Conformational and Phosphate Binding Properties of Phenylethanolamines. Crystal Structure of Ephedrine Monohydrogen Phosphate Monohydrate

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Abstract: The crystal structure of the monohydrogen phosphate salt of ephedrine, which is a phenylethanolamine, was determined by use of three-dimensional X-ray diffractometer data. Crystals of $2(C_{10}H_{16}NO)HPO_4 \cdot H_2O$ are orthorhombic, space group $P2_12_12_1$, with a = 7.094 (1), b = 11.290 (3), and c = 29.567 (5) Å. The structure was solved by a combination of statistical and Fourier methods, and was refined by full-matrix least squares to R 0.033. Ephedrine cations are hydrogen bonded to the phosphate anion through their ethanolamine moieties; the conformation of ephedrine is such that the hydroxyl and amino group can both hydrogen bond to oxygen atoms of the phosphate ion. This conformation is similar to that in the other crystal structures of phenylethanolamines, and is consistent with that predicted from spectroscopic and molecular-orbital studies. Thus it appears that phenylethanolamines generally assume a conformation that would lead to strong hydrogen-bonded interactions with phosphates. Such interactions are probably responsible for the phenylethanolamine-ATP complexes that occur in aqueous and biological systems.

Ephedrine, a phenylethanolamine, is structurally and physiologically related to epinephrine and norepinephrine, two hormones that mediate a wide variety of biological processes. Little is known about the mechanisms that might account for the biological roles of phenylethanolamines, but there is evidence that complexes of these compounds with ATP may be involved both at receptor[1] and storage sites.[2,3] Spectroscopic studies show that phenylethanolamines bind to ATP in aqueous solution, and indicate that the binding involves interaction between the ethanolamine moiety of the phenylethanolamine and the phosphate group of ATP.[4] Mechanisms that may account for this interaction have been suggested,[4] but no detailed structural studies of phenylethanolamine-phosphate complexes have been reported.

In this paper we describe the phenylethanolamine-phosphate interactions in the crystal structure of ephedrine monohydrogen phosphate, and show that ephedrine assumes a conformation which permits strong hydrogen bonding between the ethanolamine moiety and the phosphate anion. We also review structural data for other phenylethanolamines and show that these compounds generally assume a conformation that would lead to strong hydrogen bonding between their ethanolamine moieties and phosphate anions.

Experimental Section

Ephedrine phosphate was obtained by lyophilizing an aqueous solution that contained equimolar quantities of ephedrine and phosphoric acid. Slow cooling of a hot aqueous ethanol solution of ephedrine phosphate produced two types of crystals: clear needles of ephedrine dihydrogen phosphate and clear plates of ephedrine monohydrogen phosphate monohydrate. The crystal structure of the needles has been reported.[5] Weissenberg and oscillation photographs showed the plates to be orthorhombic; the space group is $P2_12_12_1$ as indicated by the systematic absence of reflections $h00$ with h odd, $0k0$ with k odd, and $00l$ with l odd. A crystal fragment with dimensions of 0.19, 0.17, and 0.08 mm was mounted on a Picker FACS-1 diffractometer with its b axis slightly inclined to the ϕ axis of the diffractometer. Unit-cell parameters were determined by a least-squares analysis of the angular settings for six high-angle (Cu Kα_1, λ 1.54051 Å) reflections measured with the diffractometer. Crystal data are listed in Table I.

Table I. Crystal Data[a]

Stoichiometry	$(C_{10}H_{16}NO^+)_2HPO_4{}^{2-} \cdot H_2O)$
Z	4
Space group	$P2_12_12_1$
a	7.094 (1) Å
b	11.290 (1) Å
c	29.567 (5) Å
ρ (calcd)	1.253 g cm^{-3}
ρ (obsd)	1.26 g cm^{-3}
μ	13.84 cm^{-1}

[a] Reported standard deviations in unit-cell parameters are three times those obtained from the least-squares analysis. Density was measured by flotation in a mixture of carbon tetrachloride and benzene.

