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where f_{HA} and f_A represent the mole fractions and δ_{HA} and δ_A the chemical shifts of the acid in its protonated and deprotonated states. The model equation for a monoprotic acid is obtained by expressing f_{HA} and f_A in terms of the acid dissociation constant, K.

$$\delta_{obs} = \frac{[H^+]\delta_{HA} + K\delta_A}{[H^+] + K} \qquad (2)$$

The following model equation for a diprotic acid is derived in the same way.

$$\delta_{obs} = \frac{[H^+]^2\delta_{H_2A} + [H^+]K_1\delta_{HA} + K_1K_2\delta_A}{[H^+]^2 + [H^+]K_1 + K_1K_2} \qquad (3)$$

Acknowledgment. This research was supported by National Institutes of Health Grant GM 37000. The NMR instrumentation was supported in part by BRSG 2 SO7 RR07010-20 awarded by Biomedical Research Resources, National Institutes of Health.

Registry No. CoA, 85-61-0; CoASSCoA, 31664-36-5; CoASSG, 6477-52-7.

The Problem of Regioselectivity in Nucleophilic Additions to Pyridinium and Related Cations. Role of Generalized Anomeric Effect

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Received October 1, 1991

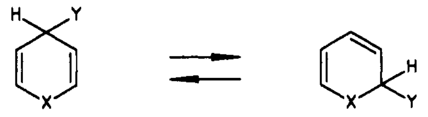
A MNDO and AM1 study of the isomerization of pyrans, thiopyrans, dihydropyridines, and their methoxy derivatives was carried out so as to clarify the nature of the effects causing the observed thermodynamic regioselectivity in nucleophilic addition to pyridinium, pyrylium and thiopyrylium cations. The results show that, in contrast to 2*H*-thiopyrans, 2*H*-pyrans and 1,2-dihydropyridines are significantly stabilized by a generalized anomeric effect when the group bonded to the 2 position is OMe. It is pointed out that in the case of reversible additions, a clear distinction should be made between the kinetic and the thermodynamic regioselectivity because, in contrast with current usage, the latter cannot be interpreted in terms of frontier orbital theory but by the presence or absence of a generalized anomeric effect. It is also pointed out that predictions of kinetic regioselectivity based on frontier orbital theory are not supported by literature data. The kinetic regioselectivity seems to be governed by the relative electron density at the carbon under attack, independent of the hard or soft character of the nucleophile.

There has been considerable interest in the regioselectivity of nucleophilic attacks on pyridinium ions, due, in part at least, to the biological importance of the reduction of NAD.[1] The first attempt to rationalize the literature data on these systems was made by Kosower,[2] who related the position of attack by a nucleophile to the possible intermediacy of a charge-transfer complex (CTC) prior to the attack. In particular, nucleophiles with a low ionization potential were presumed to proceed via a CTC which subsequently would evolve into the 4*H* adduct, while nucleophiles not forming the CTC would directly attack the 2 position.

In a more recent and theoretically-rooted approach by Klopman,[3] the regioselectivity was related to the hard/soft character of the nucleophiles. According to this view, since the total charge density in a pyridinium ion is larger at C2 than at C4, whereas the coefficient of the LUMO is larger at C4 than at C2, hard nucleophiles would attack C2 (charge control), while soft nucleophiles would attack C4 (frontier orbital control). Both of the models implicitly assume that the experimental distribution of the products is due to irreversible reactions or that, in the case of reversible reactions, the lower-energy product is formed from the lower-energy transition state. However, this assumption is critical because in many cases it has been reported that the kinetically favored product differs from the product of thermodynamic control (vide infra). In fact, these experimental findings have been overlooked and the Klopman approach to the problem of regioselectivity has gained wide acceptance,[4] though it is mainly based on equilibrium data rather than kinetic data, as required by the theory.

In order to understand the causes of the thermodynamic regioselectivity in nucleophilic additions to pyridinium and to the related pyrylium and thiopyrylium cations, we have undertaken a MNDO[5] and AM1[6] study of the equilibria reported in Scheme I. The results of this investigation are reported herein.

