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A DNMR STUDY OF ISOMERIC PHENOLS OBTAINED BY RING-OPENING, RING-CLOSURE OF 3-ISOPROPYL-2,4,6-TRIMETHYLPYRYLIUM SALTS: AN APPROACH TO THE REGIOSELECTIVITY OF THE RING-CLOSURE

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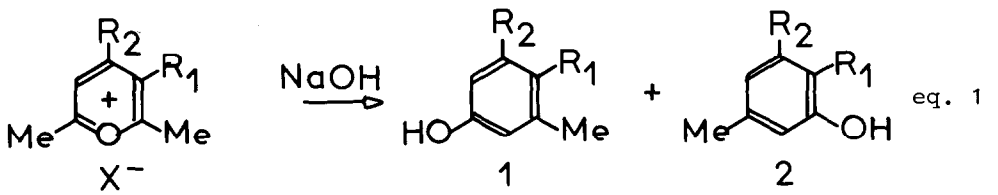
Abstract: The regioselectivity of the syntheses of phenols via dissymmetrical pyrylium salts is found to be related to the difference in steric strain in the products as determined by conformational analysis.

Pyrylium salts bearing methyl or methylene groups in positions 2 and 6 afford the corresponding phenols under treatment with alkali.[1] This time-honoured reaction[2] was used for identification of the pyrylium salts,[3] and little attention has been paid to the regioselectivity of the ring-closure when the starting pyrylium salt bears two different substituents in positions 3 and 5 leading to nonequivalence of the positions 2 and 6. Thus, 3-R_1-4-R_2-2,6-dimethylpyrylium salt gives the two isomeric phenols 1 and 2 (eq. 1) under treat-

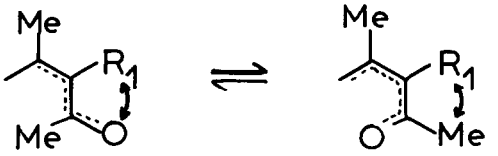


eq. 1

ment with NaOH. Under standard conditions,[4] 2,3,4,6-tetramethylpyrylium salt (R_1 = R_2 = Me) afforded 1a (R_1 = R_2 = Me) (31 %) and 2a (R_1 = R_2 = Me) (69 %), whereas 4-ethyl-2,3,6-trimethylpyrylium salt (R_1 = Me, R_2 = Et) afforded 1b (R_1 = Me, R_2 = Et) (30 %) and 2b (R_1 = Me, R_2 = Et) (70 %).

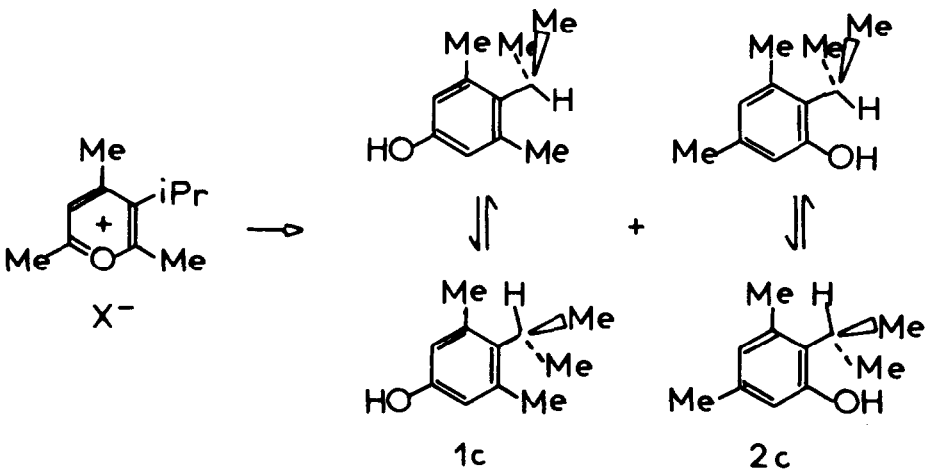
Since it appears that the more encumbered methyl group preferentially enters the ring, we suspected that the steric interaction between the methyl group in position 2 and the substituent R_1 could play a significant role in the regioselectivity of the ring-closure of the common intermediate (1,5-pentenedione). In order to observe a cyclization leading to the phenol 2, the 1,5-pentenedione must adopt a conformation in which the methyl group is transoid to the R_1 substituent whereas the cisoid conformation will not give any cyclization. The regioselectivity might arise from the difference in strain between R_1 and the oxygen on one hand and between R_1 and a methyl group on the other

hand (Scheme).



Scheme

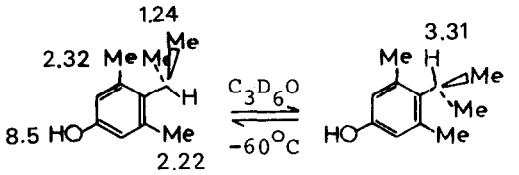
In order to check this hypothesis, we prepared the 3-isopropyl-2,4,6-trimethylpyrylium salt[5] in which the strain is expected to be substantial, and which above all provides two isomeric phenols 1c (R_1 = iPr, R_2 = Me) and 2c which can be used as rigid model for a quantitative and experimental study of the interaction of the isopropyl group and a methyl or a hydroxyl, respectively (eq. 2), through the conformational analysis of the isopropyl group in 1c and 2c. The treatment of the 3-isopropyl-2,4,6-trimethylpyrylium by NaOH gave 10 % of 1c and 90 % of 2c supporting our hypothesis.[6]