Intensity data were collected with the diffractometer by use of a scintillation counter, nickel-filtered copper radiation, and a θ–2θ scanning technique. Measurements were made for the 2403 unique reflections with $2\theta \leq 128°$. Those reflections with scan counts less than background levels were assigned intensity values of 0.0 and were retained in all subsequent calculations. The intensity values were assigned variances, $\sigma^2(I)$, according to the statistics of the scan and background counts plus an additional term $(0.03S)^2$, S being the scan counts. The intensities and variances were corrected for Lorentz and polarization factors. Absorption corrections were applied using the computer program ORABS;[6] the transmission factors ranged from 0.76 to 0.92. Structure factors and their variances were scaled by means of a Wilson plot.[7]

Trial coordinates for the phosphorus atom and the four oxygen atoms of the phosphate group were obtained by direct methods,

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(2) Reference 1, p 1235.

(3) V. S. Pai and E. W. Maynert, *Mol. Pharmacol.*, **8**, 82 (1972).

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(6) D. J. Wehe, W. R. Busing, and H. A. Levy, "ORABS, A Fortran Program for Calculating Single Crystal Absorption Corrections," Oak Ridge National Laboratory, Oak Ridge, Tenn., 1962, Report ORNL-TM-229.

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Table II. Final Heavy-Atom Parameters and Their Standard Deviations[a]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
				Ephedrine A					
C(1)	4830 (3)	2243 (2)	5985 (1)	113 (5)	71 (2)	7 (1)	7 (3)	2 (1)	2 (1)
C(2)	5423 (5)	1306 (3)	5717 (1)	202 (7)	88 (3)	9 (1)	22 (4)	7 (1)	1 (1)
C(3)	6321 (5)	1509 (4)	5307 (1)	251 (9)	131 (4)	10 (1)	16 (5)	14 (2)	3 (1)
C(4)	6629 (5)	2647 (4)	5165 (1)	197 (7)	168 (5)	8 (1)	−24 (5)	9 (1)	4 (1)
C(5)	6062 (6)	3579 (4)	5425 (1)	261 (9)	115 (4)	11 (1)	−67 (5)	−1 (2)	10 (1)
C(6)	5169 (5)	3388 (3)	5838 (1)	241 (8)	82 (3)	9 (1)	−32 (4)	3 (1)	39 (1)
C(7)	3827 (4)	1982 (2)	6425 (1)	140 (6)	47 (2)	7 (1)	−1 (3)	−3 (1)	1 (1)
C(8)	1667 (4)	1951 (2)	6360 (1)	134 (5)	64 (2)	6 (1)	−4 (3)	−2 (1)	−1 (1)
O(1)	4303 (3)	2823 (2)	6762 (1)	185 (4)	61 (2)	7 (1)	−29 (2)	−4 (1)	−1 (1)
C(9)	−1239 (4)	1367 (3)	6791 (1)	134 (6)	98 (3)	14 (1)	−42 (4)	−1 (1)	2 (1)
N(1)	0811 (3)	1667 (2)	6812 (1)	107 (4)	53 (2)	76 (1)	−9 (3)	−1 (1)	1 (1)
C(10)	0825 (5)	3087 (3)	6178 (1)	186 (7)	112 (4)	12 (1)	29 (5)	−4 (2)	16 (1)
				Ephedrine B					
C(1)	7636 (4)	7483 (3)	6045 (1)	126 (5)	82 (3)	8 (1)	−10 (3)	−4 (1)	−1 (1)
C(2)	8149 (5)	6304 (3)	5978 (1)	184 (7)	91 (3)	12 (1)	−12 (4)	7 (1)	−8 (1)
C(3)	9171 (6)	5971 (4)	5999 (1)	229 (8)	120 (4)	14 (1)	3 (5)	12 (2)	−15 (1)
C(4)	9669 (5)	6808 (4)	5286 (1)	170 (8)	179 (5)	10 (1)	32 (5)	1 (1)	−13 (1)
C(5)	9221 (5)	7967 (4)	5348 (1)	190 (7)	169 (5)	10 (1)	18 (6)	5 (2)	16 (1)
C(6)	8198 (4)	8315 (3)	5733 (1)	172 (6)	107 (4)	9 (1)	21 (4)	4 (1)	6 (1)
C(7)	6481 (4)	7817 (2)	6458 (1)	149 (6)	63 (2)	6 (1)	−4 (3)	−3 (1)	−1 (1)
C(8)	4466 (4)	7327 (3)	6419 (1)	149 (5)	68 (2)	7 (1)	−9 (3)	−2 (1)	−2 (1)
O(1)	6441 (3)	9060 (2)	6507 (1)	268 (6)	60 (2)	9 (1)	−31 (3)	7 (1)	3 (1)
C(9)	1685 (5)	6840 (4)	6902 (1)	159 (6)	106 (4)	11 (1)	−38 (4)	2 (1)	1 (1)
N(1)	3505 (3)	7477 (2)	6866 (1)	125 (4)	55 (2)	7 (2)	−5 (2)	−1 (1)	1 (1)
C(10)	3341 (5)	7932 (5)	6049 (1)	171 (7)	190 (6)	8 (1)	−26 (6)	−9 (1)	11 (1)
				Phosphate and Water					
P	5822 (1)	5164 (1)	7497 (1)	121 (1)	43 (1)	6 (1)	−1 (1)	−1 (1)	−1 (1)
O(2)	5632 (3)	6504 (1)	7512 (1)	223 (4)	46 (1)	8 (1)	2 (2)	−9 (1)	1 (1)
O(3)	6176 (3)	4875 (2)	6972 (1)	249 (1)	62 (2)	7 (1)	−31 (3)	8 (1)	−3 (1)
O(4)	7532 (2)	4758 (2)	7769 (1)	121 (3)	52 (1)	10 (1)	7 (2)	−3 (1)	−1 (1)
O(5)	4070 (3)	4510 (2)	7641 (1)	128 (4)	70 (2)	8 (1)	−11 (2)	−1 (1)	1 (1)
O(W)	0668 (4)	3701 (2)	7326 (1)	125 (4)	111 (2)	21 (1)	−1 (3)	5 (1)	−27 (1)

