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Communications

Prediction of the resonant absorption for a polar macromolecule librating in a double potential well

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The analytic theory[1,2] is applied to a hemoglobin (Hb) molecule librating in a cosine squared intermolecular potential $U(\theta)$; for long-lived librators (with a lifetime of *ca.* 1 ns) the theory predicts the appearance of narrow microwave loss/absorption lines simultaneously with the low frequency Debye spectrum; comparison is made with the constant field model.

Some progress has recently been achieved[1,2] in elaborating the analytic linear response theory of polar molecules librating in a double well potential with the profile $\cos^2\theta$. To this potential the $\cos\theta$ conservative electric field $E_{\text{cons}}(\theta)$ corresponds:

$$U(\theta) = U_0(1 - \cos^2\theta), \text{so that } E_{\text{cons}}(\theta) = (U_0/\mu)\cos\theta \quad (1)$$

Here U_0 is the well depth and θ is the angle between the dipole moment vector $\vec{\mu}$ and the symmetry axis of the potential $U(\theta)$. In ref. 2 a simple quasi-harmonic approximation was elaborated which was shown to be sufficient to enable at least a qualitative study to be made of the dielectric relaxation in a potential (equation 1).

A similar constant field model with the cosine potential $U(\theta)$, *viz*

$$E_{\text{cons}} = U_0/(2\mu) \equiv E_0, \text{so that } U(\theta) = (U_0/2)(1 - \cos\theta) \quad (2)$$

was applied[3] to the hydrated Hb molecule having rotational mobility. Here E_0, unlike $E_{\text{cons}}(\theta)$ in equation (1), does not depend on the angle θ.

This communication also considers the dielectric relaxation of the hydrated Hb molecule but for the case of the double well potential given by equation (1). This is important since:

(*a*) The double well potential is a microscopic model for a typical polar dielectric, in which the resultant dipole moment $<\vec{\mu}> = 0$, since in two neighbouring wells the averaged dipole moment vectors, corresponding to $\theta = 0$ and $\theta = \pi$, have opposite directions. We note that in the constant field model $<\vec{\mu}> \neq 0$ since all dipoles are oriented along E_0 (however, for an isotropic dielectric with different E_0 directions the average $<\vec{\mu}> = 0$).

(*b*) For the double well potential, unlike the single one, the low frequency (Debye) spectral region should appear for any frequency of collisions since it is caused by the Brownian rotational diffusion between the orientations, corresponding to $\theta = 0$ and $\theta = \pi$. Conversely, in the single well (constant field) model such Debye spectra do not appear[3] since only the equilibrium configuration exists in this model.

Experimentally the separate relaxation band has been observed[4] in the MHz region for the Hb-water solution; it was assumed[4] that this band appears because of reorientation of the protein molecules. The extended rotational diffusion model was used[5] in order to explain this result; in this model dipoles rotate freely during the lifetime τ (τ is the mean time interval between strong immediate collisions). The theory[5] agrees with experiment[4] if one supposes that the mean normalized collision frequency $y = \eta/\tau$ is large ($y \gg 1$), where $\eta = \sqrt{(I/(2k_B T))}$, I is the moment of inertia of the macromolecule, k_B is the Boltzmann constant and T is the temperature.

New and interesting features appear in the double well model reported here.

The dielectric response of an isotropic medium is characterized[1,2] by the complex susceptibility $\chi^* = \chi' + i\chi''$ (* means the complex conjugate), which is simply related to the spectral function $L(z)$ of the model, that is the sum due to sub-ensembles of 'librators' and 'hindered rotators':

$$L(z) = \check{L}(z) + \mathring{L}(z) \quad (3)$$

Using the Gross collision model, we have for the double well potential in case of an isotropic model:[2]

$$\chi^* = 2GzL(z)[x + iyL(z)]^{-1} \quad (4)$$

$$\check{L}(z) \equiv \frac{\exp(p^2/2)}{2\sqrt{\pi}pI_0(p^2/2)} \int_0^{p^2} \exp(-h) \frac{h}{\overset{*}{\gamma}} \left\{ \frac{h/(4p^2)}{4p^2 - \overset{*}{\gamma}^2 z^2} + \frac{1}{p^2 - \overset{*}{\gamma}^2 z^2} \right\} \mathrm{d}h \quad (5)$$

