	Titrimetry	1·90	
	19[d]	Titrimetry	1·97	
	20	Titrimetry	1·68	
	21	Titrimetry	1·72	
	22	Titrimetry	1·95	
	23	Titrimetry	2·30	
	24	GC	2·18	
2($n = 4$)	25	Titrimetry	1·95	$\bar{k} = 2·11 \pm 0·23$
	26	Titrimetry	1·82	
	27	Titrimetry	2·20	
	28	Titrimetry	2·20	
	29	GC	2·40	
2($n = 5$)	30	Titrimetry	1·90	$\bar{k} = 1·94 \pm 0·05$
	31	Titrimetry	1·97	

[a] For all runs (unless indicated otherwise) $[\mathbf{4}]_0$ or $[\mathbf{2}]_0 = 0·25 \pm 0·04$ M and $[KCN]_0 = 0·30 \pm 0·04$ M.
[b] Error limits are standard deviations.
[c] $[KCN]_0 = 0·16$ M.
[d] $[\mathbf{2}\ (n = 3)]_0 = 0·34$ M.

determine the concentrations of **1**, **2** and **3** as a function of time for each kinetic run (see Experimental). The overall reaction (Scheme 2) can be characterized as involving consecutive–competitive second-order reactions; all three concentrations must be known to extract the rate constants k_1 and k_2. An algorithm developed by Wideqvist,[10] which was successfully utilized in our previous study,[2] determines k_1 and $\varkappa$ directly from concentration measurements; from these, k_2 can be easily calculated. Alternatively, the value of $\varkappa$ can be determined by a computational method[3] in which the best fit is found between the experimental concentration data and those predicted theoretically, using a variation of Euler's method for numerical integration of the appropriate differential equations. The $\varkappa$ values thus determined are shown in parentheses in Table 2 and are seen to agree well with the results of the Wideqvist algorithm (deviations 1–22%).

The results for the three homologs of **1** are summarized in Table 2. For each kinetic run, the final product ratios were also determined by GC analysis at $t = \infty$, and were compared with values predicted from the independent functional groups model.[1] In Table 3, the average rate constants for each compound are expressed relative to the rate for the respective 1-bromoalkane.

As can be seen from Table 2 (runs 32–40), all three homologs of **1** deviate markedly from independent functional group behavior. They exhibit $\varkappa$ values substantially greater than 0·5, and the observed final product mixtures are significantly different than those predicted for independent behavior. The deviations are

Table 2. Kinetic and product ratio data for **1** ($n = 3$–5)[a]

Compound	Run no.	k_1[b]	$\varkappa$[b,c]	k_2[b]	r	Observed product mixtures[d] (predicted[e]) f_{X_2}	f_{XP}	f_{P_2}	Average deviation (%)[f]
1($n = 3$)	32	2·07	1·07(1·05)	2·21	1·211	0·260(0·156)	0·324(0·478)	0·416(0·367)	37
	33	2·37	1·10(1·09)	2·61	1·202	0·242(0·159)	0·290(0·480)	0·468(0·361)	41
	34	2·02	1·14(1·13)	2·30	1·152	0·288(0·180)	0·314(0·488)	0·398(0·332)	56
	35[g]	1·95	1·14(1·29)	2·22	2·000				
	36[h]	2·00	1·28(1·36)	2·56	2·000				
	Av·	2·08 ± 0·17	1·15 ± 0·08	2·38 ± 0·19					
1($n = 4$)	37	3·17	0·73(0·89)	2·31	1·190	0·246(0·164)	0·369(0·482)	0·385(0·354)	27
	38	3·10	0·80(0·94)	2·48	1·226	0·187(0·150)	0·339(0·474)	0·474(0·376)	26
	Av·	3·14 ± 0·05	0·77 ± 0·05	2·40 ± 0·12					
1($n = 5$)	39	3·28	0·57(0·70)	1·87	1·194	0·197(0·162)	0·455(0·481)	0·348(0·356)	10
	40	3·18	0·64(0·68)	2·04	1·220	0·244(0·152)	0·465(0·476)	0·292(0·372)	28
	Av·	3·23 ± 0·07	0·61 ± 0·05	1·96 ± 0·12					

