Electronic Effects in π-Facially Stereoselective Epoxidation of Phenyltrifluoromethylpropenol

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AM1, PM3 and ab initio 6-31G* calculations indicate that stereoselective epoxidation of the alkene 3 arises from stereoelectronic control exerted via a CF$_3$–C bond orientated anti to the alkene plane for steric reasons, in contrast to a previously proposed model for epoxidation of allylic fluorides in which the F–C and alkene bonds are oriented syn.

Stereoselective addition to C=C or C=O double bonds is thought to arise from orbital interactions induced by e.g. a nucleophilic reagent approaching the π-face anti to either the most electron-donating σ-bond[1] or anti to the lowest entry σ* orbital of the substrate,[2] although electrostatic π asymmetry has also been suggested[3] as contributing to π-facial selection[4] and to the unusual properties of the chiral recognition reagent 1.[5] For electrophilic addition, stabilisation of a π system by p$_\pi$ interactions with an anti periplanar low energy σ* orbital (i.e. C–Cl) is known[6] to deactivate the double bond. Accordingly, a recently proposed[7] general model for electrophilic addition

to allylic π-bonds based on epoxidation of allylic fluorides has the most electronegative C–Y bond (2, Y=F) placed syn to the C=C plane and orthogonal to the p$_\pi$ system, thus avoiding any such σ*$_{C-Y}$/p$_\pi$ deactivation of the alkene.

When the chelating effect of an OH group is included, such a model would predict that electrophilic epoxidation of the alkene 3 (R=Ph, Y=CF$_3$) should give predominantly 4a,
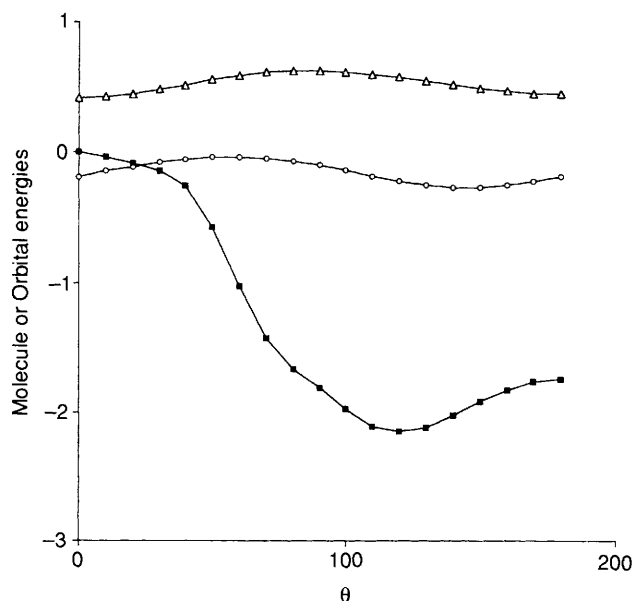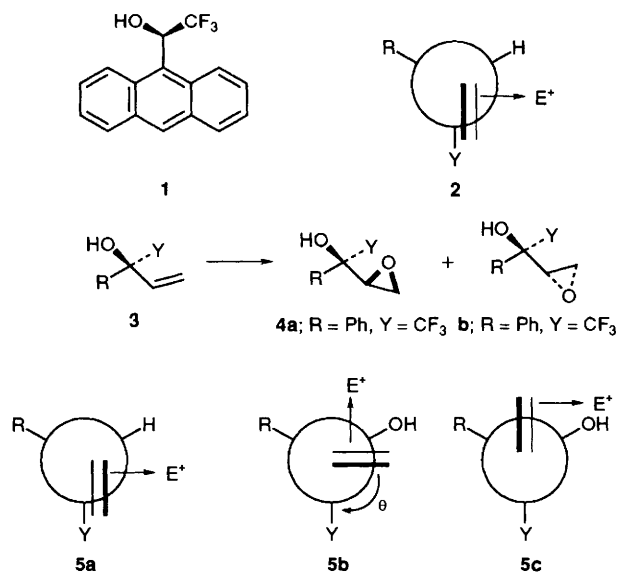

