International Journal of Pharmaceutics, 9 (1981) 97–106
Elsevier/North-Holland Biomedical Press

Deviation of dissolution behaviour of benzoic acid from theoretical predictions with lowering of temperature: limitations as a model dissolution substance

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(Received April 22nd, 1981)
(Accepted May 26th, 1981)

Summary

Benzoic acid dissolution was found to be non-ideal on lowering the dissolution temperature and serious deviation from classical diffusion was observed. Experimental dissolution rates, measured using a rotating disc apparatus, differed from the values predicted using the Levich equation, the deviations becoming more pronounced and negative as the temperature was reduced. Measurement of dissolution rates at varying rotational velocities (ω) of the disc enabled application of a test for diffusional behaviour: plots of dissolution rate against $\omega^{1/2}$ were linear only at 37°C but were curved at 25°C and below. Since the deviation was negative at high ω-values, it could not have been due to turbulence, the rate-limiting process evidently being an interfacial reaction. In further tests, the addition of a complexing agent, caffeine, to increase the dissolution rate eliminated the curvature at 25°C when the caffeine concentration was high but not at low concentrations, thus confirming the postulation of an interfacial process. Additional evidence was provided by an Arrhenius plot of the experimental data which deviated at low temperatures whereas at 25–37°C, the slope was in accord with an activation energy value suited to transport control.

Introduction

The dissolution of benzoic acid is considered to be diffusion-convection controlled in non-turbulent stirred solutions, an assumption which has led to its frequent use as a standard or model substance for testing the influence of various parameters, such as hydrodynamic flow, temperature and change in surface film thickness on dissolution. Temperature effects on dissolution were studied by Wildermann (1909), Gapon (1928) and Edwards (1951); activation energies were estimated by these authors and also by Bisaillon and Tawashi (1971).

Agitation and hydrodynamic flow effects on mass transfer were investigated using benzoic acid by Hixson and Wilkens (1933), Hixson and Baum (1941), Linton and Sherwood (1950) and more recently by Emanuel and Olander (1964), Bisaillon and Tawashi (1971) and Underwood and Cadwallader (1976). Change in surface film thickness and concentration gradients caused by chemical reaction during dissolution was studied using the acid in various reactive and alkaline media (King and Brodie, 1937; Hixson and Baum, 1944; Higuchi et al., 1958; Litt and Friedlander, 1959; Gibaldi et al., 1968).

The first to use benzoic acid discs in testing the reliability of a rotating disc apparatus for dissolution measurements using the Levich equation (1962) were Gallily and Friedlander (1965), working at 19.8°C at a low Reynolds number. A number of workers (Gapon, 1928; Edwards, 1951) found deviations between their data and the theoretically calculated values of dissolution constants. Prakongpan et al. (1976) working at 37°C obtained dissolution rates 14% below the predicted values over a wide range of rotation speeds in the laminar flow region, a discrepancy attributed to the geometry of the type of rotating disc used in their apparatus.

The present authors also obtained sub-theoretical values using benzoic acid as a test substance with a rotating disc apparatus in salicylamide dissolution studies (Donbrow and Touitou, 1977a). Since the dissolution of the latter substance occurred by an intermediate type of mechanism and shifted from diffusional towards interfacial control on temperature change, it seemed possible that a similar effect might be responsible for the discrepant dissolution rates in benzoic acid. Preliminary studies supported this possibility (Donbrow and Touitou, 1977b). In the work reported here, the temperature range was extended downwards, which would be expected to enhance interfacial rate control if this were the cause of the deviations.

Materials and methods

The apparatus used for determination of the dissolution rate is shown in Fig. 1. The disc holder was constructed of perspex and had a removeable steel rotating shaft. Benzoic acid tablets were prepared by direct compression of 500 mg of the crystallized acid at 10 tons/cm^2 in a 1.3 cm diameter die under vacuum using a laboratory press (Perkin-Elmer). They were embedded in the discs flush with the surface using paraffin wax, which prevented erosion at the sides of the tablet. To provide correct hydrodynamics within the system, the experimental conditions were in accord with those suggested by Riddiford (1966) for ensuring laminar flow. The assembly was centered and the depth of immersion and distance from disc to container wall exceeded 1 cm. A constant speed stirrer (Fisher Stedi-Speed) was used, between 98 and 900 rpm, measured by means of a tachometer (Tak-Ette, Power Instruments, IL). They were appropriate to a laminar flow regime corresponding to Reynold's numbers from 10 to 10^2, well below the transition to turbulent flow, which occurs at Reynold's numbers exceeding $10^4 - 10^5$. The quantity (400 ml) of hydrochloric acid, 0.01 N, or caffeine solution used as the dissolution medium ensured sink conditions.

