Theoretical studies on long-range substituent effects in the reduction of 7-norbornanones

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The energetics of the stereoselective reduction of norbornan-7-one derivatives have been studied by semiempirical AM1 molecular orbital calculations. It was found that the reaction is kinetically controlled; correct prediction of the selectivity is possible only on the basis of the relative energies of the transition states of the reaction. Theoretically calculated and experimental *anti–syn* product ratios are in semiquantitative agreement, in contrast to results obtained from molecular electrostatic potentials. Geometry relaxation of the transition state is essential in obtaining reliable isomer ratios.

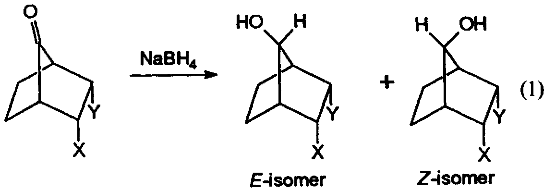
Although the diastereoselective reduction of the carbonyl group can be achieved only in special cases, the stereochemistry of diastereoselective ketone reductions has been widely investigated. Early studies attempted to provide a common interpretation both for acyclic and cyclic carbonyl reductions. However, the behaviour of cyclic ketones in diastereoselective reductions could not be rationalised by any of the models proposed for aliphatic ketones.[1] The recognition of different types of interactions involved in the corresponding transition states prompted the development of several independent models exclusively for the reduction of cyclic ketones, mainly cyclohexanone derivatives.

In the first interpretation of diastereoselectivity,[2] it was proposed that the transition state for unhindered ketones is product-like and the direction of nucleophilic attack is controlled by product stability. In spite of its deficiencies, the concept of steric-approach control became a well documented and widely accepted model. The effect of axial hydrogen atoms around the carbonyl group was first pointed out by Richer.[3] In addition to the steric effect of axial hydrogens, the rear-side approach of the nucleophile results also in a significant preference for axial attack.[4] This model was modified[5] by proposing that equatorial attack of the carbonyl group is not really inhibited by axial CH bonds but, due to the antiplanarity effect, rather the axial approach is promoted. An interpretation based on orbital effects was presented by Klein,[6] and another consequence of unfavourable steric interactions was pointed out by Wigfield and Gowland.[7] A most relevant analysis was performed by Cieplak *et al.*[8] that led to a new model in which stereoelectronic control is associated with electron donation to the σ^* vacant orbital. Royer[9] made use of molecular electrostatic potential (MEP) maps for the prediction of diastereoselectivity and proposed that the unsymmetrical nature of the map could influence the reaction, negative regions disfavouring the equatorial attack. In order to study the effect of remote substituents a new set of model compounds is required, this is why the reduction of a number of bridged cyclic ketones, in particular 2,3-bis(bromomethyl)norborn-5-en-7-one, was examined where the nucleophilic attack by the hydride anion could be designed using the MEP.[10] The relative importance of electrostatic *vs.* orbital effects on diastereoselective reduction of norbornanones,[11] benzobornanones,[12] adamantanones,[13] as well as their unsaturated analogues[14] was investigated. A simple computational procedure was developed by Ganguly *et al.*[15] that considers electrostatic effects by the calculation of the interaction energy between model ketones and a probe negative charge (charge model), while orbital effects were estimated by calculating the interaction energy between the carbonyl compound and a hydride anion (hydride model). For norbornan-7-ones both charge and hydride models predicted the same product in agreement with the experimental finding.

In this work we present a systematic semiempirical molecular orbital study of substituted norbornan-7-ones. Our goal was to decide whether diastereoselectivity can be interpreted in terms of electrostatics or orbital control alone, and furthermore, to check the reliability of the applied method for the prediction of product ratios in this specific case.

Models and methods

Reduction of 2-*endo*-monosubstituted and 2,3-*endo,endo*-bis(substituted)norbornan-7-one derivatives, **1–8** [reaction (1)] was studied where the product may exist both in *E*- and *Z*-forms.



