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Anti-Inflammatory Steroids, Lysosomal Stabilization and Parachor

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Parachor is an additive constitutive property of a molecule and is related to the molar volume and the surface tension. The parachor of a steroid can be calculated from its constituent atoms and bonds. The parachor of a biologically active molecule is related to the ability of that molecule to permeate hydrophobic regions of cells, especially cellular membranes. An examination of the parachor values of a large number of steroids shows that these values are correlated with a number of different biological activities, from independent sources. The ability of steroids to release lysosomal enzymes from isolated lysosomes *in vitro* is inversely related to the parachor of the steroid. A similar relationship holds for the release of lysosomal β-glucuronidase (EC 3.2.1.31) from isolated lysosomes of rat preputial gland following *in vivo* administration of steroids. The relative anti-inflammatory potencies of steroids by several assay methods are directly proportional to their parachors. The relative ability of corticosteroids to uncouple oxidative phosphorylation and to swell isolated mitochondria *in vitro* show a direct proportionality with the steroidal parachor. The percutaneous absorptions of steroids show good correlation with parachors, stratum corneum – water partition coefficients and amylcaproate–water partition coefficients; but not with hexadecane–water partition coefficients. The application of parachor as a structure–activity correlation parameter in drug design is likely to yield useful information. The advantages and limitations of the calculated parachor method are discussed.

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Le parachor est une propriété constitutive additive d'une molécule et il est relié au volume molaire et à la tension superficielle. Le parachor d'un stéroïde peut être calculé à partir des atomes et des liaisons qui le constituent. Le parachor d'une molécule biologiquement active est relié au pouvoir de cette molécule de rendre perméables les régions hydrophobes des cellules, spécialement les membranes cellulaires. L'examen des valeurs du parachor d'un grand nombre de stéroïdes montre que ces valeurs sont reliées à un certain nombre de différentes activités biologiques de sources indépendantes. La capacité des stéroïdes de libérer les enzymes lysosomiques des lysosomes isolés *in vitro* est reliée de façon inverse au parachor du stéroïde. Une relation semblable existe dans la libération de la β-glucuronidase (EC 3.2.1.31) lysosomique des lysosomes isolés de la glande préputiale du rat suite à l'administration *in vitro* de stéroïdes. L'efficacité anti-inflammatoire relative des stéroïdes mesurée par plusieurs méthodes est directement proportionnelle à leur parachor. La capacité relative des corticostéroïdes de découpler la phosphorylation

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oxydative et de gonfler les mitochondries isolées *in vitro* est directement proportionnelle au parachor de ces stéroïdes. L'absorption percutanée des stéroïdes montre une bonne relation avec les parachors, les coefficients de partage stratum corneum – eau, les coefficients de partage amylcaproate–eau mais non avec les coefficients de partage hexadécane–eau. L'application du parachor comme paramètre de la relation entre structure et activité dans l'étude d'une drogue est susceptible de donner des informations utiles. Les avantages et les limitations de la méthode du parachor sont discutées. [Traduit par le journal]

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Introduction

The stabilization of lysosomes by corticosteroids has been proposed as a basis for their anti-inflammatory activity (1–4). The uncoupling of oxidative phosphorylation is another biochemical action that has been considered to correlate with the anti-inflammatory effects of several drug classes. Several workers have reported that the anti-inflammatory steroids uncoupled oxidative phosphorylation *in vivo* (5–8). In the present paper, we have examined the relationship between three biological actions of some C-21 steroids, namely, anti-inflammatory potency, lysosomal stabilization, and uncoupling of oxidative phosphorylation; and a molecular physicochemical parameter, the parachor. Parachor is a molar parameter defined as the product of the molar volume and the fourth root of surface tension (9). Parachors have been experimentally determined for many compounds and the additive constitutive nature of parachor was exploited for many years as a means of structure determination. Atomic and group parachors are readily available which enable the determination of the molar parachor of a complex molecule by addition of the parachor values of individual atoms and groups (9, 10). Thus, for a proposed molecule it is not necessary to synthesize and purify the compound and to determine its parachor experimentally. This is an important consideration which means that for complex biological molecules the parachor can be readily predicted. McGowan (11) was the first to correlate biological activity with parachor for a large number of compounds when he found a linear relationship between their narcotic effect on tadpoles and their parachors. Hansch (12) subjected McGowan's data to regression analysis and confirmed that there is good correlation between the parachor and the biological activity of the reported compounds. We have demonstrated the usefulness of the parachor as a structure–activity correlation parameter in several drug classes (13).

