Through-bond and Through-space Models for Interpreting Chemical Reactivity in Organic Reactions

Keith Bowden
Department of Chemistry and Biological Chemistry, University of Essex, Wivenhoe Park, Colchester, Essex CO4 3SQ, UK

Edward J. Grubbs
Department of Chemistry, San Diego State University, San Diego, California 92182, USA

1 Introduction

Polar substituent effects have been the subject of many investigations It has been generally agreed that the major influences can be considered to be localised effects, *i e* the electrostatic field and/or inductive effects, and the delocalised effect, *i e* the resonance effect[1] The relative importance of the two mechanisms described as the electrostatic field and inductive effects has been disputed[2] Both represent approximations, but can be clearly distinguished in designed models The inductive effect relates to through bond transmission by successive polarisation of the bonds between a dipolar or charged substituent and the reaction site The effect is attenuated by each bond in a ratio described as the transmission coefficient The summation of this effect over all possible paths can be made using either a simple relation or a more complex topological approach[3] The electrostatic field approach attempts to calculate the Coulombic interaction within the molecule The more sophisticated approach requires a knowledge of the distance between the reaction site and the monopole or dipole, the dipole moment the angles between the vector relating to the dipole and the distance described above, and the effective relative permittivity[4]

Westheimer in a retrospective[5] has stated that the theory developed by Kirkwood and himself[4] 'has stood the test of time for more than half a century ' Some excellent organic texts invidious to identify, refer almost exclusively to inductive transmission of polar substitutent effects, rather than electrostatic forces Others refer to an inductive transmission acting through space, which is, by definition, not possible

Kirkwood and Westheimer[4] derived equations (1) and (2) to estimate the Gibbs free energy required for the removal of an acid proton in the presence of a monopolar or dipolar substituent, respectively In these equations, r, μ, θ and ϵ_e are the distances between the ionisable proton and the monopole or dipole, the dipole moment, the angle between the vectors relating to the dipole and distance r, and the effective relative permittivity, respectively The effective relative permittivity, ϵ_e, is a function of the geometry and relative permittivity of the molecular cavity, ϵ_i, and the solvent medium, ϵ (ϵ_0 being the relative permittivity of vacuum)[3] On the other hand the inductive effect involves propagation by successive polarisation of the bonds by a dipolar or charged substituent between the substituent and the reaction site and will diminish with chain length A quantitative treatment was suggested by Branch and Calvin[6] and developed further by McGowan[7] A simple relation is that shown in equation (3) below, where ϕ and n are the transmission coefficient for inductive effects and the number of intervening bonds, respectively A more sophisticated relation has been suggested by Exner and Fiedler,[3] in which the substituent effect on the n th atom of a straight chain molecule is expressed by the value ϕ^n The value n for any non terminal atom is related to the values of those of the neighbouring atoms by being the arithmetic mean This treatment can be applied to any atom in a branched or cyclic system summing over all neighbouring atoms as in equation (4)

$$\log (K/K_H) = Z_1 Z_2 e^2/2\;3\, RTr\,(4\pi\epsilon_0\,\epsilon_e) \qquad (1)$$

$$\log (K/K_H) = Z_1 e\mu\cos\theta/2\;3\, RTr^2\,(4\pi\epsilon_0\epsilon_e) \qquad (2)$$

$$\log (K/K_0) \propto \Sigma\phi^n \qquad (3)$$

$$n = \frac{1}{s}\sum n \qquad (4)$$

These are only simplified relations and must be applied to real and complex molecular systems Thus, there is no implicit role for solvent dependence in the inductive effect treatments described above Furthermore, this treatment cannot take account of the angular dependence of substituent effects However, the calculation of the effective relative permittivities for the electrostatic field treatment presents problems Molecular cavity shapes, that are required

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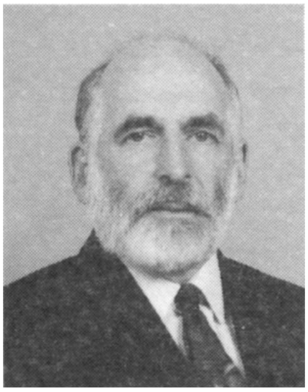
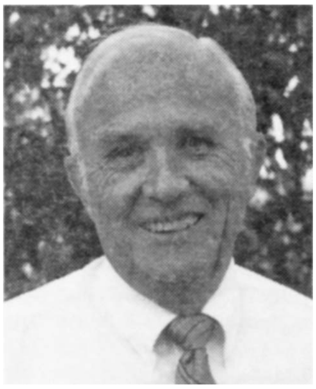