[a] All values have been multiplied by 10^4. Temperature factors are in the form $T = \exp(-\beta_{11}h^2 - \beta_{22}k^2 - \beta_{33}l^2 - 2\beta_{12}hk - 2\beta_{13}hl - 2\beta_{12}kl)$. Final value of the isotropic extinction parameter (g) is 0.28.

with the use of the computer program MULTAN.[8] The other nonhydrogen atoms were located in a Fourier map that was calculated with phase angles derived from the five heavy atoms of the phosphate group. The trial structure was refined with a SIGMA-7 computer by use of a modified version of the full-matrix least-squares program ORFLS.[9] The quantity minimized was $\Sigma w(F_o^2 - (1/k^2)F_c^2)^2$, where k is a scale factor and weight w is equal to $(1/\sigma \cdot (F_o^2))^2$. All measured reflections, regardless of their $I/\sigma(I)$ ratio, were included in the refinement. Atomic scattering factors for the nonhydrogen atoms were taken from ref 10; anomalous dispersion corrections for these atoms were those of Cromer and Liberman.[11] The hydrogen atom scattering factors were taken from Stewart, Davidson, and Simpson.[12] Hydrogen atoms were located in a difference Fourier map that was calculated during the final stages of refinement. The last cycles of refinement included all positional parameters, anisotropic temperature parameters for the hydrogen atoms, isotropic temperature factors for the hydrogen atoms, and Zachariasen's extinction parameter g[13] (as formulated by Hamilton and Coppens[14]). Because of the limited core-storage capacity of the computer, it was impracticable to refine all parameters simultaneously; consequently, the parameters were divided into three blocks, those for each of the ephedrine cations in separate blocks, and those for the phosphate ion and the water molecule in a third block. Each of these blocks also contained the scale factor and the extinction parameter. The blocks of parameters were refined in successive cycles. The final R index $(\Sigma||F_o| - |F_c||/\Sigma|F_o|)$ for all reflections is 0.033; the goodness-of-fit $(\Sigma(1/\sigma^2(F_o^2)))(F_o^2 - F_c^2/k^2)/(m - s))^{1/2}$, where m is the number of reflections used and s is the number of parameters refined, is 1.38. During the last cycle of refinement, no atomic parameter shifted more than one-fourth of its standard deviation. A final difference Fourier map showed no peaks or troughs exceeding 0.2 e/Å^3 in magnitude.

