Nitroalkanes in C–C Bond Forming Reactions: a Crystal Structure of a Complex of a Guanidine Catalyst and a Nitroalkane Substrate

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van Aken, E., Wynberg, H. and van Bolhuis, F., 1993. Nitroalkanes in C–C Bond Forming Reactions: a Crystal Structure of a Complex of a Guanidine Catalyst and a Nitroalkane Substrate. – Acta Chem. Scand. 47: 122–124.

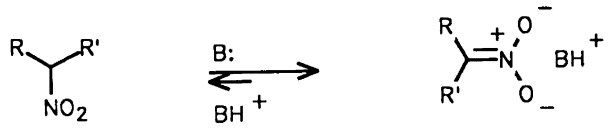
1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD), a good catalyst for nitroalkanes in C–C bond forming reactions, forms a 1:1 complex with phenylnitromethane as a substrate. The mode of complexation between the catalyst and the substrate is shown by a crystal structure **3**.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

Nitroalkanes have been used surprisingly little in catalytic enantioselective C–C bond forming reactions.[1] This is in spite of the possibly short routes to optically active amines,[2] β-amino alcohols[3] (e.g. ephedrine) and α-amino acids.[4].

Our first attempts using cinchona alkaloids[1a] as chiral basic catalysts in Michael and Henry reactions,[5] using nitroalkanes as the nucleophiles, resulted in slow conversions and low enantioselectivities in all reactions. The e.e.s did not exceed 25%. The unknown mode of complexation between the cinchona alkaloids and the nitroalkanes hampered further development of these catalysts towards higher enantioselectivities.

In our view a predictable and well defined mode of complexation between the catalyst and the nitroalkane substrate is necessary towards directed improvements of the enantioselectivity of the catalyst. In the first step of a base-catalyzed C–C bond forming reaction the achiral nitroalkane **1** is converted into the prochiral nitronate anion **2**. In Scheme 1 this first step in the reaction is depicted.



1 2

Scheme 1. The first step in a base-catalyzed addition reaction of nitroalkanes.

The nitronate anion **2**, a proposed intermediate in C–C bond forming reactions, serves as an ideal handle for the catalyst. Fixation of this nitronate anion by the catalyst is essential because, at this stage of the reaction, the stereochemistry at C_α of the product is determined. The catalyst should possess, after protonation, a structural element complementary to the structure of this nitronate anion **2**. The bicyclic guanidine, 1,5,7-triazabicyclo[4.4.0]dec-5-ene TBD, a strong base, possesses the right geometry after protonation. We used TBD as a model catalyst for testing the mode of complexation of bicyclic guanidines with nitroalkanes and its catalytic activity in C–C bond forming reactions with nitroalkanes as the nucleophiles.

Enantioselective catalysis, for introducing chirality on C_α of the nitroalkane, requires differentiation between the *Re*-site and the *Si*-site of the prochiral nitronate anion **2**. This may eventually be achieved by using the reported chiral bicyclic guanidines.[6]

Here we report a crystal structure of a complex **3** of the achiral catalyst model, 1,5,7-triazabicyclo[4.4.0]dec-5-ene TBD and phenylnitromethane (Fig. 1), establishing the mode of complexation between nitroalkane substrate and the guanidine catalyst.

The bicyclic guanidine TBD is an excellent catalyst for Michael and Henry reactions of nitroalkanes in toluene.[7] An example is the Michael addition of nitroethane to methyl vinyl ketone explored in a 0.1 M reaction using 10% TBD as the catalyst. This afforded 75% 5-nitro-2-hexanone within 5 min. With quinine as the catalyst only 75% of 5-nitro-2-hexanone is formed after 122 h of reaction time; the enantioselectivity of the product was 13%.

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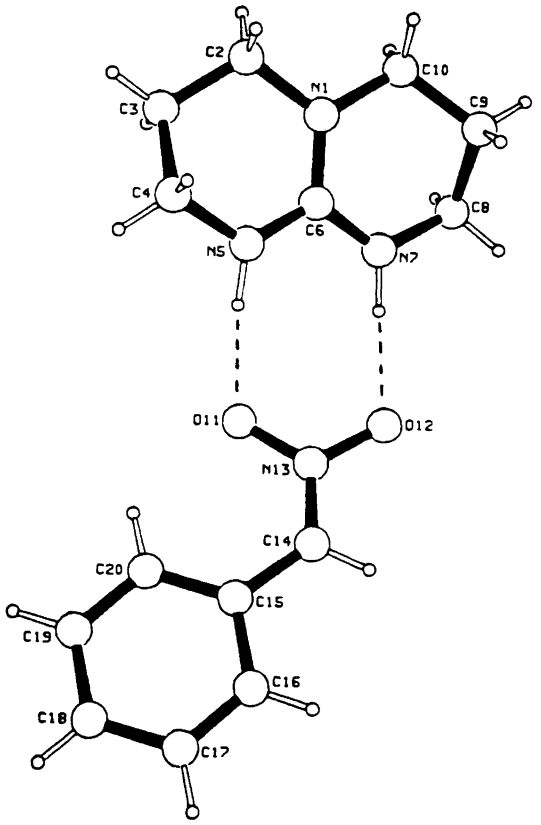