Scheme I



1a–7a 1b–7b

1, X = O, Y = H
2, X = O, Y = OMe
3, X = S, Y = H
4, X = S, Y = OMe
5, X = NMe, Y = H
6, X = NH, Y = H
7, X = NH, Y = OMe

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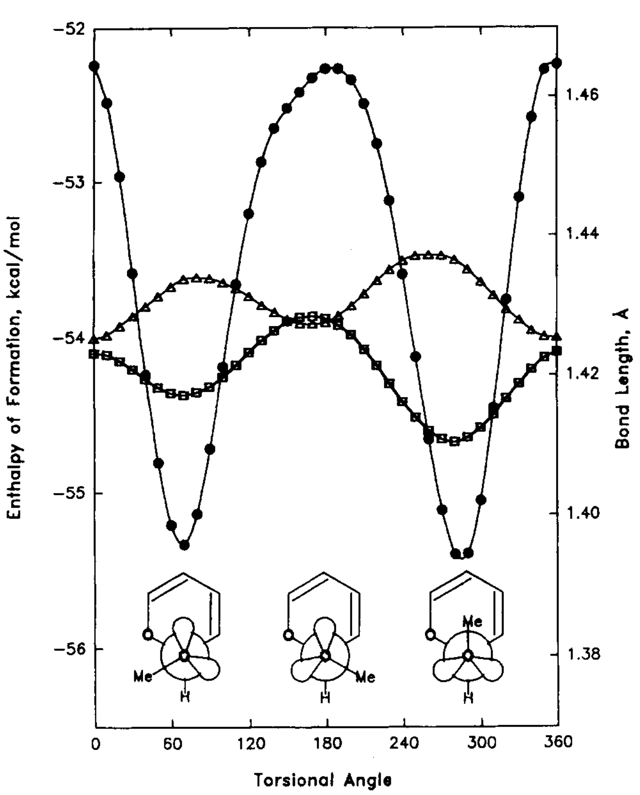

Figure 1. Enthalpy profile (●, left scale) and bond length profiles for O1--C2 (△, right scale) and for C2--OMe (□, right scale) in the case of 2-methoxy-2*H*-pyran, as calculated by the AM1 method.

Computational Procedure

Calculations were carried out on an IBM 3090/600 computer (CICS, University "La Sapienza", Roma) using MNDO[5] and AM1[6] as implemented in the AMPAC[7] package of computer programs. The block data file within AMPAC was updated with the recently introduced AM1 parameters for sulfur.[8] All the calculations were carried out with full optimization of all the geometrical variables and by adopting the option PRECISE. For the compounds without internal rotations (**1**, **3**, **6**) the option THERMO was used in order to calculate entropies at 25 °C.

For the compounds **2**, **4**, **5**, and **7** in which there are internal rotations, a preliminary search of the most stable conformation was carried out. This was accomplished by a 360° rotation, in steps of 10°, of the substituent (OMe in the compounds **2**, **4**, **7**, and Me in the compounds **5**) about the bond leading to the ring. At each step all the other internal variables were optimized. Finally, the nearest conformation to each minimum was fully optimized. A typical energy profile is reported in Figure 1 for the compound **2b**. The energy of the lowest conformational minimum was assumed to represent the heat of formation of the compound.

Results and Discussion

The semiempirical MNDO[5] and AM1[6] methods have been shown to reproduce the ground-state properties of a wide variety of neutral species in a satisfactory and convenient manner. However, before introducing the results of the present investigation, it is appropriate to consider the available experimental data about equilibria in solution.

In Table I are reported either the experimental upper limits or the experimental values of the statistically corrected standard free energies of reaction ($\Delta G°_c$) for the equilibria **1**–**7**. Numbering refers to Scheme I, so that equilibrium **1** corresponds to the equilibrium between **1a** and **1b**, and so on. The limiting values of $\Delta G°_c$ have been estimated as follows.

Table I. Experimental Free Energies ($\Delta G°_c$)[a] and Calculated Enthalpies of Reaction ($\Delta H°$) at 25 °C. Values in kcal/mol

equilibrium	$\Delta G°_c$	$\Delta H°$ (MNDO)	$\Delta H°$ (AM1)
1		1.2	−0.9
2	$\lesssim -4.7$	−6.1	−8.1
3	$\lesssim -1$	0.2	2.6
4	$\lesssim -2$	−1.4	4.9
5	2.29[b]	1.7	2.8
6	*c*	1.8	3.3
7	< -2[c]	−3.8	−0.3

[a] Corrected for the statistical factors. [b] Obtained in DMSO at 91.6°: Fowler, F. W. *J. Am. Chem. Soc.* 1972, *94*, 5926–5927. [c] Hypothetical equilibrium (see text).

