Articles

The Discovery of Crown Ethers

CHARLES J. PEDERSEN

The discovery of the crown ethers stemmed from efforts to control the catalytic activity of vanadium and copper by complexation with multidentate ligands. The first crown ether, 2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclo-octadeca-2,11-diene, was obtained in 0.4% yield during an attempt to prepare a phenolic ligand from catechol and bis(2-chloroethyl)ether. This compound, which complexed with the sodium cation, was the first compound known to display such activity and became known as dibenzo-18-crown-6, an 18-atom heterocycle containing 6 oxygen atoms. Some 60 related compounds were made involving heterocyclic rings containing 12 to 60 atoms including 4 and 10 oxygen atoms. There are optimum polyether ring sizes for the different alkali metal cations: 15 to 18 for sodium, 18 for potassium, and 18 to 21 for cesium. Complexes having polyether to cation ratios of 1:1, 3:2, and 2:1 were prepared. Solubilization of inorganic salts in aprotic solvents, especially by saturated crown ethers, was demonstrated.

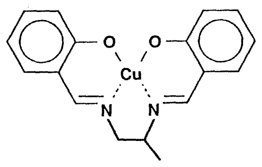
As a new scientist at the du Pont Company, I initially worked on a series of typical problems (*1–5*). I began to search for oil-soluble precipitants for copper, and I found the first good metal deactivator for petroleum products (*6–8*). As a result of this work, I developed an interest in the effects of various ligands on the catalytic properties of copper and the transition elements generally. I noticed a very unusual synergistic effect wherein a metal deactivator greatly increased the efficacy of antioxidants (*9, 10*).

As my interests in the oxidative degradation of the substrates, particularly petroleum products and rubber, increased, I gave up working on metal deactivators and coordination chemistry. In the mid-1940s, my work involved oxidative degradation and stabilization (*11–13*). During the 1940s and 1950s, I became interested in the photochemistry of new phthalocyanine adducts and of quinone-imine dioxides. I found some polymerization initiators, discovered that ferrocene was a good antiknock agent for gasoline, and made some novel polymers (*14–23*).

Discovery of the Crown Ethers

But then there arose a challenging opportunity that led me back to ligand chemistry. My colleague Herman Schroeder suggested that there was an interesting problem in the coordination chemistry of vanadium, and I began work with the initial goal of understanding factors that govern the catalytic activity of vanadium in oxidation and polymerization. It was my work in this area that led to the discovery of crown ethers.

I had studied the autoxidation of petroleum products and rubber and its retardation by antioxidants. Autoxidation is greatly catalyzed by trace metals, such as copper and vanadium. This is what led to the development of the "metal deactivators," which suppress the catalytic activity of the metal salts by converting them into inactive multidentate complexes. The first of these deactivators was *N,N'*-(1,2-propylenebis)(salicylideneimine), an excellent deactivator for copper:



In 1960 when I returned to investigations in coordination chemistry, I decided to study the effects of bi- and multidentate phenolic ligands on the catalytic properties of the vanadyl group, VO (*24*). The multidendate ligand I selected was the bis[2-(*o*-hydroxyphenoxy)ethyl]ether (**III**), whose synthesis is depicted in Fig. 1. I knew that the partially protected catechol (**I**) was contam-

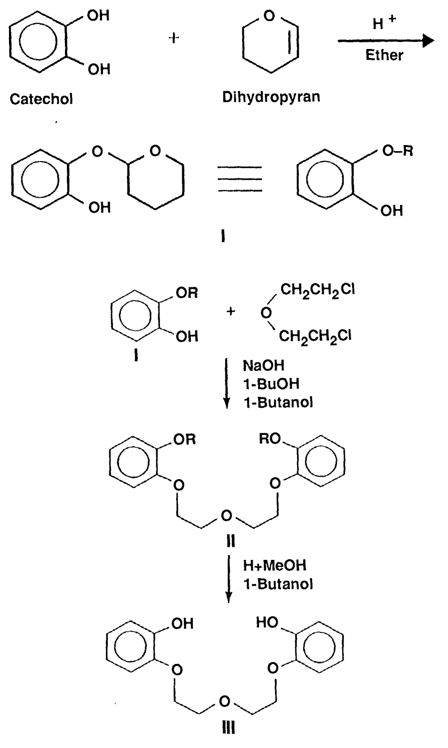


Fig. 1. Synthesis of bis[2-(*o*-hydroxyphenoxy)ethyl]ether; Bu, butyl; Me, methyl.

