Nitronate Anion Recognition and Modulation of Ambident Reactivity by Hydrogen-Bonding Receptors

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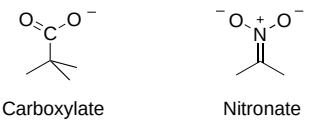
Abstract: Nitronate anions were shown to form complexes in DMSO with hydrogen-bonding receptors such as 1,3-dimethylthiourea **1** ($K_a = 120\,M^{-1}$) and bicyclic guanidinium **2** ($K_a = 3200\,M^{-1}$). A ditopic bis-thiourea exhibited increased association with substrates, that contained either two nitronates ($K_a = 7000\,M^{-1}$) or a combination of nitronate and carboxylate ($K_a = 7200\,M^{-1}$). Complexation of nitronate resulted in a change in the ambident reactivity during alkylation with *p*-nitrobenzyl bromide. The predominant reaction pathway was shifted from oxygen alkylation to carbon alkylation as receptor binding strength increased. Kinetic analysis indicated an overall inhibition of nitronate reactivity, and this suggests that greater suppression of the oxygen pathway allows carbon alkylation to predominate.

Keywords: ambident nucleophiles · anions · hydrogen bonds · molecular recognition · receptors

Introduction

While much of host–guest chemistry focuses on the static recognition of a substrate in solution, complexation of a chemically active substrate can result in receptor-induced changes in the reactivity of that guest. Nitronate, the anion produced by deprotonation adjacent to a nitro group, is one reactive species whose chemistry has been modified by receptor binding.[1–3] As part of a continuing study of anion recognition, we have utilized hydrogen-bonding receptors to form complexes with various nitronate derivatives. Additionally, this complexation leads to changes in the chemical reactivity of the nitronate anion.

The nitronate anion closely resembles a carboxylate anion in the presentation of two negatively charged geminal oxygen atoms (see anionic guest comparison below), and this suggests that receptors capable of complexing carboxylates[4–6] will also associate with nitronates through a bidentate hydrogen-bonding interaction. Both Davis[7] and Wynberg[8] have previously explored the use of amidinium- and guanidinium-based receptors to form complexes with nitronates by using X-ray crystallography to show the formation of discrete hydrogen bonds between the nitronate and receptor. The crucial nature of the bidentate interaction was verified in solution by the observation of proton transfer to form nitronates only when a bidentate receptor was present.[7] While the existence of the nitronate–receptor complex has been demonstrated, the strength of this interaction is yet to be reported.[9]



In the following sections, the association strength and thermodynamics of nitronate binding by bidentate hydrogen-bonding receptors are detailed, along with the consequences of association on ambident reactivity of the nitronate nucleophile.

Association of nitronate with hydrogen-bonding receptors: Evaluation of nitronate–receptor complexation began with the determination of binding strength and association thermodynamics. Both NMR titration and isothermal titration calorimetry were used to quantify the association of nitronate with hydrogen-bonding receptors based on thiourea and guanidinium groups. In the NMR protocol, nitronate was generated from the addition of tetrabutylammonium (TBA) hydroxide to nitroethane in DMSO. Subsequent addition of aliquots of 1,3-dimethyl-thiourea **1** caused both proton signals from the resulting TBA ethylnitronate to shift downfield, presumably due to the formation of the complexes shown in the structures illustrated. Nonlinear regression analysis[10]

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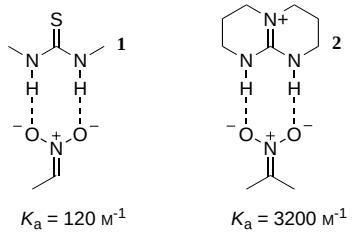


of the resulting curve indicated weak binding in DMSO ($K_a = 120 \pm 20\,\mathrm{M}^{-1}$).

