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Excitation transfer and carcinogenesis

It has been suggested recently by BIRKS[1] that the induction of cancer by conjugated hydrocarbons could be the consequence of a transfer of excitation energy by resonance from tryptophan to the carcinogen, following the formation of a protein–carcinogen complex.

The probability of a dipole–dipole energy transfer is, according to FÖRSTER's theory[2,3], proportional to the overlap integral:

$$J = \int f_S(\lambda)\varepsilon_A(\lambda)\lambda^4 d\lambda$$

where $f_S(\lambda)$ is the quantum intensity of the fluorescence emission of tryptophan and $\varepsilon_A(\lambda)$ the molar extinction coefficient of the hydrocarbon.

In fact, in order to account for the results which showed that the large non-carcinogenic hydrocarbons, pentacene and pentaphene, have high values of J (and observing that this is due to the strong overlap of their second excited singlet with the tryptophan emission) BIRKS postulates that it is only the fraction J_1 of the overlap, corresponding to the first excited singlet of the hydrocarbon, which should be important.

The values of J_1 for 17 unsubstituted aromatic hydrocarbons and for the methylated derivatives of benzanthracene were considered by BIRKS as showing a satisfactory correlation with carcinogenic activity, the only exception being 3,4-benzphenanthrene (active, although having a very small J_1). A closer examination of BIRKS' data shows, however, that in fact there are two more exceptions in them: anthracene which is inactive in spite of having J_1 larger than that of benzanthracene, and 1,2,7,8-dibenzanthracene (active although his $J_1 = 150$ instead of the value of ref. 1).

In order to check further the validity of BIRKS' proposal, we have evaluated J_1 for all the remaining fundamental aromatic hydrocarbons which have been tested for carcinogenic activity and whose absorption spectra were available[4]. These 21 molecules include the two weakly carcinogenic 1,2,5,6- and 1,2,3,4-dibenzphenanthrenes, the very potent 3,4,9,10-dibenzpyrene and 18 inactive compounds. We have also calculated J_1 values for typical isomeric members of the two benzacridine series which differ strikingly in activity[5,*]. (Our evaluation of J_1 for benzanthracene is based on the spectrum of this compound given by NORMAN-JONES[6] which seems to be the best available one. This fixes the threshold value for J_1 at 2000 instead of 1350 used by BIRKS. This technical detail is, however, of no importance in the following discussion.)

The results presented in Table I lead to a few important conclusions. Thus, in the first place, although BIRKS has taken the precaution of stating that his correlation may not be the only factor responsible for carcinogenic activity but may operate in conjunction with the necessity of formation of a carcinogen–protein complex, it must nevertheless be stressed (because this situation is not apparent in his data) that the correlation which he proposes is completely unable to distinguish between the active and inactive compounds. Thus, the two active dibenzphenanthrenes have J_1 values inferior to the threshold value, while two of the three inactive dibenzphenanthrenes have J_1 values superior to the threshold value. The extremely potent carcinogen 3,4,9,10-dibenzpyrene has a very low value of J_1 much smaller than the threshold. All the remaining inactive hydrocarbons composed of five or six fused

* The absorption spectra of benzacridines were kindly communicated to us by A. MATTHIEU-CREUTIN.