A few attempts have been made to correlate steroid biological activities with other physicochemical parameters, such as partition coefficients. Scheuplein *et al.* (14) studied the percutaneous absorption of steroids and found a correlation between the permeability constant and the diffusion constant and the partition coefficients of the steroids. Katz and Shaikh (15) reported a good correlation between the relative efficiency of percutaneous absorption and partition coefficients for the topical corticosteroids. Similar observations have been made by McKenzie (16) and Engel (17). Lien and Tong (18), using regression analysis, showed that the addition of other steric and electronic terms, such as molar refraction, Taft's polar substitution constant, molecular weight, and solubility in water, significantly improved the correlations in some cases. Recently, Wolff and Hansch (19, 20) applied for the first time the multiple parameter regression technique (21, 22) to steroids with monosubstitution. For both 9α-substituted cortisol analogs (19) and 6α-substituted Δ^6-progesterone derivatives (20), the linear correlations of steroidal activity with the Hansch π-value were low; but the addition of other parameters improved the correlation to a significant level.

In the present paper, we show some interesting and hitherto unreported correlations between lysosomal stabilization *in vitro* and *in vivo*, anti-inflammatory potency, glucocorticoid potency, percutaneous absorption, and the parachors of the steroids.

Methods

Molecular parachor values of individual steroids were calculated by the addition of atomic or group parachors. The latter were obtained from Quayle's tables of recommended parachors (10).

Statistical correlations of biological activity and parachor were carried out by step-wise regression analysis using a computer program (SPSS, version 5) of the Institute of Computer Science at the University of Guelph.

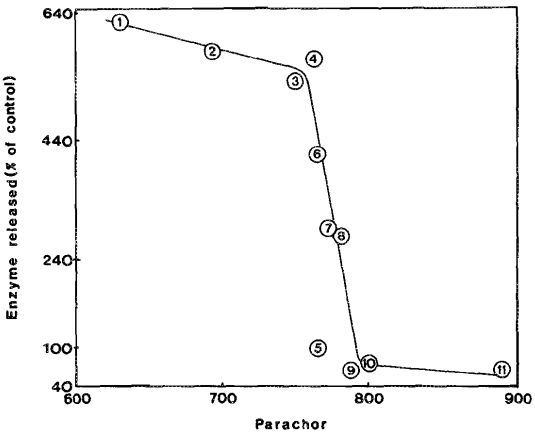

FIG. 1. Correlation between steroidal parachors and their influence on lysosomal stability *in vitro*. Enzyme released (percentage of control) refers to free acid phosphatase enzyme activity in the supernatant as released from the large granule fraction of rabbit liver after *in vitro* incubation of isolated lysosomes with the steroids (23). The steroids are (1) diethylstilbestrol, (2) etiocholanolone, (3) progesterone, (4) pregnanolone, (5) allopregnanolone, (6) deoxycorticosterone, (7) dehydroepiandrosterone acetate, (8) corticosterone, (9) cortisone, (10) cortisol, and (11) cortisone acetate.

The regression equations are:

	n	r	s	F
$A = -2.667\,P + 2366.395$	11	0.75	159.5	11.3
$A = 0.0004\,P^2 - 3.231\,P + 2577.422$	11	0.75	169.2	5.0
$1/A = 0.1004 + 0.0002\,e^P$	11	0.66	0.4	7.0

where, A is the relative release of the enzyme expressed as percentage of control; P is the parachor of the steroids. Of the statistical symbols, n is the number of data points; r is the correlation coefficient; s is the standard error and F is the Snedecor's variance ratio.

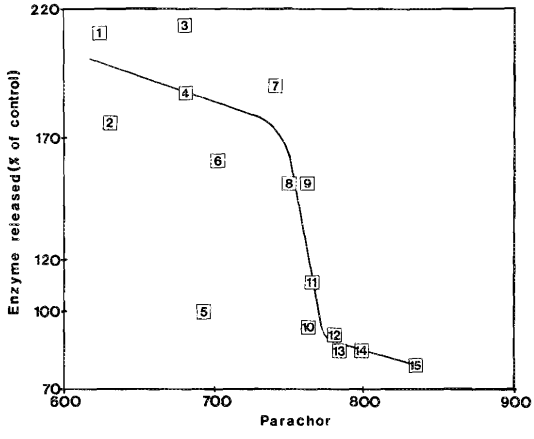

FIG. 2. Correlation between steroidal parachors and their influence on lysosomal stability *in vivo*. Enzyme released (percentage of control) refers to free β-glucoronidase enzyme activity in the supernatant from rat preputial gland homogenates after intravenous administration of the steroid *in vivo* (24). The steroids are (1) estradiol, (2) diethylstilbesterol, (3) ethinyl estradiol, (4) testosterone, (5) etiocholanolone, (6) norethisterone, (7) norgestrel, (8) progesterone, (9) pregnanolone, (10) allopregnanolone, (11) deoxycorticosterone, (12) corticosterone, (13) prednisolone, (14) cortisol, and (15) dexamethasone.