Calorimetric titration illustrated the increased binding strength of guanidinium derivative **2**. Aliquots of the lithium salt of 2-nitropropane were added to a solution of the tetraphenylborate salt of guanidinium receptor **2** to form the bidentate complexes shown above. Isothermal titration calorimetry (Microcal, Northampton, MA)[11] was used to measure the heat evolved upon the injection of nitronate into the guanidinium solution (Figure 1A). Integration of the heat produced from each injection led to the binding curve shown

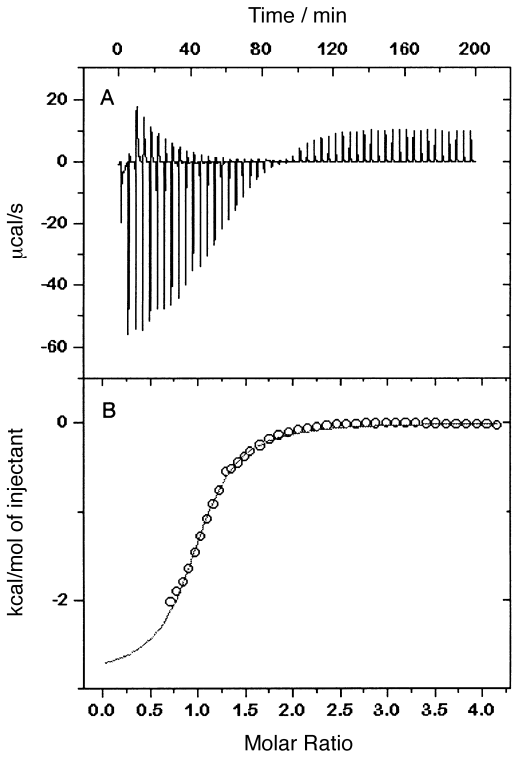
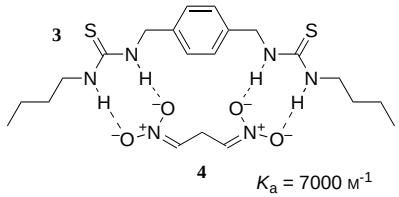
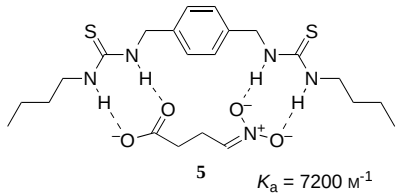


Figure 1. Calorimetric titration for the lithium salt of 2-nitropropane and guanidinium **2**. A) Raw data of heat evolution with injection of nitronate salt. B) Resulting binding curve (○) and best fit curve.

in Figure 1B. Application of a one-site binding model provided not only the association strength ($K_a = 3200 \pm 300\,\mathrm{M}^{-1}$) but also the enthalpy of association ($\Delta H = -2.9 \pm 0.1$ kcal mol^{-1}).[12]

A ditopic receptor,[4] bis-thiourea **3**, was found to be complementary to substrates that contained either two nitronates, or a combination of nitronate and a second anionic functional group. NMR titration was used to determine the binding affinity of complex **4**, formed by the bis-TBA salt of

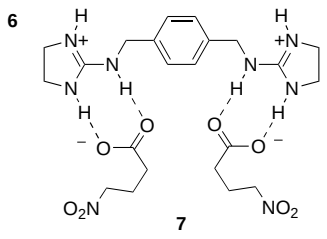




1,3-dinitropropane and bis-thiourea **3** ($K_a = 7000 \pm 200\,\mathrm{M}^{-1}$). Replacement of one nitronate with carboxylate, as in the 4-nitrobutyrate bis-TBA salt, produced an analogous complex **5** with similar binding strength ($K_a = 7200 \pm 200\,\mathrm{M}^{-1}$). As in previous examples,[4, 13, 14] the accumulation of binding sites produces greater complex stability than with monotopic hosts.

Comparison of the binding data for nitronate and carboxylate reveals similarities, as anticipated from the structural relations described above. Comparable binding experiments with the acetate TBA salt gave complexes in DMSO with thiourea receptor **1** ($K_a = 340\,\mathrm{M}^{-1}$)[4] and guanidinium **2** tetraphenylborate ($K_a = 5600\,\mathrm{M}^{-1}$; $\Delta H = -3.6$ kcal mol^{-1}),[5] each with greater binding affinity than the corresponding nitronate complex. The complex formed by ditopic complexation of the glutarate bis-TBA salt by bis-thiourea **3** ($K_a = 11\,000\,\mathrm{M}^{-1}$)[4] also showed increased association strength relative to similar nitronate complexes. This decrease in binding affinity from carboxylate to nitronate is consistent with the lower nitronic acid pK_a that results from the greater dispersion of negative charge over both oxygens and the α carbon.[15] The exothermic nature of both nitronate and carboxylate complexes suggests association is promoted by the formation of strong hydrogen bonds in DMSO.

