Computational Elucidation of the Catalytic Mechanism for Ketone Reduction by an Oxazaborolidine–Borane Adduct

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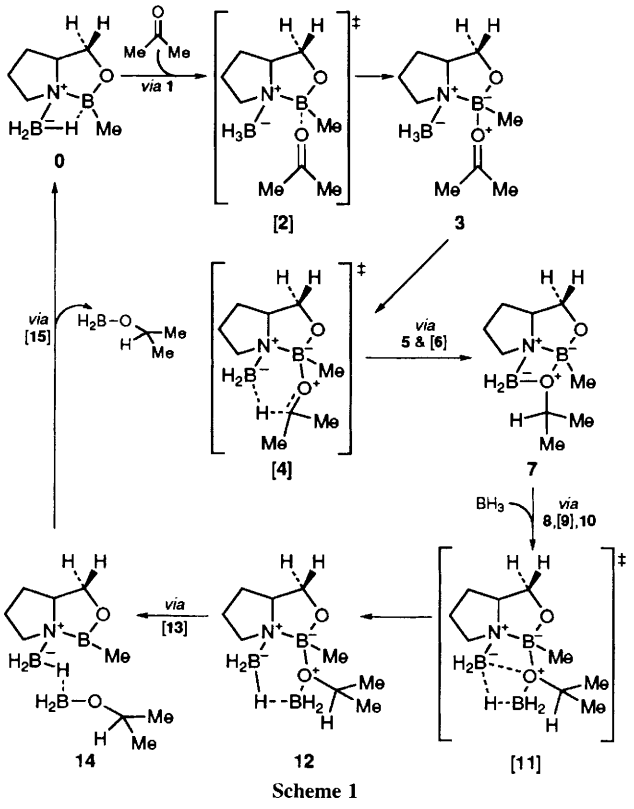
The reaction pathway around the complete catalytic cycle for THF–borane reduction of propanone catalysed by the oxazaborolidine from (*S*)-proline has been determined by AM1 semiempirical MO calculations, including characterisation of all transition structures; the transition structure for ketone coordination is almost as high in energy as that for the rate-limiting hydride-transfer step, and the calculated kinetic isotope effect for reduction by THF–[$^2H_3$]borane is in accord with experiment.

Chiral oxazaborolidine(OAB)–borane adducts are highly effective catalysts for enantioselective reduction of prochiral ketones.[1] Whilst considerable (apparently heuristic) experimentation has been directed towards development of these reagents for production of secondary alcohols in very high enantiomeric excess, rather less effort has been focused upon elucidation of the mechanism[2] as a basis for rational design of effective catalysts for asymmetric induction. Previous theoretical work has either investigated the hydride-transfer step alone,[3] or has considered only a variety of putative intermediates[4] which may or may not occur along the actual reaction path. We outline here the results of a thorough theoretical investigation of a complete catalytic cycle, including all transition structures (TSs), details of which will be presented in full elsewhere.

Scheme 1 summarises a mechanism for catalytic reduction of propanone to propan-2-ol by the borane adduct of the OAB derived from (*S*)-proline. Since the product is achiral, this system does not directly address the issue of asymmetric induction; instead this simplification allows the complete reaction pathway to be delineated, permitting identification of the rate-determining steps, and thereby providing the basis for understanding of the catalytic action and for a subsequent investigation of stereoselectivity. Each boron atom in the system has an attendant solvent molecule of THF; thus an additional two (for structures **0**–**7**) or three (for structures **8**–**15**) THF molecules are included in the model but are omitted from Scheme 1 for clarity. Coordination of THF to borane is strong and specific, but to the OAB–borane adduct it is weak and rather non-specific; however, it is essential to include the solvent molecules to achieve a realistic account of the energetics of complexation.



Scheme 1

Semiempirical MO calculations were performed using the AM1 Hamiltonian,[5] which has been shown to provide an acceptable description of hydride bridging in the OAB–borane adduct, in agreement with experiment and with the *ab initio* MP2/6-31G** method but in contrast to the *ab initio* HF/6-31G** method which neglects electron correlation.[6] Full geometry optimisation was carried out using the AMPAC 4.5 program[7] and each species was characterised as corresponding to either a minimum or a saddle point on the energy hypersurface by means of vibrational analysis: a TS possesses a single imaginary vibrational frequency whereas a minimum-energy structure has none. Intrinsic reaction-coordinate calculations were performed using the MOPAC93 program[8] in