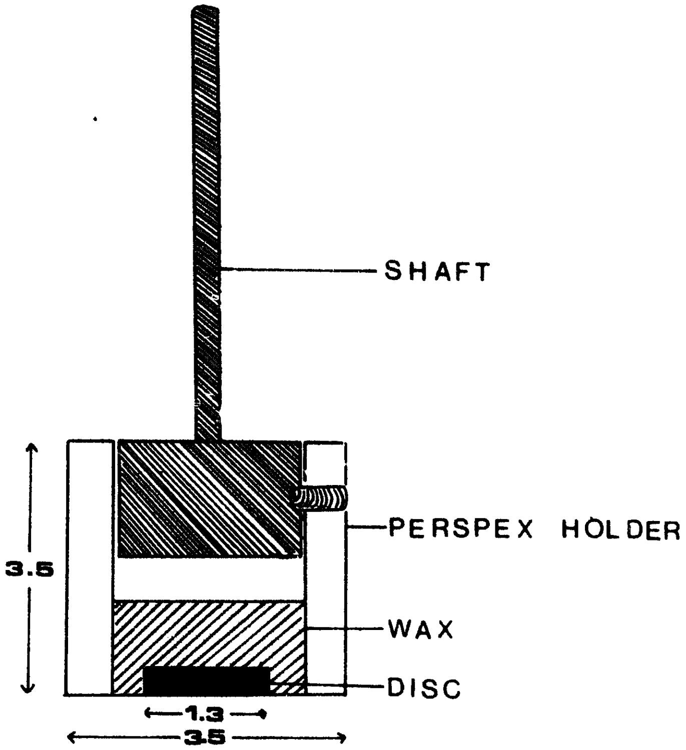

Fig. 1. Apparatus used for dissolution rate measurements.

Samples were withdrawn at 2.5-min intervals, each experiment being continued for only 10 min to minimize changes in surface characteristics of the tablet. The samples were analyzed spectrophotometrically or gas-chromatographically. The experiments were duplicated and were reproducible to within 3%. Conditioning of the benzoic acid disc in the dissolution medium for different periods up to 10 min showed that there was no time lag in the establishment of equilibrium at the surface. Shortening the stirrer shaft to 6 cm did not change the dissolution rate at 37°C, 98 rpm.

Results and Discussion

For the rotating disc in which only diffusion and convection are important, mass transport is considered to follow the Levich equation:

$$J = 0.62AD^{2/3}\nu^{-1/6}\omega^{1/2}(C_s - C_b) \tag{1}$$

where J is the dissolution rate, A is the surface area of the disc, D is the diffusion coefficient of the solute in the dissolution medium, C_s is the solute solubility, C_b the bulk concentration, ν is the kinematic viscosity of the medium and ω is the angular velocity of rotation. Introduction of the dissolution rate constant, k_t, defined appropriately for the hydrodynamic flow described by Eqn. 1 yields the equation:

$$J = k_tA(C_s - C_b) \tag{2}$$

where $k_t = 0.62\ D^{2/3}\nu^{-1/6}\omega^{1/2}$. In diffusion-convection controlled dissolution, the experimental dissolution rate should be close to that calculated using this equation.

The intermediate type of dissolution involves an additional resistance derived from an interfacial process which alters the observed dissolution rate constant, k_{obs}, the latter then being given by the following equation:

$$k_{obs} = k_i k_t / (k_i + k_t) \tag{3}$$

where k_i and k_t are the interfacial and transport rate constants, respectively. If either of the two rate constants becomes dominant, the equation simplifies to that of pure diffusional-convectional or pure interfacial control (Bircumshaw and Riddiford, 1952).