1: X,Y = CH_3 2: X,Y = CH_2CH_3 3: X,Y = $COOCH_3$ 4: X,Y = CH_2OCH_3

5: X,Y = CH_2Br 6: X = $COOCH_3$, 7: X = CN, Y = H 8: X = CCH, Y = H

We considered the reaction with $NaBH_4$ and, following the proposition of Coxon and Luibrand,[16] we used AlH_3 as a model for the borohydride anion. The reason for selection of this model is that the reduction mechanism of carbonyl compounds by $NaBH_4$ is not completely clear. Two alternative hypotheses have been reported. (*i*) The reaction takes place by hydride transfer followed by the formation of the B–O bond. In this case the transition state could not be located.[17] (*ii*) Eisenstein *et al.*[18] suggested a four-centre transition state as a superposition of the two reaction steps mentioned above. However, in protic solvents this transition state is forbidden by orbital symmetry considerations.[19] AlH_3 is known as a reducing agent for carbonyl compounds and reduction is taking place *via* hydride transfer which is similar to the first rate-determining step of the borohydride reduction, therefore it can be used as a model reagent for the latter reaction that is mechanistically unclear. Successful application of this model to 5-substituted adamantanones has also been reported by Coxon *et al.* during the preparation of our manuscript.[20]

Minimum-energy conformations of the reagent and reactant were obtained by molecular mechanics with the MM2 parametrisation[21] using the SPARTAN software.[22] Atoms defining torsional angles are: H–C2–C(substituent)–X (ω_1) and H–C3–C(substituent)–X (ω_2). X is H for **1**, C for **2** and **8**, double-bonded O for **3**, **4** and **6**, Br for **5** and N for **7**. Optimal dihedral angles for substituents were calculated by rotating them by increments of 10°, constraining their values and optimising all other geometry parameters. Thus we obtained energy maps by plotting the conformational energy for a given pair of rotational angles. For monosubstituted derivatives the above two-dimensional maps were reduced to one-dimensional torsion energy curves. The minimum-energy conformation was determined from the corresponding map or curve where we located the absolute minimum using a force criterion of 0.01 kJ mol^{-1} Å^{-1}.

MEP maps for the minimum-energy conformations, as well as optimised geometries of reactants, products and transition-state complexes (with AlH_3 as reducing agent) were determined using the semiempirical AM1 molecular orbital method[23] with the SPARTAN[22] and MOPAC softwares,[24] respectively. Initial geometries of transition-state complexes were generated on the basis of the *ab initio* structure calculated by Coxon and Luibrand[16] for the reaction between formaldehyde and AlH_3 (see Fig. 1). We optimised transition-state geometries by the algorithm proposed by Baker[25] with a force criterion of 0.001 kJ mol^{-1} Å^{-1} using the PRECISE function of MOPAC. Because of the small differences between isomer energies, transition-state structures were optimised very carefully. Those geometries were accepted for which we found just one negative value among the diagonal elements of the force-constant matrix. The SCF convergence criterion was 4×10^{-6} kJ mol^{-1}.

Product ratios were calculated from eqn. (2) where $[E]$ and

$$\ln([E]/[Z]) = -RT\Delta E^{\ddagger}_{EZ} \qquad (2)$$

$[Z]$ are the isomer concentrations and $\Delta E^{\ddagger}_{EZ}$ denotes the difference between energies of the corresponding transition states corrected for zero-point vibrations. In eqn. (2) we neglected entropy effects because the compounds investigated differ only in small substituents located far from the reaction centre. Thus we may suppose that the entropy differences between ground and transition states will not significantly alter for the series of molecules investigated in the present study.

Results and discussion

Conformational analysis

Results of the conformational energy search for the reactants are summarised as follows (optimised torsional angles are in parentheses): **1**, **2**, **5** (ω_1 = 66°, ω_2 = 293°), **3** (ω_1 = 46°, ω_2 = 63°), **4** (ω_1 = 306°, ω_2 = 53°) and **6** (ω_1 = 288°). For **7** and **8** the torsional angle is undefined because C2, C and X are collinear. In Fig. 2 we depict the torsional energy map for **4** in order to illustrate the importance of careful optimisation.

Molecular electrostatic potential maps

In contrast to our previous results for norborn-5-en-7-ones[10] we could not predict the diastereoselectivity of most of the molecules investigated on the basis of the MEP map. The only exception (beside **5**) is the dimethoxy derivative **4** (see Fig. 3). For this molecule the MEP is negative in the substituent region thus hindering the attack of a point-like negative charge from this side. This is why the formation of the *Z* isomer is favoured. Although we were successful in predicting the (slight) diastereoselectivity for **5**, MEP maps for **1–3** and **6–8** are either symmetric or indicate a steric preference just opposite to the one found experimentally. From this we conclude that pure electrostatic models are not suitable for the prediction of diastereoselectivity in the case of the reduction of 7-norbornanone derivatives *endo*-substituted in positions 2 and/or 3.

