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STUDY OF THE REPRESENTATION OF COMPETITIVE ISOTHERMS AND OF THE INTERSECTION BETWEEN ADSORPTION ISOTHERMS

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SUMMARY

   Theoretical investigations of the separation of the components of a mixture by preparative liquid chromatography require a knowledge of the competitive equilibrium isotherms of the components of the mixture between the two phases of the chromatographic system. In many instances the set of competitive Langmuir equations provide a satisfactory model. When the competitive isotherms of the two components of a binary mixture intersect each other, however, the Langmuir model becomes unsuitable. This model postulates constant selectivity for the equilibrium between the two phases of a chromatographic system.

   A modified Langmuir model is proposed, using the ratio between two second-degree polynomials. This model is supported by general results from statistical mechanics. It accounts well for some experimental data that could not be explained in terms of the Langmuir isotherm.

INTRODUCTION

   Recently, the competitive adsorption isotherms of *cis*- and *trans*-androsterone between silica (Partisil-10; Whatman, Clifton, NJ, U.S.A.) modified with a pH 6.8 phosphate buffer[1] and acetonitrile–chloroform (10:90, 15:85 and 20:80) solutions were determined at 5, 15 and 25°C[2]. The single-component isotherms and the chromatographic behaviour of mixtures of these isomers were studied by Gonzalez *et al.*[3]. When the measurements were carried out at constant relative concentrations of the two isomers, and for a certain range of composition of the isomer mixture and of the mobile phase, the isotherms intersected each other. This phenomenon may explain the unusual band profiles observed when the column is strongly overloaded. Depending on the sample size and composition, the elution order is different. With relatively small sample sizes *cis*-androsterone is eluted first, whereas with large sample sizes it is eluted last.

   This phenomenon may not be exceptional. When two compounds are closely eluted in a given chromatographic system, it is the larger, bulkier and/or heavier one that interacts more strongly with the stationary phase. Hence the slope of its adsorption isotherm is larger, and it is the more retained at low concentrations.

However, at higher concentrations, it is the same larger, heavier compound that occupies the greatest area on the adsorbent surface, and hence for which the column capacity is the smaller. Consequently, for two closely related compounds of different shape, the larger (or the flatter) molecule tends to exhibit the isotherm with the steeper tangent at the origin and the lower asymptote. As a consequence, the isotherms must cross each other at some point, and we have a situation comparable to that experienced with the androsterone isomers.

In such an event, the classical Langmuir isotherm cannot account correctly for the experimental results[2]. We propose here an improved Langmuir model, based on the assumption that the kinetics of adsorption and desorption are a linear function of each of the concentrations of the two compounds in the mobile phase. The experimental data obtained previously for *cis-* and *trans*-androsterone are fitted on the equation obtained.

THEORY

The classical Langmuir model for multi-component isotherms is as follows:

$$q_i = \frac{a_i c_i}{1 + \sum_{j=1}^{n} b_j c_j} \qquad i = 1, 2, \ldots, n \tag{1}$$

where q_i and c_i are the concentrations of the compounds studied in the stationary phase and the mobile phase, respectively.

For two components, the selectivity, α, of the phase equilibrium is defined as

$$\alpha = \frac{q_2/c_2}{q_1/c_1} \tag{2}$$

Obviously, for a Langmuir isotherm the selectivity is constant and equal to the ratio a_2/a_1. Consequently, the Langmuir model cannot account for experimental results where the selectivity changes with increasing concentration of the components of the mixture in the mobile phase. It certainly cannot account for changes in the selectivity order observed when the isotherms determined at constant relative concentration, c_2/c_1, cross each other at a certain intermediate value of the concentration. Another approach is necessary and a more complex isotherm than the classical Langmuir model must be used.

