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Stereoselective skin permeation of organic nitrates: application of partitioning and porous transport theories

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Abstract

The effect of the stereochemistry of organic nitrates on rat skin permeability was investigated. Skin permeabilities significantly differed between dinitrates and mononitrates, and also among their diastereomers. The maximum flux and permeability coefficient of dinitrate diastereomers from water were dependent on the solubility in octanol and the octanol/water partition coefficient, respectively. On the other hand, the key parameters determining the maximum flux and permeability coefficient of mononitrate isomers were the aqueous solubility and diffusivity. These results suggest that dinitrate diastereomers permeate across skin via the lipid domain of the stratum corneum according to a partitioning mechanism, and that skin permeation of mononitrate isomers occurs via an aqueous domain by a porous mechanism. Factors raising stereoselectivity in skin permeation of organic nitrates were closely related with stereostructure, especially the functional groups at the *exo* position, of diastereomers. The interaction between the functional groups and surrounding molecules thus causes the differences in physicochemical properties and skin permeability of stereoisomers.

Keywords: Stereochemistry; Stereoselectivity; Skin permeation; Organic nitrates; Partitioning transport; Porous transport

1. Introduction

The skin permeability of molecules is important both from the standpoint of estimating clinical effectiveness of drugs administered transdermally and the toxicological risk of dermal exposure to chemicals. The permeation characteristics of a number of compounds have therefore been investigated. Skin permeability has long been believed to be dependent on the structural features of the permeant (Scheuplein and Blank, 1971), but stereostructures have received scant attention. The

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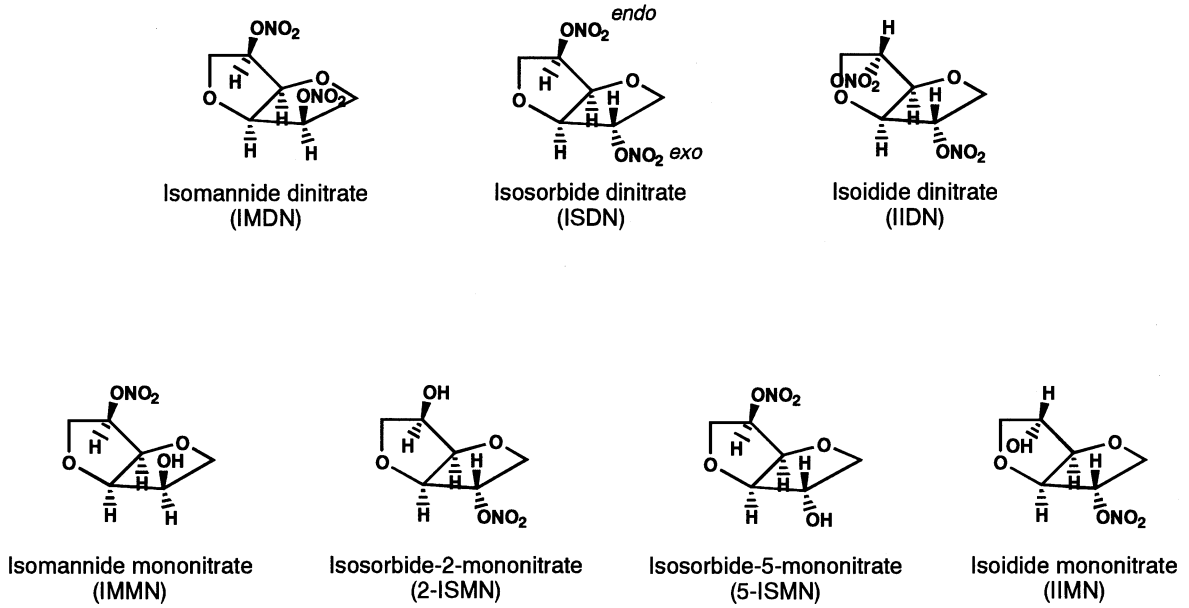

Fig. 1. Chemical structures of organic nitrates used in this study.

effect of stereochemistry on drug action and disposition has been well documented to be a consequence of stereoselective interaction with biologically active macromolecules, such as receptors and enzymes (Drayer, 1986; Jamali et al., 1989). Stereostructure can also influence physicochemical properties. Even in chiral compounds, the melting point and the solubility are different between pure enantiomers and racemic compounds (Yalkowsky, 1981; Brittain, 1990), and such differences can affect skin permeability. Investigation of the stereochemistry effects on the skin permeation process is an increasingly active and exciting field (Miyazaki et al., 1992; Wearley et al., 1993; Touitou et al., 1994; Heard and Brain, 1995).