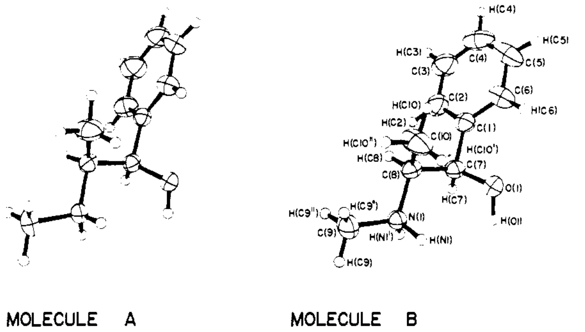

Figure 1. Conformations of the two ephedrine cations (labeled molecule A and molecule B). Heavy atoms are represented by ellipsoids, defined by the principal axes of thermal vibration, and scaled to include 50% probability. Hydrogen atoms are represented by spheres of 0.1 Å radius.

Results

Table II lists the final heavy-atom parameters and their estimated standard deviations. Table III gives the hydrogen atom parameters and their estimated standard deviations. The estimated errors in positional coordinates are less than 0.005 Å for the non-

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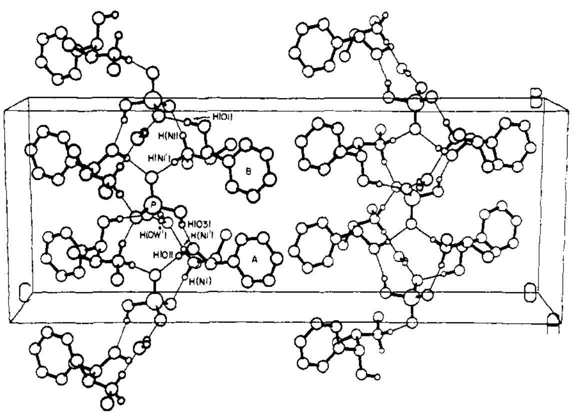

Figure 2. The crystal system viewed down the *a* axis. Thin lines represent hydrogen bonds.

Table III. Final Hydrogen-Atom Parameters and Their Estimated Standard Deviations[a]

Atom	x	y	z	β, Å^2
		Ephedrine A		
H(C2)	522 (5)	048 (3)	581 (1)	6.0 (1.0)
H(C3)	680 (5)	077 (3)	511 (1)	7.2 (1.0)
H(C4)	734 (5)	282 (3)	490 (1)	7.2 (1.0)
H(C5)	627 (5)	442 (3)	536 (1)	6.5 (0.9)
H(C6)	499 (5)	340 (3)	602 (1)	6.0 (0.9)
H(C7)	422 (4)	119 (2)	651 (1)	2.6 (0.5)
H(C8)	146 (4)	123 (2)	616 (1)	3.5 (0.6)
H(C9)	−167 (4)	104 (2)	711 (1)	3.9 (0.6)
H(C9')	−192 (7)	219 (4)	672 (1)	11.3 (1.4)
H(C9'')	−139 (5)	070 (3)	659 (1)	5.2 (0.8)
H(C10)	128 (4)	324 (3)	587 (1)	4.9 (0.7)
H(C10')	104 (4)	373 (3)	641 (1)	6.7 (0.9)
H(C10'')	−043 (5)	300 (3)	615 (1)	6.7 (1.1)
H(O1)	419 (5)	245 (3)	703 (1)	5.1 (0.7)
H(N1)	089 (4)	235 (2)	700 (1)	3.9 (0.6)
H(N1')	141 (4)	098 (3)	697 (1)	5.0 (0.7)
		Ephedrine B		
H(C2)	778 (4)	568 (3)	620 (1)	4.7 (0.7)
H(C3)	962 (5)	513 (3)	553 (1)	7.1 (1.0)
H(C4)	1036 (5)	650 (3)	502 (1)	6.1 (0.9)
H(C5)	958 (5)	860 (3)	517 (1)	6.3 (0.9)
H(C6)	800 (4)	910 (2)	579 (1)	2.7 (0.6)
H(C7)	714 (3)	751 (2)	673 (1)	2.7 (0.5)
H(C8)	465 (4)	649 (2)	638 (1)	3.4 (0.6)
H(C9)	122 (5)	689 (3)	722 (1)	7.5 (1.0)
H(C9')	090 (6)	711 (4)	670 (1)	7.8 (1.1)
H(C9'')	189 (6)	595 (4)	689 (1)	9.1 (1.2)
H(C10)	396 (6)	786 (3)	575 (1)	8.1 (1.1)
H(C10')	316 (8)	880 (4)	614 (2)	12.9 (1.9)
H(C10'')	203 (6)	762 (3)	603 (1)	6.9 (1.0)
H(O1)	628 (6)	924 (3)	682 (1)	7.9 (1.0)
H(N1)	333 (5)	836 (3)	695 (1)	5.9 (0.8)
H(N1')	442 (4)	717 (3)	710 (1)	4.5 (0.7)
		Phosphate and Water		
HO(3)	570 (6)	419 (3)	696 (1)	9.3 (1.2)
H(W)	−013 (6)	401 (3)	748 (1)	5.9 (0.9)
H(W')	168 (5)	392 (3)	743 (1)	5.3 (0.9)

