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LONG RANGE ELECTRICAL FIELD EFFECTS IN SOLVOLYSIS AND ^{13}C-NMR SHIELDING OF ANDROSTANES WITH HALOGEN, HYDROXY AND OXO SUBSTITUENTS[1]

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ABSTRACT

The solvolysis of 21 different 3- or 17-androstanyl tosylates or chlorides with halogen, hydroxy or oxo substituents in 17- or 3-position shows rate constant variations in hexafluoro isopropanol of up to 6·3 with regular differences for epimeric substituents. Similar variations are seen over a distance of ~10 Å in ^{13}C-NMR shifts at C-17 of androstan-17-ones with varied halogen substituents in C-3, whereas the shielding observed at other distant carbon atoms excludes significant through bond effects. It is shown how, on the basis of suitable Coulomb-type equations and of force field minimized geometries, both the stability variation of carbocationic transition states and the carbonyl group polarization are predictable by linear electric field effects, using the same parametrization.

The operation of polar substituent effects in aliphatic frameworks has intrigued chemists for a long time.[2] Reactivity differences in the solvolysis of a variety of aliphatic derivatives[3–14] have already provided much insight in the underlying interactions. Many problems, however, which will be exemplified below, still make it difficult to arrive at predictions beyond LFER-type of correlations between experimental observations. Long range substituent effects in steroids[10–14] are of importance not only for the corresponding reaction mechanisms but also as one possible contribution for the often drastic changes of pharmacological activity with substituent variation.[15,16] Steric long range effects even of small substituents such as fluorine were believed to intervene here with polar effects.[17] Polar interactions, however, were shown to dominate in most cases even for axial, more space demanding, orientations.[16,18]

One of the major problems pointed out by many earlier workers[2–14] is the separation of an inductive through bond from Coulomb-type through space effects. The often used description of the observed reactivities as a function of Taft-type σ-constants[19] basically does not distinguish the two transmission mechanisms, and does not take into account orientational differences between the substituents which can be substantial.[4a,5a]

These problems are approached in the present paper by a combination of substituent effect measurements on both solvolysis rates and ^{13}C-NMR shielding, which allows us also to use and to check simultaneously parametrizations and calculational procedures in the evaluation of linear electric field effects (LEF), or through space interactions, for both reactivity and NMR shielding predictions. The model is simplified, and possible through bond effects are minimized by using androstanes **1** with substituents either in the 3- or in the 17-position. The

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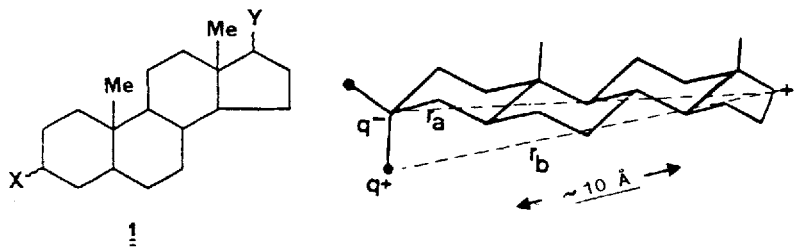

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Scheme 1

leaving group for the solvolysis, or the oxo group as a spectroscopically observable point of LEF action, were placed in the complementary position, that means as remote as possible. The intervening 8 single bonds between C-3 and C-17 will diminish any through bond interaction by $0{\cdot}6^8 \cong 0{\cdot}04$, if we assume commonly accepted attenuation factors[2,20] and on the average two pathways through the steroid skeleton.[5]

The steroids used in the present study contain halogens and oxo substituents in a conformationally well defined environment, which in contrast to hydroxy groups—which were nevertheless evaluated also—and to some less systematically varied substituents examined in the literature[14] offer several advantages: they occur only in one group conformation, they have better defined charge distributions, they don't interact with closer situated substituents,[13,14] and the halides are not as susceptible as other substituents[14] to solvent effects. Peterson and Chevli[14] have already demonstrated the significant increase of polar substituent effects on solvolysis rates with decreasing solvent nucleophilicity; in accordance with earlier observations[21] we have consistently used here the extremely weak nucleophile hexafluoroisopropanol (HFIP). In contrast to earlier investigations[2–14] we could also apply fully computerized techniques instead of manual operations with models etc. which have been shown to produce errors of up to ~500%, e.g. in related LEF calculations.[22]