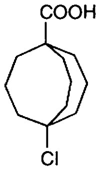
Keith Bowden was born in London England in 1936 he received his BSc and PhD (N B Chapman and J Shorter) from the University of Hull in 1959 and 1962 followed by his DSc in 1973 Following a postdoctoral fellowship (Ross Stewart) at the University of British Columbia he joined the faculty of the University of Essex where he is now professor of chemistry His research interests in physical organic chemistry include intramolecular catalysis and neighbouring group participation the transmission of polar effects strongly basic systems weak carbon acids and ring–chain tautomerism Another area of research is medicinal chemistry structure–activity relations and the mode of action of biologically active compounds



Edward Grubbs was born in Los Angeles California in 1934 He received his BA at Occidental College in 1956 He earned the PhD at MIT in 1959 working under the direction of Herbert House He worked with David Curtin (University of Illinois) as a postdoctoral associate from 1960 to 1961 He joined the faculty at San Diego State University in September 1961 and is currently professor of chemistry His research interests have included carbocation rearrangement thermal decompositions and rearrangement via *radical intermediates geometric isomerizations of imine derivatives models of transmission of dipolar substituent effects electrostatic effects in elimination reactions and intramolecular based induced eliminations* to be assumed, are often both unreal and unrealistic. Further, 'macroscopic,' rather than 'microscopic' or molecular, values for relative permittivities are used, these being the only available values.

2 Examination of the Theories using Model Systems

There are three relatively simple model systems that test the reality of the inductive and/or electrostatic field effect theories and require relatively rigid molecules with known and fixed stereochemistry to enable calculations to be performed. The first type of model systems has employed studies that contrast between the number of links available for an inductive transmission and the distance r and ϵ_e for an electrostatic field effect transmission. An ideal system would be one in which it was possible to hold one of these constant while changing the other. The second type of model systems has employed studies of the dependence of the transmission on solvent effects. For an electrostatic field effect model the dependence on the relative permittivity of the solvent can be predicted both in terms of its type and relative magnitude. The third type of model systems has employed studies of the angular dependence of substituent effects upon the angular orientations of dipoles.[8] The extreme of this model would be that originally suggested by Roberts and Carboni.[9] Molecules could be designed in which 'normal' acid-strengthening and electron-withdrawing substituents could generate a dipole which would oppose the ionisation *if* an electrostatic field effect were operating. They suggested the design of a compound to reverse a dipolar substituent effect and suggested the molecules **1** and **2** as examples. The inductive effect would be expected to be identical in **1** and **2**, whereas the electrostatic field effect would be expected to be the reverse in **2** of that in **1**. Thus, such model systems could test the prediction from the electrostatic field theory that a dipolar substituent effect can be modified by its geometrical orientation to be either 'normal,' diminished, absent or even 'reversed.'



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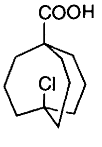
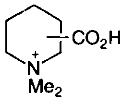


2

Grob *et al.*[10] have made a study of the effect of positive nitrogen polar substituents on the ionisation of aliphatic carboxylic acids, as in **3**, **4** and **5**.

$Me_3\overset{+}{N}(CH_2)_nCO_2H$

3



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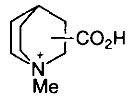

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The ΔpK_a values of the systems, corrected for steric effects estimated from uncharged model systems, are shown in Table 1. As the links are increased from one to two to three, a very modest increase in the ΔpK_a value is observed. This is quite impossible to relate to an inductive effect model, whereas an electrostatic field effect accounts for the results realistically.

The reaction constants ρ_i have been obtained[11] for the ionisation of substituted acetic **6**, *trans*-4-substituted cyclohexane-1-carboxylic **7**, 4-substituted bicyclo[2.2.2]octane-1-carboxylic **8**, and 4-substituted bicyclo[2.2.1]heptane-1-carboxylic acids **9**. The ρ_i values for the substituted acetic acids are insensitive to the medium,[12] unlike the behaviour of the 4-substituted bicyclo[2.2.2]octane-1-carboxylic and *meta-/para*-substituted benzoic acids, as would be expected from the electrostatic field theory. The model calculations for the transmission factor, ρ_i/ρ_i^0 have been made for **7**, **8** and **9**. The results for the inductive effect, using $\phi = 0.36$, and for the electrostatic field effect, using the chloro substituted acids, are shown in Table 2. The inductive models do not show general agreement between the experimental and calculated values of ρ_i/ρ_i^0, whereas the Kirkwood–Westheimer electrostatic field effect calculations result in good agreement.

