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A Comparative Study on the Ionization of Catechol Amines in Aqueous Solutions

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The acid ionization constants of four protonated catechol amines (dopa, dopamine, α-methyldopa and isoprenaline) in aqueous 0.1 M potassium chloride solutions at 25°C were determined by a potentiometric method. The results are compared with earlier results concerning the ionization of other catechol amines. The first and second protolytic constants of catechol were determined.

A simple correlation is noted between the protolytic constants of *o*-diphenols (and of the corresponding catechol amines) and the formation constants of their boric acid chelates. From this the phenolic group of the catechol amines is proved to be a stronger acid than the protonated amino group. The effect of the structure of the catechol amines on their protolysis is examined.

Although the pharmacological properties of common catechol amines are well known, their ionization and chelate formation reactions seem to have been little investigated.[1–8] In studies of chelate formation reactions of inorganic acids with di- and polyphenols [9–11] it has been found that these phenols, and the similar catechol amines, form chelates with boric acid. Boric acid has been found to stabilize aqueous solutions of the diphenolic drug, adrenaline.[4] This has been explained as due to the chelate formation between boric acid and adrenaline. In order to clarify the possible chelation reactions of the other catechol amines with boric acid it is necessary to determine the protolytic constants of these catechol amines. The evaluation of these constants is also important for an understanding of the biological activity and stability of catechol amines.

The common catechol amines may be considered as substituted diphenols, and their ionization and chelation can be compared to the corresponding properties of the diphenols studied previously.[9–11]

According to Riegelman [4] it can be assumed that the protonated form (H_2L^+) occupies a central position in the chemistry of catechol amines in aqueous solutions. Here the first phenolic group is assumed to be more acidic than the protonated amino group. According to Rajan *et al.*[6] and Karpel *et al.*,[8] however, the protonated amino groups are more acidic.

EXPERIMENTAL

The measurements were carried out at 25°C on aqueous solutions containing various concentrations of protonated (hydrochlorides) catechol amines, in which the ionic strength was stabilized by making the solutions 0.1 M in potassium chloride. Dopa, dopamine, and isoprenaline sulphate were products of Fluka AG and α-methyldopa a product from Merck Sharp & Dohme.

All solutions were prepared in distilled water free from dissolved oxygen. The vessels used for storage of the solutions were flushed with purified nitrogen to remove the air. The catechol amines studied were titrated with 0.01 – 0.1 N sodium hydroxide in solutions containing the corresponding protonated (hydrochlorides) catechol amines. The temperature was maintained at 25°C by a water bath. The pH was measured during the titrations with a Radiometer Type PHM 4c pH meter using a Beckman Type E2 No 41263 glass electrode. A Beckman Type K 100 calomel electrode was used as a reference electrode. A 0.05 M potassium hydrogen phthalate solution (pH = 4.008) was used as reference solution. The value of the apparent activity coefficient $pf_{H^+} = 0.081$ (0.1 M KCl) [12] was used when calculating the hydrogen ion concentrations from the measured pH values.

The protolytic constants were calculated by a computer program written in ALGOL.

RESULTS

The acid ionization constants (first phenolic and protonated amino groups) for the protonated catechol amines studied here were determined potentiometrically as described earlier.[9] Some of the typical titration data are presented in Tables 1 – 4, where C_A is the stoichiometric concentration of the protonated catechol amine and C_B that of the added base (0.1 N NaOH). The protolytic

Table 1. Determination of the values for the protolytic constants K_1 and K_2 of protonated dopa (DH_2^+) in aqueous 0.1 M potassium chloride solutions at 25°C.