3

Fig. 1. The crystal structure of the salt **3** of 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) and phenylnitromethane showing the atomic numbering scheme. The two H···O distances: H(5)–O(11) 1.97(3) and H(7)–O(12) 1.99 Å indicate real hydrogen bonds.

Table 1. The final positional parameters and their standard deviations of the bicyclic guanidinium/nitronate salt **3**.

Atom	*x*	*y*	*z*	*B*(A2)
O11	0.7941(2)	0.5991(2)	0.2379(1)	2.13(4)
O12	0.6114(2)	0.5825(2)	0.1374(1)	2.06(3)
N1	0.7734(2)	0.1507(2)	0.1535(1)	1.70(4)
N5	0.8080(2)	0.3368(2)	0.2445(2)	1.92(4)
N7	0.6922(2)	0.3412(2)	0.0904(2)	1.99(4)
N13	0.6774(2)	0.6410(2)	0.2118(1)	1.61(4)
C2	0.8616(3)	0.0782(2)	0.2235(2)	2.24(5)
C3	0.9525(3)	0.1629(3)	0.2865(2)	2.60(6)
C4	0.8750(3)	0.2707(2)	0.3296(2)	2.33(5)
C6	0.7581(2)	0.2758(2)	0.1624(2)	1.53(5)
C8	0.6397(3)	0.2828(2)	−0.0040(2)	2.46(6)
C9	0.5939(3)	0.1503(2)	0.0194(2)	2.60(6)
C10	0.7068(3)	0.0784(2)	0.0707(2)	2.38(5)
C14	0.6247(2)	0.7390(2)	0.2557(2)	1.62(5)
C15	0.6842(2)	0.8151(2)	0.3379(2)	1.49(4)
C16	0.6104(2)	0.9174(2)	0.3724(2)	1.76(5)
C17	0.6599(2)	0.9960(2)	0.4489(2)	1.93(5)
C18	0.7840(2)	0.9774(2)	0.4939(2)	2.08(5)
C19	0.8584(2)	0.8779(2)	0.4606(2)	2.06(5)
C20	0.8099(2)	0.7970(2)	0.3845(2)	1.71(5)
H5	0.807(3)	0.415(3)	0.241(2)	*****
H7	0.675(3)	0.411(3)	0.105(2)	*****

Experimental

General methods. The NMR spectra were recorded using a Varian VXR-300 at ambient temperature. Deuteriated benzene was used as the solvent. The addition reactions were performed in dry toluene; the products were isolated by filtration of the reaction mixture over silica gel (Merck silica gel/60) followed by evaporation of the solvent and excess reagents.

Table 2. The bond lengths (Å) and angles (°) of **3** and their estimated standard deviations.

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O11	N13	1.310(2)	N7	C8	1.465(3)	C15	C20	1.413(3)
O12	N13	1.314(2)	N7	H7	0.79(3)	C16	C17	1.383(3)
N1	C2	1.472(3)	N13	C14	1.327(3)	C17	C18	1.391(3)
N1	C6	1.344(3)	C2	C3	1.510(4)	C18	C19	1.397(3)
N1	C10	1.470(3)	C3	C4	1.527(4)	C19	C20	1.390(3)
N5	C4	1.464(3)	C8	C9	1.524(4)	O11	N5	2.792(2)
N5	C6	1.337(3)	C9	C10	1.516(4)	O12	N7	2.781(2)
N5	H5	0.83(3)	C14	C15	1.457(3)	O11	H5	1.97(3)
N7	C6	1.329(3)	C15	C16	1.421(3)	O12	H7	1.99(3)