3

4a; R = Ph, Y = CF$_3$ b; R = Ph, Y = CF$_3$

5a   5b   5c

Fig. 1 PM3 Relative enthalpy (in kcal mol^{-1}, ■), relative π-HOMO (in eV, ○) and C–CF$_3$ σ* orbital energies (in eV, ▲) in 5b (R=H, Y=CF$_3$) as a function of the angle θ (in °)
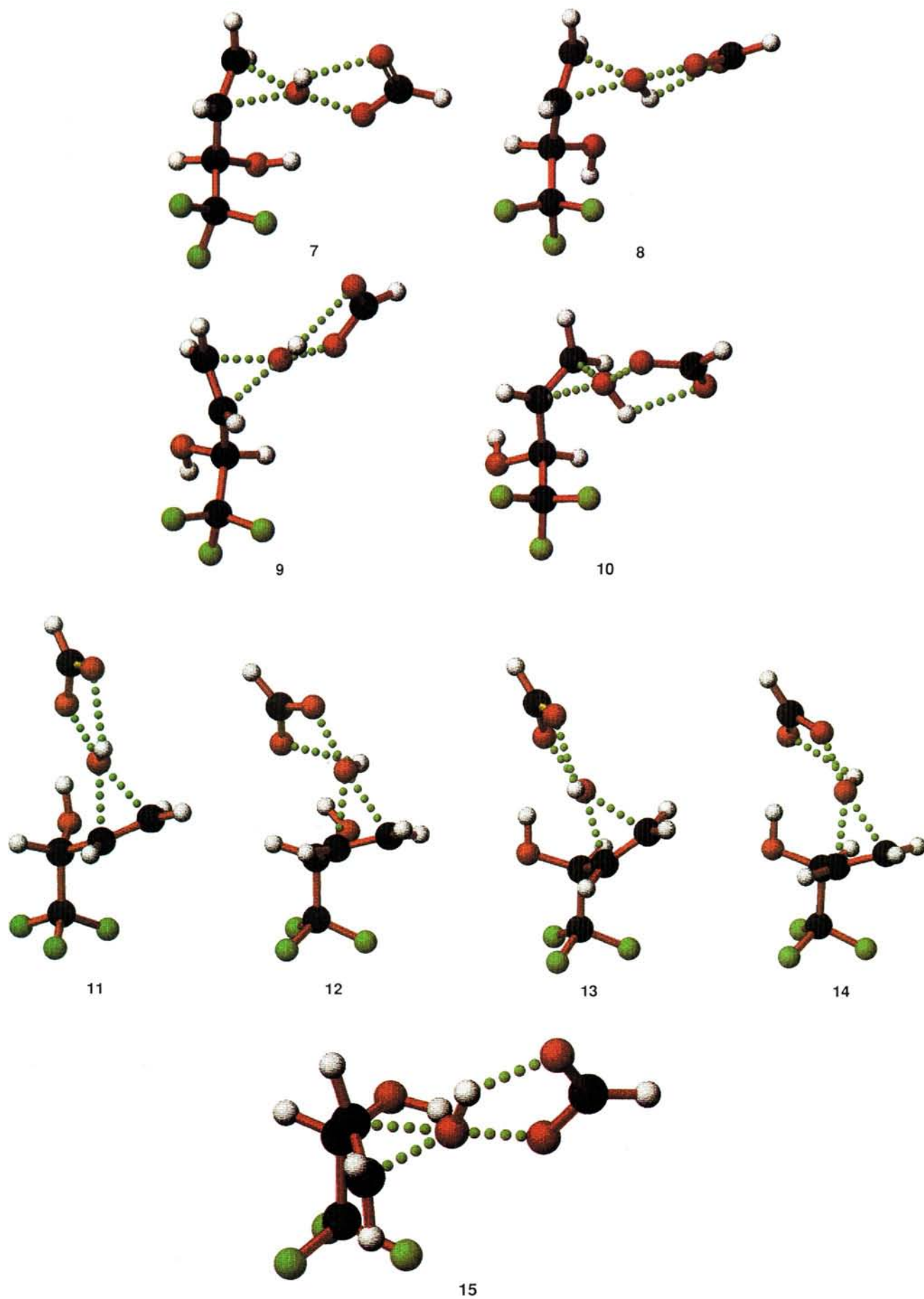
Fig. 2 Schematic structures for transition states **7–15**, indicating the relative orientations and stereochemistry

