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Rotation Barriers in Pyridinium Salts Depend on the Number of Available Ground State Conformations*

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The enthalpy and entropy of activation for the rotation about the C–N bond were measured in a series of five *N*-(1-hydroxybutan-2-yl)pyridinium salts, the 2,6-substituents being methyl, ethyl and isopropyl. Replacement of a methyl by an ethyl does not change the activation parameters, while replacement by an isopropyl increases both the activation enthalpy and the activation entropy. The latter is due to the decreased number of conformations available in the ground state. The activation entropies fit a simple model based on entropy of mixing.

Key words
pyridinium
conformation
isopropyl
activation parameters

INTRODUCTION

The low-energy conformation of the isopropyl group in isopropylbenzene is with the α-hydrogen eclipsed with the benzene ring.[1] In this conformation, the *ortho* and *meta* positions on an aromatic ring are not equivalent anymore. The NMR spectra of 1-isopropylpyridinium salts with substituents R ≠ H in positions 2 and 6 display the signals of two conformers (A and B in Figure 1) around room temperature, and the barriers to rotation about the C(sp^3) – N(sp^2) bond are in the range that can be conveniently measured by dynamic NMR. In a series of polymethyl-substituted 1-isopropylpyridinium salts the barriers to rotation decreased with increasing substitution, presumably due to better accommodation of the strain in the transition state than in the ground state.[2] It was found that the rotation barrier for a C-bonded isopropyl flanked by two methyl groups in pyridines or pyridinium salts was 46–50 kJ mol^{-1}. For a similar isopropyl bonded to the nitrogen heteroatom in pyridinium salts the barrier was 58–63 kJ mol^{-1}.[2] This difference was ascribed to the bond distance, which was shorter for C–N bonds than for C–C bonds. The influence on the barriers to rotation of an isopropyl-like substituent in position 1 of 2,4,6-trimethylpyridinium salts was also investigated, and it was found that the addition of an extra methyl group (going from 1-hydroxypropan-2-yl to 1-hydroxybutan-2-yl) increased the barrier by about 12 kJ mol^{-1}.[3] We have undertaken here a study of the influence of the substituents in positions 2 and 6 on the barriers to rotation in the five 4-methyl-2,6-dialkyl-1-(1-hydroxybutan-2-yl)pyridinium hexafluorophosphates presented in Table I.

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* Dedicated to Professor Nenad Trinajstić on the occasion of his 65th birthday.

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EXPERIMENTAL

The preparation of compounds **1** (Ref. 3), **2** (Ref. 4) and **4** (Ref. 4) *via* the corresponding pyrylium salts has been previously reported. Pyrylium salts with identical 2- and 6-substituents were prepared by alkene diacylation on adding 70 % hexafluorophosphoric acid into a mixture of carboxylic anhydride with *tert*-butanol that provided isobutene *in situ* by dehydration. When 2,4-dimethyl-6-alkylpyrylium salts were needed, they were obtained by monoacylation of mesityl oxide on adding 70 % hexafluorophosphoric acid into a mixture of carboxylic anhydride and mesityl oxide. Pyrylium salts were then converted into pyridinium hexafluorophosphates by reaction with racemic amino-1-butanol.

The NMR spectra were recorded on a Varian Inova, equipped with a 5 mm indirect detection probe, at 500 MHz for proton. Unless otherwise specified, the solvent was dmso-d_6. The chemical shifts reference was internal tetramethylsilane. The variable temperature spectra were recorded on automation. In order to achieve temperature stability, for each temperature step of 2 °C, a preacquisition delay of 5 minutes was followed by 20 minutes of shimming on the FID. The actual temperature was measured running a standard of ethylene glycol in the same conditions. A quadratic function was used to fit the actual temperature to the setting, which provided a standard error for the temperature of ±0.01 °C.

Preparation of Pyrylium Salts by Diacylation of Isobutene

To a mixture of carboxylic anhydride (420 mmol) and anhydrous *tert*-butanol (50 mmol), 60 % hexafluorophosphoric acid (50 mmol) was added dropwise under stirring at such a rate that the temperature did not raise over 90 °C. After cooling, the crystalline pyrylium salt was filtered off, washed thoroughly with diethyl ether, and recrystallized from ethanol. Yields were around 50 %.

2,6-Dialkyl-4-methylpyrylium hexafluorophosphates: Me–Me, m.p. 199 °C; Et–Et, m.p. 187 °C; iPr–iPr, m.p. 186 °C.