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
C2	N1	C6	122.3(2)	O11	N13	C14	123.4(2)	N1	C10	C9	112.1(2)
C2	N1	C10	115.6(2)	O12	N13	C14	119.5(2)	N13	C14	C15	126.6(2)
C6	N1	C10	122.0(2)	N1	C2	C3	111.7(2)	C14	C15	C16	117.1(2)
C4	N5	C6	121.8(2)	C2	C3	C4	109.2(2)	C14	C15	C20	125.4(2)
C4	N5	H5	122.(2)	N5	C4	C3	107.8(2)	C16	C15	C20	117.5(2)
C6	N5	H5	116.(2)	N1	C6	N5	120.6(2)	C15	C16	C17	121.1(2)
C6	N7	C8	122.1(2)	N1	C6	N7	120.8(2)	C16	C17	C18	120.8(2)
C6	N7	H7	115.(2)	N5	C6	N7	118.6(2)	C17	C18	C19	119.0(2)
C8	N7	H7	122.(2)	N7	C8	C9	108.7(2)	C18	C19	C20	121.1(2)
O11	N13	O12	117.2(2)	C8	C9	C10	108.4(2)	C15	C20	C19	120.5(2)

Single crystals of 3,4,6,7,8,9-hexahydro-2*H*-pyrimido-[1,2-*a*]pyrimidine phenylnitronate **3** were obtained from a solvent mixture of toluene and pentane. The crystal structure of the complex **3** shows a dihydrogen bridge bonding mode between the substrate and the catalyst. The essential hydrogen bonding atoms H5 and H7, respectively, were refined individually. The H ··· O distances of, respectively, 1.97 Å and 1.99 Å indicate real hydrogen bonds.[8]

Crystal data for 3,4,6,7,8,9-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine phenylnitronate **3**, $C_7H_{14}N_3 \cdot C_7H_6NO_2$, $M_w = 276.34$, were collected at 130 K, to give the following data: monoclinic, space group $P2_1/a$, $a = 10.338(2)$, $b = 10.627(2)$, $c = 13{,}232(3)$ Å, $\beta = 93.95(2)^\circ$ and $V = 1456.2$ Å.[3] For $Z = 4$ and $F_w = 276.34$ the $D_c = 1.266\,g\,cm^{-3}$. $\lambda = 0.71073$ Å, $\mu(Mo\text{-}K_\alpha) = 0.82\,cm^{-1}$. The final R value was $R = 0.041$ and $w_R = 0.048$ for 2470 reflections. The final atomic parameters and their estimated standard deviations for **3** are given in Table 1, the bond lengths and angles in Table 2.

Results and discussion

The dihedral angle between the guanidine plane N5 – C6 – N7 and the nitronate plane O11 – N13 – O12 is 39.6°. The 'head to head' orientation in **3** satisfies the demand for a tight and predictable complexation between the catalyst and the nitroalkane.

NMR spectroscopy studies (^1H, ^{13}C and 2D NOE experiments) also suggested a 'head to head' orientation of the two ionic components in solution. 300 MHz ^1H NMR spectroscopy of a 1:1 mixture of TBD and phenylnitromethane in benzene-d_6 showed complete deprotonation of phenylnitromethane. The signal of the C_α-methylene group ($\delta = 5.43$, s) disappeared from the spectrum. The remaining $C_\alpha - H$ shifted into the aromatic region ($\delta = 7.56$, s). A mixture of 1:2 of TBD and phenylnitromethane in benzene-d_6 showed two distinct pairs of signals for the deprotonated and complexed nitronate anion and the free phenylnitromethane. ^{13}C NMR showed distinct signals for all six aromatic carbon atoms in the 1:1 mixture, indicating a relatively slow rotation of the phenyl group, due to conjugation with the C=N double bond. 2D NOE experiments in benzene-d_6, revealed no interaction between any of the hydrogens of the two ionic components, ruling out a stacked or sandwich structure of the complex in solution.

The crystal structure **3** is, to our knowledge, the first example of a complex of a basic catalyst and a nitroalkane substrate. It combines the two aspects of recognition and catalysis. The type of complexation is analogous to the complexation of carboxylate,[9] phosphate,[9a,10] and nitrate[11] anions by the guanidinium moiety. The reported complexation of a nitrate anion by Schmidtchen[11] showed a similar binding mode.

Experiments with the chiral byclic guanidine, placed at our disposal by Prof. J. de Mendoza, are currently under investigation and will be published in due course.

Acknowledgments. The work was supported by the Dutch Foundation for Chemical Research (SON), with financial aid from the Dutch Organization for Scientific Research (NWO).

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Received December 2, 1991.