CALCULATION PROCEDURES

The geometry of all structures were individually optimized by MM2[23] energy minimizations, which have been shown to lead to realistic and usually X-ray compatible structures for these steroids.[16,18,22b,24] In line with earlier findings[16,24] introduction of substituents X = Hal, OR, =O (oxo) in the 3 or 17 position does not generate any significant geometry variations around the remote 17- or 3-position, respectively. Thus, even the 'soft' torsional angles in these areas remain constant within $\sim \pm 0{\cdot}3°$ according to the force field minimization,[24a] a result supported by ^{1}H-[24a] and ^{13}C-[24b]NMR data.

The C—X dipoles for X = Hal, OH, =O, H were represented as point charges obtained largely from group dipole moments and the optimized C—X bond length;[25] the partial charges q were placed on the C and X nuclei and were the same[26] which have been successfully applied in other LEF calculations for NMR shielding.[22,24,27] The dielectric constant was set to 2·0 in accordance with earlier investigations on alkyl systems[14,28] and can be easily varied due to its linear dependence in the Coulomb equations used. Oxo groups at the influenced position were used to represent the optimized geometry not only for the observed carbonyl ^{13}C-shielding variations but also for the carbocation in the solvolysis transition state model. This seems to be justified in view of the generally correct strain energy representation in S_N1-type reactions of

normal secondary alkyl esters, which moreover indicate the limiting case of a fully developed position charge if HFIP is the solvent.[21b]

Following the Kirkwood–Westheimer[28a] or the Buckingham[29] approach of Coulomb-type interactions, the most simple description for the LEF of a point charge q on the free energy E of the ionic transition state with a charge q' is

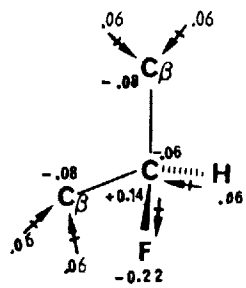
$$E = q\, q'\, r_i^{-1}\, \varepsilon^{-1} \tag{1}$$

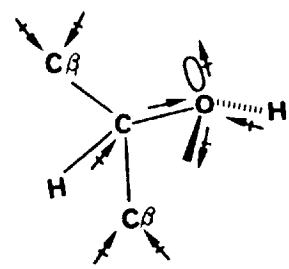
where r_i is the distance between q and q'.

The polarization of the NMR-spectroscopically observed C=O group with the polarizability P by a point charge q in the distance r_i with a field vector characterized by the angle Θ_i is

$$\sigma_{LEF} = P\, l^{-1}\, r_i^{-2} \cos(\Theta_i)\, q_i \tag{2}$$

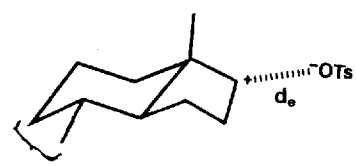
A program (COULOMB) was used for application of equation (1) and a separate one (SHIFT)[30] for application of equation (2), both accepting MM2-optimized co-ordinates and allowing for the summation of E and σ_{LEF}, respectively, for all desired positions in the steroid skeleton.





The Effect of Charge Delocalization Away from Cα on $\Delta G^*_{calc.}$:

	With:	0%	27%	36%	delocalized:
Result for:	X=3α-F	26	46	53	[cal/Mol]
	X=3α-OH	-290	-	-240	
	X=3β-OH	-230	-	-100	



The Effect of the Leaving OTs Anion on $\Delta G^*_{calc.}$:

for Distance d_e :	3Å	4Å	∞	
Resulting ΔG^* :	15.3	16	26	[cal/Mol]