Preparation of Pyrylium Salts by Acylation of Mesityl Oxide

To a mixture of carboxylic anhydride (380 mmol) and mesityl oxide (50 mmol of the commercial mixture of α,β- and β,γ-unsaturated isomers), 60 % hexafluorophosphoric acid (50 mmol) was added dropwise under stirring at such a rate that the themperature did not raise over 90 °C. After cooling, the crystalline pyrylium salt was filtered off, washed thoroughly with diethyl ether, and recrystallized from ethanol. Yields were around 40 % and the purity of the crude products was lower than for the preceding method.

2-Alkyl-4,6-dimethylpyrylium hexafluorophosphates: Et, m.p. 185 °C; iPr, m.p. 132 °C.

Conversion into Pyridinium Salts

The pyridinium salts were prepared by refluxing the ethanolic solution of the pyrylium salt with an equimolar amount of 2-amino-1-butanol for 20 minutes, adding after cooling a small amount of ammonium hydroxide (for converting any unreacted pyrylium salt into the corresponding liquid pyridine) and precipitating the product by addition of diethyl ether. Filtration, washing with diethyl ether, and recrystallization from ethanol afforded compounds **1**–**5** in 80–90 % yield. All these compounds gave correct elemental analyses for C, H, N.

(±)-2,6-Diethyl-1-(1-ethyl-2-hydroxyethyl)-4-methylpyridinium hexafluorophosphate (**3**), m.p. 157–158 °C. ^{1}H NMR

TABLE I. ^{1}H NMR chemical shifts in compounds **1**–**5**

Compound R2–R6 (conformer) Position	**1** Me–Me	**2** Me–Et **A**	**2** Me–Et **B**	**3** Et–Et	**4** Me–iPr **A**	**4** Me–iPr **B**	**5** iPr–iPr
3	7.75	7.73	7.74	7.71	7.84	7.74	7.81
4	2.48	2.50	2.50	2.53	2.52	2.52	2.54
5	7.72	7.73	7.81	7.81	7.71	7.98	7.94
OH[(a)]	5.30	–	–	5.37	5.34	5.36	–
1'	4.05, 3.89	4.05, 3.92	4.00, 3.93	4.02, 3.96	4.07, 3.92	3.99, 3.95	3.99, 3.96
2'	5.12	5.11	5.11	5.09	5.24	5.10	5.19
3'	2.02, 2.02	2.06, 2.01	2.06, 1.98	2.12, 1.98	2.03, 2.03	2.10, 1.96	2.15, 1.96
4'	0.85	0.86	0.86	0.89	0.86	0.88	0.91
1''	2.83	3.19, 3.14	2.83	3.20, 3.15	3.77	2.83	3.73
2'' *syn*[(b)]	–	1.32	–	1.34	1.36	–	1.36
2'' *anti*	–	–	–	–	1.34	–	1.34
1'''	2.83	2.84	3.12, 3.12	3.13, 3.13	2.85	3.63	3.62
2''' *syn*	–	–	1.33	1.34	–	1.34	1.34
2''' *anti*	–	–	–	–	–	1.33	1.32

[(a)] In cases of missing values, the OH was in fast exchange with the residual water in dmso-d_6.
[(b)] *syn* and *anti* refer to the relative position to the OH.

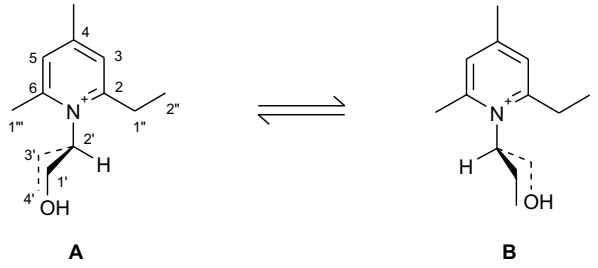

Figure 1. Conformers of 4-methyl-2,6-dialkyl-1-(1-hydroxybutan-2-yl)pyridinium hexafluorophosphates and position numbering.

(see Table I); ^{13}C NMR (dmso-d_6) δ/ppm: 161.1 (C6), 160.4 (C2), 158.0 (C4), 129.3 (C5), 127.5 (C3), 69.4 (C2'), 62.6 (C1'), 28.8 (C1''), 26.9 (C1'''), 24.8 (C3'), 21.3 (4-Me), 15.3 (C2'''), 13.8 (C2''), 11.7 (C4').