The regression equations are:

	n	r	s	F
$A = -0.629\,P + 6.001$	15	0.78	0.32	20.2
$A = -0.154\,P^2 + 1.594\,P - 1.971$	15	0.79	0.33	9.9
$1/A = 0.386 + 0.00024\,e^P$	15	0.81	0.15	24.8

where, A is the activity of the enzyme released; P is the parachor of the steroids. The statistical symbols, n, r, s and F, have the same meaning as in Fig. 1.

Results and Discussion

Figure 1 summarizes the correlation between steroid parachor values and the release of acid phosphatase (EC 3.1.3.2) from rat liver lysosomes *in vitro* in the presence of 2 m*M* steroid (23). In general, an inverse relationship exists so that steroids of low parachor are labilizing whilst those of high parachor are stabilizing. There is a correlation for 5β-H steroids, in which the A–B ring junction is *cis*, between parachor values and the labilization of lysosomes *in vitro*. It is of interest that the non-steroidal estrogen diethylstilbestrol has a labilizing effect consistent with the relationship between parachor and labilization seen for steroids.

The correlation between lysosomal stabilization and parachor holds not only for *in vitro* effects but also for steroid administered *in vivo*, as shown by the studies of Briggs (24) on the release of lysosomal β-glucuronidase (β-D-glucuronide glucuronosohydrolase, EC 3.2.1.31) from rat preputial glands, following the administration of steroids intravenously as given in Fig. 2. A similar relationship exists between the effectiveness of the steroid and its parachor value. The major discrepancy between this study and the previous *in vitro* data is the effect of etiocholanolone, which appears to be less effective *in vivo* in lysosomal labilization. The only 5α-H steroid tested in this system was allopregnanolone which, as in the *in vitro* study, shows much lower activity than its 5β-H isomer pregnanolone. Dexamethasone which has the highest parachor value among the tested steroids showed the greatest degree of lysosomal stabilization con-

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TABLE 1. Correlation between the parachors of glucocorticoids and their relative biological potencies by six different assay methods (25)

Steroids	Parachor (P)	Rat liver glycogen deposition (A_g)	Thymus involution (A_t)	Anti-granuloma (A_a)	Fibroblast assay (A_f)	Oral anti-inflammatory (A_o)	THFA assay potency (A_h)
Cortisol	796.8	1.0	1.0	1.0	1.0	1.0	1.0
Cortisone	787.3	0.5	0.5	0.5	*	0.8	*
Prednisone	774.0	2.6	0.9	1.0	*	5.0	*
Prednisolone	783.5	5.0	4.0	2.7	1.7	5.0	1.8
6α-Methylprednisolone	823.5	13.0	3.0	6.0	*	6.0	4.7
Paramethasone	834.1	23.1	45.1	63.6	11.3	12.0	*
9α-Fluoroprednisolone	794.1	27.0	4.4	17.7	*	*	*
Fluocinolone	820.3	44.0	8.5	19.7	*	*	*
Betamethasone	834.1	59.0	11.7	35.8	*	25.0	
Dexamethasone	834.1	90.4	47.0	104.0	7.5	25.0	19.0
Triamcinolone acetonide	926.7	108.0	37.7	48.5	156.0	*	33.0
Fluocinolone acetonide	937.2	138.0	263.0	446.0	440.0	*	*
Triamcinolone	809.7	*	*	*	*	6.0	0.1
Aldosterone	802.5	*	*	*	*	0.1	*
9α-Fluorocortisol	807.4	*	*	*	*	12.0	9.0

*Compounds not reported in Briggs and Brotherton (25).