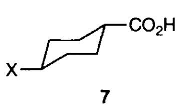
Table 1 ΔpK_a values for the systems **3**, **4** and **5** in 50% aqueous ethanol at 25 °C[10]

System	$\Delta pK_a{}^a$
3, $n = 1$	3.44
$n = 2$	1.96
$n = 3$	1.17
4, 2	3.75
3	2.08
4	1.57
5, 2	3.89
3	2.26
4	2.03

Values corrected for steric effects.

XCH_2CO_2H

6



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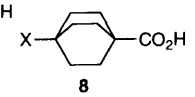

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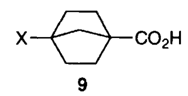

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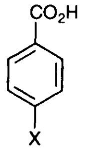
Table 2 Transmission factors, ρ_i/ρ_i^0, for the systems **7**, **8** and **9**[11]

	Exptl		Calcd		
				Electrostatic field[8]	
System	Water	50% aq. ethanol	Inductive[3] [eqn (3)]	Water	50% aq. ethanol
7	0.18_5	0.24_5	$0.09_5(0.21_5)^a$	0.16_5	0.28
8	0.21_5	0.34_5	$0.14(0.36)^a$	0.19	0.32
9	0.25_5	$(0.32_5)^b$	$0.22_5(0.41_5)^a$	0.24	$(0.40)^b$

Inductive [eqn (4)]. [b] 50% aq. methanol.

Hammett σ_P values, derived from the ionisation of *para*-substituted benzoic acids **10**, can be used successfully in the correlation of *trans*- and *cis*-3-substituted acrylic **11** and **12**, and *ortho*-substituted benzoic acids **13**.[12] For the latter two systems, **12** and **13**, compounds having 'bulky' *ortho* substituents and the parent unsubstituted compounds must be excluded from the correlation.



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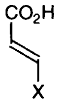

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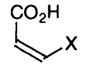

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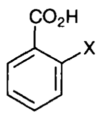

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Table 3 Hammett reaction constants, ρ, for the ionisation of the systems **11**, **12** and **13** in various solvents at 25 °C[12]

System	Water	50% aq. ethanol	80% aq. MCS[a]
10	1.00	1.47	1.66
13	2.43	2.21	2.40
12	2.25	—	2.24
11	2.45	—	3.62

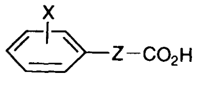
MCS = 2-methoxyethanol.

As shown in Table 3, the ρ values obtained for the *ortho*-substituted benzoic and *cis*-3-substituted acrylic acids are almost independent of the medium and comparable to each other, whereas those for the *para*-substituted benzoic and *trans*-3-substituted acrylic acids are strongly dependent on the nature of the medium. This is the result expected from an electrostatic field effect theory. For the systems **13** and **12** the solvent transmitted effect is comparable from both 'ends' of the dipole, unlike the situation in systems **10** and **11** in which the distant 'end' of the dipole is less effective in transmitting the effect *via* the high relative permittivity medium

Thus, the transmission in water is *ca* 2 4 times as effective from the *ortho*- as from the *para*-position in benzoic acids, as shown in Table 3 In Table 4 are shown the ρ values for a series of *meta-/para-* and of *ortho*-substituted systems in which the phenyl and carboxylic acid group are separated by an intervening link **14**, *i e* $[\mathrm{CH_2}]_2$, $\mathrm{OCH_2}$, *trans*-CH=CH [13] If an inductive effect is paramount, the effectiveness of *ortho*- relative to *para*-substituent effects would be expected to remain at *ca* 2,4, whereas, for an electrostatic field effect, the ratio would be expected to tend to unity as 'distance' between substituent and reaction site increases The results are clearly in accord with the latter

