(2) J. Dimaio, F. R. Ahmed, P. Schiller, and B. Belleau, in "Recent Advances in Receptor Chemistry," F. Gualtieri, M. Giannella, and C. Melchiorre, Eds., Elsevier/North-Holland Biomedical, 1979, pp. 221-234.
(3) B. Belleau and P. Morgan, *J. Med. Chem.*, **17**, 908 (1974).
(4) A. H. Beckett, A. F. Casy, and N. J. Harper, *J. Pharm. Pharmacol.*, **6**, 874 (1956).
(5) J. Fishman, E. F. Hahn, and B. I. Norton, *Nature (London)*, **261**, 64 (1976).
(6) E. F. Hahn, B. I. Norton, and J. Fishman, *Biochem. Biophys. Res. Comm.*, **89**, 233 (1979).
(7) E. F. Hahn, B. I. Norton, and J. Fishman, in "Endogenous and Exogenous Opiate Agonists and Antagonists," E. L. Way, Ed., Pergamon, New York, N.Y., 1980, pp. 529-532.
(8) P. J. Smith and C. K. Mann, *J. Org. Chem.*, **34**, 1821 (1969), and references therein.
(9) L. C. Portis, V. V. Bhat, and C. K. Mann, *J. Org. Chem.*, **35**, 2175 (1970).
(10) F. D. Lewis and T.-I. Ho, *J. Am. Chem. Soc.*, **102**, 1751 (1980), and references therein.
(11) R. B. Silverman, S. J. Hofman, and W. B. Catus III, *J. Am. Chem. Soc.*, **102**, 7126 (1980).
(12) C. Y. Meyers, W. S. Matthews, L. L. Ho, V. M. Kolb, and T. E. Parady, in "Catalysis in Organic Synthesis," G. V. Smith, Ed., Academic, New York, N.Y., 1977, pp. 217, 260-278.
(13) N. Sutin in "Oxidases and Related Redox Systems," Vol. I, T. E. King, H. S. Mason, and M. Morrison, Eds., Wiley, New York, N.Y., 1965, pp. 37-50.
(14) V. M. Kolb, *J. Pharm. Sci.*, **67**, 999 (1978).
(15) A. Korolkovas, in "Essentials of Molecular Pharmacology," Wiley-Interscience, New York, N.Y., 1970, pp. 265-288, and references therein.
(16) N. M. Lee and A. P. Smith, *Life Sci.*, **26**, 1459 (1980), and references therein.
(17) T. M. Cho, P. Y. Law, and H. H. Loh, in "Neurochemical Mechanisms of Opiates and Endorphins, Advance Biochemical Phychopharmacology," Vol. 20, H. H. Loh, and D. H. Ross, Eds., Raven, New York, N.Y., 1979, pp. 69-101, and references therein.
(18) G. R. Moore and R. J. P. Williams, *Coordination Chem. Rev.*, **18**, 125 (1976), and references therein.
(19) C. Y. Meyers and V. M. Kolb, *J. Org. Chem.*, **43**, 1985 (1978).
(20) R. Foster, "Organic Charge-Transfer Complexes," Academic, New York, N.Y., 1969, pp. 278-280, 300, and references cited therein.
(21) R. F. Collins, *Chem. Ind. (London)*, **1957**, 704.
(22) N. H. Cromwell, P. W. Foster, and M. M. Wheeler, *Chem. Ind. (London)*, **1959**, 228.
(23) R. Foster, *Chem. Ind. (London)*, (**1960**) 1354.
(24) G. J. Beichl, J. E. Colwell, and J. G. Miller, *Chem. Ind. (London)*, **1960**, 203.
(25) D. P. Stevenson and G. M. Coppinger, *J. Am. Chem. Soc.*, **84**, 149 (1962).
(26) W. J. Lautenberger, E. N. Jones, and J. G. Miller, *J. Am. Chem. Soc.*, **90**, 1100 (1968).
(27) C. J. Biaselle and J. G. Miller, *J. Am. Chem. Soc.*, **96**, 3813 (1974).
(28) D. N. Kender, *Diss. Abstr. Int. B*, **37**, 1689 (1976).
(29) S. A. Markarian and H. Fisher, *J. Chem. Soc. Chem. Commun.*, **1979**, 1055.
(30) K. M. C. Davis and M. F. Farmer, *J. Chem. Soc. B*, **1967**, 28.
(31) The Merck Index, 9th ed., Merck and Co., Rahway, N.J., 1976.

ACKNOWLEDGMENTS

Presented at the National Meeting of the American Chemical Society, Seattle, Washington, March 1983, in the Medicinal Chemistry Section, Abstract 22 (Electron-Transfer Mechanism).

This work was supported in part by the University Research Foundation, La Jolla, Calif. Discussions of the electron-transfer reactions of amines with carbon tetrachloride with Prof. Cal Y. Meyers are gratefully acknowledged.

