Kinetics of formation of zwitterionic complexes between 1,3,5-trinitrobenzene and diazabicyclo derivatives

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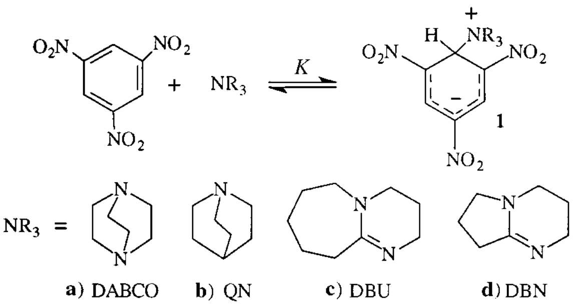
The title reactions are a simple model of nucleophilic attack of tertiary nitrogen on aromatic sp^2 carbons activated by the presence of nitro groups. The formation of the zwitterionic complexes is mildly affected by solvent changes and by addition of tetraethylammonium chloride. The reactivity of 1,4-diazabicyclo[2.2.2]octane, quinuclidine and 1,8-diazabicyclo[5.4.0]undec-7-ene is compared with that of primary and secondary amines.

The reactivity of primary and secondary amines towards activated aromatic substrates in S_NAr reactions has been extensively investigated, whilst the reactivity of tertiary amines has been studied in less detail. This lack of data is probably due to difficulties in obtaining (and in observing) the reaction products. Generally, tertiary amines are used as catalysts in the S_NAr reactions of primary and secondary amines in non-polar solvents.[1]

Previously[2] we reported ^1H NMR spectroscopic evidence for the formation of zwitterionic σ complexes **1** between 1,3,5-trinitrobenzene (TNB) and cyclic tertiary amines (or imines), such as 1,4-diazabicyclo[2.2.2]octane (DABCO), quinuclidine (QN), 1,8-diazabicyclo[5.4.0]undec-7-ene[3,4] (DBU) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), as depicted in Scheme 1.



Scheme 1

The interest in tertiary amines as nucleophiles arises from the absence of N–H protons, and therefore the absence of self association of the nucleophile and/or the absence of proton abstraction complications in the zwitterionic complexes.[5] In particular Scheme 1 illustrates a simple nucleophilic attack not only without the complications generated by proton presence, but also without those arising from the leaving group departure as is usual in S_NAr reactions. In this paper we present some kinetic data concerning the reactions between TNB and DABCO or QN in dimethyl sulfoxide (DMSO) and in THF.

Results

When solutions of TNB and DABCO (or QN) in DMSO (or THF) are mixed, a red colour rapidly develops. This colour is related to the presence of the complexes **1a** (or **1b**).[2] The maximum absorption is at $\lambda = 452$ and 562 nm in agreement with those usually observed when a σ complex is formed.[6,7] These values are satisfactorily stable for samples stored in the dark. Small variations in A_∞ (less than 4%) for samples stored in the dark with the same reaction times as those samples used in determination of k_{obs} values are observed. After the obtainment of A_∞ values, samples exposed to sunlight show a fading of the red colour, and small (and variable) A_∞ values.

Et_3N is unreactive toward TNB: diazabicyclo derivatives are particular tertiary amines, prone to attack on electrophilic carbon.

Kinetic results (k_{obs} in s^{-1}), obtained in DMSO and in THF, are collected in Table 1. The results obtained in the presence of tetraethylammonium chloride are also shown in the same table.

From the data in Table 1, k_1 and k_{-1} values are calculated using the usual eqn. (1),[8] where $[R_3N]_0$ means the initial concentration values of the amine used. k_1 and k_{-1} values are shown in Table 2, together with K values obtained by the Benesi–Hildebrand treatment of A_∞ values. DABCO data are corrected for a statistical factor of 2. In some cases K values from A_∞ values are lower than those obtained from the k_1/k_{-1} ratios. The observed discrepancies may arise from the moderate stability of the zwitterionic complexes **1**.

$$k_{obs} = k_{-1} + k_1 [R_3N]_0 \qquad (1)$$

Discussion

As expected from usual reactivity of tertiary amines, both DABCO and QN are much less reactive than primary or secondary aliphatic amines. For instance, piperidine and *n*-butylamine show k_1 values[9,10] about 10^7 times higher than k_1 for DABCO or QN.