Isosorbide dinitrate (ISDN), which has been clinically used as a transdermal drug delivery system in the treatment of angina pectoris, has two pharmacologically active diastereomers, isomannide dinitrate (IMDN) and isolodide dinitrate (IIDN). Their active metabolises, isosorbide-2-mononitrate (2-ISMN), isosorbide-5-mononitrate (5-ISMN), isomannide mononitrate (IMMN) and isolodide mononitrate (IIMN) are also diastereomers. They are structurally different in functional group, nitrate and hydroxy groups, and their *exo* and *endo* positions (Fig. 1). In light of these structural features, the effect of the stereochemistry of these organic nitrates on skin permeability was investigated. The skin permeabilities of organic nitrates in water were measured and analyzed by two basic membrane permeation mechanisms, partitioning and porous transport, to elucidate the key parameters involved in permeability. The stereoselectivity in skin permeation of these organic nitrates is discussed.

2. Materials and methods

2.1. Materials

Organic nitrates (ISDN, IMDN, IIDN, 2-ISMN, 5-ISMN, IMMN and IIMN) were synthesized and purified by Toshin Chemical Co. (Tokyo, Japan). Other chemicals and solvents were of reagent grade.

2.2. Skin permeation experiment

Rat skin was freshly excised from the abdomen of male Wistar rats (Japan SLC Inc., Hamamatsu, Japan), aged 7 weeks, after being carefully shaved. The skin samples were mounted between two diffusion half-cells with a water jacket connected to a water bath at 37°C, each having a 3.0-ml volume and 0.966-cm^2 effective diffusion area. The donor and receiver compartments were filled with distilled water and stirred at 1440 rpm with a star-head bar driven by a synchronous motor. A 14-h period of equilibration was allowed to assure constant hydration levels of the skin throughout the experiment. Then the receiver solution was replaced with fresh distilled water and the donor solution with an aqueous solution of organic nitrates. Aqueous suspensions were used as donor solution for dinitrates: 10% aqueous solution for 2-ISMN, 5-ISMN and IMMN and 5% solution for IIMN, according to their aqueous solubilities. At specified time intervals, samples (0.2 ml) were withdrawn from the receiver compartment and the same volume of fresh distilled water was added to keep the volume constant. The concentration of organic nitrates in the samples was analyzed, and the cumulative amount was plotted against time. The permeability coefficient was determined by dividing the slope of the steady-state portion (3–8 h) of these plots by the concentration of organic nitrates in the donor solution, and the maximum flux was obtained by multiplying the permeability coefficient by the solubility of organic nitrates in water. In our preliminary study, the permeability coefficients of 5-ISMN were almost constant at donor concentrations ranging from 5% to solubility. Metabolites were not detected in either the donor or the receiver solution throughout the experiment.

2.3. Determination of solubility and partition coefficient

An excess amount of organic nitrate was added to distilled water, octanol and isooctane, and the suspension was stirred in a water bath at 37°C until equilibrium. A sample of the dinitrate suspension was withdrawn and filtered immediately through a 0.45-μm cellulose acetate filter (Advantec Toyo, Tokyo) for aqueous suspension, or a 0.45-μm PTFE filter (Advantec Toyo) for octanol and isooctane suspensions. The mononitrate suspension was allowed to stand in a water bath overnight to settle and part of the supernatant was removed. The filtrate and supernatant were diluted with water and methanol for aqueous and octanol suspensions, respectively, and the concentration of organic nitrate was then determined. The isooctane suspension was evaporated to dryness under a nitrogen atmosphere followed by reconstruction with methanol before the determination of organic nitrate concentrations. Aqueous solubility of IIMN was calculated by dividing the solubility in octanol by the octanol/water partition coefficient because of liquefaction in the aqueous suspension.