Scheme 2

The influence of different parametrizations, charge localizations, etc. and resulting possible errors in the LEF calculations have been considered already with respect to NMR shielding.[22a,24,27] In view of the large distance r_i the Coulomb energy E is expected to show little dependence e.g. on the charge localization around the inducing dipole Cα—X. A redistribution of the positive charge to Cβ—Hβ, which should be prominent for X = F due to back donation[31] leads to E deviations which are smaller than errors introduced e.g. by the assumptions concerning ε (Scheme 2). This holds also for X = OH, for which, however, the ambiguities involved also with rotamer distribution and solvent interaction are prohibitive at the present time. The influence of the distance d_e separating the carbocation and the leaving group anion again is smaller than the other ambiguities involved (Scheme 2); the strongly anion-solvating HFIP warrants here the usual[14] neglect of the gegenion ($\hat{=}\ d_e = \infty$) in the calculations.

SOLVOLYSIS: KINETIC RESULTS

The introduction of strong dipoles such as X = oxo can decrease solvolysis rates in HFIP by almost an order of magnitude even when the reacting site in the steroid is as remote as possible (Table 1). The LEF calculation (equation (1)) predicts the corresponding ΔG^* increase quite correcly (Table 1), if we subtract the effect of the C ▷ H dipole which is replaced by the C ◁ X dipole. This correction was not considered by earlier workers but is of particular significance in view of the opposing C—H/C—X dipole directions.

Although it would be desirable to compare the LEF calculations also with ΔH^* and ΔS^* activation parameters our analysis must be restricted to ΔG^* comparison as it is virtually impossible to obtain sufficiently accurate $\Delta H^*/\Delta S^*$ values for the necessarily small rate differences. The correlation of experimental with calculated free activation energies ΔG^* is surprisingly good for all 5 observed oxo-derivatives and the parent tosylate with X = H, with a slope of nearly 1 (Figure 1). This indicates that the dipole moments used for X = oxo are not significantly changed by solvent interaction, and that through bond contributions are as small as predicted.

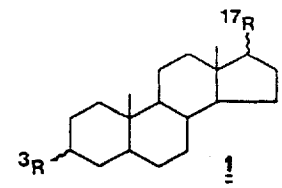
The effect of the halide dipoles are, as expected, much smaller but significant (Table 1, Figure 1). Whereas the axial 3-α-halide 17-β-tosylates correlate well with the calculated ΔG^* values, the corresponding 3β epimers do so to a much lesser degree. The reason for this could be sought for in (a) electron redistribution by back donation for eq—X = F[31] or in a specific solvation for the more polarizable eq—X = Br bond. The important result here is, that the epimers do show systematical differences over a distance of ~10 Å, and that these differences can be at least semi-quantitatively predicted by LEF calculations.

It should be noted that the correlation (Figure 1) holds independent of the leaving group orientation, which was α or β in selected cases, as well as of the leaving group itself, which was chloride instead of tosylate in 2 derivatives (Table 1). This again speaks for the presence of a solvent separated ion pair in the transition state, and for the corresponding neglect of the distant leaving group anion as assumed in the calculational model. Participation of neighbouring C—C bonds in the transition state is highly unlikely even for the 17β-tosylates[21b] and would only lead to a constant additional increment in the calculated LEF effect.

NMR-SPECTROSCOPIC RESULTS

The 8 androstan-17-ones with halogen substituents in the 3-position showed small, but regular shift variations at C-17 if necessary precautions are taken with respect to spectral dispersion