$$\mathring{L}(z) = \frac{2\exp(p^2/2)}{\sqrt{\pi}I_0(p^2/2)} \int_p^{\infty} \frac{s^2 \exp(-s^2)}{s^2 - \mathring{\gamma}^2 z^2} \frac{1 + \frac{p^2}{2s^2}}{[1 - (\frac{p}{4s})^4]\,\mathring{\gamma}} \mathrm{d}s \quad (6)$$

$$\overset{*}{\gamma} \equiv 1 + h/(4p^2); \mathring{\gamma} \equiv 1 + p^2/(4s^2); z = x + iy, x \equiv \eta/\omega, \quad (7)$$

where $I_0(\cdot)$ and further $I_1(\cdot)$ are the modified Bessel functions, z is the normalized complex frequency and

$$p = [U_0/(k_B T)]^{1/2} \quad (8)$$

is the free parameter of the model (the other one is y or $\tau = \eta/y$).

In this model the relaxation time τ_D may be estimated[1] as the function of the model parameters y and p:

$$\tau_D \approx [yL(iy)]^{-1}\eta \quad (9)$$

Similar expressions for the constant field model may be written:[3]

$$\chi^* = 2GzL(z)[x + iyL(z)/< \sigma >]^{-1}, < \sigma > = 1 - \left[\frac{I_1(2p^2)}{I_0(2p^2)}\right]^2 \quad (10)$$

$$\check{L}(z) \equiv \frac{\exp(2p^2)}{4\sqrt{\pi}pI_0(2p^2)} \int_0^{4p^2} \exp(-h) \frac{h}{\overset{*}{\gamma}^3} \left\{ \frac{h/(4p^2)}{4p^2 - \overset{*}{\gamma}^2 z^2} + \frac{1}{p^2 - \overset{*}{\gamma}^2 z^2} \right\} \mathrm{d}h \quad (11)$$

$$\mathring{L}(z) = \frac{2\exp(2p^2)}{\sqrt{\pi}I_0(2p^2)} \int_{2p}^{\infty} \frac{s^2 \exp(-s^2)}{s^2 - \mathring{\gamma}^2 z^2} \left(1 + \frac{2p^2}{s^2}\right)^2 \frac{1}{\mathring{\gamma}^3} \mathrm{d}s \quad (12)$$

$$\overset{*}{\gamma} \equiv 1 + h/(16p^2); \ \mathring{\gamma} \equiv 1 + p^2/s^2 \quad (13)$$

The multiplier 2 in equations (4) and (10) approximately takes into account the spatial statistics of the molecular ensemble since the $L(z)$ spectral function is determined for motion in a plane. Since in our approximation the internal field correction is neglected, we may use the simplified relation[1] between the susceptibility χ^* and the complex permittivity ε^*:

$$\varepsilon^* = 4\pi\chi^* + \mathrm{n}_\infty^2 \quad (14)$$

where $\mathrm{n}_\infty \equiv \mathrm{n}(\omega \to \infty)$ is the optical refraction index near the edge of the orientation–relaxation spectral region. The absorption coefficient is given by

$$\alpha = \frac{\omega\varepsilon''}{c\mathrm{n}} = 4\pi\nu Im(\sqrt{\varepsilon^*}); \ \mathrm{n} = Re(\sqrt{\varepsilon^*}), \ \nu = \frac{\omega}{2\pi c} = \frac{f}{c}, \quad (15)$$

where n is the refractive index, c is the velocity of light, ν is the wave number (frequency in cm^{-1}) and f is frequency in Hz.

The rotational mobility of a macromolecule is determined by its surroundings. We assume that the hydration of Hb is close to that used in calculations[5] for the Hb-water solution. The moment of inertia I may be calculated for a spheric top molecule: $I \equiv (2/5)M_r m_p(R_{\text{Hb}} + 2lR_{\text{H}_2\text{O}})^2$, where M_r is the molecular mass, m_p is the mass of a proton, R_{Hb} and $R_{\text{H}_2\text{O}}$ are the radii of the Hb and water molecule, respectively, and l is the number of hydration shells. Taking values $M_r = 68000$, $R_{\text{Hb}} = 32.9\,\text{A}$, $R_{\text{H}_2\text{O}} = 1.5\,\text{A}$ and $l = 1$ we have, for a hydrated Hb, $I \approx 7.42 \times 10^{-33}\,\text{g cm}^2$. In order to estimate the influence of I on the dielectric spectrum, we also calculated these for an isolated ($l = 0$) Hb molecule, for which $I_0 \approx 4.93 \times 10^{-33}\,\text{g cm}^2$. We take $\mu = 400\,\text{D}$ and $N = 10^{18}\,\text{cm}^{-3}$ as the Hb dipole moment and its concentration (which corresponds[4,5] to 10% Hb-aqueous solution); T was set at 300 K and $\mathrm{n}^2_\infty = 1.7$, the same as in liquid water.[6]