General statistical mechanics background
       The following derivation (see the next section) can be justified by some general considerations of statistical thermodynamics[4]. It is well known that the concentration of the solute in the stationary phase, q_i, is proportional to the average number of molecules present in the stationary phase at equilibrium, *i.e.*, to N_i. It has been shown[4] that this number is given by

$$N_i = \lambda_i \cdot \frac{\partial \ln \Xi}{\partial \lambda_i} \tag{3}$$

where $\varXi$ is the grand partition function of the system:

$$\varXi = \sum_{N_1} \cdots \sum_{N_k} Q(N_1, N_2, \ldots, N_k) \prod_{j=1}^{k} \lambda_j^{N_j} \tag{4}$$

Accordingly, the competitive isotherms are best represented by the ratio of two polynomials. When $k = 2$, i.e., with two components,

$$\varXi = 1 + Q_1\lambda_1 + Q_2\lambda_2 + Q_{12}\lambda_1\lambda_2 + Q_{11}\lambda_1^2 + Q_{22}\lambda_2^2 + \ldots \tag{5}$$

where Q_i and Q_{ij} are canonical partition functions and λ_i is the activity of component i. If the activity is small, $\varXi$ can be approximated by a second-order polynomial. Obviously $\lambda_i(\partial\varXi/\partial\lambda_i)$ is also a polynomial. From the above discussion, for multi-component systems the denominator of the competitive isotherm equation for each component should be the same.

Hence on a general basis, statistical mechanics predicts that competitive isotherms for multi-component systems are best represented by the ratio of two polynomials. The denominators of the isotherms are the same for all compounds. A set of second-degree polynomials is probably the best compromise between model errors (which decrease with increasing degree of the polynomial) and adjustment errors (which become significant in the fitting of experimental data with equations that have too many parameters).

The modified Langmuir model

To account for competitive multi-component adsorption, we propose to modify the Langmuir model by assuming that the rates of adsorption and desorption of each of the compounds studied are linear functions of the concentrations of both compounds in the stationary phase (rate of adsorption) and in the mobile phase (rate of desorption). This assumption permits molecular interactions in both the solution and the sorbed monolayer to be taken into account.

The corresponding kinetic equations for the two compounds involved are written as follows[5]:

$$\frac{\partial q_1}{\partial t} = K_{a1}(q_s - \alpha_{11}q_1 - \alpha_{12}q_2)c_1 - K_{d1}(c_s - \beta_{11}c_1 - \beta_{12}c_2)q_1 \tag{6}$$

$$\frac{\partial q_2}{\partial t} = K_{a2}(q_s - \alpha_{21}q_1 - \alpha_{22}q_2)c_2 - K_{d2}(c_s - \beta_{21}c_1 - \beta_{22}c_2)q_2 \tag{7}$$

where K_a and K_d are the rates of adsorption and desorption, respectively, q_i and c_i are the concentrations of the two components of the mixture used in the stationary phase and the mobile phase, respectively, q_s and c_s are the saturation concentrations in the stationary and mobile phase, respectively, and t is time.

The values of α_{ij} and β_{ij} depend on the size of the molecules of the solvent(s) and solutes involved and on the strength of the interactions between these molecules. The classical case of the competitive Langmuir isotherm corresponds to $\alpha_{ij} = 1$ and $\beta_{ij} = 0$, for all combinations of i and j.

Equilibrium between the mobile phase and the stationary phase is reached when the concentrations of the two compounds are constant. Thus, we have

$$\frac{\partial q_i}{\partial t} = 0 \qquad i = 1, 2 \tag{8}$$

Combination of eqns. 6–8 gives a system of two linear equations with two unknowns, q_1 and q_2. The classical solution of this system is

$$q_1 = \frac{\Delta_1}{\Delta}; \qquad q_2 = \frac{\Delta_2}{\Delta} \tag{9}$$

where Δ, Δ_1 and Δ_2 are the three determinants of the coefficients of the system of equations:

$$\Delta = b_0 + b_1 c_1 + b_2 c_2 + b_{11} c_1^2 + b_{22} c_2^2 \tag{10}$$

$$\Delta_1 = a_1 c_1 + a_{12} c_1 c_2 + a_{11} c_1^2 \tag{11}$$

and

$$\Delta_2 = a_2 c_2 + a_{21} c_1 c_2 + a_{22} c_1^2 \tag{12}$$

The values of the different coefficients in these three equations are the following:

$$b_0 = K_{d1} K_{d2} c_s^2 \tag{13a}$$

$$b_1 = K_{a1} K_{d2} \alpha_{11} c_s - K_{d1} K_{d2} \beta_{21} c_s - K_{d1} K_{d2} \beta_{11} c_s \tag{13b}$$

$$b_2 = K_{a2} K_{d1} \alpha_{22} c_s - K_{d1} K_{d2} \beta_{12} c_s - K_{d1} K_{d2} \beta_{22} c_s \tag{13c}$$