Table 1. Solvolysis in HFIP-kinetic results and calculated ΔG^* differences



^3R =,	^{17}R =	$k \times 10^{5a}$	$k_R/k_{H_{exp}}{}^b$	$\Delta G^*_{exp}{}^c$	$\Delta G^*_{el}{}^d$	$k_R/k_{H_{el}}{}^e$
α—OTs	H_2	311	1	—	—	—
"	=O	71	0·23	0·95	0·79	0·29
"	β—OH	255	0·72	0·21	−0·12	1·21
β—OTs	H_2	24	1	—	—	—
"	=O	5·7	0·24	0·92	0·79	0·29
"	β—OH	10·3	0·43	0·54	−0·12	1·21
H_2	α—Cl	645	1	—	—	—
=O	"	108	0·17	1·15	1·00	0·21
H_2	α—OTs	44600	1	—	—	—
=O	"	11240	0·25	0·88	1·00	0·21
β—OH	"	16316	0·37	0·63	0·23	0·70
H_2	β—OTs	3·80	1	—	—	—
=O	"	0·60	0·16	1·18	1·00	0·21
α—OH	"	2·80	0·74	0·20	−0·29	1·57
β—OH	"	1·71	0·45	0·51	0·23	0·70
α—F	"	2·92	0·77	0·18	0·03	0·96
β—F	"	1·82	0·47	0·48	0·70	0·33
α—Cl	"	2·38	0·63	0·30	0·12	0·83
β—Cl	"	1·14	0·37	0·61	0·72	0·32
α—Br	"	2·71	0·71	0·22	0·15	0·79
β—Br	"	2·20	0·58	0·35	0·71	0·33

[a]At 50·0°C; k in [sec^{-1}], ±1·5%;
[b]Substituent effect, ±5%;
[c]ΔG^* difference between substituted and unsubstituted compound, in [kcal/mol];
[d]Calculated based on equation (1), see text; in [kcal/mol];
[e]As obtained from calculations[d].

and medium effects. The C-17 shifts (Table 2) are at higher field for the 3-β epimers by a rather constant amount of a epimeric shift difference ESD ≅ 0·1 ppm. A similar difference is predicted by the LEF calculation (equation (2)); the calculated ESD values are larger by a significant, however constant, degree. This can be due to reaction field effects—related to the local dieletric constant—or to the chosen calculational procedure, in which the point of the electric field gradient action was placed at the center of the C=O bond. Nevertheless, sign and magnitude of the observed very long range effects are correctly predicted by the LEF calculation.

The other carbon NMR shifts (Table 3) agree closely with shielding values in related 3α/3β-X-substituted cholestanes.[24b] These have been analyzed in detail earlier[24b] and therefore will not be discussed here. The only important point in the context of the present paper is the result of constantly *shielding* effects of halogen substituents on all carbon atoms beyond the A-ring (with the exception of C-11 and C-19 in some derivatives). This, as well as

