First-order hyperpolarizabilities and pK_a of weak organic acids in protic solvents are linearly related

Paresh Chandra Ray and Puspendu Kumar Das
Department of Inorganic and Physical Chemistry, Indian Institute of Science, Bangalore 560 012, India

Second-order nonlinearities (β) of five weak organic acids in protic solvents have been measured by the double-quantum Rayleigh scattering (DRS) technique. β is found to bear a linear relationship to the pK_a of these compounds in those solvents. A direct implication of this observation is that the DRS technique can be used to determine the pK_a of weak organic acids in any solvent.

It has been generally recognized[1,2] that donor–acceptor-substituted organic compounds such as benzenes, stilbenes, azo dyes and polyenes possess large molecular second-order nonlinear optical (NLO) susceptibilities (β). However, ionic compounds and high dielectric constant solvents were avoided, thus far, for measurements since the electric-field-induced second-harmonic generation (EFISHG) technique[3], commonly used for determination of β, involves a high-voltage DC field to align the molecules in the direction of the field in solution. An alternate technique, the double-quantum Rayleigh scattering (DRS), rediscovered recently[4–6] allows determination of β without the above constraints. Also, the DRS technique yields an average value of β whereas the EFISH technique gives the component of β projected along the direction of alignment (normally, the dipole direction) of the molecules in solution. In this communication, we report the β values of a few amino benzoic acids and sulphonic acids in some polar protic solvents and demonstrate that β bears a linear relationship with the pK_a of these weak acids in those solvents.

Compounds a–e were purchased from Aldrich and their β values measured by the DRS technique[7] at 1.064 μm in methanol and other protic solvents. The fundamental IR light from a Q-switched Nd : YAG laser was focused on a $4 \times 4 \times 2\,cm^3$ cell containing the solution of compounds. The second-harmonic light was collected using a large-diameter and short-focal-length aspherical condenser lens and other imaging optics at the photocathode of a uv–visible photomultiplier tube (PMT) after separating the fundamental by a 532 nm interference filter of 4 nm bandwidth. The output signal from the uv–visible PMT was integrated and averaged over 10,000 laser shots in a Boxcar signal averager (SRS 250). The experiments were carried out at laser powers below the threshold for stimulated Raman and Brillouin scattering and for self-focusing and self-defocusing.

The intensities of the second-harmonic scattered light, I_{2w}, and the incident beam, I_0, are related by[8,9]

$$I_{2w} = GB^2 I_0^2 = G \sum_k N_k |\beta_k|^2 I_0^2, \quad (1)$$

where G depends upon the scattering geometry and contains the average of the products of the direction cosines and the local field corrections and also the instrumentation factor. N_k is the number density of the kth specie with second-order polarizability β_k. For a two-component system,

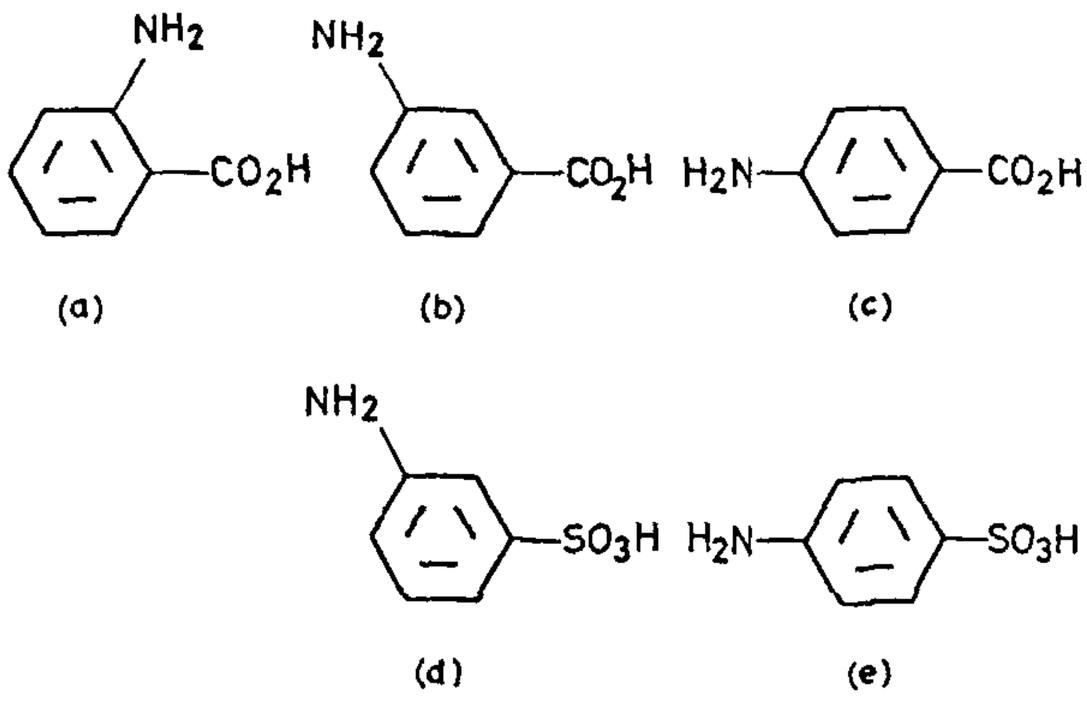
$$B^2 = N_{solvent}\, \beta^2_{solvent} + N_{solute}\, \beta^2_{solute}. \quad (2)$$