$$b_{12} = K_{a1} K_{a2} (\alpha_{11} \alpha_{22} - \alpha_{12} \alpha_{21}) + K_{d1} K_{d2} \beta_{11} \beta_{22} + K_{d1} K_{d2} \beta_{12} \beta_{21} -$$

$$K_{a1} K_{d2} \alpha_{11} \beta_{22} - K_{a2} K_{d1} \alpha_{22} \beta_{11} \tag{13d}$$

$$b_{11} = K_{d1} K_{d2} \beta_{11} \beta_{21} - K_{a1} K_{d2} \alpha_{11} \beta_{21} \tag{13e}$$

$$b_{22} = K_{d1} K_{d2} \beta_{12} \beta_{22} - K_{d1} K_{a2} \beta_{12} \alpha_{22} \tag{13f}$$

$$a_1 = K_{a1} K_{d2} c_s q_s \tag{14a}$$

$$a_{12} = K_{a1} K_{a2} q_s \alpha_{22} - K_{a1} K_{a2} \alpha_{12} q_s - K_{a1} K_{d2} q_s \beta_{22} \tag{14b}$$

$$a_{11} = -K_{a1} K_{d2} q_s \beta_{21} \tag{14c}$$

$$a_2 = K_{a2} K_{d1} c_s q_s \tag{14d}$$

$$a_{21} = K_{a1}K_{a2}q_s\alpha_{11} - K_{a1}K_{a2}\alpha_{21}q_s - K_{a2}K_{d1}q_s\beta_{11} \tag{14e}$$

$$a_{22} = -K_{a2}K_{d1}q_s\beta_{12} \tag{14f}$$

If one divides all the coefficients in the sets 10 and 11 above by the first coefficient, b_0, and let

$$K_{ij} = \frac{k_{ij}}{b_0} \tag{15}$$

where k_{ij} represents any of the coefficients a_i, a_{ij}, b_i or b_{ij}, except b_0, we may now write the equations for the two competitive isotherms of the modified Langmuir equation:

$$q_1 = \frac{A_1c_1 + A_{12}c_1c_2 + A_{11}c_1^2}{1 + B_1c_1 + B_2c_2 + B_{12}c_1c_2 + B_{11}c_1^2 + B_{22}c_2^2} \tag{16}$$

and

$$q_2 = \frac{A_2c_2 + A_{21}c_1c_2 + A_{22}c_2^2}{1 + B_1c_1 + B_2c_2 + B_{12}c_1c_2 + B_{11}c_1^2 + B_{22}c_2^2} \tag{17}$$

When $\alpha_{ij} = 1$ and $\beta_{ij} = 0$. eqns. 16 and 17 reduce to eqn. 1, the conventional Langmuir isotherm. In the general case, the two isotherm equations depend on eleven parameters, which is too many for most practical applications. It becomes very difficult to determine these parameters accurately using the conventional fitting techniques. Convergence is not assured and is rarely achieved. It would be useful, for most practical applications, to reduce the number of independent parameters in eqns. 16 and 17. We observe that four of these parameters, A_{11}, A_{22}, B_{11} and B_{22}, depend only on the original coefficients β_{12} and β_{21} and become zero if these coefficients of the kinetic equation are zero. These coefficients account for the influence of the concentration of one component of the binary mixture on the rate of desorption of the other; we can neglect this interaction, as a first approximation. We then obtain the following extension of the Langmuir equations:

$$q_1 = \frac{A_1c_1 + A_{12}c_1c_2}{1 + B_1c_1 + B_2c_2 + B_{12}c_1c_2} \tag{18}$$

and

$$q_2 = \frac{A_2c_2 + A_{21}c_1c_2}{1 + B_1c_1 + B_2c_2 + B_{12}c_1c_2} \tag{19}$$

This system is simpler than the previous one. Nevertheless, it contains seven constants, which cannot be predicted from first principles and have to be determined by a least-square fitting of the experimental data on eqns. 18 and 19. In addition to the terms of the classical Langmuir equations, it contains only cross terms, accounting for

interactions between the two components of the mixture studied. The coefficients depend on the rate constants of the adsorption and the desorption of the two components, and on the α and β coefficients, which account for molecular interactions.

One of the major advantages of the isotherm equations derived above (eqns. 16 and 17) is that the coefficients in these equations are related to the rate constants (eqns. 6 and 7). This relationship also justifies the simplification which leads from eqns. 16 and 17 to eqns. 18 and 19.