TABLE I

VALUES OF J_1 IN HYDROCARBONS AND BENZACRIDINES

Compound	J_1	Carcinogenic activity
1,2-Benzanthracene	2000	+
1,2,5,6-Dibenzphenanthrene	1380	+
1,2,3,4,-Dibenzphenanthrene	1200	+
3,4,9,10-Dibenzpyrene	160	+ + + +
Pyrene	170	−
Naphthacene	600	−
3,4,5,6-Dibenzphenanthrene	350	−
2,3,7,8-Dibenzphenanthrene	3400	−
2,3,5,6-Dibenzphenanthrene	2100	−
Perylene	4100	−
1,2-Benznaphthacene	3800	−
1,2,6,7-Dibenzpyrene	1350	−
3,4,6,7-Dibenzpyrene	5900	−
2,3-Naphtho-3,4-pyrene	8400	−
Anthanthrene	4200	−
1,2,3,4,5,6-Tribenzanthracene	4100	−
1,2,7,8-Dibenznaphthacene	6500	−
1,2,9,10-Dibenznaphthacene	3700	−
3,4-Benzpentaphene	10000	−
2',1'-Anthra-1,2-anthracene	4500	−
2,3,8,9-Dibenzperylene	8300	−
3,4,9,10-Di(2',3'-naphtho)-pyrene	4600	−
2-Methyl-5,6-benzacridine	3000	−
10-Methyl-5,6-benzacridine	3600	−
2,10-Dimethyl-5,6-benzacridine	3800	−
2,10-Dimethyl-7,8-benzacridine	3400	+ + +
3,10-Dimethyl-7,8-benzacridine	3300	+ +

benzene rings, with one exception only, have J_1 values greater than the threshold. Moreover, the three inactive 5,6-benzacridines and the two active 7,8-benzacridines have J_1 values of the same, relatively high, order of magnitude*.

BIRKS' criterion cannot therefore discriminate between active and inactive compounds. At most it could be considered as one of the numerous correlations, whose significance is uncertain if not dubious, which have been shown to exist in the limited series of the active molecules between their carcinogenic potency and different physico-chemical characteristics**. In fact, even from that point of view, BIRKS' correlation is less satisfactory than some others. The case of the very carcinogenic 3,4,9,10-dibenzpyrene is particularly illuminating in this connection: this compound behaves from the viewpoint of J_1, exactly as does the inactive pentaphene and for the same reasons.

This last example leads us to underline the obvious superiority of the K–L-regions theory of carcinogenesis[5,7] which accounts immediately, for example, for the difference in activity between the two quoted compounds. In fact this last theory permits with very few exceptions, both to select the active and inactive compounds among

* This result is further substantiated by recent calculations of J_1 for some other substituted and heterocyclic carcinogens (J. D. MEMORY, *Biochim. Biophys. Acta*, 64 (1962) 396): 6 out of the 14 compounds calculated fail to obey BIRKS' correlation.

** Such limited correlations involve *e.g.* the ionization potential of the carcinogen or the energy of the electronic transition to the lowest excited state[5].

all those quoted by BIRKS and here, and to account moreover for the relative potencies of the active molecules. It introduces explicitely the requirements for binding which is appropriate for carcinogenesis (binding through the K region) and differentiates it from other types of binding (in particular through the L region) which are not appropriate for carcinogenesis. Moreover, relating carcinogenic activity to chemical and biochemical reactivity, it seems in better direct relation with the protein-deletion hypothesis[8] or with similar theories of a direct interaction of the carcinogen with nucleic acids[9] than are the "physical" theories of the type discussed above, at least in so far as these theories do not suggest any explicit mechanism for the production of tumors. A damage produced in a protein implicated in growth-control or directly in a nucleic acid by a chemical interaction is the simplest hypothesis for the mechanism of action of the chemical carcinogens. Its soundness is to some extent substantiated by the recent results indicating that such may be the mechanism of action of the related mutagens.

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On uncertainties inherent in the determination of the efficiency of collision between virus particles and cells

Several authors (VALENTINE AND ALLISON[1], TOLMACH[2] and STENT AND WOLLMAN[3]) have recently concluded, or regarded it as established, that the efficiency of collision of virus particles with cells is near unity. In fact the methods used can only give meaningful values for the collision efficiency if this is less than 10^{-3}–10^{-4}, and are insensitive to higher values. Apart from this limitation, uncertainties in the kinetic theory of liquids prevent the exact measurement of collision efficiency under any conditions.

The literature provides an interesting example of how such a myth can come to be accepted. VALENTINE AND ALLISON[1] reached their conclusion independently; although their mathematics are correct, they failed to notice that their results are