[a] Positional parameters have been multiplied by 10^3.

hydrogen atoms and less than 0.06 Å for the hydrogen atoms. A table of observed and calculated structure factors is included in the microfilm edition of this journal.[15]

Figure 1 shows the conformations and the thermal ellipsoids of the two crystallographically independent ephedrine cations (designated ephedrine A ande phedrine B). Conformational torsion angles are shown in Figure 4, bond lengths are given in Table IV and bond angles are listed in Table V. The phenyl groups are planar within experimental error: no atoms deviate from the phenyl planes by more than 0.01 Å.

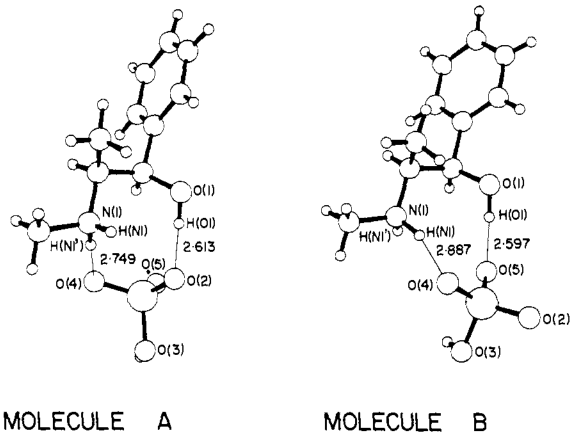

Figure 3. Hydrogen bonding between the ephedrine cations and the phosphate anion. Hydrogen bonds are represented by thin lines, and donor–acceptor distances (Å) are given.

Table IV. Bond Distances,[a] Å

Bond	Ephedrine A	Ephedrine B	Bond	Ephedrine A	Ephedrine B
C(1)–C(2)	1.386	1.394	C(2)–H(C2)	0.98	1.00
C(2)–C(3)	1.391	1.387	C(3)–H(C3)	1.06	1.02
C(3)–C(4)	1.370	1.369	C(4)–H(C4)	0.94	0.99
C(5)–C(4)	1.365	1.359	C(5)–H(C5)	0.99	0.93
C(5)–C(6)	1.390	1.407	C(6)–H(C6)	0.92	0.91
C(6)–C(1)	1.385	1.375	C(7)–H(C7)	0.96	0.99
C(1)–C(7)	1.514	1.519	C(8)–H(C8)	1.01	0.97
C(7)–O(1)	1.417	1.411	N(1)–H(N1)	0.95	1.05
C(7)–C(8)	1.545	1.537	N(1)–H(N1')	1.00	1.01
C(8)–N(1)	1.502	1.497	C(9)–H(C9)	1.05	1.00
C(8)–C(10)	1.514	1.516	C(9)–H(C9')	1.07	0.88
N(1)–C(9)	1.495	1.482	C(9)–H(C9'')	0.96	1.02
			C(10)–H(C10)	0.99	0.98
			C(10)–H(C10')	1.01	1.03
			C(10)–H(C10'')	0.90	0.98
			O(1)–H(O1)	0.91	0.96
		Phosphate and Water			
P–O(2)	1.519		O(W)–H(OW)	0.82	
P–O(3)	1.606		O(W)–H(OW')	0.80	
P–O(4)	1.526		O(3)–H(O3)	0.84	
P–O(5)	1.507				