Among the important factors which may influence experimental rates of the intermediate type is the temperature of the dissolution medium. Increase of temperature accelerates both rate constants. The temperature-dependence follows an Arrhenius-type relationship containing the appropriate energy of activation (E_i or E_t for the interfacial or transport reaction, respectively (Riddiford, 1952). When $E_i > E_t$, k_{obs} will be interfacially controlled at low temperatures and transport-controlled at high temperatures. In this situation, change of temperature will result in a shift of control and a change in the apparent energy of activation. However, when $E_t > E_i$, $k_i \gg k_t$ at all temperatures, and only transport control will be observed. When $E_t = E_i$, the rate-controlling step may not be detected solely by temperature change effects.

Agitation rate changes may also influence observed rate constants of the intermediate type, increasing the rate constant of the transport process in accordance with Eqn. 2. When $k_t \gg k_i$, k_{obs} approaches k_i (Eqn. 3) and the observed rate shifts towards that of the interfacially controlled reaction. The latter process, unlike the pure transport-controlled process, is independent of agitation rate provided the surface remains smooth and undamaged (Bircumshaw and Riddiford, 1952).

The experimental dissolution rates are obtained as the slopes of the plots of the amount of benzoic acid dissolved against the time of measurement (Fig. 2). They were constant over the whole period of the measurement at all stirring speeds and temperatures and were not altered by preliminary conditioning of the embedded tablets in water in test experiments; hence solvation and surface area change associated with roughening were not kinetic factors.

Although the slopes increase with agitation rate at a given temperature, as expected, it is evident that the influence of the agitation rate differs at the various temperatures, and is in fact much lower at 10, 15 and 25°C than at 37°C. Comparing, for example, the angles subtended between the 300 and 400 rpm lines with those between the 400 and 730 rpm lines, there is an abrupt change in their relation on lowering the temperature from 37°C to 10°C. In view of the hydrodynamic conditions used, these agitation rate effects should not be due to turbulence or electrode geometry, which is unchanged (see Experimental section).

According to the Levich equation, a plot of the dissolution rate against the square-root of ω should be linear. Positive deviation from linearity is associated with turbulence while negative deviation occurs when the dissolution process is not purely diffusion-convection controlled but involves also an interfacial resistance at the surface of the dissoluting solid, as explained earlier.

