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MASTER

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BIOMOLECULAR DYNAMICS BY COMPUTER ANALYSIS

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ABSTRACT

As numerical tools (computers and display euqipment) become more powerful and the atomic structures of important biological molecules become known, the importance of detailed computation of nonequilibrium biomolecular dynamics increases. In this manuscript we report results from a well developed study of the hydrogen bonded polypeptide crystal acetanilide, a model protein. Directions for future research are suggested.

1. Introduction

It is over ten years since Davydov[1] first suggested a self-trapping mechanism in α-helix proteins which would give rise to a soliton-like excitation on these biologically important molecules. This pioneering work has led to extensive theoretical and experimental investigations on both sides of the Atlantic. In this paper we would like to summarize some of the work carried out in this area at Los Alamos over the last 12 months. Full details of the topics discussed here will appear elsewhere.[2-5]

This study begins with an investigation into solitons in acetanilide (ACN), a crystalline material with many properties in common with α-helix proteins. This work extends in a natural manner to a theory of self-trapping, applicable to many discrete systems, described by a new set of equations which we have called the Discrete Self-Trapping (DST) equations. These equations are a discrete, generalized form of the nonlinear Schrödinger (NLS) equation. The introduction of discreteness introduces many novel mathematical features which still require further study. Although these equations were developed to describe solitons on large discrete lattices, it turns out that the same equations for a small number of lattice sites have important applications to the study of soliton-like vibrational modes of small molecules.

2. Solitons in Acetanilide

When crystalline acetanilide, $(CH_3COHNC_6H_5)_x$ or ACN, is cooled below room temperature, a new spectral line in both Raman and infrared absorption measurements is observed at 1650 cm^{-1} (see Fig. 1). This band is related to other amide-I bands (CO bond stretching) which can be explained using conventional exciton theory, but until recently this new band has been of uncertain origin.

The importance of ACN in relation to Davydov solitons on α-helix proteins is that ACN contains chains of hydrogen-bonded amide groups with similar character to those occuring in proteins, and that ACN is much more amenable to experimental work than proteins.

A recent theory[2] to account for the anomalous amide-I band proposed assigning the effect to a soliton-like excitation. The mechanism is similar to that put forward by Davydov for the α-helix, namely a self-trapping due to an interaction between the localized amide-I bond energy and lattice distortion. However in the ACN case only the hydrogen-bonded proton is displaced rather than the whole lattice structure.

This original theory[2] was based on a simple nearest-neighbor coupling model and led to reasonable agreement with experiments. In a more recent study[3] we have attempted to refine the model by including couplings between adjacent unit cells, and by a more detailed investigation of the various soliton-like modes arising in the crystal. We confine our attention to stationary solitons, i.e. those for which the modulus of probability amplitude $|a_{n\alpha}|$ for the amide-I quanta is constant in time (at least to a good approximation, i.e. slowly varying in time). Here the amplitudes are labeled by unit cell (n) and by position within the unit cell (α = 1,2,3 or 4). In this case, following an appropriately modified version of Davydov's Theory[1,2], we are led to the set of equations[3]

$$i\hbar\dot{\bar{a}}_n = \mathrm{diag}[(E_o+E_s-\gamma|a_{n1}|^2 , \ldots]\bar{a}_n \qquad (2.1)$$

$$+ [\tilde{M}\bar{a}_n + \tilde{N}\bar{a}_{n+1} + \tilde{N}^T a_{n-1}] , \; n = 1,2, \ldots$$

where $E_o + E_s$ is the exciton energy and γ is a measure of the nonlinearity of the hydrogen bond. The dot over the $\bar{a}_n$ denotes differentiation with respect to time, and 4 × 4 matrices $\tilde{M}$ and $\tilde{N}$ contain dipole coupling terms between sites in the nth and adjacent units cells respectively. The 4-vector $\bar{a}_n \equiv (a_{n1}, a_{n2}, a_{n3}, a_{n4})$. The 4 × 4 matrix $\mathrm{diag}[d_1, \ldots]$ is a real diagonal matrix with diagonal elements $d_1, \ldots$. If we work with a finite crystal with N unit cells, the Eqs. (2.1) can be written in full matrix form

$$i\dot{\bar{A}} + \gamma\,\mathrm{diag}[|a_{n1}|^2 , |a_{n2}|^2 , \ldots]\bar{A} + \varepsilon M\bar{A} = 0 \qquad (2.2)$$

Here we have scaled out $\hbar$ by $t \to \hbar t$ and scaled out $E_o + E_2$ by the transformation $\bar{A} \to \bar{A}\exp[-i(E_o+E_s)]$. The 4N vector $\bar{A}$ has elements $\bar{a}_1, \bar{a}_2, \ldots$, $\bar{a}_N$, M is the 4N × 4N block tridiagonal matrix

$$M = -\frac{1}{\varepsilon}\begin{bmatrix} \tilde{M} & \tilde{N} & & 0 & \\ \tilde{N}^T & \tilde{M} & \tilde{N} & & \\ & & \cdot & \cdot & \\ 0 & & & \tilde{N}^T & \tilde{M} \end{bmatrix} \qquad (2.3)$$

and ε is a scaling factor chosen such that the largest element of M is unity.

