Electroorganic Reactions. Part 37.† The Stereochemistry and Mechanism of the Cathodic Hydrogenation of Methyl 4-*tert*-Butylcyclohex-1-enecarboxylate

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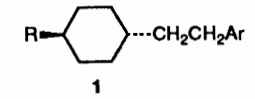
Methyl 4-*tert*-butylcyclohex-1-enecarboxylate is hydrogenated at a mercury cathode, in the presence of proton donors, in a smooth 2 F mol^{-1} process. The proportions of *cis* and *trans* isomers in the product (methyl 4-*tert*-butylcyclohexanecarboxylate) are a function of reaction conditions and detailed consideration shows that the reaction is under kinetic control. Protonation of the first-formed radical anion is probably at C-1, with little stereoselectivity. The results of base- and radical-induced epimerizations of 1,4-disubstituted cyclohexanes were used to establish the likely outcome of thermodynamic control. These results are in impressive agreement with calculations based on substituent group conformational preferences.

The electrohydrodimerisation of activated alkenes has been much studied whereas the often competing double-bond hydrogenation has received less attention because it is usually preparatively less interesting. However, the stereochemical outcome of cyclohexene reduction is of significance for synthesis. Activation of the endocyclic double bond by an electron-withdrawing group makes cathodic reduction easy. In this case the stereochemical course of the reaction will give important clues to mechanism.

An important class of liquid crystal materials (**1**) contains the *trans*-1,4-disubstituted cyclohexane unit as a key structural feature. The *trans* stereochemistry is important to give the required rigid molecular shape. Useful intermediates for commercial routes to **1** are *trans*-4-alkylcyclohexanecarboxylic acids (**2**).



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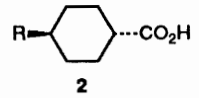

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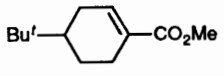

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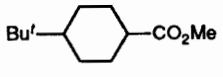

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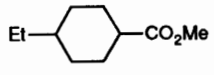

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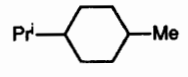

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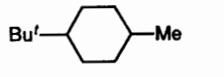

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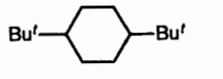

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There are few direct routes to compounds of the type **2**. Catalytic hydrogenation of 1,4-disubstituted benzenes generally gives *cis*-rich cyclohexane product mixtures. Moderate *trans* stereoselectivity has been reported from the reduction[1] of 4-isopropyl-1-methylcyclohexene with palladium on carbon (74% *trans*). The reduction of 4-*tert*-butyl-1-methylcyclohexene with a chloroplatinic acid based homogeneous catalyst gave[2] 95% of the *trans* product. The homogeneous catalytic hydrogenation of methyl 4-*tert*-butylcyclohex-1-ene carboxylate (**3**) is stereoselective; hydrogenation[3] in the presence of tris(triphenylphosphine)rhodium chloride gave 84–91% of the *trans* product with an overall yield of 56–81%.

We report here the results of experiments on the cathodic hydrogenation of methyl 4-*tert*-butylcyclohex-1-enecarboxylate (**3**) to give stereoisomers of methyl 4-*tert*-butylcyclohexanecarboxylate (**4**) under a variety of conditions. For comparison the stereoselectivity to be expected should the reactions be under thermodynamic control, is calculated using established values[4a] for conformational free-energy differences in substituted cyclohexanes.

Table 1 Calculated values[a] relating to equilibration of *cis*- and *trans*-1,4-disubstituted cyclohexanes

Compound	K_{epi}	% *trans* epimer
4	6.7	87
5	4.9	83
6	11.5	92
7	19	95
8	—	(100)

[a] Using substituent conformational free-energy difference values given in ref. 4.

Results and Discussion

Conformational Analysis.—The equilibrium constants for *cis*–*trans* epimerisation for a variety of 1,4-disubstituted cyclohexanes were calculated from conformational free-energy differences using the method originally described by Eliel[4b] and based on the additivity of conformational enthalpies. The values given in Table 1 illustrate that for reactions operating under exclusive thermodynamic control, and involving compounds with bulky substituents, very high *trans* stereoselectivities should be attainable.