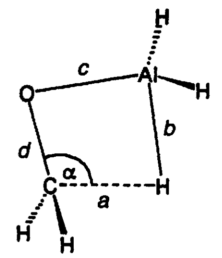


Fig. 1 Definition of geometry parameters of the transition-state complex for the reduction of **1–8** by AlH_3

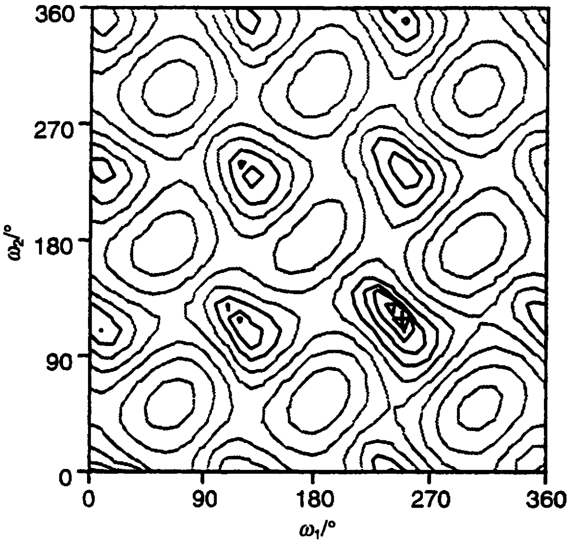


Fig. 2 Conformational energy map for **4** (rigid-rotor approximation). The minimum in the lower right region (indicated by a cross) is at −167 kJ mol^{-1}. Contour intervals are 8 kJ mol^{-1}

Product stability

In order to obtain information whether the reaction is under thermodynamic control or not, we compared experimental *Z*/*E* preferences to the relative energies of the products. Energies of *Z* and *E* isomers (the latter in parentheses) of the reduced products are (in kJ mol^{-1}): **1** −264.1 (−274.5), **2** −322.8 (−323.7), **3*** −903.0 (−905.4), **4** −598.3 (−607.8), **5** −221.6 (−229.9), **6*** −580.5 (−590.2), **7*** −100.5 (−109.3) and **8*** 3.4 (−6.9). For the compounds denoted by an asterisk the product energy difference accounts for the diastereoselectivity. As can be seen in half of the cases preference of the opposite isomer was predicted as has been found experimentally. Our failure may indicate the absence of thermodynamic control for this reaction and prompted us to look for kinetic control by performing calculations on transition-state complexes.

Transition-state complexes

In order to decide on the importance of kinetic control, we calculated relative energies of transition-state complexes too. Table 1 summarises some geometry parameters for these complexes both for *Z* and *E* isomers, while in Fig. 4 we provide the geometric model of the transition-state complex for one of

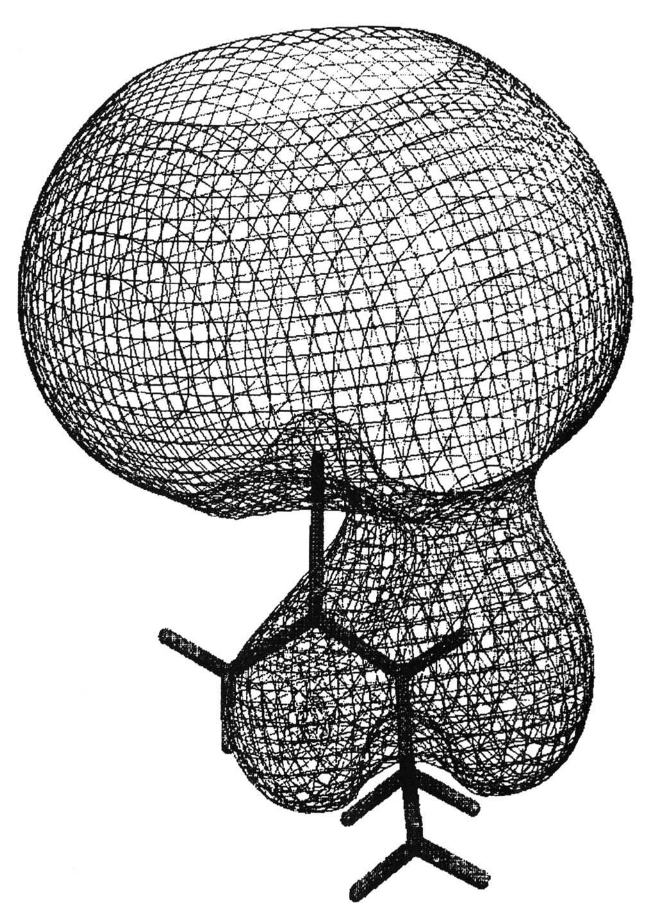


Fig. 3 Isopotential representation of the MEP map for the minimum-energy conformation of **4**. The surface envelope corresponds to −20 kJ mol^{-1}