New Insights in the Clastic Binding Hypothesis for Opiate–Receptor Interactions II: Proton-Transfer Mechanism

VERA M. KOLB ˣ and STEVE SCHEINER

Received June 22, 1983, from the *Department of Chemistry and Biochemistry, Southern Illinois University, Carbondale, IL 62901.* Accepted for publication August 12, 1983.

Abstract □ *Ab initio* (4-31G) molecular orbital calculations were performed on model systems to investigate the proton-transfer version of the clastic binding hypothesis for opiate-receptor interactions. Ammonia was chosen as the model for the nitrogen-containing portion of the opiate molecule, while ammonia and water were chosen as models for the proton acceptor at the receptor. The equilibrium position of a proton situated between the two molecules is found to be determined primarily by the orientation of the proton-donor molecule with some influence also from the other molecule. Misalignments of the lone pairs can significantly alter equilibrium populations when the proton affinities of the two molecules are similar.

Keyphrases □ Clastic binding hypothesis—proton-transfer mechanism, opiate-receptor interactions, *ab initio* molecular orbital calculations □ Opiate-receptor interactions—proton-transfer mechanism, clastic binding hypothesis, *ab initio* molecular orbital calculations □ Proton transfer—mechanism, clastic binding hypothesis, opiate-receptor interactions, *ab initio* molecular orbital calculations

Belleau *et al.* (1, 2) have presented concrete evidence that the relative spatial orientation of the lone electron pair on nitrogen (N lone pair) or morphine-type opiates is crucial for their opiate activity. On this basis they proposed the clastic binding hypothesis for opiate-receptor interactions (3). According to this hypothesis, morphine-type opiates achieve productive binding with the opiate receptor through a clastic binding process involving a stereospecific electron transfer from the nitrogen lone electron pair of the opiate to some electrophilic site at the opiate receptor. This hypothesis was recently analyzed from a chemical point of view and was found to be chemically feasible (4). An extended form of this hypothesis was proposed (4) to accommodate recent observations by Fishman *et al.* concerning the *N*-demethylation of morphines in the brain (5-7).

Belleau and co-worker (2) later proposed another version of the clastic binding hypothesis according to which the N lone pair of opiates is involved in a stereospecific proton transfer to the receptor leading to strong analgesia. For optimal analgesia, a morphine should have the N lone pair oriented properly for a facile proton transfer. This version of the clastic binding

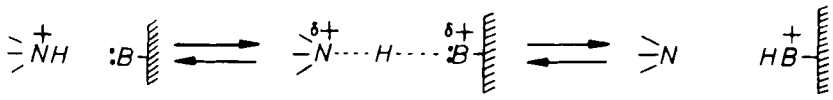


Figure 1—*Schematic representation of the proton transfer between a protonated morphine-type opiate (only nitrogen is shown) and an acceptor base (B) of the opiate receptor (shaded area) (adapted from Ref. 2).*

hypothesis shall be referred to as the proton-transfer version, as opposed to the electron-transfer version which was discussed in the previous paper (4).

We believe that the clastic binding hypothesis shows promise of explaining the mechanism of opiate-receptor interactions and, therefore, deserves further examination. The objective of this paper is to provide new insights into this hypothesis. This paper deals with the proton-transfer version of this hypothesis, while the previous paper (4) concerns the electron-transfer version. (An extensive discussion of the proton-transfer version of the clastic binding hypothesis can be found in Ref. 2.) We summarize here some crucial points with emphasis on those which we are going to investigate (*vide infra*).

BACKGROUND

Belleau and coworkers (2) visualized the proton transfer between a morphine-type opiate and the opiate receptor as shown in Fig. 1. The potency of an analgesic, according to these authors, depends on the position of the equilibrium of the proton, which is affected by the basicity of nitrogen of morphines. To account for the observed influence of the directionality of the N lone pair of morphine-type compounds on their opiate activity, it was proposed that:

1. Only the orientation of the N lone pair which allows a facile, *i.e.*, energetically favorable, proton transfer is favorable for induction of analgesia. There are other orientations of the N lone pair from which the proton transfer is energetically unfavorable.

2. The position of equilibrium of the proton will depend on the N lone pair orientation (in addition to basicity of nitrogen).

We decided to investigate the above two statements in a quantitative manner using *ab initio* quantum chemical methods. These methods are suitable for this type of study since the relative orientations of species to be studied (amine, proton, and the base at the receptor) may be precisely specified and easily varied. SCF calculations were carried out with the 4-31G basis set since this procedure furnishes proton-transfer energy barriers in excellent agreement with much more sophisticated theoretical treatments using large basis sets and configuration interactions (8–11).