Equations	n	r	s	F
[1a] $A_g = 0.807\,P - 626.408$	12	0.91	20.15	49.0
[1b] $A_g = 1592.284 \log P - 4603.108$	12	0.91	20.07	49.4
[1c] $\log A_g = 0.011\,P - 8.218$	12	0.73	0.58	11.6
[1d] $\log A_g = -0.0001\,P^2 + 0.226\,P - 99.973$	12	0.82	0.51	9.3
[1e] $\log A_t = 0.013\,P - 9.829$	12	0.83	0.48	21.9
[1f] $\log A_t = -0.0001\,P^2 + 0.161\,P - 72.836$	12	0.87	0.45	13.5
[1g] $\log A_a = 0.014\,P - 10.174$	12	0.78	0.60	15.5
[1h] $\log A_a = -0.0001\,P^2 + 0.246\,P - 109.333$	12	0.86	0.52	12.4
[1i] $\log A_f = 0.916\,P - 12.418$	6	0.98	0.21	121.8
[1j] $\log A_f = -0.00001\,P^2 + 0.023\,P - 15.371$	6	0.98	0.24	45.8
[1k] $A_o = 0.303\,P - 235.925$	11	0.73	6.37	10.5
[1l] $A_o = 0.010\,P^2 - 15.819\,P + 6267.08$	11	0.84	5.32	9.9
[1m] $A_h = 0.237\,P - 185.830$	7	0.92	5.07	29.4
[1n] $A_h = -0.0002\,P^2 + 0.628\,P - 353.191$	7	0.93	5.65	11.9

NOTE: In these equations, P is the parachor value of the steroids; A_g is the relative potency of the glucocorticoids by the rat liver glycogen deposition assay in adrenalectomized male rats; A_t is the relative potency by the thymus involution assay in adrenalectomized male rats; A_a is the relative potency by the anti-granuloma pouch assay in similar animals; A_f is the relative potency in the fibroblast assay; A_o is the oral anti-inflammatory potency and A_h is the relative potency of the steroids by the THFA assay. The biological assay data are from Briggs and Brotherton (25). Of the statistical symbols, n is the number of data points; r is the correlation coefficient; s is the standard error and F is the Snedecor's variance ratio.

sistent with its known anti-inflammatory potency. The data suggest that similar steroids of greater parachor value should be even more effective as anti-inflammatory agents.

Figures 1 and 2 indicate that for 5-β-H steroids the range of parachor of 750–800 represents a critical boundary between membrane stabilization and membrane lysis. This phenomenon may reflect a critical region for molar volume and hydrophobicity. It appears that large hydrophobic steroids contribute to the stability of the lysosomal membrane whereas smaller steroids destabilize the membrane, perhaps due to their inability to effectively replace cholesterol in the hydrophobic regions of the membrane.

Table 1 shows the biological potencies of corticosteroids as collated by Briggs and Brotherton (25). In the single-parameter linear equations [1a, 1b, 1c, 1e, 1g, 1i, 1k, 1m], the values of the correlation coefficients indicate good correlation between these biological potencies of the steroids and their parachors. The correlation coefficients obtained are 0.91 for the rat liver glycogen deposition potency [1a], 0.83 for the

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TABLE 2. Correlation between the parachors of some anti-inflammatory steroids and their effect on state 4 succinate respiration, ADP/O ratios and swelling of rat liver mitochondria (8)

Steroids	Parachor (P)	% increase in state 4 succinate respiration* at steroid concn. 10^{-5} M (A)	% increase in state 4 succinate respiration* at steroid concn. 10^{-3} M (B)	ADP/O ratios at steroid concn. 10^{-5} M (C)	ADP/O ratios at steroid concn. 10^{-3} M (D)	Mitochondrial swelling† at 10^{-3} M steroid concn. (E)
Betamethasone	834.1	16.3	52.1	1.20	0.84	−0.0067
Cortisone	787.3	15.4	21.3	1.24	0.60	‡
Cortisol	796.8	16.9	25.1	1.53	0.99	−0.0037
Dexamethasone	834.1	18.3	58.3	1.30	0.88	−0.0084
Prednisone	774.0	13.4	26.3	1.04	0.58	‡
Prednisolone	783.5	14.1	30.4	1.35	0.70	−0.0026
Triamcinolone	809.5	15.3	16.3	1.36	1.05	−0.0014

*All respiration results are expressed as nanogram atoms oxygen per minute per milligram mitochondrial protein.
†Mitochondrial swelling is measured by the decrease in absorbance at 520 nm and expressed as A_{520nm} min^{-1} (10 mg protein)$^{-1}$.
‡Compounds not reported in Symons *et al.* (8).