Since low concentrations (10^{-4}–10^{-6} M) of solute were used, we assume that its presence does not change the number density of the solvent molecules, $N_{solvent}$, significantly. Measurements at different number densities of the solute show a linear dependence of GB^2 on N_{solute}. From the intercept and slope we calculated β_{solute} and G since $\beta_{solvent}$ is known. Chloroform was calibrated with respect to carbon tetrachloride by the method described in detail by Zyss *et al.*[10], and in a similar fashion we obtained β for water, methanol, ethanol and isopropanol as 0.05, 0.52, 0.61 and 0.65, respectively, in units of 10^{-30} esu.

The β values of a–e obtained from DRS experiments in methanol, ethanol, isopropanol and water are listed in Table 1. All these compounds have an electron donor

Table 1. Quadratic hyperpolarizabilities ($\beta_{DRS} \times 10^{30}$ esu) of compounds a–e in different solvents and their calculated β ($\beta_{calc} \times 10^{30}$ esu) values

Compound	$\beta_{calc.}$	β_{DRS} Methanol	Ethanol	Isopropanol	Water
a	2.0	6 8	7.2	7.8	9 0
b	4.2	10 2	11.0	11.6	13 0
c	5.5	15 8	16.6	17.2	18.5
d	5.2	14.8	16 1	17.2	20.0
e	6 1	20.8	22.9	23.4	26.2