[a] For all runs (unless indicated otherwise) $[\mathbf{1}]_0 = 0{\cdot}25 \pm 0{\cdot}01$ M and $[KCN]_0 = 0{\cdot}30 \pm 0.01$ M.
[b] Rate constants are in units of 10^{-1} l mol^{-1} at 60 °C. $\varkappa = k_2/k_1$. Error limits are standard deviations.
[c] Values in parentheses calculated with the method in Ref. 3.
[d] At $t = \infty$.
[e] Calculated with equations relating product ratios to $[R]_0/[X_2]_0$ (Ref. 1).
[f] Average absolute deviation as a percentage of predicted value.
[g] $[\mathbf{1}]_0 = 0{\cdot}20$ M, $[KCN]_0 = 0{\cdot}40$ M.
[h] $[\mathbf{1}]_0 = 0{\cdot}15$ M, $[KCN]_0 = 0{\cdot}30$ M.

Table 3. Relative rate constants

Parameter	$H(CH_2)_nBr$ (**4**)[a] $n = 3$	$n = 4$	$n = 5$	$NC(CH_2)_nBr$ (**2**)[b] $n = 3$	$n = 4$	$n = 5$	$Br(CH_2)_nBr$ (**1**)[c] $n = 3$	$n = 4$	$n = 5$
k_1(rel.)	1·00	0·96	0·92	—	—	—	1·79	2·83	3·02
k_2(rel.)	—	—	—	1·71	1·90	1·81	2·05	2·16	1·83
$\varkappa = k_2/k_1$	—	—	—	—	—	—	1·15	0·77	0·61

[a] The values of k_1 are expressed relative to the value for **4** ($n = 3$).
[b] The values of k_2 are those directly measured (Table 1), expressed relative to the k_1 value of **4** with the same number of carbons.
[c] The values of k_1 (directly measured) and k_2 (indirectly calculated) are expressed relative to the k_1 value of **4** with the same number of carbons.

most pronounced in the case of **1** ($n = 3$) (runs 32–36), where $\varkappa = 1{\cdot}15$, and least pronounced in **1** ($n = 5$) (runs 39 and 40), where $\varkappa = 0{\cdot}61$.

It should also be noted that the directly determined values of k_2 obtained from the reactions of authentic **2** differ by an average of less than 11% from the values determined indirectly by Wideqvist's algorithm (compare runs 17–24 with 32–36, 25–29 with 37 and 38 and 30 and 31 with 39 and 40, Tables 1 and 2), which we interpret as satisfactory agreement.

Comparing the values of $k_1/2$ for the three homologs of **1** with the k values of the corresponding 1-bromoalkane **4**, it can be seen that the additional bromine in **1** ($n = 3$) causes a 10% decrease in rate constant (Table 3). By contrast, in the case of **1** ($n = 4$) and **1** ($n = 5$) there is a significant increase in $k_1/2$ (35–40%) compared with **4** ($n = 4$) and **4** ($n = 5$) respectively.

DISCUSSION

Perhaps the most important finding in this work is that even in these conformationally mobile molecules, the two functional groups in **1** and **2** depart by less than a factor of 2 from independent kinetic behavior. Nonetheless, the results in Table 3 demonstrate several things. First, in comparing the three homologs of **4**, there seems to be a slight (8%) but uniform decrease in the rate constant as the carbon chain length increases from three to five. Admittedly, however, the magnitude of this decrease essentially matches the experimental

uncertainty in the k values. Still, it is clear that the steric bulk of the hydrocarbon chain does not appear to inhibit significantly the reactivity of these three substrates. It is also clear that δ- and ε-bromo substituents, as well as γ-, δ- and ε-cyano substituents, mildly accelerate S_N2 displacement of bromide at the α-carbon relative to a similarly located hydrogen. The largest of these accelerations is 90% is caused by the cyano group of **2** ($n = 4$). By contrast, a γ-bromo substituent has a slight (*ca* 10%) retarding effect [**1** ($n = 3$)], although this difference is again at the level of experimental uncertainty in the k values. The combination of these effects results in a monotonic decrease in $\varkappa$ from 1·15 to 0·61 as the carbon chain length increases from $n = 3$ to 5. As stated before, a $\varkappa$ value of 0·5 is predicted for independent functional group behavior.[1] Our results contrast with the alternating behavior reported by others.[7]