Table 1 Calculated relative energies for transition states **7–15** (R=H, Ph)

R	No.	AM1 ΔH^a	AM1 $\Delta G^{\ddagger b}$	AM1^c ΔH	AM1^c $\Delta G^{\ddagger}$	PM3 ΔH	PM3 $\Delta G^{\ddagger}$
H	7^d	0 (31.87)	0 (43.12)	0 (31.22)	0 (43.17)	0 (13.11)	0 (25.99)
H	8	3.71	3.00	1.58	1.25	3.48	3.64
H	9	3.58	2.62	1.75	0.67	3.70	1.77
H	10	7.41	6.86	3.80	2.61	4.50	4.34
H	11^e	2.46	2.10	2.24	1.63	1.23	1.20
H	12	0.96	0.97	3.09	3.01	2.36	1.87
H	13	2.18	2.23	1.18	0.70	1.32	1.25
H	14	2.52	3.12	−0.26	−0.37	3.36	2.57
H	15^f	1.92	2.43	1.56	—	2.29	2.75
Ph	7	0 (31.64)	0 (42.92)	0 (31.78)	0 (42.52)	—	—
Ph	8	1.56	1.28	−0.53	0.88	—	—
Ph	9	4.25	4.41			—	—
Ph	10	6.28	7.18			—	—
Ph	11	1.45	2.35	1.90	3.52	—	—
Ph	12	−0.01	1.18	0.99	3.04	—	—
Ph	13	4.04	4.22	3.24	4.45	—	—
Ph	14	2.34	2.14			—	—
Ph	15	1.88	2.07	1.60	1.88	—	—

^{a} All enthalpies indicated are relative to **7** in kcal mol^{-1} with the absolute activation enthalpy in parentheses. $\Delta H(\mathbf{3 + 6}$, R=H) $= -259.96$ (AM1), -280.93 (AM1, COSMO), -261.04 (PM3). $\Delta H(\mathbf{3 + 6}$, R=Ph) $= -222.49$ (AM1), -243.67 (AM1, COSMO). ^{b} All free energies indicated relative to **7** in cal K^{-1} mol^{-1}, $\Delta S(\mathbf{3 + 6}$, R=H) $= 155.43$ (AM1), 159.19 (AM1, COSMO), 156.28 (PM3), $\Delta S(\mathbf{3 + 6}$, R=Ph) $= 177.76$ (AM1), 180.36 (AM1, COSMO). ^{c} Using the COSMO method with a relative permittivity of 10. ^{d} Ab initio 6-31G* energy -790.9781 Hartree (value including zero point thermal contributions -790.8273). ^{e} 6-31G*; -790.9789 (-790.8281). ^{f} 6-31G*; -790.9758 (-790.8247).

whereas in fact we have observed[8] a 1 : 5 ratio in favour of **4b**. We suggest here an alternative model supported by quantitative calculations in which the group Y=CF$_3$ occupies the sterically less demanding *anti* orientation **5c** relative to the alkene, rather than the *syn* position **5a** derived from the allyl fluoride model.[7]

In the standard model,[6] the alkene in conformation **5b** is stabilised and hence deactivated by interaction with the antiperiplanar C–CF$_3$ σ* bond. The calculated PM3[9] orbital energies (R=H, Y=CF$_3$, Fig. 1) indeed show that the π-orbital is initially stabilised as the dihedral angle θ tends from 180° **5c** to 0° **5a**, but this effect reaches a maximum at θ *ca.* 150°, and then reverses to give a maximum in the π-orbital energy at θ *ca.* 60° (*ca.* that for **5b**) resulting from p$_\pi$–n$_F$ repulsive interactions. The energy profile clearly shows **5c** to be lower than **5a**, but the π-HOMO (highest occupied molecular orbital) model appears to favour **5b**, perhaps because polarisation of the π-bond by the approaching electrophile is neglected. We, therefore, turned the transition state models for which recently reported *ab initio* calculations for reaction between performic acid **6** and ethene[10] served as a convenient starting point. We also wished to quantify the orientating effect of the hydroxy group on the transition state, an interaction not studied in the original calculations.[10]