In Figures 1 and 2 we present the absorption $\alpha(f)$ and loss $\varepsilon''(f)$ spectra, respectively, calculated for the field parameter $p = 4$. Hence, in the double well model the potential well depth $U_0 = 16\,k_B T$ corresponds to this p value, while for the single well the corresponding electric field $E_0 = 10^6\,\text{V cm}^{-1}$, since $p = [(\mu E_0)/(2k_B T)]^{1/2}$; this value of E_0 is typical of the conservative field produced by biomembranes.† At equilibrium the law of motion of a dipole considerably differs for such p values from that of the inertial motion (from the law of free rotation). We altered the normalized collision frequency y: in Figure 1 $y = 0.1$, 0.25, 0.5 and 0.75, *i.e.* the lifetime $\tau = \eta/y$ is equal to 3, 1.2, 0.6 and 0.4 ns for hydrated Hb and, respectively, to 2.4, 0.98, 0.49 and 0.33 ns for an isolated Hb molecule. Figure 2 shows a wide range of y parameters: $y = 0.1$, 1, 10, 100 and 1000, *i.e.* for hydrated Hb $\tau \approx 3000$, 300,

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† The comparison of equations 1 and 2 shows that for the same p value the conservative field on the bottom of the double well potential is two times less than in the single well:

$$E_{\text{cons}}^{\text{double}}(\theta = 0) = U_0/\mu = p^2 k_B T/\mu; \ E_{\text{cons}}^{\text{single}} = 2p^2 k_B T/\mu.$$

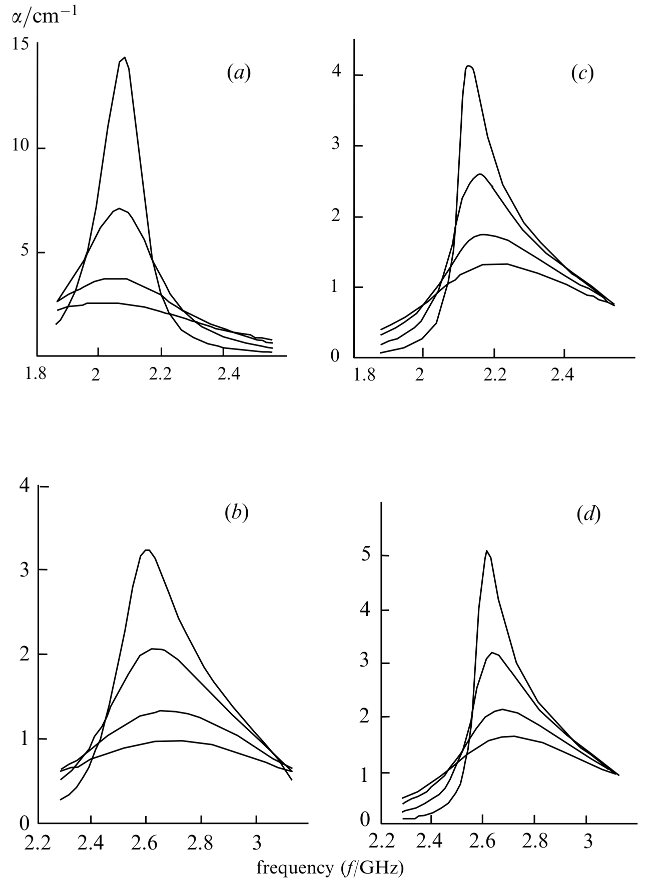

Figure 1 Frequency dependence of the absorption coefficient, calculated for the double (*a*, *b*) and single (*c*, *d*) potential. Hydrated (*a*, *c*) and isolated (*b*, *d*) Hb molecules. The field parameter $p = 4$; the normalized collision frequency $y = 0.1, 0.25, 0.5$ and 0.75 (from top to bottom).

30, 3, and 0.3 ps, respectively.

For the *double well potential* (Figures 1*a*,*b* and 2*a*) we see that:

(*a*) if collisions are rare ($y \leqslant 1$), the frequency loss/absorption dependence, $\varepsilon''(f)$ or $\alpha(f)$ has a rather sharp peak in the microwaves region (upper curves in Figures 1*a* and *b*, and curve 1 in Figure 2*a*). The normalized peak frequency $x_L \approx p$, that is,

$$f_L \approx x_L/(2\pi\eta) = (2\pi)^{-1}\sqrt{(2\mu U_0/I)}. \qquad (16)$$

The intensity of this peak is a few wavenumbers, while that of the loss peak is about 15.