Experimental verification of the calculated epimerisation equilibrium constant for methyl 4-ethylcyclohexanecarboxylate (**5**) was obtained using a free radical-induced epimerisation. Two mixtures of methyl 4-ethylcyclohexanecarboxylate (one *cis*-rich, the other *trans*-rich) were epimerised by Mazur's method,[5] *i.e.* UV irradiation in cyclohexane solution in the presence of mercury(II) bromide. The composition of the mixture was determined at intervals by GLC. The results of the photochemical epimerisation are given in Fig. 1 and clearly

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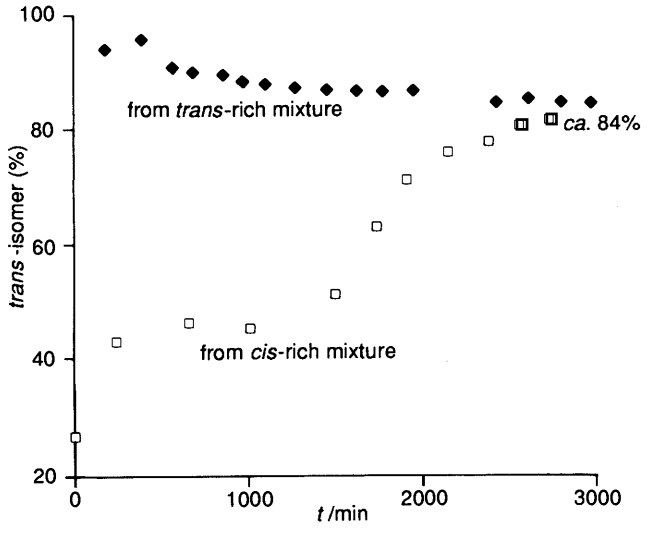


Fig. 1 Radical epimerisation of **5**

Table 2 The *trans*/*cis* equilibration of methyl 4-ethycyclohexanecarboxylate (**5**)

Source	K_{epi}	% *trans* epimer
Base-catalysed epimerisation[a]	5.2	84
Free radical-induced epimerisation[b]	4.9–5.2	83–84
Calculations based on conformational preferences[c]	4.9	83.1

[a] Experimentally determined.[6] [b] Experimentally determined (this work). [c] Calculated (this work).

illustrate that the same isomeric composition is reached when equilibrium is approached from either *cis*- or *trans*-rich mixtures; *i.e.* an equilibrium composition of 83–84% *trans* epimer. The discontinuity in the curve for epimerisation of the *cis*-isomer is merely the result of interruption of the experiment to remove deposition on the walls of the reaction vessel. Base-catalysed epimerisation of a *cis*-rich mixture of (**5**), with sodium ethoxide in ethanol at 78 °C produces[6] a mixture of epimers, with 84% of the *trans* isomer. The agreement obtained between the calculated and the two experimentally derived values (see Table 2) is very satisfactory and lends credence to the value of such calculations.

On the basis of the calculated epimerisation equilibrium constants in Table 1 it seems likely that the very high *trans* stereoselectivity (95%) observed in the aforementioned hydrogenation of 4-*tert*-butyl-1-methylcyclohexene with a chloroplatinic acid based homogeneous catalyst results from thermodynamic control of this reaction. The moderate *trans* stereoselectivity observed in the products from the catalytic hydrogenation of 4-isopropyl-1-methylcyclohexene (74%) does not reflect thermodynamic control of this reaction. The production of methyl 4-*tert*-butylcyclohexanecarboxylate (**4**) under conditions of thermodynamic control would be expected to yield a mixture with 87% of the *trans*-isomer; this has apparently been achieved[3] with homogeneous catalytic hydrogenation.