C_B/C_A	0.008 M DH_2^+ pH	0.008 M DH_2^+ pK_1	0.005 M DH_2^+ pH	0.005 M DH_2^+ pK_1	0.003 M DH_2^+ pH	0.003 M DH_2^+ pK_1	0.0015 M DH_2^+ pH	0.0015 M DH_2^+ pK_1
0.35	8.443	8.754	8.435	8.748	8.411	8.732	8.414	8.724
0.40	8.525	8.754	8.513	8.744	8.493	8.734	8.501	8.729
0.45	8.603	8.756	8.593	8.748	8.573	8.741	8.657	8.820
0.50	8.676	8.758	8.668	8.752	8.645	8.745	8.582	8.650
0.55	8.742	8.755	8.736	8.752	8.711	8.745	8.804	8.831
0.60	8.809	8.756	8.801	8.752	8.777	8.749	8.792	8.735
0.65	8.873	8.756	8.867	8.753	8.838	8.750	8.855	8.733
		pK_2		pK_2		pK_2		pK_2
0.85	9.118	9.847	9.110	9.840	9.066	9.743	9.097	9.850
0.90	9.177	9.845	9.167	9.834	9.119	9.737	9.155	9.849
0.95	9.236	9.844	9.227	9.837	9.173	9.735	9.214	9.853
1.00	9.295	9.844	9.281	9.827	9.227	9.734	9.270	9.850
1.05	9.352	9.841	9.340	9.829	9.277	9.726	9.325	9.846
1.10	9.411	9.841	9.397	9.827	9.372	9.719	9.382	9.848
1.15	9.473	9.846	9.455	9.827	9.376	9.711	9.635	10.209
Average	$pK_1 = 8.756$		8.750		8.742		8.742	
	$pK_2 = 9.844$		9.832		9.729		9.886	

Table 2. Determination of the values for the protolytic constants K_1 and K_2 of protonated dopamine (DAH_2^+) in aqueous 0.1 M potassium chloride solutions at 25°C.

C_B/C_A	0.01 M DAH_2^+ pH	0.01 M DAH_2^+ pK_1	0.005 M DAH_2^+ pH	0.005 M DAH_2^+ pK_1	0.0015 M DAH_2^+ pH	0.0015 M DAH_2^+ pK_1	0.001 M DAH_2^+ pH	0.001 M DAH_2^+ pK_1
0.10	7.881	8.839	7.890	8.849	7.895	8.858	7.923	8.888
0.15	8.076	8.835	8.087	8.848	8.088	8.854	8.112	8.879
0.20	8.230	8.840	8.242	8.854	8.229	8.848	8.256	8.875
0.25	8.350	8.838	8.358	8.848	8.347	8.846	8.374	8.873
0.30	8.455	8.837	8.465	8.850	8.453	8.846	8.477	8.872
0.35	8.551	8.838	8.558	8.849	8.543	8.846	8.570	8.872
0.40	8.640	8.840	8.645	8.849	8.624	8.842	8.655	8.872
		pK_2		pK_2		pK_2		pK_2
0.60	8.956	10.366	8.954	10.283	8.920	10.106	8.952	10.226
0.65	9.030	10.350	9.030	10.294	8.990	10.122	9.022	10.238
0.70	9.105	10.344	9.105	10.304	9.056	10.120	9.094	10.259
0.75	9.184	10.356	9.178	10.299	9.125	10.136	9.165	10.278
0.80	9.261	10.352	9.255	10.310	9.195	10.149	9.233	10.282
0.85	9.342	10.358	9.332	10.315	9.263	10.158	9.300	10.283
0.90	9.422	10.356	9.408	10.314	9.335	10.178	9.368	10.289
Average	pK_1 =	8.838		8.850		8.849		8.876
	pK_2 =	10.355		10.302		10.138		10.246

Table 3. Determination of the values for the protolytic constants K_1 and K_2 of protonated α-methyldopa (MDH_2^+) in aqueous 0.1 M potassium chloride solutions at 25°C.