(±)-2,6-Diisopropyl-1-(1-ethyl-2-hydroxyethyl)-4-methylpyridinium hexafluorophosphate (**5**), m.p. 203–204 °C. ^{1}H NMR (see Table I); ^{13}C NMR (dmso-d_6) δ/ppm: 165.4 (C6), 164.6 (C2), 158.3 (C4), 127.1 (C5), 125.3 (C3), 68.6 (C2'), 62.9 (C1'), 31.9 (C1''), 31.3 (C1'''), 25.3 (C3'), 23.9 (2xC2'''), 23.2 (C2''), 21.5 (4-Me), 11.9 (C4').

RESULTS AND DISCUSSION

Proton Spectra

The proton NMR spectra of the symmetric compounds **1**, **3** and **5** in dmso-d_6 at 25 °C display nonequivalence of the *ortho* and *meta* positions. The asymmetric compounds **2** and **4** present a mixture of conformers. We call **A** the conformer in which the larger group, Et or iPr is *syn* to the hydrogen in position 2'. The proton chemical shifts are presented in Table I. For comparison purposes, the numbering of positions 2–6 starts with position 2 being *syn* to H2'. The identification of conformers **A** or **B** and the assignment of the signals to positions 3 or 5 on one hand, or 2 or 6 on the other, were made on the basis of the nOe's seen in the NOESY spectrum. In all of the compounds, H2' displayed a strong nOe to the protons of the group in position 2, H1''. The nOe between H1'' and H3 identified the latter. Similar nOe's of protons in positions 1' and 3' to H1''' and of H1''' to H5 confirmed the assignments.

All of the chemical shifts in Table I were assigned in this way, except for H3 and H5 in **1**, which displayed overlap of the signals of positions 1'' and 1'''. These latter protons were assigned on the basis of the trend in the chemical shifts δH5 < δH3 and δH1'' < δH1''' demonstrated by compounds of this type.[2,4] The diastereotopic methyls in the isopropyl groups were assigned as *syn* or *anti* to the OH in the substituent in position 1 based on their nOe's with H1' or H3', respectively. As expected, the *syn* methyls are deshielded compared to the *anti* ones. One-bond ^{1}H–^{13}C couplings seen in the GHMQC spectrum allowed the assignment of the protonated carbons. Two or three bond ^{1}H–^{13}C couplings revealed by the GHMBC spectrum allowed the assignment of the quaternary carbons and confirmed the structural integrity of the compounds.

When in position 2, methyl or ethyl groups display line widths *ca.* 0.4 Hz larger than when they are in position 6, which provides an easy means to discriminate between H1'' and H1''' and, in the case of R2 ≠ R6, to identify conformers **A** and **B**. As demonstrated by the DQCOSY spectrum, the extra broadening is due to a through-space coupling of H2' and H1'', which are five bonds away. No such extra broadening has been seen for the isopropyl groups, which is surprising because the distance between of H2' and H1'' is supposed to be smaller for isopropyl than for methyl or ethyl. An isopropyl group *ortho* to the nitrogen in a pyridinium salt adopts an orientation with the α-hydrogen in the plane of the ring and pointing towards nitrogen.[4] In this orientation, the α-hydrogen of an isopropyl »sticks out« more than the one of a freely rotating methyl or ethyl. This repulsion between H2' and H1'' was used to explain the predominance of conformer **B** in the conformational equilibrium of compound **4**. An isopropyl group in position 6 also modifies the coupling constants of H2' and H1'. In compounds/conformers **1**, **2**, **3** and **4A** $^3J_{\mathrm{H2'–H1'deshielded}}$ = 9.8–9.3 Hz and $^3J_{\mathrm{H2'–H1'shielded}}$ = 5.2–5.4 Hz. The corresponding values in **4B** and **5** are both 7.1–7.3 Hz. The coupling pattern of H2' is diagnostic for the conformation of the compounds of this type, having one isopropyl group *ortho* to nitrogen. The chemical shift difference between the protons in position 1' is larger in the series **1**, **2**, **3** and **4A** (0.16 – 0.06 ppm) than in the series **4B** and **5** (*ca.* 0.03 ppm). The differences in coupling constants between the series suggest a difference in the populations of the conformers arising from rotation about the C1'– C2' bond.