The comparison between the reactivity of these tertiary amines and aromatic amines is difficult because the TNB and aniline alone have not been shown to produce σ complexes.[11]

Under our experimental conditions, we confirm the unreactivity of the aniline towards TNB. As a consequence, DABCO may be considered more reactive than aniline, in agreement with the higher basicity of DABCO: in water, DABCO is about 10^4 times more basic than aniline;[12] it is possible to assume that the relative pK_as of DABCO and aniline remain unchanged in DMSO with respect to water.[7]

It is important to emphasize that k_1 values of DABCO, QN and DBU refer to formation of zwitterionic complexes, while k_1 of primary and secondary amines probably refer to formation of anionic complexes.

Primary and secondary aromatic and aliphatic amines produce complexes with TNB through the catalysis of tertiary amines (Et_3N, DABCO)[9–11] which were claimed to be unreactive[13] towards TNB. The explanation of this catalytic behaviour is the proton abstraction from the zwitterionic complex by the equilibrium shown in Scheme 2, affording the σ-anionic complex **2**.

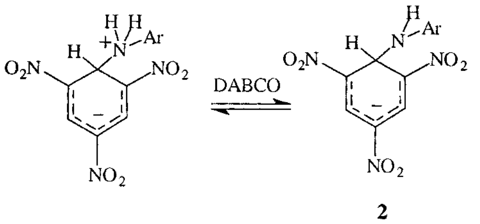
Table 1 k_{obs} values (s^{-1}) for reactions between TNB and DABCO or quinuclidine (QN) at 25 °C

Solvent = DMSO. $[TNB]_0 = 1.22 \times 10^{-4}$ mol dm^{-3}													
$[DABCO]_0/10^{-2}$ mol dm^{-3}	1.74	3.28	3.73	4.90	6.56	6.58	7.46	9.84	12.0				
$k_{obs}/10^{-4}$ s^{-1}	3.50	6.03	7.06	9.16	11.1	11.3	12.7	16.0	19.5				
Solvent = DMSO. $[TNB]_0 = 2.75 \times 10^{-4}$ mol dm^{-3}													
$[DABCO]_0/10^{-2}$ mol dm^{-3}	1.01	1.34	1.51	1.76	2.02	2.52	4.00	6.40	8.80	10.6	13.6		
$k_{obs}/10^{-4}$ s^{-1}	1.73	2.36	2.29	2.83	2.87	2.90	4.48	8.15	10.0	11.6	15.0		
Solvent = DMSO. $[TNB]_0 = 2.75 \times 10^{-4}$ mol dm^{-3} $[Et_4N^+Cl^-] = 5.00 \times 10^{-2}$ mol dm^{-3}													
$[DABCO]_0/10^{-2}$ mol dm^{-3}	1.01	1.34	1.51	1.76	2.21	3.36	4.42	5.04	6.63	6.63	7.70	10.6	13.6
$k_{obs}/10^{-4}$ s^{-1}	1.57	1.95	2.03	2.08	2.64	3.29	4.25	5.02	6.50	6.68	8.02	11.6	15.0
Solvent = THF. $[TNB]_0 = 7.9 \times 10^{-5}$ mol dm^{-3}													
$[DABCO]_0/10^{-1}$ mol dm^{-3}	0.314	0.460	0.60	0.785	0.920	1.08	1.23	1.57	1.80	1.84	2.16	3.08	
$k_{obs}/10^{-5}$ s^{-1}	1.34	2.00	2.23	2.40	3.38	3.84	4.03	5.00	6.00	6.27	7.00	9.80	
Solvent DMSO. $[TNB]_0 = 8.08 \times 10^{-5}$ mol dm^{-3}													
$[QN]_0/10^{-2}$ mol dm^{-3}	0.327	0.392	0.786	1.10	1.31	1.57	1.63						
$k_{obs}/10^{-4}$ s^{-1}	3.80	4.70	5.75	6.90	7.83	8.50	8.80						
Solvent = DMSO. $[TNB]_0 = 8.08 \times 10^{-5}$ mol dm^{-3}. $[Et_4N^+Cl^-] = 2.40 \times 10^{-2}$ mol dm^{-3}													
$[QN]_0/10^{-2}$ mol dm^{-3}	0.412	0.900	1.03	1.50	1.88								
$k_{obs}/10^{-4}$ s^{-1}	4.53	7.67	8.67	11.8	13.9								