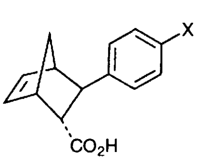
Table 4 Hammett reaction constants, ρ, for the ionisation of systems **14** in water at 25 °C[13]

Z	ρ *meta/para*	ρ *ortho*
None	1 00	2 43
$[\mathrm{CH_2}]_2$	0 24	0 26
$\mathrm{OCH_2}$	0 34	0 48
trans CH=CH	0 42	0 56

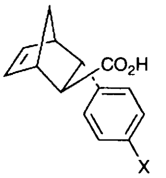


14

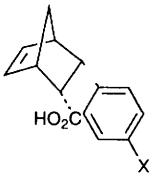
A study has been made by Beugelmans-Verrier *et al* [14] of the ionisation of a series of 3-arylnorbornene-2-carboxylic acids, **15**, **16** and **17** These results reveal the effects of *para*-substituents in the phenyl groups on the ionisation of the *endo*, *trans*-**15**, *exo*, *trans*-**16**, and *endo*, *cis*-**17**, carboxylic acids The rigid framework allows the effects to be studied with a precise knowledge of the Kirkwood–Westheimer *r* and θ values and permits a useful comparison with similarly substituted 3-phenylpropionic acids The Hammett ρ values for these systems are shown in Table 5 The relative transmission coefficients, ρ/ρ_0, have been calculated based on an inductive transmission [eqn (3)] and an electrostatic field transmission ([eqn (2) for *para*-chloro systems], as shown in Table 5 The results are in better agreement with the electrostatic field effect than with an inductive effect theory



15
endo, trans



16
exo, trans



17
endo, cis

Table 5 Hammett reaction constants, ρ, for the ionisation of 3-arylnorbornene-2-carboxylic acids in 50% (*v/v*) aqueous ethanol at 25 °C[14]

		ρ/ρ_0[12]		
			Calcd	
System	ρ	Exptl	Inductive	Field
endo, *trans* **15**	0 44	1 0	1 0	1 0
exo, *trans* **16**	0 49	1 1$_1$	1 0	1 0
endo, *cis* **17**	0 68	1 5$_5$	1 0	1 3$_5$
3-Phenylpropionic	0 37	0 8$_4$	0 9$_4$	0 8$_0$[a]

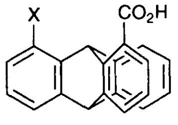
[a] *anti* Conformer

The first unequivocal example of a reversed dipolar substituent effect was considered by Golden and Stock[15] to be found in their study of a 9,10-bridged anthracene-1-carboxylic acid system Acevedo and Bowden[16] more recently studied a closely related series of 5-substituted triptycene-7-carboxylic acids and their esters **18** Their reactivities are illustrated in Table 6 The occurrence of reversed dipolar substituent effect is clear in the ionisation reaction, but the results for the esterification with diazodiphenylmethane (DDM) and the alkaline hydrolyses are more complex

Table 6 The reactivity of 5-substituted triptycene-7-carboxylic acids and their corresponding methyl esters **18**[16]

Substituent	Ionisation pK_a 80% aq MCS[a] at 25 °C	Esterification with DDM k_2/l mol^{-1} min^{-1}, MCS[a] at 30 °C	Alkaline hydrolysis of methyl esters k_2/l mol^{-1} min^{-1}, 70% aq dioxane at 30 4 °C
H	6 88	0 627	0 266
Cl	7 04	0 983	0 181
CN	7 03	0 188	0 387
OMe	7 16	0 583	0 204

[a] See Table 3



18

Grubbs and his coworkers[17] have studied 9,10-bridged 1- and 2-anthroic acids with chloro substituents in the bridges The ΔpK_a values of the isomeric dichloroethano- and chloroetheno-bridged 1- and 2-anthroic acids **19**, **20** and **21** are shown in Table 7 While the inductive effect does not predict any difference between **19b** and **19c** or **20b** or **20c**, the agreement between experimental and calculated ΔpK_a values, according to equation (2), is very good The angular orientations of the dipoles in **20c** and **21c** are responsible for the 'vanished' dipolar substituent effects

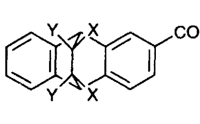
Table 7 ΔpK_a values for the 9,10-bridged 1- and 2-anthroic acids in 50% aq ethanol at 25 °C[17]

