π-Face diastereoselection: stereochemistry and reactivity of reduction reactions on conformationally rigid substrates: 5-X-adamantan-2-ones and *trans*-10-X-decal-2-ones

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Abstract—Stereochemistry and relative rates k_{ax} and k_{eq} of reduction reactions on title compounds have been measured under four different reaction conditions ($NaBH_4$ in *i*-PrOH, $LiBH_4$ and $NaAlH_4$ in THF and $LiAlH_4$ in Et_2O). Reaction sensitivities show that the Group III element has a prominent role in determining the structure of the transition state shape. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

We recently discussed[1] addition reactions on the title compounds with particular regard to the electronic contribution of remote substituents and pointed out the importance of having a better knowledge of the reaction TS when exploring questions concerned with π-face diastereoselection.[2] Simple theories such as those based on dipole–dipole interactions[3] are unable to give a satisfactory explanation, nor can theories based on ground state MO considerations.[4] Most of the difficulties encountered in trying to explain the relationship between e.g. inductive effects, changes in reagent, solvent, molecularity and π-face selection are ascribable to the fact that π-face diastereoselection has almost always been discussed in terms of k_{ax}/k_{eq} changes instead of k_{ax} and k_{eq} changes. In fact the stereochemical bias k_{ax}/k_{eq} does not indicate what is happening on the two sides of a stereogenic centre: the two faces of the molecule can behave independently from one another and suffer different effects by the remote substituent. For instance in alkylation reactions we have found that axial reactivities behave monotonically i.e. they always increase with increasing electronegativity of the X group. Instead k_{eq} changes strictly depend on the conformation of the X group and on reaction conditions.

We describe here the stereochemical and kinetic results of hydride reduction on a series of 10-X-adamantan-2-ones, namely with X=H (**1**), Ph (**2**), OH (**3**), CO_2Me (**4**), Cl (**5**) and Br (**6**). Their reactivity has been compared to that of *trans*-10-X-2-decalones: X=H (**7**), CO_2Et (**8**) and Cl (**9**),

previously investigated in the same reaction conditions[5] that are: 1) $NaBH_4$ in *i*-PrOH (20°C);[6,†] 2) $LiBH_4$ in THF (20°C); 3) $NaAlH_4$ in THF and 4) $LiAlH_4$ in Et_2O (20°C) (Fig. 1). Experiments aimed to explore the role of the Group I metal and Group III element on reaction sensitivities.
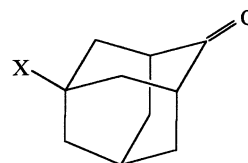
X=H (**1**); Ph (**2**); OH (**3**); CO_2Me (**4**); Cl (**5**); Br (**6**)
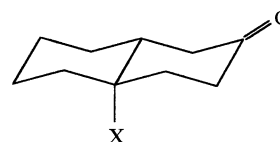
X=H (**7**); CO_2Me (**8**); Cl (**9**)

Figure 1.

The choice of a rigid molecular skeleton eliminates all questions arising from conformational uncertainty.[7–8]

2. Reaction products

Under all the above mentioned reaction conditions we obtained, besides the well known alcohol **1**′, alcohols

[†] Ref. 6 reports only the stereochemical ratios of reduction for this reaction condition. Our stereochemical ratios are in good agreement with them.
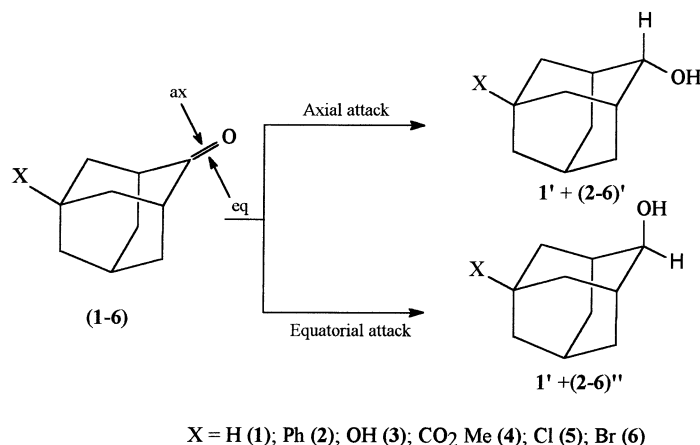
X = H (1); Ph (2); OH (3); CO$_2$ Me (4); Cl (5); Br (6)

Figure 2.