Conformational Equilibria and Rotation Barriers around the C(sp^3)–N(sp^2) Bond

Conformational Equilibria. – Proton NMR spectra of compounds **1**–**5** were carefully recorded (see experimental) every 2 °C in the temperature interval 70–130 °C. Complete lineshape analysis of the signals of H3 and H5 using gnmr[5] afforded the absolute rate for rotation (k) and, for the asymmetric compounds **2** and **4**, the constant for the conformational equilibrium (K). Reliable rate constants could be obtained below coalescence and until the absolute rate was about 1Hz, which corresponded to the temperature interval of 120 °C to 80 °C. For compound **2**, the ratio of conformers **A** and **B** was close to 1:1 throughout this temperature range, indicating that **A** and **B** have identical steric interactions and number of conformations available for the ethyl and 1-hydroxybutan--2-yl chain. For compound **4**, a plot of ln$K$ *vs.* 1/T afforded for the rotation **A** → **B** (**A** is the minor conformer) ΔH = 9.62 ± 0.17 kJ mol^{-1} and ΔS = 16.94 ± 0.17 J mol^{-1} K^{-1}.

TABLE II. Activation parameters for the rotation **B** → **A** in compounds **1**–**5**

compound	in dmso-d_6			in pyridine-d_5		
R2, R6	$\Delta H^{\neq}$ / kJ mol^{-1}	$\Delta S^{\neq}$ / J mol^{-1} K^{-1}	$\Delta G^{\neq}$ / kJ mol^{-1}	$\Delta H^{\neq}$ / kJ mol^{-1}	$\Delta S^{\neq}$ / J mol^{-1} K^{-1}	$\Delta G^{\neq}$ / kJ mol^{-1}
1, Me, Me	74.9 ± 1.7	–23.4 ± 0.8	83.7	– –	– –	–
2, Me, Et	75.3 ± 0.8	–25.1 ± 1.7	84.5	74.5 ± 0.8	–27.2 ± 0.8	84.5
3, Et, Et	76.6 ± 0.8	–24.7 ± 0.8	85.8	– –	– –	–
4, Me, iPr	81.2 ± 0.8	–16.3 ± 0.4	87.0	80.3 ± 0.8	–15.9 ± 0.4	86.2
5, iPr, iPr	80.3 ± 2.5	–11.3 ± 0.8	84.5	82.0 ± 0.8	–6.3 ± 0.4	84.1

Rotation Barriers. – Plots of ln(k/T) *vs.* 1/T for compounds **1**–**5** afforded the activation enthalpies and entropies for the rotations **B** → **A**, given in Table II.

For compounds **2**, **4** and **5**, measurements in pyridine in the temperature range 80–110 °C afforded the values presented in the last columns of Table II. These results are considered less reliable, because of the interference of the solvent's signals, which had to be taken into the simulation too. One can see that the differences between the activation parameters in the two solvents are within experimental errors, except for the activation entropy in the case of compound **5**. The $\Delta G^{\neq}$ values were calculated in the middle of the temperature interval for dmso, at 100 °C. The precision in $\Delta G^{\neq}$ is considered to be better that for the individual $\Delta H^{\neq}$ or $\Delta S^{\neq}$ because of their known tendency to internally compensate the errors, and the results indicate it to be ± 0.4 kJ mol^{-1}.

There is a trend in the $\Delta G^{\neq}$ values of compounds **1**–**4** to increase with the size of substituents. This trend is broken at compound **5**, namely replacement of a methyl with an isopropyl going from **4** to **5** drops the $\Delta G^{\neq}$ to the level of the methyl-ethyl compound **2**. The values of $\Delta G^{\neq}$ are not very differentiated and not as informative as the values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$, afforded by careful measurements. One can easily see that $\Delta S^{\neq}$ is responsible for the drop in $\Delta G^{\neq}$ from **4** to **5**, and the explanation is the extra order in the ground state introduced by an isopropyl. The activation enthalpies $\Delta H^{\neq}$ are the same within experimental errors within the series of compounds **1**, **2** and **3** on one hand and within the series **4** and **5** on the other hand, and the difference between the series is significant. This is consistent with $\Delta H^{\neq}$ being determined by the largest of the groups in positions 2 and 6, and with methyl and ethyl being about the same size and smaller than an isopropyl – an ethyl can present to the hindered region in the transition state a methyl face, while the isopropyl cannot. The activation entropies, $\Delta S^{\neq}$, are the same in the first series, and then they increase with each of the extra isopropyl groups. Assuming that the transition states for compounds **1**–**5** possess similar entropies, the increase in $\Delta S^{\neq}$ is consistent with a decrease of the ground state entropy on adding each of the isopropyl groups. The change of coupling constants $^3J_{H2'-H1'}$ when going from **1** through **4A** to **4B** and **5** suggests that an isopropyl group in position 6 (*syn* to C1') changes the populations of the conformers arising from the rotation about the C1'–C2' bond. $^3J_{H2'-H3'}$, measured by decoupling H4', did not show such a change, being in both cases 7.9–7.3 Hz.

