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BASIC STRENGTH AND HYDROGEN BONDING IN SOME AMINOALCOHOLS OF BICYCLO(2,2,2) OCTANE AND BORNANE

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Abstract—The effects are discussed of H-bonding, and steric and electronic features on pK_a values and rates of quaternization of some aminoalcohols based on the rigid, bornane and the slightly more flexible, bicyclo[2,2,2]octane structures.

INTRODUCTION

There is conflicting evidence concerning the presence of an alcoholic group in the vicinity of a basic group to increase or decrease the basic strength of the basic group.[1-6] However, it is now generally accepted that H-bonding occurs between the protonated basic group and the O atom of the alcohol (i.e. the presence of the OH group increases the basic strength when the groups are appropriately located). In the present studies, the mutual interaction of alcoholic groups and basic groups attached to a rigid structure, i.e. the bornane and the slightly more flexible structure, i.e. bicyclo[2.2.2] octane are investigated. The influence of the *cis* and *trans*-relationship of the groups is also studied.

RESULTS AND DISCUSSION

The pK_a values and rates of quaternization of the two series of amino-alcohols, aminoketones and amino-esters and rates of quaternization of aminoalcohols and aminoketones are listed in Table (1). The *cis*-compounds were stronger bases than were their corresponding *trans*-isomers. In the dimethylaminoborneols, the ΔpK_a between the *cis*-isomer (1) in which N/O H-bonding can occur and the *trans*-isomer (2) where it cannot occur is 1·70 pK_a units. Similarly, in the slightly more flexible dimethylaminobicyclo[2.2.2] octanols, the ΔpK_a between the *cis*-isomer (12) and the *trans*-isomer (13) is 1·51 pK_a units. Because bicyclo[2.2.2] octane is completely symmetrical[8] the change of the OH group from the *cis*- to the *trans*-relationship to the basic group does not change its interaction with the ring system, but replaces its interaction with the C_3–$N(CH_3)_2$ group by one with the C_3–H group. Neither the conformation of the ring system nor the inductive influence of the O atom through the bonds to the N atom, is altered by this change. Thus, the above results show that the H-bonding ($\overset{+}{N}H\ldots O$) in the *cis*-aminoalcohol is more important than N:… H–O. In the series of esters, the H bonding of the type $\overset{+}{N}H\ldots O{=}C$ accounts for the *cis*-ester (3) being a stronger base by 0·80 pK_a units than its corresponding *trans*-isomer (4) and also for the *cis*-ester (14) being a stronger base than its corresponding *trans*-isomer (15) by 0·96 pK_a units. The $\Delta pK_{a_{cis\text{-}trans}}$ values in the esters is less than in the corresponding alcohols probably because under aqueous conditions, H-bonding between the cation and the CO group is weaker than between the cation and the OH group.

H-bonding in *cis*-alcohols leads to a 5-membered ring structure whereas in the ester a 7-membered ring is involved; this leads to the *cis*-ester (3) being a weaker base than its alcohol (1) i.e. ΔpK_a 1·49 and the *cis*-ester (14) of the bicyclooctane series being a weaker base than the *cis*-alcohol (12), ΔpK_a 1·04. The electron withdrawing effect of the ester group relative to that of the OH group also plays some role because the *trans*-isomer (4), in which H-bonding is not possible, is a weaker base by 0·59 pK_a units than its corresponding *trans*-alcohol (2); also in the bicyclooctane series, the *trans*-ester (15) is only weaker by 0·49 units than the *trans*-alcohol (13).

The *cis-endo*-tertiary amino-alcohol (1) in the bornane series being a stronger base than its corresponding *cis-exo*-isomer (5) (ΔpK_a 0·23), and the *cis-endo*-ester (3) being a stronger base than its corresponding *cis-exo*-isomer (6) (ΔpK_a 0·20), is explicable in term of the steric interaction of the C_8–CH_3 group on the *exo*-side with the solvated cationic group on the same side of the molecule.

The environment of the basic group in the *trans*-tertiary amino-alcohol of the bornane and bicyclo-octane series have similar environments; this accounts for compound 2 and 13 and also 4 and 15 having similar pK_a values.

The bicyclo[2.2.2] octane ring system is slightly more flexible than is the bornane. Thus the H-bonding of the type $\overset{+}{N}H\ldots O$ in the amino-alcohols is stronger in the bornanes than it is in the bicyclo-octanes, and this accounts for the *cis-endo*-amino-alcohol (1) being a stronger base than is the *cis*-amino-alcohol (12) (ΔpK_a 0·23).