Least-square fitting

We discuss here the fitting procedure of the experimental data with eqns. 18 and 19. We have taken the data regarding the competitive adsorption isotherms of *cis*- and *trans*-androsterone measured previously[2], and fitted them with eqns. 18 and 19. The least-square fitting of data on a non-linear model for a multi-component system can be considered as a multi-variant, multi-objective, non-linear programming problem. Although the field of theoretical results in non-linear programming is rich and many methods are available, solving practical problems remains difficult.

TABLE I

FITTING OF THE FIRST COMPOUND

Note: convergence criterion met.

Non-linear least-squares summary statistics; dependent variable Q_1:

Source	Degrees of freedom	Sum of squares	Mean square
Regression	5	110763.94687	22152.78937
Residual	18	5.84413	0.32467
Uncorrected total	23	110769.79100	
Corrected total	22	50460.28589	

Parameter	Estimate	Asymptotic std. error	Asymptotic 95% confidence interval	
			Lower	Upper
A_1	8.5604	0.1041	8.3417	8.7791
A_{12}	−0.0031	0.0233	−0.0520	0.0457
B_1	0.0160	0.0012	0.0135	0.0185
B_2	0.0157	0.0042	0.0068	0.0246
B_{12}	0.0001	0.0001	−0.0001	0.0003

Asymptotic correlation matrix of the parameters:

Correlation	A_1	A_{12}	B_1	B_2	B_{12}
A_1	1.0000	0.1521	0.6052	0.3757	−0.2676
A_{12}	0.1521	1.0000	−0.6304	0.9646	0.8617
B_1	0.6052	−0.6304	1.0000	−0.4415	−0.8980
B_2	0.3757	0.9646	−0.4415	1.0000	0.7102
B_{12}	−0.2676	0.8617	−0.8980	0.7102	1.0000

We have defined our problem as the search for the set of parameters which minimizes the value of the following function:

$$\sum_{k=1}^{n} [y_{1,k} - F_1(a_i,b_i) + y_{2,k} - F_2(a_i,b_i)]^2 \tag{20}$$

where $y_{i,k}$ ($i = 1, 2$) is the concentration of component i in the stationary phase, determined during the measurement number k, n is the number of experimental points and $F_i(a_i,b_i)$ is the right-hand side of eqn. 17 ($i = 1$) or 15 ($i = 2$).
    The reason for selecting this criterion is as follows. Let

$$y_1 = F_1(a_i,b_i) + \varepsilon_1 \tag{21}$$

and

$$y_2 = F_2(a_i,b_i) + \varepsilon_2 \tag{22}$$

where ε_i ($i = 1,2$) are the errors made in the estimate of the concentration in

TABLE II

FITTING OF THE SECOND COMPOUND

Note: convergence criterion met.

Non-Linear least squares summary statistics; dependent variable Q_2:

Source	Degrees of freedom	Sum of squares	Mean square
Regression	2	92218.884725	46109.442362
Residual	21	108.826675	5.182223
Uncorrected total	23	92327.711400	
Corrected total	22	39940.694774	

Parameter	Estimate	Asymptotic std. error	Asymptotic 95% confidence interval	
			Lower	Upper
A_2	8.7174	0.1502	8.4050	9.0298
A_{21}	−0.0195	0.0075	−0.0351	−0.0039

Asymptotic correlation matrix of the parameters:

Correlation	A_2	A_{21}
A_2	1.000	−0.909
A_{21}	−0.909	1.000

the stationary phase. The condition chosen is equivalent to the minimization of

$$\sum_{k=1}^{n} (\varepsilon_{1,k} + \varepsilon_{2,k})^2.$$

From the experimental procedure[2], it is obvious that both sets of errors, $\varepsilon_{1,k}$ and $\varepsilon_{2,k}$, which have the same origin, are statistically equivalent. Accordingly, the procedure followed here will give an estimate of the parameters of the isotherm equations which is statistically equivalent to that obtained by minimizing the error made in the estimate for each component separately.

RESULTS

The results are reported in Tables I and II and Figs. 1–4. They were obtained using the SAS computer program package.