The octanol/water partition coefficients of organic nitrates, except for IIMN, were calculated as the solubility ratio in octanol/water at 37°C. The values of IIMN were determined by the conventional shaken flask method (Leo et al., 1971). Organic and aqueous phases were presaturated with each other at 37°C. Equal volumes (4 ml) of the two solvents with IIMN dissolved in the aqueous phase (50 μg/ml) were placed in a screw-capped glass tube. To obtain equilibration, the sample was vortexed for 30 s after 1 h of incubation in a water bath at 37°C, incubated for another hour and vortexed again. The sample tube was left overnight in the water bath to allow the phases to separate. After removing the organic phase, the mononitrate concentration in the aqueous phase was determined. The octanol/water partition coefficient (K_{ow}) was calculated from the equation:

$$K_{ow} = \frac{C_0 - C}{C} \quad (1)$$

where C_0 is the initial concentration in the aqueous phase and C is the concentration after partition.

2.4. Determination of ideal solubility

The melting point (T_m) and heat of fusion (ΔH) of organic nitrates were measured by differential

scanning calorimetry (DSC). DSC measurement of an organic nitrate (210 mg) was carried out in an aluminum pan at a heating rate of 10°C/min using a Rigaku DSC8230D + TAS300 system (Tokyo). The DSC curve was recorded and analyzed by Rigaku TAS300 software. The ideal solubility (a) was calculated according to the following equation:

$$\log a = \frac{\Delta H}{R}\left(\frac{1}{T_m} - \frac{1}{T}\right) \quad (2)$$

where R and T are the gas constant (8.3143 J K^{-1} mol^{-1}) and the experimental temperature (310.15 K). The ideal solubility of IIMN could not be obtained because of decomposition.

2.5. Determination of diffusion coefficient in water

The diffusion coefficient of organic nitrates in water was determined by a capillary cell method (Saraf et al., 1963). One liter of distilled water was prewarmed in a water bath at 37°C and stirred at 120 rpm with a stirring bar driven by a synchronous motor. A microliter syringe (71 ORN, Hamilton Co.) was filled with 20 μl of an organic nitrate aqueous solution (50 μg/ml) and carefully immersed in water after removing the needle port. After 12–24 h the syringe was removed and the organic nitrate remaining was immediately quantified. The diffusion coefficient in water (D_w) was calculated from an approximate equation of diffusion (Wang, 1951):

$$D_w = \frac{4L^2}{\pi^2 T}\ln\left(\frac{8C_0}{\pi^2 C}\right) \quad (3)$$

where L is the capillary length of the syringe, C is the concentration of organic nitrate at time T, and C_0 is the initial concentration.

2.6. Analytical methods

Organic nitrates were assayed by high-performance liquid chromatography (HPLC). The HPLC system consisted of a pump (LC-6A, Shimadzu, Kyoto, Japan), a 4.6 × 150-mm stainless-steel column packed with Nucleosil 100-5C18 (Machery Nagel, Duren, Germany) in a column oven (CTO-6A, Shimadzu) set at 40°C, an ultraviolet detector (SPD-6A, Shimadzu) and an integrator (C-R6A, Shimadzu). The mobile phases were acetonitrile/water (30:70) for dinitrates, methanol/water (15:85) for 2-ISMN and IMMN, and methanol/water (20:80) for 5-ISMN and IIMN. The flow rates were 1.2 and 0.6 ml/min and the internal standards were ethyl p-hydroxybenzoic acid and phenol for dinitrates and mononitrates. The detector wavelength was set at 220 nm.

3. Results and discussion

3.1. Skin permeability of stereoisomers of organic nitrates

Skin permeation data for stereoisomers of organic nitrates is summarized in Table 1. The maximum flux (J_{max}) differed by about 50-fold between the maximum value of 2-ISMN and the minimum of ISDN, and was generally higher for mononitrate diastereomers than for dinitrate ones. The permeability coefficients (P) of dinitrate isomers were 10–100 times higher than those of mononitrate isomers. Obvious differences in both permeation parameters were observed among diastereomers of the nitrates.

Table 1
Skin permeability of organic nitrates from aqueous solutions[a]

	J^b_{max} (μg/cm^2 h)	P^c ($\times 10^{-6}$ cm/s)
Dinitrates		
IMDM	42.3 ± 1.1	5.62 ± 0.15
ISDN	30.4 ± 4.4	7.29 ± 0.97
IIDN	67.9 ± 19.5	12.2 ± 3.5
Mononitrates		
IMMN	506 ± 252	0.232 ± 0.116
2-ISMN	1500 ± 365	0.453 ± 0.110
5-ISMN	115 ± 33	0.159 ± 0.046
IIMN	371 ± 13	0.270 ± 0.010

[a] Each value represents the mean ± S.D. of three to seven experiments.
[b] Maximum flux.
[c] Permeability coefficient.