Voltammetry.—Cyclic voltammetry of methyl 4-*tert*-butylcyclohex-1-enecarboxylate (**3**) (2 mmol dm^{-3}) in 0.1 mol dm^{-3} $TBABF_4$/DMF at a mercury bead cathode produced an irreversible reduction wave at sweep speeds (v) up to 1 V s^{-1}, with a peak potential of −2.30 V (*vs.* pseudo Ag wire). The reduction peak was under diffusion control, as shown by linearity of the plot of i_p *vs.* $v^{\frac{1}{2}}$ for sweep speeds between 50 and 900 mV s^{-1}. The addition of a thirty-fold excess of quinol, as a proton donor, produced no significant change in peak current or peak shape.

Coulometry.—It was important to distinguish between the hydrodimerisation and hydrogenation of **3**; the formation in preparative scale experiments of good yields of the product of hydrogenation (see below) is not, on its own, compelling evidence in the absence of complete material balance. To this end the coulometry of the closely related compound methyl cyclohex-1-enecarboxylate (**9**) was determined in both the presence and absence of proton donor. The results are given in Fig. 2 and show conclusively that when acid (quinol) is present clean 2 F mol^{-1} reduction is observed (n_{obs} = 2.04 ± 0.12) which is consistent with hydrogenation. Under aprotic conditions the predominant reaction is hydrodimerisation (1 F mol^{-1}, n_{obs} = 0.99 ± 0.02); were this to compete significantly with hydrogenation in the presence of acid then n-values intermediate between 1 and 2 would have been found. Addition of quinol did not affect the peak current in the cyclic voltammetric experiments (see above). There is, therefore, different behaviour for those fast time scale (non-steady state) conditions compared with those of the long time scale (steady state) conditions of preparative electrolysis.

Preparative Scale Reduction.—The results for the cathodic reduction of **3** at constant current with a variety of other conditions are presented in Table 3. The progress of the reaction was monitored by capillary GLC using decalin (*cis* and *trans* mixture) as an internal standard.

The low yield obtained from the reduction at platinum (entries 4 and 5) probably arises from preferential proton reduction at this low hydrogen-overvoltage material. In support of this, gas evolution was observed during this reaction.

Current efficiencies were calculated at relatively low conversion, based on the premise that alkene hydrogenation requires 2 F of charge per double bond. For reactions in which a very large excess of charge was transferred and high yields of products obtained (*e.g.* entry 3), the calculated current efficiency may be considerably lower than the optimum value. The calculated current efficiencies vary from experiment to experiment, with the highest value of 61% in entries 6 and 11. With respect to entry 8, it appears that prior to 2 F mol^{-1} of charge transfer, reduction of a species other than the ester occurs, and evidence for this includes the observation of gas evolution, the low electrode potential and the 100% recovery of starting material. Reduction of the ester occurs subsequently, but the occurrence of this competing reduction is reflected in the low current efficiency for this process (entry 9).

The similarity in the measured electrode potential for all experiments (except entries 8 and 14) and the correlation of this value with the peak potential from cyclic voltammetry is noteworthy. In one of these experiments (entry 14) the electrode potential is considerably lower, despite significant selective alkene hydrogenation.

The error associated with GLC analysis (±6.3% of determined value) should be remembered when considering the significance of differences between epimer ratios. The results indicate a range from a *cis* stereoselectivity of 79% (experiment 1) and a *trans* stereoselectivity of 67–68% (entries 3 and 7), the latter occurring when methanol was used as proton donor. The results clearly indicate that kinetic control predominates in each case; thermodynamic control would give 87% selectivity in favour of the *trans* isomer.