Bimolecular nucleophilic substitution reactions are mainly influenced by steric effects, though rate acceleration due to certain electron-withdrawing α-substituents are also well documented.[11] It is highly unlikely that the modest accelerations described above are manifestations of steric effects. Instead, the accelerations must be due to modest electron-withdrawing polar effects of the non-reacting neighboring group, thereby stabilizing the electron rich S_N2 transition state, including perhaps its solvation.[12]

Our results are fully consistent with the Swain–Lupton[13] inductive substituent parameters F (0·72 for Br and 0·90 for CN), indicating that remote CN substituents should accelerate the reaction more than comparably positioned Br substituents. However, the fact that the number of carbons between the reaction center and the electron-withdrawing substituent has relatively little effect on the magnitude of rate acceleration [compare rates of **2** ($n = 3$), **2** ($n = 4$) and **2** ($n = 5$), and also the rates of **1** ($n = 4$) and **1** ($n = 5$)] suggests that these are conformationally averaged field effects transmitted through space rather than through σ-bonds.

Although in 1,3-dibromopropane [**1** ($n = 3$)] the electron-withdrawing γ-bromine is closer to the reaction center than in **1** ($n = 4$) and **1** ($n = 5$), the reaction is slightly slower. Steric effects in this case could be responsible for overcoming any favorable electronic effect.

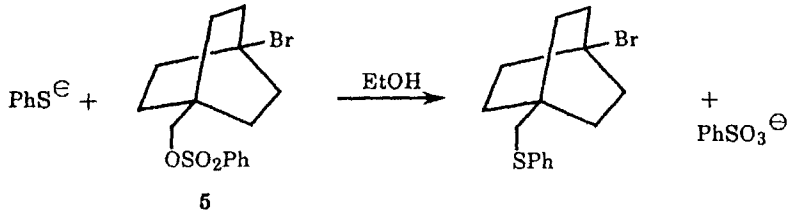
Our results are consistent with some observations of rate accelerations by remote substituents in S_N2 reactions previously reported in the literature. Conant *et al.*[14] found that chloroalkyl nitriles [$NC(CH_2)_nCl$] react 2·8 ($n = 2$), 3·7 ($n = 3$), and 2·8 ($n = 4$) times faster than 1-chlorobutane with KI in acetone. Similarly, Hine *et al.*[15] reported that displacement by thiophenoxide of the iodine in $Cl(CH_2)_nI$ exhibited the following rates relative to n-C_3H_7I: $n = 3$, 1·08; $n = 4$, 1·59; and $n = 5$, 1·52. Holtz and Stock[16] found that 4-bromo compound **5** reacts twice as fast as the unbrominated analog with thiophenoxide ion in ethanol (Scheme 5). The latter result is especially relevant, because the rigidity of these substrates allows the isolation of substituent polar effects without the influence of steric effects.

CONCLUSIONS

The reaction of three homologous α,ω-dibromoalkanes with KCN in methanol gives product ratios that are significantly different from those predicted by the independent group model. In all three cases the value of $\varkappa$ ($= k_2/k_1$) is greater than 0·5. The smallest value, $\varkappa = 0{\cdot}61$, is exhibited by the 1,5-dibromopentane system [**1** ($n = 5$)] and the largest, $\varkappa = 1{\cdot}15$ (greatest deviation from the model), is exhibited by 1,3-dibromopropane [**1** ($n = 3$)]. With the exception of the latter compound, all other homologs of **1** and **2** react significantly faster than the corresponding n-bromoalkane; these results are best explained by polar field effects of the non-reacting Br or CN functional group. Steric effects do not appear to play a significant role.