We define stationary solutions of (2.2) to be those having the form

$$\bar{A} = \bar{\phi} \exp(i\omega t) \qquad (2.4)$$

where $\bar{\phi}$ is a time independent 4N-vector. Inserting this into (2.2) we get a nonlinear eigenvalue problem for ω and $\bar{\phi}$

$$-\omega\bar{\phi} + \gamma \operatorname{diag}[|\bar{\phi}|^2]\bar{\phi} + \varepsilon M\bar{\phi} = 0 \ . \qquad (2.5)$$

Solutions of (2.5) for fixed values of γ,ε and ω can be found by Newton iterative methods[3]. Once a solution is known, it can be continued as a function of the parameters by using numerical path following techniques[6]. Some typical solutions are shown in Fig. 2. Figures 2(a) and (c) show two types of soliton-like solutions for large γ values: Fig. 2(b) shows a solution calculated for small γ. All three solutions lie on one continuous branch of solutions. Note that the four sites in each unit cell are labeled □,+,o,x respectively, and that the solitons are large γ values are much more localized than in the case where the nonlinearity is small. Numerical tests on the full evolution equations (2.2) suggest that the solution shown in Fig. 2(a) is stable but that the other solutions may be unstable to perturbations. We argue that the "anamolous amide-I" line in Fig. 1 can be explained in the presence of solitons of the type shown in Fig. 2(a), with the energy focused essentially on one peptide group in the unit cell[3].

3. The Discrete Self-Trapping Equations

In the study of the ACN problem, many other, more complicated, stationary solutions were found[3]. In addition, the evolution and self-trapping of states starting out as arbitrary nonlocalized distributions of energy was not clearly understood. It was also noticed that Eq. (2.2) applied to many other systems for which self-trapping was known to occur. With appropriate choices of the matrix M, this system can model solitons on α-helix proteins or globular proteins[7] or polarons in a crystal[8]. Furthermore, these equations could also be used to model the vibrational states of polyatomic molecules[4], a problem for which (2.2) with only a small number of sites would be appropriate. If M is chosen to be tridiagonal, with appropriately chosen coefficients, a finite difference version of the nonlinear Schrödinger (NLS) equation is obtained. In view of the general importance of (2.2), it was decided to name the system the Discrete Self-Trapping (DST) equation

$$i\dot{\bar{A}} + \gamma\, \mathrm{diag}[|\bar{A}|^2]\bar{A} + \varepsilon M\bar{A} = 0 \tag{3.1}$$

where now A is a complex n-vector, γ and ε are real parameters, and M is an arbitrary real symmetric n × n matrix[5]. In view of the application to molecular vibrational analysis for small n, and as a first step to understanding the behavior of the equations for large n, we have carried out an initial investigation of (3.1) for n = 1,2,3 and 4 and for a few specific choices of M.

Some general properties of the DST equation (3.1) are worth listing before progressing to specific examples. The DST equation can be derived from the Lagrangian

$$L = \sum_j [\tfrac{1}{2} i(A_j^* \dot{A}_j - A_j \dot{A}_j^*) + \tfrac{1}{2}\gamma |A_j|^4] + \varepsilon \sum_{j,k} m_{jk} A_j^* A_k \tag{3.2}$$

where the m_{jk} are the elements of M, $m_{jk} = m_{kj}$. The Hamiltonian (energy) is

$$H = -\tfrac{1}{4}\gamma \sum_j |A_j|^4 - \varepsilon \sum_{j,k} m_{jk} A_j^* A_k \ . \qquad (3.3)$$

If we define the number N as

$$N = \sum_j |A_j|^2 \qquad (3.4)$$

then it is straightforward to show that both H and N are constant in time.

If all the diagonal elements of M are equal ($m_{11} = \ldots = m_{nn} = m$), the phase transformation $\bar{A} = \bar{B}\exp(imt)$ gives a DST equation for $\bar{B}$ with zeros on the diagonal of M. We have considered only the case in which the diagonal elements of M are zero.

In the limit $\gamma \to 0$, (3.1) reduces to the linear, dispersive system

$$i\dot{\bar{A}} + \varepsilon M\bar{A} = 0 \qquad (3.5)$$

which is completely integrable. In the limit $\varepsilon \to 0$ (or equivalently $\gamma \to \infty$ up to a scaling of t), the equations decouple to give the nonlinear system

$$i\dot{\bar{A}} + \gamma\ \mathrm{diag}[|A|^2]A = 0 \qquad (3.6)$$

which can also be solved explicitly. We are interested in the case $\gamma,\varepsilon \neq 0$ in which there is an interaction between dispersion and nonlinearity.

As in the case of the ACN investigation, stationary solutions of the DST equations defined by (2.4) play an important role in the theory. In many cases it is possible to obtain exact solutions of (2.5) in closed form, and in many physical situations these solutions can be expected to play a major role. Even when no analytic form for a stationary solution is available, numerical path-following techniques[6] can be used to study these solutions as functions of γ or ε, using the solutions of the reduced problems (3.5) or (3.6) as starting points.

Another advantage of working with stationary solutions is that the linear stability of such solutions can easily be calculated[5,9]. In the case where $\bar{\phi}$ is real, it is necessary to examine the eigenvalues of the system

$$\det[JC-\lambda^2 I] = 0 \tag{3.7}$$

where the n × n matrix J is the Jacobian of the equations (2.5)

$$J = -\omega I + 3\gamma \,\mathrm{diag}[\phi_i^2] + \varepsilon M \tag{3.8}$$

and -C is the matrix multiplying $\bar{\phi}$ in (2.5)

$$C = \omega I - \gamma \,\mathrm{diag}[\phi_i^2] - \varepsilon M \,. \tag{3.9}$$

It is straightforward to show that if $(\omega,\bar{\phi})$ is a stationary solution to (2.5), then a <u>necessary</u> condition for the stability of this solution is that all the λ_i^2 in (3.7) are purely real and negative. Conversely, if at least one of the λ_i^2 is not purely real and negative, this is a <u>sufficient</u> condition for instability. Numerical test suggest that the necessary condition for stability is usually sufficient also. The eigenvalues of (3.7) can be evaluated numerically if necessary.

It is useful to adopt a simple notation to label the different solutions that can occur in considering stationary solutions of (3.1), i.e. those satisfying (2.4), (2.5). Firstly, note that the equations are invariant under a gauge transformation $\bar{A} \rightarrow \bar{A}\exp(i\alpha)$, so without loss of generality we can choose the first component of $\bar{\phi}$ to be real.