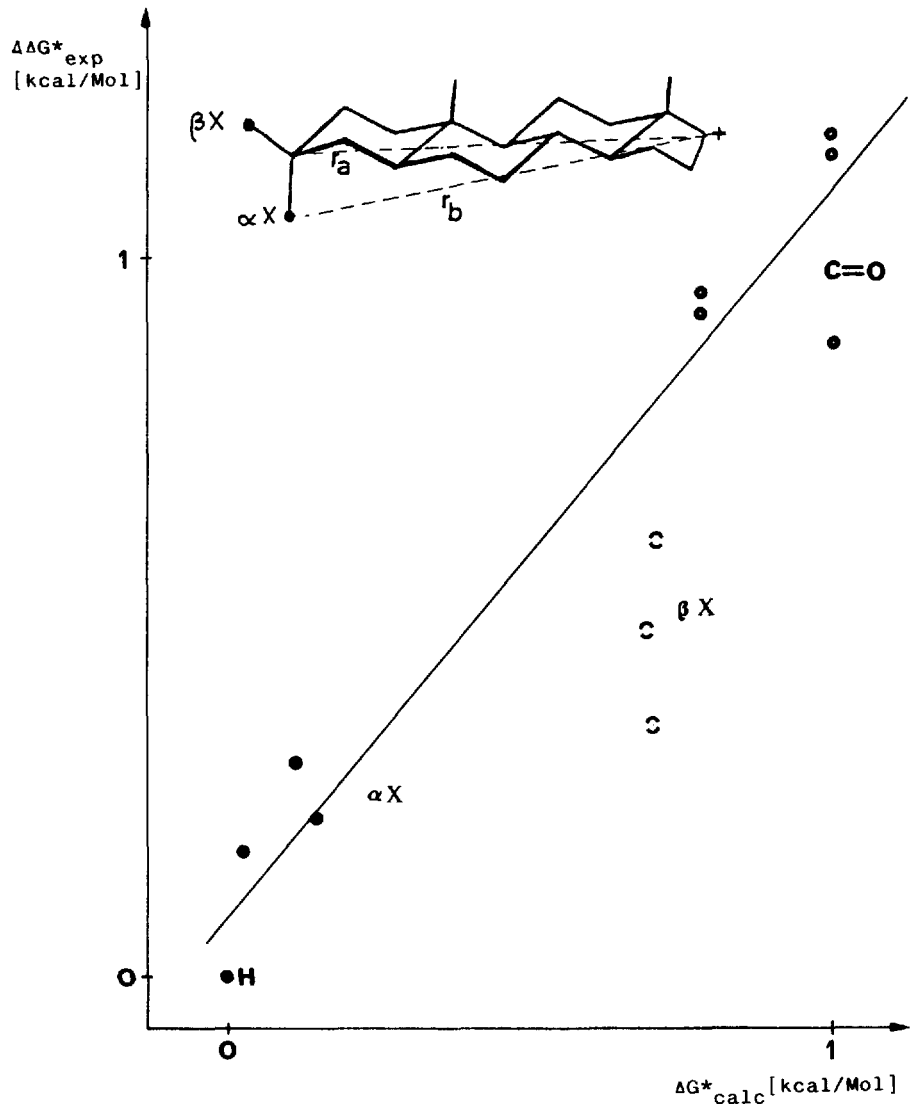


Figure 1. Solvolysis in HFIP—free activation energies ΔG^*: exp. vs. calc. values. For all systems the value for the parent unsubstituted derivative (X = H) is set $\Delta G^*=0$

the irregular shift variations along the carbon chain (Table 3) clearly speaks against any significant through bond effects which should lead to *de*shielding.

CONCLUSIONS

The results demonstrate, that C—Hal, C—OH or C=O dipoles can stereoselectively lead to sizable polarizations of carbonyl bonds and to stability variations of carbocations over a distance of 10 Å. The experimental data and the calculational agreement obtained clearly

Table 2. Comparison of epimeric shift differences (ESD[a]) observed for C-17–NMR shifts in 3α/β-X-substituted androstane-17-ones with calculated linear electric field (LEF[b]) differences

X	3α—X	3β—X	ESD	
	LEF[b]	LEF[b]	exp	calc.[b]
F	−0·07	−0·29	0·11	0·22
Cl	−0·12	−0·29	0·11	0·17
Br	−0·10	−0·28	0·11	0·18
I	−0·12	−0·25	0·08	0·13

[a]In ppm, complete exp. values see Table 3;
[b]Calculated as described in the text and converted to the ppm-scale with 400 [ppm/e].

Table 3. Substituent effects (SCS) on ^{13}C-NMR shifts in 3-X-substituted 5αH-androstan-17-ones

Atom	α—F	α—Cl	α—Br	α—I	β—F	β—Cl	β—Br	β—I
1	−6·35	−6·65	−5·94	−5·48	−2·28	−0·03	1·03	2·37
2	4·98	7·96	8·75	10·47	6·61	11·02	11·98	9·33
3	60·63	31·59	25·62	7·56	64·00	31·21	22·35	−1·57
4	5·20	7·78	8·43	9·91	6·50	10·88	11·82	14·12
5	−7·91	−8·10	−7·22	−5·36	−2·17	−0·26	0·90	2·43
6	−0·83	−1·19	−1·31	−1·47	−0·55	−0·74	−0·79	−0·96
7	−0·22	−0·32	−0·36	−0·40	−0·11	−0·18	−0·21	−0·26
8	−0·01	−0·02	−0·01	−0·01	−0·03	−0·05	−0·05	−0·06
9	−0·72	−0·89	−0·98	−1·04	−0·48	−0·52	−0·46	−0·32
10	−0·57	−0·18	−0·03	0·26	−0·74	−0·89	−0·88	−0·81
11	−0·02	−0·02	−0·01	0·01	0·50	0·33	0·26	0·11
12	−0·08	−0·10	−0·11	−0·12	−0·07	−0·10	−0·12	−0·15
13	−0·04	−0·03	−0·03	−0·04	−0·04	−0·05	−0·05	−0·05
14	−0·13	−0·14	−0·15	−0·16	−0·17	−0·18	−0·18	−0·18
15	−0·01	−0·01	−0·02	−0·02	0·02	−0·02	−0·02	−0·04
16	−0·05	−0·06	−0·06	−0·06	−0·05	−0·09	−0·12	−0·16
17	−0·13	−0·21	−0·20	−0·25	−0·24	−0·32	−0·31	−0·33
18	−0·01	0·00	0·00	0·00	−0·03	−0·04	−0·05	−0·05
19	−1·09	−0·45	0·03	1·12	0·01	0·02	0·04	0·06