On the other hand, in the ester series, the H-bonding of the type $\overset{+}{N}H\ldots O{=}C$ is stronger in the bicyclo-octanes than it is in the bornanes because in the latter, the rigid bornane structure introduces some strain in the 7-membered ring involving the H-bond. In the bicyclo-octanes, the flexibility of the bicyclic system relieves this strain and increases the strength of the H-bond. This accounts for the *cis-endo*-isomer (3) of the bornane being a weaker base than is the *cis*-isomer (14) of the bicyclo-octane (ΔpK_a 0·22).

In the tertiary aminoketone series, the rigidity of the

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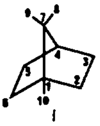
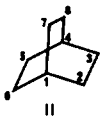
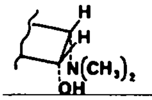
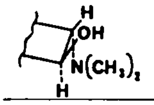
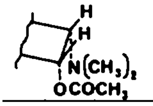
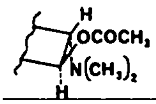
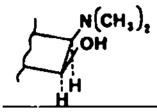
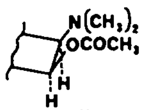
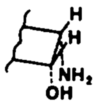
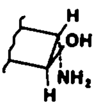
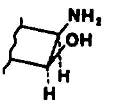
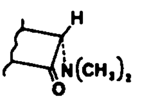
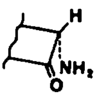
Table 1. pK_a Values and rates of quaternization of some amino-bornanes I and aminobicyclo[2.2.2] octanes II



I



II

Compound	Aminobornanes I		Aminobicyclo[2,2,2]octanes II	
	Configuration and No.	pKa and rate of quat^n	Configuration and No.	pKa and rate of quat^n
	cis-endo (1)	10.65 [1.15]	cis (12)	10.42 [3.45]
	trans-exo-OH (2)	8.95 [0.88]	trans (13)	8.91 [3.88]
	cis-endo (3)	9.16	cis (14)	9.38
	trans-exo-OCOCH$_3$ (4)	8.36	trans (15)	8.42
	cis-exo (5)	10.42 [0.69]	- -	- -
	cis-exo (6)	8.96	- -	- -
	cis-endo (7)	9.70[7]	cis (16)	9.78
	trans-exo-OH (8)	9.48[7]	trans (17)	9.25
	cis-exo (9)	9.65[7]	- -	- -
	-- (10)	7.35 [1.26]	- (18)	7.63 [7.19]
	- (11)	7.18	-	-

[ ] rates of quat^n × 10^5 sec^{-1}.

bornane ring system allows the cationic proton to be aligned with the π orbital of the CO carbon atom in a W arrangement[9,10] in the preferred conformation to facilitate proton dissociation while in the bicyclo-octanes, due to ring flexibility, the molecule spends only a short time in the favourable conformation. Thus the aminoketone (**18**) of bicyclo-octane is a weaker base than is the bornane (**10**) (ΔpK_a 0·28).

The substitution of aminoketones produces increasing conformational restraint which results in incorrect orientation of nitrogen lone pair[10] and furthermore substitution of the H atom (i.e. in the primary amine) by the (+I) Me group opposes the (−I) effect of the CO group or the OH group. This accounts for the tertiary aminoketone (**10**) being a stronger base than its corresponding primary amine (**11**) (ΔpK_a 0·17) and also for the *cis*-primary aminoalcohol (**16**) being a weaker base than its corresponding *cis*-tertiary amine (**12**) (ΔpK_a 0·64).

On the other hand, in the *trans*-amino-alcohols, the primary amine (in the cationic form) has three protons to be solvated while the tertiary amine has only one; thus, solvation results in the *trans*-primary amine of the bornanes (**8**) being a stronger base than its corresponding tertiary amine (**2**) (ΔpK_a 0·53) and also for the *trans*-primary amine of the bicyclo-octanes (**17**) being a stronger base than its corresponding tertiary amine (**13**) (ΔpK_a 0·34).

In the *cis*-compounds the tertiary amino-alcohol can form an H bonding of the type $\overset{+}{N}H \ldots O$ which stabilises the cationic proton; although in the primary aminoalcohol a similar H-bond is formed, two other protons are available for dissociation. This accounts for the *cis-endo*-primary amino-alcohol (i.e. of the bornanes) (**7**) being a weaker base than its corresponding tertiary amine (**1**) (ΔpK_a 0·95) and also for the *cis*-primary aminoalcohol (i.e. of the bicyclo-octanes) (**16**) being a weaker base than its corresponding tertiary amine (**12**) (ΔpK_a 0·64).