In many cases, all the components of $\bar{\phi}$ will be real, and it is convenient to label them according to their behavior as $\gamma \to \infty$. From (2.4) and (3.6) we deduce that in this limit (for real $\bar{\phi}$)

$$-\omega\phi_i + \gamma\phi_i^3 = 0 \quad i = 1,\ldots,n \tag{3.10}$$

so either $\phi_i = 0$ or $\pm(\omega/\gamma)^{\frac{1}{2}}$. If we further assume that the $\bar{\phi}$ has been normalized so that N in (3.4) is unity (this is always possible by a rescaling of γ), then either $\phi_i = 0$ or $\phi_i = \pm 1/\sqrt{K}$, where K is the number of nonzero components of $\bar{\phi}$ in the limit $\gamma \to \infty$. We denote these nonzero components of $\bar{\phi}$ by ↑ or ↓ respectively. The components of $\bar{\phi}$ which <u>tend</u> to zero as $\gamma \to \infty$ are denoted by the symbol •, whereas those components of $\bar{\phi}$ which are zero for all γ are denoted by 0. Finally, complex components of $\bar{\phi}$ are denoted by *. Only solutions which are independent under the permutation group of M are listed.

We now examine some special cases for various n, considering both stationary and non-stationary solutions. Recall that we are restricting ourselves to the cases where the diagonal elements of M can be transformed to zero, and we normalize N to unity in (3.4).

1) <u>The case n = 1</u>

In this case, M = 0 and there is only one solution of (3.1) the stationary solution $\underline{A} = \exp(i\gamma t)$, denoted by (↑). This stable solution corresponds to a single harmonic oscillator.

2) <u>The case n = 2</u>

In view of our restrictions on M, the only case to consider is

$$M = \begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}.$$

A straightforward analysis of (2.5) shows that the only stationary solutions of (3.1) are those shown in Table 1.

Table 1

Stationary Solutions of (3.1) for the case $n = 2$

Mode Description	Mode Amplitudes	ω	H
↑↑	$\phi_1 = \phi_2 = 1/\sqrt{2}$	$\gamma/2+\varepsilon$	$-\gamma/4-\varepsilon$
↑↓	$\phi_1 = -\phi_2 = 1/\sqrt{2}$	$\gamma/2-\varepsilon$	$-\gamma/4+\varepsilon$
↑·	$\phi_{1,2} = \{\frac{1}{2}[1\pm(1-4\varepsilon^2/\gamma^2)^{\frac{1}{2}}]\}^{\frac{1}{2}}$ $(\gamma > 2\varepsilon)$	γ	$-\gamma/2-\varepsilon^2/\gamma$

These solution curves are shown in Fig. 3, with unstable solutions shown by dotted lines. At $\gamma = 0$ there are two branches, (↑↑) and (↑↓) corresponding to the two eigenvectors of M. At $\gamma = 2\omega/\varepsilon$ the (↑↑) branch bifurcates to give an additional (↑·) branch. The (↑↓) and (↑·) branches are stable, whereas the (↑↑) branch loses stability at the bifurcation point.

In order to study non-stationary solutions of the $n = 2$ case, it is simplest to change to a new set of variables. Writing $A_1 = a \exp(i\theta_1)$, $A_2 = b \exp(i\theta_2)$, with $a^2 + b^2 = N = 1$, then it can be shown that (3.1) reduces to two equations for a and the phase difference $\Theta = \theta_1 - \theta_2$.

$$\dot{a} = \varepsilon(1-a^2)^{\frac{1}{2}} \sin\Theta$$

$$\dot{\Theta} = \gamma(2a^2-1) + \varepsilon \frac{(1-2a^2)}{a(1-a^2)^{\frac{1}{2}}} \cos\Theta \qquad (3.11)$$

The phase plane diagram for this system is equivalent to a contour plot of constant energy solutions. In these variables we have

$$H = -\tfrac{1}{4}\gamma(1+2a^4-2a^2) - 2\varepsilon a(1-a^2)^{\frac{1}{2}} \cos\theta\ . \qquad (3.9)$$

In Figs. 4 and 5 we show the $a - \theta$ phase plane for the case $\gamma > 2\varepsilon$ ($\gamma = 4\varepsilon$) and $\gamma < 2\varepsilon$ ($\gamma = \varepsilon$) respectively. The stationary solutions (Table 1) correspond to fixed points in these phase planes: $(\uparrow\uparrow)$, $(\uparrow\downarrow)$ corresponds to $a = 1/\sqrt{2}$ and $\theta = 0,\pi$ respectively, and $(\uparrow\cdot)$ (for $\gamma > 2\varepsilon$) is a fixed point at $\theta = 0$ and a equal to one of the ϕ values in Table 1.

It is clear that the solution $(\uparrow\uparrow)$ is a stable fixed point for $\gamma < 2\varepsilon$: for $\gamma > 2\varepsilon$ it turns into an unstable saddle point and the two new stable centers corresponding to the $(\uparrow\cdot)$ solution appear. The $(\uparrow\downarrow)$ fixed point is a stable center for all γ.

The n = 2 case then furnishes a nice example of a nonlinear coupled oscillator system where all the solutions are well understood.