EXPERIMENTAL

The instruments used included the following: Bruker AC250 (NMR); Hewlett-Packard Model 700 GC (8 ft × $\frac{1}{8}$ in o.d. column packed with 2·8% Carbowax 20M on Chromosorb G-HP, 80–100 mesh) with HP 3394 integrator and thermal conductivity detector; Varian Model 90-P GC (12·5 ft × $\frac{1}{4}$ in. o.d. column packed with 18% Carbowax 20M on Chromosorb W, 60–80 mesh) with disc integrator and thermal conductivity detector. The GC analyses for the reaction of **4**



5

Scheme 5

($n = 5$) and KCN were performed on the 90-P. The analyses for the reactions of **2** ($n = 3$), **1** ($n = 3$), **1** ($n = 4$) and **1** ($n = 5$) were performed with the HP700.

The calibrated response factors [RF_X = (moles X/moles standard) (signal of standard/signal of X); where the internal standard is 1, the appropriate homolog was used] for the relevant compounds (vs internal standards) are as follows: **4** ($n = 5$) 1·09 (vs *m*-xylene); **2** ($n = 3$) 1·09 (vs benzyl alcohol); **2** ($n = 4$) 1·04 (vs benzyl alcohol); **2** ($n = 3$) 1·12 (vs **1**); **2** ($n = 4$) 1·04 (vs **1**); **2** ($n = 5$) 1·05 (vs **1**); **3** ($n = 3$) 1·12 (vs **1**); **3** ($n = 4$) 0·95 (vs **1**); and **3** ($n = 5$) 1·12 (vs **1**).

Materials. Potassium cyanide, **1** ($n = 3$–5), **2** ($n = 3$, 4), **3** ($n = 4$, 5) and **4** ($n = 3$–5) were supplied by Aldrich Chemical; the KCN was pulverized and oven dried at 80 °C before use. Anhydrous methanol was prepared by refluxing reagent-grade solvent with magnesium metal and iodine, followed by distillation and storage over molecular sieves.[17] All glassware was oven dried.

Synthesis of 1,3-dicyanopropane [**3** ($n = 3$)]. To a solution of 2·08 g of **1** ($n = 3$) (10·3 mmol) in 100 ml of dry methanol were added 2·51 g of KCN (38·5 mmol). A reflux condenser was attached and the solution was stirred at 60 °C for 5 days. After this period GC analysis of the reaction mixture showed only trace amounts of **1** ($n = 3$) and **2** ($n = 3$). Rotary evaporation of the solvent and extraction of the residue with diethyl ether (3 × 75 ml) gave, after evaporation, 0·88 g of pale yellow liquid which was distilled bulb-to-bulb at 0·2 mmHg to give 0·63 g (65%) yield of colorless liquid,[18a–c] whose ^{1}H NMR spectrum matched the previously reported one.[18d]

Synthesis of 6-bromohexanenitrile [**2** ($n = 5$)]. To a solution of 48·45 g of 1,5-dibromopentane (0·211 mol) in 100 ml of MeOH were added 10·0 g of KCN (0·154 mol). A reflux condenser was attached and the solution was stirred at 70 °C for 4 days. Rotary evaporation of the solvent and fractional distillation twice of the residue under reduced pressure afforded 7·7 g (21% yield) of colorless liquid,[19] b.p. = 132 °C (18 mmHg) [lit.[8b] b.p. = 134.4 °C (15 mmHg)].

Kinetic methods. (A) NMR study. To an NMR tube containing a weighed amount of KCN in *ca* 0·4 ml of methanol-d_4 was added a weighed amount of **2** ($n = 3$) or **4** ($n = 3$). The solution was diluted with additional methanol-d_4 to bring the volume to exactly 0·50 ml, then the NMR tube was sealed and inserted into an oil-bath maintained at 60 ± 0·1 °C. Every 0·5–4 h the ^{1}H NMR spectrum was obtained. Concentrations of starting alkyl bromide and nitrile product were determined from peak integrations of central —CH_2— signals of each, and the known initial concentration of the starting bromoalkane. The concentration of CN^- was calculated from its known initial concentration and the mass balance.