Table 2
Physicochemical parameters of organic nitrates[a]

	C_w^b (mg/ml)	C_o^c (mg/ml)	C_i^d (mg/ml)	Log a^e	D_w^f ($\times 10^{-6}$ cm^2/s)	K_{ow}^g
Dinitrates						
IMDM	2.14 ± 0.07	24.3 ± 1.0	1.94 ± 0.06	-0.277	1.20 ± 0.06	11.3
ISDN	1.16 ± 0.04	19.2 ± 1.0	2.00 ± 0.02	-0.430	1.35 ± 0.04	16.6
IIDN	1.55 ± 0.07	27.9 ± 4.8	7.26 ± 0.24	-0.104	1.20 ± 0.05	18.0
Mononitrates						
IMMN	607 ± 52	60.4 ± 4.5	0.837 ± 0.056	-0.349	1.32 ± 0.03	0.995
2-ISMN	921 ± 256	137 ± 5	2.45 ± 0.23	-0.241	1.51 ± 0.08	0.149
5-ISMN	200 ± 1	84.4 ± 3.0	0.152 ± 0.010	-0.557	1.25 ± 0.03	0.422
IIMN	382	518 ± 6	0.338 ± 0.019		1.48 ± 0.06	1.36 ± 0.09

[a] Each value represents the mean $\pm$ S.D. of three to six experiments.
[b] Solubility in water at 37°C. The value of IIMN was obtained by dividing C_o by K_{ow}.
[c] Solubility in octanol at 37°C.
[d] Solubility in isooctane at 37°C.
[e] Logarithm of ideal solubility.
[f] Diffusion coefficient in water at 37°C.
[g] Octanol/water partition coefficient at 37°C. The values except for IIMN were obtained by dividing C_o by C_w.

3.2. Relationship between skin permeation and physicochemical properties

Skin permeation of stereoisomers of organic nitrates was analyzed by two basic membrane permeation mechanisms, partitioning and porous transport, to investigate the key parameters determining skin permeability. Several physicochemical parameters of organic nitrates are listed in Table 2. When the concentration of a solute in the donor solution is greater than the solubility and a sink condition is maintained in the receiver solution during the membrane permeation of the solute, the maximum flux (J_{max}) in the partitioning transport can be mathematically expressed as:

$$J_{max} = \frac{D_m K C_v}{L} \quad (4)$$

where D_m, K and C_v are the diffusion coefficient in the membrane, membrane/vehicle partition coefficient and solubility in the vehicle of the solute, and L is the membrane thickness. Because the pores in the porous transport are filled with the same liquid as the vehicle, the partition term is omitted and the maximum flux in the porous transport is expressed as follows:

$$J_{max} = \frac{D_v \epsilon C_v}{\tau L} \quad (5)$$

where D_v is the diffusion coefficient of the solute in the vehicle filling the pores, and ϵ and τ are the porosity and tortuosity of the membrane. The structural parameters of the membrane, L, ϵ and τ, can be regarded as constant in the present study, and a similar value of diffusion coefficient compared with other parameters can be expected among organic nitrates in each route because of the small differences in molecular weight (236.14 for dinitrates and 191.14 for mononitrates). Therefore, if skin permeation of stereoisomers of organic nitrates is by partitioning transport, the maximum flux should be in proportion to the product of the skin/vehicle partition coefficient and the solubility in the vehicle, that is the solubility in skin. If permeation is by porous transport, the maximum flux should depend solely on the solubility in the vehicle. The maximum flux (J_{max}) of stereoisomers was thus plotted against the solubility in various solvents (Fig. 2). The logarithm of the maximum flux of mononitrate diastereomers had a linear relationship with the logarithm of solubility in water (C_w), the vehicle, which had a slope of about 1. However, for the dinitrate diastereomers, there was a tendency for