[a] Standard deviations in bond lengths involving only nonhydrogen atoms are about 0.006 Å. Standard deviations in bond lengths involving hydrogen atoms are about 0.06 Å.

The crystal-packing and hydrogen-bonding schemes are shown in Figure 2. The hydrophobic phenyl and methyl groups are clustered together; the water molecules, the phosphate anions, and the hydroxyl and amino groups are hydrogen bonded together. The resultant packing scheme consists of alternating layers of polar and hydrophobic groups, with the layers running parallel to the *ab* plane. Table VI gives hydrogen bond distances and angles. As shown in Figure 3, each of the ephedrine cations is hydrogen bonded to the phosphate anion.

Discussion

An outstanding feature of this crystal structure is the interaction between the ephedrine cations and the phos-

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[15] See paragraph at end of paper regarding supplementary material.

Table V. Bond Angles,[a] deg

	Ephedrine A	Ephedrine B		Ephedrine A	Ephedrine B
C(6)–C(1)–C(2)	118.8	118.8	H(C6)–C(6)–C(1)	117	120
C(7)–C(1)–C(6)	122.3	121.8	H(O1)–O(1)–C(7)	107	108
C(7)–C(1)–C(2)	119.0	119.5	H(C7)–C(7)–C(1)	105	108
C(1)–C(2)–C(3)	120.7	120.7	H(C7)–C(7)–O(1)	112	106
C(2)–C(3)–C(4)	119.7	119.6	H(C7)–C(7)–C(8)	107	112
C(3)–C(4)–C(5)	120.2	120.9	H(C8)–C(8)–C(7)	104	109
C(4)–C(5)–C(6)	120.6	119.9	H(C8)–C(8)–C(10)	115	115
C(5)–C(6)–C(1)	120.0	120.1	H(C8)–C(8)–N(1)	106	107
O(1)–C(7)–C(1)	111.2	109.8	H(C10)–C(10)–C(8)	111	112
C(8)–C(7)–O(1)	111.2	110.3	H(C10′)–C(10)–C(8)	108	108
C(8)–C(7)–C(1)	111.3	110.6	H(C10′′)–C(10)–C(8)	109	112
C(7)–3(8)–3(10)	114.6	112.5	H(N1)–N(1)–C(8)	109	113
C(7)–C(8)–N(1)	107.1	108.4	H(N1)–N(1)–HN(1′)	110	104
C(10)–C(8)–N(1)	109.7	110.3	H(N1)–N(1)–C(9)	105	110
C(8)–N(1)–C(9)	113.8	113.9	H(N1′)–N(1)–C(8)	114	106
H(C2)–C(2)–C(1)	120	120	H(N1′)–N(1)–C(9)	105	110
H(C2)–C(2)–C(3)	119	119	H(C9)–C(9)–N(1)	109	109
H(C3)–C(3)–C(2)	119	125	H(C9′)–C(9)–N(1)	105	110
H(C3)–C(3)–C(4)	121	115	H(C9′′)–C(9)–N(1)	108	111
H(C4)–C(4)–C(3)	122	115	H(C10)–C(10)–H(C10′)	106	111
H(C4)–C(4)–C(5)	118	124	H(C10)–C(10)–H(C10′′)	105	110
H(C5)–C(5)–C(4)	126	127	H(C10′)–C(10)–H(C10′′)	117	103
H(C5)–C(5)–C(6)	114	113	H(C9)–C(9)–H(C9′)	111	115
H(C6)–C(6)–C(5)	123	119	H(C9)–C(9)–H(C9′′)	103	99
			H(C9′)–C(9)–H(C9′′)	121	113
		Phosphate and Water			
O(2)–P–O(3)	104.1		O(3)–P–O(5)	107.6	
O(2)–P–O(4)	110.7		O(4)–P–O(5)	111.1	
O(2)–P–O(5)	114.0		H(O3)–O(3)–P	100	
O(3)–P–O(4)	108.9		H(W)–O(W)–H(W′)	106	

[a] Standard deviations in bond angles involving only nonhydrogen atoms are about 0.3°. Standard deviations in bond angles involving hydrogen atoms are about 4°.