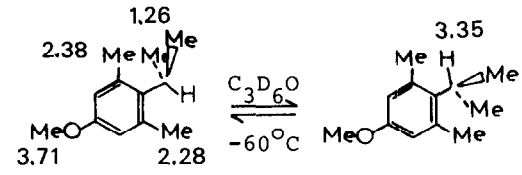
eq. 2

The DNMR study was performed on both free phenols and their methoxy derivatives[8] in C_3D_6O or freon mixture. On cooling, the rotation around the sp^2-sp^3 bond (aryl -iPr) is slowed down in 1c and 2c. Two conformers are evidenced, they differ by the orientation of the isopropyl group as it has been exemplified several times on other derivatives.[9] In 2c, the conformer with the two methyl groups of the isopropyl straddling the plane of the ring and pointing toward the hydroxy group, is far more populated than the other.[10] The conformational preference is similar in acetone and a mixture of CHF_2Cl and $CHFCl_2$. The barrier to the rotation[11] (which involves the steric requirements of the two ortho-ortho' substituents) is lower in 2c than in 1c. Barriers to rotation are known for isopropylmesitylene[9b] ($\Delta G^{\ddagger}$ = 12.88 kcal/mol (-38 °C) in acetone) and for 2,6-dimethoxy-4-methylcumene[12] ($\Delta G^{\ddagger}$ = 9.6 kcal/mol (-93 °C) in CS_2). The similarity of the barriers in 1c and isopropylmesitylene supports the assumption that electronic effect of the remote substituent does

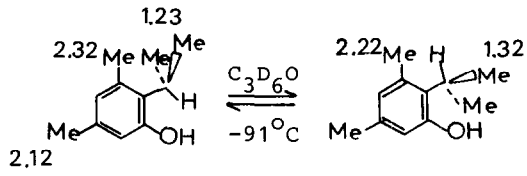
not affect the barrier height. 2c has a barrier which is between the one in isopropylmesitylene and the one in 2,6-dimethoxy-4-methylcumene as expected for the intervention in the transition state of the rotation of the steric interaction of both flanking substituents. Our experimental data on 2c disprove the barrier to rotation calculated by molecular orbital calculation on 2-iPr-3-methylphenol which was obviously erroneous.[13]



Δν(Hz)	T (K)	$k(s^{-1})$	$\Delta G^{\ddagger}$ (kcal/mol)
10.4	237.3	10.0	12.69
10.5	244.3	19.0	12.77
10.7	251.4	38.0	12.81

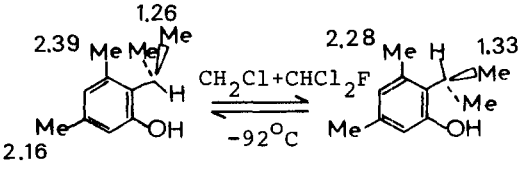


Δν(Hz)	T (K)	$k(s^{-1})$	$\Delta G^{\ddagger}$ (kcal/mol)
10.0	236.8	8.0	12.77
10.0	241.8	12.5	12.84
10.0	251.1	34.0	12.85



Δν(Hz)	T (K)	$k(s^{-1})$	$\Delta G^{\ddagger}$ (kcal/mol)
10.3	188.1		10.5 ± 0.3 (A → B)

p_A=0.03 ΔG°=1.26 p_B=0.97±0.01



Δν(Hz)	T (K)	$k(s^{-1})$	$\Delta G^{\ddagger}$ (kcal/mol)
10.9	196.0	4.0	10.75
10.9	203.3	11.1	10.76 (A → B)

p_A=0.05 ΔG°=1.05 p_B=0.95±0.01

In summary, both the conformational states and the barriers to rotation indicate that strain is lower when an isopropyl group interacts with a hydroxy than when it interacts with a methyl group.[14] This difference in strain which is to be found in all the steps leading to the ring-closure is a first approach to the regioselectivity of the syntheses of phenol via dissymmetrical pyrylium salts.

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References and Notes

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5. 2,4-diMe-2-pentanol was diacylated by Ac_2O in $HClO_4$ medium as already described for other alcohols.[4] 3-iPr-2,4,6-trimethylpyrylium ^1H NMR (CF_3COOH/$CDCl_3$ (80/20)): 1.46 (6H, d, J = 8 Hz), 2.80 (3H, s), 2.86 (3H, s), 2.96 (3H, s), 3.53 (1H, m, J = 8 Hz), 7.67 (1H, s).
6. 3,5-Dimethyl-2-isopropylphenol 2c: ^1H NMR ($CDCl_3$) 1.27 (6H, d), 2.12 (3H, s), 2.20 (3H, s), 3.20 (1H, m), 4.67 (1H, s), 6.22 (1H, s), 6.45 (1H, s). ^{13}C NMR ($CDCl_3$): 154.4 (C_1), 136.96 (C_2), 129.27 (C_3), 124.02 (C_4), 135.95 (C_5), 115.2 (C_6), 115.2 (C_6), 27.81 (CH α), 20.64 (Me β, Me-3,5); MS m/e (%) 164 (32.7), 150 (14), 149 (100), 121 (8.6), 115 (10), 105 (9.7), 91 (20), 77 (10); Red oil. 3,5-Dimethyl-4-isopropylphenol 1c, mp 108 °C (107-108.5 °C).[7] ^1H NMR ($CDCl_3$) 1.23 (6H, d), 2.56 (6H, s), 3.26 (1H, m), 4.6 (1H, b), 6.37 (2H, s). ^{13}C NMR ($CDCl_3$): 152.58 (C_1), 115.85 (C_2, C_6), 136.67 (C_3, C_5), 137.63 (C_4), 28.85 (CH), 21.53 (Me β), 21.12 (Me-3,5). MS m/e (%) 164 (37), 150 (13.7), 149 (100), 121 (8.2), 105 (5.5), 91 (5.5), 77 (5.3).
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