Yields of the saturated, hydrogenation, product **4** were above 90% in several cases and the coulometric results (above) show that even where low yields were obtained it is unlikely that alternative products are formed from **3**. The low yields obtained

Table 3 Preparative cathodic reduction[a] of methyl 4-*tert*-butylcyclohex-1-enecarboxylate (**3**)

Entry	Solvent	Proton source	Charge (F mol^{-1})	Cyclohexane (**4**, %)	*cis*:*trans*	Recovered **3** (%)	Current efficiency (%)
1	THF	H_2O[b]	2.2	24	79:21	—	22
2	THF	H_2O[b]	4.2	18	73:27	—	
3	THF	MeOH[b]	3.6	93	33:67	—	51
4[c]	THF	MeOH[b]	2.2	10	51:49	90	9
5[c]	THF	MeOH[b]	13.1	14	69:31	74	
6	DMF	MeOH[b]	2.2	67	43:57	14	61
7	DMF	MeOH[b]	4.3	78	32:68	—	
8	DMF	MeOH[b]/*p*TSA[d]	2.0	—	—	100[e]	0
9	DMF	MeOH[b]/*p*TSA[d]	4.0	76	54:46	24	38
10	DMF	MeOH[b]/*p*TSA[d]	6.0	97	45:55	3	
11	DMF	Quinol[f]	2.0	61	58:42	39	61
12	DMF	Quinol[f]	4.0	95	62:38	—	
13[g]	DMF	Quinol[f]	2.1	45	54:46	55	43
14[g]	DMF	Quinol[f]	3.9	36	40:60	47[e]	

[a] Using Hg cathode, divided cell, Ag reference electrode, [substrate] = 0.01–0.03 [decalin] = 0.08–0.1 mol dm^{-3}, constant current density = 4.2 mA cm^{-2} (cathode potential, −1.8 to −2.4 V). [b] 4.0–4.4 mol dm^{-3}. [c] Pt cathode, 10 mA cm^{-2}. [d] 0.04 mol dm^{-3}. [e] Cathode potential ≤ −1.6 V. [f] 0.05 mol dm^{-3}. [g] At 80 °C.

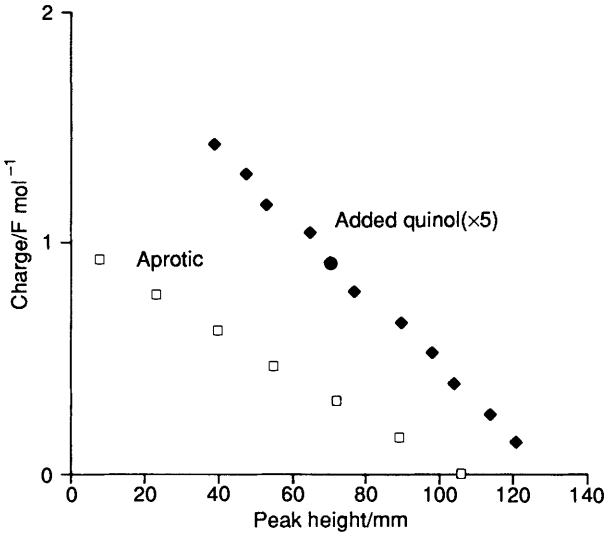


Fig. 2 Coulometry for reduction of **9**. Solvent: DMF–TBAI (0.1 mol dm^{-3}); potential: −2.2 V (Ag/AgI).

in the aqueous system probably reflect competing hydrogen evolution and ester hydrolysis.

In preliminary experiments in which no precautions were taken to eliminate water from reagents, saturation of the double bond was observed, but considerable hydrolysis of the ester to the corresponding acid also took place. For example, in an electrolysis conducted at a mercury cathode with 0.4 mol dm^{-3} TBAI/4 mmol dm^{-3} 1,4-dihydroquinone/DMF as electrolyte and after the transfer of 4.3 F mol^{-1} of charge, analysis of the catholyte by GLC showed no ester material present. However on treatment with acid, extraction with diethyl ether and methylation of the ethereal extract with diazomethane, peaks for **4** corresponding to a 70.4% yield were observed together with starting material (**3**, 22.9%). Alkaline hydrolysis of the *trans* ester is significantly faster than that of the *cis* isomer;[7] consequently in experiments with water present (Table 3, entries 1 and 2) the predominance of methyl *cis*-4-*tert*-butyl-cyclohexanecarboxylate is probably the result of selective removal of the *trans* isomer by hydrolysis.