Table 1 Some optimised geometry parameters and heats of formation (ΔH/kJ mol^{-1}) for the investigated transition-state complexes as obtained by the semiempirical AM1 molecular orbital method. For definitions of geometry parameters, see Fig. 1. Upper row: *Z*-isomer, lower row: *E*-isomer

Compound	*a*/pm	*b*/pm	*c*/pm	*d*/pm	α/degrees	ΔH/kJ mol^{-1}
1	181	152	184	128	90.8	−82.5
	185	158	187	130	94.3	−81.2
2	192	164	185	129	92.2	−134.5
	195	163	181	126	93.9	−131.5
3	187	162	185	128	94.1	−679.2
	183	158	186	130	92.3	−681.4
4	184	155	184	130	91.5	−430.8
	182	149	187	125	89.4	−427.1
5	182	160	184	128	90.2	−166.9
	187	157	185	129	93.1	−165.8
6	181	156	187	125	92.6	−403.7
	185	159	186	126	89.3	−404.7
7	183	154	186	124	93.0	82.7
	180	160	181	130	94.1	80.8
8	186	159	187	131	93.8	173.1
	181	157	182	128	94.6	172.6

the molecules studied. Table 2 contains product ratios as obtained by the AM1 molecular orbital method. As is seen, a semiquantitative agreement with experiment is achieved indicating that, at least in the present case, the AM1 semiempirical molecular orbital method is capable of providing reliable information on reaction transition states. While the approximate model of Ganguly *et al.*[15] correctly predicts diastereoselectivity in all but one case (**8** for the hydride model) due to the simplifications applied, no quantitative agreement can be anticipated. This result allows us to formulate the statement that in the case of the reduction of norbornan-7-ones simple models based on pure electrostatic or orbital control are inadequate for the quantitative prediction of diastereomer ratios. This is possible only on the basis of geometry-optimised transition-state energies.

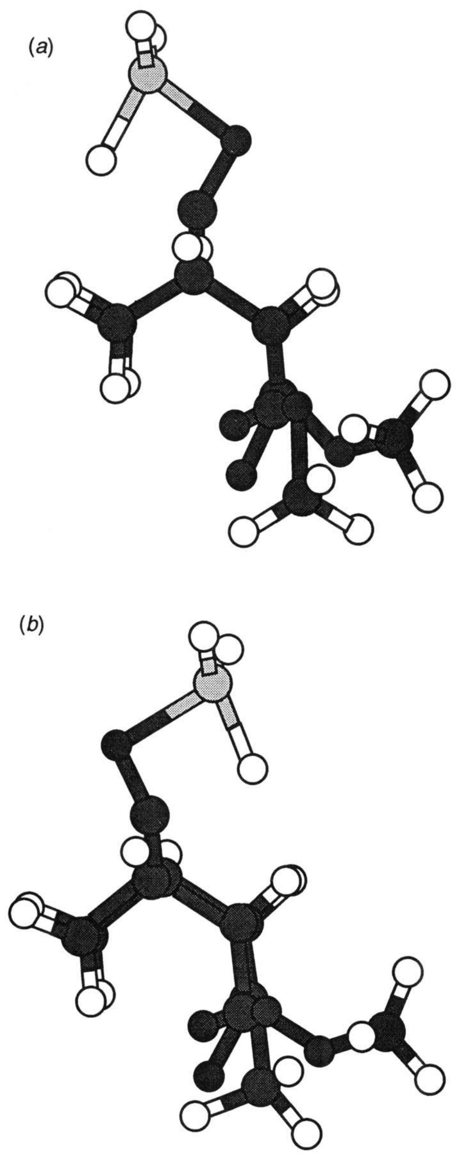


Fig. 4 Transition-state geometry of the complex between **3** and AlH_3. (*a*) *Z*-isomer, (*b*) *E*-isomer. Atom codes: large dark grey circles: C, small dark grey circles: O, large light grey circles: Al, small white circles: H

Table 2 *Z*/*E* product ratios (%) as obtained from AM1 molecular orbital calculations and experiment. *Z*/*E* preferences, predicted by the simple model of Ganguly *et al.*[15] are also indicated

	Preference		*Z*/*E* product ratio (%)	
Compound	Charge model	Hydride model	Eqn. (2)	Experiment
1	*Z*	*Z*	68:32	55:45
2	*Z*	*Z*	85:15	80:20
3	*E*	*E*	21:79	16:84
4	*Z*	*Z*	90:10	60:40
5	—	—	63:37	55:45
6	*E*	*E*	35:65	32:68
7	*E*	*E*	25:75	18:82
8	*E*	*Z*	22:78	31:69

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