The negative charge on the nitronate is crucial for strong association with hydrogen-bonding receptors. Similar NMR titrations with guests that contain the charge neutral nitro group did not show the changes in chemical shift indicative of complexation. Furthermore, no binding was observed between bis-functional 1,3-dinitropropane and either bis-thiourea **3** or bis-guanidinium **6** in DMSO or acetonitrile. Kelly[13] has observed binding to nitro groups in extremely nonpolar solvents such as carbon tetrachloride, but these are not



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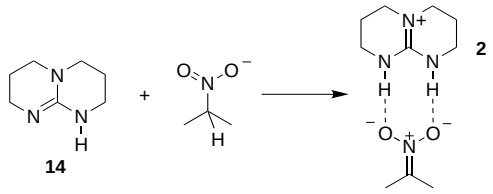
suitable in this instance due to the insolubility of receptors **3** and **6**. In an attempt to gauge the association of the neutral nitro group in an already chelated guest, the monoanion of 4-nitrobutyric acid was created by the addition of one equivalent of TBA hydroxide. Addition of this substrate to bis-guanidinium **6** bis-tetraphenylborate resulted in a biphasic binding curve indicative of multiple binding equilibria as seen for the complex **7**, making the determination of the binding data unreliable.

Receptor complexation and chemical reactivity: Deprotonation of a nitroalkane produces a nitronate functionality that can be recognized by the hydrogen-bonding receptors above, but also creates a chemically active group that can participate in a wide variety of reactions. The success of other compounds[1–3] that bring about changes in the enantioselective reactions of nitronate suggests that the hydrogen-bonding receptors above can modulate aspects of nitronate reactivity through intermolecular association. One area of reactivity is the ambident nature of the nitronate anion observed during alkylation. The delocalization of negative charge on both carbon and oxygen results in alkylation at both atoms. The extent of each pathway is controlled by electrophile structure, and oxygen alkylation occurs in most cases.[16] Association with hydrogen-bonding receptors through the bidentate interaction shown (**1** and **2**) should change both the electronic and steric nature of nitronate oxygens, and as a result modify their chemical reactivity.

Alkylation of 2-nitropropane with *p*-nitrobenzyl bromide (Scheme 1) was chosen to investigate the effect of receptor complexation on ambident reactivity. This electrophile alkylates nitronate predominantly at the oxygen, but also produces a small amount of carbon alkylate, and thus both pathways can be observed.[17] Oxygen alkylation proceeds through S_N2 attack of the nitronate oxygen on the alkyl halide; this produces an unstable nitronic ester **9**, which rapidly decomposes into aldehyde **11** and acetone oxime **13**. Additionally, the resulting aldehyde **11** reacts with a second equivalent of nitronate to form nitroaldol adduct **12**. Carbon alkylation occurs through a multistep radical chain mechanism to form **10**.[18–21] Changes in the alkylation ratio that occur with receptor addition were easily determined by NMR analysis of the resulting products **10**–**12**, and the identity of each was determined by independent synthesis. The carbon alkylation product was obtained from the reaction of nitropropane and *p*-nitrobenzyl chloride,[17] and the aldol adduct was synthesized from 2-nitropropane, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and commercially available *p*-nitrobenzaldehyde.[22]

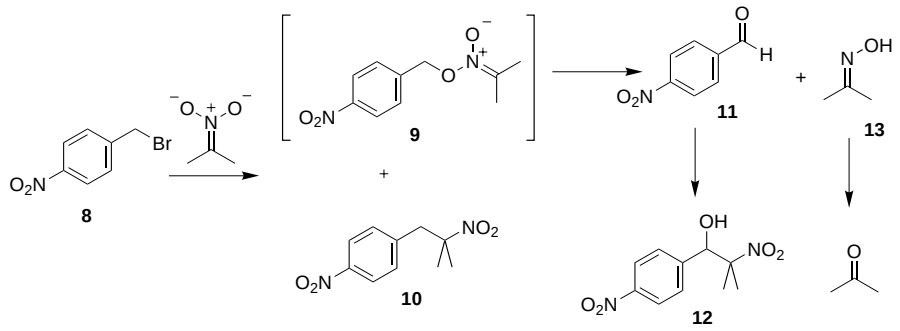
In an effort to compare bimolecular association and chemical reactivity, thiourea **1** and guanidinium **2** were employed in this study. When thiourea **1** was used an equal amount of potassium *tert*-butoxide was required to form the nitronate in situ. Guanidine **14** (Scheme 2), on the other hand,



Scheme 2. Formation of receptor–nitronate complex.

functions both to deprotonate the nitroalkane and to form guanidinium receptor **2**, which subsequently complexes the resulting nitronate (Scheme 2). Excess nitronate (1.3 equiv) was used in each case to ensure complete consumption of the halide in the presence of the competing nitroaldol reaction. All reactions were undertaken in DMF to permit comparisons with previous alkylation studies and to allow correlation with association data; this avoided possible complications caused by deprotonation of the acidic hydrogens of DMSO.