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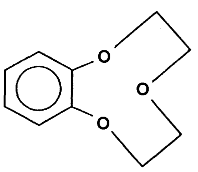
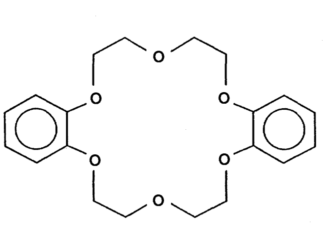
inated with about 10% unreacted catechol. I decided to use this mixture for the second step because purification would be required at the end. The reactions were carried out as outlined in Fig. 1 and gave a product mixture in the form of an unattractive goo. Initial attempts at purification gave a small yield (about 0.4% yield) of white crystals which had a silky, fibrous structure and were apparently insoluble in hydroxylic solvents.

The unknown probably was not the target compound because that would have been present in a higher yield, and, although my objective was to prepare and test a particular compound for a particular purpose, I began to study the unknown. It was fortunate that I used an ultraviolet spectrophotometer to follow the reactions of the phenols. These compounds and their ethers in neutral methanol solutions absorb in the region of 275 nm. If these compounds are treated with alkali, the absorption curve (solid curve in Fig. 2) is not significantly altered if all the hydroxyl groups are protected, but it is shifted to longer wavelengths and higher absorption if one or more hydroxyl groups are still free (dashed curve in Fig. 2).

The unknown product was only slightly soluble in methanol, and the neutral solution gave an absorption curve characteristic of a phenolic compound (Fig. 3A). The solution was made alkaline with sodium hydroxide with the expectation that the curve would either be unaffected or be shifted to longer wavelengths. The resulting spectrum, however, showed neither effect but rather the one shown in Fig. 3B. Moreover, the fibrous crystals were freely soluble in methanol in the presence of sodium hydroxide. This seemed strange because the compound did not contain a free phenolic group, a fact confirmed by its infrared and nuclear magnetic resonance spectra. I then found that the compound was soluble in methanol containing any soluble sodium salt. Thus, the increased solubility was due not to alkalinity but to sodium ions. But there was no obvious explanation for the behavior of the compound because its elementary analysis corresponded to that for a 2,3-benzo-1,4,7-trioxacyclononane,



a plausible product from the reaction of catechol and bis(2-chloroethyl)ether in the presence of sodium hydroxide. However, its molecular weight was exactly twice that of the above compound. The true structure was that of an 18-membered ring, dibenzo-18-crown-6(2,3,11,12-dibenzo-1,4,7,10,13,16-hexaoxacyclo-octadeca-2, 11-diene),



the first and most versatile of the aromatic crown compounds. The shape is that of a torus or a doughnut.

On the basis of these results, it seemed clear to me that the sodium ion had fallen into the hole in the center of the molecule and was held there by the electrostatic attraction between its positive charge and the negative dipolar charge on the six oxygen atoms symmetrically arranged around it in the polyether ring. Tests showed that other alkali metal ions and the ammonium ion behaved like the sodium ion so that, at long last, a neutral compound had been synthesized that formed stable complexes with alkali metal ions.

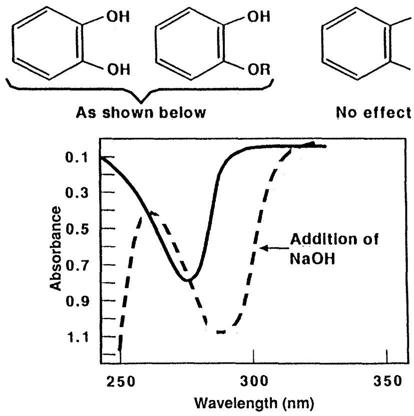


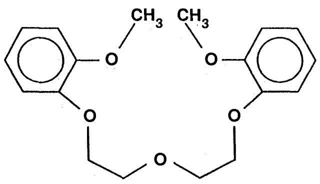
Fig. 2. Effect of sodium hydroxide on the ultraviolet spectrum of the phenols.

Until then, no one had found a synthetic compound that formed stable complexes with sodium or potassium ions.