(*b*) The bandwidth of the resonance loss/absorption curves increases with the rise of y; for $y > 1$ the absorption maximum α_L vanishes.

(*c*) If the moment of inertia I decreases, the absorption curve widens and shifts to higher frequencies approximately as $1/\sqrt{I}$ (*cf.* Figure 1*b* with Figure 1*a*).

(*d*) For rare collisions ($y < 1$) the two-humped loss curve $\varepsilon''(f)$ arises which have comparable peaks $\max[\varepsilon''(f)]$; the low-frequency loss peak ε''_D corresponds to the Debye relaxation spectra and the high frequency peak ε''_L to the microwave spectra discussed above (curves 1 and 2 in Figure 2*a*).

(*e*) For frequent collisions ($y > 1$) only the relaxation-type curve $\varepsilon''(f)$ appears, which has only one loss maximum ε''_m (curves 3, 4, 5 in Figure 2*a*).

Comparison with the *single well potential* (Figures 1*c*, *d* and 2*b*) shows that for long lifetimes ($y < 1$) the resonant (in the microwave region for Hb molecule) dielectric behaviour is similar in both models, the loss/absorption curves being narrower for the single well potential. However, for $y < 1$ the low-frequency spectrum has only one maximum (at microwaves, see curve 1 in Figure 2*b*; the low frequency loss maximum is four orders of magnitude lower). For *short lifetimes* ($y \geqslant 10$) the intensity of the loss peaks is much lower than that for the double well (*cf.* curves 3, 4, 5 in Figures 2*b* and 2*a*).

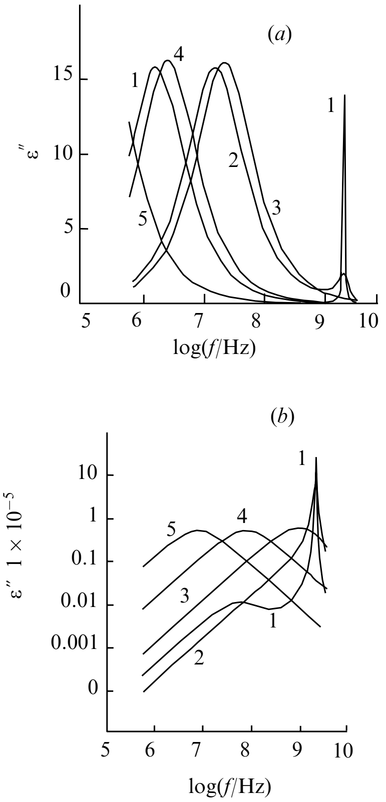

Figure 2 Dielectric loss spectra of the hydrated Hb molecule predicted for the double (*a*) and single (*b*) well potentials. The collision parameter $y = 0.1, 1, 10, 100$ and 1000 for curves 1, 2, 3, 4 and 5, respectively. The field parameter $p = 4$.

In Figure 3 the loss/absoption spectra calculated for the planar extended diffusion model is shown, to which equations 3–7 transform, for $p = 0$, to

$$L(z) = \mathring{L}(z) = \frac{2}{\sqrt{\pi}}\int_p^{\infty}\frac{s^2\exp(-s^2)}{s^2 - z^2}\mathrm{d}s,\ \check{L}(z) \equiv 0 \qquad (17)$$

For rare collisions ($y < 1$) the absorption/loss spectra are much wider than in the strong double potential and are shifted to lower frequencies; for very frequent collisions the dielectric behaviour becomes similar in both models (*cf.* curves 3, 4 and 5 in Figures 2 and 3*a* for $y = 10$, 100 and 1000, respectively). This is confirmed by comparison for $y \geqslant 10$ with the estimated relaxation times, shown in Figure 4. The experimental[4] loss peak ε''_D, at the frequency $f_D \approx 1$ MHz, is related to the relaxation time $\tau_D = (2\pi f_D)^{-1} \approx 1.6 \times 10^{-7}$ s. In the extended diffusion model we can fit the relaxation spectrum by taking a large value of y ($y \approx 268$), or correspondingly short τ ($\tau \approx 1.12$ ps). In the double well model nearly the same values of y and τ ($y \approx 248$ and $\tau \approx 1.21$ ps) also yield this τ_D value.

