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A RELATIONSHIP BETWEEN REPRESSION OF DIMETHYLNITROSAMINE-DEMETHYLASE BY POLYCYCLIC AROMATIC HYDROCARBONS AND THEIR SHAPE*

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Abstract—The quantitative relationship between the ability of polycyclic aromatic hydrocarbons to repress the mixed-function oxidase, dimethylnitrosamine-demethylase, and a parameter expressing the shape of the hydrocarbon molecules, has been studied. The shape parameter represents the ratio of the longer to shorter sides of the minimum rectangular envelope around the structure, drawn proportionally to atomic dimensions. The shape parameter allows the prediction of the relative biological activity of 23 active and 4 inactive compounds.

The molecular size of chemical compounds has often been noted to affect its biological activity: such observations have been reported by Arcos *et al.* [1, 2]. Furthermore, in a class of compounds of similar chemical properties the molecular size is related to the phase partition characteristics. The latter, in turn, determine the penetration into and transport within a biological system.

It has long been known that biological activity of chemical compounds is determined by their chemical reactivity, stereochemical features, and the oil/water partition coefficients [3]. Within a group of compounds of a similar reactivity, such as the PAH, differences in biological activity are likely to be governed by the latter two factors. Attempts of quantitative expression of the biological activity of PAH have been made by Hansch and Fujita [3], Franke [4], and by Herndon [5]. All expressions incorporate the Pullmans' electron density at the *K* and *L* regions [6], the n-octanol/water partition coefficients, and protein-binding constants or the parameter Δ defined as (24 − C) where C is the number of carbon atoms in molecule. However, in reports [3, 4] difficulties were encountered in deriving structure–activity relationships, due to adoption of a low-precision scale of carcinogenic activity. Moreover, results presented in [5] are of rather small statistical importance, since the correlation was obtained using a small number of compounds.

As some relationships have been postulated between carcinogenic activity and the capacity of PAH to repress or induce activity of certain enzymes [7], it appeared of interest to investigate the correlation between structural geometric parameters and the biological activity of PAH. In [1] a relationship has been reported between repression of dimethylnitrosamine[DMN]-demethylase and the incumbrance area of the PAH. The incumbrance area was defined [8] as a surface area of a minimal rectangular envelope and was used as a measure of the molecular size. The incumbrance area required for the maximal repressor activity range between about 85 and 150 Å^2. The magnitude of this area provides, however, only a rough estimate of the activity of PAH, since almost one-half of compounds whose areas fall within that range exhibit a low, if any, activity.

Closer inspection of the structure of the PAH reveals, however, that not only the size of these molecules, but also their shape correlates with their ability to repress DMN-demethylase. Accordingly, we propose a modification of the concept of Arcos *et al.* [1] of the minimal rectangular envelope and the use of the ratio: the longer over the shorter side of the incumbrance area rectangle, as a parameter (η) characterizing the shape of a molecule. The importance of the molecular shape has actually been considered by Arcos *et al.* [1, 2], who noted that an elongated molecular shape appears to be required for both induction and repression, while highly symmetrical, compact-shaped hydrocarbons are inactive.

METHODS

The shape parameter (η) was evaluated from the incumbrance area rectangles, calculated as described [2] for a number of unsubstituted polycyclic aromatic hydrocarbons. The data were analysed by computerized regression analysis following the general equation:

$$\log A = k_1\eta^2 + k_2\eta + k_3\Delta + k_4. \qquad (1)$$

The activities of the first 23 compounds in Table 1 were used to determine the constants in equation 1.

RESULTS AND DISCUSSION

Table 1 lists data expressed as per cent repression of DMN-demethylase (A) together with the η and Δ values. The least-square fit gave constants shown in

* Abbreviation used: PAH for polycyclic aromatic hydrocarbon(s).

Table 1. Numerical data used for correlating the shape parameter of the PAH with their repressor activity