To perform *ab initio* calculations it was necessary to model the large morphine molecules by smaller representative systems. Ammonia was chosen as the simplest model of the amine-type nitrogen-containing portion of a biologically active morphine-type opiate. Two different models were chosen to represent the base at the opiate receptor, the nature of which has not as yet been elucidated. We examine the possibility that such a base contains nitrogen or oxygen, as is frequently the case for bases encountered in biological systems (12). The first model is the nitrogen base ammonia which contains a single lone electron pair (Fig. 2). Water was used as the simplest model of an oxygen base and contains two lone pairs (Fig. 3). These two models for the base provide a wide range of basicity, which is expected to include the pK of the receptor within it.

EXPERIMENTAL

All molecular orbital calculations were performed using the *ab initio* Gaussian-70 system of programs (13). The 4-31G basis set (14) was used within the restricted Hartree-Fock formalism.

Before we present our calculations on the simple model systems (Figs. 2 and 3) it is important to define clearly all the parameters of these models in conjunction with the actual case of a morphine undergoing a proton transfer at the opiate receptor (Fig. 4). Both the morphine molecule and the hypothetical base at the receptor have been shown to be sterically fixed at the receptor: morphine by virtue of the noncovalent "lock-and-key" fit (15) and the base at the receptor by virtue of a covalent bond (Fig. 4). The example of a morphine shown in Fig. 4 is oxymorphone, a potent opiate agonist. The example of a base B at the receptor shown in Fig. 4 is a neutral base having one lone electron pair. The N lone pairs of oxymorphone and the base B are shown to be in a less than perfect alignment along the N···B internuclear axis, which is a more likely case than perfect alignment, since morphines may not be the ideal substrates for the opiate-receptor cavity [etorphine, for example, may be a better candidate (16)].

The N···B distance R is unknown. In our calculations on the model systems this distance varied from 2.75 to 3.15 Å, which is a typical range between proton donors and acceptors encountered in biologically important hydrogen-bonded systems (12). The N···B distance R shown in Fig. 4 is likely to be longer than the equilibrium N···B distance (in the absence of steric constraints), due to the postulated less-than-perfect fit between morphine and the receptor. In Figs. 2–4, r refers to the distance between the proton-donating nitrogen atom and the central proton in its equilibrium position. This parameter, r, will depend to some extent on the internitrogen distance R, as will be demonstrated below.

To study the dependence of the properties of the proton transfer on the directionality of the lone pairs, the NH_3 and base molecules (NH_3 or OH_2) were twisted, as illustrated in Figs. 2 and 3. α_1 and α_2 are angles describing the rotation of the nitrogen proton donor and the proton-acceptor B, respectively, from their optimal orientation. Both conrotatory and disrotatory misalignments were studied. For each configuration (defined by R, α_1, and α_2), the equilibrium position of the central proton was located. Scheme I conveniently summarizes the relevant features of the energetics of the proton-transfer process. The left well corresponds to the NH···B state and the right well to N···HB. Between the two is an energy barrier $E^\dagger$ over which the proton must pass. A high value of $E^\dagger$ may prevent proton transfer. ΔE refers to the energy difference between the states ($N^+H\cdots B$) and ($N\cdots H^+B$), and its value will determine the equilibrium population of the proton between the two states (assuming equilibrium is achieved).

RESULTS

$(H_3N\cdots H\cdots NH_3)^+$ System—We begin our discussion with the system in which a proton may be transferred between two ammonia molecules, one of which models the morphine base and the other represents the base at the opiate receptor (Fig. 2). We shall refer to this model as the $(H_3N\cdots H\cdots NH_3)^+$ system.

A study of the energetics of proton transfer in the $(H_3N\cdots H\cdots NH_3)^+$ system has recently been published by Scheiner (17). We summarize briefly here some conclusions of the latter work which are relevant to the objectives of this study. Calculated potential energy curves of the type shown in Scheme I are illustrated in Fig. 5. For internitrogen distances R <2.5 Å, the potential may be seen to contain a single centrally located minimum. At this distance, the preferred position of the proton is midway between the two nitrogens. However, for larger values of R, the potential acquires a symmetric double-well character. The two equivalent energy minima each correspond to a configuration in which the central proton is associated with one ammonia molecule or the other. The magnitudes of the energy barriers to proton transfer increase rather quickly as R is increased. In all configurations, for values of R ranging from 2.45 to 3.15 Å, the hydrogen bond is linear.

If one assumes that there is a meaningful parallel between the model system $(H_3N\cdots H\cdots NH_3)^+$ and the morphine-receptor complex shown in Fig. 4, an important feature emerges: there may be a significant energy barrier for the proton transfer between the morphine and the receptor which may be enlarged or reduced by increasing or decreasing, respectively, the distance R. This feature could provide a simple regulatory mechanism in case the re-

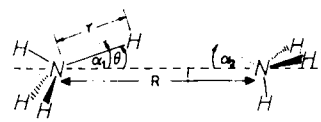


Figure 2—*Model representing a proton transfer from the protonated nitrogen of a morphine-type opiate (NH_3 on the left) and a base B at the receptor (NH_3 on the right). Both NH_3 units belong to the C_{3v} point group with r(NH) = 1.008 Å, θ(HNH) = 109.3°. The equilibrium position of the central proton is defined by the N—H distance r and the angle θ between the N—H and N···N axes. Angles α_1 and α_2 describe the rotations of the proton-donating amine and proton-accepting base, respectively, from their optimal orientations, $\alpha_1 = \alpha_2 = 0°$. Dotted lines represent the C-3 rotation axis of each molecule.*