C_B/C_A	0.008 M MDH_2^+ pH	0.008 M MDH_2^+ pK_1	0.005 M MDH_2^+ pH	0.005 M MDH_2^+ pK_1	0.003 M MDH_2^+ pH	0.003 M MDH_2^+ pK_1	0.001 M MDH_2^+ pH	0.001 M MDH_2^+ pK_1
0.10	7.913	8.874	7.916	8.880	7.902	8.866	7.970	8.941
0.15	8.120	8.884	8.122	8.890	8.101	8.869	8.150	8.926
0.20	8.263	8.880	8.448	9.081	8.253	8.874	8.289	8.920
0.25	8.391	8.889	8.892	8.897	8.377	8.880	8.404	8.918
0.30	8.489	8.883	8.495	8.900	8.479	8.881	8.496	8.910
0.35	8.584	8.887	8.585	8.900	8.566	8.877	8.590	8.916
0.40	8.666	8.885	8.667	8.901	8.651	8.880	8.665	8.911
		pK_2		pK_2		pK_2		pK_2
0.60	8.960	10.110	8.954	9.942	9.013	8.932	8.939	9.927
0.65	9.025	10.095	9.020	9.955	9.077	8.996	8.999	9.929
0.70	9.090	10.089	9.081	9.957	9.139	9.058	9.062	9.946
0.75	9.157	10.095	9.143	9.966	9.199	9.118	9.121	9.955
0.80	9.211	10.091	9.205	9.976	9.260	9.179	9.178	9.960
0.85	9.285	10.089	9.265	9.980	9.320	9.239	9.234	9.964
0.90	9.348	10.086	9.324	9.983	9.378	9.297	9.291	9.973
Average	pK_1 =	8.883		8.917		8.875		8.920
	pK_2 =	10.093		9.965		9.999		9.950

Table 4. Determination of the values for the protolytic constants K_1 and K_2 of protonated isoprenaline (IPH_2^+) in aqueous 0.1 M potassium chloride solutions at 25°C.

	0.008 M IPH_2^+		0.005 M IPH_2^+		0.003 M IPH_2^+		0.001 M IPH_2^+	
C_B/C_A	pH	pK_1	pH	pK_1	pH	pK_1	pH	pK_1
0.35	8.366	8.674	8.348	8.650	8.347	8.647	8.338	8.639
0.40	8.450	8.672	8.430	8.647	8.432	8.648	8.415	8.631
0.45	8.528	8.671	8.509	8.647	8.510	8.647	8.503	8.642
0.50	8.602	8.671	8.583	8.646	8.586	8.648	8.567	8.630
0.55	8.669	8.667	8.656	8.648	8.658	8.648	8.646	8.638
0.60	8.737	8.666	8.724	8.646	8.727	8.646	8.714	8.636
0.65	8.806	8.668	8.795	8.648	8.793	8.643	8.780	8.634
		pK_2		pK_2		pK_2		pK_2
0.85	9.068	9.926	9.059	9.880	9.063	9.905	9.048	9.865
0.90	9.131	9.926	9.127	9.886	9.131	9.910	9.116	9.870
0.95	9.195	9.930	9.192	9.884	9.198	9.911	9.182	9.870
1.00	9.254	9.922	9.258	9.885	9.264	9.911	9.246	9.866
1.05	9.314	9.920	9.323	9.884	9.324	9.900	9.305	9.854
1.10	9.375	9.922	9.387	9.882	9.389	9.900	9.368	9.851
1.15	9.432	9.918	9.452	9.883	9.455	9.903	9.430	9.847
Average	$pK_1 = 8.670$		8.647		8.647		8.636	
	$pK_2 = 9.924$		9.883		9.905		9.860	

constants of the four catechol amines studied here are collected in Table 5. In Table 6 the protolytic constants of some common catechol amines are compared to the protolytic constants of catechol and pyrogallol.[13] The protolytic constant of catechol has been previously determined by several investigators, but their results are divergent.[14–24] Hence the protolytic constants of catechol were redetermined using the potentiometric method described earlier.[9] The results are shown in Table 7.