The NMR product ratios from the reaction of *p*-nitrobenzyl bromide under various conditions are listed in Table 1. Compounds **11** and **12** are both oxygen alkylation products and were combined into a single value as a result of the variable extent of the nitroaldol reaction. In the absence of any receptor in DMF, only 10% carbon alkylation was observed. Addition of the weakly coordinating thiourea receptor increased carbon alkylation to 28%, and this increased to 40% when five equivalents of receptor were added. Guanidinium **2**, which displays stronger association than thiourea **1**, also produced increased carbon alkylation. In polar DMF, 42% carbon alkylation was

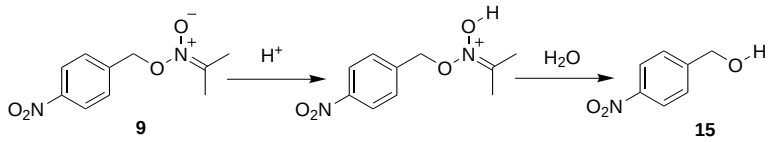


Scheme 1. Reaction of *p*-nitrobenzyl bromide with the nitronate salt of 2-nitropropane.

Table 1. NMR product ratios from *p*-nitrobenzyl bromide alkylation of 2-nitropropane.

	Base	Solvent	C Alkylation [%]	O Alkylation [%]
none	KO*t*Bu	DMF	10	90
1 (1 equiv)	KO*t*Bu	DMF	28	72
1 (5 equiv)	KO*t*Bu	DMF	40	60
2	**14**	DMF	42	58
2	**14**	CH_2Cl_2	77	23
2	**14**	THF	82	18

observed, but this propensity increased further when the reaction was performed in nonpolar solvents. When the identical reaction was performed in dichloromethane, 77% carbon alkylation was observed, which increased to 82% when tetrahydrofuran was used as a solvent. Control reactions with no receptor in nonpolar conditions (and binding experiments) proved impossible as a result of the insolubility of uncomplexed nitronate salts in these solvents.



Scheme 3. Formation of *p*-nitrobenzyl alcohol.

In addition to being dependent on receptor binding strength and solvent, product ratios are also concentration dependent. Various concentrations of *p*-nitrobenzyl bromide were allowed to react with a twofold excess of the guanidinium–nitronate complex formed in Scheme 2. As the concentration of reactants increased, so did the ratio of carbon alkylation observed (Table 2). Similar experiments with no receptor showed no dependence on concentration over the same range. The resulting alkylation ratios indicated that the more concentrated solutions favor carbon alkylation, which increases by 40% over the given concentration range.

Table 2. Alkylation of 2-nitropropane by *p*-nitrobenzyl bromide in the presence of guanidinium receptor **2** in DMF.

Halide [mM]	Nitronate [mM]	C Alkylation [%]	O Alkylation [%]
200	400	53	47
150	300	42	58
100	200	39	61
40	80	30	70
25	50	13	87

This reversal in ambident reactivity correlates with the strength of receptor complexation. Increased carbon alkylation is observed in solvents that promote stronger complex formation and in solutions that are highly concentrated or contain excess receptor; in each case, nitronate binding by the receptor is favored. As nitronate is more tightly complexed by receptor, the percentage of carbon alkylation rises, and this indicates the direct role of receptor complexation in the change in ambident reactivity.

Kinetic analysis of nitronate alkylation: Further insight into the source of receptor-induced changes in ambident reactivity was gained through kinetic analysis of the alkylation reaction.[23] After addition of the halide to the nitronate/receptor solution, aliquots of the reaction mixture were removed at regular intervals and quenched by addition to aqueous hydrobromic acid. Changes in the order of addition of starting materials did not alter the resulting kinetic profile. The reaction products were analyzed from NMR product ratios as before, with the additional observation of two minor reaction products, *p*-nitrobenzyl alcohol and *p*-nitrobenzoic acid.