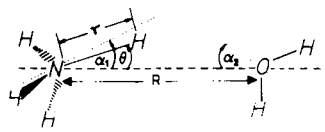


Figure 3—*Analogous to Fig. 2, except that the proton-accepting base at the receptor is modeled by OH_2 with r(OH) = 0.95 Å, θ(HOH) = 111.3°. The corresponding dotted line indicates the C-2 symmetry axis of OH_2.*

ceptor has a point of flexibility (dashed line on the boundary of the receptor in Fig. 4).

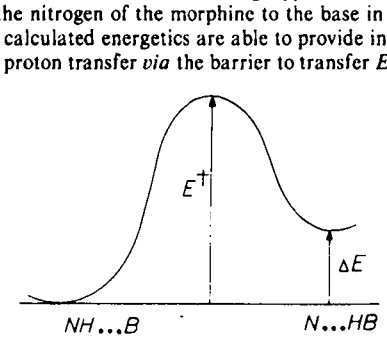
Belleau's claim that only certain orientations of the N lone pair in the system shown in Fig. 1 allow a facile (*i.e.*, energetically favorable) proton transfer is supported to some extent by the study of the energetics in the $(H_3N\cdots H\cdots NH_3)^+$ system in terms of α_1 and α_2 for a range of R values (17). Thus, Scheiner has found that for each R studied (2.73, 2.95, and 3.15 Å) the activation barriers of the systems having $\alpha \neq 0$, *i.e.*, the N lone pair(s) misaligned relative to their optimal orientation, are larger than those of the systems in which the N lone pair(s) are optimally oriented, *i.e.*, $\alpha = 0$. The magnitude of the energy barrier depends on the type of misalignment between the two N lone pairs, and is largest for disrotatory misalignments (*e.g.*, 42.0 kcal/mol for $\alpha_1 = -40°$, $\alpha_2 = 40°$, and $R = 3.15$ Å). Misalignments of 20° produce barrier increases in the range of 1–2 kcal/mol, while much more drastic increases are observed for greater misalignments of the N lone pairs.

In this paper we focus on the influence of the relative spatial orientation of the N lone pairs on the equilibrium position of the central proton and the relative equilibrium populations of the $(H_3NH\cdots NH_3)^+$ and $(H_3N\cdots HNH_3)^+$ states.

Table I contains a summary of the equilibrium position of the central proton in the $(H_3NH\cdots NH_3)^+$ state for a range of intermolecular configurations specified by R, α_1, and α_2. We note that the equilibrium NH distance r remains virtually the same, ~1 Å (1.002–1.087), for all α values and R values studied. As R increases the proton is slightly closer to the NH_3, the proton donor, which is expected since the influence of the other NH_3, the proton acceptor (ammonia on right in Fig. 2), becomes weaker as the distance R increases. The only exception to this trend is found in the last entry of Table I, namely for the largest misalignment studied ($\alpha_1 = 40°$ and $\alpha_2 = -40°$), in which the distance r actually increases very slightly with the increased R. With changing α values the proton is rotated at approximately constant r so that it partially follows the N lone pair of the NH_3, the proton donor. This is seen, for example, in entries 4 and 5 of Table I, which show that when the NH_3 proton donor is rotated by 20° and 40°, the proton is rotated off the N···N axis by 11.9° and 30.3°, respectively, for $R = 2.75$ Å. If we consider the N lone pair as lying along the C-3 symmetry axis of NH_3, α may be thought of as a measure of the "directionality" of the lone pair. [However, this correspondence is only true near the nucleus, as the N lone pair may undergo "bending" toward the proton as illustrated in similar examples (18, 19).]

The calculated values of Θ are a compromise between the left NH_3 which attempts to pull the proton along the lone pair direction (α_1) and the right NH_3 which pulls the proton toward the N···N axis (0°). The difference between α_1 and θ, listed in Table I, provides a measure of the strength of the latter attraction. As the distance R increases, θ becomes closer to α_1, *i.e.*, the proton follows the N lone pair of the proton-donating NH_3 more closely, since the influence of the proton-accepting ammonia diminishes for greater R. The only exception, again, is the case of the largest misalignment, presented in entry 9. In conclusion, the equilibrium position of the proton depends primarily on the direction of the donor lone pair and to a lesser extent on the relative position of the acceptor lone pair. The equilibrium N···H distance, r, generally remains within a narrow range, ~1.05 Å.