Degani et al. isolated 2-methoxy-2*H*-thiopyran (**4b**) as the only product of the reaction of thiopyrylium ion with a methanolic solution of $NaHCO_3$.[9] Since the methoxide attachment in methanol to thiopyrylium ions is a reversible process,[10] the isolation of only the 2*H* adduct indicates that its yield is greater than 98% or, in other words, that $\Delta G°_c$ for the equilibrium **4** is lower than −2 kcal/mol. However, the value of $\Delta G°_c$ should not be significantly lower than this limit because the equilibria for isomerization of the symmetrical substituted 2,4,6-triphenyl-4-methoxy-4*H*-thiopyran and 2,4,6-tri-*tert*-butyl-4-methoxy-4*H*-thiopyran in MeOH at 25 °C have $\Delta G°_c = -2.1$ and −0.9 kcal/mol, respectively.[10]

Experimental data for the equilibrium **3** are not available; however, a comparison of the equilibrium data for the isomerization of a number of variously substituted thiopyrans in CD_3CN, with analogous data referring to the isomerization of the corresponding methoxythiopyrans in MeOH, has shown that the equilibrium constants for Y = H are slightly lower than those for Y = OMe, the difference being less than a factor of 5 in all of the cases.[10] Thus, adding $RT \ln 5$ (≈ 1 kcal/mol) to the $\Delta G°_c$ limit for the equilibrium **4**, we can estimate that $\Delta G°_c$ for the equilibrium **3** is $\lesssim -1$ kcal/mol.

In a previous paper, it was concluded that the equilibrium involving methoxypyrans is 2.7 kcal/mol more exothermic than that involving the corresponding methoxythiopyrans;[11] thus, $\Delta G°_c$ for the equilibrium **2** is given by $\Delta G°_c$ for the equilibrium **4** less 2.7 kcal/mol, i.e., $\lesssim -4.7$ kcal/mol.

The hypothetical equilibrium **7**, which is supposed to resemble the equilibria involving N-substituted dihydropyridines, was chosen because it offers the advantage of greater simplicity of calculations (vide infra). From the observation that *N*-aryl-[12] and *N*-*tert*-butoxypyridinium[13] ions react reversibly with MeO^- in MeOH to yield exclusively the corresponding 2-methoxy-1,2-dihydropyridines, it follows that, on the analogy of equilibrium **4**, $\Delta G°_c$ should be < -2 kcal/mol for the equilibrium **7** also.

No data are available on the equilibrium **1**, involving the isomerization of pyrans, because 2*H*-pyran (**2b**) is an unstable species that undergoes a fast ring-opening reaction.[14]

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[7] Dewar, M. J. S. QCPE, Program No. 539.

[8] (a) Dewar, M. J. S.; Yuan, Y.-C. *Inorg. Chem.* 1990, *29*, 3881–3890. (b) Note that a considerable number of papers reported "AM1" results on sulfur compounds prior to the publication of ref 8a. In fact these results were obtained by using MNDO parameters in AM1, a procedure that, according to Dewar, is wholly unacceptable.[8a]

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[14] Schiess, P.; Chia, H. L. *Helv. Chim. Acta* 1970, *53*, 485–495.

Table I also shows the standard enthalpy of reaction (ΔH°) for the equilibria 1–7, calculated by both MNDO and AM1 methods. Since the entropies of reaction calculated for the compounds without internal rotations (1, 3, 6) were negligible when allowance was made for the statistical factors, it was assumed that the same holds for the other equilibria. Therefore, ΔH° can be identified with $\Delta G^\circ{}_c$.

Comparison of the calculated data for the equilibria 5 and 6 shows that *N*-methyl substitution does not significantly affect the ΔH° value, thus justifying the choice of equilibria 7 to represent the behavior of N-substituted dihydropyridines.

In the case of equilibrium 1, MNDO and AM1 indicate a different order of stability for 2*H*- and 4*H*-pyran; however, because enthalpy differences are small (ca. 1 kcal/mol), the two methods substantially agree and indicate a similar stability for the two isomers. A large increase in the heat of reaction (ca. 7 kcal/mol) is calculated with both the methods when Y = OMe (see data for the equilibrium 2). A lower increment (ca. 3–6 kcal/mol) is observed in the case of dihydropyridines by comparing the data for equilibrium 5 (or 6) with that of equilibrium 7. A still lower increment (1.6 kcal/mol) is observed in the case of thiopyrans (equilibria 3 and 4), as far as the MNDO results are concerned. The AM1 results in this case are significantly overestimated and do not seem reliable.