For each conformation **5a–c**, two orientations of the incoming performic acid O–H group are possible, as well as non-chelating forms. These possibilities are all included in transition states **7–15**, R=H, Ph, Y=CF$_3$, which were initially located† using the semiempirical AM1 and PM3 methods,[9]

followed by reoptimisation at the *ab initio* 6-13G* basis set level[11] for **7** (≡**5c**), **11** (≡**5b**) and **15** (≡**5a**) for R=H, Y=CF$_3$ only. Our semiempirical and *ab initio* calculated geometries‡ (Fig. 2) are in good accord with the previous study.[10]

The calculated energies show that **7**, Y=CF$_3$ is 1.9–2.3 (AM1, PM3) or 1.4–1.6 kcal mol^{-1} (1 cal = 4.184 J) (6-31G*) more stable than **15** and similar to (6-31G*) or more stable (AM1, PM3) than **11** (Table 1). The activation enthalpies are significantly smaller with PM3 than AM1, the former appearing more realistic for a reaction that readily occurs at room temperature. Entropic effects are negligible (Table 1).§ The calculations also indicate that chelation control *via* hydrogen-bonding interaction between the incoming peracid and **3** results in a stabilisation of *ca.* 3–4 kcal mol^{-1}, *viz.* **7** *vs.* **9**. To evaluate the effect that a typical organic solvent (ε *ca.* 10) may have on the stereoselectivity, the transition states were fully reoptimised at the semiempirical level using the recently described COSMO[14] continuum model for solvation. The chelating effect is reduced as expected, but **7** is still lower in energy than either **11** or **15**, in agreement with experimental observation (Table 1).

The stereoelectronic role of the CF$_3$ group in **7**, **11** and **15** can be probed by inspecting the localised orbitals.[15] These

† Geometries were optimised at the AM1, AM1(COSMO), PM3 or 6-31G* levels using the AMPAC-4,[9a] MOPAC-6, MOPAC-93[9b] or GAUSSIAN-92 programs.[11] Transition states were located using the eigenvector following method and were shown to have one negative eigenvalue with the correct displacement coordinates in the Hessian matrix as required of a transition state. Molecular entropies were calculated from the normal vibrational frequencies obtained from the mass-weighted Hessian matrix. Molecular structures were inspected on CAChe Scientific or Silicon Graphics Indigo Elan workstations, on the latter using the AVS system or locally written Iris Explorer/EyeChem Modules. Conversion to Quicktime video animation format was done on an Apple Macintosh system.

‡ Binary files in Quicktime video animation format playable on either Macintosh or Microsoft Windows systems, which illustrate the three-dimensional properties of the transition states **7**, **11** and **15** are available for public access from the Gopher$^+$ server *argon-fddi.ch.ic.ac.uk* (Internet IP address 155.198.1.33) along with coordinate text files for all the structures **7–15**.

These files will reside in the Royal_Society_of_Chemistry/Chemical_Communications/3_02351F directory for a period of at least two years from the publication of this paper. A brief description of how to acquire and visualise such materials is available as a text file from the same source. We welcome comments on the suitability of this method of providing supplementary information.

§ Several anomalies in the semiempirical results do appear. Thus, **12** at the AM1 level is excessively stabilised by some 1–2 kcal mol^{-1} owing to formation of a bisected hydrogen bonding structure.[12] Similarly, the PM3 method artificially favours very short H–H (*ca.* 1.7 Å) contacts as in *e.g* methane dimer,[13] an error that occurs in several of the transition states involving **3**, R=Ph and which are excluded here for this reason.

show a three-centre alkene–oxygen transition-state bond (R=H, AM1: -15.30 eV/7, $-15.21/11$, $-15.41/15$; PM3: $-16.12/7$, $-16.03/11$, $-16.17/15$), which is least stable in orientation **11**, supporting the hypothesis that alignment of the C–CF$_3$ axis with the forming carbon–electrophile bonds destabilises the formation of C–O bonding, and also indicating that the higher overall energy of **15** is due to steric rather than to electronic factors. We conclude that π-facial stereoselection in even a relatively simple system such as **3** results from a combination of steric, stereoelectronic and hydrogen-bonding effects in which the need for transition-state models is emphasised.

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