As mentioned above, the clastic binding hypothesis requires a proton transfer from the nitrogen of the morphine to the base in order to initiate analgesia. The calculated energetics are able to provide information about the rate of this proton transfer *via* the barrier to transfer $E^\dagger$. In addition, it



Scheme I

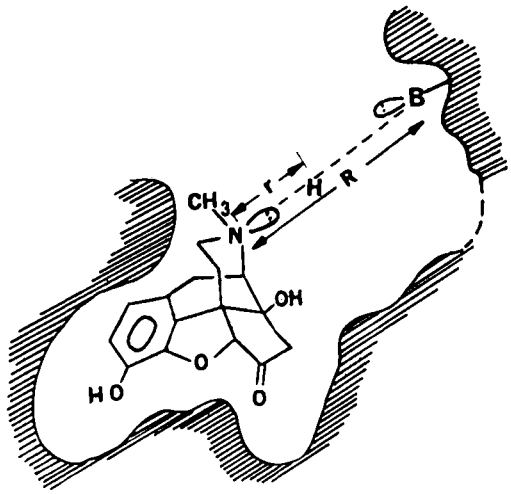


Figure 4—*Schematic representation of a proton transfer from the nitrogen of a morphine-type opiate (oxymorphone) to a hypothetical base B at the opiate receptor. The latter is shown as a shaded area whose shape should not be taken literally. The broken boundary of the receptor indicates a point of possible receptor flexibility and leads to uncertainty in distance R. The lone pairs of oxymorphone and the base B are shown to be in a less-than-perfect alignment along the N···B internuclear axis for reasons discussed in the text.*

would be useful to know something about the relative populations of the NH···B and N···HB states as it is only the latter that leads to analgesia. Information of this type is available from the difference in energy between these two states, corresponding to ΔE in Scheme I. At thermodynamic equilibrium the ratio of relative populations is given by:

$$K = \frac{n(\text{N}\cdots\text{HB})}{n(\text{NH}\cdots\text{B})} = \exp(-\Delta G°/RT)$$

where $\Delta G°$ refers to the difference in Gibbs free energy between the two states. By equating our calculated values of ΔE to $\Delta G°$ we make the following assumptions: (*a*) the difference in entropy between the two states is negligible and (*b*) the zero-point vibrational energies of the two states are about the same. The lack of any major changes in bonding structure, with the exception of the proton motion, would lead one to expect these assumptions to be reasonable.

For the angularly undistorted system ($\alpha_1 = \alpha_2 = 0°$), the symmetry of the potential energy curve leads to a value of $\Delta E = 0$ and therefore to $K = 1$. The same is true for both conrotatory and disrotatory distortions where $\alpha_1 = \pm\alpha_2$. In all of these cases, we would expect equal populations of NH···B and N···HB. However, when one molecule is rotated and the other is not, the symmetry is destroyed and $\Delta E \neq 0$. The calculated values of ΔE in cases where the proton-donor molecule is rotated by α and the acceptor molecule is left undistorted are provided in Table II. Along with these calculated energy differences are included the associated equilibrium constants K. For distortions of only 20°, the ΔE values are quite small and K is thus nearly equal to 1. However, for greater distortions of 40°, the energy differences are greater than 1 kcal/mol and K is of the order of 0.1. We thus see that for such distortions, the population of state NH···B is an order of magnitude greater than that of N···HB. In other words, the equilibrium of the two states is shifted toward that configuration in which the proton is associated with the lone pair with the misalignment.

$(H_3N\cdots H\cdots OH_2)^+$ System—The second system we studied is $(H_3N\cdots H\cdots OH_2)^+$ in which the morphine base is represented by H_3N and the proton acceptor at the receptor is modeled by H_2O (Fig. 3). The latter base has two lone electron pairs, thus providing an electronically different environment than that of the aforementioned NH_3 system. In addition, H_2O has a different basicity than NH_3.

A study of the energetics of proton transfer in the $(H_3N\cdots H\cdots OH_2)^+$ system as a function of R, α_1, and α_2 has recently been published (10, 20). The results of these studies are qualitatively parallel to that of the $(H_3N\cdots H\cdots NH_3)^+$ system, except that the asymmetry of the former system leads to two activation barriers. one for the proton transfer from NH_4^+ to H_2O ($E^\dagger_{NH\to O}$) and one for the proton transfer from H_3O^+ to NH_3 ($E^\dagger_{OH\to N}$). The latter barrier is smaller than the former. The values of activation barriers for proton transfers from NH_4^+ to H_2O vary from 29.1 kcal/mol for the optimally aligned system ($\alpha_1 = \alpha_2 = 0°$) to 52.2 kcal/mol for the system with the greatest misalignment studied ($\alpha_1 = 40°$ and $\alpha_2 = -40°$). The corre-

Table I—Equilibrium Position of Proton as Function of α in the $(H_3N\cdots H\cdots NH_3)^+$ System for R Values of 2.75, 2.95, and 3.15 Å