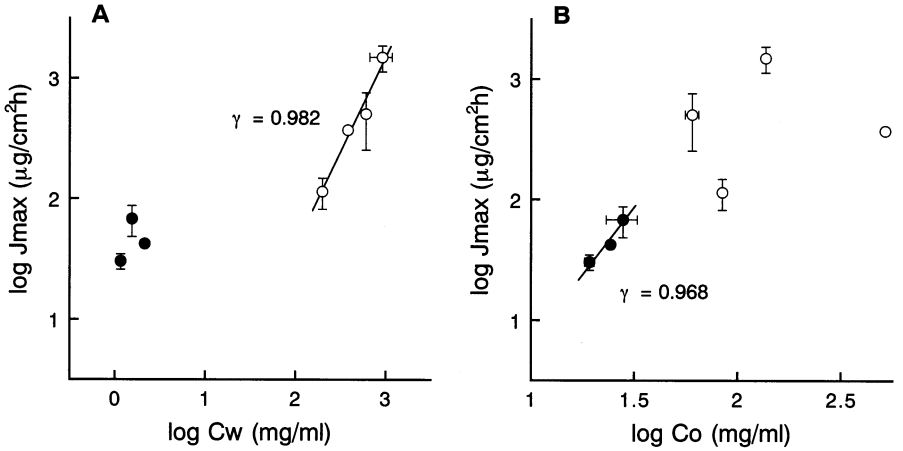

Fig. 2. Relationships of maximum flux of dinitrate (●) and mononitrate (○) diastereomers from water with the solubilities in water (A) and octanol (B). Each point represents the mean ± S.D. of three to seven experiments.

the maximum flux to relate to the solubility in octanol (C_o), a solvent which has a similar solubility parameter as the lipid domain of the stratum corneum (Liron and Cohen, 1984). These results suggest that the skin permeation of these compounds in water is controlled by a porous or a partitioning mechanism for mononitrate and dinitrate diastereomers, respectively. Under our experimental conditions, rat skin was fully hydrated so that an aqueous domain might be created in the stratum corneum in addition to the lipid domain (Lambert et al., 1989). Therefore, lipophilic dinitrate diastereomers should permeate across skin via the lipid domain according to a partitioning mechanism, whereas skin permeation of hydrophilic mononitrate isomers should occur via the aqueous domain through a porous mechanism.

From a thermodynamic point of view, Eq. (4) and Eq. (5) can be transformed into Eq. (6) and Eq. (7):

$$J_{max}\frac{D_m a_v}{\gamma_m L} \tag{6}$$

$$J_{max}=\frac{D_v \epsilon a_v}{\tau \gamma_v L} \tag{7}$$

where a_v is the thermodynamic activity of the solute in the vehicle, and γ_m and γ_v are the activity coefficients in the membrane and vehicle. Both equations show that the maximum flux is proportional to the activity in the vehicle regardless of the transport mechanism, and that the proportional coefficients differ among the mechanisms if the differences in the diffusion and activity coefficients among solutes are insignificant. The solubility in isooctane (C_i) and ideal solubility (a) of stereoisomers of organic nitrates were measured as indicators of the activity in the vehicle (Rytting et al., 1972), and the logarithmic relations with maximum flux are plotted in Fig. 3. Different straight lines among dinitrate and mononitrate isomers can be drawn for each activity indicator. The result does not contradict different permeation mechanisms, although this is not direct proof.

Based on Eq. (4) and Eq. (5), the permeability coefficient (P) is given by Eq. (8) and Eq. (9):

$$P=\frac{D_m K}{L} \tag{8}$$

$$P=\frac{D_v \epsilon}{\tau L} \tag{9}$$

Due to the constancy of the membrane structure, the permeability coefficient should change dependent on the product of the diffusion coefficient in the membrane (D_m) and the membrane/vehicle partition coefficient (K) for partitioning transport, but only on the diffusion coefficient in the vehicle (D_v) for porous transport. The relationships between the permeability coefficient of stereoisomers of organic nitrates and several physicochemical