Table 1. Stereochemical product ratios (k_{ax}/k_{eq}) for 10-X-adamantan-2-ones (**1–6**)

Reaction conditions	Stereochemical product ratios (k_{ax}/k_{eq})					
	1′, σ_I=0.00	**2′/2″**, σ_I=0.12	**3′/3″**, σ_I=0.25	**4′/4″**, σ_I=0.32	**5′/5″**, σ_I=0.47	**6′/6″**, σ_I=0.47
1) NaBH$_4$, *i*-PrOH, 20°C	1	1.28	1.05	1.37	1.38	1.23
2) LiBH$_4$, THF, 20°C	1	1.22	1.06	1.12	1.34	1.19
3) NaAlH$_4$, THF, 20°C	1	1.09	1.18	1.30	1.41	1.38
4) LiAlH$_4$, Et$_2$O, 20°C	1	1.27	1.10	1.25	1.12	1.23

(**2–6**)′ that derived from axial attack of the reduction agents, and (**2–6**)″ derived from equatorial attack (Fig. 2).

All our attempts to separate alcohols **2′** and **3′** from alcohols **2″** and **3″**, respectively, were unsuccessful: we characterised them in the epimeric mixture via ^{1}H and ^{13}C NMR by comparison with literature data.[6,9] In particular the axial hydroxyl diastereoisomers exhibit the carbinol ^{13}C quaternary carbon signal at higher fields with respect to the equatorial diastereomers,[10] and have higher propensities towards loss of water from parent ion in mass spectrometry.[11] Alcohols derived from 5-X-adamantan-2-ones (**4–6**) were separated from each other by HPLC and individually characterised by comparison with literature data.[6,12]

3. Results

3.1. Stereochemistry: relative axial and equatorial reactivity

For each set of reaction conditions we determined the stereochemistry of reduction reactions by GLC. Table 1 collects the stereochemical outcome of several reactions (five experiments at least for each substrate under all reaction conditions).

The stereochemical results do not show a great difference between either substrates or reaction condition: we have a rather small constant increase of the k_{ax}/k_{eq} ratio with the increasing electronegativity of substituents[13] which means either that there are no large rates changes on the two diastereotopic faces of the molecule, or that we are looking at parallel rates variations. We can infer what happens on

the two sides of the ketonic group only from kinetic data and therefore performed competitive reaction sets on equimolecular mixtures of compounds **1** and **2–6**, respectively.

Competitive kinetic experiments provided highly reproducible results largely independent of the concentration of the reactants. The relative reaction rates were obtained by GLC determination of the reaction yields.[‡] Relative rates k_{ax} and k_{eq} were computed taking the overall rate of compound **1** ($k_{ax} = k_{eq} = 1$) as two, and by assuming that all reactions are first order in ketone and the same order in reducing agent for all ketones[§] and are reported in Table 2 as a mean of at least five separate experiments.

Reactions of Table 2 give fairly good LFER collected in Table 3 in decreasing ρ value order.

Competitive reactions were also performed on equimolecular mixtures of compounds **1** and **7**; **4** and **8**; **5** and **9** (that is admantanones and decalones bearing the same substituent). The experimental data are collected in Table 4.

[‡] We measured the areas of starting materials and products; each area was divided by the corresponding molecular weight. Preliminary experiments showed that GLC responses of compounds (**1–6**) on the one hand and the alcohols (**1–6**)′ and (**2–6**)″ on the other were very close to each other. Thus no correction was introduced. Although yields varied from run to run, the material balance (i.e. the sum of starting and final products) was always greater than 90% of the starting material.