Entry	α_1	α_2	R = 2.75 Å			R = 2.95 Å			R = 3.15 Å		
			r, Å	θ, °	$\alpha_1 - \theta$ °	r, Å	θ, °	$\alpha_1 - \theta$, °	r Å	θ, °	$\alpha_1 - \theta$, °
1	0	0	1.087	0	0	1.062	0	0	1.048	0	0
2	0	20	1.076	3.0	−3.0	1.057	2.2	−2.2	1.045	1.7	−1.7
3	0	40	1.059	5.6	−5.6	1.046	4.1	−4.1	1.037	3.1	−3.1
4	20	0	1.068	11.9	8.1	1.051	13.5	6.5	1.039	14.8	5.2
5	40	0	1.028	30.3	9.7	1.024	32.2	7.8	1.021	33.8	6.2
6	20	20	1.069	14.7	5.3	1.051	15.6	4.4	1.041	16.4	3.6
7	40	40	1.036	33.4	6.6	1.030	34.5	5.5	1.025	35.5	4.5
8	20	−20	1.055	10.0	10.0	1.041	12.2	7.8	1.033	13.9	6.1
9	40	−40	1.002	35.3	4.7	1.007	35.3	4.7	1.010	35.8	4.2

Table II—Energy Differences and Relative Populations [a] for $(H_3N\cdots H\cdots NH_3)^+$

α	R = 2.75 Å		R = 2.95 Å		R = 3.15 Å	
	ΔE, kcal/mol	K	ΔE, kcal/mol	K	ΔE, kcal/mol	K
20°	−0.126	1.23	−0.107	1.19	−0.032	1.052
40°	1.192	0.145	1.161	0.152	1.321	0.119

[a] For t = 27° C.

sponding values for the barriers for proton transfer from H_3O^+ to NH_3 are much smaller: 2.7 and 16.9 kcal/mol.

The comparison between the values for the energy barriers for the proton transfer from NH_4^+ to H_2O and to NH_3 reveals that the latter are much smaller than the former. This difference is undoubtedly due chiefly to the difference in the electronegativities of nitrogen and oxygen atoms (10, 20). The activation barriers for the proton transfer in the $(H_3N\cdots H\cdots OH_2)^+$ system depend on the misalignments between the proton donor and acceptor in a manner very similar to that observed for the $(H_3N\cdots H\cdots NH_3)^+$ system (10, 20).

We report here the effect of the relative spatial orientation of the lone electron pairs in the $(H_3N\cdots H\cdots OH_2)^+$ system on the equilibrium position of the proton (Table III). The analysis of data presented in Table III reveals a picture analogous to that of the $(H_3N\cdots H\cdots NH_3)^+$ system. The r distance, again, is essentially constant and is ~1 Å (1.000–1.046 Å). This distance again decreases slightly with increased R, except for the case of the largest misalignment (entry 9 of Table III), in which r increases slightly. θ Follows α_1 again (*cf.* entries 4 and 5) and to a smaller extent α_2 (*cf.* entries 2 and 3). The $\alpha_1 - \theta$ difference here is as large as 7.3°.

DISCUSSION

While it would be presumptuous to generalize our data on the $(H_3N\cdots H\cdots NH_3)^+$ and $(H_3N\cdots H\cdots OH_2)^+$ systems and claim that they are directly applicable to the situations where the proton is being transferred between the morphine-type opiates and the opiate receptor, we believe that our findings should be considered qualitatively when picturing morphine–receptor interactions in conjunction with the clastic binding hypothesis of Belleau. The previously published calculations of the energetics of proton transfer in the $(H_3N\cdots H\cdots NH_3)^+$ and $(H_3N\cdots H\cdots OH_2)^+$ systems as a function of the distance and the relative spatial orientation of the species between which the proton is being transferred (10, 17, 20) support the claim by Belleau and co-workers (2) that the ease of proton transfer depends on the directionality of the N lone pair (2).

We have presented calculations which show that the equilibrium position of the proton depends on both the N lone pair direction and the orientation of the proton-acceptor molecule. We have shown in both model systems—$(H_3N\cdots H\cdots NH_3)^+$ and $(H_3N\cdots H\cdots OH_2)^+$—that the proton "follows" the N lone pair of the proton donor, and to a lesser extent that of the acceptor. The result is that if the "directionality" of the N lone pair is changed by a certain angle α_1, the proton will change its position by an angle θ, which may differ from α_1 by up to 10° in our model systems. The distance r between the proton and the proton-donating NH_3 stays pretty much constant at ~1 Å. However, the equilibrium populations of the proton on the two molecules may depend significantly on the N lone pair directions. This dependence is maximized in a system such as $(H_3N\cdots H\cdots NH_3)^+$ where the proton-donor and -acceptor molecules have identical proton affinities. When the proton affinities are significantly different there is little dependence on angular characteristics for the following reasons. Even in the angularly undistorted case, ΔE is quite different from 0. In the case of $(H_3N\cdots H\cdots OH_2)^+$, this quantity is about 38 kcal/mol. The equilibrium population of $N\cdots HO$ relative to $NH\cdots O$ is negligible (10^{-28}). Angular distortions of the two groups may increase or decrease ΔE by only a small amount relative to the original 38 kcal/mol. For example, a reduction of ΔE by 2 kcal/mol would only change K from 10^{-28} to 10^{-26}, an increase of 100-fold, but still a negligible amount of $N\cdots HO$. Therefore, for the angular orientations of the lone pairs to have a major effect on the relative populations of the two states, it would be necessary for the morphine and receptor base to have very similar proton affinities.