In the extended diffusion model the loss curve $\varepsilon''(\omega)$ has the only maximum for any y (or τ); in the case of rare collisions ($y < 1$) the absorption spectrum $\alpha(\omega)$ is quasi-resonant since on the level 1/2 its bandwidth Δf_L is comparable with the peak frequency f_L; the normalized bandwidth $\gamma = \Delta f_L/f_L$ is thus approximately 1. In the double well model, as seen above, for $y < 1$ the loss/absorption curves appear to be resonant ones. There exists a second lifetime τ to which the aforementioned τ_D corresponds, namely $\tau \approx 4.79$ ns or $y \approx 0.0625$. This is shown in Figure 4 where the dashed horizontal line crosses the calculated $\tau_D(\tau)$ solid curve in two places. Conversely, in the case of the extended diffusion model (dashed curve in Figure 4) there is only one point of intersection, at which $\tau \approx 1.12$ ps.

In conclusion, a polar macromolecule may be influenced by

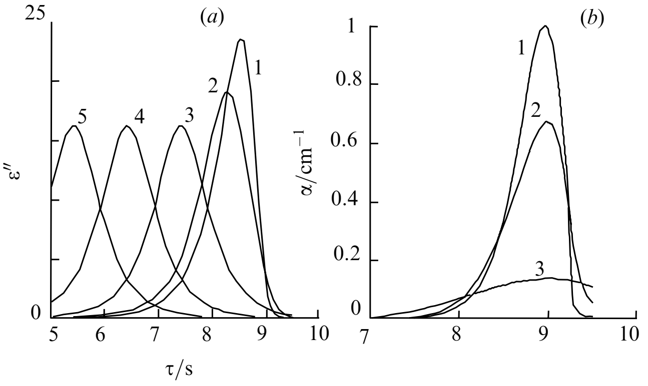

Figure 3 The loss (*a*) and absorption (*b*) spectra of the hydrated Hb molecule, calculated for the extended diffusion model ($p = 0$). Curves 1, 2, 3, 4 and 5 for $y = 0.1$, 1, 10, 100 and 1000, respectively.

a conservative potential well having a specific profile. We have estimated the dielectric response of the hydrated Hb librating in strong double and single well potentials (equations 1 and 2, respectively).

For the double well potential we predict the appearance of a rather narrow ($\gamma \approx 0.2$ for the lifetime $\tau \approx 3$ ns) absorption curve $\alpha(f)$ whose peak frequency f_L ($f_L \approx 2.1$ GHz) is about p times larger than that calculated in the absence of the $U(\theta)$ potential ($p = 4$). Previously only quasi-resonant spectra corresponding to the extended diffusion model have been described[5] for a similar water–protein system (in the extended diffusion model $\gamma \approx 1$).

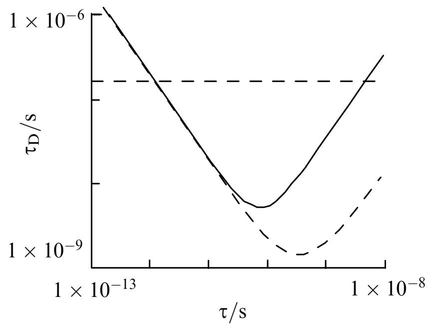

Figure 4 The relaxation time τ_D *versus* lifetime τ, estimated for $p = 4$ (solid line) and $p = 0$ (dashed line). The horizontal line corresponds to the observed[4] τ_D value.

The predicted appearance of the Debye relaxation spectrum due to the long-lived librations (for $\tau \approx 4.8$ ns) is close to the observed[4] one.

In the double well potential model the additional possibility of obtaining the desired relaxation time is related to the short lifetime τ (*ca.* 1.2 ps), that is three orders of magnitude less than the above value (4.8 ns). For very frequent collisions the influence of the U potential on the dielectric behaviour is negligible, thus the results of our calculations are close to those obtained earlier[3] for the extended diffusion model [we note that in ref. 5 a more complicated calculation scheme, corresponding to equation (17), was used]. It would be very interesting to know, which of the two discussed mechanisms (related to long or short lifetimes of the librational state) could actually be realized.

We note that for important components such as free water, the simple $\cos^2\theta$ potential is inapplicable and thus another molecular model (probably for the 'hat'-like potential profiles[6]) should be elaborated.

The calculation scheme given by equations (10)–(15) could be applied to 'simple' nonassociated liquids studied extensively experimentally[7] (with use of the confined rotator model).[1] By applying the double potential model it is possible to estimate the well-depth U_0 and related parameters of particles, librating /rotating in condensed polar fluids.

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