Tables I and II show the results determined by the SAS program for the isotherm of the first and second components, respectively. Using the values of the parameters in these tables, we calculated the theoretical isotherms corresponding to the three sets of
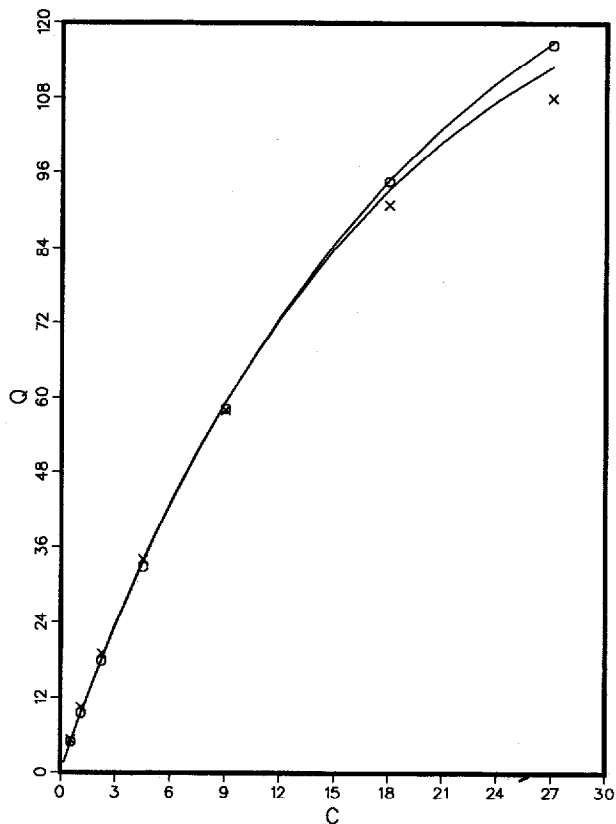

Fig. 1. Comparison between the experimental isotherm data (points) measured by frontal analysis, using solutions of constant relative composition of the two isotherms, and the result of the least-square fitting of these data with eqns. 18 and 19. ○, *cis*-; +, *trans*-Androsterone. Relative concentrations, *cis*- to *trans*-androsterone = 1:1. Concentrations in mg/ml.
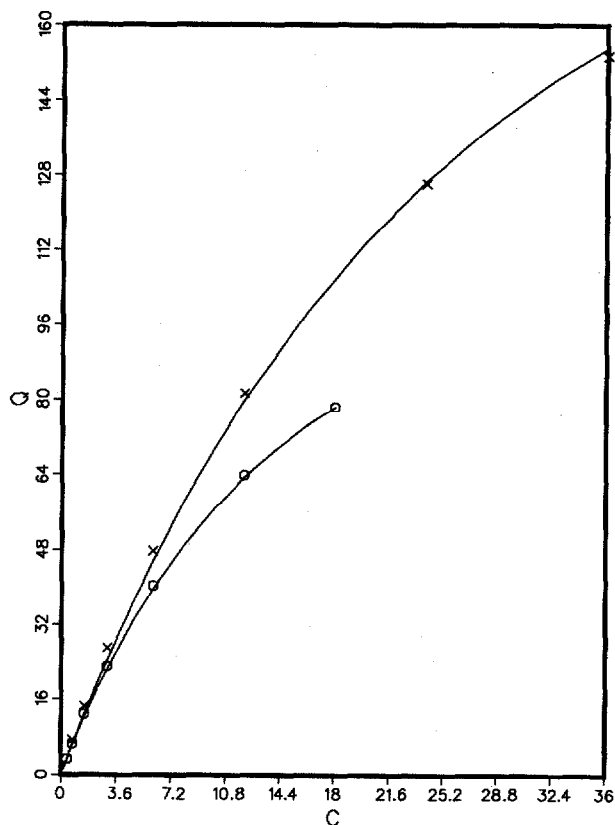
Fig. 2. As Fig. 1 with relative concentrations *cis*- to *trans*-androsterone = 1:2.

data points which had been determined previously[2]. These sets are obtained by frontal analysis[6], using increasingly concentrated steps of binary mixtures of the two isomers with constant relative concentrations of the two isomers (2:1, 1:1 and 1:2).