The increase in the heat of reaction on passing from Y = H to Y = OMe may well be due to stabilizing geminal interactions between the methoxy group and the ring heteroatom in 2*H* adducts (**2b**, **4b**, **7b**). Indeed, it is known that when two significantly electronegative atoms such as N, O, F, and, to a lesser extent, S are bonded to the same tetrahedral carbon a stabilization occurs (generalized anomeric effect) which is due to inductive and negative hyperconjugation effects.[15,16] The stereoelectronic prerequisite for hyperconjugative contributions is that an electron pair of a donor atom Y is oriented antiperiplanar to a polar C–X bond. The geometrical consequences, which are easily understood in terms of "double-bond–no-bond" resonance ($\mathrm{Y{-}CR_2{-}X} \leftrightarrow \mathrm{Y^+{=}CR_2\ X^-}$), are the shortening of the C–Y bond and the lengthening of the C–X bond. In order to verify the presence of hyperconjugative contributions, we have studied the effects of rotation of the methoxy group in **2b**, **4b**, and **7b**. The results obtained in the case of **2b** with AM1 are displayed, by way of illustration, in Figure 1. Three curves are shown; one refers to the enthalpy of formation of **2b** and the others to the lengths of the bonds O1–C2 and C2–OMe, respectively. The enthalpy profile shows two minima corresponding to the structures in which an oxygen lone pair of the methoxy group is antiperiplanar to O1. In the regions where the enthalpy is minimal, the bond length curves for O1–C2 and C2–OMe show a maximum and a minimum, respectively, in agreement with a double-bond–no-bond resonance effect. It is interesting to note that at 0° and 180°, where the effect of negative hyperconjugation is presumably very small, the bond lengths of O1–C2 and C2–OMe are almost the same. Similar effects were found in the case of 2-methoxy-1,2-dihydropyridine (**7b**), whereas in the case of 2-methoxy-2*H*-thiopyran (**4b**), where the stabilizing interactions are smaller, a third minimum of comparable energy was detected at ca. 180°.

Turning to the problem of regioselectivity in nucleophilic addition to pyridinium cations, an important observation was made by Lyle and Gauthier[17] who showed that in the reversible addition of cyanide ion to some pyridinium ions, the principal product of kinetic control, the 1,2-dihydropyridine, is different from that of thermodynamic control, the 1,4-dihydropyridine; i.e, the lower-energy product is formed from the higher-energy transition state.

It appears, therefore, that in the case of reversible reactions, a *clear distinction* should be made between the kinetic regioselectivity and the thermodynamic regioselectivity because only the former can possibly be interpreted by models based on perturbation theory,[3,4] whereas the latter only depends on those factors affecting the stability of the products.

A typical case is that regarding the addition of cyanide ion (a soft nucleophile) and methoxide ion (a hard nucleophile) to pyridinium ions. Both the reactions are reversible,[12,13,17,18–20] and both nucleophiles have shown a kinetic regioselectivity contrasting with the thermodynamic one.[17,19] In the case of methoxide ion, this behavior has also been shown in the addition to pyrylium and thiopyrylium cations.[21] Despite these precedents, the thermodynamically controlled formation of the 1,4-dihydropyridine, in the case of cyanide ion, and of the 2 isomer, in the case of methoxide ion,[22] is often justified on the basis of the hard/soft concept.[23] Since it has been shown that the CN group does not give significant geminal interactions with the N atom,[15b] we suggest that cyanide ion gives the 4 isomer simply because this is the intrinsically more stable isomer (see the data for the equilibrium 5), whereas methoxide ion gives the 2 isomer because of the anomeric effect (see the data for the equilibrium 7). In most of the cases the attacking atom of hard nucleophiles is O or N, while that of soft nucleophiles is C or S; therefore, it is easily understood why the thermodynamic regioselectivity, caused by the presence or absence of anomeric effects in the products, has been erroneously attributed to hard/soft interactions in the transition states.[1]

One can wonder if the frontier orbital theory provides at least a rationale for the kinetic regioselectivity. To the best of our knowledge, there is not a single example of nucleophilic addition to the 4 position of the pyridinium ring which can be ascribed with any certainty to kinetic control and which is not forced by differential steric and conjugative effects between positions 2 and 4. Kinetically controlled distributions can be obtained with certainty either by irreversible reactions or by kinetic studies of those reversible reactions that show a kinetic distribution of products *different* from the thermodynamic one. Indeed if a reaction is reversible, the observation of the 4 isomer as the only reaction product does not imply that it is also the product of kinetic control because a very fast isomerization converting the kinetically favored 2 isomer into

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[22] In some cases, due to the presence of substituents on the pyridinium ring, the formation of the 4 isomer at equilibrium can be significant also for the methoxide ion addition. However, to our knowledge, the cyanide ion addition on the same pyridinium ions always produces a larger quantity of the 4 isomer (cf. refs 19 and 20).