3) <u>The case n = 3</u>

We have studied only the case

$$M = \begin{bmatrix} 0 & 1 & 1 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \end{bmatrix} \qquad (3.10)$$

corresponding to three sites interacting with equal strengths. This system is invariant to any permutations of the three sites, so the distinct asymptotic stationary solutions turn out to be $(\uparrow\cdot\cdot)$, $(\uparrow\uparrow\cdot)$, $(\uparrow\downarrow 0)$, $(\uparrow\uparrow\uparrow)$, $(\uparrow\uparrow\downarrow)$, and $(\uparrow\ast\ast)$. It is possible to show that there is only one complex solution $(\uparrow\ast\ast)$: $\phi_1 = 1$, $\phi_2 = \phi_3^* = 1/\sqrt{3}\, \exp(2\pi i/3)$, $\omega = \gamma/3 - \varepsilon$. Two of the real solutions have analytic forms: $(\uparrow\uparrow\uparrow)$, $\phi = \phi = \phi = 1/\sqrt{3}$, $\omega = \gamma/3 + 2\varepsilon$; $(\uparrow\downarrow o)$, $\phi = -\phi = 1/\sqrt{2}$, $\phi = 0$, $\omega = \gamma/2 - \varepsilon$. No analytic solutions for the other three real solutions known have been found.

Solution curves for the real solutions are shown in Fig. 6. There is a bifurcation point at $(\omega,\gamma) = (7\varepsilon/2, 9\varepsilon/2)$. The $(\uparrow\cdot\cdot)$ branch becomes stable at the point at which $\partial\gamma/\partial\omega = 0$. The $(\uparrow\downarrow o)$ branch is unstable in the interval $3.5385\ldots < \omega/\varepsilon < 8$, where the first number is the only root of $x^3 - 8x - 16 = 0$. Stability calculations suggest that the complex stationary solution $(\uparrow**)$ is stable for all γ.

Numerical integrations of (3.1) for a variety of initial conditions have been made to study non-stationary solutions. A range of periodic, quasi-periodic, and chaotic solutions have been found[4,5]. It is possible that a different choice of M in the n = 3 case would give an integrable system, but this possibility is still an open question.

4) The case $n = 4$

Two cases have been studied for $n = 4$. One is an "equal-strength" interaction matrix with zeros on the diagonal and unit elements elsewhere. The other is a "nearest neighbor" interaction with $m_{ij} = 0$ if $|i - j| = 0,2$ and $m_{ij} = 1$ elsewhere. Detailed bifurcation diagrams for the stationary solutions in this case are reported elsewhere[5].

5) Higher values of n

The solutions described above for $n = 2,3,\ldots$ can be used to generate period $2,3,\ldots$ solutions to higher order problems with appropriate symmetries.

It is clear that one of the most interesting solutions will be the one corresponding to the single stationary soliton-like solution $(\uparrow\cdot\cdot\cdot\cdot\cdot\cdot\cdot)$. Experience with the ACN solutions suggest that this is always the one with the highest binding energy.

When this approach is applied to arbitrary globular proteins, the interaction matrix M is essentially random. In this case the energy of the single soliton localized at one site will vary from site to site. An important problem, as yet poorly understood, is how an arbitrary nonlocal energy distribution becomes focused into a single soliton or some similar mode. In more regular structures such as ACN the initial mechanism for self trapping is the Benjamin-Feir Instability[3], but there is no theory as yet for more random structures.

In considering the DST equation (3.1) for smaller n values, although the localized soliton states are stable, the "basin of attraction" for such states is small. Initial homogeneous energy distributions behave in a stochastic manner, and the energy does not become localized at any one site for any appreciable period. Presumably as n is increased, the tendency to self-trap becomes stronger, since it is known from the ACN and NLS studies that this occurs for large n. Further studies are under way to investigate this effect for both regular and random structures.

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References

1. A. S. Davydov and N. I. Kislukha, Phys. Status Solidi (b) 1973, 59, p. 465. See also A. S. Davydov, Phys. Scr., 1979, 20, p. 387, and the proceedings of this symposium for more recent results and bibliographies.

2. G. Careri, U. Buontempo, F. Carta, E. Gratton and A. C. Scott, Phys. Rev. Letts., 51 (1983), p. 304.

3. J. C. Eilbeck, P. S. Lomdahl and A. C. Scott, "Soliton Structure in Crystalline Acetanilide," Report LA-UR-84-785, to be published in Phys. Rev. B.

4. A. C. Scott, P. S. Lomdahl and J. C. Eilbeck, "Between the Local Mode and Normal Mode Limits," Report LA-UR-84-1604, submitted for publication.

5. J. C. Eilbeck, P. S. Lomdahl and A. C. Scott, "The Discrete Self-Trapping Equations," in preparation.

6. D. W. Decker and H. B. Keller, Comm. Pure and Appl. Math., 1981, 34, p. 149, M. Kubícek and M. Marek, "Computational Methods in Bifurcation Theory and Dissipative Structures," 1983, Springer-Verlag, New York.

7. P. S. Lomdahl, "Nonlinear Dynamics of Globular Proteins," Report LA-UR-82-2252; to appear in "Nonlinear Electrodynamics in Biological Systems," 1984, eds. W. R. Adey and A. F. Lawrence, Plenum Press, New York.

8. T. Holstein, Ann. Phys., 1959, 8, p. 325, p. 343.

9. J. Carr and J. C. Eilbeck, "Stability of Stationary Solutions of the Discrete Self-Trapping Equations," in preparation.

Figure Captions

Fig. 1 Infrared absorption spectrum of acetanilide.

Fig. 2 Some solutions of (2.5).

Fig. 3 Stationary solutions of DST for $n = 2$.

Fig. 4 Phase plane plot of DST for $n = 2$ and $\gamma > 2\varepsilon$.

Fig. 5 Phase plane plot of DST for $n = 2$ and $\gamma < 2\varepsilon$.

Fig. 6 Stationary solution of DST for $n = 3$ and M as in (3.10).