[a]SCS = δ_{RX}–δ_{RH} in [ppm]; measurements with 0·06 M solutions in d_{12}-cyclohexane at 24 °C.

indicate through space electric field effects as responsible mechanisms. Such long range through space field effects can play an important rôle not only for organic reactions or for the binding of steroids in protein receptors but also for host–guest interactions or for substrate binding and activation in enzymes and other biological systems, for which such electrostatic effects are increasingly invoked.[32]

EXPERIMENTAL DETAILS

^{13}C-NMR spectra

These were recorded with a Bruker AM 400 spectrometer at 100·6 MHz with a digital resolution of ±0·01 ppm in 0·06 M d_{12}-cyclohexane solutions with 0·2% int. TMS at 24 °C. Earlier measurements at lower dispersion (at 20 MHz) and in more concentrated deuterochloroform solutions failed to give reproducible and regular long range substituent effects.

Kinetic measurements

These were carried out by conductometry and automatic data processing as described earlier.[21a] The rate constants k, usually obtained over 2–5 half lives were mostly accurate within ±2%. For some systems the temperature dependence was measured, which yielded the desired k (Table 1) as well as selected ΔH^* and ΔS^* values (Table 4).

Tosylates

The tosylates were prepared by reaction of the hydroxy steroids[24a] (e.g. ~0·3 mmol) with *p*-toluenesulfonylchloride (0·33 mmol) in 1 ml pyridine under ice-chilling and stirring at room temperature over night. After the usual work up with ice water, dilute hydrochloric acid, sodium bicarbonate and water, and recrystallization usually from methanol one obtained 50–90% product; for analytical data see Table 5.

Table 4. Activation parameters ΔH^{*a} and ΔS^{*b} from temperature dependence of rate constants k^c in HFIP

^{3}R	^{17}R	ΔH^*	ΔS^*	Temperature and Rate Constants						
H_2	α—OTs	14·1	−17	0·0	14·6	15·0	20·3	30·3		°C
				0·60	2·51	2·85	4·75	9·2		$10^2\,sec^{-1}$
=O	α—OTs	14·7	−17	15·5	21·7	25·4	30·9	34·6	40·2	°C
				0·63	1·19	1·62	2·76	3·53	4·95	$10^2\,sec^{-1}$
H_2	α—Cl	14·0	−26	10·0	20·0	30·0	40·0	50·0		°C
				0·26	0·62	1·43	3·05	6·45		$10^3\,sec^{-1}$
=O	α—Cl	15·0	−26	18·8	19·2	30·4	40·2	50·0		°C
				0·72	0·78	1·91	4·47	10·8		$10^4\,sec^{-1}$

[a] ΔH^0 in [kcal/mol], ±3%;
[b] ΔS^0 in [cal/mol], ±3 units (errors from Eyring plots).