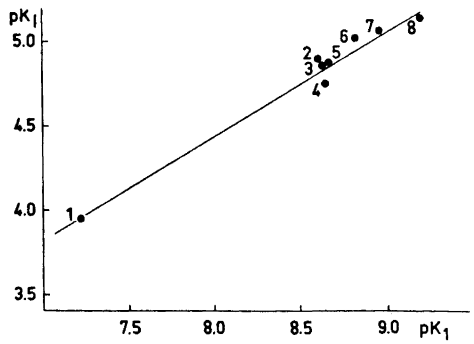

Fig. 1. The dependence of *o*-diphenol-boric acid chelate formation on the protolysis of the first phenolic group in *o*-diphenols. 1 Protocatechualdehyde. 2 DL-Noradrenaline. 3 L-Noradrenaline. 4 Adrenaline. 5 Gallic acid. 6 Protocatechuic acid. 7 Pyrogallol. 8 Catechol.

In Fig. 1 is shown the relationship between the first protolytic constants of some *o*-diphenols and the formation constants of the boric acid chelates of the corresponding phenols [9] (points 1, 5 – 8). According to this the formation of the boric acid chelates of the phenols is promoted by the acid strength of the ligand. Because the catechol amines considered in this paper also form such boric acid chelates,[9] the same correlation should be expected to hold for them too. In Fig. 1, the points 2 – 4 depict the catechol amines studied earlier with the first protolytic constant of the catechol amine taken as the protolytic constant. If, on the other hand, the corresponding second protolytic constants were used, the expected correlation would not be realized (*cf.* Table 6). It is obvious from this that the first protolytic constant of the catechol amines is due to the phenolic group and the second one to the protonated amino group. Riegelman [5] has earlier come to the same conclusion, whereas Rajan [6] and Karpel [8] have taken the opposite view.

An examination of the results in Table 6 reveals that the catechol amines are stronger acids than the simple *o*-diphenols. An amine chain attached to the diphenol ring thus clearly strengthens the acidic character of the phenolic group. Changes in the amine chain, however, seem to have a clear effect only on the second protolytic constant of the catechol amines (protonated amino

Table 5. Values of the protolytic constants (protonated amino and phenolic groups) of four protonated catechol amines in aqueous solutions at various concentrations (0.1 M KCl, 25°C).

	Dopamine			α-Methyldopa	
$[DAH_2^+]$	pK_1	pK_2	$[MDH_2^+]$	pK_1	pK_2
0.001	8.876	10.264	0.001	8.926	9.950
	8.858	10.072		8.845	9.965
0.005	8.850	10.302		8.890	10.038
0.015	8.849	10.138	0.003	8.875	9.999
0.010	8.838	10.355	0.005	8.917	9.965
	8.865	10.357	0.008	8.868	10.035
	8.865	10.375		8.883	10.093
	8.851	10.477	Average	8.886	9.996
	8.850	10.336			
	8.836	10.378			
	8.838	10.282			
	8.890	10.402			
Average	8.855	10.312			
	Dopa			Isoprenaline	
$[DH_2^+]$	pK_1	pK_2	$[IPH_2^+]$	pK_1	pK_2
0.0015	8.742	9.886	0.001	8.670	9.924
0.003	8.742	9.729	0.003	8.647	9.906
0.005	8.750	9.832		8.647	9.905
	8.766	9.830	0.005	8.647	9.883
Average	8.750	9.819		8.657	9.915
			0.008	8.636	9.860
			Average	8.651	9.899

Table 6. The protolytic constants (phenolic and protonated amino groups) of catechol, pyrogallol, and some common protonated catechol amines.