The production of *p*-nitrobenzyl alcohol **15** (Scheme 3) from nitronate alkylation was not observed during the alkylation reactions above, and occurred only when the incomplete reaction was quenched by acid. After the reaction was complete (>10 min), no alcohol was formed from acid quenching. This suggests that the product arises from hydrolysis of the protonated nitronic ester intermediate **9** formed under acidic conditions (Scheme 3). Additionally, treatment of *p*-nitrobenzyl bromide under identical acidic conditions without the presence of the nitronate resulted in the recovery of only starting material, and this excluded the possibility of hydrolysis without the involvement of the nitronic acid intermediate.

The formation of a small amount of nitrobenzoic acid was also observed. This side product was presumed to form from the reaction of *p*-nitrobenzaldehyde **11** with an additional equivalent of nitronate. Typically aldehydes react with the carbon atom of nitronates through the nitroaldol reaction as in Scheme 1. This pathway was observed in the production of 2-methyl-2-nitro-1-(*p*-nitrophenyl)propanol (**12**) in an 87% yield from the reaction of *p*-nitrobenzaldehyde, 2-nitropropane, and a catalytic amount of DBU in THF. A similar reaction of *p*-nitrobenzaldehyde **11** with the lithium salt of 2-nitropropane in DMF, however, produces *p*-nitrobenzoic acid in 73% yield. This alternate product is thought to arise from the reaction of the aldehyde with the oxygen of nitronate and subsequent oxidation–reduction; this is reminiscent of the mechanism of aldehyde formation in Scheme 1. As nitronic ester **9** can undergo internal oxidation–reduction to form aldehyde **11**,[17] the aldehyde–nitronate adduct may form *p*-nitrobenzoic acid through a similar mechanism. Curiously, only *p*-nitrobenzaldehyde produced acid products; under identical conditions, all other aldehydes tested produced only nitro-aldol products. The nitroaldol reaction is reversible, and presumably the equilibrium is shifted by the irreversible acid formation that occurs only with this activated aldehyde.

A kinetic profile of the nitronate alkylation was obtained by periodic removal of aliquots of the reaction mixture, which were quenched with aqueous hydrobromic acid. Products were isolated by dichloromethane extraction, and the alkylation ratios were determined from NMR analysis of product mixtures. Results are displayed as a percentage of reaction products versus time; halide is consumed, and both oxygen and carbon alkylation products are formed. Aldehyde **11**, alcohol **15**, and nitroaldol **12** products are included in the total oxygen alkylation percentage. A moderate *p*-nitrobenzyl bromide concentration (40 mM) was chosen to allow visualization of both alkylation pathways in the NMR spectra, and reaction times were less than four minutes to minimize formation of *p*-nitrobenzoic acid.

Reaction in the absence of receptor produced the kinetic profile shown in Figure 2A. Nitrobenzyl bromide (◆), which reacted with the lithium salt of 2-nitropropane in DMF, was consumed inside four minutes with concomitant production of oxygen alkylation (■) and carbon alkylation (○) products. As seen in previous results, oxygen alkylation predominated. A

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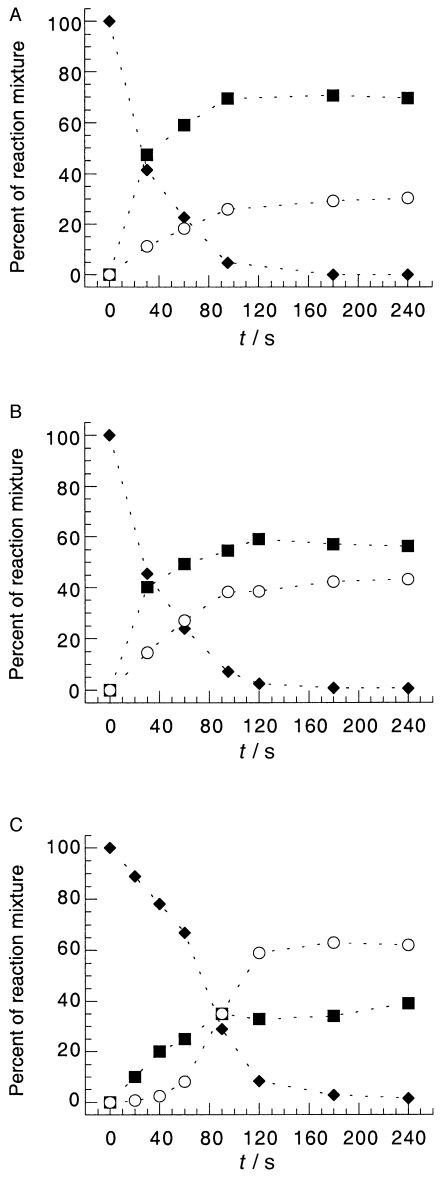