	Equations (the number of cases $n = 7$)	r	s	F
[2a]	$A = 0.055\,P - 28.597$	0.80	1.10	8.73
[2b]	$A = -0.001\,P^2 + 1.525\,P - 620.936$	0.82	1.15	4.23
[2c]	$\log A = 0.002\,P - 0.037$	0.80	0.03	8.92
[2d]	$\log A = -0.00003\,P^2 + 0.049\,P - 19.189$	0.84	0.03	4.66
[2e]	$B = 0.502\,P - 370.498$	0.76	11.45	6.71
[2f]	$B = 0.023\,P^2 - 37.135\,P + 14797.644$	0.94	6.75	14.83
[2g]	$C = 0.001\,P + 0.518$	0.15	0.16	0.12
[2h]	$C = -0.0003\,P^2 + 0.529\,P - 212.154$	0.83	0.10	4.47
[2i]	$D = 0.005\,P - 3.174$	0.58	0.18	2.51
[2j]	$D = -0.0003\,P^2 + 0.485\,P - 196.556$	0.80	0.15	3.50
[2k]	$E = -0.0001\,P + 2.091$	0.87	0.01	15.94
[2l]	$E = -0.00001\,P^2 + 0.003\,P - 1.0003$	0.89	0.01	7.99

NOTE: In these equations, P is the parachor value of the steroid; A and B are the percentage increases in state 4 succinate respiration at steroid concentrations of 10^{-5} M and 10^{-3} M, respectively; C and D are the ADP/O ratios at 10^{-5} M and 10^{-3} M steroid concentrations, respectively; and E is the relative swelling of the rat liver mitochondria at 10^{-3} M steroid concentration. The experimental data are from Symons *et al.* (8). The statistical symbols: n, r, s, and F have the same meaning as in Table 1.

thymus involution potency [1e], 0.78 for the antigranuloma potency [1g], 0.98 for the fibroblast assay potency [1i], 0.73 for the oral anti-inflammatory potency [1k], and 0.92 for the tetrahydrofurfurylalcohol (THFA) assay potency [1m]. The use of an additional term, such as P^2 [1d, 1f, 1h, 1j, 1l, 1n] or log P [1b] affects the correlation to a small extent. Table 2 is prepared from the data of Symons *et al.* (8) on the effect of some anti-inflammatory steroids on state 4 succinate respiration, ADP/O ratios and swelling of rat liver mitochondria. In the single-parameter linear equations, the values of the correlation coefficients indicate good correlation between the steroidal parachor and their effects on the state 4 succinate respiration and swelling of rat liver mitochondria, but not with the ADP/O ratio, which, however, gives good correlation in the two-parameter squared-term equations, indicating a curvilinear relationship. The data of Scheuplein *et al.* (14) on the percutaneous absorption of some C-21 steroids and their partition coefficients in three systems are given in Table 3. In the single-parameter linear equations [3a–3j], the values of the correlation coefficients obtained show that both the permeability constant and diffusion constant for the percutaneous absorption of these steroids correlate well with parachor, stratum corneum – water partition coefficient, amylcaproate – water partition coefficient, and the flux observed experimentally. However, the hexadecane – water partition coefficient does not correlate well. The use of the squared [3k, 3m, 3n, 3p] or log term [3l, 3m, 3o, 3p] improves the correlation to some extent. In other linear equations [3q, 3r, 3s], it

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TABLE 3. Correlations among the permeability constants for the percutaneous absorption of steroids, their partition coefficients and their parachor values (14)

Steroids	Parachor (P)	K_{sc}	K_{ac}	K_{hex}	J_s(exp)	k_p	D
Progesterone	751.3	104	56	17.0	30	1500	160
Pregnenolone	747.1	50	52	4.2	51.3	1500	220
Hydroxypregnenolone	761.4	43	49	1.6	17	600	155
Hydroxyprogesterone	765.6	40	46	2.5	60	600	166
Cortexone	768.2	37	30	3.0	10.9	450	135
Cortexolone	782.5	23	11.2	0.1	7.5	75	36.1
Corticosterone	781.2	17	6.8	0.02	1.04	60	39.2
Cortisone	787.3	8.5	1.52	0.28	0.10	10	13.1
Cortisol	796.8	7	1.3	0.01	0.06	3	4.8
Aldosterone	802.5	6.8	—	—	0.02	3	4.9