The calculated isotherms and the data points are plotted on Figs. 1–3. There is good agreement between the experimental data and the calculated isotherms (see the statistical data in the tables and figures). The model permits a good representation of the experimental results obtained at high concentrations, which is not surprising with 7 degrees of freedom instead of 4 for a Langmuir isotherm. The agreement between the model and the experimental data is less good at low concentrations, however. The relative retention determined from the retention times of very small size samples of the two androsterones isomers is 1.2; the model gives $\alpha_2/\alpha_1 = 1.02$ instead. All attempts at forcing the least-square fit procedure to give a larger ratio A_2/A_1 in order to obtain a larger relative retention at low concentrations gave poor fits of the experimental data at high concentrations. This lack of a good fit between the experimental data and the model would create problems in the simulation of the elution and separation of large-size samples of binary mixtures of these isomers.

Fig. 4 shows a three-dimensional plot of the two isotherms, in a space (C_1, C_2,
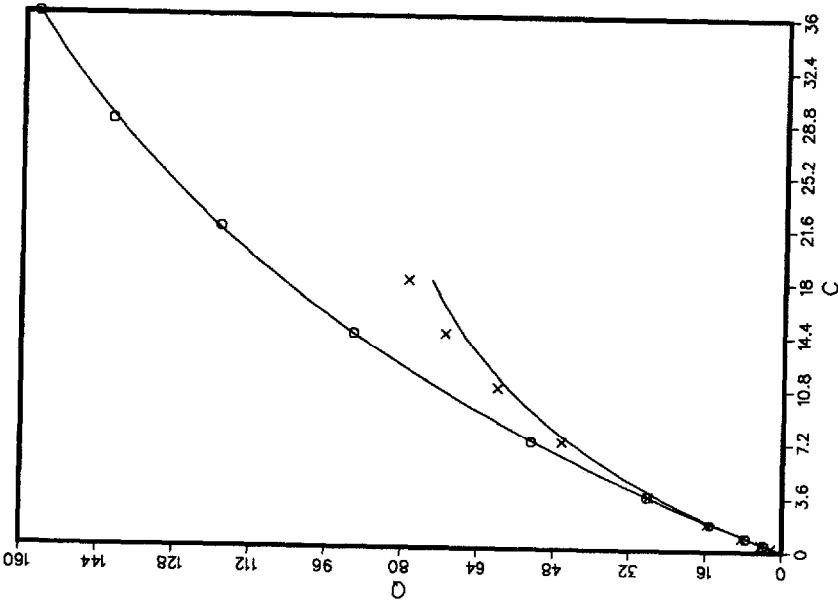
Fig. 3. As Fig. 1 with relative concentrations *cis*- to *trans*-androsterone = 2:1.
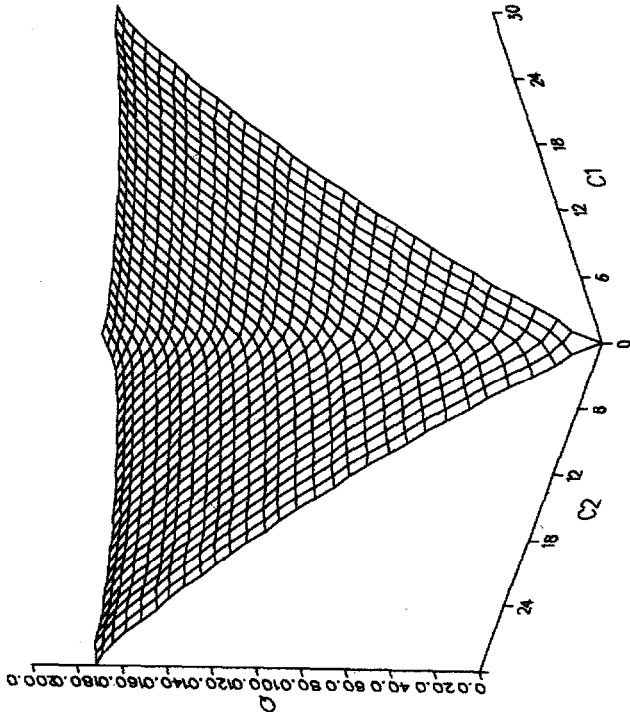
Fig. 4. Three-dimensional plot of the two component isotherms, showing the slightly twisted intersection line.

Q_i). The isotherms of the two isomers in a vertical plane ($C_2/C_1 = a$) intersect because the curve which is the intersection between the two isotherm surfaces is twisted and not planar. The Langmuir isotherm predicts a planar intersection between these two surfaces and could not be used to account for experimental results in this instance[2].

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