Table 5. Analytical data for steroid tosylates

Starting Compound	mp [°C]	C found(calc.)	H found(calc.)	Proton NMR Data[a] 18—H_3	19—H_3	3—H(W/2)[b]	17—H(W/2)[b]
3αF-5α-Androstan-17βol	138–140	76·95 (77·55)	10·58 (10·54)	0·74	0·79	4·84 (8Hz)	3·65 (18Hz)
3βF- " " "	152–153	77·01 (77·55)	10·54 (10·54)	0·74	0·83	4·95 (22Hz)	3·65 (18Hz)
3αCl- " " "	150–151	72·93 (73·42)	9·97 (9·98)	0·74	0·80	4·52 (8Hz)	3·64 (18Hz)
3βCl- " " "	161–162	73·35 (73·42)	9·94 (9·98)	0·74	0·84	3·80 (22Hz)	3·64 (18Hz)
3αBr- " " "	133–135	63·81 (64·23)	8·74 (8·73)	0·74	0·80	4·74 (8Hz)	3·65 (18Hz)
3βBr- " " "	155–156	63·60 (64·23)	8·73 (8·73)	0·74	0·86	4·05 (22Hz)	3·64 (18Hz)

[a]Shifts in [ppm] from int. TMS;
[b]Half height width in [Hz].

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REFERENCES

1. Alicyclic Reaction Mechanisms, Part 12; Part. 11: H.-J. Schneider, U. Buchheit and G. Schmidt, *J. Chem. Res. (S)*, 92 (1987).
2. For a review see L. N. Ferguson, *Organic Molecular Structure*, Willard Grant Press, Boston, 1975, p. 72.
3. See, e.g.: (a) P. v. R. Schleyer and C. W. Woodworth, *J. Am. Chem. Soc.* **90**, 6528 (1968) (Bicyclo [2.2.2] octane systems); (b) T. M. Gund, P. v. R. Schleyer, G. D. Unruh and G. J. Gleicher, *J. Org. Chem.* **39**, 2995 (1974) (Adamantane derivatives).
4. (a) D. S. Noyce and B. E. Johnston, *J. Org. Chem.* **34**, 1252 (1969); (Decalins); (b) D. S. Noyce, B. N. Bastian, P. T. S. Lau, R. S. Monson and B. Weinstein, *J. Org. Chem.* **34**, 1247 (1969) (Cyclohexanes).
5. (a) H. Tanida, S. Yamamoto and K. Takeda, *J. Org. Chem.* **38**, 2077 (1973); (b) K. Takeda, H. Tanida and K. Horiki, *J. Org. Chem.* **31**, 734 (1966) (Decalin derivatives).
6. For a recent study on acyclic derivatives see C. A. Grob and A. Waldner, *Helv. Chim. Acta* **62**, 1736 (1979).
7. (a) C. A. Grob, *Angew. Chem.* **94**, 87 (1982); C. A. Grob, *Angew. Chem., Int. Ed. Engl.* **21**, 87 (1982); (b) C. A. Grob, *Accts. Chem. Res.* **16**, 426 (1983) (Norbornanes).
8. (a) D. Lenoir and R. M. Frank, *Chem. Ber.* **118**, 753 (1985); (Polycyclic compounds); (b) D. Lenoir, W. Roell, E. Weiss and G. Wenke, *Tetrahedron Lett.* **23**, 1991 (1976) (Norbornane derivatives).
9. For further references see reviews on solvolytic displacement reactions: (a) T. W. Bentley, *Ann. Rep. Progr. Chem., Sect. B.* **71**, 111 (1974); (b) J. M. Harris *Prog. Phys. Org. Chem.* **11**, 89 (1974); (c) T. W. Bentley and P. v. R. Schleyer, *Adv. Phys. Org. Chem.* **14**, 1 (1977); (d) W. Kirmse, *Top. Curr. Chem.* **80**, 125 (1979).
10. For a review on substituent effects in steroids see: R. T. Blickenstaff and K. Sophasan, *Tetrahedron* **28**, 1945 (1972).
11. J. Mathieu, M. Legrand and J. Valls, *Bull. Soc. Chim. France* 549 (1960).
12. D. J. Noyce and G. A. Selter, *J. Org. Chem.* **36**, 3458 (1971).
13. K. Takeda, H. Tamida and K. Horiki, *J. Org. Chem.* **31**, 734 (1966).
14. P. E. Peterson and D. M. Chevli, *J. Org. Chem.* **39**, 3684 (1974).
15. (a) C. M. Weeks, W. L. Duax and M. E. Wolff, *J. Am. Chem. Soc.* **95**, 2865 (1973); (b) P. A. Kollman, D. D. Giannini, W. L. Duax, S. Rothenberg and M. W. Wolff, *J. Am. Chem. Soc.* **95**, 2869 (1973).
16. H.-J. Schneider, U. Buchheit, W. Gschwendtner and M. Lonsdorfer in: *Molecular Structure and Biological Activity*, J. F. Griffin, W. L. Duax, (eds), Elsevier, 1982, p. 165; for comparison to X-ray structures see also: N. L. Allinger, *Adv. Phys. Org. Chem.* **13**, 1 (1976); J. P. Schmit and G. G. Rousseau, *J. Steroid Biochem.* **9**, 921 (1978); R. Bucourt, N. C. Cohen and G. Lemoine, *Bull. Soc. Chim. France* 903 (1975).
17. See e.g. W. L. Duax, V. Cody, J. F. Griffin, D. C. Rohrer and C. M. Weeks, *J. Toxicol. Environm. Health* **4**, 205 (1978).
18. H.-J. Schneider, W. Gschwendtner and E. F. Weigand, *J. Am. Chem. Soc.* **101**, 7195 (1979).
19. For new approaches see C. A. Grob, *Angew. Chem.* **88**, 621 (1976); *Angew. Chem., Int. Ed. Engl.* **15**, 569 (1976).
20. L. Radom, J. A. Pople and P. v. R. Schleyer, *J. Am. Chem. Soc.* **94**, 5936 (1972).
21. (a) H.-J. Schneider, G. Schmidt and F. Thomas, *J. Am. Chem. Soc.* **105**, 3556 (1983); (b) H.-J. Schneider, N. Becker, G. Schmidt and F. Thomas, *J. Org. Chem.* **51**, 3602 (1986); and references cited therein.
22. (a) H.-J. Schneider, W. Freitag, G. Gschwendtner and G. Maldener, *J. Magn. Res.* **36**, 273 (1979); (b) H.-J. Schneider, W. Gschwendtner and U. Buchheit, *J. Magn. Res.* **26**, 175 (1977).
23. N. L. Allinger, *J. Am. Chem. Soc.* **99**, 8127 (1977).