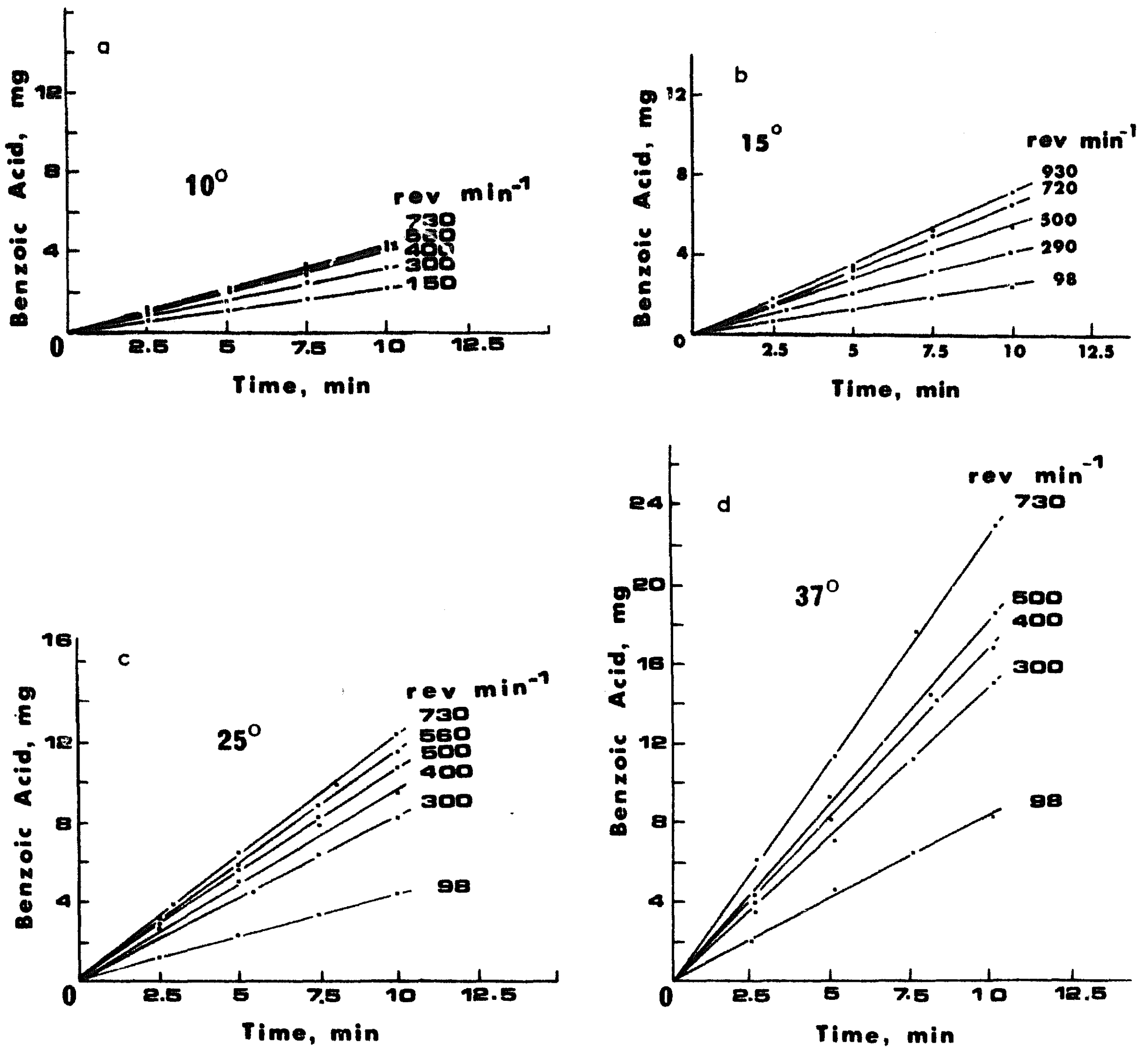

Fig. 2. Benzoic acid dissolution rates in 0.01 N HCl at various temperatures and rotational velocities.

In the experimental plots testing the effect of agitation rate (Fig. 3), negative deviation is outstanding at 10 and 15°C in acid medium and at 25°C in both acid medium and a medium containing a low concentration of caffeine *. However, at 37°C in acid and at 25°C in complexing medium containing a high concentration of caffeine the plot is linear. The presence of a complexing medium can raise the dissolution rate and shift the control mechanism from interfacial to transport (Donbrow and Touitou, 1977). Log-log J-ω plots, which should be linear with slope 0.5 in dissolution processes, in accord with Eqn. 1, observed this criterion only at 37°C or in the high caffeine concentration medium at 25°C. Under all other conditions used, the slope was significantly lower than 0.5 (e.g. 5°C, 0.21; 10°C, 0.37; 15°C, 0.43).

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* Similar negative deviation was obtained at lower temperatures, e.g. at 5°C in acid medium.

Benzoic acid dissolution rates at 10, 15, 25 and 37°C over a range of rpm values were calculated using Eqn. 1 for comparison with experimental values and are plotted in Fig. 3. It is evident that whereas at 37°C the experimental and theoretical values are in accord, at 10, 15 and 25°C the former are significantly lower than the values predicted by the equation. The deviation is accentuated as the temperature is lowered, as, for example, can be seen in Table 1 for data measured at 300 rpm. D-values used in the calculation were based on the Stokes–Einstein equation using the molar volume of benzoic acid obtained from functional group values (Flynn et al., 1974). They were in agreement with some (King and Brodie, 1937; Higuchi et al., 1965), but not all literature values,which were found in fact to fluctuate over a range (Bisaillon and Tawashi, 1971; Goldberg and Higuchi, 1968; Eisenberg et al., 1955). The important aspect is that whatever value is taken for D, the trend of increasing negative deviation on lowering the temperature remains.