	ΔpK_a	
Compound	Exptl	Calc[a]
19b	0 58	
19c	0 18	
20b	0 47	0 36
20c	0 02	0 01
21b	0 22	0 29
21c	0 04	0 13

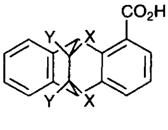
[a] Kirkwood–Westheimer theory with Tanford modification

[2 2]Paracyclophane is a very good template for the evaluation of the angular dependence of dipolar substituent effects With the reactive group in one ring and the substituent in the other, the four isomers represented by **22** can be studied [18] As shown in Table 8, the ΔpK_a values of isomeric pseudo substituted bromo-4-carboxy[2 2]paracyclophanes are given An inductive effect theory would predict a value of *ca* − 0 1 for ΔpK_a of all isomers The electrostatic field effect calculations shown in Table 8 are in good agreement with the experimental results which have been obtained for a wide range of pseudo substituted 4-carboxy[2 2]paracyclophanes more recently [19]

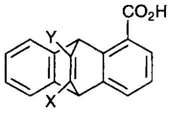
Roberts and Carboni[9] had suggested that an ideal model for the observation of reversed dipolar substituent effects would be the 1-(8-substituted 1-naphthyl)propynoic acids **23**, which were



19 a X = H, Y = H
b X = H, Y = Cl
c X = Cl, Y = H



20 a X = H, Y = H
b X = H, Y = Cl
c X = Cl, Y = H



21 a X = H, Y H
b X = Cl, Y = H
c X = H, Y – Cl

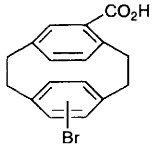


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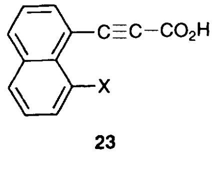
Table 8 The ΔpK_a values of the bromo-4-carboxy[2 2]paracyclophanes **22**, in 80% aqueous MCS[a] at 25 °C [18]

Substituent	ΔpK_a Expt	 Calcd [b]
pseudo *gem*	0 40	0 73
pseudo *ortho*	0 16	0 06
pseudo *meta*	− 0 31	− 0 33
pseudo *para*	− 0 35	− 0 31

[a] See Table 3 [b] Kirkwood–Westheimer spherical point dipole theory

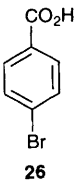
subsequently prepared and studied by Bowden and Hojatti [20] The ΔpK_a values for the 8-bromo or chloro acid **23** of *ca* 0 4 pK_a unit in 80% aqueous 2-methoxyethanol can be compared with a value of *ca* − 0 5 pK_a unit for the 3-halo substituted propynoic acids **24** in water [21] The reversal of the dipolar substituent effect is almost complete The results agree with the electrostatic field effect, whereas an inductive effect would be estimated to give an effect of *ca* − 0 2 pK_a unit



23

$X-C\equiv C-CO_2H$

24



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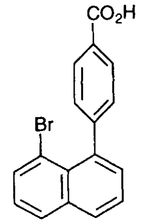
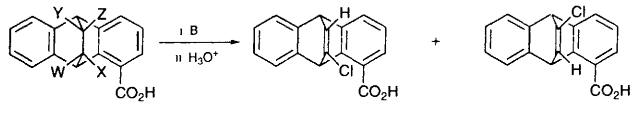


25

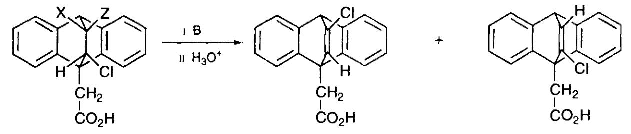
A 'simple' system is the 8-substituted 1-phenylnaphthalene system in which the 1-phenylnaphthalene will be 'locked' in a conformation with the two aryl groups almost orthogonal The 4-(8-bromo-1-naphthyl)benzoic acid **25** can be considered to be a 'reversed' model of 4-bromobenzoic acid[22] **26** The ΔpK_a values in 80% aqueous MCS for **25** and **26** are 0 49 and − 0 53 pK_a unit, respectively This is an almost complete reversal of the dipolar substituent effect and is in full accord with the electrostatic field effect