The three-dimensional structure of the compound is shown in the computer-simulated model in Fig. 4. I applied the name "crown" to the first member of this class of macrocyclic polyethers because its molecular model looked like one and, with it, cations could be crowned and uncrowned without physical damage to either as shown for the potassium complex in Fig. 5. I developed the system of crown nomenclature chiefly because the International Union of Pure and Applied Chemistry names for the crown ethers were so complex. This system of abbreviated names, devised solely for the ready identification of the macrocyclic polyethers, has been retained by the scientific establishment. Figure 6 illustrates how the system of nomenclature is derived from the side-ring substituents, the total number of oxygen atoms in the main ring, and the size of the ring.

In ordinary organic reactions only rings of five, six, or seven members form easily. By contrast, in these compounds a ring of 18 atoms had been formed in a single operation by the reaction of two molecules of catechol, which was present as a minor impurity, with two molecules of bis(2-chloroethyl)ether. Further experiments revealed that dibenzo-18-crown-6 can be synthesized from these intermediates in a 45% yield without the need for high-dilution techniques. I concluded that the ring-closing step, initiated either by a second molecule of catechol or by a second molecule of bis(2-chloroethyl)ether, was facilitated by the sodium ion, which, by ion-dipole interaction, "wrapped" the molecular pieces around itself to form a three-quarter circle and disposed them for the final ring closure in much the same way as in the synthesis of the porphyrins and phthalocyanines. Later experiments supported this hypothesis.

The yields of dibenzo-18-crown-6 are higher when it is prepared with sodium or potassium hydroxide than when lithium or tetramethylammonium hydroxide is used. Lithium and the quaternary ammonium ions are not strongly complexed by the polyether. The best complexing agents are rings of 15 to 24 atoms including 5 to 8 oxygen atoms. They are formed in higher yields than smaller or larger rings or rings of equal sizes with only 4 oxygen atoms. Even open-chain polyethers such as 3,4,12,13-dibenzo-2,5,8,11,14-pentaoxapentadeca-3,12-diene



were found to form complexes with sodium and potassium ions (*25, 26*).

I was especially interested in the stability of the "complexes" and

Table 1. Diameters of holes in polyether rings in angstrom units.

Macrocyclic polyether	Diameter
All 14-crown-4	1.2–1.5
All 15-crown-5	1.7–2.2
All 18-crown-6	2.6–3.2
All 21-crown-7	3.4–4.3

Table 2. Complexable cations and their diameters in angstrom units.

Group I		Group II		Group III		Group IV	
Li^+	1.36						
Na^+	1.94						
K^+	2.66	Ca^{2+}	1.98				
Cu(I)	1.92	Zn^{2+}	1.48				
Rb^+	2.94	Sr^{2+}	2.26				
Ag^+	2.52	Cd^{2+}	1.94				
Cs^+	3.34	Ba^{2+}	2.68	La^{3+}	2.30		
Au(I)	2.88	Hg(II)	2.20	Tl(I)	2.80	Pb(II)	2.40
Fr^+	3.52	Ra^{2+}	2.80				
NH_4^+	2.86						

the reasons for their behavior. For example, I found that for maximum stability of its salt complex, each cation has an optimum polyether ring size. A complex can form even if the fit is not the best by means of a sandwich complex consisting of two molecules of polyether per cation. The thermal stability of some salt complexes, for example, that with potassium thiocyanate (KSCN), is attested to by the fact that melting points of the complexes are higher than those of the components.

Preparation and Properties of Macrocyclic Polyethers

Spurred by curiosity regarding the factors that induced the stability of the salt complexes (such as the relative sizes of the hole and the cation, and the number and symmetrical arrangement of the oxygen atoms in the polyether ring), I initiated an extensive program of syntheses. Ultimately, about 60 macrocyclic polyethers were prepared, each containing 12 to 60 atoms in a polyether ring, including 4 to 10 oxygen atoms, and some with nitrogen and sulfur atoms. Many of these compounds were found to be useless as complexing agents, but they served to define the effective ones, which are compounds containing 5 to 10 oxygen atoms in the ring, each separated from the next by 2 carbon atoms. Even whole molecules such as the thioureas formed complexes with some crown compounds.