Figure 2. Reaction kinetics. A) No host in DMF. B) Guanidinium **2** in DMF. C) Guanidinium **2** in THF. Nitrobenzyl bromide (◆), oxygen alkylation (■), and carbon alkylation (○). All reactions are performed at 25 °C.

small change in the kinetic profile was observed when guanidine **14** was used to create the receptor–nitronate complex as in Scheme 2. Alkylation with *p*-nitrobenzyl bromide in the presence of guanidinium **2** in DMF (Figure 2B) proceeds with a slightly reduced rate of halide consumption (◆) coupled with a greater production of the carbon alkylation products (○).

When the reaction solvent was changed to tetrahydrofuran (THF), stronger host–guest association resulted, and a new kinetic profile was observed, shown in Figure 2C. The consumption of starting material no longer followed the exponential decay seen previously in DMF; instead there was an initial slow reaction followed by a fast depletion of halide. New trends were seen in the percentage of alkylation products as well. Oxygen alkylation proceeded during the slow phase but leveled during the subsequent fast reaction. Carbon alkylation, by contrast, was nominal during the slow initial phase, but rapidly approached the final amount during the fast reaction. It follows that the initial slow reaction is primarily due to oxygen alkylation, while the secondary fast reaction produces mainly carbon alkylation.

Rate constants for the three kinetic profiles were determined to quantify the effect of receptor complexation on the progress of nitronate alkylation. In each case, alkylation follows second-order kinetics with regard to the consumption of halide and nitronate. The concentration of *p*-nitrobenzyl bromide was determined directly from NMR product analysis, while nitronate concentration was inferred from the decreases that occur from both alkylation pathways as well as nitroaldol formation. Rate constants determined from this data (Table 3) indicate a slight decrease in the rate of reaction with the addition of the guanidinium receptor in DMF, with a more significant rate decrease observed in THF.

Table 3. Second-order rate constants for reactions in Figure 2.

Figure 2	Receptor	Solvent	k [$M^{-1}sec^{-1}$]
A	none	DMF	8.1×10^{-3}
B	**2**	DMF	7.0×10^{-3}
C	**2**	THF	1.2×10^{-3}

The delicate balance between the rates of oxygen alkylation and carbon alkylation was further demonstrated by reactions at lower temperature. Kinetic analysis at 0 °C showed a slower consumption of halide, complete only after ten minutes, with minimal carbon alkylation (< 10 %). Once again, addition of receptor **2** reduced the reaction rate further, but in this instance no carbon alkylate was formed. In both cases, the initial consumption of starting materials demonstrated second-order kinetics, with rate constants $0.072\,M^{-1}sec^{-1}$ with no receptor and $0.032\,M^{-1}sec^{-1}$ with added receptor **15**. The reduction in the overall rate of reaction without an increase in carbon alkylation suggests the intrinsic rate of carbon alkylation at 0 °C is too small to be drastically affected by receptor complexation. While association reduces the rate of oxygen alkylation, the inherent rate of carbon alkylation is too low to compete, even though association slows the oxygen alkylation pathway.

Previous analysis of nitronate alkylation demonstrated a dependence between product ratios and leaving group.[23] More active leaving groups produced mainly oxygen alkylation, while less reactive leaving groups produced carbon alkylation. Determination of rate constants from product ratios indicated that the rate of oxygen alkylation was highly sensitive to reaction conditions, while the rate of carbon alkylation was largely invariant. A similar mechanism may also pertain to the effect of receptor complexation. Nitronate oxygen nucleophilicity should be reduced by the formation of hydrogen bonds, and this results in a decrease in the rate of oxygen alkylation. The role of association in the carbon alkylation pathway is as yet unclear. This increase in carbon alkylation with concomitant reduction in the overall rate of halide depletion resembles the effect of the leaving group, and this suggests association reduces the rate of oxygen alkylation such that the carbon alkylation pathway predominates.