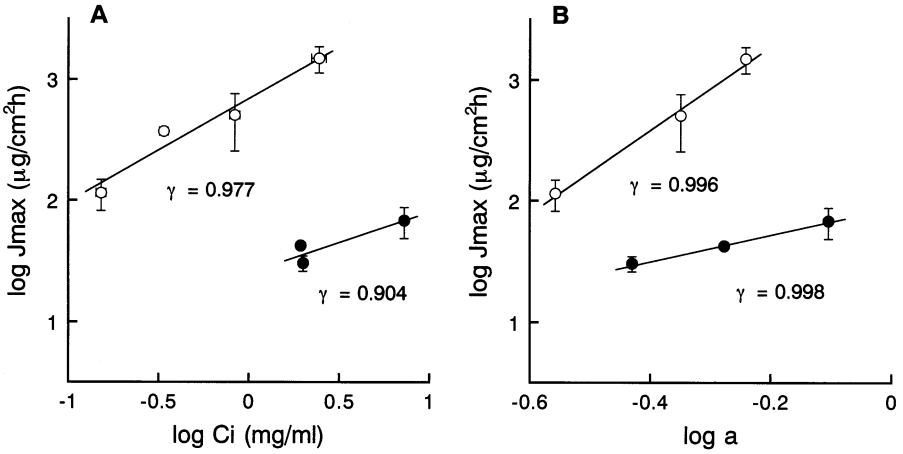

Fig. 3. Relationships of maximum flux of dinitrate (●) and mononitrate (○) diastereomers from water with the solubilities in isooctane (A) and ideal solubility (B). Each point represents the mean ± S.D. of three to seven experiments.

parameters relating to diffusivity and lipophilicity are shown in Fig. 4. The permeability coefficient of mononitrate isomers increased with increase in the diffusion coefficient in water (D_w), which may reflect the diffusion coefficient in the aqueous domain of the stratum corneum, and be independent of the octanol/water partition coefficient (K_{ow}), which is a general index for the partition from water to the stratum corneum lipid. In contrast, the permeability coefficient of dinitrate isomers increased with increase in the octanol/water partition coefficient. These results are consistent with porous transport of mononitrate isomers and partitioning transport of dinitrate ones, as mentioned above.

From the several relationships between skin permeability of stereoisomers of organic nitrates and the physicochemical parameters, we have deduced that dinitrate diastereomers permeate across skin via the lipid domain of the stratum corneum according to a partitioning mechanism, and that skin permeation of mononitrate isomers occurs via an aqueous domain by a porous mechanism. The main determinants are the solubility in the lipid domain, the lipid domain/water partition coefficient for maximum flux, the permeability coefficient of dinitrate isomers, the solubility and diffusion coefficient in water for maximum flux, and the permeability coefficient of mononitrate isomers.

3.3. Diastereomeric difference in skin permeation of organic nitrates

After confirming the main determinants of skin permeability of organic nitrates, we focused on the relationship of stereostructure with skin permeation parameters and their determinants to clarify the mechanisms increasing the diastereomeric differences in skin permeation. For dinitrate diastereomers, the permeability coefficient increased with increase in the number of nitrate groups at the *exo* position (Fig. 1 and Table 1). The octanol/water partition coefficient, which is an indicator of the lipid domain/water partition coefficient, had the same tendency (Fig. 1 and Table 2). It has been reported that the nitrate group at the *endo* position interacts with the lone-pair electrons of the oxygen atom in the adjacent ring (Hayward et al., 1967). Due to the intramolecular interactions of dinitrate isomers, the contribution of the nitrate group at the *exo* position to solute–solvent interactions is larger than that of the same group at the *endo* position. Therefore, the increase in number of lipophilic nitrate groups in the *exo* position might facilitate the movement of isomer from water to octanol and lipid domain of the stratum corneum.

The maximum flux and the solubility in octanol, which is an indicator of solubility in the lipid domain, of dinitrate diastereomers were