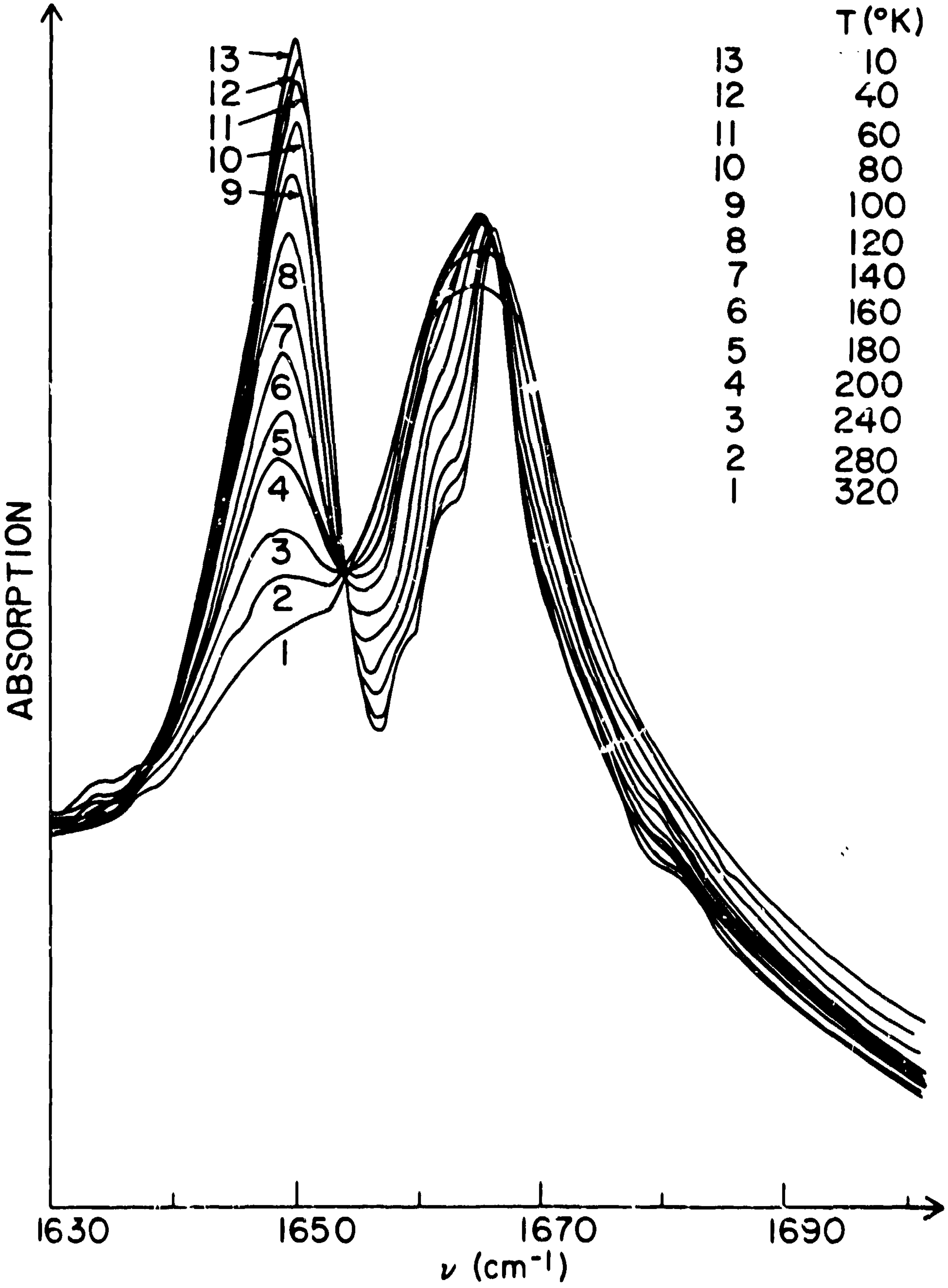
ABSORPTION
ν (cm⁻¹)
1630
1650
1670
1690
13
12
11
10
9
8
7
6
5
4
3
2
1
T (°K)
13 10
12 40
11 60
10 80
9 100
8 120
7 140
6 160
5 180
4 200
3 240
2 280
1 320