Widespread use of receptor association to alter the ambident nature of the nitronate nucleophile is limited, however. The electrophile chosen in this study inherently produces some carbon alkylate, whereas most do not.[17] Application of these receptors to unsubstituted benzyl halides failed to significantly change the ratio of products formed. Presumably the carbon alkylation pathway is just too slow to compete even with receptor assistance, and this limits the synthetic generality of this approach. Receptor complexation is most effective when the competing rates of reaction are initially close, and association shifts the reaction from one pathway to another.

In summary, simple hydrogen-bonding receptors formed complexes with nitronate anions in DMSO; the binding of guanidinium receptors is stronger than that for thiourea receptors. The exothermic nature of this association suggests the strong bidentate hydrogen-bonding interaction previously seen in crystal structures. This complexation resulted in a change in the ambident nature of the nitronate nucleophile in the reaction with *p*-nitrobenzyl bromide, and stronger complexation produced a shift from oxygen alkylation to carbon alkylation. Kinetic analysis suggested hydrogen bonding reduced the rate of oxygen alkylation such that carbon alkylation predominated. The effect of receptor binding on other aspects of nitronate reactivity remains to be determined.

Experimental Section

Determination of association by NMR titration: An array (10) of solutions was prepared that contained nitroalkane and receptor in DMSO. Nitroalkane concentration was held constant (typically 1 mM), and receptor concentration varied from 0 – 10 equivalents. Nitronate complexes were formed by the addition of one equivalent of tetrabutylammonium hydroxide in DMSO for monoanions and two equivalents for dianions. After this was allowed to equilibrate for several minutes, NMR spectra were acquired. The changes in chemical shifts for nitronate protons were plotted as a binding isotherm and modeled with nonlinear least squares regression analysis to determine association constants.[10]

Isothermal titration calorimetry: An isothermal titration calorimeter from Microcal (Northampton, Mass.) was used in this study.[11] A solution (5 mM) of guanidinium **2** tetraphenylborate salt was placed in the sample cell. As the lithium salt of 2-nitropropane was added in a series of fifty injections (5 μL), the heat that evolved was recorded. Heat produced from the dilution of nitronate in DMSO was quantified in a second experiment and subtracted from the binding data. The final curve was modeled using one-site nonlinear regression analysis.[11] This analysis provided both an association constant and enthalpy of association from a single curve fit.

Product analysis protocol: The compounds 2-nitropropane (0.50 g, 5.61 mM) and *p*-nitrobenzyl bromide (0.30 g, 1.39 mM) were dissolved in the chosen solvent (10 mL). Base and receptor (1.80 mM each) were added as needed, and the solution was stirred for thirty minutes. The solution was poured into dichloromethane (50 mL) and extracted with HBr (5%), sat. $NaHCO_3$ (aq), and water. The organic layer was dried with Na_2SO_4 and concentrated to dryness. Product ratios were determined by NMR integration of the aldehyde proton of **11**, the benzylmethine of **12**, and the methylene of **15**.

Concentration dependence protocol: Solutions of *p*-nitrobenzyl bromide, 2-nitropropane, and bicyclic guanidine **14** in DMF were mixed such that final halide concentrations were 200, 150, 100, 40, and 25 mM, while nitropropane and guanidine concentrations were twice that amount. In each case, the halide was added last to ensure nitronate – guanidinium equilibration. After being stirred for thirty minutes, the solution was added to dichloromethane (50 mL) and quenched with aqueous HBr (5%). The organic layer was washed with sat. $NaHCO_3$ (aq), brine, and water, dried with Na_2SO_4, and then was concentrated to dryness under reduced pressure. Product ratios were determined by NMR integration of the aldehyde proton of **11**, the benzylmethine of **12**, and the methylene of **15**.

Kinetic protocol:[23]

No receptor: The lithium salt of 2-nitropropane (95 mg, 1.00 mM) was dissolved in DMF (7.5 mL). A second solution was prepared that contained *p*-nitrobenzyl bromide (108 mg, 0.50 mM) in solvent (5 mL). As the two solutions were added, a stopwatch was started upon half addition. At specific intervals, ≈0.5 mL was removed and immediately poured into a separatory funnel with dichloromethane (10 mL) and aqueous HBr (5%, 20 mL). The organic layer was separated, washed with brine to remove DMF, dried with Na_2SO_4, and concentrated to dryness.

With receptor: The compounds 2-nitropropane and guanidine **14** were mixed in reaction solvent (7.5 mL, DMF or THF) and allowed to stand for 5 min. *p*-Nitrobenzyl bromide solution (5 mL) was added, and the reaction proceeded as above. Changes in the order of addition resulted in no distinguishable changes in the kinetic profiles.