[§] Yields varied in competition experiments depending on quenching times. In order to minimize errors in computing the relative rates, we used only data from reactions with yields ranging from 15 to 85%: outside this range, either the errors in reading the GLC peaks of products originated from less reactive competitors, or those in reading areas of unreacted substances increase up to unacceptable limits.

Table 2. Overall ratio of rates and relative rates for 5-X-adamantan-2-ones

Reaction conditions	Overall ratio of rates	Relative rates											
		k_{ax}						k_{eq}					
	$k_1/k_2/k_3/k_4/k_5/k_6$[a]	1	2	3	4	5	6	1	2	3	4	5	6
1) NaBH$_4$, i-PrOH	1/2.32/2.63/4.55/12.5/12.5	1	2.6	2.7	5.3	14.5	13.8	1	2.1	2.6	3.8	10.5	11.2
2) LiBH$_4$, THF	1/2.27/1.78/2.94/10.2/6.67	1	2.5	1.8	3.1	11.7	7.2	1	2.0	1.7	2.8	8.7	6.1
3) NaAlH$_4$, THF	1/1.64/2.16/1.83/2.80/4.12	1	1.0	1.0	1.4	1.9	2.9	1	0.9	0.9	1.1	1.4	2.1
4) LiAlH$_4$, Et$_2$O	1/1.28/1.31/1.39/2.10/1.73	1	1.2	0.9	1.4	1.9	2.0	1	1.0	0.9	1.1	1.7	1.7

[a] Mean standard deviation: 0.02.

Table 3. LFER data (ρ in decreasing order and corresponding r^2) in different reaction conditions

Reaction conditions	Attack	ρ	r^2
1) NaBH$_4$, i-PrOH, 20°C	Ax.	2.35	0.96
	Eq.	2.15	0.97
2) LiBH$_4$, THF, 20°C	Ax.	1.92	0.86
	Eq.	1.75	0.89
3) NaAlH$_4$, THF, 20°C	Ax.	0.86	0.76
4) LiAlH$_4$, Et$_2$O, 20°C	Ax.	0.63	0.72
3) NaAlH$_4$, THF, 20°C	Eq.	0.54	0.52
4) LiAlH$_4$, Et$_2$O, 20°C	Eq.	0.54	0.66

Table 4. Relative rates (k_{ax} and k_{eq}) of 5-X-adamantan-2-ones and *trans*-10-X-decal-2-ones

Reaction conditions	Relative rates											
	$k_{ax\ (adam.)}$			$k_{ax\ (dec.)}$			$k_{eq\ (adam.)}$			$k_{eq\ (dec.)}$		
	1	4	5	7	8	9	1	4	5	7	8	9
1) NaBH$_4$, i-PrOH	1	5.3	14.5	3.7	10.1	38.2	1	3.8	10.5	0.5	0.7	0.0
2) LiBH$_4$, THF	1	3.1	11.7	2.2	4.1	20.8	1	2.8	8.7	0.3	0.2	0.0
3) NaAlH$_4$, THF	1	1.4	1.9	1.6	1.3	1.9	1	1.1	1.4	0.2	0.1	0.0
4) LiAlH$_4$, Et$_2$O	1	1.4	1.9	2.2	3.0	4.7	1	1.1	1.7	0.3	0.2	0.0

4. Discussion

The kinetic data in Tables 2 and 3 show that:

1. both k_{ax} and k_{eq} slightly increase on increasing substituent electronegativity;
2. the small positive stereochemical bias (Table 1) is due to a greater increase for axial reactivity (Table 2);
3. the fastest reaction (k_{ax}) is also the most sensitive one towards the effect of substituent; the attack is nucleophilic on both sides of the molecule;[||]
4. Table 3 clearly shows that ρ values group in two sets: the boron and the aluminium set. This sharp division suggests that the solvent change (i.e. i-PrOH→THF) does not produce kinetic effects larger than those produced by the B→Al change. Instead the solvent effect (i.e. THF→Et$_2$O) may be in the range of those produced by the Na→Li change as possibly suggested by the mixing of values in the aluminium set;
5. this means that the reaction sensitivity mainly depends on

the identity of the third group metal being higher with boron reactants than with aluminium and with changes of the first group metal being of less importance. It also means that the boron TSs are more polar than the aluminium ones. Some data in the literature indicate that the first group metal has a role in determining the overall reaction rate with reactions using LiBH$_4$ being much faster than those with NaBH$_4$.[14,15] The same holds for literature data concerning LiAlH$_4$ vs NaAlH$_4$ rates.[16] In conjunction with experiments we are describing here, those data depict for the first time, as far as we know, the two different roles of I and III Group metal in determining, respectively, reaction rates and sensitivity.

For what concerns the decalones series (axial substituent), Table 4, one can observe:

Axial reactivity:

1. as in the adamantanone series, reactions rates increase with increasing the substituent electronegativity;
2. as in the adamantanone series, the greatest effect of changing substituent electronegativity is again observed in reaction conditions 1) and 2);
3. these effects have the same magnitude of those observed in the adamantanone series ($\approx$ ten times in passing from H to Cl in reaction conditions 1) and 2) and two times in reaction conditions 3) and 4));
4. the change from B to Al has a larger effect on the reaction sensitivity when Group I metal is Na.

Point 1 strictly parallels what we already described for addition reactions and has the same rationale: the LUMO carbonyl orbital is more extended on the axial face both under the influence of β-C–C bond hyperconjugation and C$_4$–X bonds irrespective of their axial or equatorial

[||] We found[5] that substrates bearing an axial substituent show, in analogous reducing conditions, that k_{eq} decreases on increasing the substituents electronegativity (see $k_{eq(dec)}$ in Table 4): this is peculiar for a reaction 'electrophilic' in nature.

conformation: this more rigidly preserves the nucleophilic character of axial attack with changing reactant.

Equatorial reactivity:

The influence of a C_4–X axial substituent is far less predictable. In the present case we observe a decrease in reactivity with increasing substituent electronegativity in all reduction conditions: an electrophilic behaviour is mimicked and therefore, one must imagine the TS with the O–metal bond more developed than the C–H bond. In the alkylation reaction[1] the equatorial attack was instead 'nucleophilic' or 'electrophilic' depending on the used reactant. This is not schizophrenic behaviour: it depends on that the HOMO carbonyl orbital suffer opposite distortion effects from the β-C–C and the axial C_4–X bond hyperconjugation. The balance is determined by the identity of the X group and the reaction outcome, nucleophilic or electrophilic, could depend on the reactant in a way till now unexplored. In similar cases, the need of precise TS knowledge is more evident. In our opinion many of the uncertainties and debates in the literature concerning π-face diastereoselection on less rigid substrates are due to the fact that products ascribed to axial attack partly originate from the more equivocal equatorial attack on the C_4–X axial conformation.[7]

5. Conclusions

We determined the axial and equatorial rates of attack on 5-X-adamantan-2-ones and *trans*-10-X-decal-2-ones in reduction reactions. Changes of Group I metals (Li and Na) only have a small influence on the reaction sensitivity: this mainly depends on the Group III element, being larger for reducing agents containing boron with respect to those containing aluminum. This means that the transition state shape is mainly determined by the Group III element. The TS is more polar, trapezoidal with boron reactants and has the O···B bond less developed than the C···H bond. Aluminum hydrides generate a more square, pericyclic TS. Solvent changes do not produce kinetic effects larger than those produced by the Group III element change. A comparison of axial and equatorial conformation of substituents (adamantanones and decalones series) shows for axial reactivity similar behaviour in the two series; on the other side, equatorial reactivity shows a different and less predictable behaviour when the substituent is axial.

6. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a GEMINI 200. GC–MS analyses were performed with a GC–MS HP 5970 Chemstation Mass Selective Detector connected with a HP 5890 gas chromatograph and on a HP G1800A GCD System gas chromatograph. GLC analyses were carried out on a Carlo Erba HRGC Mega Series 5300 apparatus using a 30 m, 0.25 mm i.d. fused silica capillary column (stationary phase O.V.1), He flow=0.5 ml/min. We report, in sequence, the elution order of compounds from each mixture and the most suitable temperature conditions (in parentheses T_{oven}°C) for, respectively,: **1**, **1**′ (160); **4**, **4**′, **4**″ (170); **5**,

5′, **5**″ (170); **6**, **6**′, **6**″ (160); **7**, **7**′, **7**″ (150); **8**, **8**′, **8**″ (170); **9**, **9**′, **9**″ (170) and (in parentheses T_{oven}, initial isotherm, $T_{increase}$, T_{final}) for **2**, **2**′, **2**″ (170, 5 min, 20°C/min, 220); **3**, **3**′, **3**″ (80, 1 min, 10°C/min, 220); $T_{inj}=T_{det}=230$°C.

6.1. Starting materials

2-Adamantanone is commercially available (Aldrich) and was used as such. Published procedures were used for the preparation of 5-phenyl-adamantan-2-one **2** and 5-hydroxy-adamantan-2-one **3**,[17] 5-carbomethoxy-adamantan-2-one **4**,[18] 5-chloro-adamantan-2-one **5** and 5-bromo-adamantan-2-one **6**,[19] *trans*-decal-2-one **7**,[20] *trans*-10-carbethoxy-decal-2-one **8**[21] and *trans*-10-chloro-decal-2-one **9**.[5]

6.2. Preparation of reagents

1 M solns of NaBH$_4$, LiBH$_4$ and LiAlH$_4$, respectively, in anhydrous *i*-PrOH, THF and Et$_2$O were prepared, kept under dry N$_2$ and titrated[22] before use. Commercial solns (1 M) of NaAlH$_4$ in THF (Aldrich) were titrated and diluted to the desired concentration just before use.

6.3. Reactions

All the reactions were carried out under a pure dry nitrogen atmosphere and the glassware was carefully flamed and flushed with dry nitrogen before use. Typically: a solution of the reducing reagent (0.1 M) was added via a syringe into a flask containing a solution 0.1 M of each substrate in the suitable anhydrous solvent, with *n*-hexadecane as internal standard. Reactions lasted a few minutes. After this time, the reaction mixtures were slowly hydrolysed with satd. aq. NH$_4$Cl and extracted three times with Et$_2$O. The ethereal solns washed with water were combined, dried over Na$_2$SO$_4$, filtered and evaporated. Analyses of reaction mixtures by GLC were carried out as described.

6.4. Competition experiments

Three flasks (10 ml) were equipped with magnetic stirrer and connected by means of a three-point star-rotating receiver to a graduated burette, gas inlet and CaCl$_2$ tube. The apparatus was carefully dried by flaming it under a nitrogen flow. Each flask contained an equimolecular mixture of **1** and **3** or, respectively, depending on the chosen partner for that particular experiment, **1**, **4**, **5**, or **1**, **2**, **6**, or **1**, **7** or **4**, **8**, or **5**, **9**);[¶] 0.1 mmol of each substance were used and dissolved in 2 or 3 ml of anhydrous solvent (*i*-PrOH, Et$_2$O or THF) depending on whether the competition reaction was with two or three competitors. The graduated burette was filled via a syringe with the suitable, conveniently diluted, reactant, and the equimolar amount of it was added to the substrates mixtures under vigorous stirring. Reaction mixtures were then hydrolysed and worked up under standard methods, and finally examined by GLC in order to measure the relative amounts of products and starting materials.

¶ As a consequence of peaks overlapping in the GLC analysis it was not possible to perform competition experiments in which all products were present at the same time.

Acknowledgements

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