Fig. 1

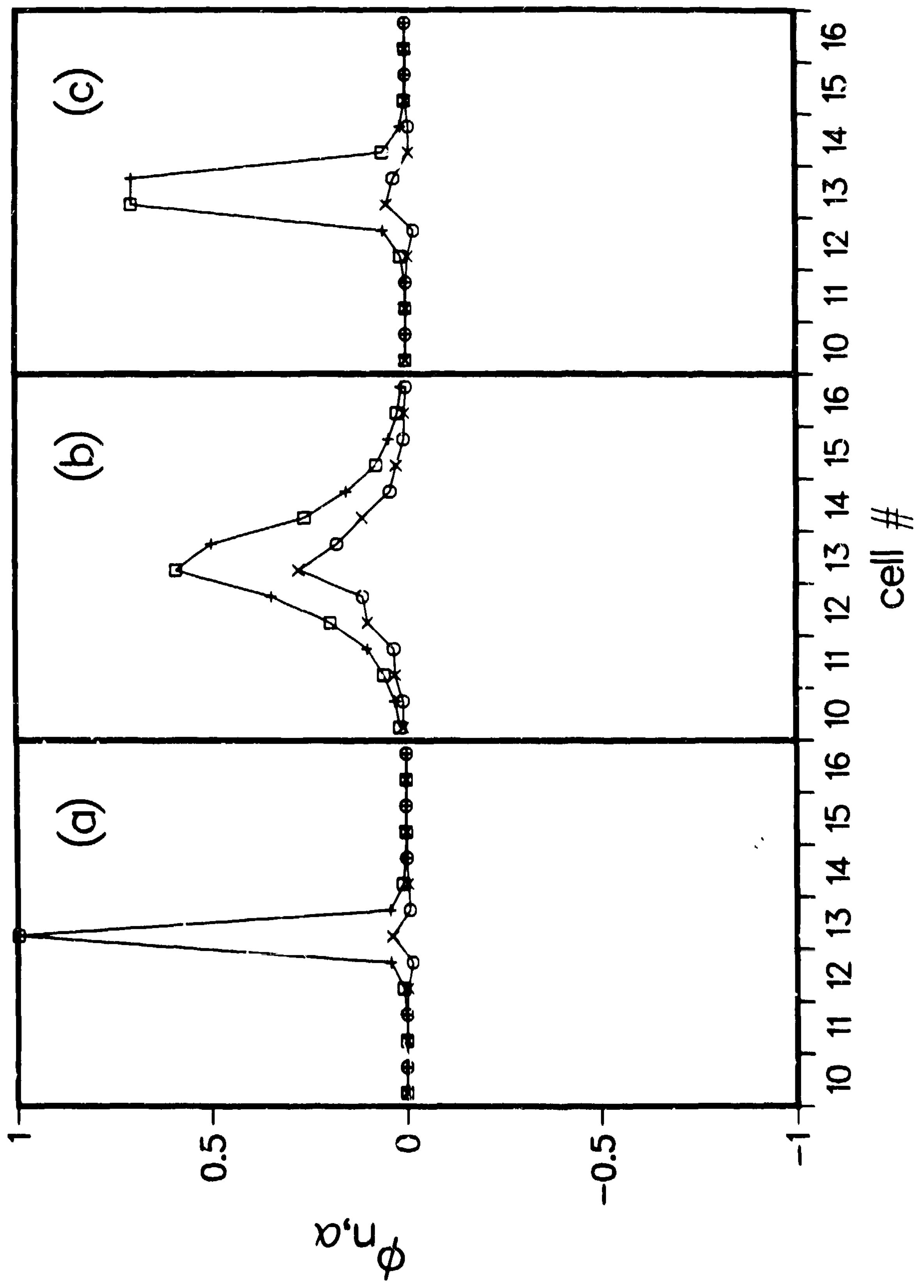

FIG. 2

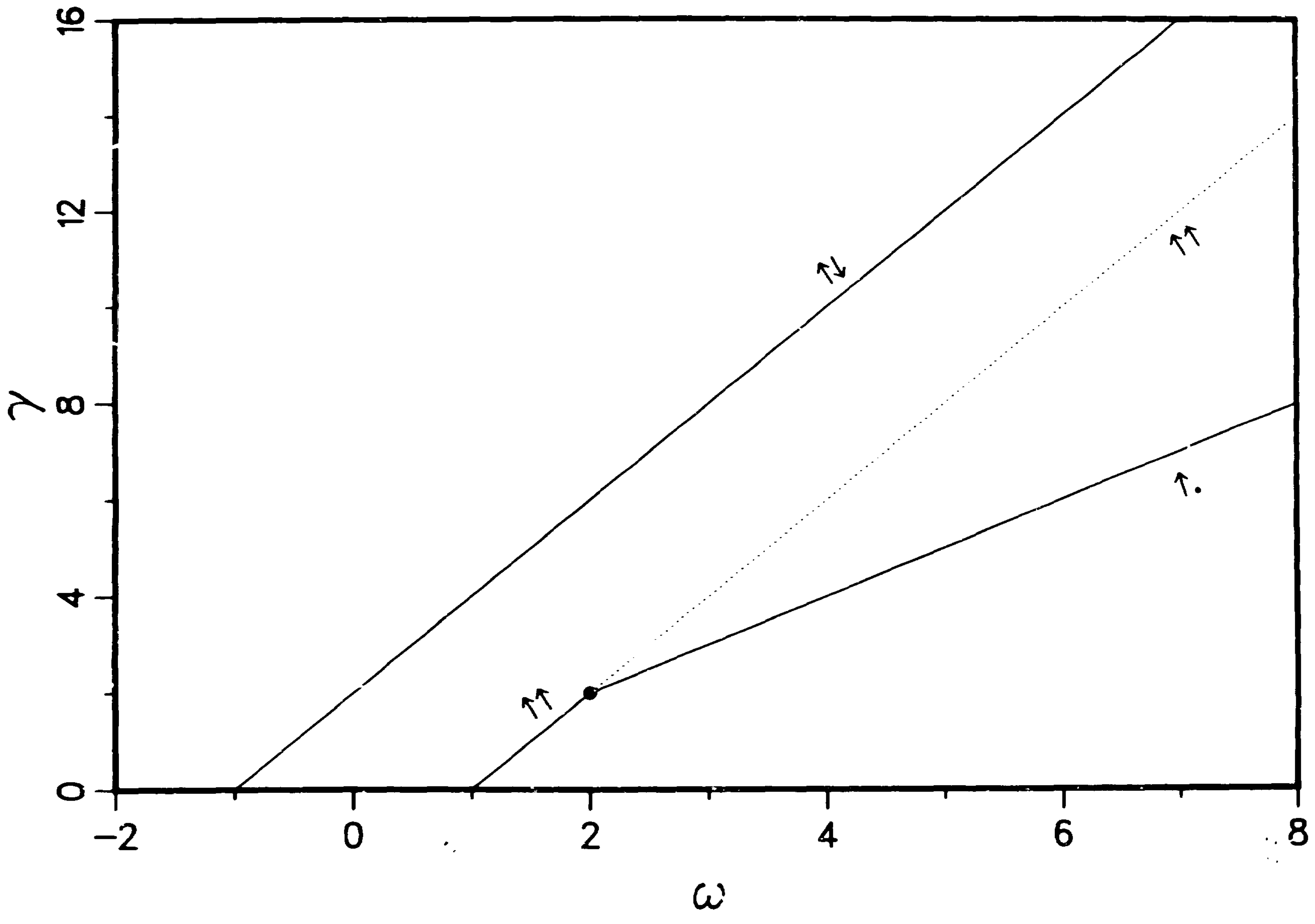