The aromatic macrocyclic polyethers have the following properties. They are neutral, colorless compounds with sharp melting points. They are only slightly soluble in water and alcohols, fairly soluble in aromatic solvents, and very soluble in methylene chloride and chloroform. They undergo substitution reactions characteristic of aromatic ethers (halogenation and nitration) and form formaldehyde resins when treated with paraformaldehyde under acid conditions. They are decomposed by reactions that cause the scission of ethers.

The saturated macrocyclic polyethers are obtained most simply by catalytically hydrogenating the aromatic compounds with ruthenium catalyst. Bridge-bond isomers are obtained from compounds containing two or more aromatic side-ring substituents. For example, dibenzo-18-crown-6 gives a mixture of stereoisomers of dicyclohexyl-18-crown-6. The saturated polyethers are colorless, viscous oils or solids of low melting points. They are thermally stable but, like the aromatic compounds, must be protected from oxygen at high temperatures. They are, as a group, very much more soluble than the aromatic compounds in all solvents, and most of them are even soluble in petroleum ether.

The unique property of the macrocyclic polyethers as complexing agents is their preference for alkali metal ions, which do not form complexes with the numerous ligands used for the transition metal ions. The crown compounds form stable crystalline complexes and solutions of the complexes with some or all of the cations of alkali and alkaline-earth metals plus ammonium ions and others. Some of them, for example, dicyclohexyl-18-crown-6, also form complexes with Co(II) and certain other transition metal ions. The saturated compounds are better complexing agents than the corresponding aromatic compounds.

Three criteria have been used to determine whether complexes form between macrocyclic polyethers and salts: (i) isolation of the complexes as crystals; (ii) characteristic changes in the ultraviolet spectra of the aromatic compounds; and (iii) changes in the solubilities of the polyethers and salts in different solvents.

These compounds have holes of different diameters in the center of the polyether rings (Table 1). The uncomplexed cations also differ in size (Table 2). Depending, therefore, on the relative sizes of the hole and the cation, crystalline complexes with polyether:cation ratios of 1:1, 3:2, and 2:1 have been prepared (Table 3). The aromatic macrocyclic polyethers tend to give high-melting complexes that are not readily soluble in aprotic solvents, whereas the saturated compounds give lower melting complexes that are more

Table 3. Crystalline complexes of polyethers.

Crystalline complex	Mole ratio*
Benzo-15-crown-5	
NaI	1:1
KSCN	2:1
Dibenzo-15-crown-5	
KSCN	2:1
Dibenzo-18-crown-6	
KSCN	1:1
NH_4SCN	1:1
RbSCN	1:1
RbSCN	2:1
CsSCN	2:1
CsSCN	3:2
Dicyclohexyl-18-crown-6	
KI_3	1:1
CsI_3	3:2
Dibenzo-24-crown-8	
KSCN	1:1
KSCN	1:2
Dibenzo-30-crown-10	
KSCN	1:1
NaSCN	1:2

*Polyether:salt.

Table 4. Extraction results. A two-phase liquid extraction was used, methylene chloride and water.

Polyether	Picrate extracted (%)			
	Li^+	Na^+	K^+	Cs^+
Dicyclohexyl-14-crown-4	1.1	0	0	0
Cyclohexyl-15-crown-5	1.6	19.7	8.7	4.0
Dibenzo-18-crown-6	0	1.6	25.2	5.8
Dicyclohexyl-18-crown-6	3.3	25.6	77.8	44.2
Dicyclohexyl-21-crown-7	3.1	22.6	51.3	49.7
Dicyclohexyl-24-crown-8	2.9	8.9	20.1	18.1

soluble. Most of the pure complexes are decomposed by water, the rate and extent of decomposition depending on the proportion of water and the temperature.

It was postulated from the beginning that complexes of macrocyclic polyethers containing fewer than seven oxygen atoms consisted of a cation surrounded by the oxygen atoms arranged symmetrically in a plane. The essential correctness of this view of the structure was confirmed by Truter and her collaborators, who were the first to determine the structures of a number of crystalline salt complexes of crown compounds by x-ray diffraction methods (*27*).