With regard to the accuracy of the particular quantum chemical method used here, we do not expect our results to be changed in any major way by use of larger basis sets or inclusion of electron correlation. While the specific r(NH) distances in Tables I and III may be somewhat altered, our finding of very small changes in this distance with variations of the hydrogen-bond configuration is expected to be verified. The energetics calculated with the 4-31G basis set at the Hartree–Fock level are also expected to be little changed with more sophisticated procedures, as has been demonstrated previously (8–11, 17, 20).

We may use our results to draw some inferences about the effects of modifications of the relative orientation of the morphine and receptor in Fig. 4. A rotation of the morphine molecule as a whole, with the nitrogen atom as a stationary "pivot" would correspond to twisting of the proton-donor molecule (α_1) in Figs. 2 and 3. α_2,Rotation of the proton acceptor, would be effected by a translatory motion of the entire morphine molecule to bring the nitrogen atom more out of line with the base lone pair. Our results provide evidence that small rotations of these types, *i.e.*, $\leq$20°, would not significantly alter the populations of the "untransferred" state $NH\cdots B$ and the "transferred" state $N\cdots HB$. On the other hand, a large rotation was shown above to lead to a preferential population of the proton on the group with the misaligned lone pair. We therefore infer that a rotation of the morphine about its nitrogen atom (α_1) will inhibit transfer of its proton to the base. This transfer would, however, be enhanced by a translation of the morphine off the base lone pair direction (α_2).

The reader is cautioned that these conclusions are based only on equilibrium populations. Equilibrium might not be achieved in these systems. Secondly, while the equilibrium population of the $N\cdots HB$ state might be increased by the second motion described above, the angular distortion also produces an enlargement of the energy barrier to proton transfer which would act to inhibit

Table III—Equilibrium Position of Proton as Function of α in the $(H_3N\cdots H\cdots OH_2)^+$ System for R Values of 2.75, 2.95, and 3.15 Å

Entry	α_1	α_2	R = 2.75 Å			R = 2.95 Å			R = 3.15 Å		
			r, Å	θ, °	$\alpha_1 - \theta$ °	r, Å	θ, °	$\alpha_1 - \theta$, °	r Å	θ, °	$\alpha_1 - \theta$, °
1	0	0	1.046	0	0	1.039	0	0	1.033	0	0
2	0	20	1.042	2.3	−2.3	1.037	1.7	−1.7	1.031	1.3	−1.3
3	0	40	1.032	4.6	−4.6	1.030	3.4	−3.4	1.026	2.6	−2.6
4	20	0	1.037	14.2	5.8	1.032	15.3	4.7	1.027	16.2	3.8
5	40	0	1.017	33.3	6.7	1.017	34.5	5.5	1.016	35.6	4.4
6	20	20	1.039	16.1	3.9	1.033	16.7	3.3	1.028	17.4	2.6
7	40	40	1.025	35.1	4.9	1.022	36.0	4.0	1.020	36.8	3.2
8	20	−20	1.030	12.7	7.3	1.026	14.2	5.8	1.023	15.5	4.5
9	40	−40	1.000	36.1	3.9	1.005	36.3	3.7	1.008	36.8	3.2