FIG. 3

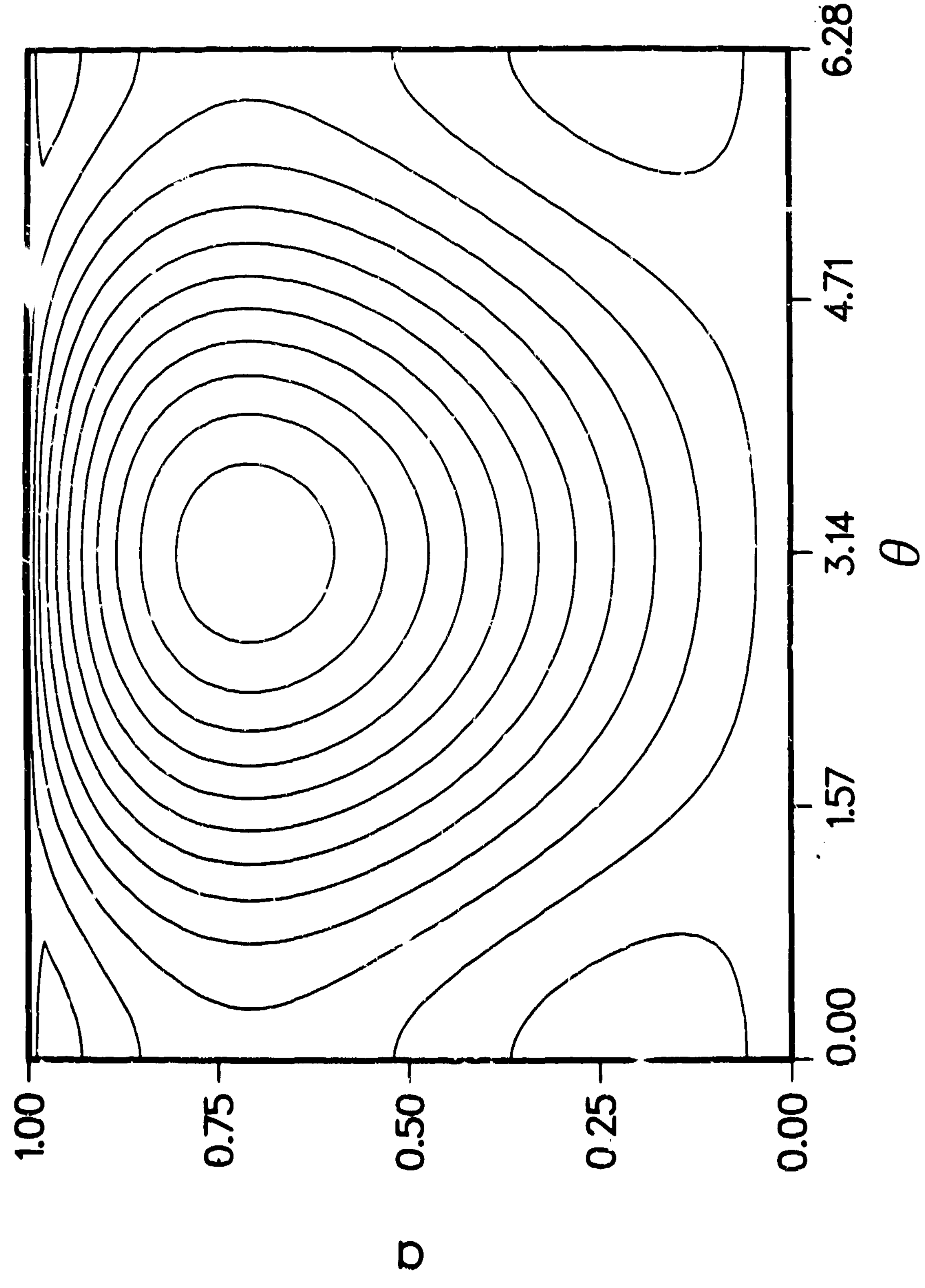

FIG. 4