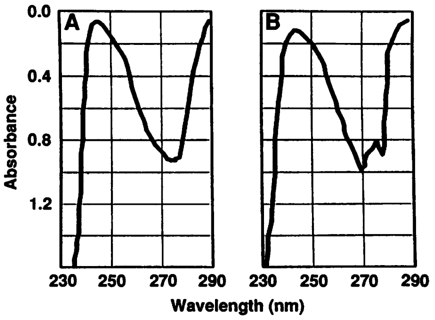
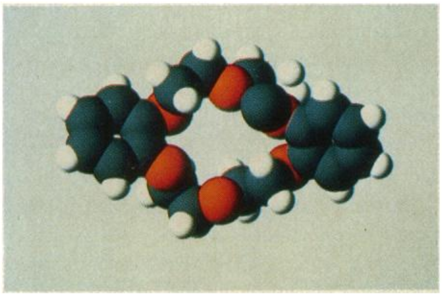


Fig. 3. Effect of sodium hydroxide on the ultraviolet spectrum of dibenzo-18-crown-6 in methanol: (**A**) neutral solution; (**B**) excess hydroxide.



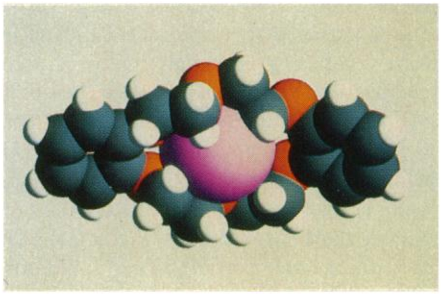


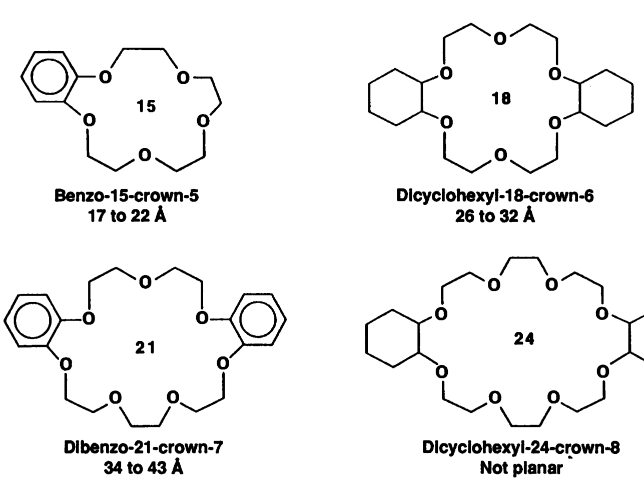
Fig. 4 (**top**). Three-dimensional structure of dibenzo-18-crown-6. **Fig. 5** (**bottom**). Structure of its potassium complex.

All macrocyclic polyethers containing one or more benzo groups have a characteristic absorption maximum at 275 nm in methanol, and the shapes of the curves are altered by the addition of complexable salts (Fig. 3). The spectral evidence is nearly always confirmed by the other two criteria.

Macrocyclic polyethers and complexable salts mutually increase their solubilities in solvents wherein the complexes are soluble. The solubility of the KSCN complex is about 0.1 mol per liter, a 100-fold increase over the solubility of the aromatic compound. Some of the saturated polyethers, such as dicyclohexyl-18-crown-6, solubilize alkali metal salts, particularly those of potassium, in aprotic solvents. Crystals of potassium permanganate, potassium *tert*-butoxide, and potassium palladous tetrachloride ($PdCl_2 + 2KCl$) can be made to dissolve in liquid aromatic hydrocarbons merely by adding dicyclohexyl-18-crown-6. This process is dramatic for the crown complex of potassium permanganate, which colors toluene purple. Benzylpotassium is rendered soluble in *n*-heptane by the polyether, but the polyether ring is gradually decomposed by this organometallic compound. The solubilizing power of the saturated macrocyclic polyethers permits ionic reactions to occur in aprotic media. It is expected that this property will find practical use in catalysis, enhancement of chemical reactivity, separation and recovery of salts, electrochemistry, and analytical chemistry.

One can rank the complexing efficiencies of saturated macrocyclic ethers numerically by measuring the relative distribution of a colored alkali metal salt (such as picrate) between an immiscible organic solvent and water in the presence of the crown ether. If the polyether is ineffective as a complexing agent, the organic phase will be colorless; if the polyether is very powerful, most of the color will be in the organic phase. The efficiencies of most polyethers will lie between these two limits (Table 4) (*28–35*).