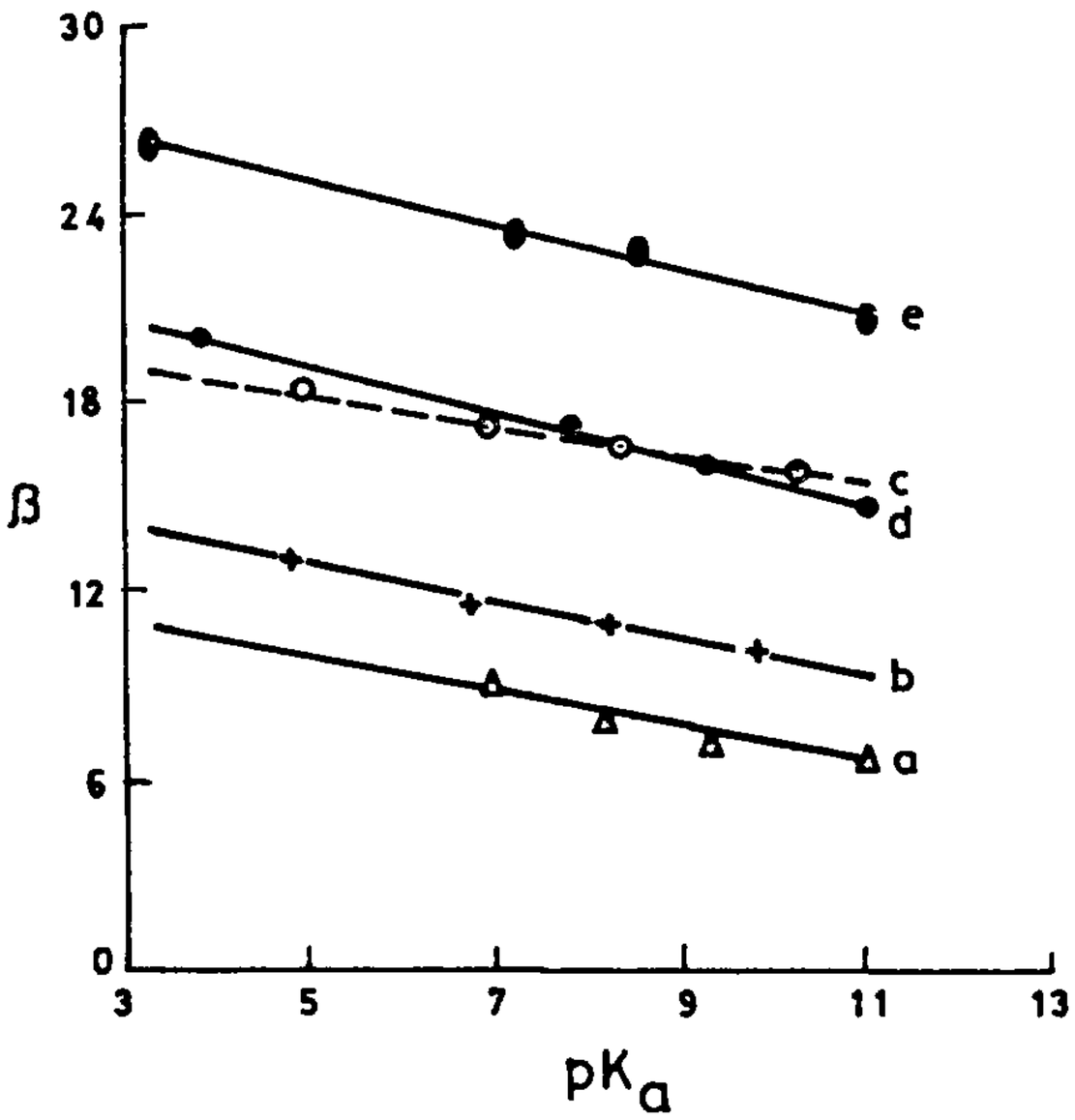


Figure 1. pK_a vs β_{DRS} ($\times 10^{-30}$ esu) plot for compounds a–e. The straight line is a linear least-squares fit through the experimental points. The intercepts (at $pK_a = 3.0$) and slopes are: *a*, 10 6, −0.53; *b*, 14 0, −0.55; *c*, 22 7, −0.72, *d*, 20.4, −0 65; and *e*, 28 4, −0 68, respectively.

and an electron acceptor group. As a result, the contribution from the canonical quinonoid structure in the ground state is high. Since delocalization of electrons is most favoured when the donor–acceptor are para to each other, the para-compounds show large nonlinearities and the order is para > meta > ortho for a fixed pair of donor–acceptor substituents[11, 12]. For the common amino donor we expect the sulfonic-acid-substituted derivative to exhibit higher β values than analogous carboxylic acid derivatives since the former is a better electron acceptor than the latter. This is actually observed experimentally (see Table 1). We have also computed finite-field β for these compounds using the PM3 parametrization within the MOPAC[13, 14] package with full geometry optimization. The calculated β values are purely gas phase numbers and do not include the solvent effects. But the experimental trend in β is nicely reproduced in the calculation although the calculated results are always lower. This may be explained by recalling the well-established notion that in solution specific interactions with solvent molecules[15–18] may alter the NLO characteristics (i.e. β) and we can write various components of β as

$$\beta = \beta_g + \beta_{hb} + \beta_{int}, \qquad (3)$$

where β_g is the quadratic polarizability of the molecules in the gas phase (i.e. isolated) and β_{hb} and β_{int} correspond to hydrogen bonding (intermolecular and intramolecular) and intermolecular interaction (dipole–dipole, ion–dipole, ion–ion, etc.) contributions to β, respectively. For different solvents these components of β will be different and the stability of the solvated conjugate base (anion) will determine the dissociation constant in solution. For acids with low pK_a values in solution the amino group will be protonated and the concentration of the zwitterionic specie will influence the equilibrium constant. Insofar as the trend in β is concerned, it is not at all surprising that we find that water > isopropanol > ethanol > methanol, although their polarity varies as water > methanol > ethanol > isopropanol. We also find that pK_a (ref. 19–21) of a–e (which are weak acids) in these solvents correlates linearly with their β in solution (Figure 1). This indirectly points out that the driving forces which lead to a higher degree of dissociation and improvement on the quadratic polarizability (since the slope of all the plots in Figure 1 is negative) in solution are the same. Thus, we propose that the DRS technique may be used as a probe for measuring pK_a of weak organic acids.