Rates of quaternization. Relative pK_a values depend upon the relative accessibility of a solvated proton to a basic group and to the relative differences between the internal steric interaction of the larger solvated cation and the smaller solvated base.[11,12]. On the other hand, rates of quaternization depend primarily upon the accessibility of the lone pair of the N atom to an alkyl cation.[11,12] It is therefore to be expected that relative rates of quaternization may not reflect relative pK_a values of a series of compounds.

A comparison of relative pK_a values and rates of quaternization in the present series is illustrative of these differences. The aminoketones (**18** and **10**), despite being weaker bases than their corresponding alcohols (**12, 13** and **1, 2** and **5**) respectively, are quaternized faster possibly because the CO group gives less steric hindrance than does the OH group and also the CO group can facilitate the attraction of the CH_3^+ group towards the N atom.

On the other hand, the *trans*-amino-alcohol of the bornane (**2**) with approximately the same pK_a value as the *trans*-amino-alcohol of the bicyclo-octane (**13**) is quaternized much less rapidly. This is probably because of the greater rigidity of the former compound.

In the aminobornanes, the *cis-endo*-isomer (**1**) is a slightly stronger base than is the *cis-exo*-isomer (**5**) but is quaternized much more quickly, because the C_8–CH_3 group in **5** sterically hinders the approach to the N atom.

In the aminobornane series, the *cis-endo*-isomer (**1**) pK_a 10·65 is quaternized faster than its corresponding *trans*-isomer (*endo*-basic group) (**2**) pK_a 8·95, not only because it is a stronger base but because although the OH group in the *cis*-compound (**1**) is much larger than is the *endo*-H atom on C_2, the electronic effect of the OH group may help to attract the CH_3^+ group and thus counterbalance the steric hindrance of the OH group. In contrast in the bicyclo-octane series, the *trans*-isomer (**13**) pK_a 8·91 is quaternized faster than the corresponding *cis*-isomer (**12**) pK_a 10·42 (i.e. the strongly basic isomer) because the flexibility of the ring now results in the O atom of the OH group not being located in the direction to provide electronic assistance to the attract of the CH_3^+ on the N atom.

In all compounds [Table 1], the aminobicyclo-octanes were quaternized faster than were the corresponding aminobornanes, probably because the relative flexibility of the bicyclo-octanes facilitated the accommodation of the cation better than did the more rigid bornane ring system.

EXPERIMENTAL

Compounds **1–10**[13] and **12–18**[8] have been described. Compound **11** was prepared from 3-hydroxyiminobornan-2-one[14] which was prepared from (+)-bornan-2-one [(+)-Camphor] B.D.H.

pK_a Values were determined using a pH meter with an automatic titrator TTT II and autoburette ABU 12 (Radiometer Ltd. Copenhagen). A standard combined calomel and glass electrode (type GK 2320C) was used which was standardized with a phthalate buffer (pH 6·50 ± 0·02). A jacketted glass reaction vessel (5 ml) was maintained in a thermostatically controlled water bath at 25 ± 0·1°. The reaction media was stirred and CO_2-free N_2 passed on top of the soln in the vessel through a side inlet and was passed throughout the titration.

Rates of quaternization were determined using a Cambridge Conductance bridge with a conventional conductivity cell having black platinized electrodes with a large surface-area (about 2 cm^2). The electrodes were platinized before the measurements and were kept under distilled water when not in use. The cell was maintained in a thermostatically controlled water bath at 25 ± 0·2C.

Determination of pK_a *values.* The compounds were used as water soluble hydrochlorides, which were dried over $CaCl_2$ in a desiccator for a few days, weighed immediately in a 5 ml volumetric flask and dissolved in CO_2-free distilled water to give 0·005N solns. An aliquot (3 ml) was transferred to the reaction vessel and was stirred in a thermostat at 25° ± 0·1 under a stream of CO_2-free N_2. One tenth of equivalent of N/10 NaOH (CO_2-free) was added from an autoburette, the pH reading was taken 2 min after each addition and the pK_a values determined from the pH of half neutralization. Some determinations were replicated and results were ±0·04 pK_a units accurate.

Determination of the rates of quaternization. MeI(BDH) was distilled twice and kept in a brown bottle over mercury to remove any iodine impurity.

MeOH (spectral grade) was distilled twice and used as the solvent.

The tertiary amine (4 mg) was dissolved in MeOH (10 ml) in the conductivity cell and the conductivity recorded until a constant reading was obtained; then MeI (0·5 ml; excess) was added from a microburette and a stop clock was started simultaneously. The conductivity was measured at 1 min intervals for 10 min, at 5 min intervals for 50 min, then at 10 min intervals for 40 min; an infinity reading was obtained after 3 days. Quaternization rates were calculated.[11]

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