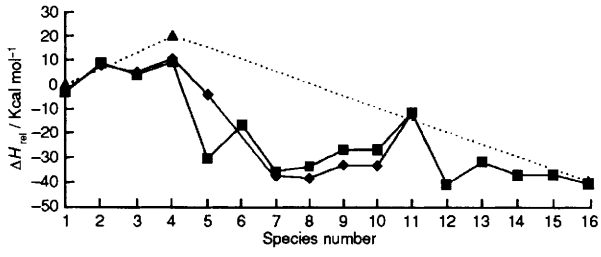


Fig. 1 Relative AM1 calculated enthalpies for species along the pathways for OAB-catalysed (–◆– *via* boat TS, –■– *via* chair TS) and uncatalysed (···▲···) reduction of propanone by THF–borane

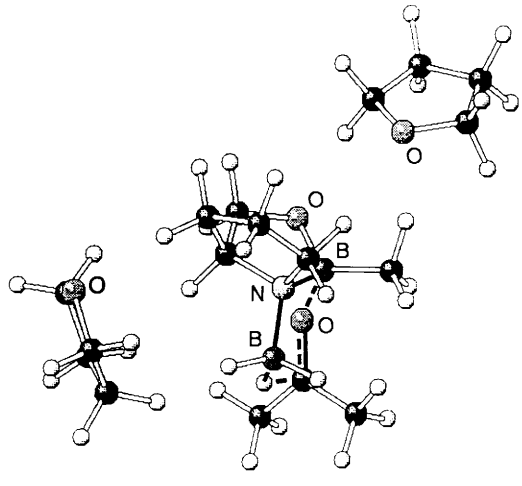


Fig. 2. AM1 optimized geometry for hydride-transfer chair transition structure [4], showing THF solvent molecules

order to determine the existence of a continuous path connecting each saddle point with its adjacent energy minima. This procedure is necessary to verify the sequence of steps for the catalytic mechanism as shown in Scheme 1.

Fig. 1 shows the AM1 calculated enthalpy for each stationary structure along the catalysed reaction path (relative to OAB–borane·2THF + propanone + THF–borane) together with the reactant and product complexes and TS for the uncatalysed reaction (relative to propanone + THF–borane). Species **1** is a loosely coordinated complex of propanone with the solvated OAB–borane adduct **0**; formation of the tightly coordinated complex **3** involves a TS [**2**] rather close in energy to [**4**] for the hydride-transfer step, which may therefore not be entirely rate-determining. The structure of [**4**] is shown in Fig. 2. There are parallel pathways *via* either a boat or a chair conformer of [**4**] all the way through to [**11**], the key TS for regeneration of the catalytic complex. Formation of the oxazadiboretane species **7** occurs more or less directly by means of the slightly higher-energy boat TS [**4**] but *via* a ring-opened species **5** along the path through the preferred chair TS [**4**]. Addition of THF–borane to **7** regenerates the catalyst by means of a six-membered hydride-bridged-ring structure **12** followed by a ring-opened species **14** which readily loses 2-propoxyborane; the latter is the product complex for the uncatalysed reaction. We were unable to locate a route for loss of the alkoxyborane moiety directly from **7**, prior to catalyst regeneration by addition to THF–borane to free OAB. The mechanism leading to the formation of a dialkoxyborane, in which the alkoxyborane product complex itself acts as the hydride donor for a subsequent catalytic cycle, has not been considered here.

The kinetic isotope effect k_H/k_{D3} = 1.8 (23 °C) calculated for the catalysed reaction of propanone with THF–[$^2H_3$]borane agrees well with the experimental value of 1.7 reported for OAB-catalysed reduction of acetophenone[2a] and lends support for this mechanism. This contrasts with k_H/k_{D3} = 1.3 calculated for the uncatalysed reduction of propanone by THF–[$^2H_3$]borane. The enthalpy of activation for the catalysed reaction is about 11 kcal mol^{-1} less than for the uncatalysed reaction, corresponding to a rate enhancement of $\approx 2 \times 10^7$ at room temperature. Catalysis is achieved in effect by conversion of a four-membered cyclic TS into a six-membered cyclic TS by means of a favourable interaction between the dipolar endocyclic N–B bond of the OAB and the zwitterion-like charge distribution of the uncatalysed TS.

Calculations are underway on the diphenyl derivative of the (*S*)-proline OAB to determine which structural features facilitate the reduction of prochiral ketones to optically pure secondary alcohols.

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