Further evidence of the dissolution mechanism is revealed by the Arrhenius plot. If the rate were purely transport-controlled throughout, the reciprocal temperature

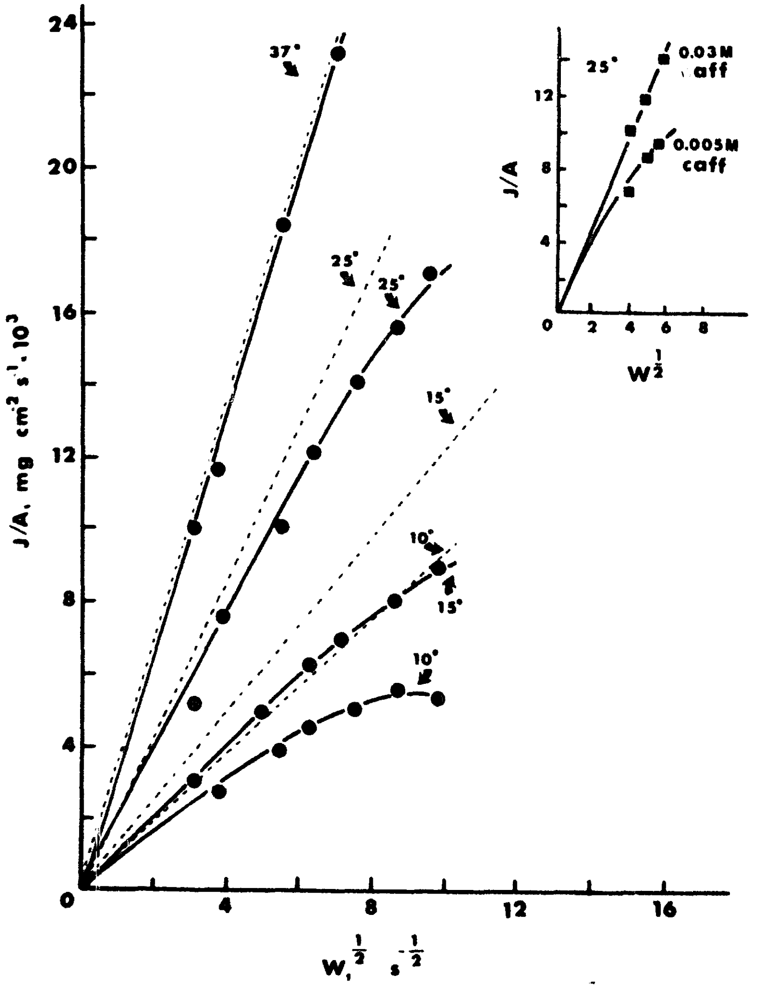

Fig. 3. Relation between dissolution rate (J/A) and square-root of rotation velocity ($\omega^{1/2}$) at different temperatures in HCl and caffeine media. ●, in 0.01 N HCl medium; ■, in caffeine medium; - - - - - -, theoretical; ————, experimental.

TABLE 1

NEGATIVE DEVIATION OF EXPERIMENTAL FROM THEORETICAL BENZOIC ACID DISSOLUTION RATES IN 0.01 N HCl AT 300 rpm.

Temperature (°C)	Dissolution rate [a] ($g\,cm^{-2}\,s^{-1} \times 10^6$)	Dissolution rate [b] ($g\,cm^{-2}\,s^{-1} \times 10^6$)	$-\Delta$ (%)
10	3.87	5.37	28
15	5.16	6.59	22
25	10.00	12.10	17
37	18.30	19.51	6

[a] Experimental.

[b] Theoretical, calculated by means of Eqn. 1.

would be linearly related to log of the dissolution rate constant. The experimental results give curves, however, and a negative deviation, accentuated at lower temperatures, is evident as shown at two selected rpm values in Fig. 4. Bisaillon and Tawashi's straight line, which fits transport control, was measured at a satisfactorily low rotation speed but within a narrow range of high temperatures. Our results in this temperature region could also be considered a straight line. Edwards, working on crystals under different hydrodynamic flow conditions, obtained reasonable