We propose here a model in which the number of conformations accessible to the 1-hydroxybutan-2-yl substituent (with much lower rotation barriers than those involving the C–N bond) is four in the ground state for conformers **1**–**4A**, one for conformers **4B**–**5**, and one in the transition state in all of the cases. The four ground state conformations for **1**–**4A**, presented in Figure 2, are those in which neither the OH in position 1' nor the CH_3 in position 4' are intercalated between the pyridinium and the rest of the butan-2-yl chain.

An isopropyl group in position 6 makes the pyridinium group appear larger, and the only conformation accessible to **4B** and **5** is the one in which both the methyl on C3' and the hydroxyl on C1' are *anti* to the pyridinium. This is also the only conformation available in the transition state. The entropy gained when releasing the 1-hydroxybutan-2-yl substituent from one conformation into four would be the entropy of mixing: $S_{mix} = -R\,\Sigma n_i^{-1}\ln(n_i^{-1}) = -8.31[4*0.25*\ln(0.25)] = 11.46$ J mol^{-1} K^{-1}, where n_i is the number of available conformations. The entropy for the rotation **4B** → **4A** is ΔS = 16.74 J mol^{-1} K^{-1}, which is more than that gained by releasing the substituent in position 1 into four conformations. The difference has to come from releasing the

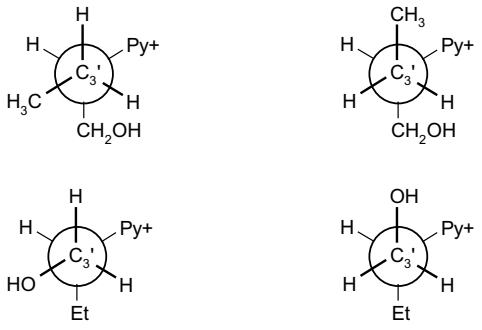

Figure 2. Conformations available for the 1-hydroxybutan-2-yl substituent in position 1.

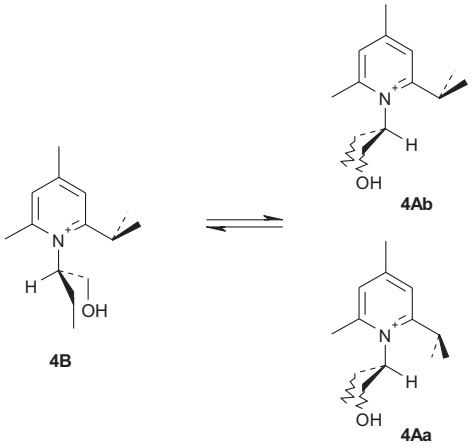

Figure 3. Ground-state conformations available to compound **4**.

isopropyl group in position 6 into two conformations (Figure 3). In this case: S_{mix} = –8.31[8*0.125*ln(0.125)] = 17.2 J mol^{-1} K^{-1}, within the experimental error from the measured value.

Averaging with conformations in which H1" of the isopropyl points away from H2' also explains the lack of coupling (or a coupling too small to be seen) between these two protons in **4A** and **5**. In terms of ΔG for the reaction **4B** → **4A**, at 100 °C, ΔS accounts for –373*16.7/1000 = –6.3 kJ mol^{-1} and ΔH for 9.6 kJ mol^{-1}.

The difference in $\Delta S^{\neq}$ between compounds **1**–**3** and **4B** (8.8 J mol^{-1} K^{-1}) comes mainly from the restriction of the substituent in position 1 to one conformation in the latter, which accounts for 11.5 J mol^{-1} K^{-1}. The rest could be due to some residual conformational freedom of the substituent in position 1 in the transition states of the less hindered compounds, but in a first approximation, one can say that the transition states in the two cases are of comparable entropies. For compound **5** the transition state should be even closer in entropy to the one of **4B**, because an extra isopropyl group would limit even further the conformational mobility of the 1-hydroxybutan-2-yl substituent. In this case, assuming that the isopropyl in position 2 in **5** can adopt two conformations, as in **4A**, one would expect the entropy of the ground state of **5** to be higher than the one of **4B** by S_{mix} = –8.31[2*0.5ln(0.5)] = 5.7 J mol^{-1} K^{-1}. In fact, the ground state of **5** is lower than the one of **4B** by about the same amount (5.0 J mol^{-1} K^{-1}) which would be possible if in the ground state of **5** one had complete gearing and in the transition state one of the isopropyl groups would still be conformationally mobile. It is possible for the groups in positions 1 and 2 to be geared in **5** and not in **4A** – the extra isopropyl group in position 6 of **5**, while gearing with the group in position 1, bends the C2'–N bond towards the group in position 2. The chemical shifts of H1" and H2' are higher in **4A** than in **5**, which is consistent with reduced steric strain in the latter, achieved by gearing.