In conclusion, we have demonstrated that pK_a and β of weak organic acids in solution are linearly connected. Since we have chosen the solvents and NLO chromophores randomly, we believe that this inference is general. Currently, we are developing a more generalized model for describing this dependence quantitatively.

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Intranasally delivered microdoses of bromocriptine (BCR) effectively reduces serum prolactin levels in hyperprolactinaemic patients

R. Suresh, K. M. Prasanna Kumar* and N. R. Moudgal†

Center for Reproductive Biology and Molecular Endocrinology, Indian Institute of Science, Bangalore 560 012, India
*Department of Endocrinology, M. S. Ramaiah Medical Teaching Hospital, Bangalore 560 054, India

It is well known that hyperprolactinaemia in the human leads to infertility. The therapy of choice in India has been the administration of bromocriptine (BCR) as tablets. This mode of administration is generally accompanied by undesirable side-effects such as giddiness, nausea, vomiting and postural hypotension. We demonstrate here the efficacy of microdoses of BCR administered intranasally (IN) to hyperprolactinaemic patients ($n = 6$) in reducing significantly the elevated serum prolactin levels and maintain them within the normal range. The IN mode of BCR administration, in addition to reducing the effective dose of the drug by 4–20-fold, results in little or no side-effects otherwise associated with oral therapy.

HYPERPROLACTINAEMIA could be a result of pituitary stalk compression (hypothalamo-pituitary disconnection), the presence of a pituitary tumour, or unexplained idiopathic causes. One of the principal effects of high concentrations of prolactin secretion is the inhibition of gonadotropin pulsatality, probably due to an effect at the hypothalamic GnRH pulse generator[1]. Hyperprolactinaemia-associated reproductive dysfunctions in the human female are known to result in menstrual irregularities like oligomenorrhea or amenorrhea, spontaneous or expressive galactorrhea and inhibition of ovarian steroidogenesis. The effect of hyperprolactinaemia in man, on the other hand, is yet to be clearly understood; but it is known to cause decrease in libido, leading to infertility.

Bromocriptine (BCR), a potent dopamine agonist that inhibits prolactin secretion from the pituitary, is the drug of choice in effective reduction of prolactin (PRL) concentration in the management of hyperprolactinaemic patients. However, being an ergot alkaloid, oral BCR (O-BCR) therapy results in side-effects such as nausea, vomiting and postural hypotension[2] in a large percentage of patients; the less common side-effects are headache, fatigue, abdominal cramps and constipation. Attempts at developing new agonists that are long-acting as well as have less adverse effects have been on the anvil in the recent past[1]. Hitherto, in India, BCR is available only in tablet form and the administered dose ranges from 5–20 mg or more per day.

Earlier studies from our laboratory and others have clearly demonstrated that intranasal (IN) administration of microdoses of steroids/drugs are effective in acting at the hypothalamo-pituitary axis and as such serve as a potential alternate method to achieve blockage of hormone release[3–9]. In the present pilot study we have sought to determine (a) whether IN-BCR treatment (in microdoses compared to the relatively larger doses of O-BCR) can effectively reduce the PRL concentration and maintain it within normal range (< 25 µg/l) in hyperprolactinaemic patients and (b) if the marked reduction in therapeutic dose results in a significant decrease in side-effects and better patient compliance.

Five female and one male hyperprolactinaemic patients volunteered to enter the study, which was cleared by the Ethics Committee of M. S. Ramaiah Medical Teaching Hospital, Bangalore. A written, informed consent was obtained from all of the volunteer-patients. The details of their age, diagnosis and clinical manifestations are provided in Table 1. Since all the patients were on O-BCR, they underwent a washout period of two weeks, during which time they were asked to stop taking the BCR tablets and were taught the precise use of the nasal spray device. The nebulizer used was obtained from Pfeiffer GmbH and Co. KG, Radolfzell, Germany, and delivers ~ 100 µl solvent/spray with an efficiency of > 90% as determined using a labelled [^{3}H] steroid. The solvent (vehicle) used to dissolve crystalline BCR (kindly provided by Serum Institute of India, Pune) comprised of ethanol/propylene glycol/distilled water in a ratio of 3 : 3 : 4. This solvent has earlier been successfully used to deliver steroid hormones in human volunteers[5].

Following the washout period, the volunteers were subjected to a two-week pretreatment schedule when the vehicle alone was delivered by IN route. Resting levels of serum PRL were determined from three blood samples collected on day 14, 7 and 1 of this phase of

†For correspondence.