3 Other Reactive Consequences of Electrostatic Field Effects

Acidity measurements and other reactive properties of carboxylic acids and their derivatives have traditionally served as the principal probes of the transmission of substituent effects However there is a growing array of reaction phenomena which is revealing the importance of through-space, charge–charge and charge–dipole effects in a variety of chemical systems Thus, Grubbs and coworkers[23] have studied the regioselectivities in the base-induced eliminations of HCl from the four isomeric acids **27a—d** The selectivities were quantitatively accounted for in terms of differences in charge–charge repulsions dominated by interactions between the carboxylate anion and the partially charged alkoxide ion in the competing transition states Similarly the high degree of regioselectivity in the *tert*-butoxide-induced dehydrochlorinations of isomers **28a** and **28b** (**29**/**30** from **28a** = 98/2, **29**/**30** from **28b** = 95/5) could be attributed to related charge–charge repulsive energy differences in competing transition states And for the two homologues of **28a** and **28b** in which the carboxylate is attached directly to the bridgehead carbon (CH_2 removed) the based-induced eliminations lead exclusively to the formation of the homologue of **29** as a result of minimizations of charge–charge repulsive interactions



27a X = Z = Cl W = Y = H
b X = Z = H W = Y = Cl
c X = Y = H W = Z = Cl
d X = Y = Cl W = Z = H



28a X = H Z = Cl
b X = Cl Z = H

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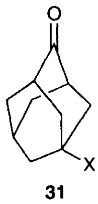
30

Stereoselectivities of electrophilic additions to substituted 7-isopropylidenebenzonorbornenes have been studied by Paquette *et al* [24] The so-called 'weak' electrophiles, such as *meta*-chloroperbenzoic acid (*m*-CPBA) and *N*-bromosuccinimide (NBS), exhibit preferential *anti* (to the aromatic ring) attack They bear lone-pair electrons and have high electron densities on their 'surfaces ' The moderate (dichlorocarbene) to strong (CH_3CO^+ and HCO^+) electrophiles have modest or large positive charges at the attacking atom and approach preferentially from the *syn* direction Thus, for 7-isopropylidenebenzonorbornene (9-isopropylidenemethano-1,4-dihydronaphthalene), the reaction with *m*-CPBA or NBS leads to *anti syn* ratios of 83 17 and 81 19, respectively By contrast, $:CCl_2$ and CH_3CO^+ (from AcCl–$AlCl_3$) give *syn anti* product ratios of 65 35 and 100 0, respectively Although differing from the explanation originally offered, Houk and coworkers[21] argue convincingly that what they call 'negative' electrophiles (such as *m*-CPBA and NBS) give *anti* addition because of the electrostatic repulsion between the electrophile (*i e* the nonbonding electrons of the attacking atom) and the electron-rich aromatic ring in the *syn* transition structure This differs from the earlier[24] explanations since it emphasizes that *syn* addition is disfavoured, not that *anti* addition is stabilized by 'backside' involvement of the aromatic π electrons With a positive electrophile, *syn* attack is believed to be favoured by both torsional effects and electrophile–π-electron-region attractions

Additional experimental support for the primacy of electrostatic effects in the π-facial selectivity of nucleophilic substitutions in cyclohexanone derivatives comes from the recent work of Adcock and coworkers [25] Their investigations were of a series of 5-substituted adamantyl derivatives **31** and included ^{13}C (carbonyl carbon) chemical shifts, π-facial selectivities in $NaBH_4$ reductions and



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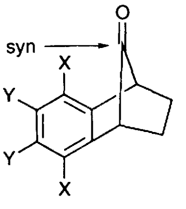
methyllithium additions, and correlations with polar field parameters They concluded that electrostatic field interactions exert a major effect in determining these π-facial competitive reactions

Similar electrostatic effects appear important in other related systems Okada and coworkers[26] reported that $LiAlH_4$ reductions of **32** in tetrahydrofuran (THF) yielded 62% *syn* addition of hydride when X and Y are H, but this increased to 92% and 100% when X and Y are Cl and F, respectively By contrast the *anti* addition is slightly favoured when X is methoxy The same general charge–dipole phenomena appear to account for the preferred direction of hydride additions to 2,2-diarylcyclopentanones[27] **33** and the substituted norbornanone[28] **34**



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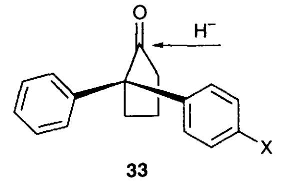