Table 2 Reactions between TNB and 1,8-diazabicyclo[2.2.2]octane (DABCO)[a] or quinuclidine (QN) at 25 °C, in DMSO (or THF). $[TNB]_0 = 1.2 \times 10^{-4}$ mol dm^{-3} (unless otherwise indicated)

	Solvent	k_1/s^{-1} mol^{-1} dm^3	k_{-1}/s^{-1}	K[b]	R[c]	n[d]	K[e]	R[c]	n[d]	ε/dm^3 mol^{-1} cm^{-1}	λ/nm[f]
DABCO	DMSO	$(7.65 \pm 0.1) \times 10^{-3}$	$(1.17 \pm 0.2) \times 10^{-4}$	65	0.997	9	42	0.999	9	6.3×10^3	514
DABCO[g]	DMSO	$(5.24 \pm 0.1) \times 10^{-3}$	$(7.29 \pm 1) \times 10^{-5}$	72	0.997	11	36	0.993	9	4.4×10^3	516
DABCO[h]	DMSO	$(4.49 \pm 0.1) \times 10^{-3}$	$(5.69 \pm 1) \times 10^{-5}$	79	0.997	11	51	0.997	9	7.3×10^3	516
QN	DMSO	$(3.60 \pm 0.002) \times 10^{-2}$	$(2.95 \pm 0.2) \times 10^{-4}$	122	0.994	7	107	0.997	10	1.3×10^4	522
QN[i]	DMSO	$(6.50 \pm 0.002) \times 10^{-2}$	$(1.93 \pm 0.2) \times 10^{-4}$	336	0.999	5	193	0.994	11	1.2×10^4	522
DABCO[j]	THF	$(1.53 \pm 0.04) \times 10^{-4}$	$(3.7 \pm 1) \times 10^{-6}$	41	0.997	12	36	0.994	9	1.6×10^4	562
DBU[k]	DMSO	0.70	3.9×10^{-5}	1.8×10^4							

[a] Data are corrected by a statistical factor of 2. [b] K/mol^{-1} $dm^3 = k_1/k_{-1}$. [c] Correlation coefficient. [d] Number of points. [e] Calculated by Benesi–Hildebrand treatment. [f] Used in the determinations. [g] $[TNB]_0 = 2.8 \times 10^{-4}$ mol dm^{-3}. [h] In the presence of $Et_4N^+Cl^-$ (0.050 mol dm^{-3}). [i] In the presence of $Et_4N^+Cl^-$ (0.024 mol dm^{-3}). [j] $[TNB]_0 = 7.9 \times 10^{-5}$ mol dm^{-3}. [k] Ref. 3.



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Scheme 2

Other explanations of the observed catalysis may be worthy of consideration, such as non-covalent interactions and TNB–amine,[5] or amine–amine hydrogen bonding formation.[14]

The nucleophilic power of DABCO (as measured by k_1 values) (see Table 1) is lower than that of DBU ($k_1^{DBU}/k_1^{DABCO} \approx 100$). The nucleophilic power of the sp^2 nitrogen has been the subject of less research than that of sp^3 nitrogen and the present data show another instance[15] of the higher nucleophilicity of imines with respect to the nucleophilicity of amines.

The stability of complex **1c** (TNB–DBU) in DMSO is higher than that of complexes **1a** and **1b**. $K^{DBU}/K^{DABCO} = 260$, $K^{DBU}/K^{QN} = 150$. This difference may be attributable to the delocalization of the positive charge in the case of the complex with DBU.[2]

The data in Table 2 show that QN is more reactive than DABCO ($k_1^{QN}/k_1^{DABCO} \approx 5$) in agreement (at least from the qualitative point of view) with the higher basicity (in water) of QN ($pK_a = 10.95$)[16] with respect to the basicity of DABCO ($pK_a = 8.19$).[17] Furthermore the stability of complexes **1** is higher for QN than for DABCO ($K^{QN}/K^{DABCO} \approx 2$). These differences confirm the importance of the inductive electron-withdrawing effect of the second nitrogen atom in depressing the electron availability in the first nitrogen atom.[18]