Synthesis:

Lithium salt of 2-nitropropane:[23] Lithium wire (0.36 g, 51.86 mM) was slowly added to absolute ethanol (100 mL) at 0 °C. This was stirred for one hour, or until the wire was completely consumed, and a homogeneous solution remained. The compound 2-nitropropane (9.30 g, 104.5 mM) was added, and the solution was stirred for eight hours and allowed to warm to room temperature. After the volume of the solution was reduced (to 25 mL) under reduced pressure, diethyl ether (200 mL) was added; this resulted in the formation of a white precipitate. This was collected by filtration and washed with diethyl ether. Remaining solvent was removed under high vacuum to yield a white powder (4.73 g, 96%). ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.80$ (s); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta =$ 111.0 (s), 18.3 (q); $C_3H_6LiNO_2 \cdot H_2O$ (113.04): calcd C 31.88, H 7.13, N 12.39; found C 31.90, H 7.11, N 12.36.

2-(p-Nitrobenzyl)-2-nitropropane (***10***): *p*-Nitrobenzyl chloride (0.10 g, 0.58 mM) was dissolved in DMF (10 mL). The lithium salt of 2-nitropropane (0.11 g, 1.16 mM) was added, and this resulted in an immediate red color. After being stirred for eight hours, the solution was poured into HCl (10%, 100 mL) and washed twice with dichloromethane. The combined organic layers were washed several times with water, once with brine, dried with Na_2SO_4, and concentrated to dryness. A yellow oil remained (0.11 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.06$ (d, $J = 7.7$ Hz, 2H; Ar), 7.21 (d, $J =$ 7.7 Hz, 2H; Ar), 3.24 (s, 2H; CH_2), 1.53 (s, 6H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.4$, 142.4, 130.9, 123.6, 88.2, 46.0, 25.6; MS (EI): *m*/*z* (%): $C_{10}H_{12}N_2O_4$: calcd 224.0797; found 224.0786; $C_{10}H_{12}N_2O_4$ (224.22): calcd C 53.57, H 5.39, N 12.49; found C 54.09, H 5.37, N 11.96.

2-Methyl-2-nitro-1-(p-nitrophenyl)propanol (***12***): *p*-Nitro-benzaldehyde (0.50 g, 3.31 mM) and 2-nitropropane (0.60 g, 6.73 mM) were dissolved in THF (30 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.10 g, 0.72 mM) was added, and this resulted in an immediate yellow color. After being stirred for four hours, the solvent was removed under reduced pressure, and the residue was partitioned between dichloromethane and HCl (10%). The organic layer was washed with water, dried with Na_2SO_4, and concentrated to dryness. The residue was triturated with diethyl ether to yield a yellow solid (0.69 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.23$ (d, $J = 8.5$ Hz, 2H; Ar), 7.58 (d, $J = 8.5$ Hz, 2H; Ar), 5.44 (s, 1H; CH), 1.58 (s, 3H), 1.48 (s, 3H); MS (EI): *m*/*z* (%): $C_{10}H_{12}NO_3$ [$M - NO_2$]: calcd 194.0817; found 194.0816; $C_{10}H_{12}N_2O_5$ (240.22): calcd C 50.00, H 5.03, N 11.66; found C 50.57, H 5.04, N 11.24.

Oxidation of p-nitrobenzaldehyde to p-nitrobenzoic acid: *p*-Nitrobenzaldehyde (0.50 g, 3.31 mM) was dissolved in DMF (20 mL). Addition of the lithium salt of 2-nitropropane (0.63 g, 6.63 mM) immediately resulted in a red color. After this was stirred for four hours, the solution was poured into HCl (10%, 100 mL). This cloudy solution was washed twice with dichloromethane, and the combined organic fractions were washed twice with water and once with brine. The organic solution was extracted with sat. $NaHCO_3$ (50 mL). The basic aqueous layer was removed and acidified with HCl before it was extracted with dichloromethane. This organic layer was dried with Na_2SO_4 and concentrated to dryness to yield a tan solid (0.40 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.29$ (d, $J = 8.9$ Hz, 2H), 8.23 (d, $J =$ 8.9 Hz, 2H); $C_7H_5NO_4$ (167.12): calcd C 50.31, H 3.02, N 8.38; found C 50.37, H 2.99, N 8.40.

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