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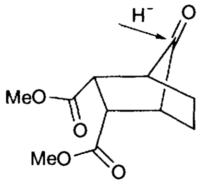
X	% *cis*
NO	79
Cl	63
Br	63
OCH_3	43
O^-	30
NH_2	36



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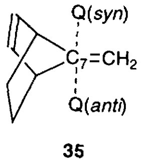
It should be noted with regard to stereofacial selectivities that there remains some controversy regarding the validity of various stereoelectronic theories employed in the analyses of these processes A detailed review of alternative theories has been presented[29] However, the results appear to be predominantly accommodated by an electrostatic field theory[25]

4 Computational Approaches

Ab initio calculations of transition structures are attracting growing interest in probing electrostatic effects in a variety of reactive systems Several examples will illustrate the general approach Houk *et al*[21] have investigated the electrostatic potentials of 7-methylenenorborene as well as energies for 7-methylenebenzonorbornene interacting with a point charge as a model for electrophilic additions For methylenenorbornene, the electrostatic potentials range from − 27 kcal mol ^{1} (1 cal = 4 184 J) over the π system to + 23 kcal mol ^{1} near the hydrogens (calculations at the 6-31G* level) The surface potentials indicate that charged species should attack preferentially from the *syn* (to cyclopentene double bond) direction due to electrostatic effects Negatively charged species will preferentially attack the *anti* face to minimize repulsive interactions Thus, the results of computations of energies (again at the 6-31G* level) for 7-methylenenorbornene possessing an added charge (representing an attacking electrophile or nucleophile) of 0 2 e placed 2 0 Å 'above or below' C 7 are shown with structure **35** This indicates that the cyclopentene double bond stabilizes a positively charged attacking species and destabilizes a negatively charged one Similar conclusions are drawn for attacking charged species interacting with 7-methylenebenzonorbornene

Charge	E_{el}/kcal mol ^{1}
$Q(syn)$ + 0 2	− 5 9
$Q(anti)$ + 0 2	− 2 7
$Q(syn)$ − 0 2	3 3
$Q(anti)$ − 0 2	− 0 3



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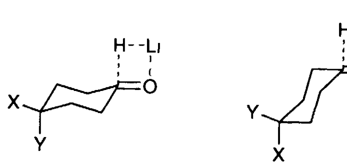
Houk and coworkers[30] have also explored transition structures for the axial and equatorial additions of lithium hydride to cyclohexanone with full optimization using the 3-21G basis set

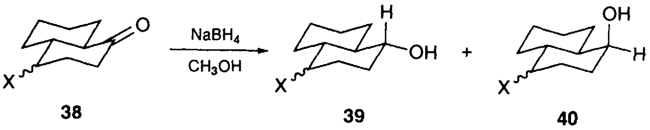


36 **37**

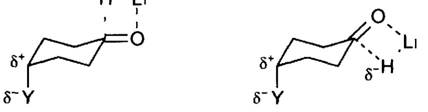
(calculations performed with Pople's GAUSSIAN suite programs) The calculated axial preference (structure **36**, X = Y = H) over equatorial hydride transfer (structure **37**), specifically 1 8 kcal mol ^{1} (when calculations are performed with the 6-31 G* basis set on the 3-21G geometries), is in qualitative agreement with experimental observations of an axial–equatorial hydride transfer ratio of about 90 10 for the lithium aluminium hydride reduction of 4-*tert*-butylcyclohexanone When a substituent is situated equatorial at the 4-position, the calculations predicted very small variations in stereoselectivity When the substituent is axial (X = H), the calculations indicated a substantial additional stabilization for transition structure **36** in every case Thus, when Y = F, the ΔE value favouring **36** is 2 5 kcal mol ^{1}, when Y = Cl, the difference is 2 9 kcal mol ^{1}, (calculated ΔE values for Y = OH or NH_2 are conformationally dependent, with respect to rotation about the C—O and C—N bonds, but similar in magnitude when the lone-pair electrons are in the conformationally more stable orientation 'inside' a vertical projection of the ring) An experimental system for which these calculations serve as a model is the borohydride reduction of 4-substituted *trans*-decalones, the results of which are shown in Table 9

Table 9 Stereoselectivities in the reduction of 4-substituted *trans*-decalones with excess sodium borohydride in methanol at 25 °C[30]