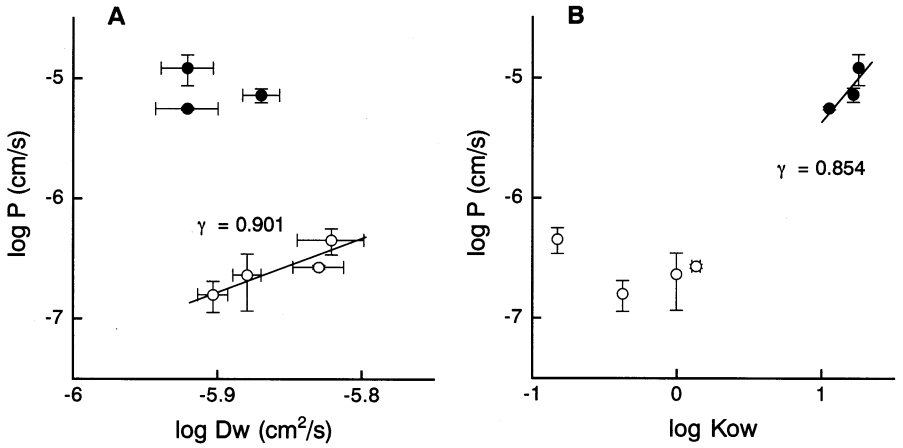

Fig. 4. Relationships of permeability coefficient of dinitrate (●) and mononitrate (○) diastereomers from water with the diffusion coefficient in water (A) and octanol/water partition coefficient (B). Each point represents the mean ± S.D. of three to seven experiments.

highest for IIDN followed by IMDN and ISDN, and the order was different from that of the permeability coefficient and octanol/water partition coefficient (Tables 1 and 2). Generally, the solubility of a crystalline solute is determined by the intrinsic properties of the crystalline lattice, as well as molecular interactions between the solute and solvent. Low crystalline lattice energy of the solute results in high solubility (Hildebrand and Scott, 1964). The heat of fusion, a parameter reflecting the crystalline lattice energy, were 12.8, 20.5 and 27.6 kJ/mol: one nitrate group at the *exo* position produces a compact molecular fitting in the crystal, but two results in a loose crystalline lattice because of steric hindrance. The lower the heat of fusion, the higher were the solubility in octanol and maximum flux of dinitrate isomers. This suggests that the differences in the specific interactions in the crystal rather than solute–solvent interactions might be the cause of differences in solubility in the octanol and lipid domain of the stratum corneum, and thus the maximum flux of dinitrate isomers.

The permeability coefficient and maximum flux of mononitrate diastereomers and their determinants, the diffusion coefficient and solubility in water, also seemed to be closely related with functional groups at the *exo* position. A nitrate group at the *exo* position increased diffusion and dissolution in water and thus skin permeation of mononitrate isomers, while a hydroxy group at the same position was inhibitory (Fig. 1, Tables 1 and 2). The hydroxy groups at the *endo* position also were involved in intramolecular interactions via a hydrogen bond to an oxygen atom in the same ring (Anteunis and Verhegghe, 1971). Therefore, interactions of functional groups at the *exo* position with surrounding water molecules might produce diastereomeric differences in the diffusivity and solubility in water, and thus skin permeability. Unfortunately, it is difficult to discuss such solute–water interactions due to the unique properties of water as solvent (Frank and Evans, 1945). Even dissolution in water is a complex phenomenon involving self-association of solute or water and hydration of solute. Taken alone, our data do not offer useful information about the mechanism of stereoselective skin permeation of mononitrate isomers.

The skin permeation of solutes via the aqueous domain of the stratum corneum is still a subject of considerable controversy. Although some investigators have suggested the existence of an aqueous pathway (Hatanaka et al., 1994; Peck et al., 1994; Ruland et al., 1994; Sznitowska et al., 1995), the concept is not fully accepted by others. A typical disproof is that the lipid domain of the stratum corneum alone can fully characterize the barrier properties of skin when the dependence of permeability coefficient on permeant size and lipophilic-

ity is considered (Potts and Guy, 1992). Four mononitrates used in this study, however, were diastereomers with the same molecular weight. The van der Waals radii calculated based on the stereostructure also ranged from 7.100 to 7.905 Å, which are too similar to account for the differences in skin permeability among the diastereomers. Moreover, 2-ISMN had the highest permeability coefficient (Table 1) in spite of its low partition to lipid (Table 2). It is unlikely that the isomer has the highest diffusion coefficient in the lipid domain of the stratum corneum because it has the largest radius among diastereomers. We therefore conclude that an aqueous domain exists in the stratum corneum at least under our experimental conditions, where rat skin was fully hydrated.

4. Conclusions

We have demonstrated the stereoselective skin permeation of organic nitrates. The stereoselectivity was caused by differences in physicochemical properties of solubility, lipophilicity and diffusivity, and these properties are closely related to the stereostructure of the diastereomers. Because the factors resulting in the stereoselectivity were not intrinsic to skin permeation, they should also affect other pharmacokinetics and pharmacodynamics. Although organic nitrates are only one example of a drug having stereoisomers, the results here provide instructive information for the design of drugs and pharmaceutical formulations.

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