Table VI. Hydrogen Bond Distances (Å) and Angles (deg)

			Distances		
Donor atom	Hydrogen atom	Acceptor atom[a]	Donor–acceptor	Acceptor–hydrogen	Donor–hydrogen–acceptor angle
		Molecule A			
O(1)	H(O1)	O(2) (I)	2.61	1.72	166
N(1)	H(N1)	O(W)	2.75	1.59	170
N(1)	H(N′)	O(4) (I)	2.75	1.75	179
		Molecule B			
O(1)	H(O1)	O (5) (II)	2.60	1.64	178
N(1)	H(N1)	O(4) (II)	2.89	1.88	163
N(1)	H(N1′)	O(2)	2.64	1.67	170
		Phosphate and Water			
O(W)	H(OW′)	O(5)	2.74	1.93	175
O(W)	H(OW)	O(4) (III)	2.85	2.06	170
O(3)	H(O3)	O(1)	2.74	1.93	163

[a] Symmetry codes: (I) $1 - x, y - {}^1/_2, {}^3/_2 - z$; (II) $1 - x, y + {}^1/_2, {}^3/_2 - z$; (III) $x - 1, y, z$.

phate anion (Figure 3). Both of the crystallographically independent ephedrine cations form hydrogen bonds from the hydroxyl and amino groups of their ethanolamine moieties to oxygen atoms of the phosphate anion. This hydrogen bonding results in a cohesive interaction between the ethanolamine moieties and the phosphate anion, with two hydrogen bonds that are nearly linear and hydroxyl–phosphate contacts that are unsually short. Thus, the conformations of the ethanolamine moieties in this crystal structure are such that their hydroxyl and amino groups are in an orientation that is suitable for strong interactions with phosphates.

A comparison of the conformation observed in this structure with that found in other crystal structures of phenylethanolamines indicates that these compounds usually assume conformations closely related to that found for ephedrine. Seven other independent determinations of phenylethanolamine crystal structures,[5,16–18] as well as a theoretical calculation of the conformation of ephedrine,[19] have been reported. Pertinent conformational features from these other structural studies are shown in Figure 4. The conformations of phenylethanolamines are conveniently represented by four torsion angles, which we designate as τ, ψ, ω, and χ. These torsion angles[20] are defined as follows: τ which describes the conformation about the C(1)–C(7) bond, is defined by atoms C(2)–C(1)–C(7)–O(1); ω which describes the conformation about the C(7)–C(8) bond is defined by atoms O(1)–C(7)–C(8)–N(1); χ which describes the conformation about the N(1)–C(8) bond is defined by atoms R′–N(1)–C(8)–C(7); and ψ which describes the conformation about the O(1)–C(7) bond is defined by atoms H(O1)–O(1)–C(7)–C(8). As shown in Figure 4, these conformational angles are clustered within relatively narrow ranges, and the values for the other phenylethanolamines are in general agreement with those for ephedrine.

The torsion angle about the C(7)–C(8) bond of the ethanolamine moieties is of particular interest. As shown in Figure 4, this torsion angle (ω) falls into the