(B) Gas chromatographic and titration analyses. To a 20 ml volumetric flask containing *ca* 8 ml of dry methanol and a weighed amount of KCN was added a weighed amount of **1**, **2** or **3** (and a weighed amount of internal standard, where appropriate). The volumetric flask was filled to the mark with dry methanol and, after complete mixing, the solution was transferred into a 20 ml round-bottomed flask with stirring bar, which was then sealed and inserted in an oil-bath maintained at 60 ± 0·1 °C. Aliquots (1·0 ml) of the solution were withdrawn every 0·5–4 h until the reaction was *ca* 70% complete, then also after *ca* 48 h ($t = \infty$). The reaction mixtures were homogeneous until *ca* 50% completion, at which point a white precipitate (presumably KBr) formed. Each aliquot was mixed in an Erlenmeyer flask with 50 ml of water and 1–2 ml of 1 M $NaHCO_3$ and titrated with standard iodine solution (0·05 M) until a light yellow color persisted for *ca* 10 s. This iodine solution was prepared and standardized weekly against $Na_2S_2O_3$ solution (which in turn was standardized against KIO_3 solution).[9c] In the case of dibromoalkane substrates (**1**), 1·0–2·0 μl of the same aliquot was analyzed simultaneously by GC and the ratio [**1**]/[**2**] ($\equiv a$) was determined from GC integrations corrected for response factors. The concentrations of **1**, **2**, **3** and CN^- were calculated from the following equations:

$$[\mathbf{1}] = a\left(\frac{[CN^-]_0 - [CN^-] - 2[\mathbf{1}]_0}{-1 - 2a}\right)$$

$$[\mathbf{2}] = \frac{[CN^-]_0 - [CN^-] - 2[\mathbf{1}]_0}{-1 - 2a}$$

$$[\mathbf{3}] = [\mathbf{1}]_0 - (a+1)\frac{[CN^-]_0 - [CN^-] - 2[\mathbf{1}]_0}{-1 - 2a}$$

$$[CN^-] = [CN^-]_0 - [\mathbf{2}] - 2[\mathbf{3}]$$

which are readily derived from the mass balance. The aliquot corresponding to $t = \infty$ was analyzed only by GC and the absolute concentrations of **1**, **2** and **3** were determined from GC integrations (corrected for response factors) and the known initial concentration of **1**.

In the case of monobromo substrates (**2** or **4**), GC analysis of each aliquot gave directly the concentration of starting material from its peak integration, the peak integration of the internal standard, the response factor correction and the known concentration of the internal standard. The concentration of CN^- in this case was determined by mass balance.

Determination of rate constants. (A) Monobrominated substrates (**2** and **4**). The rate constant k was determined as the slope of the plot of the standard integrated second-order rate law.

(b) Dibromoalkane substrates (**1**). The graphical integration method of Wideqvist[2,10] was used. For each timed aliquot (data point) the concentrations [**1**], [**2**], [**3**] and [CN^-] were determined by GC and titrimetry as described above. For each data point the values of $\ln([\mathbf{1}]_0/[\mathbf{1}])$, $[\mathbf{2}]/[\mathbf{1}]$, $[\mathbf{1}]_0 - [\mathbf{1}]$, θ and u were calculated where θ and u are defined by the following equations and were determined by graphical integrations:

$$\theta = \int_0^t [CN^-]\, dt$$

$$u = \int_0^{[\mathbf{1}]_0 - [\mathbf{1}]} \frac{[\mathbf{2}]}{[\mathbf{1}]}\, d([\mathbf{1}]_0 - [\mathbf{1}])$$

The value of k_1 was found as the slope of a linear plot of $\ln([\mathbf{1}]_0/[\mathbf{1}])$ versus θ (as abscissa). The value of $\varkappa$ was found as the slope of a linear plot of $[\mathbf{2}]/[\mathbf{1}]$ versus u (as abscissa). The value of k_2 was calculated as $\varkappa k_1$.

Alternatively, the value of $\varkappa$ can be determined by varying $\varkappa$ to locate the best fit of the experimental concentration data for each run to the data predicted by the numerical solution of the appropriate differential equations.[3]