	Equations (the number of cases n = 10)	r	s	F
[3a]	$k_p = -28.763\,P + 22753.863$	0.91	258.5	38.8
[3b]	$k_p = 17.781\,K_{sc} - 117.871$	0.89	286.7	30.0
[3c]	$k_p = 22.425\,K_{ac} - 89.104$	0.90	277.8	32.5
[3d]	$k_p = 90.199\,K_{hex} + 221.113$	0.79	380.3	13.6
[3e]	$k_p = 19.918\,J_s(\text{exp}) + 125.739$	0.75	413.7	10.3
[3f]	$D = -4.159\,P + 3314.211$	0.95	25.9	80.2
[3g]	$D = 2.074\,K_{sc} + 23.645$	0.75	57.0	10.3
[3h]	$D = 3.340\,K_{ac} + 8.627$	0.97	22.2	113.3
[3i]	$D = 8.419\,K_{hex} + 69.237$	0.54	72.8	3.2
[3j]	$D = 3.125\,J_s(\text{exp}) + 37.819$	0.85	45.2	21.2
[3k]	$k_p = 0.761\,P^2 - 1207.25\,P + 478888.99$	0.99	99.6	154.2
[3l]	$\log k_p = -0.055\,P + 44.676$	0.97	0.3	127.7
[3m]	$\log k_p = -0.001\,P^2 + 0.807\,P - 288.819$	0.98	0.2	98.5
[3n]	$k_p = -0.115\,K_{sc}^2 + 29.887\,K_{sc} - 304.387$	0.91	277.4	16.8
[3o]	$\log k_p = 0.029\,K_{sc} + 1.035$	0.81	0.6	15.5
[3p]	$\log k_p = -0.001\,K_{sc}^2 + 0.092\,K_{sc} + 0.066$	0.99	0.2	145.8
[3q]	$K_{sc} = -1.323\,P + 1058.028$	0.84	17.1	18.9
[3r]	$K_{ac} = -1.198\,P + 952.843$	0.95	7.9	72.5
[3s]	$K_{hex} = -0.180\,P + 142.181$	0.65	4.2	5.8
[3t]	$J_s(\text{exp}) = -0.906\,P + 719.019$	0.76	15.3	11.0

NOTE: In the table and the equations, P is the calculated parachor value of the steroid; K_{sc} is the stratum corneum – water partition coefficient; K_{ac} is the amylcaproate–water partition coefficient; K_{hex} is the hexadecane–water partition coefficient; J_s(exp) is the flux observed experimentally, expressed as mol cm^{-2} h^{-1} × 10^{-13}; k_p ist he permeability constant in cm h^{-1} × 10^{-6} and D is the diffusion constant in cm^2 s^{-1} × 10^{-13}. The experimental data are from Scheuplein *et al.* (14). The statistical symbols, n, r, s, and F, have the same meaning as in Table 1.

appears that the partition coefficients in two systems: stratum corneum – water and amylcaproate – water correlate well with the parachor for the steroids; whereas the hexadecane – water partition coefficient does not. The good correlation obtained between the steroidal parachor and their partition coefficients in the stratum corneum – water and amylcaproate – water systems strengthens the case for the parachor to be used as a structure-activity correlation parameter in drug design. By analogy with the Hansch multiparameter regression technique (21), the additional use of appropriate electronic or steric correction factors, in conjunction with the parachor, should produce better correlations in structure–activity studies. As already shown by us, the parachor yields better correlations than the partition coefficients in several drug classes (13). The immediate advantage of parachor values over experimentally-determined partition coefficients is that the former can be readily calculated from existing compilations of atomic parachors, without the necessity of synthesis and physical measurements on newly-designed molecules which may not be readily available. The disadvantage in this calculated method is that the calculated parachor values for optical isomers are the same although their biological potencies vary greatly in many cases. It remains to be seen whether experimentally-determined

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surface tensions of optical isomers are different, and consequently whether the observed discrepancies for steroid optical isomers could be corrected.

The application of correlations between the parachors and the observed biological activities of steroids may yield new insights into the mode of action of steroids, particularly in those cases in which hydrophobic interactions may be rate-limiting. Evidence has been presented by Szego (26) and Jackson and Chalkley (27) that steroid hormone receptor proteins are compartmentalized in the membranes of target cells within a hydrophobic environment. Hydrophobic binding between steroids and proteins is likely to be an important factor in steroid hormone action. We have examined the data for a number of independent competition studies using purified corticosteroid hormone receptors for different steroids for a correlation with the parachors of the competing steroids, and have found a consistent pattern of correlation (Ahmad, P., and Mellors, A.: manuscript submitted). Our results suggest that an extensive evaluation of the parachor as a structure–activity correlation parameter should yield useful information about the nature of steroid–cell interactions.

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