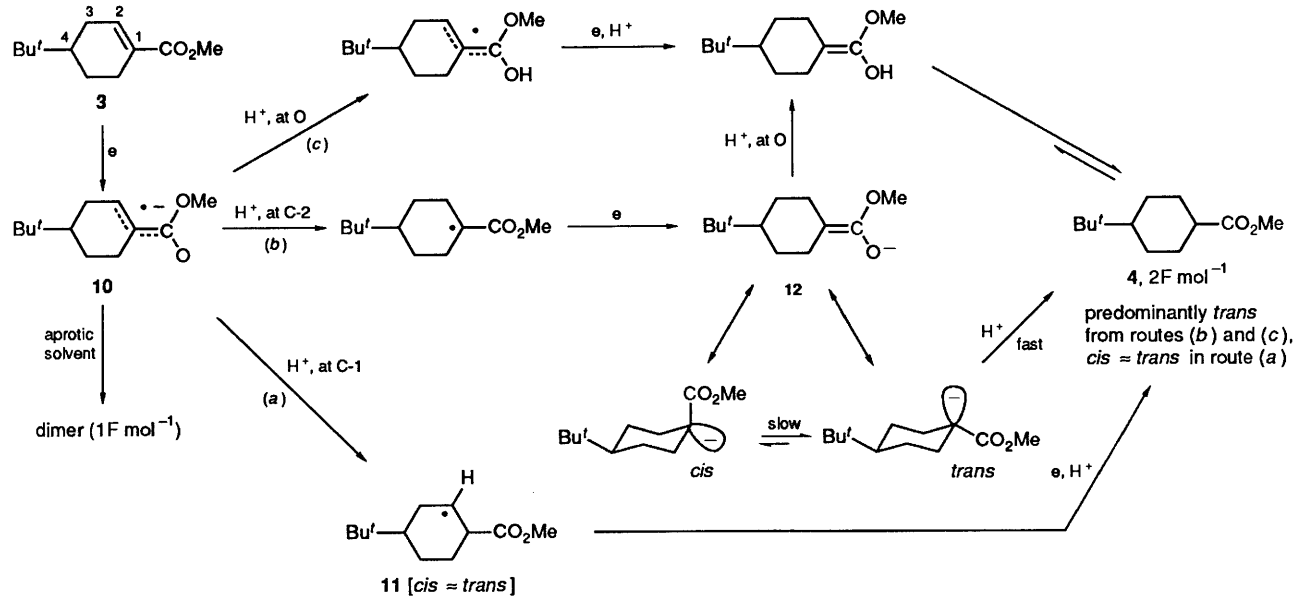
Mechanistic Rationalisation.—Key features of the results presented in Table 3 are: (i) where there is good material balance and incomplete conversion, *e.g.* entries 4, 6, 9, 11, 13, the ratio of *cis*:*trans* isomers is *ca.* 1:1; (ii) *cis*-rich mixtures are obtained at low conversions to the cyclohexane, *e.g.* entries 1, 2 and 5; (iii) *trans*-rich mixtures are obtained in cases where charge significantly in excess of the required 2 F mol^{-1} is passed, *e.g.* entries 3 and 7 or, as in 14, when excess charge is combined with a higher temperature. At equilibrium *ca.* 87% of the *trans* isomer would be expected—this is not approached in any of the experiments.

The results are best interpreted in terms of there being little or no stereoselectivity. In those cases where a preponderance of *cis* isomer is found the most likely reason is that preferential hydrolysis of the *trans* isomer has taken place (see above). An excess of the *trans* isomer is associated with extended electrolysis during which it is also probable that epimerisation of the product takes place, promoted by electrogenerated base (compare entries 6 and 7).

A consistent explanation is summarised in Scheme 1, which indicates the likely stereochemical consequences of protonation at the three possible sites (O, C-1 and C-2) following initial formation of the radical anion **10**. In aprotic conditions the radical anion is undoubtedly formed, on the basis of the coulometric experiments. Each of the routes (*a*), (*b*) and (*c*) given in the scheme correspond to an overall ECE mechanism consistent with the requirement for 2 F mol^{-1} reduction. Radical anions such as **10** are relatively long-lived and diffuse into bulk solution, where protonation and further reduction take place. Because in such cases the reducing agent is another molecule of **10** the mechanism is probably best described by the terms DISP or ECE_h where E denotes electron transfer, C a chemical step and DISP a disproportionation. The particular mechanistic description chosen does not affect the following stereochemical arguments.