No.	Hydrocarbon	Shape parameter (η)	$\Delta = (24 - C)$	Per cent repression of DMN-demethylase Obs.	Calc.
Compounds considered for derivation of regression equation 2					
1.	Coronene	1.000	0	9.1	3.0
2.	1,2,3,4-Dibenzopyrene	1.013	0	3.8	3.3
3.	1,12-Benzoperylene	1.113	2	1.2	5.5
4.	Triphenylene	1.111	6	4.9	3.5
5.	Pyrene	1.119	8	2.2	3.0
6.	1,2,7,8-Dibenzoperylene	1.206	4	4.9	7.9
7.	1,2,6,7-Dibenzopyrene	1.311	0	17.2	20.9
8.	1,2,4,5,8,9-Tribenzopyrene	1.351	4	13.1	16.1
9.	1,2,3,4,5,6-Tribenzonaphthacene	1.321	5	6.0	12.7
10.	Anthanthrene	1.342	2	28.7	19.2
11.	Naphthalene	1.242	14	6.0	3.2
12.	Phenanthrene	1.459	10	6.5	12.2
13.	1,2,7,8-Dibenzanthracene	1.479	2	37.1	31.0
14.	1,2-Benzanthracene	1.572	6	36.2	24.6
15.	Chrysene	1.683	6	31.9	27.8
16.	1,2,5,6-Dibenzanthracene	1.782	2	56.2	42.8
17.	3,4-Benzotetraphene	1.347	2	32.5	19.7
18.	1,2-Benzopentacene	1.980	2	17.2	30.5
19.	1,2,7,8-Dibenzophenanthrene	1.989	2	43.1	29.8
20.	1,2,8,9-Dibenzopentacene	2.150	6	10.4	10.4
21.	Naphthacene	1.872	6	34.2	25.0
22.	Quaterylene	2.174	16	3.2	3.1
23.	2',1'-Anthra-1,2-anthracene	2.296	2	6.0	7.3
Inactive compounds					
24.	1,2,3,4,5,6,7,8-Tetrabenzonaphthalene	1.000	2	inactive	2.4
25.	1,2-Benzopyrene	1.149	4	inactive	5.5
26.	Benzocoronene	1.182	4	inactive	6.8
27.	Ovalene	1.206	8	inactive	5.0
28.	Perylene	1.268	4	inactive	10.9
29.	1,2,7,8-Dibenzocoronene	1.361	8	inactive	10.8
Compounds which obeyed poorly equation 2					
30.	1,2,3,4-Dibenzanthracene	1.118	2	54.5	5.6
31.	1,2,4,5-Dibenzopyrene	1.090	0	37.8	5.8
32.	3,4-Benzopyrene	1.347	4	41.6	15.8
33.	3,4,8,9-Dibenzopyrene	1.614	0	16.9	50.0
34.	3,4,9,10-Dibenzopyrene	1.724	0	5.4	54.0
35.	Anthracene	1.559	10	1.4	15.5

equation 2:

$$\log A = -2.3939\eta^2 + 8.2663\eta - 0.0475\Delta - 5.4026.$$
$$n = 23, s = 0.2655, R = 0.8564. \quad (2)$$

where n is the number of compounds considered, s is the standard deviation and R is the correlation coefficient.

Neglecting the parameter Δ lowers the statistical significance of the correlation to give the following equation:

$$\log A = -2.3181\eta^2 + 7.9224\eta - 5.2877.$$
$$n = 23, s = 0.3331, R = 0.7464. \quad (3)$$

Examination of the relationship between log A and the shape parameter, η, gave:

$$\log A = 0.3965\eta + 0.4463. \quad (4)$$
$$n = 23, s = 0.4592, R = 0.3379.$$

A comparison of the statistical significance of equations 3 and 4 reveals the importance of the squared term, η^2, and confirms the existence of a region of η values in which biological activity attains a maximum.

The affect of the parameter Δ (which is related to size) on the activity of a molecule is small, as seen in equation 5:

$$\log A = -0.0346\Delta + 1.2094. \quad (5)$$
$$n = 23, s = 0.4636, R = 0.3117.$$

Yet, introduction of Δ into equation 2 resulted in a statistically significant difference.

Since log 0 is meaningless, inactive compounds 24–29 may, in principle, not be considered when deriving equation 2. Nonetheless, their activity calculated from equation 2 is low. Equation 2 allows satisfactory prediction of the biological activity of compounds 1–27, while compounds 28–35 obey poorly the equation. Nonetheless, the correlation between η and repressor activity toward DMN-demethylase generally supports the suggestion of Arcos [1, 2] regarding the importance of steric fit between the hydrocarbon molecule and its cellular receptor site. The total lack of correlation between η and the activities of 3,4,9,10-dibenzopyrene and 1,2,3,4-dibenzanthracene is possibly due either to the lack of versatility of the shape parameter or to differences in the mechanism of action of these compounds.

as compared to those of other PAH. However, the primary objective of this study was to focus attention to a parameter correlating molecular shape of PAH with their biological activity. For a more precise description of the activity, introduction of additional parameters relating to chemical reactivity and possibly of data from quantum chemical calculations would be useful. Application of conclusions drawn from this study to results of other biological studies with PAH, e.g. involving topical application of PAH in carcinogenesis studies, may be inappropriate as in these studies activity may be overwhelmingly determined by partition between the aqueous and organic phases.

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