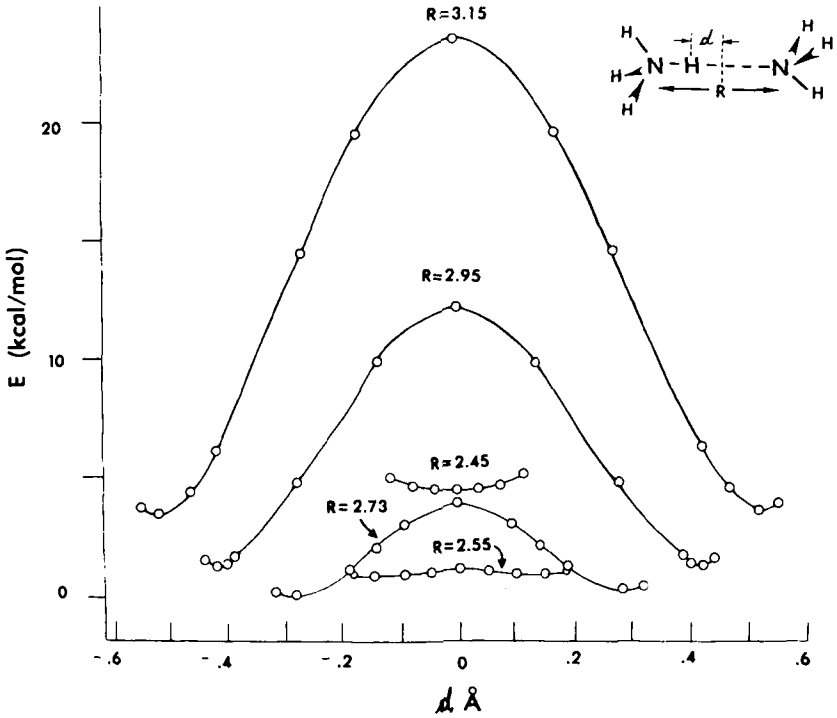


Figure 5—*Energetics of proton transfer in the* $(H_3N\cdots H\cdots NH_3)^+$ *system for various internitrogen distances* R. *Energies are all shown relative to that of the fully optimized structure* (R = 2.73 Å, r = 1.087 Å, E = −112.6132 a.u.).

this transfer. Finally, the changes in relative populations would be greatly reduced if the basicities of the morphine and receptor are different. It remains, of course, to elucidate the biological details, such as how the opiate response is elicited by the proton transfer and how the equilibrium population of the proton mediates the opiate activity.

REFERENCES

(1) B. Belleau, T. Conway, F. R. Ahmed, and A. D. Hardy, *J. Med. Chem.*, **17**, 907 (1974).

(2) J. Dimaio, F. R. Ahmed, P. Shiller, and B. Belleau, in "Recent Advances in Receptor Chemistry," F. Gualtieri, M. Giannella, and C. Melchiorre, Eds., Elsevier/North Holland Biomedical Press, 1979, pp. 221–234.

(3) B. Belleau and P. Morgan, *J. Med. Chem.*, **17**, 908 (1974).

(4) V. M. Kolb, *J. Pharm. Sci.*, **73**, 715 (1984).

(5) J. Fishman, E. F. Hahn, and B. I. Norton, *Nature (London)*, **261**, 64 (1976).

(6) E. F. Hahn, B. I. Norton, and J. Fishman, *Biochem. Biophys. Res. Commun.*, **89**, 233 (1979).

(7) E. F. Hahn, B. I. Norton, and J. Fishman, in "Endogenous and Exogenous Opiate Agonists and Antagonists," E. L. Way, Ed., Pergamon, New York, N.Y., 1980, pp. 529–532.

(8) S. Scheiner, *J. Am. Chem. Soc.*, **103**, 315 (1981).

(9) S. Scheiner and L. B. Harding, *J. Am. Chem. Soc.*, **103**, 2169 (1981).

(10) S. Scheiner and L. B. Harding, *J. Phys. Chem.*, **87**, 1145 (1983).

(11) S. Scheiner, M. M. Szcześniak, and L. D. Bigham, *Int. J. Quant. Chem.*, **23**, 739 (1983).

(12) S. N. Vinogradov, in "Molecular Interactions," Vol. 2, H. Ratajczak and W. J. Orville-Thomas, Eds., Wiley, New York, N.Y., 1980, pp. 179–229 (see pp. 181–185 for a summary of information on lengths of hydrogen bonds in peptides and related molecules).

(13) W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton, and J. A. Pople, *Quantum Chemistry Program Exchange*, **11**, 236 (1973).

(14) R. Ditchfield, W. J. Hehre, and J. A. Pople, *J. Chem. Phys.*, **54**, 724 (1971).

(15) S. H. Snyder and S. Matthysse, "Opiate Receptor Mechanisms," The MIT Press, Cambridge, Mass., 1975, pp. 63–65, 78, 137.

(16) S. H. Snyder and S. Matthysse, "Opiate Receptor Mechanisms," The MIT Press, Cambridge, Mass., 1975, p. 77.

(17) S. Scheiner, *J. Phys. Chem.*, **86**, 376 (1982).

(18) V. M. Kolb and S. Scheiner, *J. Pharm. Sci.*, **73**, 389 (1984).

(19) S. Scheiner and V. M. Kolb, *Proc. Natl. Acad. Sci. USA*, **77**, 5602 (1980).

(20) S. Scheiner, *J. Chem. Phys.*, **77**, 4039 (1982).

ACKNOWLEDGMENTS

This work was supported in part by grants from the University Research Foundation (La Jolla, California) to V. M. K. and from the National Institutes of Health (GM 29391), the Research Corporation, and NIH (Research Career Development Award, 1982–1987) to S. S.

Presented at the National Meeting of the American Chemical Society, Seattle, Washington, March 1983, in the Medicinal Chemistry Section: Abstract 22 (Electron-Transfer Mechanism) and Abstract 27 (Proton-Transfer Mechanism).

A generous allocation of computer time from the Computing Center of Southern Illinois University is gratefully acknowledged.