We propose that the stereochemical results are compelling evidence for reaction predominantly *via* route (*a*). According to this it is easy to understand the lack of discrimination; protonation at C-1 is irreversible and determines the *cis*:*trans* ratio prior to second electron transfer and further protonation. The final *cis*:*trans* ratio is that of the intermediate **11**. The reason for the lack of discrimination is that the radical anion **10** is planar and has only one hydrogen at C-2. There is therefore little hindrance to protonation at C-1 from either face, especially as rapid protonation will have a reactant-like transition state with a relatively long C–H bond.

Scheme 1 also shows that reaction by routes (*b*) and (*c*) would lead to *trans*-rich mixtures, probably at the equilibrium value. For (*b*) protonation of **10** at C-2, with rapid second electron transfer, would lead to the carbanion intermediate **12**, probably



Scheme 1 Pathways for the cathodic hydrogenation of **3**

predominantly in the enolate form. This would be protonated rapidly to give the enolic form of the product **4** and because this would be in equilibrium with the ester form (albeit at insignificant concentration) would give a highly *trans*-rich product. For anions protonation at oxygen is much faster than at carbon, even in non-aqueous solvents. However, should rapid protonation of the slowly-inverting carbanions be significant then, according to the Curtin–Hammett Principle, the ratio of isomeric products **4** will reflect the position of the conformational equilibrium of **12**. This will also greatly favour formation of the *trans* isomer.

In route (*c*) we explore the consequences of initial protonation of **10** at the carbonyl oxygen. This would eventually lead to the enolic form of the product **4** which for the reasons given above would give a highly *trans*-rich product.

Experimental

Materials.—Methyl 4-ethylcyclohexanecarboxylate (**5**) samples were supplied by BDH Ltd. (now Merck). Cyclohexane (BDH, Spectrosol) was dried over $CaCl_2$ before use. *N,N*-Dimethylformamide (BDH, Analar) was stored under nitrogen in the dark and used directly. Tetrahydrofuran was refluxed over sodium and benzophenone under nitrogen, distilled and used immediately. Methanol was refluxed over magnesium and distilled.[8] Quinol (1,4-dihydroquinone) and *p*-toluenesulfonic acid (*p*TSA) were dried over silica gel at 100 °C (1 mmHg) and 60 °C (3 mmHg) respectively, for 16 and 20 h, respectively. Methyl 4-*tert*-butylcyclohex-1-enecarboxylate (**3**) was prepared by esterification of a sample of the corresponding acid from earlier work in this laboratory; the sample was purified by column chromatography and its identity confirmed by ^1H NMR spectroscopy and high resolution mass spectrometry. Tetrabutylammonium tetrafluoroborate ($TBABF_4$, Fluka) was recrystallised from dichloromethane–anhydrous diethyl ether for voltammetric experiments, and dried over silica gel at 90–100 °C and 0.5–1 mmHg for 20–30 h. $TBABF_4$ used in preparative experiments was dried only.

Free Radical-induced Epimerisation.—The ester (4 mmol), cyclohexane (300 cm^3) and mercury(II) bromide (9 mmol) were placed in a photochemical reactor fitted into a medium pressure mercury lamp (Applied Photophysics Ltd). Flushing with nitrogen was carried out prior to starting the reaction and this flow continued during irradiation. Samples were removed at intervals and analysed by GLC (GLC column 5% D.E.G.S.-Chromosorb 80/100, oven temperature 75 °C, nitrogen flow rate 11 cm^3 min^{-1}). The glass jacket surrounding the lamp was cleaned with acetone before continuing the reaction.