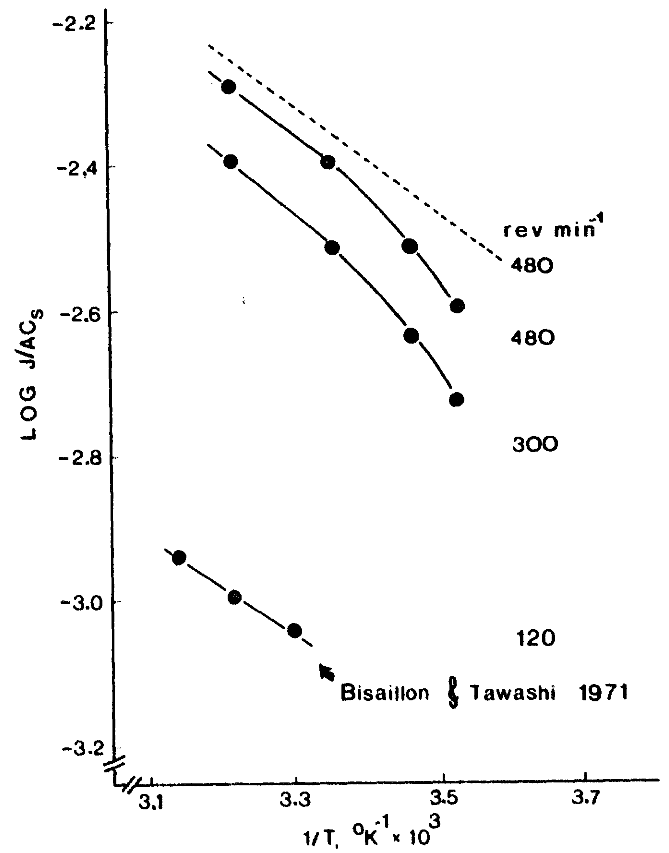

Fig. 4. Temperature dependence of dissolution rate constant (J/AC_s) of benzoic acid (Arrhenius plot).

linearity between 25 and 45°C but his 20°C result deviated, giving a lower dissolution rate than expected. Incidentally, the theoretical Arrhenius curve, in which dissolution rate constants were calculated from Eqn. 2 using appropriate values of D and ν over the temperature range, lies parallel to the line through the upper temperature points of the experimental curve and gives a slope of $-800°K$ which corresponds to an activation energy of 3.66 kcal mol^{-1}. The hypothetical regression line through all the experimental temperatures would give a higher slope.

The 3.66 kcal mol^{-1} value is close to those reported for rotating disc measurements for transport control in the laminar flow region, viz. 3.3–3.5 kcal mol^{-1}, by Nogami et al. (1966) and Bisaillon and Tawashi (1971). Energies between 5.2 and 5.7 kcal mol^{-1} were obtained by Wildermann (1909), Edwards (1951) and Griffiths and Mitchell (1971) using apparatus and methods in which the hydrodynamics were undefined and turbulence could be present, their values comparing with turbulent flow data of 4.4–4.6 kcal measured by Levich (1962) and Bisaillon and Tawashi (1971) with different types of agitation.

The question arising is why at 37°C in acid and at 25°C in caffeine media the dissolution behaviour of benzoic acid approaches close to the theoretical diffusional model, whereas at 25, 15 and 10°C in acid media there is increasingly negative deviation? It seems that at 37°C and in complexing medium the dissolution rate is controlled mainly by transport of the solute. Since lowering of temperature influences dissolution mechanisms of the intermediate type by its differential effect on the interfacial and transport rate constants (which have different temperature coefficients), the point is eventually reached at which the interfacial process becomes rate-controlling. For benzoic acid, drastic temperature lowering is necessary to reveal the interfacial resistance step clearly. Thus, while benzoic acid may observe transport behaviour close to the theoretical at 37°C under suitable experimental conditions, it is not recommended for use as a model in studies at low temperatures.

It is also worth recalling that evidence of dissolution rate limitation by interfacial reaction has now been presented for aspirin (Mitchell and Saville, 1969), *m*-aminobenzoic acid (Wurster and Kildsig, 1965) and salicylamide (Donbrow and Touitou, 1977), as well as for benzoic acid, so that it may be a more widespread phenomenon in aromatic acid derivatives than was hitherto realized and perhaps also in other compounds which show lower dissolution rates than expected from their water solubility (Hamlin et al., 1965). Such deviations occur at differing temperatures, including 37°C, and may be significant in drug delivery, particularly when high agitation rates are operative.

Acknowledgements

The authors are grateful to Mrs. Dalia Gilhar for her technical assistance.

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