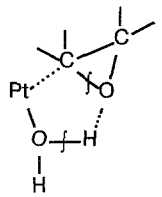

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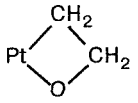

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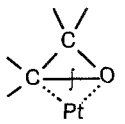

E

many metal-centered nucleophiles, we can understand why the reactivities of RI and ROTs toward the above mentioned and "normal" nucleophiles are essentially different. The higher relative rates of the reactions of RI with metal-centered nucleophiles result from the additional nucleophilic assistance to heterolysis, whereas in the case of ROTs, the leaving group has no affinity to metal complexes, and therefore, only nucleophilicity of the latter is significant.

References

1. S. L. Litvinenko, V. V. Zamashchikov, V. I. Shologon, and S. V. Bilobrov, *Metalloorg. Khim.*, 1991, **4**, 1130 [*Organomet. Chem. USSR*, 1991, **4** (Engl. Transl.)].
2. R. G. Pearson and P. E. Figdore, *J. Am. Chem. Soc.*, 1980, **102**, 1541.

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Intermolecular interactions in aqueous solutions of mebicar

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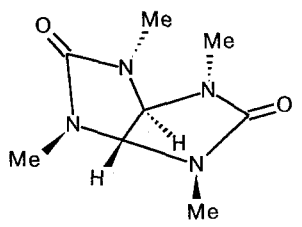
2,4,6,8-Tetramethyl-2,4,6,8-tetraazabicyclo[3.3.0]-octane-2,7-dione (mebicar, **1**) is an efficient daytime tranquilizer with a broad spectrum of activity.[1]



1

Mebicar is extremely soluble in media of various polarities (g L^{-1}): 530 (H_2O), 225 (MeOH), 155 (DMSO), 250 (CH_2Cl_2), 90 ($CHCl_3$). It has been suggested that the amphiphilic nature of **1** may be associated with its pharmacological activity.[2] We studied the effects of **1** on the structure of water and on the structures and activities of model macromolecular biological systems of a protein nature.

By differential scanning calorimetry we found that **1** can be hydrated by various mechanisms simultaneously. The specific heat capacity of **1** in a 1 % aqueous solution and its temperature increment (298—373 K) are $\bar{c}_p^{25} = 2.88$ J g^{-1} K^{-1} and $\Delta c_p \cdot \Delta T_m^{-1} = 1.46 \cdot 10^{-3}$ J g^{-1} K^{-2}. The value of the increment for **1** is comparable to that for *L*-leucine (**2**) $\Delta c_p \cdot \Delta T_m^{-1} = 1.1 \cdot 10^{-3}$ J g^{-1} K^{-2} (in the hydration of **2**, hydrophobic effects predominate). The low value of $\bar{c}_p^{25}$ for this compound, as also that for urea (**3**) ($\bar{c}_p^{25} = 1.55$ J g^{-1}), characterizes the ability of these substances to break the structure of water; for compound **2**, $\bar{c}_p^{25} = 1.92$ J g^{-1} K^{-1}.

Using millimeter absorption spectroscopy[4] we quantitatively evaluated the composition of the hydration shell of molecule **1**. We measured absorption (α/dB mm^{-1}) of electromagnetic radiation by aqueous solutions of **1** at the frequencies ν = 1.05, 1.40, 1.71 cm^{-1} and in the 4—7 cm^{-1} range in the 287—333 K temperature interval. The $\alpha(\nu)$ dependence at 293 K indicates that molecule **1** binds nine water molecules with lifetimes in the hydration shell $\tau \geq 10$ ps. As measurements

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at low frequencies show, at least two water molecules incorporated in the hydration shell retain their rotational mobility, as has been observed for hydration of compound **3** (see Ref. 4). The decrease in absorption indicates hydrophobic immobilization of two or three water molecules, most likely, around the bridging HC—CH group and the four methyl groups. Up to four water molecules are bound according to a mechanism of positive polar hydration through the formation of H-bonds with the carbonyl O atoms.

The rate of enzymatic hydrolysis of *N*-acetyl-L-tyrosine ethyl ester catalyzed by α-chymotrypsin was also studied. The rate noticeably increases in the presence of **1** ([**1**] ≤ 0.15 mol L^{-1}): the rate constant of hydrolysis of the acyl-enzyme intermediate is $k = k_{c,1} + k_{c,2}$ [**1**], where $k_{c,1} = 2.5\ s^{-1}$ is the rate constant of the hydrolysis in the absence of **1**, and $k_{c,2}$ is the second-order rate constant taking into account the effect of **1** on the rate of the enzymatic reaction. When [**1**] ≤ 0.15 mol L^{-1}, no structural changes of α-chymotrypsin or its ability to bind **1** were detected; therefore, the accelerating effect of **1** can be attributed mostly to the activation of water as a nucleophilic reagent (generation of additional reactive H_2O molecules with high mobilities[4]).

The denaturing activity of **1** was studied by differential UV spectrophotometry.[5] Up to the concentration $[\mathbf{1}]_{cr} = 0.7$ mol L^{-1} the globular protein (chymotrypsinogen A) is conformationally stable. At higher concentrations of compound **1** denaturation of the protein is observed. Previously[5] it was shown that denaturation of proteins in aqueous solutions of organic nonelectrolytes occurs in those cases where they are able to break the structure of water and also in the case of exhaustion of the bulk water. Denaturation of chymotrypsinogen A was observed at $[H_2O]_{cr} = 49$ mol L^{-1}, which practically coincides with the value $[H_2O]_{cr} = 48$ mol L^{-1} obtained for compound **3** and guanidine chloride.[5] Hence, compound **1** activates the aqueous component and can thus affect the static and dynamic structures of physiologically active proteins as well as their biological activity.

The results obtained and also the suggestion concerning the activation of biological membranes[2] may be favorable for understanding the contributions of solvent effects to the mechanisms of pharmacological activity of **1** and similar materials.

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References

1. USSR Pat. 491619, *Byul. Izobret.*, 1975, No. 42, p. 59.
2. Yu. I. Khurgin, O. V. Lebedev, and E. Yu. Maksareva, *Millimetrovye volny v biologii i meditsine* [*Millimeter Waves in Biology and Medicine*],1994, No. 4, 28 (in Russian).
3. P. L. Privalov and S. J. Gill, *Advances in Protein Chemistry*, 1988, **42**, 191.
4. Yu. I. Khurgin, V. A. Kudryashova, V. A. Zavizion, and O. V. Betskii, *Adv. Chem. Phys.*, 1994, **87**, 483.
5. Yu. I. Khurgin and E. Yu. Maksareva, *FEBS Lett.*, 1993, **315**, 149.

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Palladium-catalyzed homocoupling of aryl halides in a aqueous-organic microemulsion through the action of hydrogen

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Previously[1,2] we studied hydrogenolysis of water-soluble aryl halides in aqueous alkaline solutions through the action of $NaBH_4$ in the presence of $PdCl_2$ as catalyst and showed that the process occurs chemoselectively to give the corresponding arenes. However, aryl halides insoluble in water virtually did not undergo hydrogenolysis under the same conditions even in the presence of a phase-transfer catalyst. A number of techniques for the reduction of water-insoluble aryl halides in aqueous-organic media in the presence of catalysts

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