Voltammetry and Coulometry.—Cyclic voltammetric experiments were run in an undivided cell using a Hg bead working electrode. A combined preparative/voltammetric cell was used to conduct the coulometric experiments. For coulometry (see Fig. 2) the reductions were carried out in DMF solution, substrate concentration 0.011 mol dm^{-3}, electrolyte Bu_4NI (0.1 mol dm^{-3}), controlled potential (−2.2 V *vs.* Ag/AgI). A five-fold molar excess of quinol was added for the run with proton donor.

Preparative Scale Reductions.—Conventional glass cells were used, equipped with water jackets for cooling, with the anode and cathode compartments separated by medium porosity sintered glass or, better, by Celgard 2500 microporous polypropylene film. The reactions were kept under an inert atmosphere by the slow bubbling of dry nitrogen through the electrolyte. The catholyte volume was typically 30 cm^3 containing 0.13–0.19 g of starting material and usually decalin as an internal GLC standard. $TBABF_4$ (0.5 mol dm^{-3}) was used as supporting electrolyte in all experiments, together with a variety of solvents and proton donors (see Table 3 for details). The catholyte was magnetically stirred.

Electrolyses were conducted at constant current density (4–10 mA cm^{-2}) and electrode potentials (*vs.* pseudo Ag wire) monitored during experiments. Samples were taken at intervals and analysed, usually in triplicate, within a short time by GLC.

Analysis.—The GLC procedure allowed good separation of the starting material, internal standard and each of the methyl 4-*tert*-butylcyclohexanecarboxylate epimers. Conditions were: capillary column 25 m × 0.32 mm (ID) fused silica open tubular with bonded polydiphenyldimethylsiloxane; oven temperature 45 °C (7 min), ramp 20 °C min^{-1}, final oven temperature 80 °C (40 min); helium pressure 420 kPa.

The response factor for the starting material relative to decalin was calculated for each experiment, from the catholyte solution prior to electrolysis, and values are given in Table 4 GLC analysis of solutions was in triplicate and response factors calculated from the areas of the chromatograph peaks, using the decalin isomer of longer retention time on all occasions. As can

Table 4 GLC response factors calculated for methyl 4-*tert*-butylcyclohex-1-ene carboxylate (**4**) relative to decalin, for a variety of catholyte solutions

Experiment number (*cf.* Table 3)	Electrolyte composition	Mean response factor (± range)[a]
1, 2	$TBABF_4/H_2O/THF$	1.87 (±0.17)
3	$TBABF_4$/MeOH/THF	1.71 (±0.06)
4, 5	$TBABF_4$/MeOH/THF	1.65 (±0.03)
6, 7	$TBABF_4$/MeOH/DMF	2.21 (±0.12)
8–10	$TBABF_4$/MeOH/pTSA/DMF	1.79 (±0.05)
11, 12	$TBABF_4$/1,4-dihydroquinone/DMF	2.00 (±0.06)
13,14	$TBABF_4$/1,4-dihydroquinone/DMF	1.98 (±0.06)
Standard	Na dried Et_2O	1.43 (±0.16)

[a] The consequences of these errors in response factors, combined with errors in determination of product peak areas, was an estimated error of ±(8–12%) of the value of the yield determined (Table 3).

be seen the response factors vary considerably depending on the electrolyte composition. The assumption was made that the same response factor applied to both starting material and product, and applied to both product isomers. This was supported by the observation that the response factors for methyl 4-*tert*-butylcyclohex-1-enecarboxylate (**3**) and methyl 4-*tert*-butylcyclohexanecarboxylate (**4**, *cis*/*trans* mixture) relative to decalin, and calculated from standard solutions in sodium dried diethyl ether, were 1.43 (±0.16) and 1.58 (±0.18), respectively. The response factors in Table 4 were used to calculate the recovery of starting material and the yields of cyclohexyl esters during electrolyses.

The stereoisomeric composition of the mixture was also checked in one case by 250 MHz ^1H NMR spectroscopy and agreed well with the GLC method. Assignment of stereochemistry was by ^1H NMR spectroscopic analysis.

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