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REFERENCES

1. R. S. Macomber and T. T. Bopp, *Synth. Commun.* **10**, 767 (1980).
2. I. Constantinides, M. Lourdes-Guerra and R. S. Macomber, *J. Phys. Org. Chem.* **3**, 789 (1990).
3. R. S. Macomber and I. Constantinides, *J. Chem. Educ.* **68**, 985 (1991).
4. (a) C. C. Leznoff, *Acc. Chem. Res.* **11**, 327 (1978); (b) M. M. Srebnik, T. E. Cole and H. C. Brown, *J. Org. Chem.* **55**, 5051 (1990); (c) H. Ogawa and K. P. Spina, *J. Am. Chem. Soc.* **107**, 1365 (1985); (d) A. T. Costello and D. J. Milner, *Synth. Commun.* **17**, 219 (1987); (e) M. Prashad, J. C. Tomesch and W. J. Houlihan, *Synthesis* 477 (1990).
5. (a) *The Hydrophobic Interaction*, Faraday Symposium, Chemical Society Symposium No. 17, Royal Society of Chemistry, London, 1982; (b) B. M. Trost, D. O'Kronghly and J. L. Belletire, *J. Am. Chem. Soc.* **102**, 7595 (1980); (c) D. A. Evans, K. J. Chapman, D. T. Hung and A. T. Kawaguchi, *Angew. Chem., Int. Ed. Engl.* **26**, 1184 (1987).
6. (a) R. S. Macomber and T. C. Hemling, *J. Am. Chem. Soc.* **108**, 343 (1986); (b) D. A. Kersman, T. C. Hemling and R. S. Macomber, *J. Chem. Res. (S)* 270 (1989); *J. Chem. Res. (M)* 2001 (1989).
7. (a) D. T. Mowry, *Chem. Rev.* **42**, 189 (1948); (b) K. Friedrich and K. Wallenfels, in *The Chemistry of the Cyano Group*, edited by Z. Rappoport, p. 79. Interscience, New York (1970).
8. (a) F. Salmon-Legagneur and C. Neveu, *Bull. Soc. Chem. Fr.* 1345 (1956); (b) J. Cason, L. Wallcave and C. N. Whitesides, *J. Org. Chem.* **14**, 35 (1949); (c) J. J. Harrower, *J. Chem. Soc.* 2048 (1931); (d) L. Rapoport, A. Smith and M. S. Newman, *J. Am. Chem. Soc.* **69**, 693 (1947); (e) Vereinigte Glanzstaff-Fabriken AG, *Br. Pat.* 768 303 (1957); *Chem. Abstr.* **51**, 16515 (1948).
9. (a) F. Sutton, *A Systematic Handbook of Volumetric Analysis*, 11th ed., p. 220. Churchill, London (1924); (b) S. J. M. Auld, *J. Chem. Soc.* **93**, 1251 (1908); (c) D. A. Skoog and D. M. West, *Fundamentals of Analytical Chemistry*, 5th ed., pp. 779–782. Saunders, New York (1988).
10. (a) S. Wideqvist, *Acta Chem. Scand.* **16**, 1119 (1962); (b) S. Wideqvist, *Ark. Kemi* **8**, 545 (1955).
11. T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., pp. 376–379. Harper and Row, New York (1987).
12. T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd ed., pp. 379–381. Harper and Row, New York (1987).
13. G. C. Swain, S. H. Unger, N. R. Rosenquist and M. S. Swain, *J. Am. Chem. Soc.* **105**, 492 (1983).
14. J. B. Conant, W. R. Kirnes and R. E. Hussey, *J. Am. Chem. Soc.* **47**, 188 (1925).
15. J. Hine, S. J. Ehrenson and W. H. Brader, *J. Am. Chem. Soc.* **78**, 2282 (1956).
16. H. D. Holtz and L. M. Stock, *J. Am. Chem. Soc.* **87**, 2404 (1965).
17. A. I. Vogel, *A. Textbook of Practical Organic Chemistry*, 3rd ed., p. 167. Wiley, New York (1956).
18. (a) G. Sosnovsky, J. A. Krogh and S. G. Umhoefer, *Synthesis* 722 (1979); (b) F. L. Cook, C. W. Bowers and C. L. Liotta, *J. Org. Chem.* **39**, 3416 (1974); (c) G. Simchen and H. Kobler, *Synthesis* 605 (1975); (d) *NMR Standard Spectra Collection*, No. 251. Sadtler Research Laboratories, Philadelphia (1969).
19. V. Gundula Voss and H. Gerlach, *Helv. Chim. Acta* **66**, 2294 (1983).