[23] See, for example: Katritzky, A. R.; Chen, J.-L.; Wittmann, D. K.; Marson, C. M. *J. Org. Chem.* **1986**, *51*, 2481–2485.

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the 4 isomer could have taken place. Another possibility could be that even though the rate constant for the formation of the 2 isomer is greater than that of the 4 isomer, the 2 isomer could not even form as a transient species, simply because its equilibrium of formation is shifted toward the reagents under the reaction conditions.[24,25]

Among the commonly studied nucleophiles (complex hydrides, organometallic reagents, cyanide, hydroxide, alkoxides, dithionite, thiolates, amines, stabilized carbanions derived from nitromethane, ethyl acetoacetate, ethyl cyanoacetate, etc.), only the reactions of complex hydrides and organometallic reagents with a pyridinium ring can be considered to be irreversible; in both cases the nucleophilic attack occurs preferentially at the 2 position.[1]

In conclusion, the available experimental data suggest, as proposed by Lyle and Gauthier,[17] that the kinetic regioselectivity in nucleophilic addition to pyridinium and related cations is governed by the relative electron density at the carbon under attack, independent of the hard or soft character of the nucleophile.[26] This view is also supported by the work of Ritchie on cation–anion combination reactions.[27] Ritchie showed that the rates of combination of a large collection of nucleophiles (including hard and soft ones) with preformed carbocations follow the simple "constant selectivity" N_+ relationship (eq 1), in which k

$$\log k = \log k_0 + N_+ \tag{1}$$

is the rate constant for the reaction of a cation with a given nucleophilic system (i.e., a given nucleophile in a given solvent), k_0 is the rate constant for a reference nucleophile and is dependent only on the identity of the cation, and N_+ is a parameter dependent only on the nucleophilic system. If the nucleophilic attack at the 2 and 4 positions were rate determining (this has been shown to be the case for the methoxide addition to thiopyrylium and pyrylium cations),[11,25] each site should independently follow the Ritchie equation. This would imply that the regionselectivity is constant, i.e., independent of the nature of the nucleophile. Of course since the N_+ relationship encompasses a wide reactivity range, a scatter that would be insignificant for eq 1 could involve a significantly different regioselectivity. However, the Ritchie equation strongly indicates that frontier orbital interactions are not significant in determining the reactivity of cation–anion combination reactions[28] and thus the kinetic regioselectivity of nucleophilic attack to pyridinium and related cations.

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(24) An analogous kinetic behavior has been shown in the reaction of 2,6-di-*tert*-butyl-4-(*p*-(dimethylamino)phenyl)thiopyrylium ion with methoxide in methanol (see ref 25).

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(26) These conclusions refer to a polar mechanism. Should an electron transfer occur between a nucleophile and pyridinium ion, then recombination of the formed radicals would occur preferentially at the 4 position because of its higher spin density. For the evaluation of spin densities in pyridinium ion, see: Zeldes, H.; Livingston, R. *J. Phys. Chem.* **1972**, *76*, 3348–3355.

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A Theoretical Study Using ab Initio Methods of Tautomerism in Cytosine in the Gas Phase and in Water

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Received March 5, 1992

The four lowest energy tautomers of cytosine have been modeled in the gas phase and in aqueous solution using ab initio methods. A basis set that includes polarization functions on all atoms is needed to predict the correct ordering of the tautomers in the gas phase. The effect of solvent has been modeled using both the self-consistent reaction field and polarized continuum methods. The results are consistent and agree with experiment for all but the 3(*H*)-amino–oxo form, where only the self-consistent reaction field method is in accord with experimental observations.

There is continuing interest in an accurate evaluation of the tautomeric behavior of the purine and pyrimidine bases due in large measure to the biological implications of mispairing by the rare tautomeric forms of these bases.[1] While gas-phase studies are of fundamental interest, the effect of the environment, such as solvation, must also be considered if molecular modeling studies on these molecules are to have relevance in a biological context. It is well-known that solvent and solid-state effects can be critical in determining the tautomeric equilibrium in such heterocyclic systems. The tautomerism in cytosine has been extensively studied both experimentally[2] and theoretically.[3-6] Of the six possible tautomers of this molecule, four have been identified experimentally and are generally considered to be of lower energy than the remaining two. It is these four species, **1**, **2**, **4**, and **5** (to be consistent with the labeling of Kwiatkowski et al.[4]), which are studied theoretically in this paper.

A recent IR study of cytosine isolated in a low-temperature matrix has resulted in spectral assignments in terms of the amino–oxo form (**1**) and amino–hydroxy form (**4**).[7] We have shown that IR frequencies computed for

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