Pedersen and Frensdorff determined the stabiliy constants for 1:1 complexes of many macrocyclic polyethers with alkali metal ions by potentiometry with cation-selective electrodes. Selectivity toward the different cations varies with polyether ring size, the optimum ring size being such that the cation just fits into the hole, that is, 15 to 18 for sodium ion, 18 for potassium ion, and 18 to 21 for cesium ion (*33*).



Benzo-15-crown-5
17 to 22 Å

Dicyclohexyl-18-crown-6
26 to 32 Å

Dibenzo-21-crown-7
34 to 43 Å

Dicyclohexyl-24-crown-8
Not planar

Fig. 6. Some macrocyclic polyethers. The number in the center of the structure is the number of atoms in the polyether ring. The estimated diameter of the hole is given below each structure.

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Social Relationships and Health

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Recent scientific work has established both a theoretical basis and strong empirical evidence for a causal impact of social relationships on health. Prospective studies, which control for baseline health status, consistently show increased risk of death among persons with a low quantity, and sometimes low quality, of social relationships. Experimental and quasi-experimental studies of humans and animals also suggest that social isolation is a major risk factor for mortality from widely varying causes. The mechanisms through which social relationships affect health and the factors that promote or inhibit the development and maintenance of social relationships remain to be explored.

> . . . *my father told me of a careful observer, who certainly had heart-disease and died from it, and who positively stated that his pulse was habitually irregular to an extreme degree; yet to his great disappointment it invariably became regular as soon as my father entered the room.*—Charles Darwin (*1*)

SCIENTISTS HAVE LONG NOTED AN ASSOCIATION BETWEEN social relationships and health. More socially isolated or less socially integrated individuals are less healthy, psychologically and physically, and more likely to die. The first major work of empirical sociology found that less socially integrated people were more likely to commit suicide than the most integrated (*2*). In subsequent epidemiologic research age-adjusted mortality rates from all causes of death are consistently higher among the unmarried than the married (*3–5*). Unmarried and more socially isolated people have also manifested higher rates of tuberculosis (*6*), accidents (7), and psychiatric disorders such as schizophrenia (*8, 9*). And as the above quote from Darwin suggests, clinicians have also observed potentially health-enhancing qualities of social relationships and contacts.

The causal interpretation and explanation of these associations has, however, been less clear. Does a lack of social relationships cause people to become ill or die? Or are unhealthy people less likely to establish and maintain social relationships? Or is there some other factor, such as a misanthropic personality, which predisposes people both to have a lower quantity or quality of social relationships and to become ill or die?

Such questions have been largely unanswerable before the last decade for two reasons. First, there was little theoretical basis for causal explanation. Durkheim (*2*) proposed a theory of how social relationships affected suicide, but this theory did not generalize to morbidity and mortality from other causes. Second, evidence of the association between social relationships and health, especially in general human populations, was almost entirely retrospective or cross-sectional before the late 1970s. Retrospective studies from death certificates or hospital records ascertained the nature of a person's social relationships after they had become ill or died, and cross-sectional surveys of general populations determined whether people who reported ill health also reported a lower quality or quantity of relationships. Such studies used statistical control of potential confounding variables to rule out third factors that might produce the association between social relationships and health, but could do this only partially. They could not determine whether poor social relationships preceded or followed ill health.

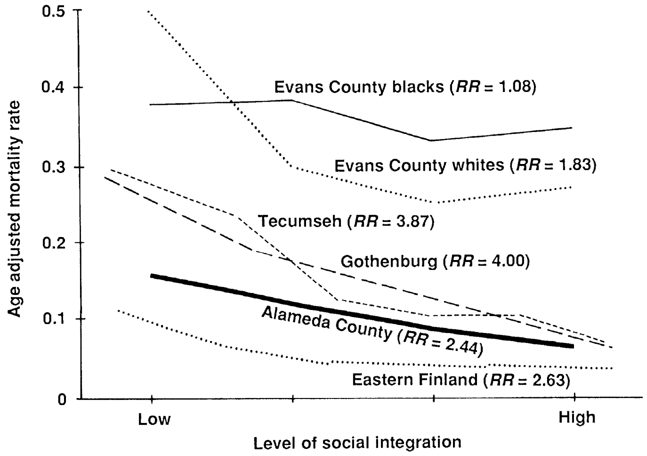

Fig. 1. Level of social integration and age-adjusted mortality for males in five prospective studies. *RR*, the relative risk ratio of mortality at the lowest versus highest level of social integration.

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