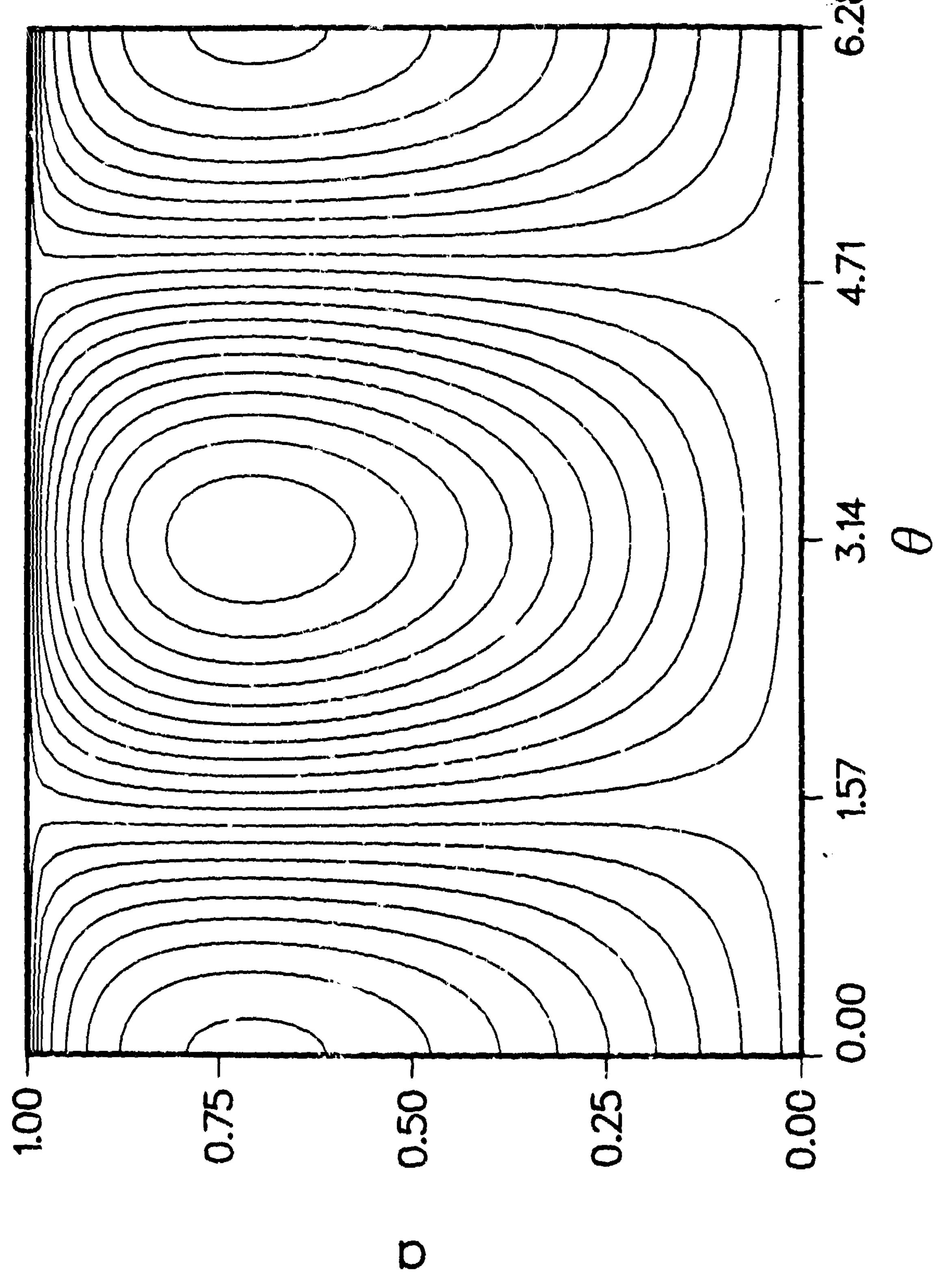

FIG. 5

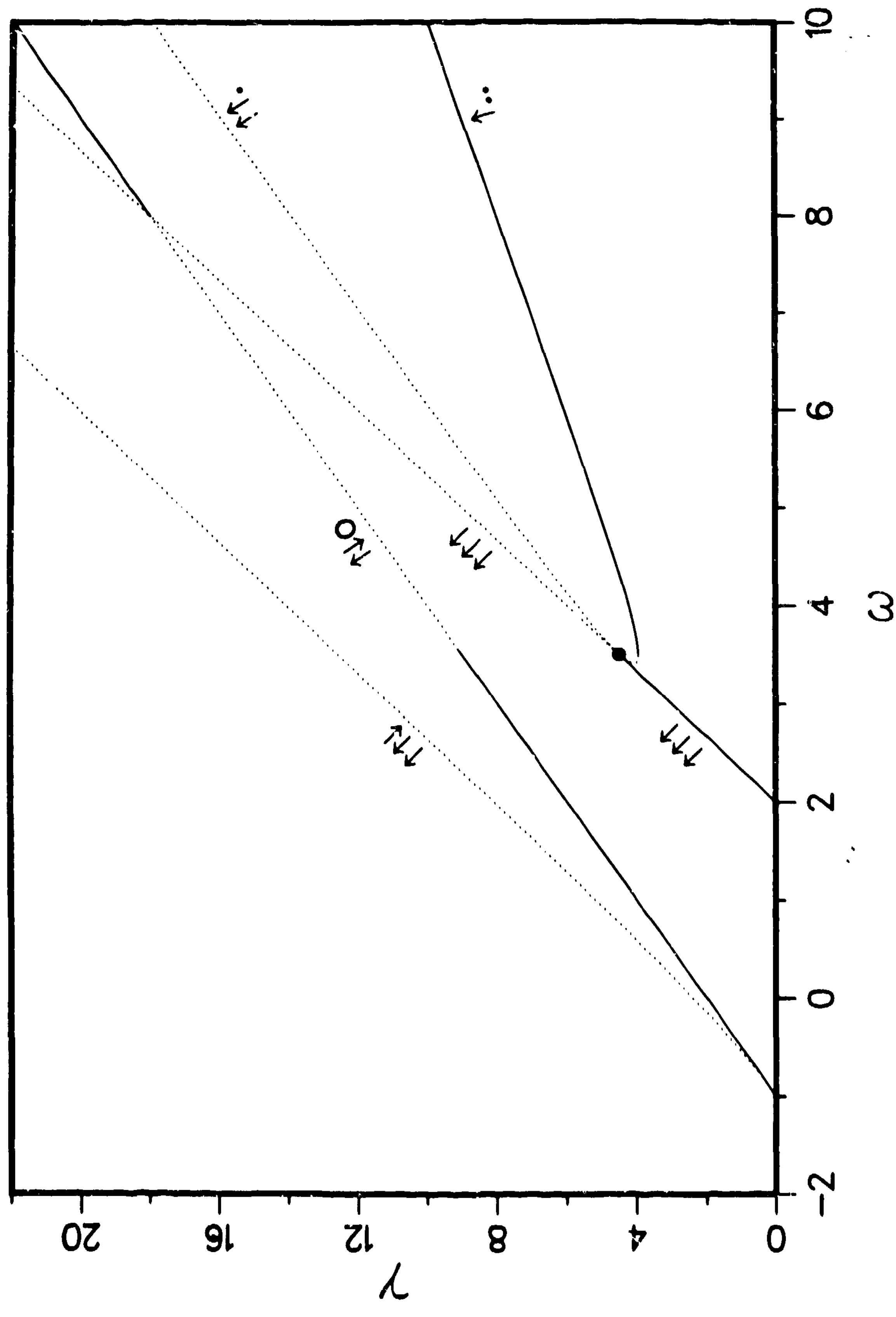

FIG. 6