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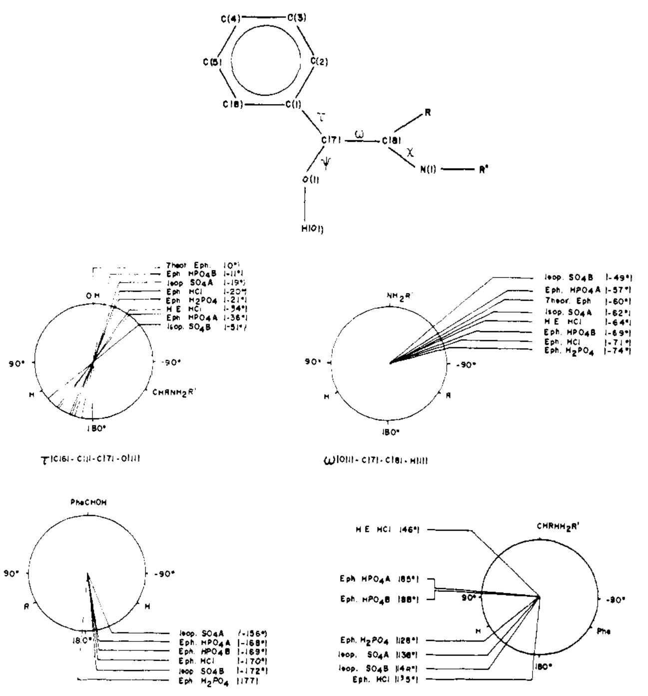

Figure 4. Conformational maps depicting the torsion angles in phenylethanolamines. Each torsion angle is described by four atoms, A–B–C–D, and is defined as the angle that A–B makes with respect to C–D when viewed down the B–C bond. The angle is zero if A–B and C–D are eclipsed, and is positive if A–B must be rotated clockwise to eclipse C–D. Each drawing shows the trace of A–B as viewed down B–C. Abbreviations for the compounds are: Theor. Eph., molecular orbital calculation for ephedrine; Eph. HPO_4A and Eph. HPO_4B, the A and B molecules in the crystal structure of ephedrine monohydrogen phosphate monohydrate (present study); Isop. SO_4A and Isop. SO_4B, the A and B molecules in the crystal structure of isoproterenol sulfate; Eph. H_2PO_4, crystal structure of ephedrine dihydrogen phosphate; N E HCl, crystal structures of norepinephrine hydrochloride.

narrow range $-74 < \omega < -49°$ for all of the phenylethanolamines that we examined. Therefore, in all cases, the amino group is situated gauche with respect to the hydroxyl group. This finding is consistent with other crystallographic,[21,22] solution,[23] and gas-phase studies,[24] all of which indicate the gauche conformation to be the most stable for a variety of ethanolamines and related compounds.

Since the conformation of ephedrine is closely related to that of other phenylethanolamines, the same type of ethanolamine–phosphate hydrogen bonding that occurs in the crystal structure of ephedrine monohydrogen phosphate should also be possible for other phenylethanolamines. In particular, interactions of this type might be predicted for epinephrine and norepinephrine, two phenylethanolamines that function as hormones and neurotransmitters. In biological systems, epinephrine and norepinephrine are released from storage vesicles from which they diffuse to the appropriate receptor sites.[25] Various studies have indicated that these compounds are complexed with ATP in storage vesicles,[2] and it has been suggested that complexes with ATP are also formed at the receptor sites.[1] Spectroscopic studies show that phenylethanolamines form complexes with ATP in aqueous solution,[3,4] and demonstrate that similar complexes also occur *in vivo* in adrenal medullary storage granules.[3]

The spectroscopic studies show that the ethanolamine moiety hydrogen bonds to the triphosphate group of ATP,[3,4] with stacking interactions between adenine and phenyl rings contributing little or nothing to the binding process.[4] Since phenylethanolamines bind as strongly to AMP as to ATP,[4] the interaction apparently involves a single phosphate group in the triphosphate moiety of ATP. The spectroscopic studies also show that the hydroxyl group of phenylethanolamines is required for the binding to ATP, thus indicating that the interaction is not simply due to coulombic attraction between the protonated amino groups and the negatively charged phosphate moiety of ATP.[4] Our results show that phenylethanolamines can interact with PO_4 groups by forming hydrogen bonds from the hydroxyl and amino groups of their ethanolamine moieties to two oxygen atoms of the phosphate. It is reasonable to assume that this type of ethanolamine–phosphate hydrogen bonding is also responsible for the phenylethanolamine–ATP complexes that have been observed in aqueous and biological systems.

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Supplementary Material Available. A table of observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JACS-73-7150.

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