From Table 2 it is possible to see the effect of the presence of $Et_4N^+Cl^-$. The stability of zwitterionic complexes is expected to be enhanced by the presence of salt, because the charge separation in **1** is higher than in separate reagents. The presence of salt is also expected to enhance the value of k_1, because the reaction starts from neutral reagents to produce a transition state showing strong charge separation.[19] However, K (calculated either from kinetic data or from Benesi–Hildebrand treatment) for DABCO values is unaffected by the addition of $Et_4N^+Cl^-$. K values related to QN show a moderate salt effect which arises from an increase of k_1 value [$k_1(\text{salt})/k_1 = 1.8$], and a small decrease of k_{-1} value. These small effects are in agreement with the salt effect observed in the reactions (in DMSO) between TNB and DBU.[2] In agreement with the mild salt effect, the increase of the polarity of solvent shows a moderate effect on the stability of **1** ($K^{DMSO}/K^{THF} = 1.7$) for DABCO (values calculated from kinetic data).

The stability of zwitterionic complexes TNB–piperidine or butylamine in DMSO are 9 and 2 respectively: more stable complexes are formed by DABCO, QN and DBU.

Addition of dioxane to DMSO reduces the stability of complexes of primary and secondary amines, while the complex TNB–DABCO is more stable in THF than in DMSO. The fact that zwitterionic complex stability is mildly affected by the medium's polarity changes indicates that the charge separation in the zwitterionic complex is 'self-assisted'. This conclusion conflicts with the idea that the zwitterionic complexes (or intermediate in S_NAr reactions) are much less favoured from the energetic point of view than the σ anionic complex **2**.

Contrary to previously reported data concerning the reactions between DBU and TNB in toluene, the solvents used here show no kinetic autocatalytic behaviour. The presence of molecular complexes (involving non-covalent interactions, see Experimental section) does not affect the rate of attack of the nucleophile, probably because in these solvents, complex and 'free' substrate show the same reactivity.

Experimental

Materials

TNB (Carlo Erba RPE) was recrystallized from anhydrous methanol (mp 123 °C).[20] DABCO (Fluka) was purified by crystallization from anhydrous toluene and by sublimation *in vacuo*. QN (Fluka) was purified by sublimation. THF (Carlo Erba) dried over sodium and distilled was redistilled from $LiAlH_4$, immediately before use, under nitrogen atmosphere.[21] DMSO was purified using the usual procedures.[21] $[^2H_6]$DMSO was treated with molecular sieves (Carlo Erba 4 Å). *Visible spectra* were recorded with Perkin-Elmer Lambda 5 and Lambda 12 spectrophotometers. *NMR data* were recorded on a Varian Gemini 300 MHz spectrometer. *Kinetic runs* were performed (by usual procedure) by following the appearance of the reaction product at 560 nm. The reproducibility of k_{obs} values was ±4%. At the end of the reactions, A_∞ values were compared with A_∞ values of a sample stored in the dark and runs with differences in A_∞ values higher than 4% were eliminated.

Inspection of mixtures at zero reaction time and presence of molecular complexes

As far as the possibility of interactions between TNB and amines by an equilibrium preceding the attack of the nucleophile in DMSO are concerned, we obtained small indications (by the UV–VIS spectroscopic method) of absorption (at zero reaction time) which cannot be related either to starting materials or to zwitterionic complex **1**. In THF, by monitoring the reaction mixtures at $\lambda = 452$ nm, there is evidence of the presence of a molecular complex TNB–DABCO. Its stability was evaluated by Benesi–Hildebrand treatment: $K = 0.81 \pm 0.2$ ($mol^{-1}\ dm^3$, error is evaluated from standard deviations, $\varepsilon = 500$, number of points = 12). In $[^2H_6]$DMSO the ^1H NMR spectrum of mixtures TNB–DABCO (or QN) shows the presence of the σ complex **1** and the proton signal of the remaining TBN ($\delta = 9.25$) becomes a broad signal, as required if a rapid equilibrium formation (donor–acceptor like) takes place.

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