	pK_1	pK_2	Medium (I and °C)	References
Catechol	9.43	13	0.1 – 0.15, 20	20
	9.15	11.23	0.06, 25	14
	9.17	13.4	0.1, 18 – 22	21
	9.37	12.8	0.1, 25	17
	9.33	12.62	0.1, 25	20, 23
	9.25	–	0.09, 25	15
	9.85	–	?, 26	16
	9.20	11.93	0.1, 25	18
	9.39	13.1	0.1, 25	19
	9.21	11.70	0.1, 25	This work
Pyrogallol	8.82	11.09	?, ?	22
	9.01	11.64	?, ?	23
	9.05	11.19	0.1, 20	24
	8.98	–	0.1, 25	13
Adrenaline	8.71	9.90	0.1, 25	25
	8.66	9.95	0.1, 25	17
	8.78	10.02	0.06, 25	26
	8.73	10.17	1.0, 25	6
	8.62	10.05	0.1, 25	9
L-Noradrenaline	8.82	9.98	0.06, 25	26
	8.57	9.93	1.0, 25	6
	8.64	9.70	0.1, 25	17
	8.62	9.64	0.1, 25	9
DL-Noradrenaline	8.57	9.73	1.0, 25	6
	8.60	9.62	0.1, 25	9
Dopamine	8.96	10.50	1.0, 25	6
	8.86	10.31	0.1, 25	This work
Isoprenaline	8.65	9.90	0.1, 25	This work
Dopa	9.19	10.24	?, ?	3
	8.71	9.74	1.0, 25	7
	8.67	9.88	0.0, 25	2
	8.75	9.82	0.1, 25	This work
α-Methyldopa	9.12	10.61	?, ?	3
	8.87	10.00	0.1, 25	This work

group). It can be noted, *e.g.*, that methylation of the amino group clearly weakens the acidic character of the protonated amino group (*cf.* adrenaline/noradrenaline), but seems to have no effect on the protolysis of the phenolic group. This effect on the protonated amino group is readily understood by analogy with the basic protolytic constants of alkyl amines. The attachment

Table 7. Determination of the values for the protolytic constants K_1 and K_2 of catechol in aqueous 0.1 M potassium chloride solutions at 25°C.

C_B/C_A	0.008 M Catechol pH	0.008 M Catechol pK_1	0.005 M Catechol pH	0.005 M Catechol pK_1	0.003 M Catechol pH	0.003 M Catechol pK_1
0.35	8.934	9.210	8.950	9.226	8.735	9.220
0.40	9.022	9.208	9.034	9.218	8.908	9.220
0.45	9.109	9.208	9.124	9.221	9.061	9.221
0.50	9.193	9.208	9.210	9.222	9.199	9.217
0.55	9.273	9.205	9.295	9.223	9.336	9.216
0.60	9.354	9.202	9.378	9.221	9.475	9.214
0.65	9.435	9.198	9.465	9.219	9.622	9.211
		pK_2		pK_2		pK_2
0.85	9.798	11.161	9.864	11.821	9.622	11.604
0.90	9.909	11.199	9.991	11.910	9.783	11.626
0.95	10.035	11.261	10.121	11.897	9.965	11.716
1.00	10.168	11.315	10.269	12.009	10.156	11.774
1.05	10.312	11.386	10.404	12.027	10.342	11.852
1.10	10.468	11.488	10.530	12.069	10.499	11.895
1.15	10.614	11.584	10.638	12.093	10.629	11.942
Average		$pK_1 = 9.206$ $pK_2 = 11.342$		$pK_1 = 9.221$ $pK_2 = 11.975$		$pK_1 = 9.217$ $pK_2 = 11.773$

of an alkyl group to the amine markedly strengthens the basic character of the latter, or correspondingly weakens the acidic character of the protonated amino group. It is just this weakening of protolysis that is observed in passing from noradrenaline to adrenaline. Moreover, by comparing isoprenaline and adrenaline, it can be observed that the radical attached to nitrogen has no significant effect on the protolytic constants. Neither here nor in the case of alkyl amines has the size of the alkyl group any substantial effect on the protolytic constants.

It may be noted as a general feature of this argument that the structure of the amine chain on the whole has but little effect on the protolysis of the catechol amines. A remarkable exception, however, is a methyl group in the α-position (*cf.* dopa and dopamine), which quite clearly exerts an influence on both the phenolic and the protonated amino group by decreasing their corresponding protolytic constants. On the other hand, changes in the structure of the amine chain affect primarily the protolysis of the protonated amino group.

One of the authors (P. J. A.) shortly intends to continue investigating the formation of boric acid chelates of the catechol amines.

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