The activation enthalpies are the same for compounds **4B** and **5**. In the transition state the N-substituent rotates with one of the β carbons past one of the *ortho* isopropyl groups, which is conformationally locked. The other isopropyl group, further away from the other β carbon, may still be mobile.

Molecular Structure of Compound 2 Determined by X-ray Diffraction

The molecular structure of compound **2** is presented in Figure 4. One can see that in the crystal the 1-hydroxybutan-2-yl group has a staggered zig-zag (*anti*, or W-type) conformation, and the plane of the pyridinium ring bisects the W-shaped hydroxybutyl moiety. The crystal structure agrees with the model we proposed for the ground state conformations – neither the OH in position 1' nor the CH_3 in position 4' are intercalated between the pyridinium and the rest of the butan-2-yl chain. The pyridinium ring bisecting the W-shaped hydroxybutyl moiety agrees with the structures of the conformers of Figure 1. The oxygen atom deviates from the plane of the butyl group by –159.3°. The orientation of the 1-hydroxybutan-2-yl group is such that the two ethyl groups (one belonging to the 1-hydroxybutan-2-yl group and the other being a pyridinium substituent) are close to each other, whereas the hydroxymethyl group is oriented towards the methyl substituent of the pyridinium ring. The larger thermal ellipsoids of the methyl groups in the ethyl substituents indicate that the position of these groups fluctuates more than that of other groups.

CONCLUSIONS

In conclusion, the activation enthalpies and entropies, afforded by careful dynamic NMR experiments, allowed an insight into the ground state and transition state conformations of 2,6-dialkyl-1-(1-hydroxybutan-2-yl)pyridinium

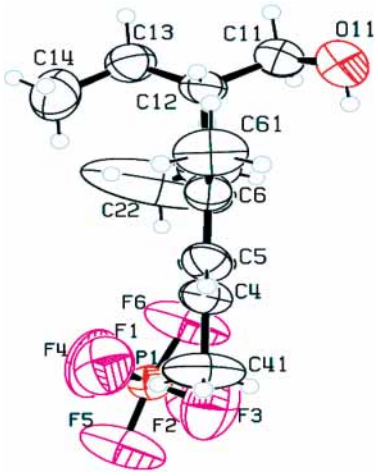

Figure 4. The conformation of compound **2** in solid state, as determined by X-ray crystallography.

salts. It was found that in the transition state there is little if any conformational mobility of the substituent in position 1 and of the bulkier of the substituents in positions 2 and 6. In the ground state, all four conformations of the 1-hydroxy-2-pyridiniumbutan which do not have the hydroxy or the terminal methyl intercalated between the pyridinium and the rest of the butan-2-yl chain are available, as long as the substituent in position 1 is not geared with an isopropyl group. In this latter case, the only conformation available is the one with these terminal groups *anti* to the pyridinium. An isopropyl group in position 6 (*anti* to H2') was found to be geared to the substituent in position 1, as opposed to the situation when the isopropyl is in position 2. However, isopropyl groups in both positions 2 and 6 will be all geared.

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SAŽETAK

Rotacijske barijere kod piridinijevih soli ovise o broju raspoloživih konformacija osnovnoga stanja

Ion Ghiviriga, Edmund W. Czerwinski i Alexandru T. Balaban

Izmjerene su entalpija i entropija aktivacije za rotaciju oko C–N veze u nizu od pet *N*-(1-hidroksibutan-2-il)piridinijevih soli s metilom, etilom i izopropilom kao 2,6-supstituentima. Zamjena metila s etilom ne mijenja aktivacijske parametre, dok zamjena metila s izopropilom povećava i entalpiju aktivacije i entropiju aktivacije. Ovaj drugi rezultat je posljedica smanjivanja broja raspoloživih konformacija osnovnoga stanja. Entropije aktivacije podupiru jednostavan model temeljen na entropiji mješanja.