24. (a) H.-J. Schneider, U. Buchheit, N. Becker, G. Schmidt and U. Siehl, *J. Am. Chem. Soc.* **107**, 7027 (1985); (b) H.-J. Schneider and W. Gschwendtner, *J. Org. Chem.* **47**, 4216 (1982), and references cited therein.
25. (a) V. I. Minkin and S. Zhdanov *Dipole Moments in Organic Chemistry*, Plenum Press, New York, 1970, p. 196; (b) S. W. Benson and M. Luria, *J. Am. Chem. Soc.* **75**, 704 (1975) (C—H dipole data).
26. See Suppl. Material to Reference 24a, Table L*.
27. For similar LEF parametrizations see H.-J. Schneider and W. Freitag, *J. Am. Chem. Soc.* **99**, 8363 (1982); H.-J. Schneider *et al.*, in preparation.
28. (a) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.* **6**, 506 (1938); (b) C. Tanford, *J. Am. Chem. Soc.* **79**, 5348 (1957); (c) W. H. Ortung, *J. Am. Chem. Soc.* **100**, 4369 (1978); (d) P. H. Owens, G. J. Gleicher and L. M. Smith, *J. Am. Chem. Soc.* **90**, 4122 (1968), and references cited therein.
29. A. D. Buckingham, *Canad. J. Chem.* **38**, 300 (1960); for later literature see Reference 24.
30. H.-J. Schneider and G. Schmidt, *J. Chem. Soc. Perkin Trans. II* 2027 (1985).
31. J. A. Pople and M. Gordon, *J. Am. Chem. Soc.* **89**, 4253 (1967).
32. See e.g.: (a) A. Warshel, *Biochemistry* **20**, 3167 (1981); (b) D. Van Belle, I. Couplet, M. Prevost and S. J. Wodak, *J. Mol. Biol.* **198**, 721 (1987), and references cited.