Comp	X	%**39**	%**40**
38a	H	60	40
38b	*eq* OH	61	39
38c	*eq* OAc	71	29
38d	*eq* Br	66	34
38e	*eq* Cl	71	29
38f	*ax* OH	85	15
38g	*ax* OAc	83	17
38h	*ax* Cl	88	12
38i	*ax* F	87	13

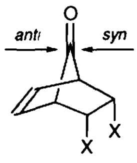


Thus, as with the computational cyclohexanone models, axial electron-withdrawing substituents at C-4 in decalone cause larger increases in the axial borohydride addition than when in equatorial positions Houk and coworkers[30] argue that electrostatic effects are a principal cause of these observations As illustrated in **41** and **42**, equatorial attack by the hydride is destabilized by electrostatic repulsive interaction with the axial substituent



41 **42**

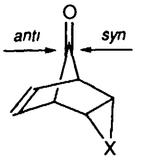
Williams and Paddon-Row[31] have computed energy differences between *anti* and *syn* directions of attack by LiH on the norbornenones **43** The results show a preferred *syn* attack for all substituents The electrostatic basis for these calculated selectivities (repulsive interactions between the hydride component of LiH and the C=C double bond) was supported by conducting



X = SiH$_3$, Me, H, CH$_2$OH, CN

43

point-charge calculations in which the LiH moiety was in each case replaced by a point negative charge located at the position vacated by the hydride (and assigned a charge equal to the Mulliken charge of the vacated hydride) The *anti–syn* energy differences [HF/6-31G(d) computations] paralleled those for the real transition structures Related computational studies[28 32] have been reported for π-facial selectivities for hydride (LiH) attack on **43a** where X=CO$_2$CH$_3$ or the corresponding dialdehyde **43b**, and on **44** including the systems X=O and X=CH$_2$ Computational studies (based upon PM3-derived molecular electrostatic potentials) reveal significant electrostatic field contributions to stereofacial selectivities in the reaction of dichlorocarbene with **45**,[33] stereochemical selectivities in nucleophilic additions to vinylic sulfoxides,[34] electrophilic reactions with allylic alochols and ethers,[35] and to the regiochemistry and stereochemistry of electrophilic additions to other variously substituted allylic double bonds [36]



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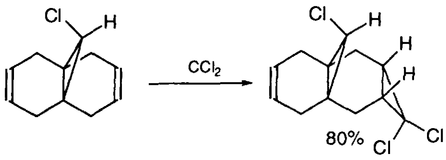
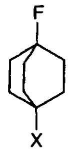


45 **46**

5 NMR Studies

The results from ^{19}F NMR studies[37] are more complex Thus, the ^{19}F NMR substituent chemical shifts of 4-substituted bicyclo[2 2 2]octan-1 yl fluoride **47** were considered to be dependent on both the electrostatic field and electronegativity effects The latter effect was considered to be identical to the σ-inductive effect and not significant after the first atom of attachment *Then* the electronegativity contribution was ascribed to a 'through-three-bond' electron delocalization mechanism This was supported by a study of the 4-substituted bicyclo[2 2 1]heptan-1-yl fluorides **48**, which revealed an electronegativity contribution of the opposite sign to that observed for **47** What is very clear is that ^{19}F NMR substituent effects involve both through-bond and through-space effects However, the effects are not always the same as those associated with studies of reactivity



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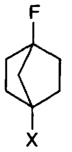

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6 Conclusions

In this account, we have given an overview of a variety of chemical reactivity phenomena The results appear to be consistently explained in terms of an electrostatic field effect, but not by the classical inductive effect The Kirkwood–Westheimer theory, even with the modifications available, is not entirely satisfactory A comparative study[38] of the gas-phase acidities of substituted quinuclidinium and bicyclo[2 2 2]octanylammonium ions indicated a field effect transmission, but the fall-off observed between the two series is considerably less than that expected from a simple electrostatic theory However, it appears likely that future generations of theoretical treatments will allow calculations for molecules even more complex than those discussed here

The following quotation seems highly relevant to the present position of the classical inductive effect regarding reactivity studies

'Is there any other point to which you would wish to draw my attention?'

'To the curious incident of the dog in the night-time '

'The dog did nothing in the night-time '

'That was the curious incident,' remarked Sherlock Holmes [39]

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